Table of Contents

EDWARDS LIFESCIENCES CORPORATION

NOTES TO CONSOLIDATED FINANCIAL STATEMENTS (Continued)

13. EMPLOYEE BENEFIT PLANS (Continued)

The following benefit payments, which reflect expected future service, as appropriate, at December 31, 2019, are expected to be paid (in millions):

2020	$ 4.0
2021	3.6
2022	4.1
2023	5.7
2024	5.1
2024-2026	28.1

As of December 31, 2019, expected employer contributions for 2020 are $1.9 million.

Defined Contribution Plans

The Company's employees in the United States and Puerto Rico are eligible to participate in a qualified defined contribution plan. In the United States, participants may contribute up to 25% of their eligible compensation (subject to tax code limitation) to the plan. Edwards Lifesciences matches the first 4% of the participant's annual eligible compensation contributed to the plan on a dollar-for-dollar basis. Edwards Lifesciences matches the next 2% of the participant's annual eligible compensation to the plan on a 50% basis. In Puerto Rico, participants may contribute up to 25% of their annual compensation (subject to tax code limitation) to the plan. Edwards Lifesciences matches the first 4% of participant's annual eligible compensation contributed to the plan on a 50% basis. The Company also provides a 2% profit sharing contribution calculated on eligible earnings for each employee. Matching contributions relating to Edwards Lifesciences employees were $31.4 million, $26.6 million, and $19.9 million in 2019, 2018, and 2017, respectively.

The Company also has nonqualified deferred compensation plans for a select group of employees. The plans provide eligible participants the opportunity to defer eligible compensation to future dates specified by the participant with a return based on investment alternatives selected by the participant. The amount accrued under these nonqualified plans was $88.7 million and $68.5 million at December 31, 2019 and 2018, respectively.

14. COMMON STOCK

Treasury Stock

In November 2017, the Board of Directors approved a stock repurchase program authorizing the Company to purchase up to $1.0 billion of the Company's common stock. In May 2019, the Board of Directors approved a new stock repurchase program authorizing the Company to purchase up to an additional $1.0 billion of the Company's common stock. The repurchase programs do not have an expiration date. Stock repurchased under the programs may be used to offset obligations under the Company's employee stock-based benefit programs and stock-based business acquisitions, and will reduce the total shares outstanding.

During 2019, 2018, and 2017, the Company repurchased 1.5 million, 5.5 million, and 7.7 million shares, respectively, at an aggregate cost of $263.3 million, $795.5 million, and $763.3 million, respectively, including shares purchased under the accelerated share repurchase ("ASR") agreements described below and shares acquired to satisfy tax withholding obligations in connection with the vesting of restricted stock units issued to employees. The timing and size of any future stock repurchases are subject to a variety of factors, including expected dilution from stock plans, cash capacity, and the market price of the Company's common stock.

Accelerated Share Repurchase

During 2019, 2018, and 2017, the Company entered into ASR agreements providing for the repurchase of the Company's common stock based on the volume-weighted average price ("VWAP") of the Company's common stock during the term of the

Table of Contents

EDWARDS LIFESCIENCES CORPORATION

NOTES TO CONSOLIDATED FINANCIAL STATEMENTS (Continued)

14. COMMON STOCK (Continued)

agreements, less a discount. The following table summarizes the terms of the ASR agreements (dollars and shares in millions, except per share data):

		Initial Delivery			Final Settlement		
Agreement Date	Amount Paid	Shares Received	Price per Share (a)	Value of Shares as % of Contract Value	Settlement Date	Total Shares Received	Average Price per Share (a)
November 2017	$ 150.0	1.1	$ 109.86	80%	December 2017	1.3	$ 114.85
April 2018	$ 400.0	2.5	$ 127.36	80%	July 2018	2.8	$ 142.37
October 2018	$ 250.0	1.4	$ 139.22	80%	November 2018	1.7	$ 150.54
May 2019	$ 150.0	0.7	$ 178.66	80%	May 2019	0.8	$ 178.42
May 2019	$ 100.0	0.5	$ 170.02	80%	June 2019	0.6	$ 178.46

The ASR agreements were accounted for as two separate transactions: (1) the value of the initial delivery of shares was recorded as shares of common stock acquired in a treasury stock transaction on the acquisition date and (2) the remaining amount of the purchase price paid was recorded as a forward contract indexed to the Company's own common stock and was recorded in "*Additional Paid-in Capital*" on the consolidated balance sheets. The initial delivery of shares resulted in an immediate reduction of the outstanding shares used to calculate the weighted-average common shares outstanding for basic and diluted earnings per share. The Company determined that the forward contract indexed to the Company's common stock met all the applicable criteria for equity classification and, therefore, was not accounted for as a derivative instrument.

Employee and Director Stock Plans

The Edwards Lifesciences Corporation Long-term Stock Incentive Compensation Program (the "Program") provides for the grant of incentive and non-qualified stock options, restricted stock, and restricted stock units for eligible employees and contractors of the Company. Under the Program, these grants are awarded at a price equal to the fair market value at the date of grant based upon the closing price on that date. Options to purchase shares of the Company's common stock granted under the Program generally vest over predetermined periods of between three to four years and expire seven years after the date of grant. Service-based restricted stock units of the Company's common stock granted under the Program generally vest over predetermined periods ranging from three to four years after the date of grant. Market-based restricted stock units of the Company's common stock granted under the Program vest over three years based on a combination of certain service and market conditions. The actual number of shares issued will be determined based on the Company's total stockholder return relative to a selected industry peer group. Performance-based restricted stock units vest based on a combination of certain service conditions and upon achievement of specified milestones. Under the Program, the number of shares of common stock available for issuance under the Program was 109.2 million shares. No more than 11.2 million shares reserved for issuance may be granted in the form of restricted stock or restricted stock units.

The Company also maintains the Nonemployee Directors Stock Incentive Compensation Program (the "Nonemployee Directors Program"). Under the Nonemployee Directors Program, annually each nonemployee director may receive up to 40,000 stock options or 16,000 restricted stock units of the Company's common stock, or a combination thereof, provided that in no event may the total value of the combined annual award exceed $0.2 million. These grants generally vest over one year from the date of grant. Under the Nonemployee Directors Program, an aggregate of 2.8 million shares of the Company's common stock has been authorized for issuance.

The Company has an employee stock purchase plan for United States employees and a plan for international employees (collectively "ESPP"). Under the ESPP, eligible employees may purchase shares of the Company's common stock at 85% of the lower of the fair market value of Edwards Lifesciences common stock on the effective date of subscription or the date of purchase. Under the ESPP, employees can authorize the Company to withhold up to 12% of their compensation for common stock purchases, subject to certain limitations. The ESPP is available to all active employees of the Company paid from the United States payroll and to eligible employees of the Company outside the United States, to the extent permitted by local law. The ESPP for United States employees is qualified under Section 423 of the Internal Revenue Code. The number of shares of common stock authorized for issuance under the ESPP was 15.3 million shares.

Table of Contents

EDWARDS LIFESCIENCES CORPORATION

NOTES TO CONSOLIDATED FINANCIAL STATEMENTS (Continued)

14. COMMON STOCK (Continued)

The fair value of each option award and employee stock purchase subscription is estimated on the date of grant using the Black-Scholes option valuation model that uses the assumptions noted in the following tables. The risk-free interest rate is estimated using the U.S. Treasury yield curve and is based on the expected term of the award. Expected volatility is estimated based on a blend of the weighted-average of the historical volatility of Edwards Lifesciences' stock and the implied volatility from traded options on Edwards Lifesciences' stock. The expected term of awards granted is estimated from the vesting period of the award, as well as historical exercise behavior, and represents the period of time that awards granted are expected to be outstanding. The Company uses historical data to estimate forfeitures and has estimated an annual forfeiture rate of 6.4%.

The Black-Scholes option pricing model was used with the following weighted-average assumptions for options granted during the following periods:

Option Awards

	2019	2018	2017
Average risk-free interest rate	2.3%	2.9%	1.8%
Expected dividend yield	None	None	None
Expected volatility	30%	29%	33%
Expected life (years)	5.1	5.0	4.6
Fair value, per share	$ 54.51	$ 42.51	$ 33.74

The Black-Scholes option pricing model was used with the following weighted-average assumptions for ESPP subscriptions granted during the following periods:

ESPP

	2019	2018	2017
Average risk-free interest rate	2.4%	1.7%	0.8%
Expected dividend yield	None	None	None
Expected volatility	32%	33%	33%
Expected life (years)	0.6	0.6	0.6
Fair value, per share	$ 49.29	$ 36.53	$ 25.69

The fair value of market-based restricted stock units was determined using a Monte Carlo simulation model, which uses multiple input variables to determine the probability of satisfying the market condition requirements. The weighted-average assumptions used to determine the fair value of the market-based restricted stock units during the years ended December 31, 2019, 2018, and 2017 included a risk-free interest rate of 2.2%, 2.7%, and 1.7%, respectively, and an expected volatility rate of 29.4%, 29.7%, and 30.2%, respectively.

EDWARDS LIFESCIENCES CORPORATION

NOTES TO CONSOLIDATED FINANCIAL STATEMENTS (Continued)

14. COMMON STOCK (Continued)

Stock option activity during the year ended December 31, 2019 under the Program and the Nonemployee Directors Program was as follows (in millions, except years and per-share amounts):

	Shares	Weighted-Average Exercise Price	Weighted-Average Remaining Contractual Term	Aggregate Intrinsic Value
Outstanding as of December 31, 2018	7.2	$ 73.42		
Options granted	0.7	179.53		
Options exercised	(2.2)	49.59		
Outstanding as of December 31, 2019	5.7	96.57	3.4 years	$ 780.9
Exercisable as of December 31, 2019	3.8	72.07	2.5 years	611.4
Vested and expected to vest as of December 31, 2019	5.4	94.13	3.3 years	756.7

The following table summarizes nonvested restricted stock unit activity during the year ended December 31, 2019 under the Program and the Nonemployee Directors Program (in millions, except per-share amounts):

	Shares	Weighted-Average Grant-Date Fair Value
Nonvested as of December 31, 2018	1.0	$ 113.86
Granted (a)	0.3	182.70
Vested	(0.3)	90.78
Forfeited (b)	(0.1)	118.74
Nonvested as of December 31, 2019	0.9	140.68

(a) The shares granted includes 33,225 shares of market-based restricted stock units granted during 2019, which represents the targeted number of shares to be issued.

(b) The shares forfeited includes 10,660 shares related to the cancellation of market-based restricted stock units since the payout percentage achieved at the end of the performance period was less than target. As described above, the actual number of shares ultimately issued is determined based on the Company's total stockholder return relative to a selected industry peer group.

The intrinsic value of stock options exercised and restricted stock units vested during the years ended December 31, 2019, 2018, and 2017 were $382.1 million, $281.1 million, and $205.2 million, respectively. The intrinsic value of stock options is calculated as the amount by which the market price of the Company's common stock exceeds the exercise price of the option. During the years ended December 31, 2019, 2018, and 2017, the Company received cash from exercises of stock options of $110.4 million, $103.7 million, and $77.6 million, respectively, and tax benefits from exercises of stock options and vesting of restricted stock units of $85.1 million, $62.5 million, and $66.9 million, respectively. The total grant-date fair value of stock options vested during the years ended December 31, 2019, 2018, and 2017 were $31.2 million, $29.0 million, and $26.3 million, respectively.

As of December 31, 2019, the total remaining unrecognized compensation expense related to nonvested stock options, restricted stock units, and employee stock purchase subscriptions amounted to $126.3 million, which will be amortized over the weighted-average remaining requisite service period of 30 months.

Table of Contents

EDWARDS LIFESCIENCES CORPORATION

NOTES TO CONSOLIDATED FINANCIAL STATEMENTS (Continued)

15. ACCUMULATED OTHER COMPREHENSIVE LOSS

Presented below is a summary of activity for each component of "*Accumulated Other Comprehensive Loss*" for the years ended December 31, 2019, 2018, and 2017.

	Foreign Currency Translation Adjustments	Unrealized Gain (Loss) on Hedges	Unrealized Gain (Loss) on Available-for-sale Investments	Unrealized Pension Costs (a)	Total Accumulated Other Comprehensive Loss
			(in millions)		
December 31, 2016	$ (197.6)	$ 16.7	$ 0.1	$ (17.6)	$ (198.4)
Other comprehensive income (loss) before reclassifications	84.1	(43.5)	(8.3)	9.7	42.0
Amounts reclassified from accumulated other comprehensive loss	—	(6.5)	3.1	(5.1)	(8.5)
Deferred income tax benefit (expense)	13.4	19.4	0.5	(1.1)	32.2
December 31, 2017	(100.1)	(13.9)	(4.6)	(14.1)	(132.7)
Impact from adoption of ASU 2016-16 and ASU 2018-02	(4.9)	(2.9)	—	—	(7.8)
January 1, 2018	(105.0)	(16.8)	(4.6)	(14.1)	(140.5)
Other comprehensive (loss) income before reclassifications	(36.7)	35.1	(3.1)	7.6	2.9
Amounts reclassified from accumulated other comprehensive loss	—	19.1	2.9	(6.7)	15.3
Deferred income tax expense	(1.9)	(13.8)	(0.2)	(0.3)	(16.2)
December 31, 2018	(143.6)	23.6	(5.0)	(13.5)	(138.5)
Other comprehensive (loss) income before reclassifications	(1.5)	27.9	7.9	(3.2)	31.1
Amounts reclassified from accumulated other comprehensive loss	(6.6)	(44.2)	0.4	0.7	(49.7)
Deferred income tax (expense) benefit	(3.1)	5.2	(1.6)	0.6	1.1
December 31, 2019	$ (154.8)	$ 12.5	$ 1.7	$ (15.4)	$ (156.0)

Table of Contents

EDWARDS LIFESCIENCES CORPORATION

NOTES TO CONSOLIDATED FINANCIAL STATEMENTS (Continued)

15. ACCUMULATED OTHER COMPREHENSIVE LOSS (Continued)

(a) For the years ended December 31, 2019, 2018, and 2017, the change in unrealized pension costs consisted of the following (in millions):

	Pre-Tax Amount	Tax (Expense) Benefit	Net of Tax Amount
2019			
Prior service credit arising during period	$ 4.6	$ (0.6)	$ 4.0
Amortization of prior service credit	(0.2)	0.1	(0.1)
Net prior service credit arising during period	4.4	(0.5)	3.9
Net actuarial loss arising during period	(6.9)	1.1	(5.8)
Unrealized pension costs, net	$ (2.5)	$ 0.6	$ (1.9)
2018			
Prior service credit arising during period	$ 3.3	$ (0.9)	$ 2.4
Amortization of prior service credit	(0.1)	—	(0.1)
Net prior service credit arising during period	3.2	(0.9)	2.3
Net actuarial loss arising during period	(2.3)	0.6	(1.7)
Unrealized pension credits, net	$ 0.9	$ (0.3)	$ 0.6
2017			
Prior service credit arising during period	$ 3.5	$ (0.4)	$ 3.1
Amortization of prior service cost	0.2	—	0.2
Net prior service credit arising during period	3.7	(0.4)	3.3
Net actuarial gain arising during period	0.9	(0.7)	0.2
Unrealized pension credits, net	$ 4.6	$ (1.1)	$ 3.5

Table of Contents

EDWARDS LIFESCIENCES CORPORATION

NOTES TO CONSOLIDATED FINANCIAL STATEMENTS (Continued)

15. ACCUMULATED OTHER COMPREHENSIVE LOSS (Continued)

The following table provides information about amounts reclassified from "*Accumulated Other Comprehensive Loss*" (in millions):

Details about Accumulated Other Comprehensive Loss Components	Years Ended December 31, 2019	2018	Affected Line on Consolidated Statements of Operations
Foreign currency translation adjustments	$ 6.6	$ —	Other (income) expense, net
	(1.6)	—	Provision for income taxes
	$ 5.0	$ —	Net of tax
Gain (loss) on hedges	$ 40.9	$ (17.3)	Cost of sales
	1.9	(2.3)	Selling, general, and administrative expenses
	1.4	0.5	Other (income) expense, net
	44.2	(19.1)	Total before tax
	(11.0)	4.4	Provision for income taxes
	$ 33.2	$ (14.7)	Net of tax
Gain (loss) on available-for-sale investments	$ (0.4)	$ (2.9)	Other (income) expense, net
	(0.3)	0.2	Provision for income taxes
	$ (0.7)	$ (2.7)	Net of tax
Amortization of pension adjustments	$ —	$ 7.1	Special (gains) charges, net
	(0.7)	(0.4)	Other (income) expense, net
	(0.7)	6.7	Total before tax
	0.1	(0.6)	Provision for income taxes
	$ (0.6)	$ 6.1	Net of tax

16. OTHER (INCOME) EXPENSE, NET

	Years Ended December 31, 2019	2018	2017
		(in millions)	
Foreign exchange (gains) losses, net	$ (5.9)	$ (6.7)	$ 5.4
(Gain) loss on investments	(0.5)	1.7	2.7
Non-service cost components of net periodic pension benefit cost (credit)	0.2	(0.1)	(6.1)
Other	(2.0)	1.1	(0.6)
Total other (income) expense, net	$ (8.2)	$ (4.0)	$ 1.4

Table of Contents

EDWARDS LIFESCIENCES CORPORATION

NOTES TO CONSOLIDATED FINANCIAL STATEMENTS (Continued)

17. INCOME TAXES

The Company's income before provision for income taxes was generated from United States and international operations as follows (in millions):

	Years Ended December 31,		
	2019	2018	2017
United States	$ 383.4	$ 266.1	$ 491.5
International, including Puerto Rico	783.1	495.3	543.4
	$ 1,166.5	$ 761.4	$ 1,034.9

The provision for income taxes consists of the following (in millions):

	Years Ended December 31,		
	2019	2018	2017
Current			
United States:			
Federal	$ 31.3	$ 10.9	$ 330.8
State and local	48.7	13.6	32.8
International, including Puerto Rico	29.1	35.9	60.6
Current income tax expense	$ 109.1	$ 60.4	$ 424.2
Deferred			
United States:			
Federal	$ 28.3	$ (16.1)	$ 39.3
State and local	(18.3)	(22.4)	(3.8)
International, including Puerto Rico	0.5	17.3	(8.4)
Deferred income tax expense (benefit)	10.5	(21.2)	27.1
Total income tax provision	$ 119.6	$ 39.2	$ 451.3

Table of Contents

EDWARDS LIFESCIENCES CORPORATION

NOTES TO CONSOLIDATED FINANCIAL STATEMENTS (Continued)

17. INCOME TAXES (Continued)

The components of deferred tax assets and liabilities are as follows (in millions):

	December 31,	
	2019	2018
Deferred tax assets		
Compensation and benefits	$ 91.6	$ 71.4
Benefits from uncertain tax positions	22.5	22.2
Net tax credit carryforwards	108.4	94.4
Net operating loss carryforwards	57.6	42.1
Accrued liabilities	6.1	57.9
Inventories	12.9	7.2
State income taxes	0.5	0.6
Investments	1.5	1.6
Lease liability obligations	18.4	—
Other	1.9	4.1
Total deferred tax assets	321.4	301.5
Deferred tax liabilities		
Property, plant, and equipment	(22.6)	(24.5)
Cash flow and net investment hedges	(6.8)	(4.5)
Deferred tax on foreign earnings	(0.1)	(0.6)
Right-of-use assets	(17.5)	—
Inventories	—	(3.9)
Other intangible assets	(71.0)	(77.1)
Other	(2.2)	(0.1)
Total deferred tax liabilities	(120.2)	(110.7)
Valuation allowance	(65.8)	(46.7)
Net deferred tax assets	$ 135.4	$ 144.1

During 2019, net deferred tax assets decreased $8.7 million, including items that were recorded to stockholders' equity and which did not impact the Company's income tax provision.

The valuation allowance of $65.8 million as of December 31, 2019 reduces certain deferred tax assets to amounts that are more likely than not to be realized. This allowance primarily relates to the net operating loss carryforwards of certain non-United States subsidiaries and certain non-United States credit carryforwards.

EDWARDS LIFESCIENCES CORPORATION

NOTES TO CONSOLIDATED FINANCIAL STATEMENTS (Continued)

17. INCOME TAXES (Continued)

Net operating loss and capital loss carryforwards and the related carryforward periods at December 31, 2019 are summarized as follows (in millions):

	Carryforward Amount	Tax Benefit Amount	Valuation Allowance	Net Tax Benefit	Carryforward Period Ends
United States federal net operating losses	$ 35.9	$ 7.5	$ —	$ 7.5	2030-2037
United States federal net operating losses	11.3	2.4	—	2.4	Indefinite
United States state net operating losses	32.1	2.1	(2.1)	—	2026-2039
United States state net operating losses	1.0	—	—	—	Indefinite
Non-United States net operating losses	52.4	4.7	(4.1)	0.6	2020-2027
Non-United States net operating losses	239.1	40.7	(35.2)	5.5	Indefinite
United States capital losses	34.1	0.5	(0.5)	—	2022
Total	$ 405.9	$ 57.9	$ (41.9)	$ 16.0	

Certain tax attributes are subject to an annual limitation as a result of the acquisitions of Harpoon Medical, Inc. and CAS Medical Systems, Inc. (see Note 8), which constitute a change of ownership as defined under Internal Revenue Code Section 382.

The gross tax credit carryforwards and the related carryforward periods at December 31, 2019 are summarized as follows (in millions):

	Carryforward Amount	Valuation Allowance	Net Tax Benefit	Carryforward Period Ends
California research expenditure tax credits	$ 124.4	$ —	$ 124.4	Indefinite
Federal research expenditure tax credits	1.5	—	1.5	2026-2039
Puerto Rico purchases credit	21.8	(21.8)	—	Indefinite
Total	$ 147.7	$ (21.8)	$ 125.9	

The Company has $124.4 million of California research expenditure tax credits it expects to use in future periods. The credits may be carried forward indefinitely. Based upon anticipated future taxable income, the Company expects that it is more likely than not that all California research expenditure tax credits will be utilized, although the utilization of the full benefit is expected to occur over a number of years and into the distant future. Accordingly, no valuation allowance has been provided. The Company has $21.8 million of Puerto Rico purchases credit. Throughout its history and into the future, the Puerto Rico operations generate or are expected to generate credits each year in excess of its ability to utilize credits in those years. As a result, even though the credits have an indefinite life, the Company continues to record a valuation allowance on the credit carryforwards.

On December 22, 2017, Public Law 115-97, commonly referred to as the Tax Cuts and Jobs Act (the "2017 Act"), was signed into law. The 2017 Act (1) reduced the U.S. federal corporate tax rate from 35 percent to 21 percent for tax years beginning after December 31, 2017, (2) required companies to pay a one-time mandatory deemed repatriation tax on the cumulative earnings of certain foreign subsidiaries that were previously tax deferred, and (3) created new taxes on certain foreign earnings in future years.

On December 22, 2017, Staff Accounting Bulletin No. 118 ("SAB 118") was issued to address the application of generally accepted accounting principles in the United States of America in situations when a registrant does not have the necessary information available, prepared, or analyzed (including computations) in reasonable detail to complete the accounting for certain income tax effects of the 2017 Act. In accordance with SAB 118, as of December 31, 2017, the Company had estimated provisional amounts for (1) $3.3 million of tax benefits in connection with the remeasurement of certain tax assets and liabilities, (2) $297.4 million of net tax expense (discussed below) in connection with the one-time mandatory deemed repatriation tax on cumulative earnings of certain foreign subsidiaries, and (3) $32.3 million of tax benefits associated with a tax reform related restructuring. In accordance with SAB 118, during 2018 the Company adjusted the provisional amounts as described below.

Table of Contents

EDWARDS LIFESCIENCES CORPORATION

NOTES TO CONSOLIDATED FINANCIAL STATEMENTS (Continued)

17. INCOME TAXES (Continued)

As a result of Internal Revenue Service ("IRS") guidance issued subsequent to the 2017 Act, the $32.3 million of tax benefits associated with the tax reform related restructuring mentioned above were reversed in 2018. In addition, during 2018, the Company recorded a $12.8 million reduction in the repatriation tax and an additional benefit of $3.7 million in connection with the remeasurement of deferred tax assets. In accordance with SAB 118, the Company completed its accounting for the 2017 Act during the fourth quarter of 2018. In addition, the Company elected to pay the repatriation tax in installments over eight years.

The Company asserts that $1.1 billion of its foreign earnings continue to be indefinitely reinvested and it intends to repatriate $140.7 million of its foreign earnings as of December 31, 2019. The estimated net tax liability (after credits) on the indefinitely reinvested earnings if repatriated is $13.6 million.

The Company has received tax incentives in certain non-U.S. tax jurisdictions, the primary benefit for which will expire in 2029. The tax reductions as compared to the local statutory rates were $157.6 million ($0.75 per diluted share), $144.9 million ($0.70 per diluted share), and $81.0 million ($0.39 per diluted share) for the years ended December 31, 2019, 2018, and 2017, respectively.

A reconciliation of the United States federal statutory income tax rate to the Company's effective income tax rate is as follows (in millions):

	Years Ended December 31,		
	2019	2018	2017
Income tax expense at U.S. federal statutory rate	$ 245.0	$ 159.9	$ 362.2
Foreign income taxed at different rates	(75.0)	(16.2)	(106.9)
State and local taxes, net of federal tax benefit	11.9	6.8	11.5
Tax credits, federal and state	(42.9)	(36.7)	(25.8)
Build (release) of reserve for prior years' uncertain tax positions	5.0	(35.5)	(7.7)
U.S. tax on foreign earnings, net of credits	(2.9)	(12.2)	(30.3)
Tax on global intangible low-taxed income	32.0	—	—
Foreign-derived intangible income deduction	(7.2)	(6.6)	—
Deductible employee share-based compensation	(57.6)	(41.8)	(48.2)
Nondeductible employee share-based compensation	3.2	2.8	3.9
Impact related to 2017 U.S. Tax Reform	2.8	15.8	294.1
Other	5.3	2.9	(1.5)
Income tax provision	$ 119.6	$ 39.2	$ 451.3

The Company's effective tax rate for 2019 increased in comparison to 2018 primarily because of the increase in the U.S. tax on global intangible low-taxed income and the tax benefit in 2018 from audit settlements.

Uncertain Tax Positions

As of December 31, 2019 and 2018, the gross uncertain tax positions were $203.1 million and $150.7 million, respectively. The Company estimates that these liabilities would be reduced by $50.1 million and $42.7 million, respectively, from offsetting tax benefits associated with the correlative effects of potential transfer pricing adjustments, state income taxes, and timing adjustments. The net amounts of $153.0 million and $108.0 million, respectively, if not required, would favorably affect the Company's effective tax rate.

Table of Contents

EDWARDS LIFESCIENCES CORPORATION

NOTES TO CONSOLIDATED FINANCIAL STATEMENTS (Continued)

17. INCOME TAXES (Continued)

A reconciliation of the beginning and ending amount of uncertain tax positions, excluding interest, penalties, and foreign exchange, is as follows (in millions):

	December 31,		
	2019	2018	2017
Uncertain gross tax positions, January 1	$ 150.7	$ 225.6	$ 245.5
Current year tax positions	55.4	37.8	77.7
Increase in prior year tax positions	0.8	13.9	63.7
Decrease in prior year tax positions	(3.8)	(78.8)	(65.0)
Settlements	—	(46.5)	(95.3)
Lapse of statutes of limitations	—	(1.3)	(1.0)
Uncertain gross tax positions, December 31	$ 203.1	$ 150.7	$ 225.6

The table above summarizes the gross amounts of uncertain tax positions without regard to reduction in tax liabilities or additions to deferred tax assets and liabilities if such uncertain tax positions were settled.

The Company recognizes interest and penalties, if any, related to uncertain tax positions in the provision for income taxes. As of December 31, 2019, the Company had accrued $9.3 million (net of $3.5 million tax benefit) of interest related to uncertain tax positions, and as of December 31, 2018, the Company had accrued $4.6 million (net of $1.9 million tax benefit) of interest related to uncertain tax positions. During 2019, 2018, and 2017, the Company recognized interest expense (benefit), net of tax benefit, of $4.7 million, $(2.8) million, and $(7.3) million, respectively, in "*Provision for Income Taxes*" on the consolidated statements of operations.

The Company strives to resolve open matters with each tax authority at the examination level and could reach agreement with a tax authority at any time. While the Company has accrued for matters it believes are more likely than not to require settlement, the final outcome with a tax authority may result in a tax liability that is more or less than that reflected in the consolidated financial statements. Furthermore, the Company may later decide to challenge any assessments, if made, and may exercise its right to appeal. The uncertain tax positions are reviewed quarterly and adjusted as events occur that affect potential liabilities for additional taxes, such as lapsing of applicable statutes of limitations, proposed assessments by tax authorities, negotiations between tax authorities, identification of new issues, and issuance of new legislation, regulations, or case law. Management believes that adequate amounts of tax and related penalty and interest have been provided in income tax expense for any adjustments that may result from these uncertain tax positions.

At December 31, 2019, all material state, local, and foreign income tax matters have been concluded for years through 2008. During 2018, the Company signed agreements with the IRS to settle tax years 2009 through 2014, including transfer pricing matters and the tax treatment of a portion of a litigation settlement payment received in 2014. The IRS began its examination of the 2015 and 2016 tax years during the fourth quarter of 2018 and its examination of the 2017 tax year during the first quarter of 2019.

During 2018, the Company executed an Advance Pricing Agreement ("APA") between the United States and Switzerland governments for tax years 2009 through 2020 covering various transfer pricing matters . Certain intercompany transactions covering tax years 2015 through 2019 were not resolved and those related tax positions remain uncertain. These transfer pricing matters may be significant to the Company's consolidated financial statements. Based upon the information currently available and numerous possible outcomes, the Company cannot reasonably estimate what, if any, changes in its existing uncertain tax positions may occur in the next 12 months and, therefore, has recorded the gross uncertain tax positions as a long-term liability.

In addition, the Company executed other APAs as follows: during 2017, an APA between the United States and Japan covering tax years 2015 through 2019; and during 2018, APAs between Japan and Singapore and between Switzerland and Japan covering tax years 2015 through 2019. The Company is evaluating filing to renew some or all of these APAs for the years 2020 and forward. The execution of some or all of these APAs depends on a number of variables outside of the Company's control.

Table of Contents

EDWARDS LIFESCIENCES CORPORATION

NOTES TO CONSOLIDATED FINANCIAL STATEMENTS (Continued)

18. LEGAL PROCEEDINGS

On January 28, 2019, Abbott Cardiovascular Systems, Inc. and Evalve, Inc., both subsidiaries of Abbott Laboratories (collectively "Abbott") filed a lawsuit against Edwards Lifesciences Corporation and Edwards Lifesciences, LLC, ("Edwards") in the Federal District Court in the District of Delaware alleging that the *Edwards PASCAL* heart valve repair system infringes certain claims of Abbott's U.S. Patent Nos. 7,288,097, 6,752,813, 7,563,267, 7,736,388, and 8,057,493, seeking unspecified monetary damages and preliminary and permanent injunctive relief. Thereafter, Abbott sought a preliminary injunction and a temporary restraining order and the court denied these requests. Trial is scheduled for May 6, 2020.

On January 28, 2019, Abbott and its Abbott Medical UK Limited subsidiary (inclusively and collectively also "Abbott") filed a lawsuit in the United Kingdom in the High Court of Justice, Chancery Division, Patents Court, against Edwards Lifesciences Limited, alleging that the *Edwards PASCAL* heart valve repair system infringes certain claims of Abbott's UK national patents arising from EP 1 624 810 B1 (the " '810 patent") and EP 1 408 850 B1 (the " '850 patent"). Abbott requested a preliminary injunction and the High Court denied this request. Trial proceedings began on December 9, 2019, and a decision is expected in early 2020.

On January 28, 2019, Abbott Medical GmbH (inclusively and collectively also "Abbott") filed a lawsuit in the District Court in Düsseldorf, Germany against Edwards Lifesciences Corporation and its German subsidiary, Edwards Lifesciences Services GmbH, alleging that the *Edwards PASCAL* heart valve repair system infringes certain claims of Abbott's German national patents arising from the '810 and '850 European patents. The District Court has scheduled trial for March 19, 2020 for the '810 patent and for July 14, 2020 for the '850 patent. On March 15, 2019, Edwards filed a lawsuit in the German Patent Court in Munich, Germany, alleging that Abbott's '850 patent is invalid. The Abbott '810 patent is subject to opposition proceedings at the European Patent Office, where a first instance opposition panel determined that the '810 patent was valid with amendment. Edwards will appeal.

On January 28, 2019, Abbott and Abbott Medical AG (inclusively and collectively also "Abbott") filed a lawsuit in the Federal Patent Court in St. Gallen, Switzerland against Edwards Lifesciences AG, Edwards Lifesciences Technology Sàrl, Edwards Lifesciences IPRM AG, and Mitral Valve Technologies Sàrl, alleging that the *Edwards PASCAL* heart valve repair system infringes Abbott's Swiss national patents arising from the same European patents. The court subsequently granted Abbott's request for a preliminary injunction on the '850 patent and Edwards has appealed.

On January 28, 2019, Abbott Cardiovascular System Inc., Abbott Medical Italia S.p.A and Evalve Inc. (inclusively and collectively also "Abbott") filed a lawsuit in the Civil Court of Milan, Italy against Edwards Lifesciences Corporation, Edwards Lifesciences LLC, and Edwards Lifesciences Italia SpA, alleging that the *Edwards PASCAL* heart valve repair system infringes Abbott's Italian national patent arising from its '850 European patent. The lawsuit seeks a preliminary injunction. The Company intends to defend itself vigorously in all of the above matters.

On February 22, 2019, Edwards Lifesciences Corporation and Edwards Lifesciences, LLC filed a lawsuit against Abbott Cardiovascular Systems, Inc. in the Federal District Court in the Central District of California alleging that Abbott's *MITRACLIP* device infringes Edwards' U.S. Patent Nos. 6,719,767, 7,011,669, and 8,062,313 related to heart implant technology and seeking unspecified monetary damages. A trial date has not yet been scheduled.

Because the ultimate outcome of the above matters involve judgments, estimates, and inherent uncertainties, charges related to such matters could have a material adverse impact on the Company's consolidated financial results. The Company records accruals for loss contingencies to the extent it is probable that a liability has been incurred and the amount of the related loss can be reasonably estimated. Where a loss is reasonably possible (including potential losses in excess of the amounts accrued by the Company), the Company will disclose a reasonable estimate of the amount of loss or range of possible losses with respect to the loss contingency (including potential losses in excess of the amounts accrued by the Company), unless the Company is not able to reasonably estimate the amount or range of reasonably possible losses. With respect to the matters above, the Company is not able to estimate the amount or range of any loss for these matters.

In addition, the Company is or may be a party to, or may otherwise be responsible for, pending or threatened lawsuits including those related to products and services currently or formerly manufactured or performed, as applicable, by the Company, workplace and employment matters or governmental investigations (the "Other Lawsuits"). The Other Lawsuits raise

EDWARDS LIFESCIENCES CORPORATION

NOTES TO CONSOLIDATED FINANCIAL STATEMENTS (Continued)

18. LEGAL PROCEEDINGS (Continued)

difficult and complex factual and legal issues and are subject to many uncertainties, including, but not limited to, the facts and circumstances of each particular case or claim, the jurisdiction in which each suit is brought, and differences in applicable law. Management does not believe that any loss relating to the Other Lawsuits would have a material adverse effect on the Company's overall financial condition, results of operations or cash flows. However, the resolution of one or more of the Other Lawsuits in any reporting period, could have a material adverse impact on the Company's financial results for that period. The Company is not able to estimate the amount or range of any loss for legal contingencies related to the Other Lawsuits for which there is no reserve or additional loss for matters already reserved.

The Company is subject to various environmental laws and regulations both within and outside of the United States. The Company's operations, like those of other medical device companies, involve the use of substances regulated under environmental laws, primarily in manufacturing and sterilization processes. While it is difficult to quantify the potential impact of continuing compliance with environmental protection laws, management believes that such compliance will not have a material impact on the Company's financial results.

19. SEGMENT INFORMATION

The Company conducts operations worldwide and is managed in the following geographical regions: United States, Europe, Japan, and Rest of World. All regions sell products that are used to treat advanced cardiovascular disease.

The Company's geographic segments are reported based on the financial information provided to the Chief Operating Decision Maker (the Chief Executive Officer). The Company evaluates the performance of its geographic segments based on net sales and operating income. The accounting policies of the segments are substantially the same as those described in Note 2. Segment net sales and segment operating income are based on internally derived standard foreign exchange rates, which may differ from year to year, and do not include inter-segment profits. Because of the interdependence of the reportable segments, the operating profit as presented may not be representative of the geographical distribution that would occur if the segments were not interdependent. Net sales by geographic area are based on the location of the customer.

Certain items are maintained at the corporate level and are not allocated to the segments. The non-allocated items include net interest expense, global marketing expenses, corporate research and development expenses, manufacturing variances, corporate headquarters costs, special gains and charges, stock-based compensation, foreign currency hedging activities, certain litigation costs, changes in the fair value of contingent consideration liabilities, and most of the Company's amortization expense. Although most of the Company's depreciation expense is included in segment operating income, due to the Company's methodology for cost build-up, it is impractical to determine the amount of depreciation expense included in each segment, and, therefore, a portion is maintained at the corporate level. The Company neither discretely allocates assets to its operating segments, nor evaluates the operating segments using discrete asset information.

Table of Contents

EDWARDS LIFESCIENCES CORPORATION

NOTES TO CONSOLIDATED FINANCIAL STATEMENTS (Continued)

19. SEGMENT INFORMATION (Continued)

The table below presents information about Edwards Lifesciences' reportable segments (in millions):

	Years Ended December 31,		
	2019	2018	2017
Segment Net Sales			
United States	$ 2,532.7	$ 2,055.2	$ 1,907.6
Europe	926.1	826.4	800.7
Japan	441.4	398.4	356.5
Rest of World	433.3	396.0	357.3
Total segment net sales	$ 4,333.5	$ 3,676.0	$ 3,422.1
Segment Operating Income			
United States	$ 1,742.3	$ 1,368.1	$ 1,242.3
Europe	472.0	394.8	378.4
Japan	272.3	237.0	201.1
Rest of World	127.9	115.6	92.8
Total segment operating income	$ 2,614.5	$ 2,115.5	$ 1,914.6

The table below presents reconciliations of segment net sales to consolidated net sales and segment operating income to consolidated income before provision for income taxes ("pre-tax income") (in millions):

	Years Ended December 31,		
	2019	2018	2017
Net Sales Reconciliation			
Segment net sales	$ 4,333.5	$ 3,676.0	$ 3,422.1
Foreign currency	14.5	46.8	13.2
Consolidated net sales	$ 4,348.0	$ 3,722.8	$ 3,435.3
Pre-tax Income Reconciliation			
Segment operating income	$ 2,614.5	$ 2,115.5	$ 1,914.6
Unallocated amounts:			
Corporate items	(1,439.7)	(1,058.1)	(903.5)
Special charges, net	(64.6)	(116.2)	(9.7)
Intellectual property litigation (expenses) income, net	(33.4)	(214.0)	73.3
Change in fair value of contingent consideration liabilities, net	6.1	5.7	9.9
Foreign currency	63.9	15.3	4.8
Consolidated operating income	1,146.8	748.2	1,089.4
Non-operating income (expense)	19.7	13.2	(54.5)
Consolidated pre-tax income	$ 1,166.5	$ 761.4	$ 1,034.9

Table of Contents

EDWARDS LIFESCIENCES CORPORATION

NOTES TO CONSOLIDATED FINANCIAL STATEMENTS (Continued)

19. SEGMENT INFORMATION (Continued)

Enterprise-Wide Information

Enterprise-wide information is based on actual foreign exchange rates used in the Company's consolidated financial statements.

	As of or for the Years Ended December 31,		
	2019	2018	2017
	(in millions)		
Net Sales by Geographic Area			
United States	$ 2,532.7	$ 2,055.3	$ 1,907.6
Europe	941.2	885.1	831.0
Japan	444.7	396.8	350.3
Rest of World	429.4	385.6	346.4
	$ 4,348.0	$ 3,722.8	$ 3,435.3
Net Sales by Major Product Area			
Transcatheter Aortic Valve Replacement	$ 2,737.9	$ 2,283.8	$ 2,023.8
Transcatheter Mitral and Tricuspid Therapies	28.2	2.9	3.4
Surgical Structural Heart	841.7	761.6	807.1
Critical Care	740.2	674.5	601.0
	$ 4,348.0	$ 3,722.8	$ 3,435.3
Long-lived Tangible Assets by Geographic Area			
United States	$ 849.1	$ 642.1	$ 608.7
Europe	101.5	36.6	28.4
Japan	21.7	6.7	7.6
Rest of World	269.4	214.4	139.7
	$ 1,241.7	$ 899.8	$ 784.4

Table of Contents

EDWARDS LIFESCIENCES CORPORATION

NOTES TO CONSOLIDATED FINANCIAL STATEMENTS (Continued)

20. QUARTERLY FINANCIAL RESULTS AND MARKET FOR THE COMPANY'S STOCK (UNAUDITED)

Years Ended December 31,	First Quarter	Second Quarter	Third Quarter	Fourth Quarter	Total Year
	(in millions, except per share data)				
2019					
Net sales	$ 993.0	$ 1,086.9	$ 1,094.0	$ 1,174.1	$ 4,348.0
Gross profit	761.2	782.9	801.6	887.9	3,233.6
Net income (a)	249.7	242.3	274.7	280.2	1,046.9
Earnings per common share (a):					
Basic	1.20	1.16	1.32	1.34	5.03
Diluted	1.18	1.14	1.30	1.32	4.93
Market price:					
High	$ 197.86	$ 195.00	$ 228.19	$ 247.64	$ 247.64
Low	140.86	165.69	183.01	213.23	140.86
2018					
Net sales	$ 894.8	$ 943.7	$ 906.6	$ 977.7	$ 3,722.8
Gross profit	661.2	697.5	681.7	743.0	2,783.4
Net income (b)	206.6	282.7	225.9	7.0	722.2
Earnings per common share (b):					
Basic	0.98	1.35	1.08	0.03	3.45
Diluted	0.96	1.32	1.06	0.03	3.38
Market price:					
High	$ 143.22	$ 155.22	$ 175.00	$ 174.99	$ 175.00
Low	110.68	123.00	134.53	136.44	110.68

(a) The first quarter of 2019 includes a $24.0 million charge related to the acquisition of early-stage transcatheter intellectual property and associated clinical and regulatory experience, the second and third quarters of 2019 include a $46.2 million and $26.9 million charge, respectively, related to the write off of inventory, and the fourth quarter of 2019 includes a $40.6 million charge related to the impairment of certain in-process research and development assets.

(b) The fourth quarter of 2018 includes a $116.2 million charge related to the impairment of certain developed technology and in-process research and development assets and a $180.0 million charge related to a litigation settlement.

Table of Contents

EDWARDS LIFESCIENCES CORPORATION

NOTES TO CONSOLIDATED FINANCIAL STATEMENTS (Continued)

21. VALUATION AND QUALIFYING ACCOUNTS

	Balance at Beginning of Period	Additions: Charged to Costs and Expenses	Additions: Charged to Other Accounts	Deductions From Reserves	Balance at End of Period
			(in millions)		
Year ended December 31, 2019					
Allowance for doubtful accounts (a)	$ 13.6	$ 4.7	$ 0.2	$ (3.8)	$ 14.7
Tax valuation allowance (b)	46.7	18.9	0.2	—	65.8
Year ended December 31, 2018					
Allowance for doubtful accounts (a)	$ 13.7	$ 2.2	$ 1.0	$ (3.3)	$ 13.6
Tax valuation allowance (b)	41.6	7.1	(1.8)	(0.2)	46.7
Year ended December 31, 2017					
Allowance for doubtful accounts (a)	$ 12.8	$ 2.9	$ —	$ (2.0)	$ 13.7
Tax valuation allowance (b)	47.7	(8.9)	2.8	—	41.6

(a) The deductions related to allowances for doubtful accounts represent accounts receivable which are written off.

(b) The tax valuation allowances are provided for other-than-temporary impairments and unrealized losses related to certain investments that may not be recognized due to the uncertainty of the ready marketability of certain impaired investments, and net operating loss and credit carryforwards that may not be recognized due to insufficient taxable income.

Item 9. Changes in and Disagreements With Accountants on Accounting and Financial Disclosure

None.

Item 9A. Controls and Procedures

Evaluation of Disclosure Controls and Procedures. The Company's management, including the Chief Executive Officer and Chief Financial Officer, performed an evaluation of the effectiveness of the design and operation of the Company's disclosure controls and procedures (as defined in Rules 13a-15(e) and 15d-15(e) under the Securities Exchange Act of 1934, as amended) as of December 31, 2019.

Based on their evaluation, the Chief Executive Officer and Chief Financial Officer have concluded as of December 31, 2019 that the Company's disclosure controls and procedures are designed at a reasonable assurance level and are effective in providing reasonable assurance that the information required to be disclosed by the Company in the reports it files or submits under the Securities Exchange Act of 1934, as amended, is recorded, processed, summarized, and reported within the time periods specified in the SEC's rules and forms, and that such information is accumulated and communicated to the Company's management, including the Chief Executive Officer and Chief Financial Officer, as appropriate, to allow timely decisions regarding required disclosure.

Management's Report on Internal Control Over Financial Reporting. The Company's management, including the Chief Executive Officer and Chief Financial Officer, is responsible for establishing and maintaining adequate internal control over financial reporting, as such term is defined in Rules 13a-15(f) and 15d-15(f) under the Securities Exchange Act of 1934, as amended. Under the supervision and with the participation of the Company's management, including the Chief Executive Officer and Chief Financial Officer, the Company conducted an evaluation of the effectiveness of its internal control over financial reporting based on the framework in *Internal Control—Integrated Framework (2013)* issued by the Committee of Sponsoring Organizations of the Treadway Commission (COSO). Based on that evaluation, the Company's management concluded that its internal control over financial reporting was effective as of December 31, 2019. The effectiveness of the

Table of Contents

Company's internal control over financial reporting as of December 31, 2019 has been audited by PricewaterhouseCoopers LLP, an independent registered public accounting firm, as stated in their report which appears herein.

Changes in Internal Control Over Financial Reporting. There have been no changes in the Company's internal control over financial reporting that occurred during the Company's fourth fiscal quarter of 2019 that have materially affected, or are reasonably likely to materially affect, the Company's internal control over financial reporting.

Item 9B. Other Information

None.

Table of Contents

PART III

Item 10. Directors, Executive Officers and Corporate Governance

Certain information required by this Item will be set forth under the headings "Corporate Governance Policies and Practices," "Executive Compensation and Other Information—Executive Officers," and "Other Matters and Business—Additional Information" and "—Delinquent Section 16(a) Reports" in the definitive proxy materials to be filed in connection with the Company's 2020 Annual Meeting of Stockholders (the "Proxy Statement") (which Proxy Statement will be filed with the SEC within 120 days of December 31, 2019). The information required by this Item to be contained in the Proxy Statement is incorporated herein by reference. The Company has adopted a code of ethics that applies to all directors and employees, including the Company's principal executive officer, principal financial officer and controller or persons performing similar functions. The code of ethics (business practice standards) is posted on the Company's website, which is found at www.edwards.com under "Investors-Corporate Governance-Corporate Responsibility-Global Integrity Program." To the extent required by applicable rules of the SEC and the New York Stock Exchange, the Company intends to disclose on its website any amendments to, or waivers from, any provision of its code of ethics that apply to the Company's directors and executive officers, including the principal executive officer, principal financial officer or controller or persons performing similar functions.

Item 11. Executive Compensation

The information contained under the heading "Executive Compensation and Other Information" in the Proxy Statement is incorporated herein by reference.

Item 12. Security Ownership of Certain Beneficial Owners and Management and Related Stockholder Matters

The information contained under the headings "Security Ownership of Certain Beneficial Owners and Management" and "Equity Compensation Plan Information" in the Proxy Statement is incorporated herein by reference.

Item 13. Certain Relationships and Related Transactions, and Director Independence

The information contained under the heading "Other Matters and Business—Related Persons Transactions" and under the heading "Corporate Governance Policies and Practices—Director Independence" in the Proxy Statement is incorporated herein by reference.

Item 14. Principal Accounting Fees and Services

The information contained under the heading "Audit Matters—Fees Paid to Principal Accountants" in the Proxy Statement is incorporated herein by reference.

Table of Contents

PART IV

Item 15. Exhibits and Financial Statement Schedules

(a) The following documents are filed as part of this report:

1. Consolidated Financial Statements. See “Index to Consolidated Financial Statements” in Part II, Item 8 herein.

2. Financial Statement Schedules. Other schedules are not applicable and have not been included herein.

3. Exhibits.

Exhibit No.	Exhibit No.
3.1	Amended and Restated Certificate of Incorporation of Edwards Lifesciences Corporation dated May 16, 2013 (incorporated by reference to Exhibit 3.1 in Edwards Lifesciences' report on Form 8-K dated May 17, 2013)
3.2	Bylaws of Edwards Lifesciences Corporation amended and restated as of February 25, 2016 (incorporated by reference to Exhibit 3.1 in Edwards Lifesciences' report on Form 8-K dated March 2, 2016)
4.1	Specimen form of certificate representing Edwards Lifesciences Corporation common stock (incorporated by reference to Exhibit 4.1 in Edwards Lifesciences' Registration Statement on Form 10 (File No. 001-15525) filed on March 15, 2000)
4.2	Description of Edwards Lifesciences Corporation's Capital Stock
4.3	Indenture, dated as of September 6, 2013, between Edwards Lifesciences Corporation and Wells Fargo Bank, National Association, as trustee (incorporated by reference to Exhibit 4.5 in Edwards Lifesciences' Registration Statement on Form S-3 (File No. 333-191022) filed on September 6, 2013) (the "Indenture")
4.4	First Supplemental Indenture, dated as of October 3, 2013, to the Indenture (incorporated by reference to Exhibit 4.1 in Edwards Lifesciences' report on Form 8-K, filed on October 3, 2013)
4.5	Second Supplemental Indenture, dated as of June 15, 2018, to the Indenture (incorporated by reference to Exhibit 4.2 in Edwards Lifesciences' report on Form 8-K, filed on June 15, 2018) ("Second Supplemental Indenture")
4.6	Form of Global Note for the 4.300% Senior Notes due 2028 (incorporated by reference to Exhibit A in the Second Supplemental Indenture filed as Exhibit 4.2 in Edwards Lifesciences' report on Form 8-K, filed on June 15, 2018)
10.1	Five-Year Credit Agreement, dated as of April 30, 2018, among Edwards Lifesciences Corporation and certain of its subsidiaries, as Borrowers, the lenders signatory thereto, Bank of America, N.A., as Administrative Agent, JPMorgan Chase Bank, N.A., as Syndication Agent, and Morgan Stanley MUFG Loan Partners, LLC, Deutsche Bank Securities Inc., HSBC Bank USA, National Association, and Wells Fargo Bank, National Association, as Co-Documentation Agents (incorporated by reference to Exhibit 10.1 in Edwards Lifesciences' report on Form 8-K, filed on April 30, 2018)
#10.2	Settlement Agreement, dated May 19, 2014, between Edwards Lifesciences Corporation and Medtronic, Inc. (incorporated by reference to Exhibit 10.2 in Edwards Lifesciences' report on Form 10-Q for the quarterly period ended June 30, 2014)
*10.3	Edwards Lifesciences Corporation Form of Employment Agreement (incorporated by reference to Exhibit 10.8 in Edwards Lifesciences' report on Form 10-Q for the quarterly period ended March 31, 2003)
*10.4	Edwards Lifesciences Corporation Amended and Restated Employment Agreement for Michael A. Mussallem dated March 30, 2009 (incorporated by reference to Exhibit 10.2 in Edwards Lifesciences' report on Form 10-Q for the quarterly period ended March 31, 2009)
*10.5	Edwards Lifesciences Corporation Amended and Restated Chief Executive Officer Change-in-Control Severance Agreement, dated October 9, 2012 (incorporated by reference to Exhibit 10.1 in Edwards Lifesciences' report on Form 10-Q for the quarterly period ended September 30, 2012)
*10.6	Edwards Lifesciences Corporation Form of Change-in-Control Severance Agreement (incorporated by reference to Exhibit 10.2 in Edwards Lifesciences' report on Form 10-Q for the quarterly period ended September 30, 2012)
*10.7	Edwards Lifesciences Corporation 2018 Edwards Incentive Plan (incorporated by reference to Exhibit 10.7 in Edwards Lifesciences report on Form 10-K for the fiscal year ended December 31, 2018)
*10.8	Edwards Lifesciences Corporation Long-Term Stock Incentive Compensation Program, as amended and restated as of February 23, 2017 (incorporated by reference to Appendix A in Edwards Lifesciences' Definitive Proxy Statement filed on March 30, 2017)
*10.9	Edwards Lifesciences Corporation Form of Participant Stock Option Statement and related Long-Term Stock Program Global Nonqualified Stock Option Award Agreement for awards granted prior to May 2015 (incorporated by reference to Exhibit 10.1 in Edwards Lifesciences' report on Form 10-Q for the quarterly period ended March 31, 2011)

Table of Contents

Exhibit No.	Exhibit No.
*10.10	Edwards Lifesciences Corporation Form of Participant Restricted Stock Unit Statement and related Long-Term Stock Program Global Restricted Stock Unit Award Agreement for awards granted prior to May 2015 (incorporated by reference to Exhibit 10.2 in Edwards Lifesciences' report on Form 10-Q for the quarterly period ended March 31, 2011)
*10.11	Edwards Lifesciences Corporation Form of Long-Term Stock Incentive Compensation Program Global Nonqualified Stock Option Award Agreement for awards granted beginning May 2015 (incorporated by reference to Exhibit 10.3 in Edwards Lifesciences' report on Form 10-Q for the quarterly period ended June 30, 2015)
*10.12	Edwards Lifesciences Corporation Form of Long-Term Stock Incentive Compensation Program Global Restricted Stock Unit Award Agreement for awards granted beginning May 2015 (incorporated by reference to Exhibit 10.4 in Edwards Lifesciences' report on Form 10-Q for the quarterly period ended June 30, 2015)
*10.13	Edwards Lifesciences Corporation Form of Performance-Based Restricted Stock Unit Award Statement and related Long-Term Stock Program Global Performance-Based Restricted Stock Unit Award Agreement for awards granted beginning May 2015 (incorporated by reference to Exhibit 10.5 in Edwards Lifesciences' report on Form 10-Q for the quarterly period ended June 30, 2015)
*10.14	Edwards Lifesciences Corporation Nonemployee Directors Stock Incentive Program, as amended and restated as of February 25, 2016 (incorporated by reference to Exhibit 10.1 in Edwards Lifesciences' report on Form 10-Q for the quarterly period ended March 31, 2016)
*10.15	Edwards Lifesciences Corporation Form of Participant Stock Option Statement and related Nonemployee Directors Stock Incentive Program Nonqualified Stock Option Award Agreement (incorporated by reference to Exhibit 10.2 in Edwards Lifesciences' report on Form 10-Q for the quarterly period ended June 30, 2013)
*10.16	Edwards Lifesciences Corporation Form of Nonemployee Directors Stock Incentive Program Restricted Stock Units Agreement (incorporated by reference to Exhibit 10.4 in Edwards Lifesciences' report on Form 10-Q for the quarterly period ended March 31, 2011)
*10.17	Edwards Lifesciences Corporation Form of Nonemployee Directors Stock Incentive Program Restricted Stock Agreement (incorporated by reference to Exhibit 10.5 in Edwards Lifesciences' report on Form 10-Q for the quarterly period ended March 31, 2011)
*10.18	Edwards Lifesciences Corporation Severance Pay Plan, restated effective January 1, 2013 (incorporated by reference to Exhibit 10.1 in Edwards Lifesciences' report on Form 10-Q for the quarterly period ended March 31, 2013)
*10.19	Amendment No. 1 to the Edwards Lifesciences Corporation Severance Plan, dated February 24, 2017 (incorporated by reference to Exhibit 10.5 in Edwards Lifesciences' report on Form 10-Q for the quarterly period ended March 31, 2017)
*10.20	Amendment No. 2 to the Edwards Lifesciences Corporation Severance Plan, dated April 26, 2017 (incorporated by reference to Exhibit 10.2 in Edwards Lifesciences' report on Form 10-Q for the quarterly period ended June 30, 2017)
*10.21	Edwards Lifesciences Corporation Executive Deferred Compensation Plan, as amended and restated effective November 9, 2011 (incorporated by reference to Exhibit 10.7 in Edwards Lifesciences' report on Form 10-K for the fiscal year ended December 31, 2011)
*10.22	Edwards Lifesciences Technology SARL Retirement Savings Plan, as amended and restated January 1, 2011 (incorporated by reference to Exhibit 10.17 in Edwards Lifesciences' report on Form 10-K for the fiscal year ended December 31, 2012)
*10.23	Amendment No. 1 to the Edwards Lifesciences Technology SARL Retirement Savings Plan, dated June 25, 2013 (incorporated by reference to Exhibit 10.3 in Edwards Lifesciences' report on Form 10-Q for the quarterly period ended March 31, 2017)
*10.24	Amendment No. 2 to the Edwards Lifesciences Technology SARL Retirement Savings Plan, dated February 24, 2017 (incorporated by reference to Exhibit 10.4 in Edwards Lifesciences' report on Form 10-Q for the quarterly period ended March 31, 2017)
*10.25	Amendment No. 3 to the Edwards Lifesciences Technology SARL Retirement Savings Plan, dated February 14, 2018 (incorporated by reference to Exhibit 10.27 in Edwards Lifesciences' report on Form 10-K for the fiscal year ended December 31, 2017)
*10.26	Amendment No. 4 to the Edwards Lifesciences Technology SARL Retirement Savings Plan, dated November 14, 2018 (incorporated by reference to Exhibit 10.26 in Edwards Lifesciences report on Form 10-K for the fiscal year ended December 31, 2018)
*10.27	Edwards Lifesciences Corporation 401(k) Savings and Investment Plan, restated effective January 1, 2016 (incorporated by reference to Exhibit 10.2 in Edwards Lifesciences' report on Form 10-Q for the quarterly period ended March 31, 2016)
*10.28	Amendment No. 1 to the Edwards Lifesciences Corporation 401(k) Savings and Investment Plan, dated May 2, 2016 (incorporated by reference to Exhibit 10.1 in Edwards Lifesciences' report on Form 10-Q for the quarterly period ended June 30, 2016)
*10.29	Amendment No. 2 to the Edwards Lifesciences Corporation 401(k) Savings and Investment Plan, dated December 19, 2016 (incorporated by reference to Exhibit 10.24 in Edwards Lifesciences' report on Form 10-K for the fiscal year ended December 31, 2016

Table of Contents

Exhibit No.	Exhibit No.
*10.30	Amendment No. 3 to the Edwards Lifesciences Corporation 401(k) Savings and Investment Plan, dated February 24, 2017 (incorporated by reference to Exhibit 10.1 in Edwards Lifesciences' report on Form 10-Q for the quarterly period ended March 31, 2017)
*10.31	Amendment No. 4 to the Edwards Lifesciences Corporation 401(k) Savings and Investment Plan, dated February 24, 2017 (incorporated by reference to Exhibit 10.2 in Edwards Lifesciences' report on Form 10-Q for the quarterly period ended March 31, 2017)
*10.32	Amendment No. 5 to the Edwards Lifesciences Corporation 401(k) Savings and Investment Plan, dated October 27, 2017 (incorporated by reference to Exhibit 10.33 in Edwards Lifesciences' report on Form 10-K for the fiscal year ended December, 31, 2017)
*10.33	Amendment No. 6 to the Edwards Lifesciences Corporation 401(k) Savings and Investment Plan, dated December 19, 2017 (incorporated by reference to Exhibit 10.34 in Edwards Lifesciences' report on Form 10-K for the fiscal year ended December, 31, 2017)
*10.34	Amendment No. 7 to the Edwards Lifesciences Corporation 401(k) Savings and Investment Plan, dated December 19, 2017 (incorporated by reference to Exhibit 10.35 in Edwards Lifesciences' report on Form 10-K for the fiscal year ended December, 31, 2017)
*10.35	Amendment No. 8 to the Edwards Lifesciences Corporation 401(k) Savings and Investment Plan, dated April 17, 2018 (incorporated by reference to Exhibit 10.1 in Edwards Lifesciences' report on Form 10-Q for the quarterly period ended March 31, 2018)
*10.36	Amendment No. 9 to the Edwards Lifesciences Corporation 401(k) Savings and Investment Plan, dated October 5, 2018 (incorporated by reference to Exhibit 10.1 in Edwards Lifesciences' report on Form 10-Q for the quarterly period ended September 30, 2018)
*10.37	Amendment No. 10 to the Edwards Lifesciences Corporation 401(k) Savings and Investment Plan, dated April 23, 2019 (incorporated by reference to Exhibit 10.1 in Edwards Lifesciences' report on Form 10-Q for the quarterly period ended March 31, 2019)
*10.38	Amendment No. 11 to the Edwards Lifesciences Corporation 401(k) Savings and Investment Plan, dated July 1, 2019 (incorporated by reference to Exhibit 10.1 in Edwards Lifesciences' report on Form 10-Q for the quarterly period ended June 30, 2019)
*10.39	Edwards Lifesciences Corporation 2001 Employee Stock Purchase Plan for United States Employees, as amended and restated February 23, 2017 (incorporated by reference to Appendix B in Edwards Lifesciences' Definitive Proxy Statement filed on March 30, 2017)
*10.40	Edwards Lifesciences Corporation 2001 Employee Stock Purchase Plan for International Employees, as amended and restated February 20, 2014 (incorporated by reference to Appendix B in Edwards Lifesciences' Definitive Proxy Statement filed on March 28, 2014)
*10.41	Edwards Lifesciences Corporation Officer Perquisite Program Guidelines, as of February 20, 2013 (incorporated by reference to Exhibit 10.25 in Edwards Lifesciences' report on Form 10-K for the fiscal year ended December 31, 2012)
*10.42	Edwards Lifesciences Corporation Form of Indemnification Agreement (incorporated by reference to Exhibit 10.20 in Edwards Lifesciences' report on Form 10-K for the fiscal year ended December 31, 2011)
21.1	Subsidiaries of Edwards Lifesciences Corporation
23	Consent of Independent Registered Public Accounting Firm
31.1	Certification Pursuant to Section 302 of the Sarbanes-Oxley Act of 2002
31.2	Certification Pursuant to Section 302 of the Sarbanes-Oxley Act of 2002
+32	Certification Pursuant to 18 U.S.C. Section 1350, as Adopted Pursuant to Section 906 of the Sarbanes-Oxley Act of 2002
101.INS	XBRL Instance Document - the instance document does not appear in the Interactive Data File because its XBRL tags are embedded within the Inline XBRL document
101.SCH	XBRL Taxonomy Extension Schema Document
101.CAL	XBRL Taxonomy Extension Calculation Linkbase Document
101.DEF	XBRL Taxonomy Extension Definition Linkbase Document
101.LAB	XBRL Taxonomy Extension Label Linkbase Document
101.PRE	XBRL Taxonomy Extension Presentation Linkbase Document
104	Cover Page Interactive Data File (formatted as inline XBRL and contained in Exhibit 101)

Pursuant to a request for confidential treatment, confidential portions of this exhibit have been redacted and have been filed separately with the Securities and Exchange Commission
* Represents management contract or compensatory plan
+ Furnished herewith

Table of Contents

Item 16. Form 10-K Summary

None.

Table of Contents

SIGNATURES

Pursuant to the requirements of Section 13 or 15(d) of the Securities Exchange Act of 1934, the Registrant has duly caused this report to be signed on its behalf by the undersigned thereunto duly authorized.

EDWARDS LIFESCIENCES CORPORATION

February 14, 2020 By: /s/ MICHAEL A. MUSSALLEM

Michael A. Mussallem
Chairman of the Board and
Chief Executive Officer

Pursuant to the requirements of the Securities Exchange Act of 1934, this report has been signed below by the following persons on behalf of the registrant and in the capacities and on the dates indicated.

Signature	Title	Date
/s/ MICHAEL A. MUSSALLEM Michael A. Mussallem	Chairman of the Board and Chief Executive Officer (Principal Executive Officer)	February 14, 2020
/s/ SCOTT B. ULLEM Scott B. Ullem	Corporate Vice President, Chief Financial Officer (Principal Financial Officer)	February 14, 2020
/s/ ROBERT W.A. SELLERS Robert W.A. Sellers	Vice President, Corporate Controller (Principal Accounting Officer)	February 14, 2020
/s/ KIERAN T. GALLAHUE Kieran T. Gallahue	Director	February 14, 2020
/s/ LESLIE S. HEISZ Leslie S. Heisz	Director	February 14, 2020
/s/ WILLIAM J. LINK, PH.D. William J. Link, Ph.D.	Director	February 14, 2020
/s/ STEVEN R. LORANGER Steven R. Loranger	Director	February 14, 2020
/s/ MARTHA H. MARSH Martha H. Marsh	Director	February 14, 2020
/s/ WESLEY W. VON SCHACK Wesley W. von Schack	Director	February 14, 2020
/s/ NICHOLAS J. VALERIANI Nicholas J. Valeriani	Director	February 14, 2020

Exhibit 4.2

DESCRIPTION OF CAPITAL STOCK

References to "we," "us" and "our" refer to Edwards Lifesciences Corporation.

General

This section summarizes the rights of our capital stock, certain provisions of our amended and restated certificate of incorporation (our "certificate of incorporation") and our bylaws, as amended and restated (our "bylaws"), and certain provisions of applicable law. The following description is only a summary and is qualified by reference to our certificate of incorporation and our bylaws, which are filed as exhibits to our Annual Report on Form 10-K for the year ended December 31, 2019 filed with the Securities and Exchange Commission.

Authorized Capitalization

Our authorized capital stock consists of:

- 350,000,000 shares of common stock, with a par value of $1.00 per share; and
- 50,000,000 shares of preferred stock, with a par value of $0.01 per share, of which 3,500,000 shares have been designated as "Series A Junior Participating Preferred Stock."

As of December 31, 2019, 218.1 million shares of our common stock were issued and 209.1 million shares of our common stock were outstanding, and no shares of our preferred stock were issued and outstanding. As of December 31, 2019, we also had approximately 112 million shares of our common stock reserved to be issued upon exercise of outstanding stock options and restricted stock units granted to employees and directors.

Common Stock

The holders of our common stock are entitled to one vote for each share on all matters submitted to a vote of stockholders and do not have cumulative voting rights with respect to the election of directors. Holders of our common stock are entitled to receive ratably such dividends as may be declared from time to time by our board of directors out of legally available assets. In the event of our liquidation, dissolution or winding up, holders of common stock are entitled to share ratably in all assets remaining after payment of all debts and other liabilities and any amounts due to any holders of preferred stock. Holders of our common stock have no preemptive or conversion rights. No redemption or sinking fund provisions apply to our common stock. The rights, preferences and privileges of holders of our common stock are subject to the rights of the holders of shares of any series of preferred stock which we may issue. All of our outstanding shares of common stock are fully paid and non-assessable.

Preferred Stock

Our board of directors has the authority, without stockholder approval, to issue up to 50,000,000 shares of our preferred stock in one or more series and to determine, with respect to any such series, the powers, preferences and rights of the shares of such series, and the qualifications, limitations and restrictions thereof, including, without limitation, voting rights, dividend rights, conversion rights, terms of redemption, liquidation preference, sinking fund terms and the number of shares constituting any series and the designation thereof.

Our board of directors can issue, without stockholder approval, preferred stock with voting and conversion rights that could adversely affect the voting power of the holders of common stock and reduce the likelihood that such holders will receive dividend payments or payments upon liquidation. Such issuance could have the effect of decreasing the market price of the common stock. The issuance of preferred stock or even the ability to issue preferred stock could also have the effect of delaying, deterring or preventing a change of control or other corporate action.

Anti-Takeover Effects of Delaware Law and Our Certificate of Incorporation and Bylaw Provisions

Our certificate of incorporation and bylaws contain certain provisions that may make it more difficult to acquire control of us by means of a tender offer, open market purchase, proxy fight or otherwise. These provisions and certain provisions of Delaware law are expected to discourage coercive takeover practices and inadequate takeover bids.

These provisions are intended to enhance the likelihood of continued stability in the composition of our board of directors and its policies and to discourage certain types of transactions that may involve an actual or threatened acquisition of us. The provisions also are intended to discourage certain tactics that may be used in proxy fights. However, such provisions could have the effect of discouraging others from making tender offers for our shares and, as a consequence, could deprive stockholders of opportunities to realize takeover premiums for their shares.

Set forth below is a summary of the relevant provisions of our certificate of incorporation and bylaws and certain applicable sections of the General Corporation Law of the State of Delaware. For additional information we refer you to the provisions of our certificate of incorporation, our bylaws and those sections of the General Corporation Law of the State of Delaware.

Delaware Anti-Takeover Statute

We are subject to the provisions of Section 203 of the General Corporation Law of the State of Delaware regulating corporate takeovers. In general, Section 203, subject to certain exceptions, prohibits a publicly-held Delaware corporation from engaging in any business combination with any interested stockholder for a period of three years following the date that such person or entity became an interested stockholder, unless:

- prior to that date, the board of directors of the corporation approved either the business combination or the transaction which resulted in the stockholder becoming an interested stockholder;
- upon consummation of the transaction that resulted in the stockholder becoming an interested stockholder, the interested stockholder owned at least 85% of the voting stock of the corporation outstanding at the time the transaction commenced, excluding specified shares; or
- at or subsequent to that date of the transaction that resulted in a person or entity becoming an interested stockholder, the business combination is approved by the board of directors and authorized at an annual or special meeting of stockholders, and not by written consent, by the affirmative vote of at least 662⁄3% of the outstanding voting stock that is not owned by the interested stockholder.

The application of Section 203 may limit the ability of stockholders to approve a transaction that they may deem to be in their best interests. In addition, Section 203 makes it more difficult for an interested stockholder to effect various business combinations with a corporation for a three-year period, although the stockholders may, by adopting an amendment to our certificate of incorporation or bylaws, elect not to be governed by this section, effective 12 months after adoption.

In general, Section 203 defines “business combination” as:

- any merger or consolidation involving the corporation and the interested stockholder;
- any sale, lease, exchange, mortgage, pledge, transfer or other disposition of 10% or more of the assets of the corporation to or with the interested stockholder;
- subject to certain exceptions, any transaction which results in the issuance or transfer by the corporation of any stock of the corporation to the interested stockholder;
- any transaction involving the corporation that has the effect of increasing the proportionate share of the stock of any class or series of the corporation beneficially owned by the interested stockholder; or
- the receipt by the interested stockholder of the benefit of any loans, advances, guarantees, pledges or other financial benefits provided by or through the corporation.

In general, Section 203 defines an "interested stockholder" as any person that is:

- the owner of 15% or more of the outstanding voting stock of the corporation;
- an affiliate or associate of the corporation and was the owner of 15% or more of the outstanding voting stock of the corporation at any time within three years immediately prior to the relevant date; or
- an affiliate or associate of the above.

Our certificate of incorporation and bylaws do not exclude us from the restrictions imposed under Section 203. We anticipate that the provisions of Section 203 may encourage companies interested in acquiring us to negotiate in advance with our board of directors because the stockholder approval requirement would be avoided if a majority of the directors then in office approve either the business combination or the transaction that resulted in the stockholder becoming an interested stockholder.

Our Board of Directors

Our certificate of incorporation provides that the number of directors may be fixed from time to time by the board of directors, subject to the rights of holders of shares of any series of preferred stock to elect additional directors under specific circumstances. The size of our board of directors is currently fixed at eight directors. Each elected director holds office until his or her successor is duly elected and qualified, or until his or her earlier death, resignation, disqualification or removal.

Our certificate of incorporation and bylaws do not authorize cumulative voting with regard to the election of directors.

Board Vacancies

Our certificate of incorporation and bylaws provide that any vacancy in our board of directors may be filled only by a majority of the directors then in office, though less than a quorum, or by our sole remaining director. Each director so elected shall hold office until his or her successor is duly elected and qualified, or until his or her earlier death, resignation, disqualification or removal.

Advance Notice Requirements for Stockholder Proposals and Director Nominees

Our bylaws provide that stockholders seeking to make nominations of candidates for election as directors, or to bring other business before an annual or special meeting of the stockholders, must provide timely notice of their intent in writing. To be timely, a stockholder's notice must be delivered to and received at our principal executive offices not less than 90 days nor more than 120 days prior to the meeting. However, in the event that the date of the annual meeting is more than 25 days before or more than 25 days after the first anniversary date of the preceding year's annual meeting, or in the event of a special meeting of stockholders called for the purpose of electing directors, a stockholder's notice must be delivered to our principal executive offices not later than the close of business on the 10th day following the earlier of the date on which such notice of the date of the meeting was mailed or such public disclosure of the date of the meeting was made. Our bylaws also specify certain requirements as to the form and content of a stockholder's notice. These provisions may restrict the ability of our stockholders to bring business before our annual meeting of stockholders or to make nominations for directors at our annual meeting or any special meeting of stockholders.

Proxy Access

Our bylaws permit an eligible stockholder or group of stockholders to include up to a specified number of director nominees in our proxy materials for an annual meeting of stockholders. To qualify, the stockholders (or group of up to thirty stockholders) must have continuously owned for at least three years 3% or more of our outstanding shares of capital stock. The maximum number of stockholder nominees permitted under the proxy access provisions of our bylaws is generally the greater of (i) two or (ii) 20% of the total number of our directors in office as of the last day on which notice of a nomination may be delivered.

Notice of a nomination under our proxy access bylaw provisions must generally be submitted to our principal executive offices not less than 120 days nor more than 150 days prior to the first anniversary of the date that we first mailed our proxy statement to stockholders for the immediately preceding annual meeting of stockholders. The notice must contain certain information specified in our bylaws.

Blank Check Preferred Stock

Our certificate of incorporation provides that our board of directors can issue, without stockholder approval, up to 50,000,000 shares of our preferred stock in one or more series and to determine, with respect to any such series, the powers, preferences and rights of the shares of such series, and the qualifications, limitations and restrictions thereof, including, without limitation, voting rights, dividend rights, conversion rights, terms of redemption, liquidation preference, sinking fund terms and the number of shares constituting any series and the designation thereof.

Stockholder Action by Written Consent

Our certificate of incorporation provides that all actions requiring the vote or consent of stockholders must be taken at a regular or special meeting of stockholders and cannot be taken by written consent without a meeting.

Choice of Forum

Our bylaws provide that, unless we consent in writing to the selection of an alternative forum, the Court of Chancery of the State of Delaware will be, to the fullest extent permitted by law, the sole and exclusive forum for any derivative action or proceeding brought on our behalf; any action asserting a claim of breach of fiduciary duty; any action asserting a claim against us arising pursuant to the Delaware General Corporation Law; or any action asserting a claim against us that is governed by the internal affairs doctrine. This exclusive forum provision is intended to apply to claims arising under Delaware state law and would not apply to claims brought pursuant to the Securities Exchange Act of 1934 or Securities Act of 1933, or any other claim for which the federal courts have exclusive jurisdiction.

Transfer Agent and Registrar

Computershare is the transfer agent and registrar for our common stock.

Listing

Our common stock is listed on the NYSE under the symbol “EW.”

Exhibit 21.1

The following is a list of subsidiaries of Edwards Lifesciences Corporation, omitting subsidiaries which, considered in the aggregate as a single subsidiary, would not constitute a significant subsidiary as of December 31, 2019:

Legal Entity		State of Incorporation/ Formation		Country of Incorporation/ Formation
Edwards Lifesciences Innovation Holding LLC		Delaware		U.S.
Edwards Lifesciences LLC		Delaware		U.S.
Edwards Lifesciences Services GmbH				Germany
Edwards Lifesciences (Japan) Limited				Japan
Edwards Lifesciences Holding B.V.				The Netherlands
Edwards Lifesciences AG				Switzerland

Exhibit 23

CONSENT OF INDEPENDENT REGISTERED PUBLIC ACCOUNTING FIRM

We hereby consent to the incorporation by reference in the Registration Statements on Form S-8 (Nos. 333-33054, 333-33056, 333-40434, 333-52334, 333-52346, 333-60670, 333-98219, 333-105961, 333-127260, 333-150810, 333-154242, 333-168462, 333-183106, 333-192229, 333-195853, 333-204180, 333-211333, and 333-217909) and Form S-3 (No. 333-232866) of Edwards Lifesciences Corporation of our report dated February 14, 2020 relating to the financial statements and the effectiveness of internal control over financial reporting, which appears in this Form 10-K.

/s/ PricewaterhouseCoopers LLP
Irvine, California
February 14, 2020

Exhibit 31.1

EDWARDS LIFESCIENCES CORPORATION
CERTIFICATIONS PURSUANT TO
SECTION 302 OF
THE SARBANES-OXLEY ACT OF 2002
CERTIFICATION

I, Michael A. Mussallem, certify that:

1. I have reviewed this annual report on Form 10-K of Edwards Lifesciences Corporation;

2. Based on my knowledge, this report does not contain any untrue statement of a material fact or omit to state a material fact necessary to make the statements made, in light of the circumstances under which such statements were made, not misleading with respect to the period covered by this report;

3. Based on my knowledge, the financial statements, and other financial information included in this report, fairly present in all material respects the financial condition, results of operations and cash flows of the registrant as of, and for, the periods presented in this report;

4. The registrant's other certifying officer(s) and I are responsible for establishing and maintaining disclosure controls and procedures (as defined in Exchange Act Rules 13a-15(e) and 15d-15(e)) and internal control over financial reporting (as defined in Exchange Act Rules 13a-15(f) and 15d-15(f)) for the registrant and have:

   (a) Designed such disclosure controls and procedures, or caused such disclosure controls and procedures to be designed under our supervision, to ensure that material information relating to the registrant, including its consolidated subsidiaries, is made known to us by others within those entities, particularly during the period in which this report is being prepared;

   (b) Designed such internal control over financial reporting, or caused such internal control over financial reporting to be designed under our supervision, to provide reasonable assurance regarding the reliability of financial reporting and the preparation of financial statements for external purposes in accordance with generally accepted accounting principles;

   (c) Evaluated the effectiveness of the registrant's disclosure controls and procedures and presented in this report our conclusions about the effectiveness of the disclosure controls and procedures, as of the end of the period covered by this report based on such evaluation; and

   (d) Disclosed in this report any change in the registrant's internal control over financial reporting that occurred during the registrant's most recent fiscal quarter (the registrant's fourth fiscal quarter in the case of an annual report) that has materially affected, or is reasonably likely to materially affect, the registrant's internal control over financial reporting; and

5. The registrant's other certifying officer(s) and I have disclosed, based on our most recent evaluation of internal control over financial reporting, to the registrant's auditors and the audit committee of the registrant's board of directors (or persons performing the equivalent functions):

   (a) All significant deficiencies and material weaknesses in the design or operation of internal control over financial reporting which are reasonably likely to adversely affect the registrant's ability to record, process, summarize and report financial information; and

   (b) Any fraud, whether or not material, that involves management or other employees who have a significant role in the registrant's internal control over financial reporting.

By: /s/ MICHAEL A. MUSSALLEM
Michael A. Mussallem
Chairman of the Board and Chief Executive Officer

February 14, 2020

Exhibit 31.2

EDWARDS LIFESCIENCES CORPORATION
CERTIFICATIONS PURSUANT TO
SECTION 302 OF
THE SARBANES-OXLEY ACT OF 2002
CERTIFICATION

I, Scott B. Ullem, certify that:

1. I have reviewed this annual report on Form 10-K of Edwards Lifesciences Corporation;

2. Based on my knowledge, this report does not contain any untrue statement of a material fact or omit to state a material fact necessary to make the statements made, in light of the circumstances under which such statements were made, not misleading with respect to the period covered by this report;

3. Based on my knowledge, the financial statements, and other financial information included in this report, fairly present in all material respects the financial condition, results of operations and cash flows of the registrant as of, and for, the periods presented in this report;

4. The registrant's other certifying officer(s) and I are responsible for establishing and maintaining disclosure controls and procedures (as defined in Exchange Act Rules 13a-15(e) and 15d-15(e)) and internal control over financial reporting (as defined in Exchange Act Rules 13a-15(f) and 15d-15(f)) for the registrant and have:

   (a) Designed such disclosure controls and procedures, or caused such disclosure controls and procedures to be designed under our supervision, to ensure that material information relating to the registrant, including its consolidated subsidiaries, is made known to us by others within those entities, particularly during the period in which this report is being prepared;

   (b) Designed such internal control over financial reporting, or caused such internal control over financial reporting to be designed under our supervision, to provide reasonable assurance regarding the reliability of financial reporting and the preparation of financial statements for external purposes in accordance with generally accepted accounting principles;

   (c) Evaluated the effectiveness of the registrant's disclosure controls and procedures and presented in this report our conclusions about the effectiveness of the disclosure controls and procedures, as of the end of the period covered by this report based on such evaluation; and

   (d) Disclosed in this report any change in the registrant's internal control over financial reporting that occurred during the registrant's most recent fiscal quarter (the registrant's fourth fiscal quarter in the case of an annual report) that has materially affected, or is reasonably likely to materially affect, the registrant's internal control over financial reporting; and

5. The registrant's other certifying officer(s) and I have disclosed, based on our most recent evaluation of internal control over financial reporting, to the registrant's auditors and the audit committee of the registrant's board of directors (or persons performing the equivalent functions):

   (a) All significant deficiencies and material weaknesses in the design or operation of internal control over financial reporting which are reasonably likely to adversely affect the registrant's ability to record, process, summarize and report financial information; and

   (b) Any fraud, whether or not material, that involves management or other employees who have a significant role in the registrant's internal control over financial reporting.

By: /s/ SCOTT B. ULLEM

Scott B. Ullem
Corporate Vice President,
Chief Financial Officer

February 14, 2020

Exhibit 32

EDWARDS LIFESCIENCES CORPORATION
CERTIFICATION PURSUANT TO
18 U.S.C. SECTION 1350,
AS ADOPTED PURSUANT TO
SECTION 906 OF THE SARBANES-OXLEY ACT OF 2002

In connection with the Annual Report of Edwards Lifesciences Corporation (the "Company") on Form 10-K for the year ended December 31, 2019 as filed with the Securities and Exchange Commission on the date hereof (the "Report"), we, Michael A. Mussallem, Chairman of the Board and Chief Executive Officer of the Company, and Scott B. Ullem, Corporate Vice President, Chief Financial Officer, certify, pursuant to 18 U.S.C. 1350, as adopted pursuant to Section 906 of the Sarbanes-Oxley Act of 2002, that:

(1) The Report fully complies with the requirements of section 13(a) or 15(d) of the Securities Exchange Act of 1934; and

(2) The information contained in the Report fairly presents, in all material respects, the financial condition and results of operations of the Company.

/s/ MICHAEL A. MUSSALLEM

Michael A. Mussallem
Chairman of the Board and Chief Executive Officer

February 14, 2020

/s/ SCOTT B. ULLEM

Scott B. Ullem
Corporate Vice President,
Chief Financial Officer

February 14, 2020

EXHIBIT 41

2020 Investor Conference

December 10, 2020



Edwards

Opening Remarks

Michael A. Mussallem
Chairman and CEO

Edwards

Our Credo

Through our actions, we will become trusted partners with customers, colleagues, and patients – creating a community unified in its mission to improve the quality of life around the world. Our results will benefit customers, patients, employees and shareholders.

We will celebrate our successes, thrive on discovery, and continually expand our boundaries. We will act boldly, decisively, and with determination on behalf of people fighting cardiovascular disease.



At Edwards Lifesciences, we are dedicated to providing innovative solutions for people fighting cardiovascular disease.

Helping Patients is Our Life's Work, and *life is now*

Our Aspirations



Edwards is a global leader dedicated to…

Fostering an **inclusive culture** where all employees grow and thrive

Transforming patient lives with **breakthrough** medical technologies

Excelling as a **trusted partner** through distinguished quality and integrity

Passionate engagement that strengthens our communities

Delivering exceptional **shareholder value**

Helping Patients Around the World



*Source: 2020 engagement survey results of global professional employees

Patient-Focused Innovation Strategy

Focus

Singular focus on the large unmet needs of structural heart and critically ill patients



Leadership

Lead groundbreaking standards of care through trusted relationships

Innovation

Pioneer breakthrough technologies with compelling evidence

Edwards' patient-focused innovation strategy has produced sustained underlying sales growth

Global Transcatheter Opportunity

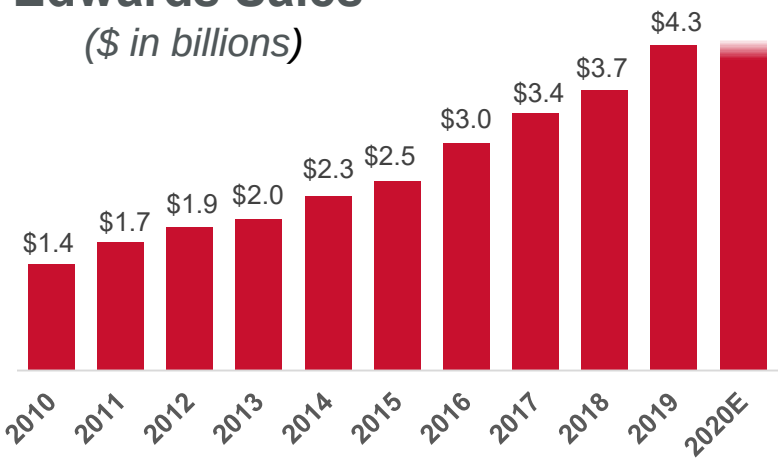
$10B+ by 2025

Focused on opportunities where **patient demand** is very large



Edwards Sales

($ in billions)



Long-term investments have yielded high-value, organic growth

Track record of **triple wins**:

- Improved outcomes
- Enhanced quality of life
- Cost effectiveness

Edwards
2021 and Beyond



2021 expected to be a year of significant growth and investment in our future

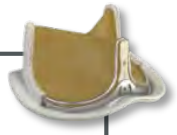
2021 Expectations

Mid-teens Underlying net sales growth	**$2.00 - $2.20** Adjusted EPS



TAVR

- Therapy expansion
- Technology advances
- Geographic expansion



Surgical

- Surgeon partnership
- Leading pipeline
- Growth segment focus



TMTT

- Differentiated portfolio
- Clinical evidence
- Real-world outcomes



Critical Care

- HemoSphere growth
- Smart technologies
- Portfolio expansion

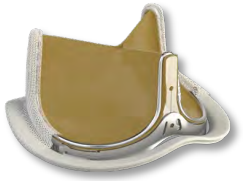
2021 Product Group Milestones

THE EARLY TAVR TRIAL

EARLY TAVR Asymptomatic
Enrollment Completion



Japan TAVR
Low Risk Approval





INSPIRIS
China Launch



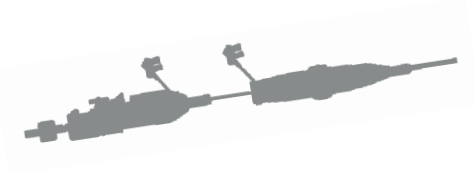
MITRIS
US and Japan Launch



Critical Care
Viewfinder
Connectivity
Solution



Alterra
Adaptive Prestent



Next Generation
PASCAL Delivery System
Initial Clinical Experience



Expanded
Launch
of KONECT



Launching
Moderate AS Trial



Next Generation
EVOQUE Mitral System
Initial Clinical Experience



SAPIEN X4
Clinical Trial Launch

2020 Investor Conference Agenda

Transcatheter Aortic Valve Replacement	Larry Wood and Huimin Wang, M.D.
Surgical Structural Heart	Daveen Chopra
Advanced Technologies	Todd Brinton, M.D.
Transcatheter Mitral and Tricuspid Therapies	Bernard Zovighian and Jean-Luc Lemercier
Critical Care	Katie Szyman
Financial Outlook	Scott Ullem
Closing Remarks	Mike Mussallem
Question and Answer Session	

Edwards' Executive Leadership Team



Michael Mussallem
Chairman & CEO



Donald Bobo, Jr.
Strategy & Corporate Development



Todd Brinton, M.D.
Chief Scientific Officer



Daveen Chopra
Surgical Structural Heart



Dirksen Lehman
Public Affairs



Jean-Luc Lemercier
EMEA, Canada and Latin America



Christine McCauley
Human Resources



Gary Sorsher
Quality, Regulatory, Clinical



Joseph Nuzzolese
Global Supply Chain



Arnold Pinkston
General Counsel



Katie Szyman
Critical Care



Scott Ullem
Chief Financial Officer



Huimin Wang, M.D.
Japan, Asia and Pacific



Larry Wood
Transcatheter Aortic Valve Replacement



Bernard Zovighian
Transcatheter Mitral & Tricuspid Therapies

Long-tenured expert healthcare executives

Highly strategic and collaborative team

Incentives aligned with shareholders



Edwards

Helping Patients is Our Life's Work, and life is now

2020 Investor Conference

Transcatheter Aortic Heart Valves

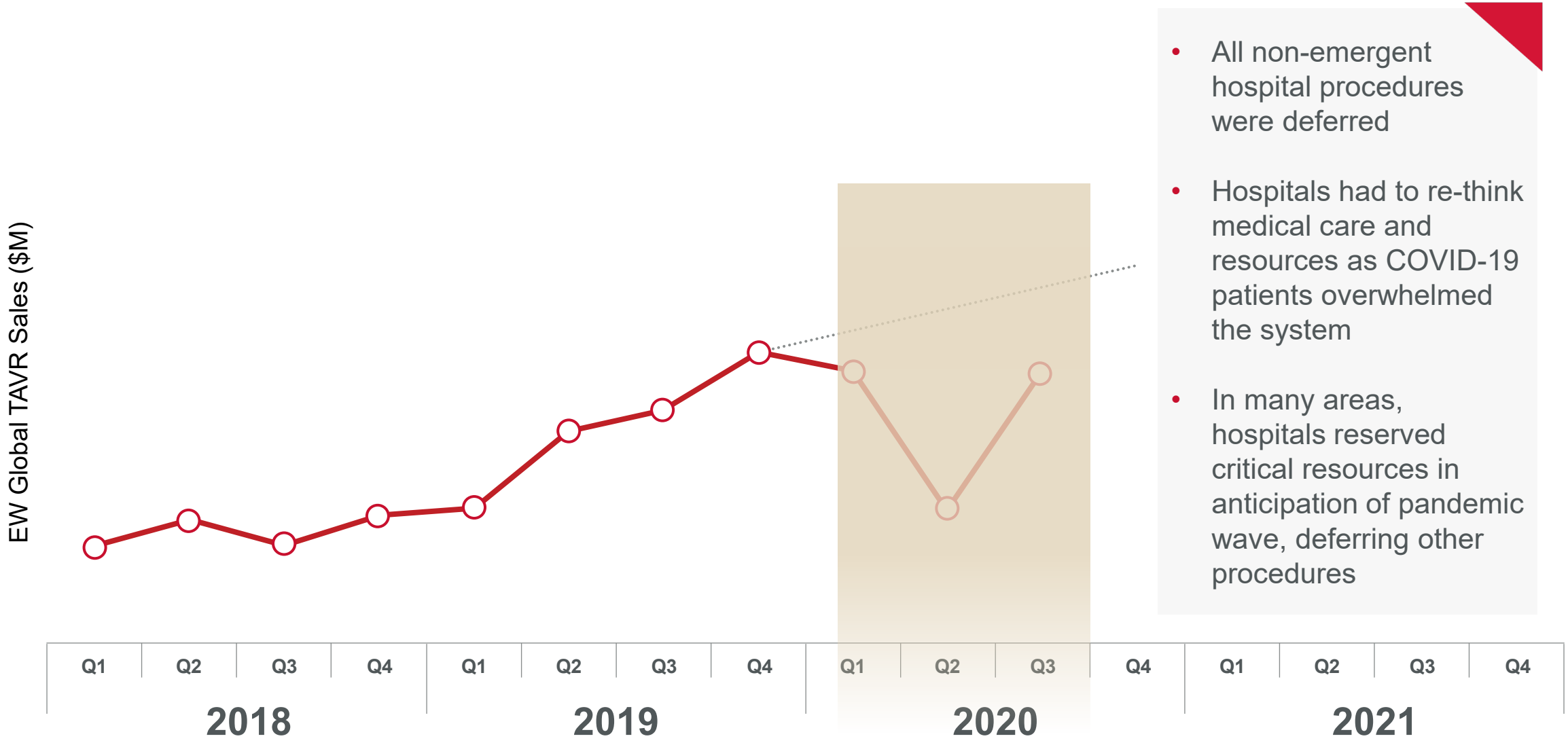
Edwards

We entered 2020 with strong momentum on a path to exceed our goals…



- PARTNER 3 results demonstrated SAPIEN 3 is the only valve superior to surgery
- Low-risk approval in U.S. and EU
- In U.S., revised NCD drove therapy access
- Strong trajectory in the first 10 weeks of 2020

…then the pandemic hit



- All non-emergent hospital procedures were deferred
- Hospitals had to re-think medical care and resources as COVID-19 patients overwhelmed the system
- In many areas, hospitals reserved critical resources in anticipation of pandemic wave, deferring other procedures

But we did not stop…

Severe Aortic Stenosis is a deadly disease

Severe AS patients' mortality rates increase drastically as patients wait for treatment

Helping patients remains our top priority



We remain laser focused on patient care and clinical partnership

Bicuspid precaution removed

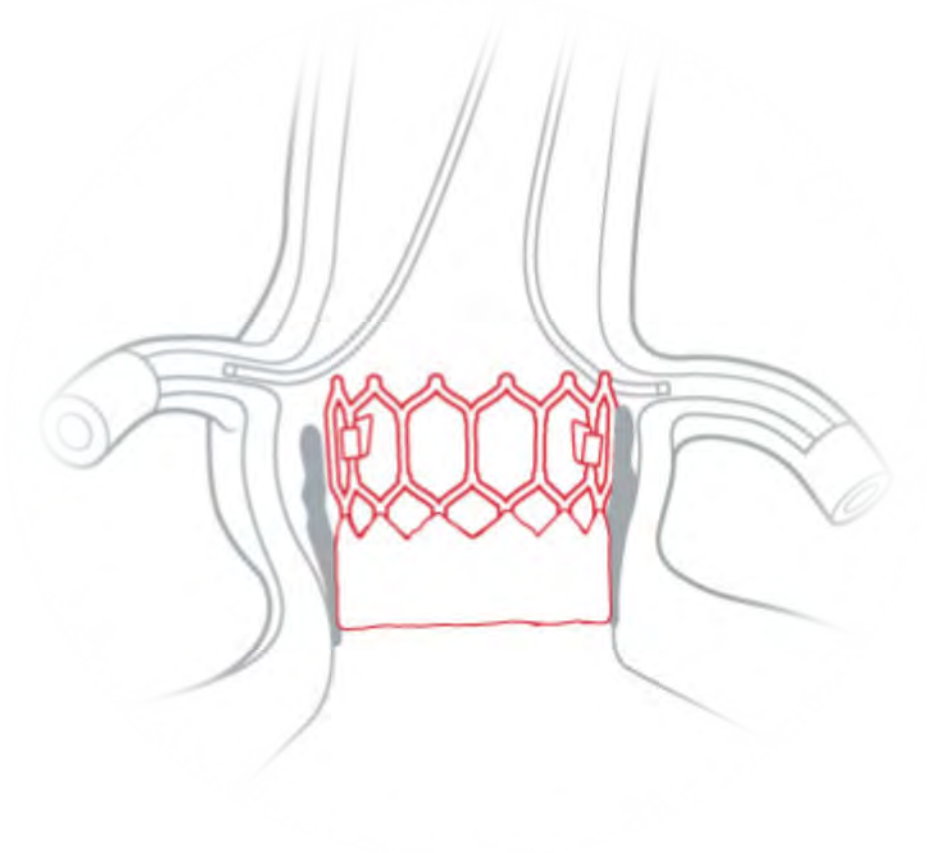
Provides further confidence for low risk, younger patients

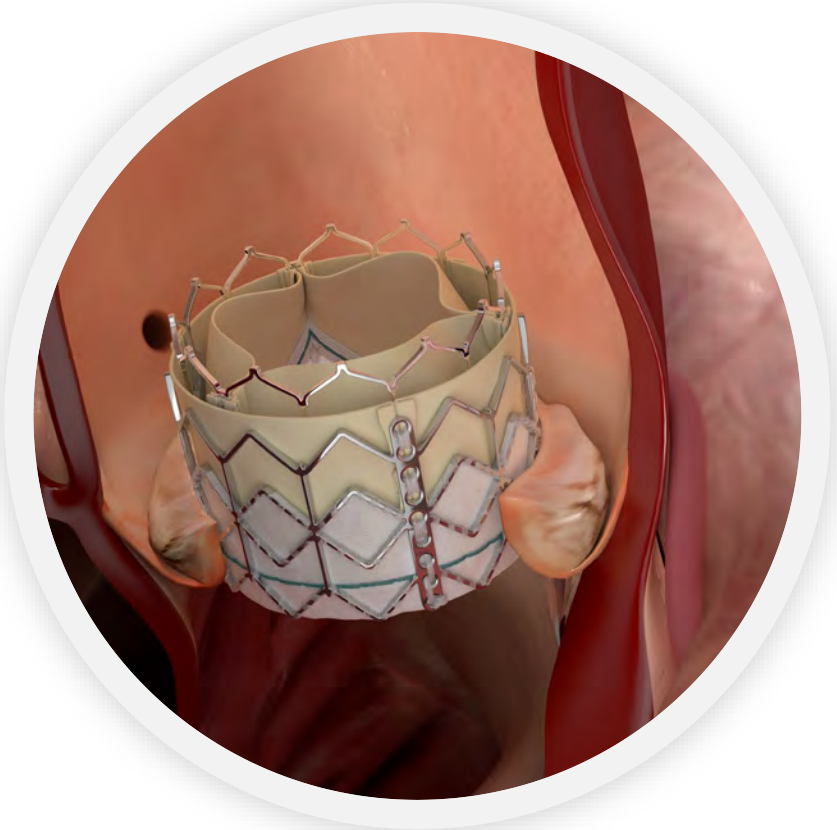


Low rates of complications that matter most to bicuspid patients[1]		
CEC-adjudicated Event	30 Days (n=71)	1 Year (n=71)
All-cause mortality	0%	1.4%
All stroke	2.8%	2.8%
Disabling stroke	0%	0%
New permanent pacemaker	9.9%	11.3%
Moderate/severe PVL	1.4%	0%

1. PARTNER 3 bicuspid nested registry analysis
2. FDA precaution removal letter dated 22nd July 2020

Edwards SAPIEN 3 TAVR Now Approved for TAVR-in-TAVR Indication





Provides long-term treatment option for patients with AS and reflects our dedication to long-term care

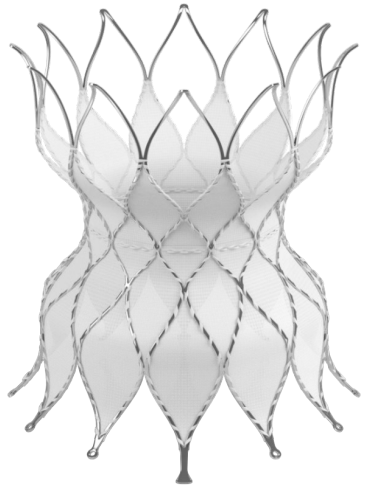
Expanding Options for Congenital Pulmonic Heart Disease Patients

- SAPIEN 3 now approved for pulmonic patients (direct valve replacement)
- Alterra Adaptive Prestent and SAPIEN 3 Pulmonic System expands therapy
- Alterra U.S. Approval anticipated in 2H 2021



SAPIEN 3 Valve

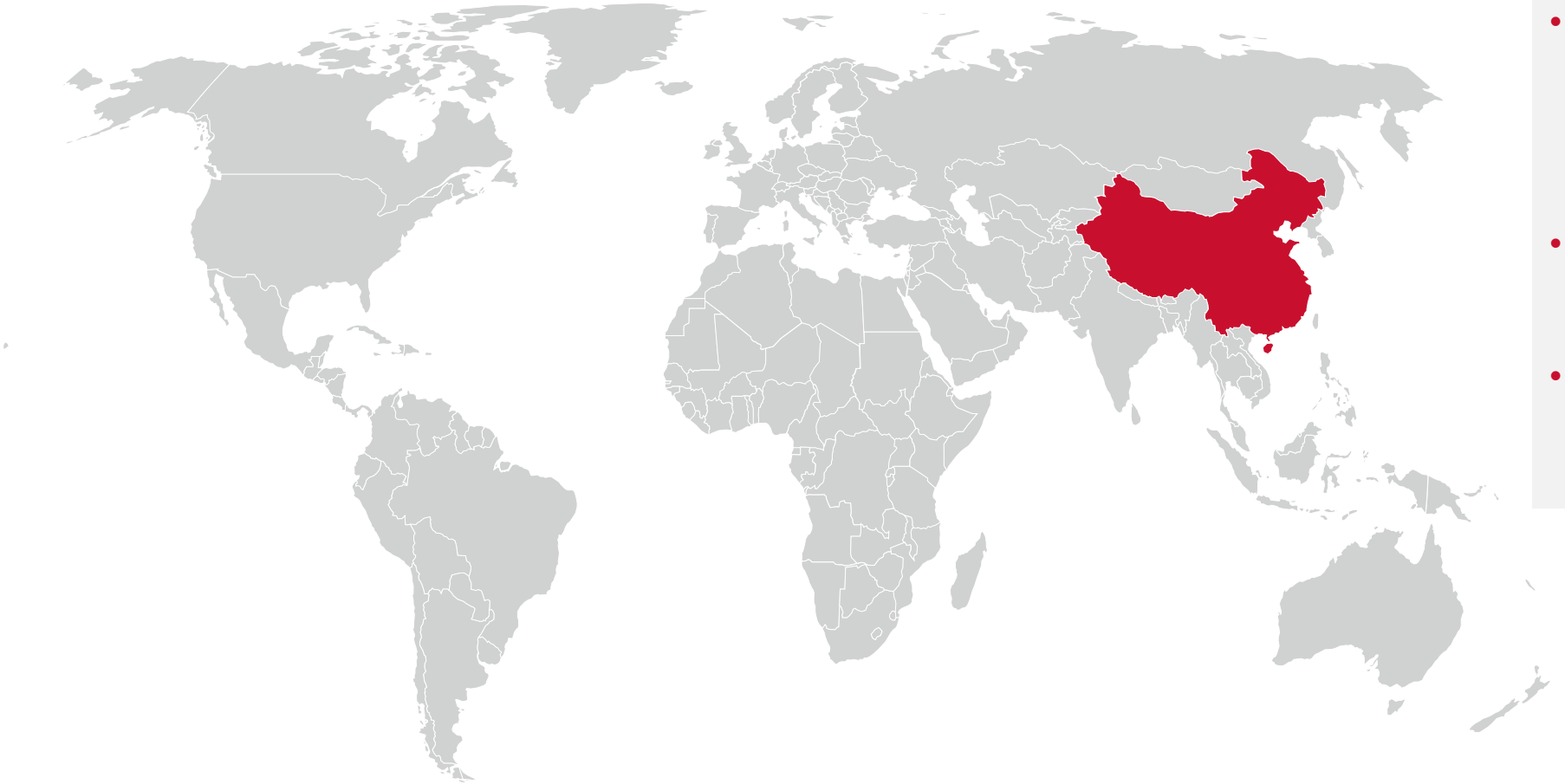
+



Alterra Adaptive Prestent

Congenital Pulmonary Valve disease is a serious issue, and these patients have unique challenges

SAPIEN 3 Now Approved in China For High Risk Patients



- Focused on establishing strong relationships to become the trusted clinical partner
- Patient outcomes remain the priority
- Contributor to long-term growth



The COVID-19 experience helped to inform our future



- Patients with Aortic Stenosis don't wait well, and TAVR is an essential procedure
- High-touch model remains valued
- We expect hospitals to adapt to local outbreaks and prioritize structural heart procedures until the pandemic subsides
- TAVR outcomes and efficiencies will continue to be highly valued

Data from New York City and Switzerland demonstrate risks of waiting

In the first study from New York City, 10% of patients awaiting aortic valve replacement at a busy structural heart program ended up undergoing urgent TAVR or died during in the first 30 days after elective procedures were halted. By 3 months, more than one-third of patients affected by the ban on elective procedures required an urgent intervention or died, the vast majority sent for TAVR because of worsening symptoms.



Across the pond, Swiss researchers reported that nearly one in five patients scheduled for aortic valve replacement who had the procedure delayed reported to hospital with valve-related symptoms or worsening heart failure. Thomas Pilgrim, MD (Bern University Hospital), senior researcher of the prospective Aortic Stenosis Defer (AS-DEFER) study, said elective procedures were halted in Switzerland on March 20, 2020, but they knew they'd have to take on selected patients given their risk.



PARTNER 3 Best-in-Class Outcomes

99%
Freedom from death and disabling stroke at 1 year

96%
of patients discharged home

90%
did not need to be rehospitalized within 2 years



Low pacemaker rates

Low rates of PVL

Edwards' TAVR allows hospitals to treat patients with confidence

Low complication rates

Short length-of-stay

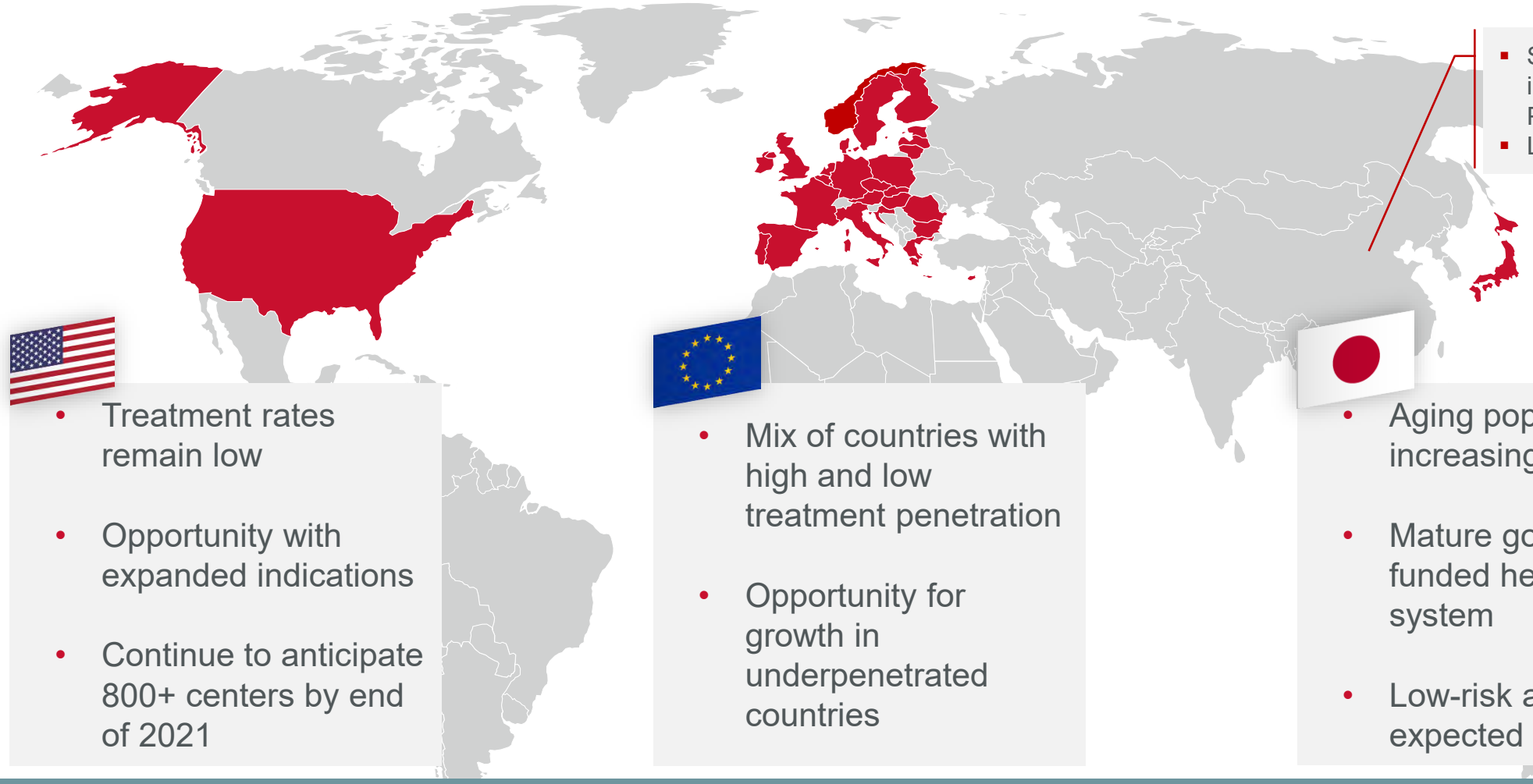
Patients discharged home

Low re-hospitalization rates



TAVR has become a healthcare priority and Edwards' TAVR advantage is now stronger than ever

TAVR fundamentals remain strong in developed markets around the world



- SAPIEN 3 now approved in China For High-Risk Patients
- Long-term opportunity

- Treatment rates remain low
- Opportunity with expanded indications
- Continue to anticipate 800+ centers by end of 2021

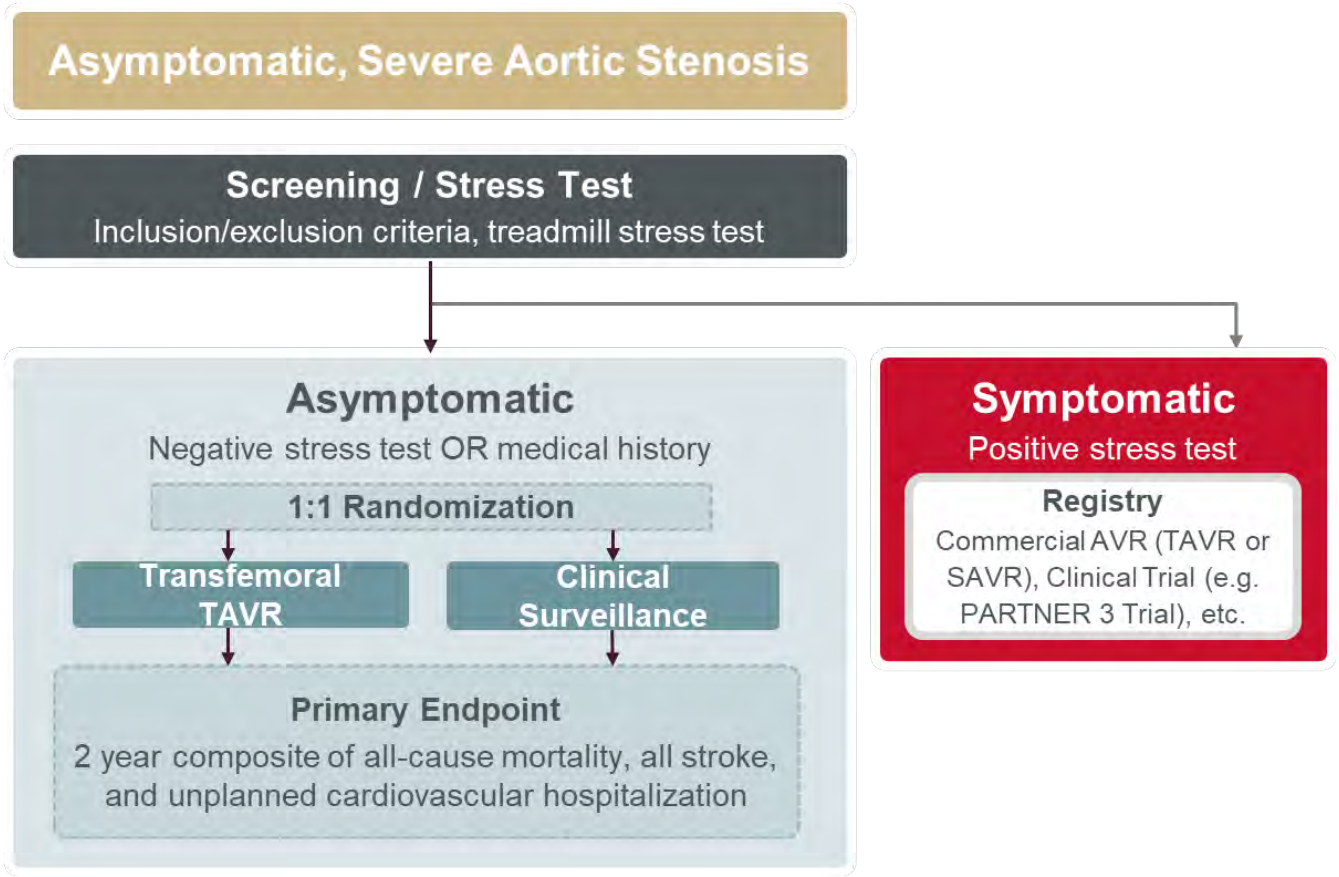
- Mix of countries with high and low treatment penetration
- Opportunity for growth in underpenetrated countries

- Aging population increasing rapidly
- Mature government-funded healthcare system
- Low-risk approval expected in 2021

We Continue to Expect the Global TAVR Market Opportunity to Exceed $7B by 2024

Asymptomatic and Moderate Risk Clinical Trials

Expected to add significant growth beyond 2024



- Beyond Severe Aortic stenosis, we believe our TAVR therapy may benefit patients with Moderate Aortic Stenosis
- Currently working closely with KOLs on a pivotal trial design

Anticipate completion of EARLY TAVR enrollment in 2021

Anticipate FDA approval to start the Moderate AS trial in 2021

Our portfolio is constantly evolving



SAPIEN 3



SAPIEN 3 Ultra

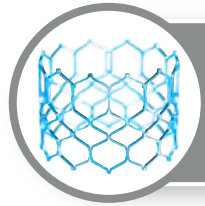
U.S. and EU launches evolutionary advancements

Next-Generation



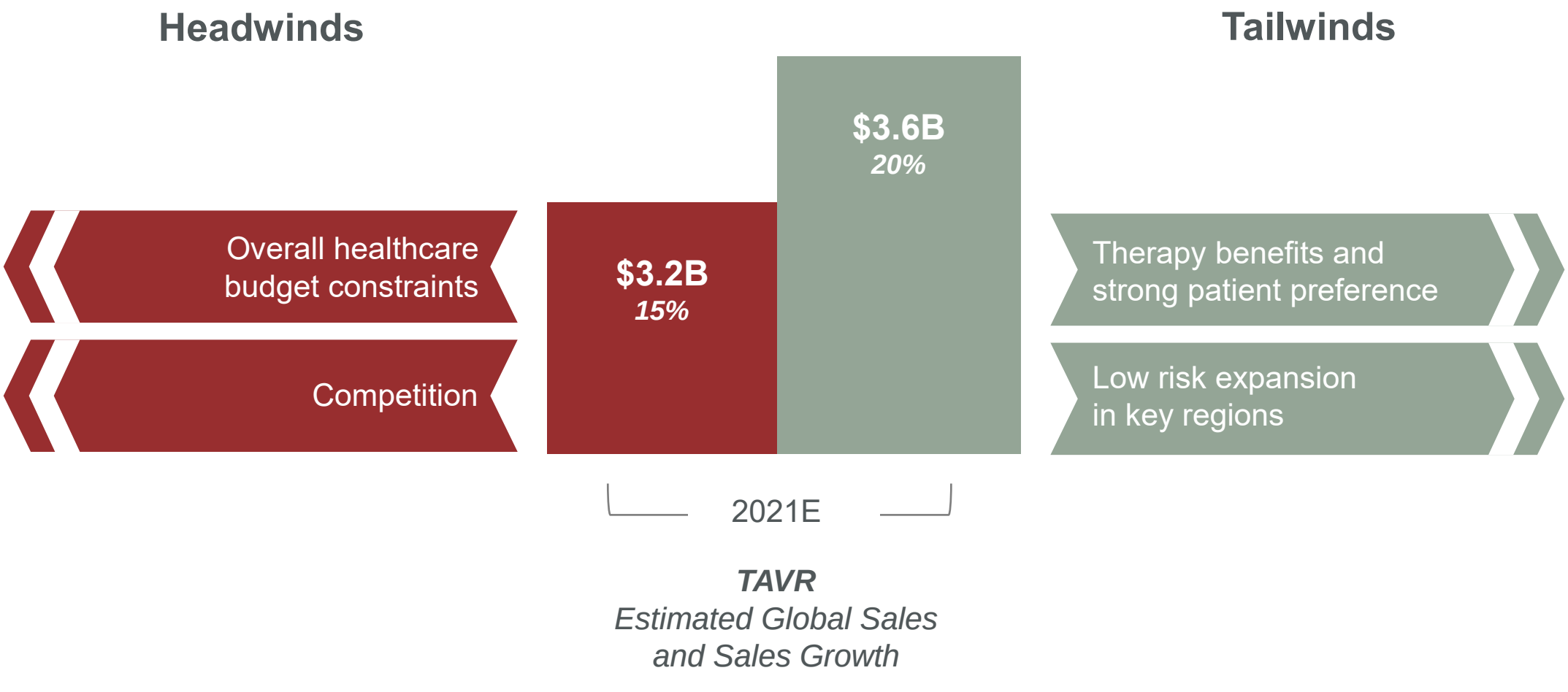
SAPIEN X4

Clinical work expected to begin in U.S. in 2021



Revolutionary platform

2021 Global Sales Outlook



TAVR
Estimated Global Sales and Sales Growth

Executive Summary

- **Aortic Stenosis is a deadly disease** and timely treatment is paramount
- Globally, **diagnosis and treatment rates of AS remain low** providing opportunity for low-double digit TAVR growth long-term
- We have **learned from the pandemic** and Edwards' TAVR therapy **fundamentals remain strong**
- Continued **investment in groundbreaking trials** beyond severe symptomatic aortic stenosis and transformational technologies to treat patients

CAUTION: Federal (United States) law restricts these devices to sale by or on the order of a physician. See instructions for use for full prescribing information, including indications, contraindications, warnings, precautions and adverse events.

Edwards SAPIEN 3 THV System and Edwards SAPIEN 3 Ultra THV System

Indications: The Edwards SAPIEN 3 Transcatheter Heart Valve System and Edwards SAPIEN 3 Ultra Transcatheter Heart Valve System are indicated for relief of aortic stenosis in patients with symptomatic heart disease due to severe native calcific aortic stenosis who are judged by a Heart Team, including a cardiac surgeon, to be appropriate for the transcatheter heart valve replacement therapy.

The Edwards SAPIEN 3 Transcatheter Heart Valve System and Edwards SAPIEN 3 Ultra Transcatheter Heart Valve System are indicated for patients with symptomatic heart disease due to failure (stenosed, insufficient, or combined) of a surgical bioprosthetic aortic or mitral valve who are judged by a heart team, including a cardiac surgeon, to be at high or greater risk for open surgical therapy (i.e., predicted risk of surgical mortality ≥ 8% at 30 days, based on the STS risk score and other clinical co-morbidities unmeasured by the STS risk calculator). Contraindications: The valves and delivery systems are contraindicated in patients who cannot tolerate an anticoagulation/antiplatelet regimen or who have active bacterial endocarditis or other active infections.

Warnings: Observation of the pacing lead throughout the procedure is essential to avoid the potential risk of pacing lead perforation. There may be an increased risk of stroke in transcatheter aortic valve replacement procedures, as compared to balloon aortic valvuloplasty or other standard treatments in high or greater risk patients. Incorrect sizing of the valve may lead to paravalvular leak, migration, embolization, residual gradient (patient-prosthesis mismatch), and/or annular rupture. Accelerated deterioration of the valve due to calcific degeneration may occur in children, adolescents, or young adults and in patients with an altered calcium metabolism. Prior to delivery, the valve must remain hydrated at all times and cannot be exposed to solutions other than its shipping storage solution and sterile physiologic rinsing solution. Valve leaflets mishandled or damaged during any part of the procedure will require replacement of the valve. Caution should be exercised in implanting a valve in patients with clinically significant coronary artery disease. Patients with pre-existing bioprostheses should be carefully assessed prior to implantation of the valve to ensure proper valve positioning and deployment. Do not use the valve if the tamper-evident seal is broken, the storage solution does not completely cover the valve, the temperature indicator has been activated, the valve is damaged, or the expiration date has elapsed. Do not mishandle the delivery system or use it if the packaging or any components are not sterile, have been opened or are damaged (e.g., kinked or stretched), or if the expiration date has elapsed. Use of excessive contrast media may lead to renal failure. Measure the patient's creatinine level prior to the procedure. Contrast media usage should be monitored. Patient injury could occur if the delivery system is not un-flexed prior to removal. Care should be exercised in patients with hypersensitivities to cobalt, nickel, chromium, molybdenum, titanium, manganese, silicon, and/or polymeric materials. The procedure should be conducted under fluoroscopic guidance. Some fluoroscopically guided procedures are associated with a risk of radiation injury to the skin.

These injuries may be painful, disfiguring, and long-lasting. Valve recipients should be maintained on anticoagulant/antiplatelet therapy, except when contraindicated, as determined by their physician. This device has not been tested for use without anticoagulation. Do not add or apply antibiotics to the storage solution, rinse solution, or to the valve. Balloon valvuloplasty should be avoided in the treatment of failing bioprostheses as this may result in embolization of bioprosthesis material and mechanical disruption of the valve leaflets. Failure to use slow, controlled inflation and prescribed nominal inflation volumes may result in balloon rupture, and lead to patient death or serious injuries associated with difficulty retrieving the delivery system and surgical intervention.

Precautions: Safety, effectiveness, and durability have not been established for THV-in-THV procedures. Long-term durability has not been established for the valve. Regular medical follow-up is advised to evaluate valve performance. Limited clinical data are available for transcatheter aortic valve replacement in patients with a congenital bicuspid aortic valve who are deemed to be at low surgical risk. Anatomical characteristics should be considered when using the valve in this population. In addition, patient age should be considered as long-term durability of the valve has not been established. Glutaraldehyde may cause irritation of the skin, eyes, nose, and throat. Avoid prolonged or repeated exposure to, or breathing of, the solution. Use only with adequate ventilation. If skin contact occurs, immediately flush the affected area with water; in the event of contact with eyes, seek immediate medical attention. For more information about glutaraldehyde exposure, refer to the Safety Data Sheet available from Edwards Lifesciences. To maintain proper valve leaflet coaptation, do not overinflate the deployment balloon. Appropriate antibiotic prophylaxis is recommended post-procedure in patients at risk for prosthetic valve infection and endocarditis. Additional precautions for transseptal replacement of a failed mitral valve bioprosthesis include, the presence of devices or thrombus or other abnormalities in the caval vein precluding safe transvenous femoral access for transseptal approach; and the presence of an Atrial Septal Occluder Device or calcium or abnormalities in the atrial septum preventing safe transseptal access. Special care must be exercised in mitral valve replacement if chordal preservation techniques were used in the primary implantation to avoid entrapment of the subvalvular apparatus. Safety and effectiveness have not been established for patients with the following characteristics/comorbidities: non-calcified aortic annulus; severe ventricular dysfunction with ejection fraction < 20%; congenital unicuspid aortic valve; pre-existing prosthetic ring in any position; severe mitral annular calcification (MAC); severe (> 3+) mitral insufficiency, or Gorlin syndrome; blood dyscrasias defined as leukopenia (WBC < 3000 cells/mL), acute anemia (Hb < 9 g/dL), thrombocytopenia (platelet count < 50,000 cells/mL), or history of bleeding diathesis or coagulopathy;hypertrophic cardiomyopathy with or without obstruction (HOCM); echocardiographic evidence of intracardiac mass, thrombus, or vegetation; a known hypersensitivity or contraindication to aspirin, heparin, ticlopidine (Ticlid), or clopidogrel (Plavix), or sensitivity to contrast media, which cannot be adequately premedicated; significant aortic disease, including abdominal aortic or thoracic aneurysm defined as maximal luminal diameter 5 cm or greater, marked tortuosity (hyperacute bend), aortic arch atheroma (especially if thick [> 5 mm], protruding, or ulcerated) or narrowing (especially with calcification and surface irregularities) of the abdominal or thoracic aorta, severe “unfolding” and tortuosity of the thoracic aorta; bulky calcified aortic valve leaflets in close proximity to coronary ostia; a concomitant paravalvular leak where the failing bioprosthesis is not securely fixed in the native annulus or is not structurally intact (e.g., wireform frame fracture); or a partially detached leaflet of the failing bioprosthesis that in the aortic position may obstruct a coronary ostium. For Left axillary approach, a left subclavian takeoff angle ~ ≥ 90° from the aortic arch causes sharp angles, which may be responsible for potential sheath kinking, subclavian/axillary dissection and aortic arch damage. Ensure there is flow in Left Internal Mammary Artery (LIMA)/Right Internal Mammary Artery (RIMA) during procedure and monitor PA pressure in homolateral radial artery. Residual mean gradient may be higher in a “THV-in-failing bioprosthesis” configuration than that observed following implantation of the valve inside a native aortic annulus using the same size device. Patients with elevated mean gradient post procedure should be carefully followed. It is important that the manufacturer, model and size of the preexisting bioprosthetic valve be determined, so that the appropriate valve can be implanted and a prosthesis-patient mismatch be avoided. Additionally, pre-procedure imaging modalities must be employed to make as accurate a determination of the inner diameter as possible.

Potential Adverse Events: Potential risks associated with the overall procedure, including potential access complications associated with standard cardiac catheterization, balloon valvuloplasty, the potential risks of conscious sedation and/or general anesthesia, and the use of angiography: death; stroke/transient ischemic attack, clusters, or neurological deficit; paralysis; permanent disability; respiratory insufficiency or respiratory failure; hemorrhage requiring transfusion or intervention; cardiovascular injury including perforation or dissection of vessels, ventricle, atrium, septum, myocardium, or valvular structures that may require intervention; pericardial effusion or cardiac tamponade; thoracic bleeding; embolization including air, calcific valve material, or thrombus; infection including septicemia and endocarditis; heart failure; myocardial infarction; renal insufficiency or renal failure; conduction system defect which may require a permanent pacemaker; arrhythmia; retroperitoneal bleed; arteriovenous (AV) fistula or pseudoaneurysm; reoperation; ischemia or nerve injury or brachial plexus injury; restenosis; pulmonary edema; pleural effusion; bleeding; anemia; abnormal lab values (including electrolyte imbalance); hypertension or hypotension; allergic reaction to anesthesia, contrast media, or device materials; hematoma; syncope; pain or changes at the access site; exercise intolerance or weakness; inflammation; angina; heart murmur; and fever.

Additional potential risks associated with the use of the valve, delivery system, and/or accessories include: cardiac arrest; cardiogenic shock; emergency cardiac surgery; cardiac failure or low cardiac output; coronary flow obstruction/transvalvular flow disturbance; device thrombosis requiring intervention; valve thrombosis; device embolization; device migration or malposition requiring intervention; left ventricular outflow tract obstruction; valve deployment in unintended location; valve stenosis; structural valve deterioration (wear, fracture, calcification, leaflet tear/tearing from the stent posts, leaflet retraction, suture line disruption of components of a prosthetic valve, thickening, stenosis); device degeneration; paravalvular or transvalvular leak; valve regurgitation; hemolysis; device explants; nonstructural dysfunction; mechanical failure of delivery system and/or accessories; and non-emergent reoperation.

Edwards Axela Sheath

Indications: The Edwards Axela sheath is indicated for the introduction and removal of devices used with the Edwards SAPIEN 3 Ultra delivery system.

Contraindications: There are no known contraindications.

Warnings: The devices are designed, intended, and distributed for single use only. Do not resterilize or reuse the devices. There are no data to support the sterility, nonpyrogenicity, and functionality of the devices after reprocessing.

Precautions: Caution should be used in vessels that have diameters less than 5.5 mm as it may preclude safe placement of the 14F Edwards Axela sheath. For subclavian/axillary vessels with the 29 mm Edwards SAPIEN 3 Ultra delivery system, caution should be used in vessels that have diameters less than 6.0 mm as it may preclude safe placement of the 14F Edwards Axela sheath. Use caution in tortuous or calcified vessels that would prevent safe entry of the sheath. Do not use the Edwards Axela sheath if the packaging sterile barriers and any components have been opened or damaged or the expiration date has elapsed. When inserting, manipulating or withdrawing a device through the sheath, always maintain sheath position. When puncturing, suturing or incising the tissue near the sheath, use caution to avoid damage to the sheath.

Potential Adverse Events: Complications associated with standard catheterization and use of angiography include, but are not limited to, injury including perforation or dissection of vessels, thrombosis and/or plaque dislodgement which may result in emboli formation, distal vessel obstruction, hemorrhage, infection, and/or death.

Edwards Crimper

Indications: The Edwards crimper is indicated for use in preparing the Edwards SAPIEN 3 Ultra transcatheter heart valve and the Edwards SAPIEN 3 transcatheter heart valve for implantation. Contraindications: There are no known contraindications. Warnings: The devices are designed, intended, and distributed for single use only. Do not resterilize or reuse the devices. There are no data to support the sterility, nonpyrogenicity, and functionality of the devices after reprocessing. Precautions: For special considerations associated with the use of the Edwards crimper prior to THV implantation, refer to the THV Instructions for Use. Potential Adverse Events: There are no known potential adverse events associated with the Edwards crimper.

Edwards Lifesciences devices placed on the European market meeting the essential requirments referred to in Article 3 of the Medical Device Directive 93/42/EEC bear the CE marking of conformity.

For professional use. For a listing of indications, contraindications, warnings, precautions and adverse events, please refer to the Instructions for Use (consult eifu.edwards.com where applicable).



Edwards

Helping Patients is Our Life's Work, and *life is now*

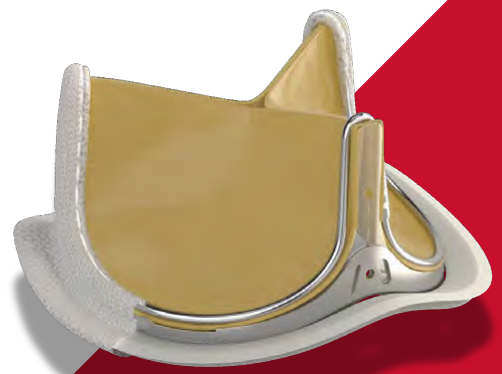
2020 Investor Conference

Surgical Structural Heart

Edwards

Surgical Structural Heart brings leading innovation

- Current $1.8B surgical structural heart market expected to grow **mid-single digits through 2026**
- **We extended our leadership** as the partner of choice for cardiac surgeons with three product launches in 2020
- **We continue to bring life-saving surgical innovation** to patients best-treated surgically



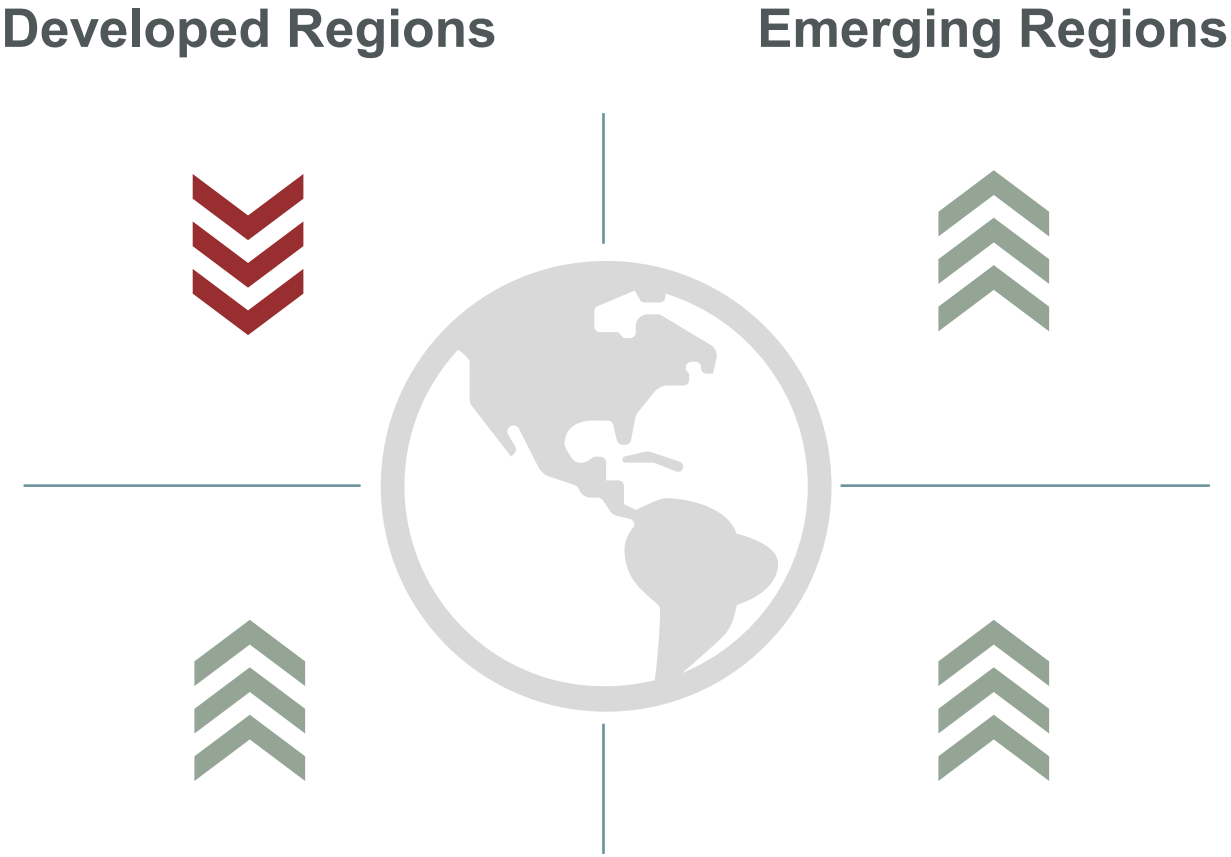
Adult cardiac surgery continues to grow mid-single digits driven by awareness and an aging population

Surgical Aortic Valve Replacement

Growth in emerging regions equally offset decline in developed regions

Surgical Mitral Valve Replacement and Repair

Continued global mid-single digit growth



Surgical aortic cases continue to grow in segments and emerging regions with less TAVR impact

Surgical Aortic Procedures (U.S. & EU)

Growth (20-26)

- **Isolated ssAS[1]** ↓
- **Combined ssAS[1]** ↘
- **Combined Moderate AS** →
- **Severe Aortic Regurgitation** →

2020E

Aortic Patients Best Treated Surgically



Younger, active patients who do not want the burden of anticoagulation



Patients with complex disease who require combined procedures



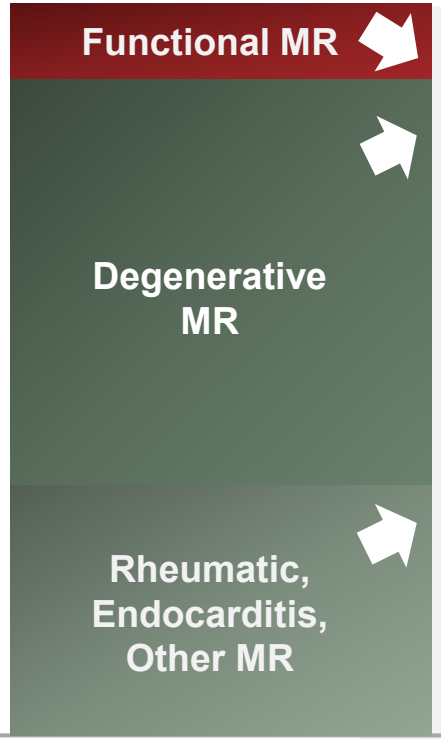
Patients with aortic regurgitation who require a surgical approach

[1] Severe Symptomatic Aortic Stenosis

Less than 2% of mitral valve disease patients are treated today, with minimal transcatheter cannibalization

Surgical Mitral Procedures (U.S. & EU)

Growth (20-26)



Mitral Patients Best Treated Surgically



Surgical low risk degenerative patients where surgery remains the gold standard



Patients with complex disease who require combined procedures

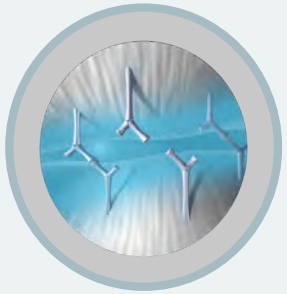


Patients with rheumatic or endocarditis diseases who require a surgical approach

We continue to generate robust clinical evidence for our leading RESILIA tissue technology

RESILIA Tissue Technology

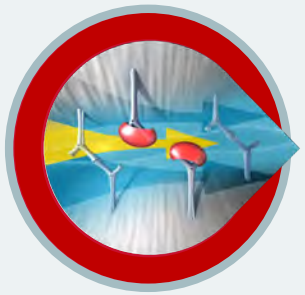
Anti-calcification to improve tissue durability



Residual aldehydes on tissue attract calcium



RESILIA permanently caps residual aldehydes



Capped aldehydes block calcium

Long-Term RESILIA Tissue Clinical Evidence

EU Feasibility Study

133 patients across 2 centers in Poland

5yr follow-up showed 0% structural valve deterioration (SVD)

COMMENCE Aortic

694 patients across 27 centers in U.S. & Poland

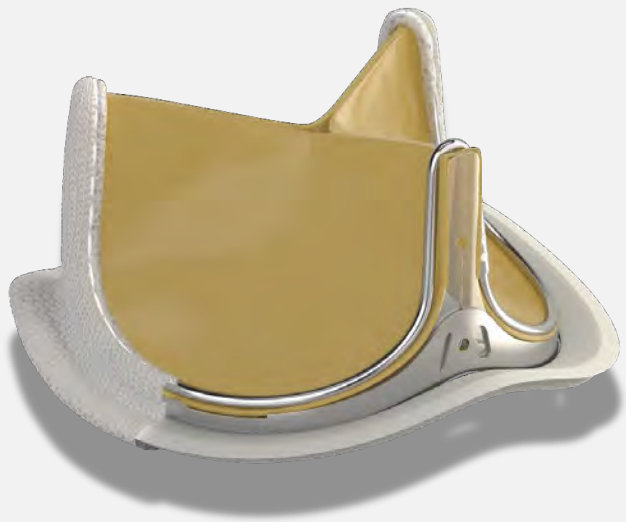
4yr follow-up showed 0% SVD 5yr outcomes in early 2021

RESILIENCE

Long term follow up in <65 year old COMMENCE aortic patients

Follow-up through 11yrs

INSPIRIS is now the leading aortic surgical valve in the world



- **Provides RESILIA tissue and VFit technology** for potential future valve-in-valve procedures
- **#1 implanted aortic surgical valve** in the U.S. and Japan, **launching in China in 2021**
- **Continuing adoption** across U.S. and Europe

KONECT addresses key unmet needs of patients and drives growth in 2021



- **Launched in the U.S. in June 2020** as the first pre-assembled, ready-to-implant tissue conduit
- Designed for **complex aortic valve patients with combined aortic root disease**
- **Impacts ~7,500 surgical procedures annually in the U.S.**, growing in the high single-digits

MITRIS is designed for active mitral patients who might otherwise receive a mechanical valve



- **Differentiating RESILIA tissue, ease-of-use enhancements**, and valve-in-valve compatibility
- **Growth opportunity** as 60% of global mitral valve replacement patients receive a mechanical valve
- **Launching in the U.S. and Japan in 2021**

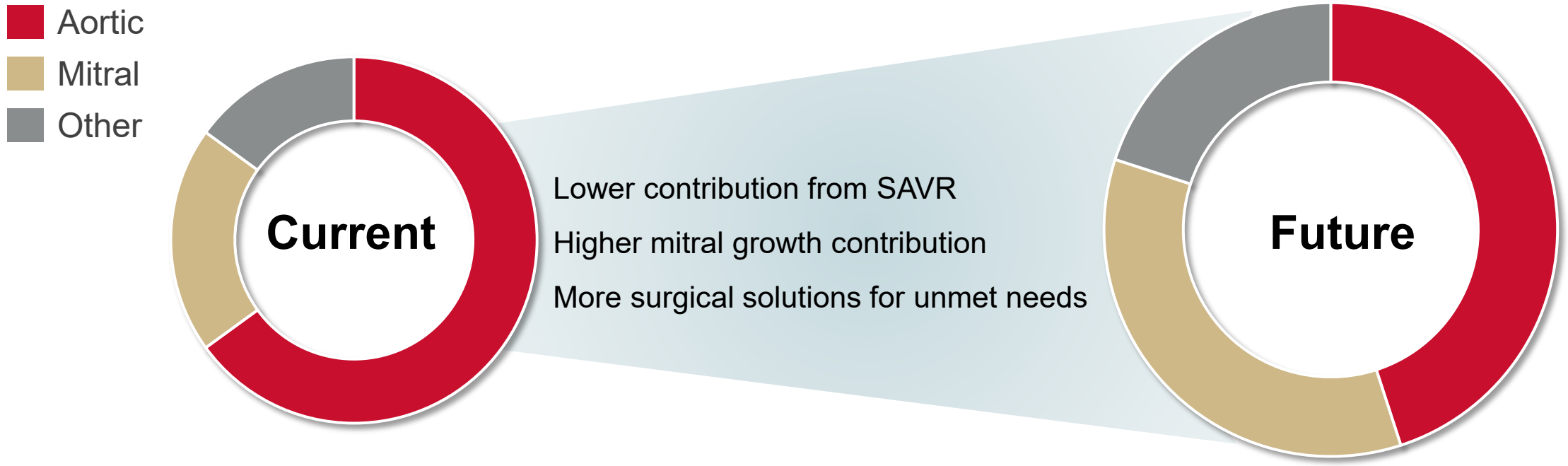
HARPOON transforms surgery for many patients with degenerative mitral regurgitation



- Standardizing mitral repair with an **echo-guided, beating-heart procedure**
- **Launched in 2020** with potential to convert ~20k surgical repair patients across the U.S., Europe, and Japan
- **Started the RESTORE U.S. pivotal trial,** a unique, non-randomized study with a one-year endpoint

Our strategy will provide a balanced portfolio and will extend patient impact

Surgical Structural Heart Revenue by Segment



2021 Global Sales Outlook

Headwinds

- Continued TAVR conversion in U.S. & EU
- Overall healthcare budget constraints



Tailwinds

- Adoption of RESILIA products
- Accelerated mech-to-tissue conversion

Surgical Structural Heart
Estimated Global Sales

Executive Summary



- The **Surgical Structural Heart market is forecast to grow** in areas with unmet patient needs

- Our **innovation strategy focuses on transforming surgical patients' lives** with life-saving surgical technologies

Important Safety Information:
INSPIRIS RESILIA Aortic Valve

Indications: For use in replacement of native or prosthetic aortic heart valves.
Contraindications: There are no known contraindications with the use of the INSPIRIS RESILIA aortic valve.

Complications and Side Effects: Thromboembolism, valve thrombosis , hemorrhage, hemolysis, regurgitation, endocarditis, structural valve deterioration, nonstructural dysfunction, stenosis, arrhythmia, transient ischemic attack/stroke, congestive heart failure, myocardial infarction, any of which could lead to reoperation, explantation, permanent disability, and death.

Warnings: DO NOT ADJUST THE VALVE DIAMETER BY EXPANDING THE BAND PRIOR TO/OR DURING IMPLANTATION OF THE SURGICAL VALVE. The expandable band is not designed to allow for compression or expansion during implantation of the surgical valve. This will cause damage to the valve and may result in aortic incompetence. DO NOT PERFORM STAND-ALONE BALLOON AORTIC VALVULOPLASTY PROCEDURES ON

THIS VALVE FOR THE SIZES 19 – 25 mm as this may expand the valve causing aortic incompetence, coronary embolism or annular rupture. Valve-in-valve sizing in the INSPIRIS valve has only been tested with specific Edwards transcatheter heart valves. Use of other transcatheter valves may result in embolization of transcatheter devices anchored within or result in annular rupture.

CAUTION: Federal (USA) law restricts this device to sale by or on the order of a physician. See instructions for use for full prescribing information. KONECT RESILIA Aortic Valved Conduit

Indications: For use in replacement of native or prosthetic aortic heart valves and the associated repair or replacement of a damaged or diseased ascending aorta.

Contraindications: There are no known contraindications with the use of the KONECT RESILIA Aortic Valved Conduit.

Complications and Side Effects: Thromboembolism, valve thrombosis, hemorrhage, hemolysis, regurgitation, endocarditis, structural valve deterioration, nonstructural dysfunction, stenosis, arrhythmia, transient ischemic attack/stroke, congestive heart failure, myocardial infarction, any of which could lead to reoperation, explanation, permanent disability, and death. Adverse events potentially associated with the use of polyester vascular grafts include hemorrhage, thrombosis, graft infection, embolism, aneurysm, pseudoaneurysm, seroma, occlusion (anastomotic intimal hyperplasia), immunological reaction to collagen (shown to be a weak immunogen; infrequent, mild, localized and self-limiting), intimal peel formation, and conduit dilatation.

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Edwards

Helping Patients is Our Life's Work, and *life is now*

2020 Investor Conference

Transcatheter Mitral and Tricuspid Therapies

Edwards

TMTT is guided by our vision to lead and transform treatment for patients with mitral and tricuspid valve disease

Today, patients with **Mitral and Tricuspid regurgitation remain undertreated** and suffer poor quality of life and high mortality

TMTT is delivering a **portfolio of therapies –** including leaflet repair, annular reduction, and valve replacement – to **address the diversity and complexity of Mitral and Tricuspid disease**

To achieve this vision, TMTT is focused on 3 key value drivers

1. Our **portfolio of differentiated therapies**
2. **Positive** results from our **pivotal trials**
3. **Favorable real-world outcomes**

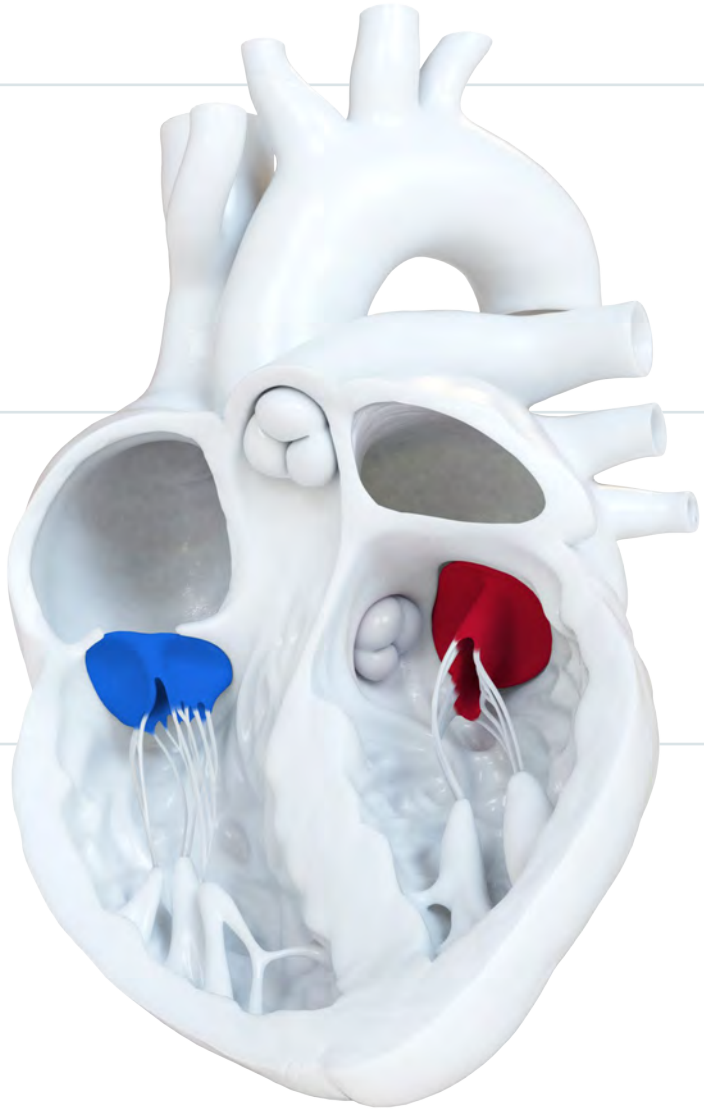
TMTT will double revenue in 2021

Ongoing innovation & clinical evidence will support the development of a **$3B MR/TR opportunity in 2025**, with significant growth beyond 2025



TMTT is innovating a broad transcatheter portfolio

	TRICUSPID		MITRAL	
Leaflet Repair	 PASCAL	 PASCAL Ace	 PASCAL	 PASCAL Ace
Annular Reduction	 Cardioband			 Cardioband
Valve Replacement	 EVOQUE		 SAPIEN M3	 EVOQUE



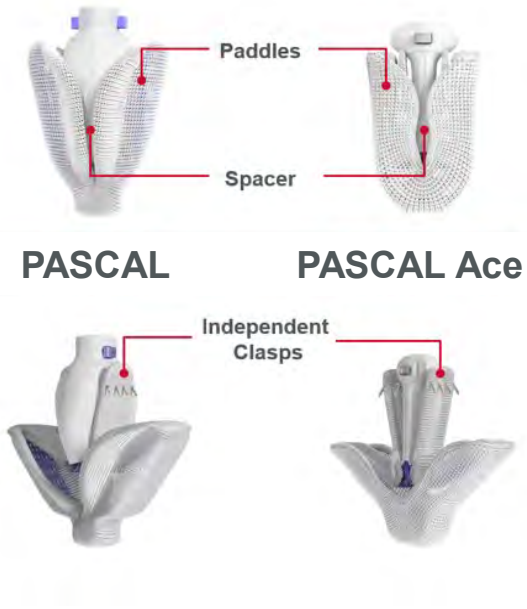
Mitral Innovations: PASCAL for Leaflet Repair



PASCAL Ace

CE Marked in 2020

New implant with **narrower profile** and spacer to achieve optimal outcomes for more patients



PASCAL & PASCAL Ace share **differentiated features**

A **nitinol design** to allow strong and yet flexible closure

A **central spacer** to bridge the coaptation gap and prevent backflow across the valve

The **ability to elongate** the device to navigate dense chords

Independent clasps, which can be used without restriction, to optimize MR reduction

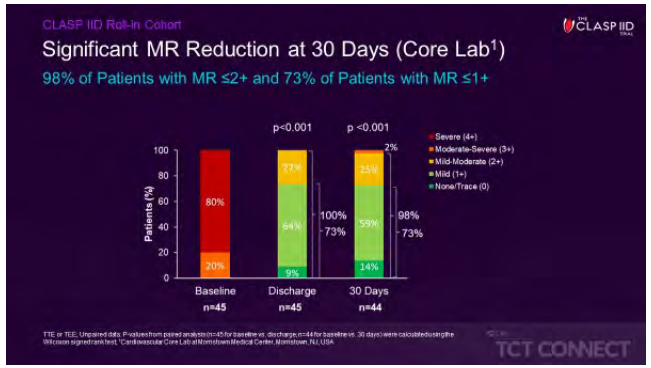
Bringing a consistent cadence of advancements to the PASCAL platform, including a next-gen delivery system in 2021

High rates of MR reduction are achieved with PASCAL, starting from physicians' earliest experience

CLASP IID Roll-In Data

73%

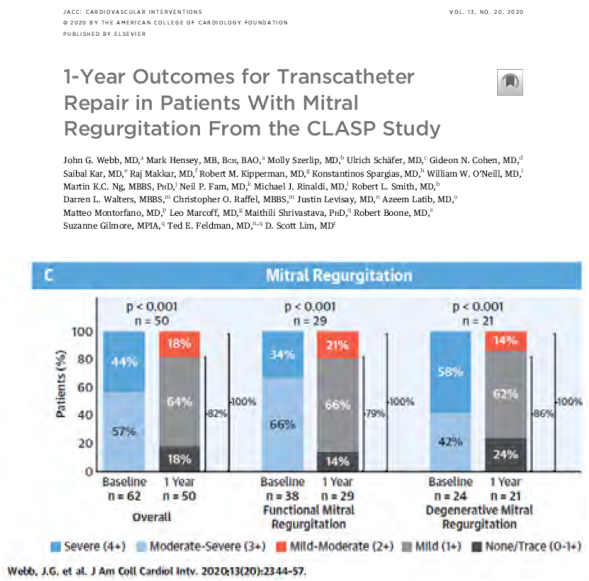
Percentage of patients with MR ≤0/1+ at 30 days [1]



CLASP CE Mark Study

82%

Percentage of patients with MR ≤0/1+ at 1 year[2]


JACC: CARDIOVASCULAR INTERVENTIONS VOL. 13, NO. 20, 2020
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1-Year Outcomes for Transcatheter Repair in Patients With Mitral Regurgitation From the CLASP Study

John G. Webb, MD,[a] Mark Hensey, MB, BCh, BAO,[a] Molly Szerlip, MD,[b] Ulrich Schäfer, MD,[c] Gideon N. Cohen, MD,[d] Saibal Kar, MD,[e] Raj Makkar, MD,[f] Robert M. Kipperman, MD,[g] Konstantinos Spargias, MD,[h] William W. O'Neill, MD,[i] Martin K.C. Ng, MBBS, PhD,[j] Neil P. Fam, MD,[k] Michael J. Rinaldi, MD,[l] Robert L. Smith, MD,[b] Darren L. Walters, MBBS,[m] Christopher O. Raffel, MBBS,[m] Justin Levisay, MD,[n] Azeem Latib, MD,[o] Matteo Montorfano, MD,[p] Leo Marcoff, MD,[q] Maithili Shrivastava, PhD,[q] Robert Boone, MD,[a] Suzanne Gilmore, MPIA,[a] Ted E. Feldman, MD,[r,s] D. Scott Lim, MD[r]

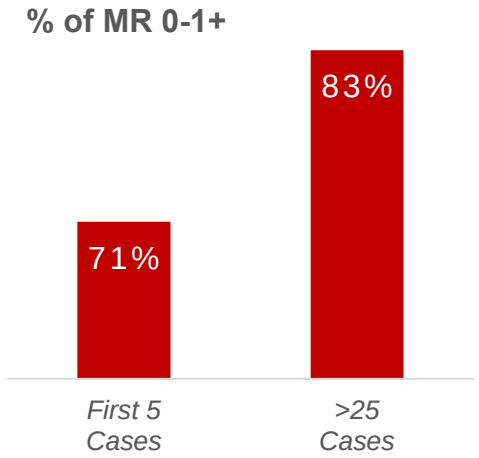
Webb, J.G. et al. J Am Coll Cardiol Intv. 2020;13(20):2344-57.

Real-World Experience

83%

Percentage of patients with MR ≤0/1+ at discharge[3]

after 25 case experience



Expect a steady cadence of evidence from CLASP, CLASP IID/IIF, and post market studies

1. Lim, TCT Connect, 2020; 2. Webb, JACC: Cardiovascular Interventions, 2020 3. Edwards data on file

Mitral Innovations: Two-platform strategy positions TMTT for transfemoral replacement leadership



SAPIEN M3

Leverages the **proven SAPIEN valve**, coupled with a novel docking system



EVOQUE

Delivers a **dedicated mitral valve replacement** therapy

Both transfemoral delivery systems are

<30F

ensuring **safety and ease-of-use** during femoral puncture and septal crossing

"The **strength of the Edwards mitral program is the diverse portfolio**…
to be able to treat a wide range of patients percutaneously and be able to discharge them as soon as the next day."

Dr. Raj Makkar
Cedars-Sinai Medical Center



We have initiated the ENCIRCLE pivotal study for SAPIEN M3, and will begin clinical experience with our next generation EVOQUE mitral system early next year

Innovations & Evidence In Tricuspid Repair



PASCAL

Differentiated leaflet repair leverages mitral platform



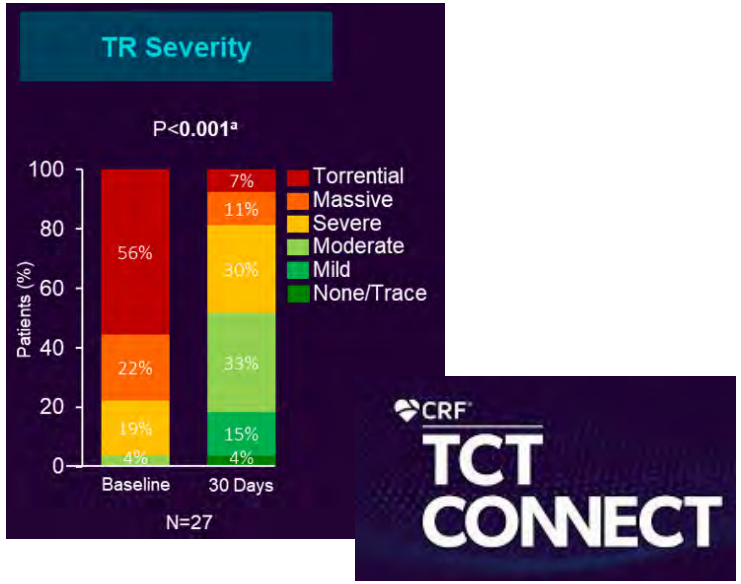
Cardioband

Strong and durable results to 2 years; investing in next generation system

PASCAL: CLASP TR EFS Study

70%

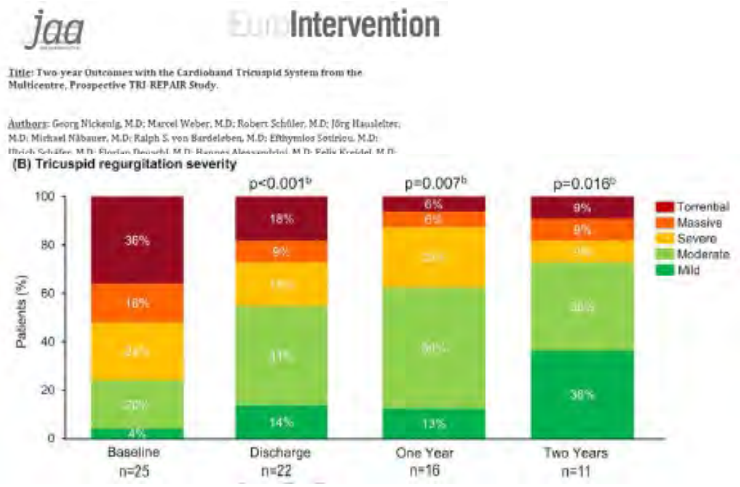
Percentage of patients with ≥ 2 TR grade reduction[1]



Cardioband: Tri-Repair CE Mark Study

72%

Percentage of patients with TR ≤ moderate at 30 days[2]



Experience with next generation PASCAL expected next year

Innovations & Evidence In Tricuspid Valve Replacement



EVOQUE

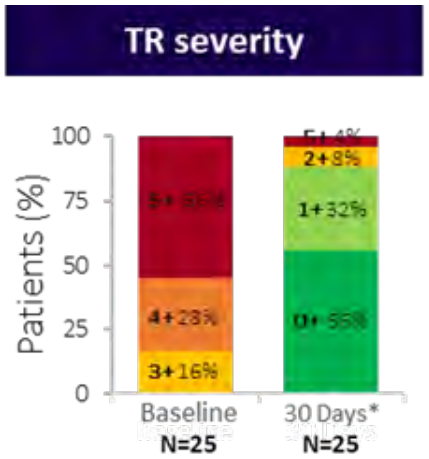
Tricuspid platform with three valve sizes to address diverse tricuspid anatomy

All three valves use the same <30F **transfemoral delivery** system

EVOQUE Compassionate Use

88%

Percentage of patients with TR ≤0/1+ at 30 days[1]



*Mean TV gradient: 3.2 ± 0.6 mmHg

Average procedure time of ~1 hour

2020 PCR e-Course

*"Having **all of these options** simultaneously in your toolbox **expands dramatically the number of patients you are able to treat."***

Dr. Stephan vonBardeleben

Heart Valve Center, Mainz Germany



Initiating the TRISCEND II randomized pivotal study based on the FDA's breakthrough designation pathway

1. Fam, Euro PCR, 2020

A dedicated team of talented people executing our high touch model to deliver outstanding patient outcomes

The TMTT high touch model

- Commitment to initial and ongoing physician training
- Highly trained clinical specialists providing full case coverage and support



Transforming treatment for patients with mitral and tricuspid valve disease to change standard of care

What to expect from TMTT in 2021

Additional Innovations

Continued innovations on each platform

Initial clinical experience with our:

- Next generation EVOQUE Mitral System
- Next generation PASCAL Delivery System

Clinical Evidence

Expanding our body of **clinical evidence**, including:

- Continued enrollment in our 5 pivotal trials
- Meaningful follow-up data publications and presentations across the portfolio

TMTT Revenue

Doubling TMTT revenue led by PASCAL and PASCAL Ace for both mitral and tricuspid patients

And in late 2022 – expect U.S. approval for PASCAL DMR and EU approval for EVOQUE Tricuspid

2021 Global Sales Outlook

Headwinds

- Slower adoption of novel TMTT therapies
- Competition for clinical trial enrollment

Doubling 2020 to ~$80M

2021E

TMTT

Estimated Global Sales

Tailwinds

- PASCAL differentiation driving faster site activation in Europe
- Rapid enrollment in CLASP IID trial

Executive Summary



- Patients with Mitral and Tricuspid regurgitation **remain undertreated** and suffer from poor quality of life
- TMTT is delivering a **portfolio of therapies, backed by clinical evidence**, to address the diversity and complexity of Mitral and Tricuspid disease
- **Doubling revenue** in 2021

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Helping Patients is Our Life's Work, and life is now

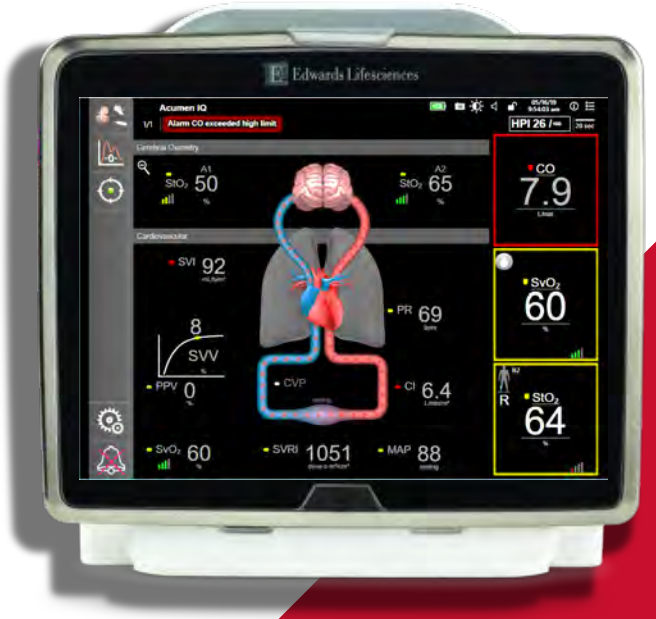
2020 Investor Conference

Critical Care

Edwards

Critical Care improving the quality of care for patients

- Continuing to **shift product mix** towards Smart Recovery, which has **highest growth** potential of our product groups
- Focusing on three **key building blocks** to advance Smart Recovery patient penetration from **5% to 15% by 2026**
- Deploying **right technologies**, generating **clinical evidence** and creating **product awareness** to drive us towards our goal



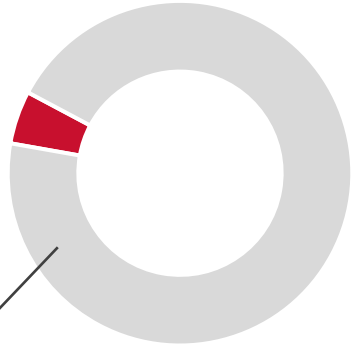
We are shifting focus of business to Smart Recovery



- Will **shift mix towards Smart Recovery**, which has highest growth potential
- This will lead to Smart Recovery becoming **largest part of our portfolio**
- **Core monitoring** largest contributor to overall revenue
- Core monitoring products support clinical efforts in fight against COVID

Three Key Building Blocks for Smart Recovery

Today

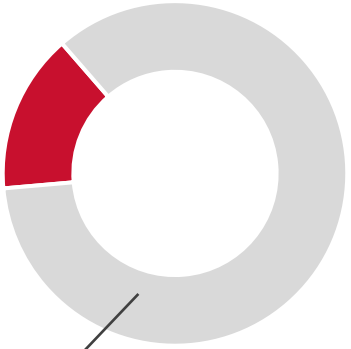


5%
penetration
700k patients

14M patients
could benefit from Smart Recovery



2026

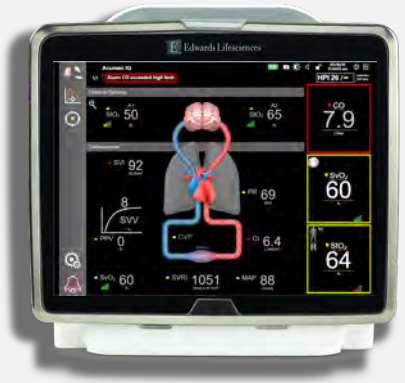


15%
penetration
2.7M patients

18M patients
could benefit from Smart Recovery

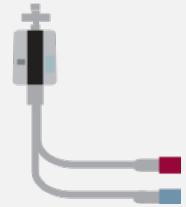
Having the Right Technologies Deployed in Hospitals

CAPITAL PLATFORM



HemoSphere

SENSORS



Acumen IQ Sensor



ForeSight



Acumen IQ Cuff

SOFTWARE

Hypotension Prediction Index (HPI)



Viewfinder
Remote View



Long-term growth can only be accomplished if we have our advanced monitoring platform in place

Generating Compelling Clinical Evidence

Intraoperative Hypotension (IOH) Matters

Both studies demonstrate IOH linked to:

Acute kidney injury	Myocardial injury	30-day mortality

Intraoperative hypotension and the risk of postoperative adverse outcomes: a systematic review

E. M. Wesselink[1,*], T. H. Kappen[1], H. M. Torn[1], A. J. C. Slooter[2] and W. A. van Klei[1]

[1]Department of Anesthesiology, Utrecht, The Netherlands and [2]Department of Intensive Care Medicine, University Medical Center Utrecht, Utrecht University, Utrecht, The Netherlands

ORIGINAL CLINICAL RESEARCH REPORT

Intraoperative Hypotension Is Associated With Adverse Clinical Outcomes After Noncardiac Surgery

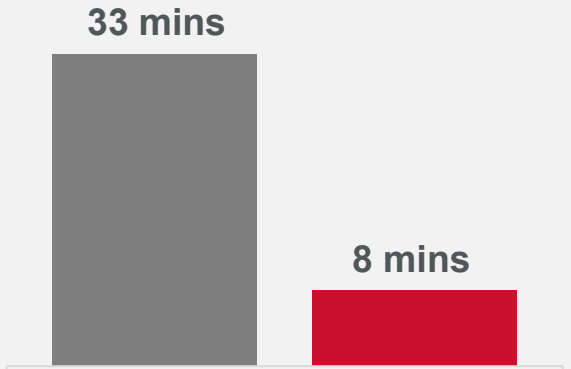
Anne Gregory, MD, MSc, FRCPC,* Wolf H. Stapelfeldt, MD,† Ashish K. Khanna, MD, FCCP, FCCM,‡§ Nathan J. Smischney, MD, MSc,‖ Isabel J. Boero, MD, MS,¶ Qinyu Chen, MS,¶ Mitali Stevens, PharmD, BCPS,# and Andrew D. Shaw, MB, FRCPC*,**

Edwards HPI Software Can Reduce IOH

without Acumen HPI software with Acumen HPI software

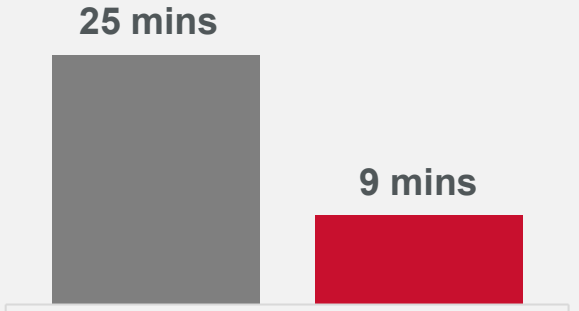
HYPE Trial

76%
Decrease in IOH



Edwards Trial

65%
Decrease in IOH



Creating Awareness for our Products Through Evidence



"HPI was high…and 10 minutes later there was hypotension. I didn't see it coming at all."

– Simon Davies, MD MBChB FRCA



"We were able to decrease the rate of hypotension by about 50%, which is quite impressive I think."

– Michael Sander, MD, PhD



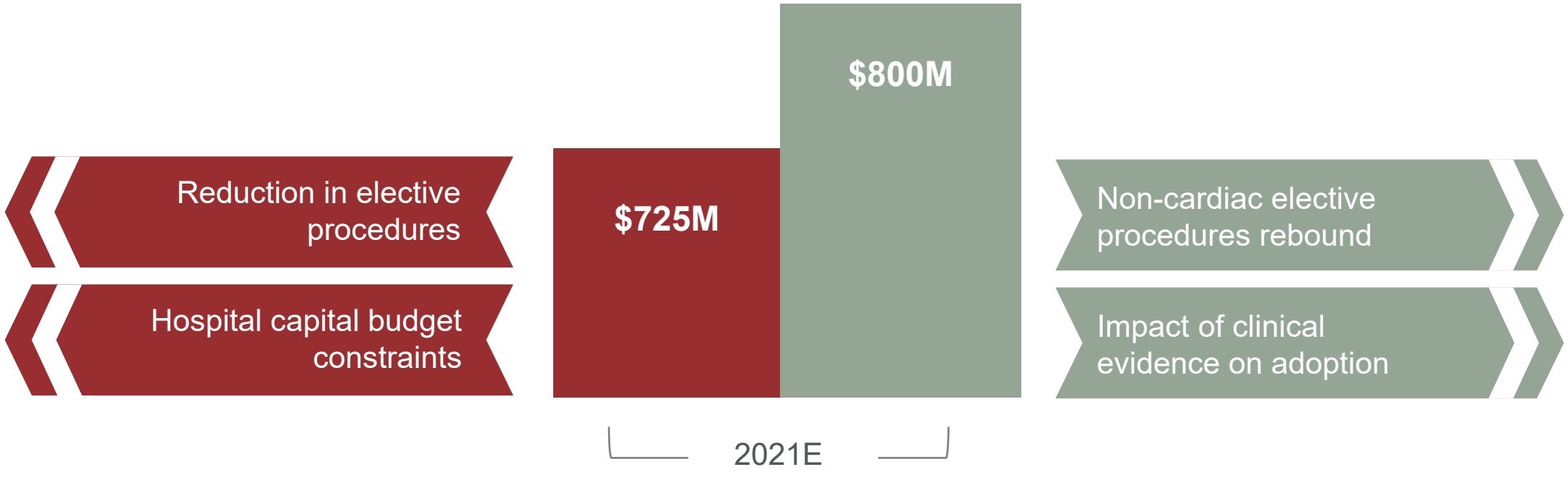
"My doctor said to me, 'I can do anesthesia in a special way using Acumen HPI.' Now, thank God, I can walk again."

– Juan Gil Garcia, HPI Patient



We believe the increased evidence around hypotension will drive awareness

2021 Global Sales Outlook



Critical Care
Estimated Global Sales

Executive Summary

- Shift product mix towards **higher growth Smart Recovery**
- Advance Smart Recovery **penetration from 5% to 15%**
- Implement building blocks: **technology, evidence, awareness**

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Helping Patients is Our Life's Work, and *life is now*

Financial Outlook

Scott Ullem
Chief Financial Officer

Edwards

Edwards has delivered strong financial performance



Edwards Financial Objectives



STRONG SALES GROWTH EXCEEDING MEDTECH SECTOR

- Sales growth fueled by successful long-term investments in R&D and advancements of breakthrough innovations
- Sustained leadership position supported by strong evidence base of value to patients and clinicians
- Addressing large, growing unmet patient needs

COVID significantly impacted 2020 financial performance

(Excludes special items; $ in millions except earnings per share)

Adjusted Item	2019 Investor Conference	October Guidance
Sales	$4,500-5,000	Year-over-year growth below plan
FX Impact on Sales	~$(40) (~1% downside to sales)	Neutral impact
Gross Profit Margin	76-77%	Year-to-date Q3: 75.6%
Earnings Per Share	$2.02-2.10 (adjusted for 3-for-1 split)	$1.85-1.95
Free Cash Flow	$1,000-1,100	Below plan

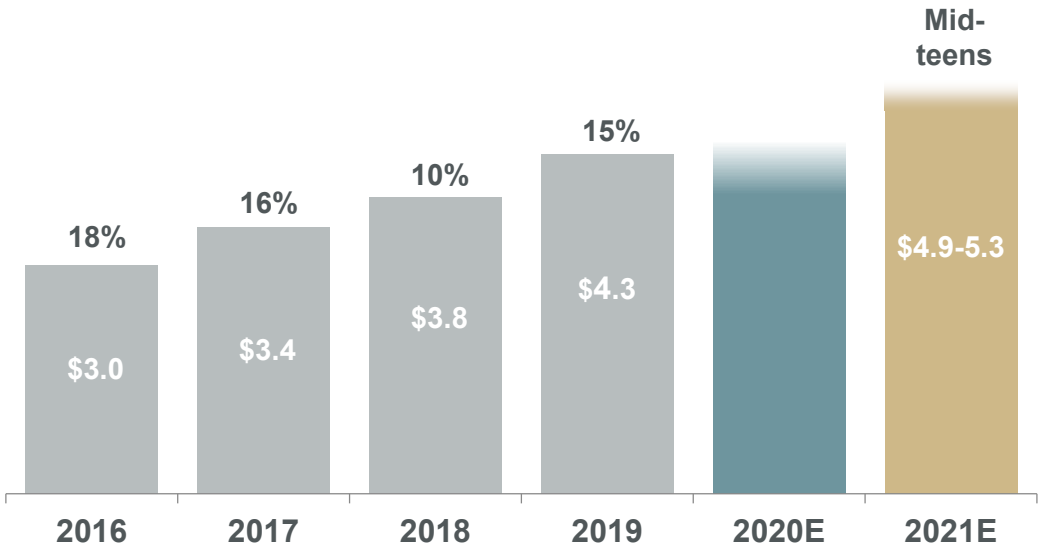
2020 Sales Guidance Comparison

Total company year-over-year Q4 growth rate trending lower than Q3 due to COVID

	2019 Investor Conference	Current Guidance
Transcatheter Aortic Valve Replacement	12-15%	Higher End (5%)-5%
Transcatheter Mitral & Tricuspid Therapies	$50-$70M	Around $40M
Surgical Structural Heart	0-3%	(15%)-(5%)
Critical Care	6-9%	(5%)-0%
Total Edwards	10-12%	Q3 YTD: ~1%

Mid-teens sales growth expected in 2021

(Adjusted sales $ in billions; underlying growth rates)



2021 EXPECTATIONS

- Hospitals continue to face headwinds from COVID
- Growth in all regions with expectations for interruptions due to COVID
- FX impact expected to be approximately 1% favorable in 2021 at current rates
- Expect high variability in quarterly growth rates

2021 Sales Guidance – Product Group

($ in millions at current exchange rates)

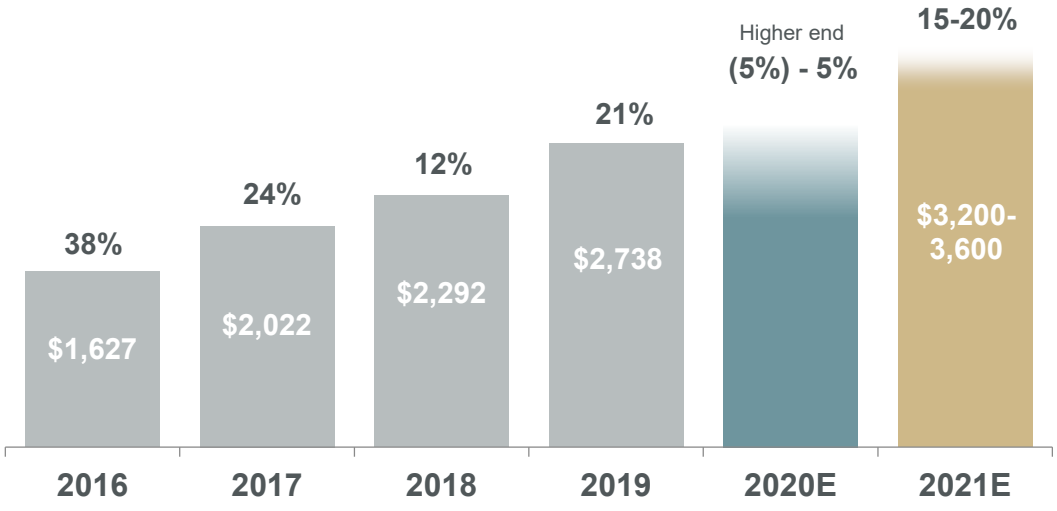
	Underlying Sales
Transcatheter Aortic Valve Replacement	$3,200-3,600 (Underlying growth 15-20%)
Transcatheter Mitral & Tricuspid Therapies	~$80 (Approximately 2x 2020)
Surgical Structural Heart	$800-900
Critical Care	$725-800
Total Edwards	$4,900-5,300 (Mid-teens underlying growth)

2021 Guidance Assumptions

- COVID continues to stress the global healthcare system
- COVID impact lessens after winter flu season
- Effective vaccine becomes widely available by mid-2021
- Hospitals continue to improve ability to treat structural heart patients

TAVR to return to double-digit sales growth in 2021

(Adjusted sales $ in millions; underlying growth rates)

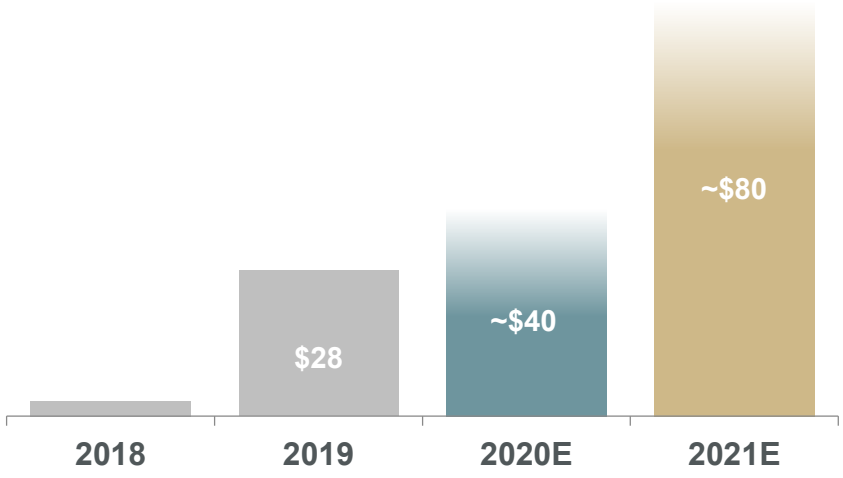


2021 HIGHLIGHTS

- Procedure growth driven by improved TAVR adoption
- EARLY TAVR enrollment complete
- FDA approval to start Moderate AS pivotal trial
- Japan low-risk approval late 2021
- Alterra approval
- SAPIEN X4 clinical trial initiated

TMTT has strong momentum going into 2021

(Adjusted sales $ in millions)

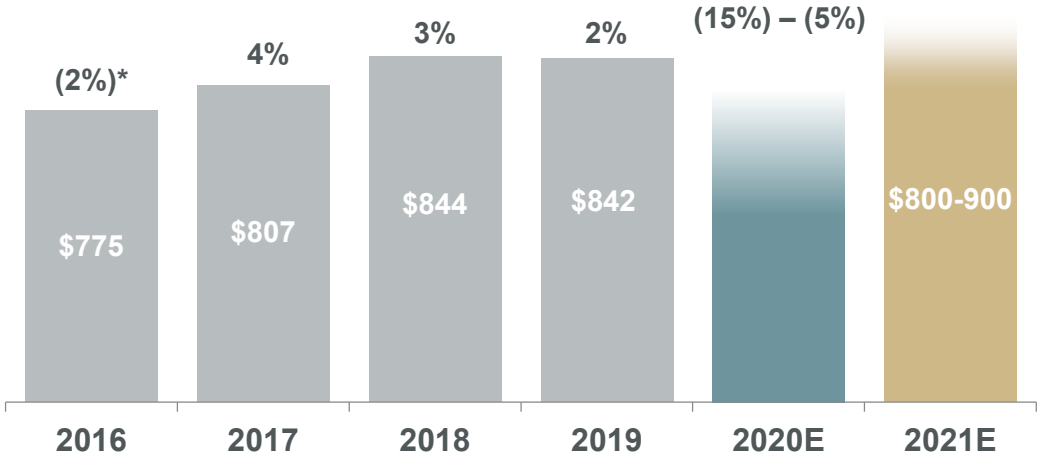


2021 HIGHLIGHTS

- Doubling 2020 global revenue led by PASCAL and PASCAL Ace for both mitral and tricuspid patients
- Enrolling 5 pivotal studies: SAPIEN M3 (ENCIRCLE); EVOQUE TR (TRISCEND II); and PASCAL (CLASP IID, IID, and IITR)
- 1st clinical experience with next generation PASCAL delivery system
- 1st clinical experience with next generation EVOQUE MR

Surgical Structural Heart brings leading innovation

(Adjusted sales $ in millions; underlying growth rates)



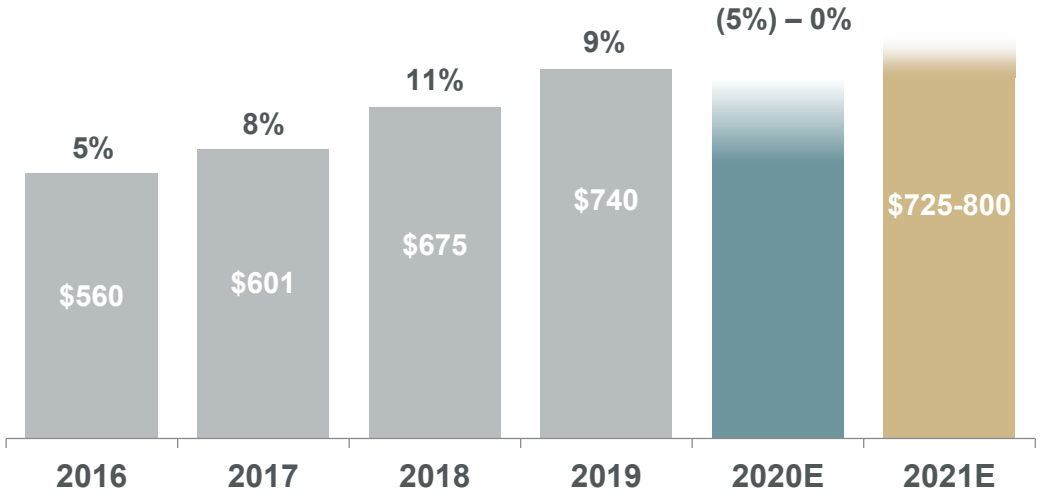
2021 HIGHLIGHTS

- Drive adoption of our RESILIA products, INSPIRIS and KONECT
- INSPIRIS China launch
- MITRIS US and Japan launch
- HARPOON U.S. pivotal trial enrolling (RESTORE)

* The PARTNER II Intermediate Risk clinical trial data.

Critical Care shifting focus to Smart Recovery

(Adjusted sales $ in millions; underlying growth rates)



2021 HIGHLIGHTS

- Drive growth with capital equipment and Smart Recovery products
- Focus on advancing Smart Recovery and improving quality of care with the expansion of HPI technology
- Viewfinder connectivity solution available in 2021

2021 Product Group Milestones

TAVR

- Procedure growth driven by improved TAVR adoption
- EARLY TAVR enrollment complete
- FDA approval to start Moderate AS pivotal trail
- Japan low-risk approval in late 2021
- Alterra approval H2 2021
- SAPIEN X4 clinical trial initiated

TMTT

- Double 2020 global revenue led by PASCAL and PASCAL Ace for both mitral and tricuspid patients
- Enrolling 5 pivotal studies
- Initial clinical experience with the next-generation PASCAL delivery system
- Initial clinical experience with the next-generation EVOQUE mitral system

Surgical Structural Heart

- RESILIA product adoption (INSPIRIS and KONECT)
- INSPIRIS China launch
- MITRIS US and Japan launch
- HARPOON U.S. pivotal trial enrolling (RESTORE)

Critical Care

- Global expansion of HPI technology
- Viewfinder connectivity solution available
- Increased clinical evidence to drive adoption

Edwards Financial Objectives



HEALTHY PROFITABILITY

- Generating strong gross profit and operating margins
- Funding growing field organization and strengthening global supply chain
- Investing aggressively for profitable organic growth
- Maintaining efficient tax structure

2021 Gross Profit Margin Outlook

	Year-over-Year	
Sales Mix	+	Mix benefit from TAVR growth Some lower-volume new product margins below the corporate average Modest price compression driven by volume discounts
Optimizing Global Supply Chain	+/–	Creating business continuity across our global manufacturing network Increasing capacity and improving efficiency Upgrading manufacturing systems across plant network Enhancing supplier network
Foreign Exchange	–	At current FX rates, expect modest negative impact
Net Impact	=	**Adjusted Gross Margin forecast to be 76-77%**

Plan to invest aggressively in 2021 for future growth despite expected COVID disruptions

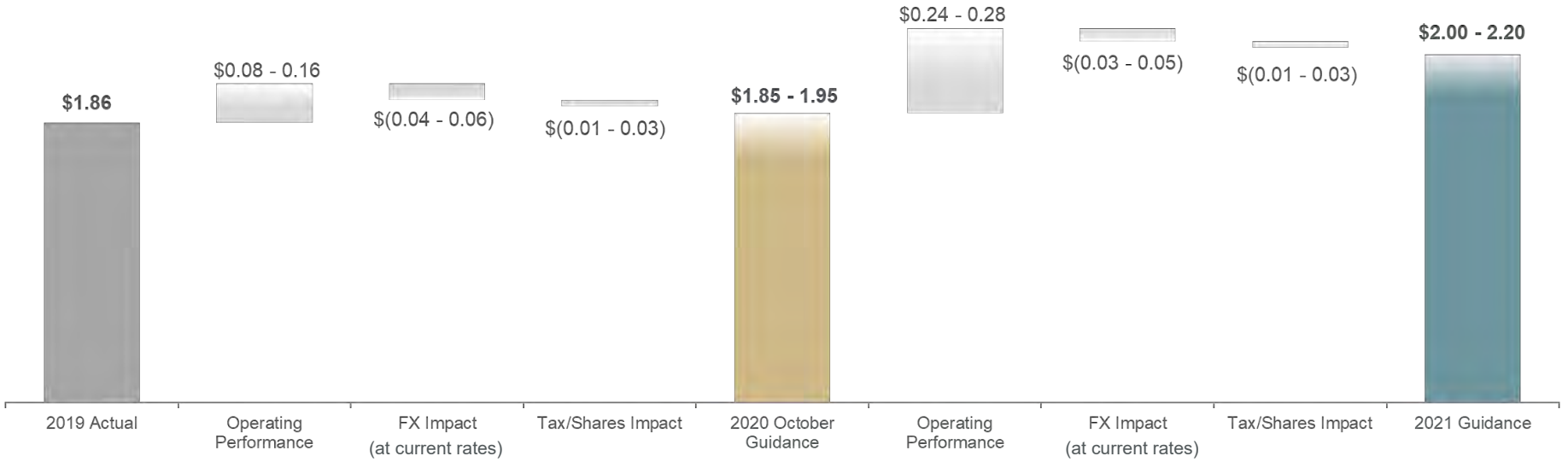
R&D

- TAVR and TMTT investments focused on developing new technologies and generating evidence to expand indications
- Enrolling 7 pivotal trials
- Approximately 1/3 of R&D investment is allocated to clinical evidence generation
- Targeted investments to grow core businesses

SG&A

- Continuing to support high-touch model for U.S. TAVR
- Ongoing build-out of commercial and clinical teams to support TMTT
- Travel resumes as COVID permits

Operating performance drives adjusted EPS growth



Edwards Financial Objectives



ROBUST CASH FLOW AND DISCIPLINED CAPITAL DEPLOYMENT

- Enables aggressive R&D investments
- Internal growth supplemented by smaller strategic acquisitions
- Investing in expanding global capacity
- Commitment to returning capital to shareholders through opportunistic share repurchase

Cash Flows and Capital Deployment

2016 - 2019

Nearly

$4B

of cash generated from operations

funded

$2.5B	**Share Repurchases**
$0.8B	**CAPEX**
$0.3B	**Upfront Acquisition Payments**

2021 HIGHLIGHTS

- Continued growth results in significant cash flows that fund future internal and external opportunities
- 2021 capital expenditures expected around $350 million as capacity expansion continues
- EPS model assumes flat diluted shares outstanding of 630 million

2021 Guidance Summary

(Excludes special items; $ and shares in millions except earnings per share)

Adjusted Item	FY 2021	Adjusted Item	FY 2021
Sales	$4,900-5,300	**Operating Margin**	29-30%
Underlying growth	Mid-teens	**Tax rate**	11-15% (~5pp ETB benefit)
FX Impact on Sales	~$35 (1% upside to sales)	**Earnings Per Share**	$2.00-$2.20
Gross Profit Margin	76-77%	**CAPEX**	~$350M
SG&A % of Sales	Similar to pre-COVID	**Shares Outstanding**	Modeled to be flat with 2020 levels of 630 million
R&D % of Sales			

Longer-Term Guidance

Underlying Sales Growth	Innovation expected to drive organic growth that exceeds medtech sector
Gross Margin	Mix and efficiencies expected to benefit longer-term margin
R&D % of Sales	Significant investments in clinical trials to expand indications and develop new technologies
SG&A % of Sales	Disciplined focus on leveraging our scale and controlling G&A expenses, partially offset by investments to support growth initiatives
Operating Margin	Investing to gradually expand margin over time
Tax Rate %	Upward pressure and less predictability due to stock option accounting
Outstanding Shares	Routine share repurchases to offset dilution from employee shares Opportunistically reduce net shares outstanding

Edwards Financial Objectives





Edwards

Helping Patients is Our Life's Work, and *life is now*

Closing Remarks

Michael A. Mussallem
Chairman and CEO

Edwards

Patient-Focused Innovation Strategy

Focus

Singular focus on the large unmet needs of structural heart and critically ill patients



Leadership

Lead groundbreaking standards of care through trusted relationships

Innovation

Pioneer breakthrough technologies with compelling evidence

2021 expected to be a year of significant growth and investment in our future

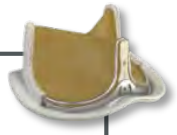
2021 Expectations

Mid-teens	$2.00 - $2.20
Underlying net sales growth	Adjusted EPS



TAVR

- Therapy expansion
- Technology advances
- Geographic expansion



Surgical

- Surgeon partnership
- Leading pipeline
- Growth segment focus



TMTT

- Differentiated portfolio
- Clinical evidence
- Real-world outcomes



Critical Care

- HemoSphere growth
- Smart technologies
- Portfolio expansion

Edwards' Board is diverse and accomplished


Michael A. Mussallem


Kieran T. Gallahue


Leslie S. Heisz


Paul A. LaViolette


William J. Link Ph.D.


Steven R. Loranger


Martha H. Marsh


Ramona Sequeira


Nicholas J. Valeriani

- **Leading governance** practices
- Proactive shareholder **engagement**
- **Performance-based compensation** philosophy based on:
  - Financial performance
  - Key operating drivers
  - Shareholder value creation

Edwards is committed to good corporate citizenship

Forbes | JUST Capital
2021 America's Most JUST Companies

2020 America's Most Responsible Companies

2020 World's Most Ethical Companies

Investor's Business Daily
50 Best ESG Companies in 2020, 2019

America's Best Large Employers 2019

2019 Management Top 250

2019 Best Performing CEOs in the World

MEMBER OF Dow Jones Sustainability Indices In Collaboration with RobecoSAM

- DJSI World
- DJSI North America

2019 Constituent MSCI ESG Leaders Indexes

FTSE4Good Index Series Constituent

ISS E&S Disclosure QualityScore
Pillar Score of 1 in Environmental and Social Disclosure

Edwards is committed to giving back



EVERY HEARTBEAT MATTERS

Launched new goal to improve lives of **2.5M** additional underserved structural heart and critically ill patients by the end of 2025



COVID-19 RESPONSE

Edwards Lifesciences Foundation issued emergency grants to more than **20** partner organizations around the world

Edwards is poised for long-term value creation

Patient-Focused Culture
motivates and guides our global team

Sustainable Growth
organic revenue



Large Populations
of under-served patients

Credibility and Trust
with clinicians, regulators, payors and patients

Innovative R&D
produces breakthrough therapies and drives shareholder returns



Edwards

Helping Patients is Our Life's Work, and

life is now

2020 Investor Conference

Forward-looking statements and disclaimers

Edwards

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Statements of past performance, efforts, or results about which inferences or assumptions may be made can also be forward-looking statements and are not indicative of future performance or results. Forward-looking statements are based on estimates and assumptions made by management of the company and are believed to be reasonable, though they are inherently uncertain, difficult to predict, and may be outside of the company’s control. The company's forward-looking statements speak only as of the date on which they are made and the company does not undertake any obligation to update any forward-looking statement to reflect events or circumstances after the date of the statement. If the company does update or correct one or more of these statements, investors and others should not conclude that the company will make additional updates or corrections.

Forward-looking statements involve risks and uncertainties that could cause actual results or experience to differ materially from that expressed or implied by the forward-looking statements. Factors that could cause actual results to differ from that expressed or implied by the forward-looking statements are detailed in the Company’s periodic reports filed with the Securities and Exchange Commission.

The opinions expressed by our guest clinicians are their own and do not necessarily reflect the views of Edwards Lifesciences.

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- A reconciliation of non-GAAP historical financial measures to the most comparable GAAP measure is available on the “Investors” page at www.edwards.com
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Edwards

Helping Patients is Our Life's Work, and life is now

EDWARDS LIFESCIENCES CORPORATION

Non-GAAP Financial Information

To supplement the consolidated financial results prepared in accordance with Generally Accepted Accounting Principles (“GAAP”), the Company uses non-GAAP historical financial measures. Management makes adjustments to the GAAP measures for items (both charges and gains) that (a) do not reflect the core operational activities of the Company, (b) are commonly adjusted within the Company’s industry to enhance comparability of the Company’s financial results with those of its peer group, or (c) are inconsistent in amount or frequency between periods (albeit such items are monitored and controlled with equal diligence relative to core operations).The Company uses the term "adjusted sales" or “underlying growth rate” when referring to non-GAAP sales information, which excludes foreign exchange rate fluctuations, the conversion to a consignment inventory system for surgical structural heart ("Surgical"), the positive impact of transcatheter aortic valve replacement ("TAVR") stocking sales in Germany and the negative impact of de-stocking, sales return reserves associated with TAVR product upgrades, and includes the prior year proforma sales results of a business acquisition. The Company uses the term “adjusted” to also exclude intellectual property litigation income and expenses, amortization of intangible assets, fair value adjustments to contingent consideration liabilities arising from acquisitions, impairments of long-lived assets, and the purchase of intellectual property.

Management uses non-GAAP financial measures internally for strategic decision making, forecasting future results, and evaluating current performance. These non-GAAP financial measures are used in addition to, and in conjunction with, results presented in accordance with GAAP and reflect an additional way of viewing aspects of the Company's operations by investors that, when viewed with its GAAP results, provide a more complete understanding of factors and trends affecting the Company's business and facilitate comparability to historical periods.

Non-GAAP financial measures are not prepared in accordance with GAAP; therefore, the information is not necessarily comparable to other companies and should be considered as a supplement to, and not as a substitute for, or superior to, the corresponding measures calculated in accordance with GAAP. A reconciliation of non-GAAP historical financial measures to the most comparable GAAP measure is provided in the tables below.

Fluctuations in exchange rates impact the comparative results and sales growth rates of the Company's underlying business. Management believes that excluding the impact of foreign exchange rate fluctuations from its sales growth provides investors a more useful comparison to historical financial results.

Guidance for sales and sales growth rates is provided on an "underlying basis," and projections for diluted earnings per share, net income and growth, gross profit margin, taxes, and free cash flow are also provided on a non-GAAP basis as adjusted for the items identified above due to the inherent difficulty in forecasting such items. The Company is not able to provide a reconciliation of the non-GAAP guidance to comparable GAAP measures due to the unknown effect, timing, and potential significance of special charges or gains, and management's inability to forecast charges associated with future transactions and initiatives.

Management considers free cash flow to be a liquidity measure which provides useful information to management and investors about the amount of cash generated by business operations, after deducting payments for capital expenditures, which can then be used for strategic opportunities or other business purposes including, among others, investing in the Company's business, making strategic acquisitions, strengthening the balance sheet, and repurchasing stock.

The items described below are adjustments to the GAAP financial results in the reconciliations that follow:

TAVR Inventory Write Off - The Company recorded a $73.1 million charge in 2019 primarily comprised of the write off of inventory in response to strategic decisions regarding its TAVR portfolio.

Intellectual Property Litigation (Income) Expenses, net - In 2019, the Company incurred intellectual property litigation expenses of $33.4 million.

Change in Fair Value of Contingent Consideration Liabilities - In 2019, the Company recorded a net gain of $6.1 million related to changes in the fair value of its contingent consideration liabilities arising from acquisitions.

Amortization of Intellectual Property - In 2019, the Company recorded amortization expense of $4.6 million related to developed technology, patents and trademarks.

Impairment of Long-lived Assets - The Company recorded a $40.6 million charge in 2019 related to the other-than-temporary impairment of certain in-process research and development assets acquired as part of the acquisition of Valtech Cardio Ltd.

Purchase of Intellectual Property - The Company recorded a $24.0 million charge in 2019 related to the acquisition of early-stage transcatheter intellectual property and associated clinical and regulatory experience.

Adjusted Free Cash Flow - The Company defines free cash flow as cash flows from operating activities less capital expenditures. During 2019, the Company excluded from its calculation payments related to a litigation settlement, net of the associated tax benefit. During 2018, the Company excluded from its calculation payments related to tax audit settlements and the repatriation tax resulting from U.S. tax law changes. During 2017, the Company excluded from its calculation a receipt of a litigation payment and the amount of an escrow deposit related to the purchase of a building.

Unaudited Reconciliation of GAAP to Non-GAAP Financial Information

Twelve months ended December 31 (in millions, except per share and percentage data)

RECONCILIATION OF GAAP TO ADJUSTED NET INCOME

	2019
GAAP Net Income	$1,046.9
Non-GAAP adjustments:	
TAVR inventory write-off	73.1
Intellectual property litigation expenses, net	33.4
Change in fair value of contingent consideration liabilities, net	(6.1)
Amortization of intangible assets	4.6
Impairment of long-lived assets	40.6
Purchased in-process research and development	24.0
Provision for income taxes:	
Tax effect on non-GAAP adjustments	(33.6)
Adjusted Net Income	$1,182.9

RECONCILIATION OF GAAP TO ADJUSTED DILUTED EARNINGS PER SHARE

GAAP Diluted Earnings Per Share	$ 1.64
Non-GAAP adjustments:	
TAVR inventory write-off	0.09
Intellectual property litigation expenses, net	0.04
Change in fair value of contingent consideration liabilities, net	(0.01)
Amortization of intangible assets	0.01
Impairment of long-lived assets	0.06
Purchased in-process research and development	0.03
Adjusted Diluted Earnings Per Share	$ 1.86

Note: Numbers may not calculate due to rounding

EDWARDS LIFESCIENCES CORPORATION
Reconciliation of GAAP to Non-GAAP Financial Information
Adjusted Free Cash Flow *

(in millions)	Year Ended December 31, 2019	2018	2017	2016
Net cash provided by operating activities	$1,179.4	$926.8	$1,000.7	$704.4
Capital expenditures	(254.4)	(238.7)	(168.1)	(176.1)
Litigation settlements	138.3	-	(112.5)	-
Tax audit settlements	-	56.7	-	-
Repatriation tax payments	-	41.0	-	-
Deposit of cash in escrow	-	-	(25.0)	-
Adjusted Free Cash Flow	$ 1,063.3	$ 785.8	$ 695.1	$ 528.3

* See description of "Adjusted Free Cash Flow" on the Non-GAAP Financial Information page.

EDWARDS LIFESCIENCES CORPORATION

Unaudited Reconciliation of Sales by Product Group and Region

($ in millions)

					2019 Adjusted	2018 Adjusted				
Sales by Product Group (YTD)	**2019**	**2018**	**Change**	**GAAP Growth Rate***	**2019 Adjusted Sales**	**CASMED Acquisition**	**Surgical Consignment Conversion**	**Germany Stocking**	**FX Impact**	**2018 Adjusted Sales**	**Underlying Growth Rate ***
Transcatheter Aortic Valve Replacement	**$ 2,737.9**	**$ 2,283.8**	**$ 454.1**	**19.9%**	$ 2,737.9	$ -	$ -	$ 8.0	$ (32.7)	$ 2,259.1	21.2%
Transcatheter Mitral and Tricuspid Therapies	**28.2**	**2.9**	**25.3**	**NM**	28.2	-	-	-	(0.1)	2.8	NM
Surgical Structural Heart	**841.7**	**761.6**	**80.1**	**10.5%**	841.7	-	82.5	-	(14.5)	829.6	1.5%
Critical Care	**740.2**	**674.5**	**65.7**	**9.7%**	740.2	15.3		-	(9.1)	680.7	8.8%
Total Sales	**$ 4,348.0**	**$ 3,722.8**	**$ 625.2**	**16.8%**	**$ 4,348.0**	**$ 15.3**	**$ 82.5**	**$ 8.0**	**$ (56.4)**	**$ 3,772.2**	**15.3%**

* Numbers may not calculate due to rounding.

EDWARDS LIFESCIENCES CORPORATION

Unaudited Reconciliation of Sales by Product Group and Region

($ in millions)

Sales by Product Group (YTD)	2018	2017	Change	GAAP Growth Rate*	2018 Adjusted: Surgical Consignment Conversion	2018 Adjusted: Germany Stocking	2018 Adjusted: 2018 Adjusted Sales	2017 Adjusted: Germany Stocking	2017 Adjusted: FX Impact	2017 Adjusted: 2017 Adjusted Sales	Underlying Growth Rate *
Transcatheter Aortic Valve Replacement	**$ 2,283.8**	**$ 2,023.8**	**$ 260.0**	**12.8%**	$ -	$ 8.0	$ 2,291.8	$ (1.4)	$ 20.0	$ 2,042.4	12.2%
Transcatheter Mitral and Tricuspid Therapies	**2.9**	**3.4**	**(0.5)**	**(14.7%)**	-	-	2.9	-	-	3.4	(14.7%)
Surgical Structural Heart	**761.6**	**807.1**	**(45.5)**	**(5.6%)**	82.5	-	844.1	-	9.2	816.3	3.4%
Critical Care	**674.5**	**601.0**	**73.5**	**12.2%**	-	-	674.5	-	5.1	606.1	11.3%
Total Sales	**$ 3,722.8**	**$ 3,435.3**	**$ 287.5**	**8.4%**	**$ 82.5**	**$ 8.0**	**$ 3,813.3**	**$ (1.4)**	**$ 34.3**	**$ 3,468.2**	**10.0%**

* Numbers may not calculate due to rounding.

EDWARDS LIFESCIENCES CORPORATION

Unaudited Reconciliation of Sales by Product Group and Region

($ in millions)

Sales by Product Group (YTD)	2017	2016	Change	GAAP Growth Rate*	2017 Adjusted: Germany Stocking	2017 Adjusted: 2017 Adjusted Sales	2016 Adjusted: Sales Return Reserve	2016 Adjusted: FX Impact	2016 Adjusted: 2016 Adjusted Sales	Underlying Growth Rate *
Transcatheter Aortic Valve Replacement	**$ 2,023.8**	**$ 1,628.2**	**$ 395.6**	**24.3%**	$ (1.4)	$ 2,022.4	$ (1.7)	$ 5.2	$ 1,631.7	24.1%
Transcatheter Mitral and Tricuspid Therapies	**3.4**	**0.3**	**3.1**	**NM**	-	3.4	-	-	0.3	NM
Surgical Structural Heart	**807.1**	**774.9**	**32.2**	**4.2%**	-	807.1	-	0.8	775.7	4.0%
Critical Care	**601.0**	**560.3**	**40.7**	**7.2%**	-	601.0	-	(1.0)	559.3	7.5%
Total Sales	**$ 3,435.3**	**$ 2,963.7**	**$ 471.6**	**15.9%**	**$ (1.4)**	**$ 3,433.9**	**$ (1.7)**	**$ 5.0**	**$ 2,967.0**	**15.7%**

* Numbers may not calculate due to rounding.

EDWARDS LIFESCIENCES CORPORATION

Unaudited Reconciliation of Sales by Product Group

($ in millions)

Sales by Product Group (YTD)	2016	2015	Change	GAAP Growth Rate*
Transcatheter Aortic Valve Replacement	$ 1,628.2	$ 1,180.1	$ 448.1	38.0%
Transcatheter Mitral and Tricuspid Therapies	0.3	0.2	0.1	NM
Surgical Structural Heart	774.9	785.0	(10.1)	(1.3%)
Critical Care	560.3	528.4	31.9	6.0%
Total Sales	**$ 2,963.7**	**$ 2,493.7**	**$ 470.0**	**18.8%**

2016 Adjusted		2015 Adjusted			
Sales Returns Reserve	2016 Adjusted Sales	Sales Returns Reserve	FX Impact	2015 Adjusted Sales	Underlying Growth Rate *
$ (1.7)	$ 1,626.5	$ 1.7	$ (2.5)	$ 1,179.3	37.9%
-	0.3	-	-	0.2	45.0%
-	774.9	-	2.2	787.2	(1.6%)
-	560.3	-	5.0	533.4	5.0%
$ (1.7)	**$ 2,962.0**	**$ 1.7**	**$ 4.7**	**$ 2,500.1**	**18.5%**

* Numbers may not calculate due to rounding.

EXHIBIT 42

Edwards Lifesciences

39th Annual J.P. Morgan Healthcare Conference

January 11, 2021

Edwards

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Our Credo

Through our actions, we will become trusted partners with customers, colleagues, and patients – creating a community unified in its mission to improve the quality of life around the world. Our results will benefit customers, patients, employees and shareholders.

We will celebrate our successes, thrive on discovery, and continually expand our boundaries. We will act boldly, decisively, and with determination on behalf of people fighting cardiovascular disease.



At Edwards Lifesciences, we are dedicated to providing innovative solutions for people fighting cardiovascular disease.

Helping Patients is Our Life's Work, and *life is now*

Helping Patients Around the World



*Source: 2020 engagement survey results of global professional employees

Patient-Focused Innovation Strategy

Focus
Singular focus on the large unmet needs of structural heart and critically ill patients

Leadership
Lead groundbreaking standards of care through trusted relationships



Innovation
Pioneer breakthrough technologies with compelling evidence

Edwards' patient-focused innovation strategy has produced sustained underlying sales growth

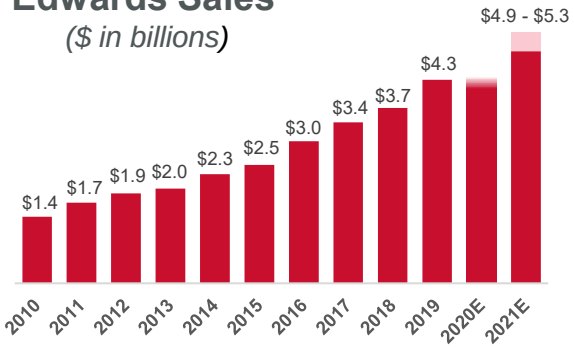
Global Transcatheter Opportunity

$10B+ by 2025

Focused on opportunities where **patient demand** is very large



Edwards Sales
($ in billions)



Long-term investments have yielded high-value, organic growth

Track record of **triple wins**:

- Improved outcomes
- Enhanced quality of life
- Cost effectiveness

Business Overview

Strong Leadership Positions and
Significant Growth Opportunities



Leader in $4B+ Global Transcatheter Aortic Valve Replacement Market

Primary global growth drivers: **indication expansion**, **therapy awareness**, and **technology advances**

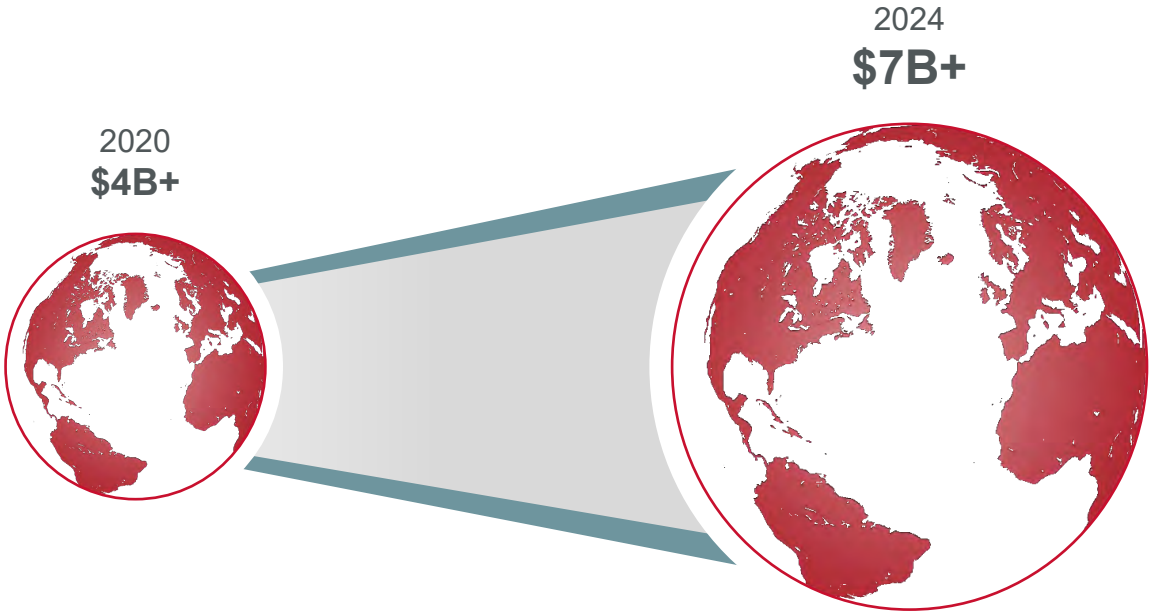
Globally, **diagnosis and treatment rates of AS remain low** providing opportunity for low-double digit TAVR growth long-term

Continued **investment in groundbreaking trials** beyond severe symptomatic aortic stenosis and transformational technologies to treat patients



$7B+ Estimated Global TAVR Opportunity by 2024

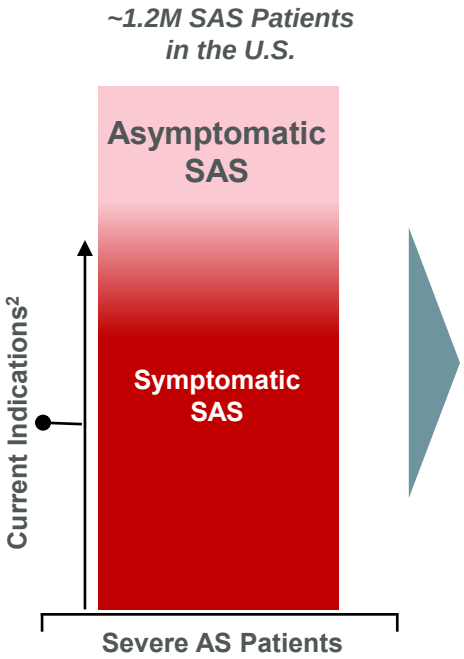
- **Indication Expansion**
- **Increasing Awareness**
- **Technology**



We anticipate the global TAVR opportunity to grow at low double-digit CAGR through 2024

Asymptomatic and Moderate Risk Clinical Trials

Expected to add significant growth beyond 2024



- **Treating severe AS before symptoms may:[1]**
  - Prevent irreversible myocardial damage
  - Reduce risk of sudden death
  - Early treatment may lead to better outcomes

- Beyond Severe Aortic stenosis, we believe our TAVR therapy may benefit patients with Moderate Aortic Stenosis
- Currently working closely with KOLs on a pivotal trial design

Anticipate completion of EARLY TAVR enrollment in 2021

Anticipate FDA approval to start the Moderate AS trial in 2021

[1] Genereux P. Natural history, diagnostic approaches and therapeutic strategies for patients with asymptomatic severe AS. JACC 2016: 2263-88.
[2] Including low-risk indication.

Our portfolio is constantly evolving

SAPIEN 3 Ultra System

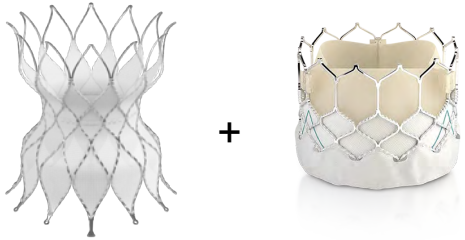
Further elevates the performance benchmark of SAPIEN 3



- **99%** Freedom from death and disabling stroke at 1 year
- **96%** of patients discharged home
- **90%** did not need to be rehospitalized within 2 years
- **Low pacemaker rates**
- **Low rates of PVL**

SAPIEN 3 Pulmonic + Alterra

Pulmonic platform expands therapy for Congenital Heart Disease patients



- Alterra Adaptive Prestent and SAPIEN 3 Pulmonic System expands therapy
- Alterra U.S. Approval anticipated in 2H 2021

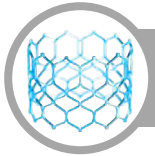
Next Generation TAVR



SAPIEN X4

Clinical work expected to begin in U.S. in 2021

- Enhanced control and precision
- Enables best-in-class safety and efficacy outcomes



Revolutionary Platform

TMTT focused on leading and transforming treatment for patients with mitral and tricuspid valve disease

Three key value drivers: a portfolio of differentiated therapies, positive results from pivotal clinical trials and favorable real-world clinical outcomes

Patients with Mitral and Tricuspid regurgitation remain **undertreated** and suffer from poor quality of life

TMTT is delivering a **portfolio of therapies**, backed by clinical evidence, to address the diversity and complexity of Mitral and Tricuspid disease

$3B global opportunity by 2025 with significant longer-term growth

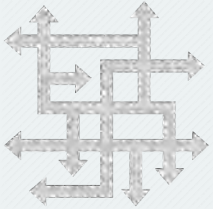


Diverse and complex patients need better treatment options

DIVERSE

Mitral and tricuspid regurgitation are complex diseases

No two patients are alike



PREVALENT

10+%

people in the U.S. over 65 **suffer from moderate or severe MR/TR**



DEADLY

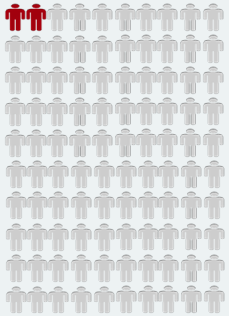
Untreated patients have **poor quality of life** and **high mortality rates**



UNDERTREATED

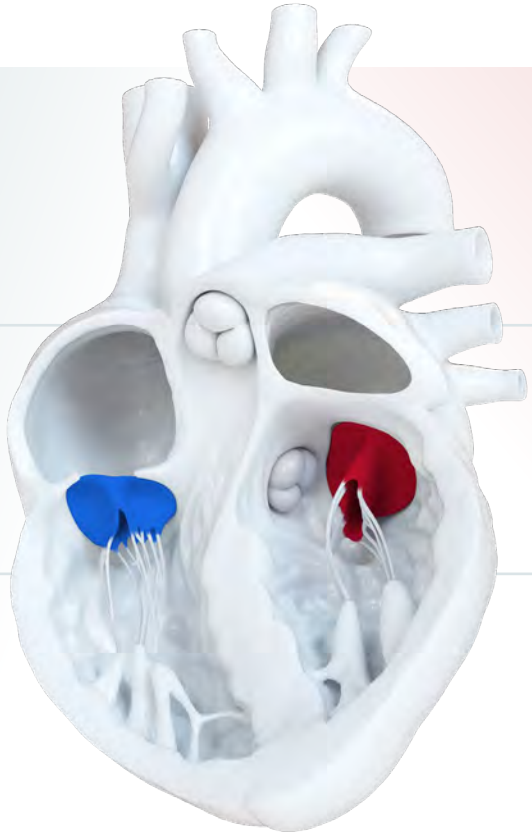
<2%

patients receive an intervention today



TMTT is innovating a broad transcatheter portfolio

	TRICUSPID		MITRAL	
Leaflet Repair	 PASCAL	 PASCAL Ace	 PASCAL	 PASCAL Ace
Annular Reduction	 Cardioband			 Cardioband
Valve Replacement	 EVOQUE		 SAPIEN M3	 EVOQUE



Building clinical evidence to transform standard of care

5 Pivotal Studies



THE CLASP IID TRIAL



PASCAL
Degenerative MR

THE CLASP IIF TRIAL



PASCAL
Functional MR

THE CLASP II TR TRIAL



PASCAL
Tricuspid

THE ENCIRCLE TRIAL



SAPIEN M3
Mitral

THE TRISCEND II PIVOTAL TRIAL



EVOQUE
Tricuspid

Strong evidence is central to expanding patient treatment

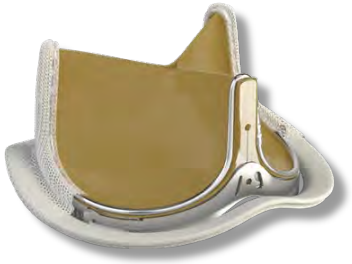
Surgical Structural Heart brings leading innovation

Current surgical structural heart market expected to **grow mid-single digits through 2026**

Extending our leadership as the partner of choice for cardiac surgeons with three product launches in 2020

Continuing to bring **life-saving surgical innovation** to patients best-treated surgically

Extend leadership in $1.8B global surgical opportunity



INSPIRIS is the world's leading aortic surgical valve

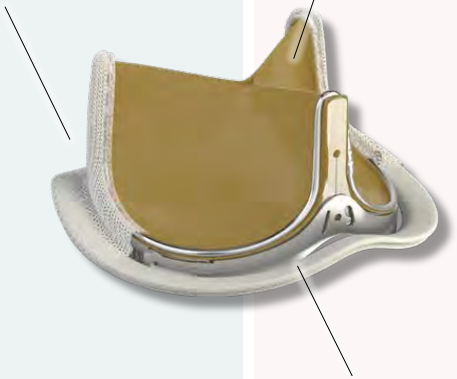
Trusted Platform

Magna Ease
Proven PERIMOUNT Platform

Active patients can avoid anticoagulation required with mechanical valves

Resilient Valve Class

RESILIA
Resilient Tissue Technology



VFit technology
Designed for potential future valve-in-valve procedures

- **#1 implanted aortic surgical valve** in the U.S. and Japan, **China launch in 2021**
- **Continuing adoption** across U.S. and Europe
- Provides **RESILIA tissue and VFit technology** for potential future valve-in-valve procedures

Our surgical portfolio strategy enables sustained growth through innovation

KONECT RESILIA
Aortic Valved Conduit



- First pre-assembled, ready-to-implant tissue conduit
- For complex aortic valve patients with combined aortic root disease
- Impacts ~7,500 surgical procedures annually in the U.S., growing in the high single-digits

MITRIS RESILIA
Surgical Mitral Valve



- Differentiating RESILIA tissue, ease-of-use enhancements, and valve-in-valve compatibility
- 60% of global mitral valve replacement patients currently receive a mechanical valve
- U.S. and Japan launch in 2021

HARPOON
Mitral Valve Repair System



- Standardizing mitral repair
- Launched in 2020 with potential to convert ~20,000 surgical repair patients across the U.S., Europe, and Japan
- RESTORE pivotal trial underway

Critical Care improving the quality of care for patients

Continuing to **shift product mix** towards Smart Recovery, which has highest growth potential of our product groups

Focusing on **three key building blocks** to advance Smart Recovery patient penetration from 5% to 15% by 2026

Deploying **right technologies**, generating **clinical evidence** and creating **product awareness** to drive us towards our goal

Critical Care products benefit millions of patients every year



We are the global leader in hemodynamic monitoring impacting more than 14 million patients per year[1]

[1] Incudes pulmonary artery catheters and pressure monitoring products, excludes capital.

Three Key Building Blocks for Smart Recovery

TECHNOLOGY

CAPITAL PLATFORM



HemoSphere

+

SENSORS



Acumen IQ Sensor



ForeSight



Acumen IQ Cuff

+

SOFTWARE

Hypotension Prediction Index (HPI)

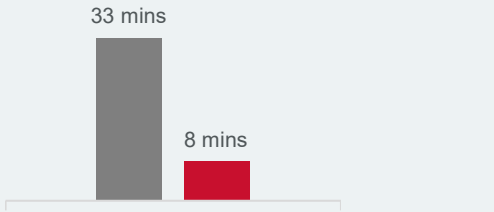


Viewfinder
Remote View



EVIDENCE

Edwards HPI Software Can Reduce Intraoperative Hypotension – HYPE TRIAL



AWARENESS



"HPI was high and 10 minutes later there was hypotension. I didn't see it coming at all."

– Simon Davies, MD MBChB FRCA



"We were able to decrease the rate of hypotension by about 50%, which is quite impressive I think."

– Michael Sander, MD, PhD

Financial Outlook



2021 expected to be a year of significant growth and investment in our future

2021 Expectations

Mid-teens	$2.00 - $2.20
Underlying net sales growth	Adjusted EPS



TAVR
- Therapy expansion
- Technology advances
- Geographic expansion



Surgical
- Surgeon partnership
- Leading pipeline
- Growth segment focus



TMTT
- Differentiated portfolio
- Clinical evidence
- Real-world outcomes



Critical Care
- HemoSphere growth
- Smart technologies
- Portfolio expansion

Edwards is poised for long-term value creation

Patient-Focused Culture
motivates and guides our global team

Sustainable Growth
organic revenue



Large Populations
of under-served patients

Credibility and Trust
with clinicians, regulators, payors and patients

Innovative R&D
produces breakthrough therapies and drives shareholder returns



Edwards

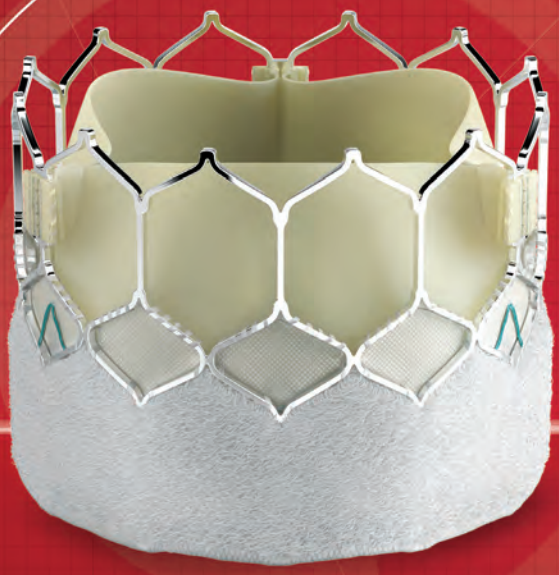
Helping Patients is Our Life's Work, and *life is now*

EXHIBIT 43

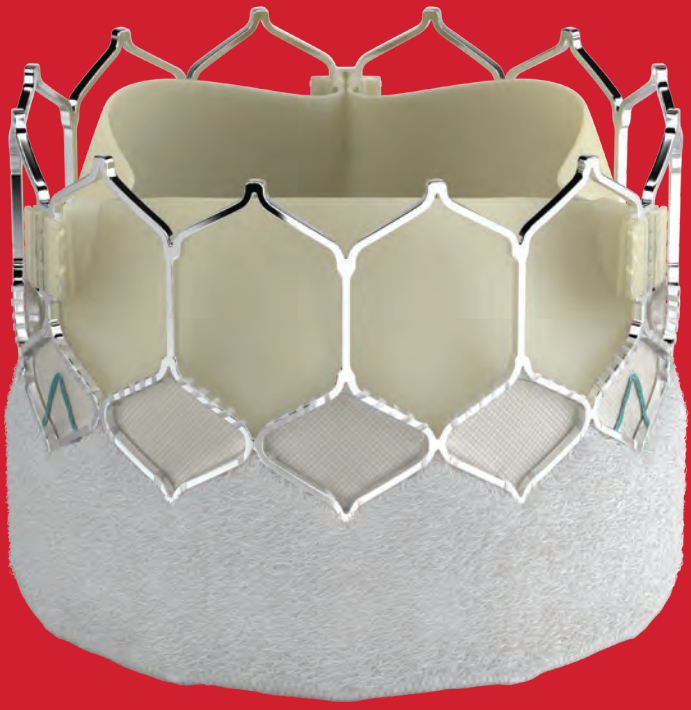
Introducing the

SAPIEN 3 Ultra valve

Edwards Engineering for Tomorrow's TAVI



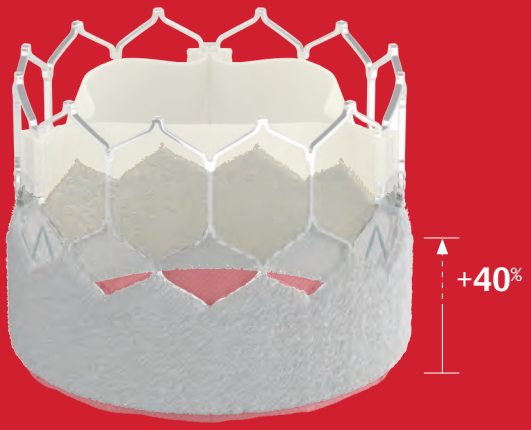
Edwards



An evolution of the valve you know and trust

Edwards Lifesciences' commitment to innovation continues with the SAPIEN 3 Ultra valve.

Built upon the proven SAPIEN platform, the SAPIEN 3 Ultra transcatheter heart valve was designed with patient needs in mind.

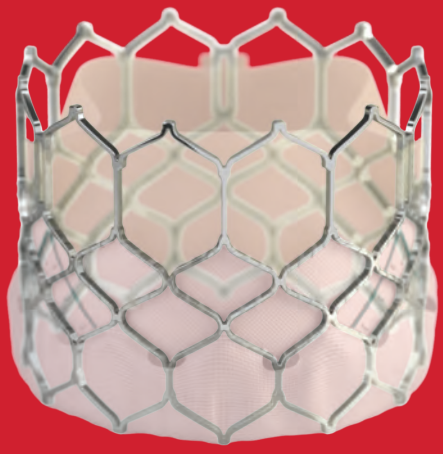


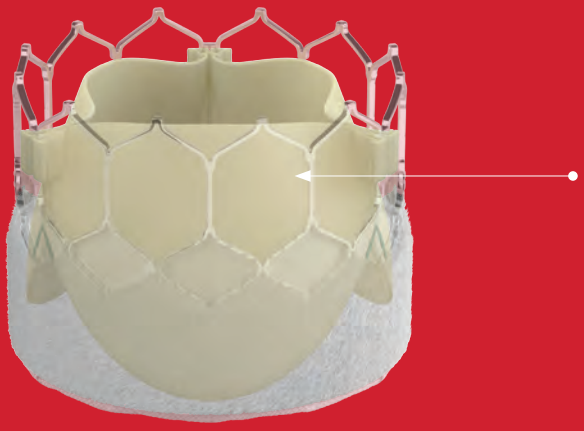
Sealing skirt technology

SAPIEN 3 Ultra valve features an approximately 40% taller*, textured PET outer skirt

Enhanced frame design

Frame geometry designed for high radial strength; short frame height facilitates future coronary access[2]





Valve tissue

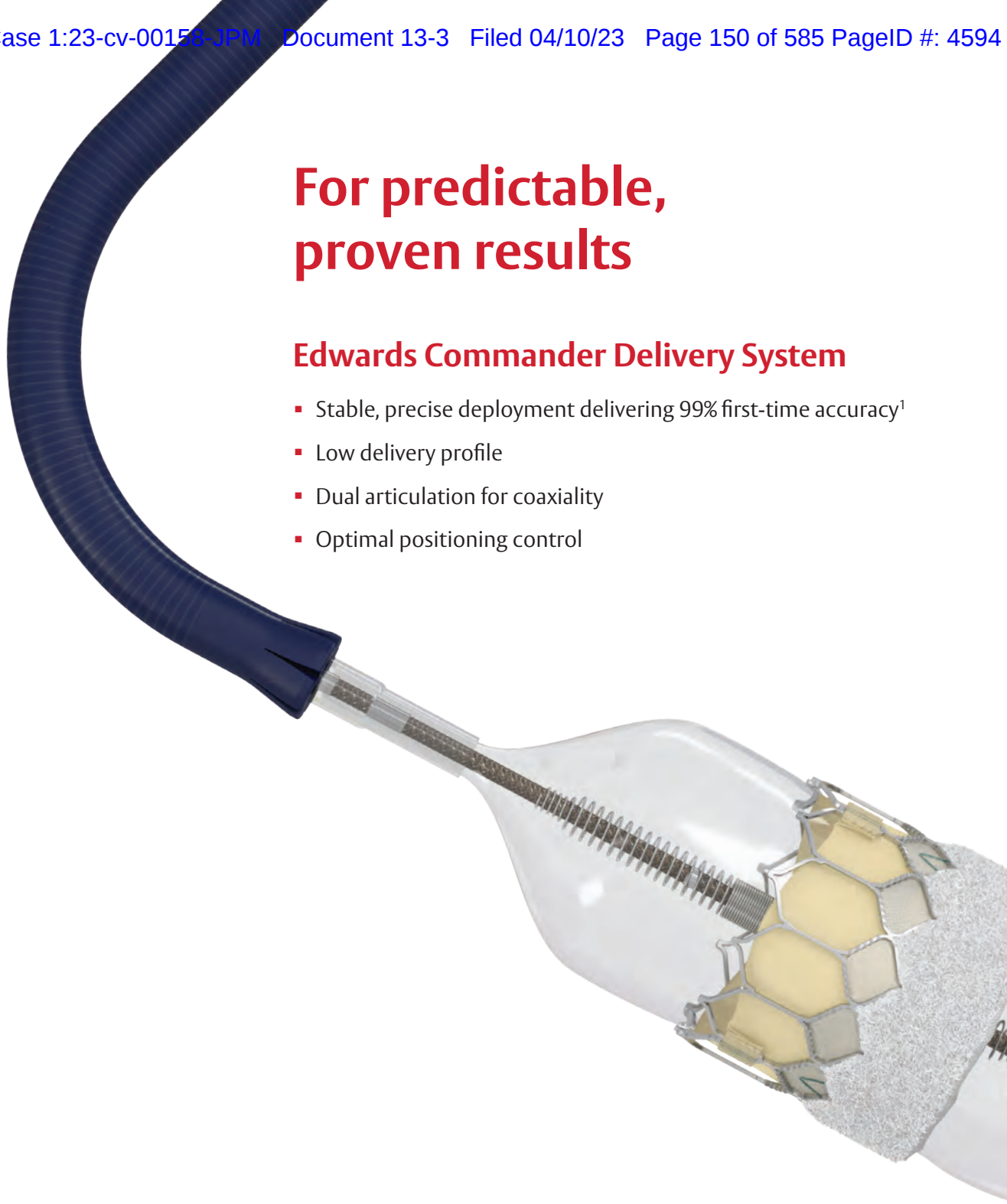
Uses same bovine pericardium tissue and process as the SAPIEN 3 valve

*Compared with the Edwards SAPIEN 3 valve. Available in 20, 23 and 26mm sizes.

For predictable, proven results

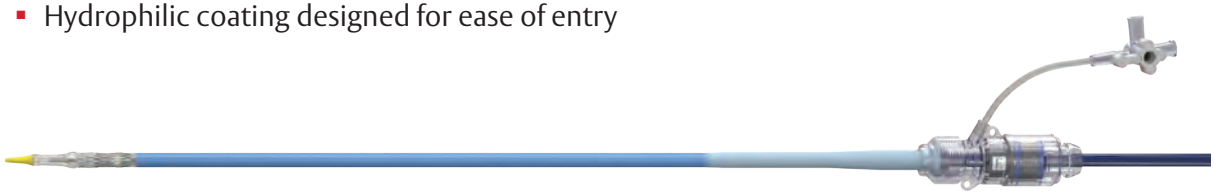
Edwards Commander Delivery System

- Stable, precise deployment delivering 99% first-time accuracy[1]
- Low delivery profile
- Dual articulation for coaxiality
- Optimal positioning control



Edwards eSheath Introducer Set

- 14F compatibility
- Dynamic Expansion Mechanism (DEM) for low-profile access
- Hydrophilic coating designed for ease of entry



The SAPIEN 3 Ultra valve is available with the Edwards Commander delivery system and Edwards eSheath Introducer helping you achieve consistent performance and controlled deployment.



Tomorrow's TAVI is here today.

- Future TAVI patients need systems designed for performance. Choose SAPIEN 3 Ultra TAVI for your patients and their severe aortic stenosis.

References:

1. The PARTNER II Trial intermediate-risk cohort 30-day unadjusted clinical event rates for TAVR with the SAPIEN 3 valve, AT population (n=1077).
2. Tarantini G, Fovino LN, Leprince P, et al. Predictors, feasibility and outcomes of coronary intervention up to 3 years after TAVI with a balloon-expandable valve: results from a large European multicenter registry. Presented at: ESC Congress 2019; September 2019; Paris, France.

For professional use. For a listing of indications, contraindications, precautions, warnings, and potential adverse events, please refer to the Instructions for Use (*consult eifu.edwards.com where applicable*). Edwards devices placed on the European market meeting the essential requirements referred to in Article 3 of the Medical Device Directive 93/42/EEC bear the CE marking of conformity.

Edwards, Edwards Lifesciences, the stylized E logo, Edwards Commander, Edwards eSheath, eSheath, PARTNER, PARTNER II, Edwards SAPIEN, Edwards SAPIEN 3, Edwards SAPIEN 3 Ultra, SAPIEN, SAPIEN 3, and SAPIEN 3 Ultra are trademarks or service marks of Edwards Lifesciences Corporation or its affiliates. All other trademarks are the property of their respective owners.

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Edwards

EXHIBIT 44

Edwards

Edwards SAPIEN 3 Ultra Transcatheter Heart Valve System

SAPIEN 3 and SAPIEN 3 Ultra Transcatheter Heart Valve
SAPIEN 3 Ultra Delivery System

Instructions for Use

CAUTION: Federal (USA) law restricts these devices to sale by or on the order of a physician.

Implantation of the transcatheter heart valve should be performed only by physicians who have received Edwards Lifesciences training. The implanting physician should be experienced in balloon aortic valvuloplasty.

Please verify that you have the latest version of the instructions for use prior to using the device by visiting http://THVIFU.edwards.com or by calling 1.800.822.9837. In order to access the instructions for use, an IFU Code will be required.

STERILE: The valve is supplied sterilized with glutaraldehyde solution. The delivery system, Sheath, and crimper are supplied sterilized with ethylene oxide gas.

Edwards, Edwards Lifesciences, the stylized E logo, Carpentier-Edwards, Certitude, Edwards eSheath, Edwards SAPIEN, Edwards SAPIEN XT, Edwards SAPIEN 3, Edwards SAPIEN 3 Ultra, eSheath, PARTNER, PARTNER II, PARTNER 3, Qualcrimp, SAPIEN, SAPIEN XT, SAPIEN 3, SAPIEN 3 Ultra, and ThermaFix are trademarks of Edwards Lifesciences Corporation. All other trademarks are the property of their respective owners.

1.0 Device Description

Edwards SAPIEN 3 Ultra Transcatheter Heart Valve (THV) System

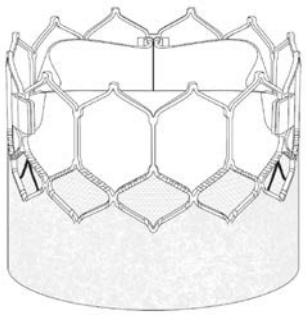
The Edwards SAPIEN 3 Ultra Transcatheter Heart Valve system consists of the Edwards SAPIEN 3 and SAPIEN 3 Ultra transcatheter heart valves and delivery systems.

- **Edwards SAPIEN 3 Ultra Transcatheter Heart Valve – (Figure 1)**

The Edwards SAPIEN 3 Ultra transcatheter heart valve is comprised of a balloon-expandable, radiopaque, cobalt-chromium frame, trileaflet bovine pericardial tissue valve, and polyethylene terephthalate (PET) inner and outer fabric skirts. The leaflets are treated according to the Carpentier-Edwards ThermaFix process.

- **Edwards SAPIEN 3 Transcatheter Heart Valve – (Figure 2)**

The Edwards SAPIEN 3 transcatheter heart valve is comprised of a balloon-expandable, radiopaque, cobalt-chromium frame, trileaflet bovine pericardial tissue valve, and polyethylene terephthalate (PET) fabric skirt. The leaflets are treated according to the Carpentier-Edwards ThermaFix process.



9750TFX

Figure 1. Edwards SAPIEN 3 Ultra Transcatheter Heart Valve

Table 1

Valve Size	Valve Height
20 mm	15.5 mm
23 mm	18 mm
26 mm	20 mm



9600TFX

Figure 2. Edwards SAPIEN 3 Transcatheter Heart Valve

Table 2

Valve Size	Valve Height
20 mm	15.5 mm
23 mm	18 mm
26 mm	20 mm
29 mm	22.5 mm

Sizing recommendations for implanting the Edwards SAPIEN 3 Ultra transcatheter heart valve and the Edwards SAPIEN 3 transcatheter heart valve in a native annulus are provided in the table below:

Table 3

Native Valve Annulus Size (TEE)	Native Valve Annulus Size (CT)		THV Size
	Area	Area Derived Diameter	
16 – 19 mm	273 – 345 mm^2	18.6 – 21 mm	20 mm
18 – 22 mm	338 – 430 mm^2	20.7 – 23.4 mm	23 mm
21 – 25 mm	430 – 546 mm^2	23.4 – 26.4 mm	26 mm
24 – 28 mm	540 – 683 mm^2	26.2 – 29.5 mm	29 mm
Valve size recommendations are based on native valve annulus size, as measured by transesophageal echocardiography (TEE) or computed tomography (CT). Patient anatomical factors and multiple imaging modalities should be considered during valve size selection. Note: Risks associated with undersizing and oversizing should be considered.			

Sizing recommendations for implanting the Edwards SAPIEN 3 Ultra transcatheter heart valve and the Edwards SAPIEN 3 transcatheter heart valve in a failing surgical bioprosthesis are provided in the table below:

Table 4

Surgical Valve True Inner Diameter (ID)[1]	THV Size
16.5 – 19.0 mm	20 mm
18.5 – 22.0 mm	23 mm
22.0 – 25.0 mm	26 mm
25.0 – 28.5 mm	29 mm

NOTE: Surgical valve 'True ID' may be smaller than the labeled valve size. For a failing stentless bioprosthesis, consider sizing recommendations for a native annulus. The dimensions of the failed bioprosthesis should be determined so that the appropriate THV size can be implanted; and is best determined by using computed tomography, magnetic resonance imaging, and/or transesophageal echocardiography.

NOTE: Exact volume required to deploy the THV may vary depending on the bioprosthesis inner diameter. Factors such as calcification and pannus tissue growth may not be accurately visualized in imaging and may reduce the effective inner diameter of the failing bioprosthesis to a size smaller than the 'True ID'. These factors should be considered and assessed in order to determine the most appropriate THV size to achieve nominal THV deployment and sufficient anchoring. Do not exceed the rated burst pressure. See Table 5 for inflation parameters.

- **Edwards SAPIEN 3 Ultra Delivery System (Figure 3)**

The Edwards SAPIEN 3 Ultra delivery system facilitates the placement of the bioprosthesis. The delivery system consists of a Flex Catheter to aid in tracking and valve positioning. The delivery system includes a tapered tip to facilitate crossing of the valve. The handle contains a Flex Wheel to control flexing of the Flex Catheter and Fine Adjustment Wheel to facilitate valve positioning within the target location. A stylet is included within the guidewire lumen of the delivery system. A radiopaque Positioning Marker in the balloon is provided to assist with valve positioning. The inflation parameters for valve deployment are:

Table 5

Model	Nominal Balloon Diameter	Nominal Inflation Volume	Rated Burst Pressure (RBP)
9630TF20	20 mm	11 mL	7 atm
9630TF23	23 mm	17 mL	7 atm
9630TF26	26 mm	23 mL	7 atm
9630TF29	29 mm	33 mL	7 atm

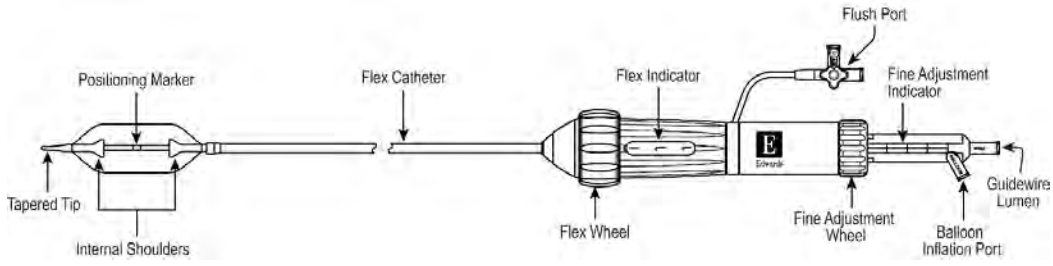


Figure 3. Edwards SAPIEN 3 Ultra Delivery System

Additional Accessories

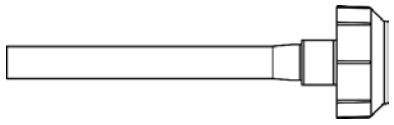


Figure 4. Loader

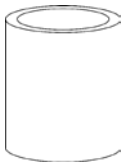


Figure 5. Qualcrimp Crimping Accessory

- **Edwards Sheath**

Refer to the provided Edwards sheath instructions for use for device description.

- **Edwards Crimper**

Refer to the Edwards Crimper instructions for use for device description.

2.0 Indications

1) The Edwards SAPIEN 3 Ultra Transcatheter Heart Valve system is indicated for relief of aortic stenosis in patients with symptomatic heart disease due to severe native calcific aortic stenosis who are judged by a Heart Team, including a cardiac surgeon, to be appropriate for the transcatheter heart valve replacement therapy.
2) The Edwards SAPIEN 3 Ultra Transcatheter Heart Valve system is indicated for patients with symptomatic heart disease due to failure (stenosed, insufficient, or combined) of a surgical bioprosthetic aortic or mitral valve who are judged by a heart team, including a cardiac surgeon, to be at high or greater risk for open surgical therapy (i.e., predicted risk of surgical mortality ≥ 8% at 30 days, based on the STS risk score and other clinical co-morbidities unmeasured by the STS risk calculator).

3.0 Contraindications

The valve and delivery systems are contraindicated in patients who cannot tolerate an anticoagulation/antiplatelet regimen or who have active bacterial endocarditis or other active infections.

4.0 Warnings

- Observation of the pacing lead throughout the procedure is essential to avoid the potential risk of pacing lead perforation.
- There may be an increased risk of stroke in transcatheter aortic valve replacement procedures, as compared to balloon aortic valvuloplasty or other standard treatments in high or greater risk patients.
- The devices are designed, intended, and distributed for single use only. **Do not resterilize or reuse the devices.** There are no data to support the sterility, nonpyrogenicity, and functionality of the devices after reprocessing.
- Incorrect sizing of the valve may lead to paravalvular leak, migration, embolization, residual gradient (patient-prosthesis mismatch) and/or annular rupture.
- Accelerated deterioration of the valve due to calcific degeneration may occur in children, adolescents, or young adults and in patients with an altered calcium metabolism.
- Prior to delivery, the valve must remain hydrated at all times and cannot be exposed to solutions other than its shipping storage solution and sterile physiologic rinsing solution. Valve leaflets mishandled or damaged during any part of the procedure will require replacement of the valve.
- Caution should be exercised in implanting a valve in patients with clinically significant coronary artery disease.
- Patients with pre-existing bioprostheses should be carefully assessed prior to implantation of the valve to ensure proper valve positioning and deployment.
- Do not use the valve if the tamper evident seal is broken, the storage solution does not completely cover the valve, the temperature indicator has been activated, the valve is damaged, or the expiration date has elapsed.
- Do not mishandle the delivery system or use it if the packaging or any components are not sterile, have been opened or are damaged (e.g. kinked or stretched), or the expiration date has elapsed.
- Use of excessive contrast media may lead to renal failure. Measure the patient's creatinine level prior to the procedure. Contrast media usage should be monitored.
- Patient injury could occur if the delivery system is not un-flexed prior to removal.
- Care should be exercised in patients with hypersensitivities to cobalt, nickel, chromium, molybdenum, titanium, manganese, silicon, and/or polymeric materials.
- The procedure should be conducted under fluoroscopic guidance. Some fluoroscopically guided procedures are associated with a risk of radiation injury to the skin. These injuries may be painful, disfiguring, and long-lasting.
- Valve recipients should be maintained on anticoagulant/antiplatelet therapy, except when contraindicated, as determined by their physician. This device has not been tested for use without

anticoagulation.

- Do not add or apply antibiotics to the storage solution, rinse solutions, or to the valve.
- Balloon valvuloplasty should be avoided in the treatment of failing bioprostheses as this may result in embolization of bioprosthesis material and mechanical disruption of the valve leaflets.

5.0 Precautions

- Safety, effectiveness, and durability have not been established for THV-in-THV procedures.
- Long-term durability has not been established for the valve. Regular medical follow-up is advised to evaluate valve performance.
- Glutaraldehyde may cause irritation of the skin, eyes, nose and throat. Avoid prolonged or repeated exposure to, or breathing of, the solution. Use only with adequate ventilation. If skin contact occurs, immediately flush the affected area with water; in the event of contact with eyes, seek immediate medical attention. For more information about glutaraldehyde exposure, refer to the Material Safety Data Sheet available from Edwards Lifesciences.
- To maintain proper valve leaflet coaptation, do not overinflate the deployment balloon.
- Appropriate antibiotic prophylaxis is recommended post-procedure in patients at risk for prosthetic valve infection and endocarditis.
- Additional precautions for transseptal replacement of a failed mitral valve bioprosthesis include, presence of devices or thrombus or other abnormalities in the caval vein precluding safe transvenous femoral access for transseptal approach; presence of Atrial Septal Occluder Device or calcium or abnormalities in the atrial septum preventing safe transseptal access.
- Special care must be exercised in mitral valve replacement if chordal preservation techniques were used in the primary implantation to avoid entrapment of the subvalvular apparatus.
- Safety and effectiveness have not been established for patients with the following characteristics/comorbidities:
  - Non-calcified aortic annulus
  - Severe ventricular dysfunction with ejection fraction < 20%
  - Congenital unicuspid aortic valve
  - Congenital bicuspid aortic valve at low surgical risk
  - Pre-existing prosthetic ring in any position
  - Severe mitral annular calcification (MAC), severe (> 3+) mitral insufficiency, or Gorlin syndrome
  - Blood dyscrasias defined as: leukopenia (WBC < 3000 cells/mL), acute anemia (Hb < 9 g/dL), thrombocytopenia (platelet count < 50,000 cells/mL), or history of bleeding diathesis or coagulopathy
  - Hypertrophic cardiomyopathy with or without obstruction (HOCM)
  - Echocardiographic evidence of intracardiac mass, thrombus, or vegetation
  - A known hypersensitivity or contraindication to aspirin, heparin, ticlopidine (Ticlid™), or clopidogrel (Plavix™), or sensitivity to contrast media, which cannot be adequately premedicated
  - Significant aortic disease, including abdominal aortic or thoracic aneurysm defined as maximal luminal diameter 5 cm or greater; marked tortuosity (hyperacute bend), aortic arch atheroma (especially if thick [> 5 mm], protruding, or ulcerated) or narrowing (especially with calcification and surface irregularities) of the abdominal or thoracic aorta, severe “unfolding” and tortuosity of the thoracic aorta
  - Access characteristics that would preclude safe placement of the Edwards sheath, such as severe obstructive calcification or severe tortuosity
  - Bulky calcified aortic valve leaflets in close proximity to coronary ostia

  - A concomitant paravalvular leak where the failing bioprosthesis is not securely fixed in the native annulus or is not structurally intact (e.g. wireform frame fracture)
  - A partially detached leaflet of the failing bioprosthesis that in the aortic position may obstruct a coronary ostium
- For Left axillary approach, a left subclavian takeoff angle ~ ≥ 90° from the aortic arch causes sharp angles, which may be responsible for potential sheath kinking, subclavian/axillary dissection and aortic arch damage.
- Ensure there is flow in Left Internal Mammary Artery (LIMA)/Right Internal Mammary Artery (RIMA) during procedure and monitor PA pressure in homolateral radial artery.
- Residual mean gradient may be higher in a “THV-in-failing bioprosthesis” configuration than that observed following implantation of the valve inside a native aortic annulus using the same size device. Patients with elevated mean gradient post procedure should be carefully followed. It is important that the manufacturer, model and size of the preexisting bioprosthetic valve be determined, so that the appropriate valve can be implanted and a prosthesis-patient mismatch be avoided. Additionally, pre-procedure imaging modalities must be employed to make as accurate a determination of the inner diameter as possible.

6.0 Potential Adverse Events

Potential risks associated with the overall procedure including potential access complications associated with standard cardiac catheterization, balloon valvuloplasty, the potential risks of conscious sedation and/or general anesthesia, and the use of angiography:

- Death
- Stroke/transient ischemic attack, clusters or neurological deficit
- Paralysis
- Permanent disability
- Respiratory insufficiency or respiratory failure
- Hemorrhage requiring transfusion or intervention
- Cardiovascular injury including perforation or dissection of vessels, ventricle, atrium, septum, myocardium or valvular structures that may require intervention
- Pericardial effusion or cardiac tamponade
- Thoracic bleeding
- Embolization including air, calcific valve material or thrombus
- Infection including septicemia and endocarditis
- Heart failure
- Myocardial infarction
- Renal insufficiency or renal failure
- Conduction system defect which may require a permanent pacemaker
- Arrhythmia
- Retroperitoneal bleed
- Arteriovenous (AV) fistula or pseudoaneurysm
- Reoperation
- Ischemia or nerve injury or brachial plexus injury
- Restenosis
- Pulmonary edema
- Pleural effusion

- Bleeding
- Anemia
- Abnormal lab values (including electrolyte imbalance)
- Hypertension or hypotension
- Allergic reaction to anesthesia, contrast media, or device materials
- Hematoma
- Syncope
- Pain or changes at the access site
- Exercise intolerance or weakness
- Inflammation
- Angina
- Heart murmur
- Fever

Additional potential risks associated with the use of the valve, delivery system, and/or accessories include:

- Cardiac arrest
- Cardiogenic shock
- Emergency cardiac surgery
- Cardiac failure or low cardiac output
- Coronary flow obstruction/transvalvular flow disturbance
- Device thrombosis requiring intervention
- Valve thrombosis
- Device embolization
- Device migration or malposition requiring intervention
- Left ventricular outflow tract obstruction
- Valve deployment in unintended location
- Valve stenosis
- Structural valve deterioration (wear, fracture, calcification, leaflet tear/tearing from the stent posts, leaflet retraction, suture line disruption of components of a prosthetic valve, thickening, stenosis)
- Device degeneration
- Paravalvular or transvalvular leak
- Valve regurgitation
- Hemolysis
- Device explants
- Nonstructural dysfunction
- Mechanical failure of delivery system, and/or accessories
- Non-emergent reoperation

7.0 Directions for Use

7.1 System Compatibility

Table 6

Product Name	20 mm System	23 mm System	26 mm System	29 mm System
	Model			
Edwards SAPIEN 3 Ultra Transcatheter Heart Valve	9750TFX20	9750TFX23	9750TFX26	
Edwards SAPIEN 3 Transcatheter Heart Valve	9600TFX20	9600TFX23	9600TFX26	9600TFX29
Edwards SAPIEN 3 Ultra Delivery System	9630TF20	9630TF23	9630TF26	9630TF29
Sheath provided by Edwards Lifesciences				
Inflation device, Qualcrimp crimping accessory, Crimp Stopper and Loader provided by Edwards Lifesciences				
Edwards Crimper	9600CR			

Additional Equipment:

- Balloon catheter, per the discretion of the physician
- 20 cc syringe or larger
- 50 cc syringe or larger
- High-pressure 3-way stopcock (x2)
- Standard cardiac catheterization lab equipment
- Fluoroscopy (fixed, mobile or semi-mobile fluoroscopy systems appropriate for use in percutaneous coronary interventions)
- Transesophageal or transthoracic echocardiography capabilities
- Exchange length 0.035 inch (0.89 mm) extra-stiff guidewire
- Temporary pacemaker (PM) and pacing lead
- Instrumentation for transseptal access and septostomy, as applicable
- Sterile rinsing basins, physiological saline, heparinized saline, 15% diluted radiopaque contrast medium
- Sterile table for valve and device preparation

7.2 Valve Handling and Preparation

Follow sterile technique during device preparation and implantation.

7.2.1 Valve Rinsing Procedure

Before opening the valve jar, carefully examine for evidence of damage (e.g. a cracked jar or lid, leakage, or broken or missing seals).

CAUTION: Valves from containers found to be damaged, leaking, without adequate sterilant, or missing intact seals must not be used for implantation.

Step	Procedure
1	Set up two (2) sterile bowls with at least 500 mL of sterile physiological saline to thoroughly rinse the glutaraldehyde sterilant from the valve.
2	Carefully remove the valve/holder assembly from the jar without touching the tissue. Verify the valve serial identification number with the number on the jar lid and record in the patient information documents. Inspect the valve for any signs of damage to the frame or tissue.
3	Rinse the valve as follows: Place the valve in the first bowl of sterile, physiological saline. Be sure the saline solution completely covers the valve and holder. With the valve and holder submerged, slowly agitate (to gently swirl the valve and holder) back and forth for a minimum of 1 minute. Transfer the valve and holder to the second rinsing bowl of sterile physiological saline and gently agitate for at least one more minute. Ensure the rinse solution in the first bowl is not used. The valve should be left in the final rinse solution until needed to prevent the tissue from drying. **CAUTION: Do not allow the valve to come into contact with the bottom or sides of the rinse bowl during agitation or swirling in the rinse solution. Direct contact between the identification tag and valve is also to be avoided during the rinse procedure. No other objects should be placed in the rinse bowls. The valve should be kept hydrated to prevent the tissue from drying.**

7.2.2 Prepare the Components

Refer to the Edwards sheath and Edwards Crimper instructions for use for device preparation.

Step	Procedure
1	Visually inspect all components for damage. Ensure the delivery system is fully unflexed and the balloon catheter is fully retracted in the flex catheter. **NOTE: The delivery system is packaged with a balloon cover placed over the balloon and should not be removed until instructed to do so.**
2	Use the fine adjustment wheel to advance the catheter and flush flex catheter with heparinized saline through the flush port.
3	Unscrew the loader cap from the loader tube and flush the loader cap. Place the loader cap over the proximal balloon cover and onto the flex catheter with the inside of the cap oriented towards the distal tip.
4	Attach a 3-way stopcock to the balloon inflation port. Partially fill a 50 cc or larger syringe with 15-20 mL diluted contrast medium and attach to the 3-way stopcock.
5	Fill the inflation device provided by Edwards Lifesciences with excess volume relative to the indicated inflation volume. Lock the inflation device and attach to the 3-way stopcock.
6	Close the 3-way stopcock to the inflation device provided by Edwards Lifesciences and de-air the system using the 50 cc or larger syringe. Slowly release the plunger and leave zero-pressure in the system.
7	Close the stopcock to the delivery system and de-air the inflation device. By rotating the knob of the inflation device provided by Edwards Lifesciences, transfer the contrast medium into the syringe to achieve the appropriate volume required to deploy the valve.
8	Close the stopcock to the 50 cc or larger syringe. Remove the syringe. Verify that the inflation volume is correct and lock the inflation device provided by Edwards Lifesciences.

Step	Procedure
	CAUTION: Maintain the inflation device provided by Edwards Lifesciences in the locked position until valve deployment.

7.2.3 Mount and Crimp the Valve on the Delivery System

Step	Procedure
1	Carefully remove the distal balloon cover from the delivery system.
2	Set up two (2) additional sterile bowls with at least 100 mL of sterile physiological saline to thoroughly rinse the Qualcrimp crimping accessory.
3	Completely submerge the Qualcrimp crimping accessory in the first bowl and gently compress it to ensure complete saline absorption. Slowly swirl the Qualcrimp crimping accessory for a minimum of 1 minute. Repeat this process in the second bowl.
4	Remove the valve from the holder and remove the ID tag.
5	Attach the 2-piece crimp stopper to the base of the crimper and click into place.
6	With the crimper in the open position, gently place the valve into the crimper aperture. Gradually crimp the valve until it fits into the Qualcrimp crimping accessory.
7	Place the Qualcrimp crimping accessory over the valve making sure the valve is parallel to the edge of the Qualcrimp crimping accessory.
8	Place the valve and Qualcrimp crimping accessory in crimper aperture. Insert the delivery system coaxially within the valve with the orientation of the valve on the delivery system as described below: **Antegrade approach:** Inflow (outer skirt end) of the valve towards the proximal end of the delivery system. **Retrograde approach:** Inflow (outer skirt end) of the valve towards the distal end of the delivery system.
9	Crimp the valve between the internal shoulders until it reaches the Qualcrimp Stop located on the 2-piece Crimp Stopper. **NOTE: Do not crimp over the *proximal* internal shoulder during this step.**
10	Gently remove the Qualcrimp crimping accessory from the valve. Remove the Qualcrimp Stop from the Final Stop, leaving the Final Stop in place.
11	Ensure the valve is within the crimper aperture and fully crimp the valve until it reaches the Final Stop and hold for 5 seconds. **NOTE: Ensure the valve is coaxial within the crimper aperture and remains between the two internal shoulders of the delivery system.** **NOTE: Do not crimp over the *proximal* internal shoulder during this step.**
12	Ensure the valve is within the crimper aperture and repeat the full crimp of the valve and hold for 5 seconds. **NOTE: Do not crimp over the *proximal* internal shoulder during this step.**
13	Align the valve so that only the outer skirt is within the crimper aperture and crimp to the Final Stop and hold for 5 seconds.
14	Align the valve so that only half of the outer skirt is within the crimper aperture and crimp to the Final Stop and hold for 5 seconds.
15	Align the valve so that the entire valve is within the crimper aperture and crimp to the Final Stop and hold for 5 seconds.

Step	Procedure
	NOTE: Do not crimp over the *distal* internal shoulder for the final crimp.
16	Flush the loader with heparinized saline. Immediately advance the valve into the loader until the tapered tip of the delivery system is exposed. **CAUTION: To prevent possible leaflet damage, the valve should not remain fully crimped and/or in the loader for over 15 minutes.**
17	Attach the loader cap to the loader, re-flush the flex catheter through the flush port and close the stopcock to the delivery system. Remove the stylet and flush the guidewire lumen of the delivery system. **CAUTION: Keep the valve hydrated until ready for implantation.** **CAUTION: The physician must verify correct orientation of the valve prior to its implantation.**
18	Prior to implantation use the fine adjustment wheel to fully retract the catheter and ensure proper placement of the loader. **WARNING: The physician must verify correct orientation of the valve prior to its implantation.**

7.3 Valvuloplasty and Valve Delivery

Valvuloplasty and valve delivery should be performed under conscious sedation and/or general anesthesia with hemodynamic monitoring in a catheterization lab/hybrid operating room with fluoroscopic and echocardiographic imaging capabilities.

Administer heparin to maintain the ACT at ≥ 250 sec during the procedure.

Balloon valvuloplasty should be avoided in the treatment of failing bioprostheses as this may result in embolization of bioprosthesis material and mechanical disruption of the valve leaflets.

CAUTION: Use of excessive contrast media may lead to renal failure. Measure the patient's creatinine level prior to the procedure. Contrast media usage should be monitored.

CAUTION: Procedure may require an arterial cut-down with surgical closure of the puncture site due to the size of the arteriotomy.

7.3.1 Baseline Parameters

Step	Procedure
1	Perform an angiogram with fluoroscopic view perpendicular to the valve.
2	Evaluate the distance of the left and right coronary ostia from the aortic annulus in relation to the valve frame height.
3	Introduce a pacemaker (PM) lead and position appropriately.
4	Set the stimulation parameters to obtain 1:1 capture, and test pacing.

7.3.2 Valvuloplasty

Pre-dilate the native aortic valve, per the discretion of the physician, according to the instructions for use for the selected balloon aortic valvuloplasty catheter.

CAUTION: Valve implantation should not be carried out if the balloon cannot be fully inflated during valvuloplasty.

7.3.3 Valve Delivery

Step	Procedure
1	Gain access using standard catheterization techniques.

Step	Procedure
2	Prepare and insert the Edwards sheath. Refer to the Edwards sheath IFU for information on device preparation and handling.
3	Insert the loader into the sheath until the loader stops.
4	Advance the delivery system, with the Edwards logo in the proper orientation (the delivery system articulates in a direction opposite from the flush port), through the sheath until the valve exits the sheath. **NOTE: Maintain the proper orientation of the flex catheter throughout the procedure. The delivery system articulates in a direction opposite from the flush port.** **CAUTION: For iliofemoral access, the valve should not be advanced through the sheath if the sheath tip is not past the bifurcation.** **CAUTION: To prevent possible leaflet damage, the valve should not remain in the sheath for over 5 minutes.**
5	Advance the catheter and use the flex wheel, if needed, and cross the valve. **NOTE: Verify the orientation of the Edwards logo to ensure proper articulation. The delivery system articulates in a direction opposite from the flush port.**
6	Verify the correct position of the valve with respect to the target location.
7	As necessary, utilize the Flex Wheel to adjust the co-axiality of the valve and the Fine Adjustment Wheel to adjust the position of the valve.
8	Begin valve deployment: • Unlock the inflation device provided by Edwards Lifesciences. • Begin rapid pacing; once systolic blood pressure has decreased to 50 mmHg or below, balloon inflation can commence. • Deploy the valve by inflating the balloon with the entire volume in the inflation device provided by Edwards Lifesciences, hold for 3 seconds and confirm that the barrel of the inflation device is empty to ensure complete inflation of the balloon. • Deflate the balloon. When the balloon catheter has been completely deflated, turn off the pacemaker. **WARNING: Failure to use slow, controlled inflation and prescribed nominal inflation volumes may result in balloon rupture, difficulty retrieving the delivery system, and may require subsequent conversion to surgical intervention.**

7.3.4 System Removal

Step	Procedure
1	Completely unflex the delivery system, retract the loader and remove the delivery system and loader from the sheath. **NOTE: If using the 29 mm SAPIEN 3 Ultra system with the Edwards eSheath introducer, retract the delivery system into an appropriate anatomical location where the balloon can be partially inflated. Partially inflate the balloon with 10 cc and then partially deflate so that 3 cc remains in the balloon. Retrieve the balloon until the balloon positioning marker band is aligned with the eSheath introducer marker band. Fully deflate the balloon before retrieving the remainder of the system through the sheath.** **WARNING: Failure to utilize this technique may result in sheath or balloon damage and may result in vessel damage.** **CAUTION: Patient injury could occur if the delivery system is not unflexed prior to removal.** **NOTE: If there is difficulty removing the delivery system balloon into the top of the sheath, push the delivery system forward, rotate and attempt again. Repeat as necessary.**
2	Remove all devices when the ACT level is appropriate. Refer to the Edwards sheath instructions for use for device removal.
3	Close the access site.

8.0 How Supplied

STERILE: The valve is supplied sterilized with glutaraldehyde solution. The delivery system is supplied sterilized with ethylene oxide gas.

8.1 Storage

The valve must be stored at 10 °C to 25 °C (50 °F to 77 °F). Each jar is shipped in an enclosure containing a temperature indicator to detect exposure of the valve to extreme temperature.

The delivery system should be stored in a cool, dry place.

9.0 MR Safety



MR Conditional

Non-clinical testing has demonstrated that the Edwards SAPIEN 3 Ultra transcatheter heart valve and the Edwards SAPIEN 3 transcatheter heart valve are MR Conditional. A patient with this device can be scanned safely, immediately after placement of this device under the following conditions:

- Static magnetic field of 1.5T or 3.0T
- Maximum spatial gradient field of 2500 gauss/cm (25 T/m) or less
- Maximum MR system reported, whole body averaged specific absorption rate (SAR) of 2 W/kg (Normal Operating Mode)

Under the scan conditions defined above, the transcatheter heart valve is expected to produce a maximum temperature rise of 3.0 °C after 15 minutes of continuous scanning.

In non-clinical testing, the image artifact caused by the device extends as far as 14.5 mm from the implant for spin echo images and 30 mm for gradient echo images when scanned in a 3.0T MRI system. The artifact obscures the device lumen in gradient echo images.

The implant has not been evaluated in MR systems other than 1.5T or 3.0T.

For valve-in-valve implantation or in the presence of other implants, please refer to the MRI safety information for the surgical valve or other devices prior to MR imaging.

10.0 Patient Information

Patient education brochures are provided to each site and should be given to the patient to inform them of the risks and benefits of the procedure and alternatives in adequate time before the procedure to be read and discussed with their physician. A copy of this brochure may also be obtained from Edwards Lifesciences by calling 1.800.822.9837. A patient implant card request form is provided with each transcatheter heart valve. After implantation, all requested information should be completed on this form. The serial number may be found on the package and on the identification tag attached to the transcatheter heart valve. The original form should be returned to the Edwards Lifesciences address indicated on the form and upon receipt, Edwards Lifesciences will provide an identification card to the patient.

11.0 Recovered Valve and Device Disposal

The explanted valve should be placed into a suitable histological fixative such as 10% formalin or 2% glutaraldehyde and returned to the company. Refrigeration is not necessary under these circumstances. Contact Edwards Lifesciences to request an Explant Kit.

Used delivery system may be disposed of in the same manner that hospital waste and biohazardous materials are handled. There are no special risks related to the disposal of these devices.

Edwards

Edwards SAPIEN 3 Ultra Transcatheter Heart Valve System

SAPIEN 3 and SAPIEN 3 Ultra Transcatheter Heart Valve Edwards Certitude Delivery System

Instructions for Use

CAUTION: Federal (USA) law restricts these devices to sale by or on the order of a physician.

Implantation of the transcatheter heart valve should be performed only by physicians who have received Edwards Lifesciences training. The implanting physician should be experienced in balloon aortic valvuloplasty.

Please verify that you have the latest version of the instructions for use prior to using the device by visiting http://THVIFU.edwards.com or by calling 1.800.822.9837. In order to access the instructions for use, an IFU Code will be required.

STERILE: The valve is supplied sterilized with glutaraldehyde solution. The delivery system, introducer sheath set, and crimper are supplied sterilized with ethylene oxide gas.

Edwards, Edwards Lifesciences, the stylized E logo, Carpentier-Edwards, Certitude, Edwards SAPIEN, Edwards SAPIEN XT, Edwards SAPIEN 3, Edwards SAPIEN 3 Ultra, PARTNER, PARTNER II, PARTNER 3, Qualcrimp, SAPIEN, SAPIEN XT, SAPIEN 3, SAPIEN 3 Ultra, and ThermaFix are trademarks of Edwards Lifesciences Corporation. All other trademarks are the property of their respective owners.

1.0 Device Description

Edwards SAPIEN 3 Ultra Trancatheter Heart Valve (THV) system

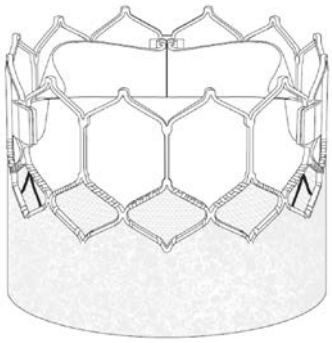
The Edwards SAPIEN 3 Ultra Transcatheter Heart Valve system consists of the Edwards SAPIEN 3 and SAPIEN 3 Ultra transcatheter heart valves and delivery systems.

- **Edwards SAPIEN 3 Ultra Transcatheter Heart Valve – (Figure 1)**

The Edwards SAPIEN 3 Ultra transcatheter heart valve is comprised of a balloon-expandable, radiopaque, cobalt-chromium frame, trileaflet bovine pericardial tissue valve, and polyethylene terephthalate (PET) inner and outer fabric skirts. The leaflets are treated according to the Carpentier-Edwards ThermaFix process.

- **Edwards SAPIEN 3 Transcatheter Heart Valve – (Figure 2)**

The Edwards SAPIEN 3 transcatheter heart valve is comprised of a balloon-expandable, radiopaque, cobalt-chromium frame, trileaflet bovine pericardial tissue valve, and polyethylene terephthalate (PET) fabric skirt. The leaflets are treated according to the Carpentier-Edwards ThermaFix process.

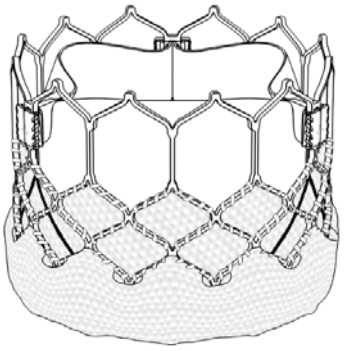


9750TFX

Figure 1. Edwards SAPIEN 3 Ultra Transcatheter Heart Valve

Table 1

Valve Size	Valve Height
20 mm	15.5 mm
23 mm	18 mm
26 mm	20 mm



9600TFX

Figure 2. Edwards SAPIEN 3 Transcatheter Heart Valve

Table 2

Valve Size	Valve Height
20 mm	15.5 mm
23 mm	18 mm
26 mm	20 mm
29 mm	22.5 mm

Sizing recommendations for implanting the Edwards SAPIEN 3 Ultra transcatheter heart valve and the Edwards SAPIEN 3 transcatheter heart valve in a native annulus are provided in the table below:

Table 3

Native Valve Annulus Size (TEE)	Native Valve Annulus Size (CT)		THV Size
	Area	Area Derived Diameter	
16 – 19 mm	273 – 345 mm^2	18.6 – 21 mm	20 mm
18 – 22 mm	338 – 430 mm^2	20.7 – 23.4 mm	23 mm
21 – 25 mm	430 – 546 mm^2	23.4 – 26.4 mm	26 mm
24 – 28 mm	540 – 683 mm^2	26.2 – 29.5 mm	29 mm
Valve size recommendations are based on native valve annulus size, as measured by transesophageal echocardiography (TEE) or computed tomography (CT). Patient anatomical factors and multiple imaging modalities should be considered during valve size selection. **NOTE:** Risks associated with undersizing and oversizing should be considered.			

Sizing recommendations for implanting the Edwards SAPIEN 3 Ultra transcatheter heart valve and the Edwards SAPIEN 3 transcatheter heart valve in a failing surgical bioprosthesis are provided in the table below:

Table 4

Surgical Valve True Inner Diameter (ID)[1]	THV Size
16.5 – 19.0 mm	20 mm
18.5 – 22.0 mm	23 mm
22.0 – 25.0 mm	26 mm
25.0 – 28.5 mm	29 mm

NOTE: Surgical valve 'True ID' may be smaller than the labeled valve size. For a failing stentless bioprosthesis, consider sizing recommendations for a native annulus. The dimensions of the failed bioprosthesis should be determined so that the appropriate THV size can be implanted; and is best determined by using computed tomography, magnetic resonance imaging, and/or transesophageal echocardiography.

NOTE: Exact volume required to deploy the THV may vary depending on the bioprosthesis inner diameter. Factors such as calcification and pannus tissue growth may not be accurately visualized in imaging and may reduce the effective inner diameter of the failing bioprosthesis to a size smaller than the 'True ID'. These factors should be considered and assessed in order to determine the most appropriate THV size to achieve nominal THV deployment and sufficient anchoring. Do not exceed the rated burst pressure. See Table 5 for inflation parameters.

- **Edwards Certitude Delivery System (Figure 3)**

The Edwards Certitude delivery system facilitates the placement of the bioprosthesis. The delivery system consists of a Flex Catheter to aid in tracking and valve positioning. The delivery system includes a tapered tip to facilitate crossing of the valve. The handle contains a Flex Wheel to control flexing of the balloon catheter. A stylet is included within the guidewire lumen of the delivery system. A radiopaque Center Marker in the balloon is provided to assist with valve positioning. The inflation parameters for valve deployment are:

Table 5

Model	Nominal Balloon Diameter	Nominal Inflation Volume	Rated Burst Pressure (RBP)
9630TA20 9600SDS20	20 mm	12 mL	7 atm
9630TA23 9600SDS23	23 mm	17 mL	7 atm
9630TA26 9600SDS26	26 mm	23 mL	7 atm
9630TA29 9600SDS29	29 mm	30 mL	7 atm

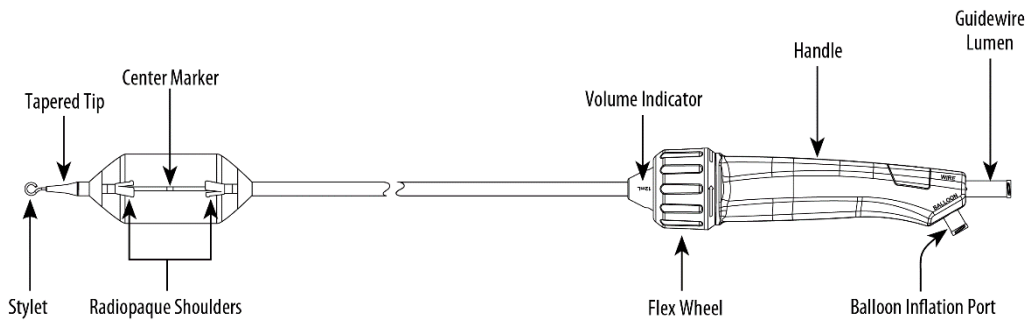


Figure 3. Edwards Certitude Delivery System

Additional Accessories

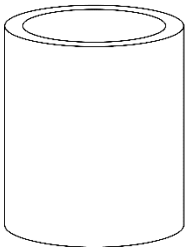


Figure 4. Qualcrimp Crimping Accessory

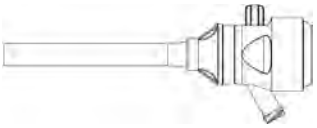


Figure 5. Loader

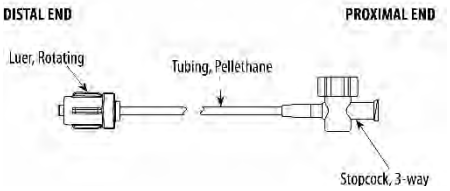


Figure 6. Extension Tubing

- **Edwards Certitude Introducer Sheath Set (Figure 7)**

The Edwards Certitude introducer sheath set facilitates the introduction and removal of devices utilized with the SAPIEN 3 and SAPIEN 3 Ultra transcatheter heart valves. The sheath has a radiopaque marker for visualization of the sheath tip and non-radiopaque depth markings on the distal end of the body of the sheath. The proximal end of the sheath includes a flush tube and three hemostasis valves. An introducer is supplied with the sheath. The entire introducer is radiopaque.

1. Housing
2. Flush Tube with Stopcock
3. Sheath
4. Radiopaque Marker
5. Non-Radiopaque Depth Markers
6. Introducer

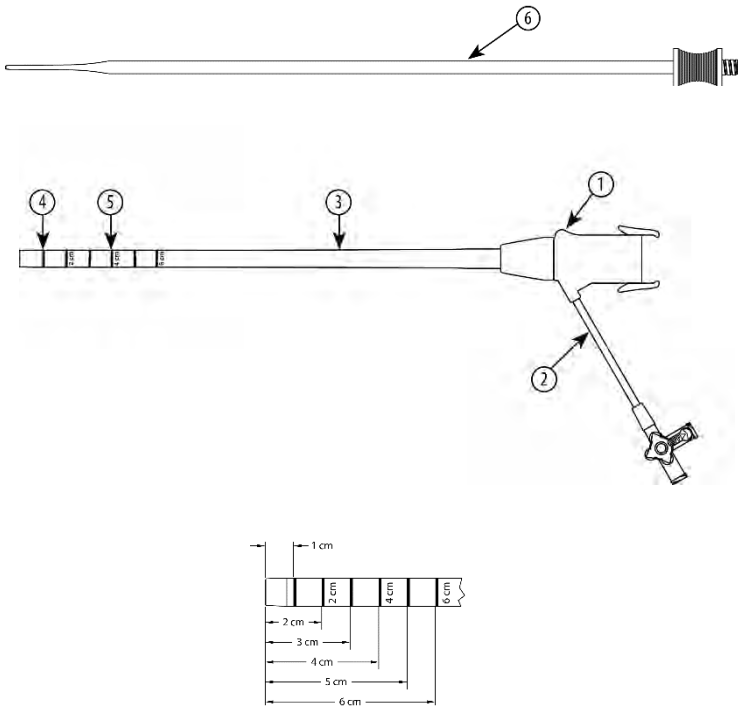


Figure 7. Edwards Certitude Introducer Sheath Set

- **Edwards Crimper**

Refer to the Edwards Crimper instructions for use for device description.

2.0 Indications

1) The Edwards SAPIEN 3 Ultra Trancatheter Heart Valve system indicated for relief of aortic stenosis in patients with symptomatic heart disease due to severe native calcific aortic stenosis who are judged by a Heart Team, including a cardiac surgeon, to be appropriate for the transcatheter heart valve replacement therapy.
2) The Edwards SAPIEN 3 Ultra Trancatheter Heart Valve system is indicated for patients with symptomatic heart disease due to failure (stenosed, insufficient, or combined) of a surgical bioprosthetic aortic or mitral valve who are judged by a heart team, including a cardiac surgeon, to be at high or greater risk for open surgical therapy (i.e., predicted risk of surgical mortality ≥ 8% at 30 days, based on the STS risk score and other clinical co-morbidities unmeasured by the STS risk calculator).

3.0 Contraindications

The valve and delivery systems are contraindicated in patients who cannot tolerate an anticoagulation/antiplatelet regimen or who have active bacterial endocarditis or other active infections.

4.0 Warnings

- Observation of the pacing lead throughout the procedure is essential to avoid the potential risk of pacing lead perforation.
- There may be an increased risk of stroke in transcatheter aortic valve replacement procedures, as compared to balloon aortic valvuloplasty or other standard treatments in high or greater risk patients.
- The devices are designed, intended, and distributed for single use only. **Do not resterilize or reuse the devices.** There are no data to support the sterility, nonpyrogenicity, and functionality of the devices after reprocessing.
- Incorrect sizing of the valve may lead to paravalvular leak, migration, embolization, residual gradient (patient-prosthesis mismatch) and/or annular rupture.
- Accelerated deterioration of the valve due to calcific generation may occur in children, adolescents, or young adults and in patients with an altered calcium metabolism.
- Prior to delivery, the valve must remain hydrated at all times and cannot be exposed to solutions other than its shipping storage solution and sterile physiologic rinsing solution. Valve leaflets mishandled or damaged during any part of the procedure will require replacement of the valve.
- Caution should be exercised in implanting a valve in patients with clinically significant coronary artery disease.
- Patients with pre-existing prostheses should be carefully assessed prior to implantation of the valve to ensure proper valve positioning and deployment.
- Do not use the valve if the tamper evident seal is broken, the storage solution does not completely cover the valve, the temperature indicator has been activated, the valve is damaged, or the expiration date has elapsed.
- Do not mishandle the delivery system or use it if the packaging or any components are not sterile, have been opened or are damaged (e.g. kinked or stretched), or the expiration date has elapsed.
- Use of excessive contrast media may lead to renal failure. Measure the patient’s creatinine level prior to the procedure. Contrast media usage should be monitored.
- Care should be exercised in patients with hypersensitivities to cobalt, nickel, chromium, molybdenum, titanium, manganese, silicon, and/or polymeric materials.
- The procedure should be conducted under fluoroscopic guidance. Some fluoroscopically guided procedures are associated with a risk of radiation injury to the skin. These injuries may be painful, disfiguring, and long-lasting.

- Valve recipients should be maintained on anticoagulant/antiplatelet therapy, except when contraindicated, as determined by their physician. This device has not been tested for use without anticoagulation.
- Do not add or apply antibiotics to the storage solution, rinse solutions, or to the valve.
- Balloon valvuloplasty should be avoided in the treatment of failing bioprostheses as this may result in embolization of bioprosthesis material and mechanical disruption of the valve leaflets.

5.0 Precautions

- Safety, effectiveness, and durability have not been established for THV-in-THV procedures.
- Long-term durability has not been established for the valve. Regular medical follow-up is advised to evaluate valve performance.
- Glutaraldehyde may cause irritation of the skin, eyes, nose and throat. Avoid prolonged or repeated exposure to, or breathing of, the solution. Use only with adequate ventilation. If skin contact occurs, immediately flush the affected area with water; in the event of contact with eyes, seek immediate medical attention. For more information about glutaraldehyde exposure, refer to the Material Safety Data Sheet available from Edwards Lifesciences.
- To maintain proper valve leaflet coaptation, do not overinflate the deployment balloon.

  Appropriate antibiotic prophylaxis is recommended post-procedure in patients at risk for prosthetic valve infection and endocarditis.Special care must be exercised in mitral valve replacement if chordal preservation techniques were used in the primary implantation to avoid entrapment of the subvalvular apparatus.

- Safety and effectiveness have not been established for patients with the following characteristics/comorbidities:
  - Non-calcified aortic annulus
  - Severe ventricular dysfunction with ejection fraction < 20%
  - Congenital unicuspid aortic valve
  - Congenital bicuspid aortic valve at low surgical risk
  - Pre-existing prosthetic ring in any position
  - Severe mitral annular calcification (MAC), severe (> 3+) mitral insufficiency, or Gorlin syndrome
  - Blood dyscrasias defined as: leukopenia (WBC < 3,000 cells/mL), acute anemia (Hb < 9 g/dL), thrombocytopenia (platelet count < 50,000 cells/mL), or history of bleeding diathesis or coagulopathy
  - Hypertrophic cardiomyopathy with or without obstruction (HOCM)
  - Echocardiographic evidence of intracardiac mass, thrombus, or vegetation
  - A known hypersensitivity or contraindication to aspirin, heparin, ticlopidine (Ticlid™), or clopidogrel (Plavix™), or sensitivity to contrast media, which cannot be adequately premedicated
  - Excessive calcification at access site
  - Bulky calcified aortic valve leaflets in close proximity to coronary ostia
  - A concomitant paravalvular leak where the failing bioprosthesis is not securely fixed in the native annulus or is not structurally intact (e.g. wireform frame fracture)
  - A partially detached leaflet of the failing bioprosthesis that in the aortic position may obstruct a coronary ostium
  - Residual mean gradient may be higher in a “THV-in-failing bioprosthesis” configuration than that observed following implantation of the valve inside a native aortic annulus using the same

size device. Patients with elevated mean gradient post procedure should be carefully followed. It is important that the manufacturer, model and size of the preexisting bioprosthetic valve be determined, so that the appropriate valve can be implanted and a prosthesis-patient mismatch be avoided. Additionally, pre-procedure imaging modalities must be employed to make as accurate a determination of the inner diameter as possible.

6.0 Potential Adverse Events

Potential risks associated with the overall procedure including potential access complications associated with standard cardiac catheterization, balloon valvuloplasty, the potential risks of conscious sedation and/or general anesthesia, and the use of angiography:

- Death
- Stroke/transient ischemic attack, clusters or neurological deficit
- Paralysis
- Permanent disability
- Respiratory insufficiency or respiratory failure
- Hemorrhage requiring transfusion or intervention
- Cardiovascular injury including perforation or dissection of vessels, ventricle, atrium, myocardium or valvular structures that may require intervention
- Pericardial effusion or cardiac tamponade
- Embolization including air, calcific valve material or thrombus
- Infection including septicemia and endocarditis
- Heart failure
- Myocardial infarction
- Renal insufficiency or renal failure
- Conduction system defect which may require a permanent pacemaker
- Arrhythmia
- Retroperitoneal bleed
- Arteriovenous (AV) fistula or pseudoaneurysm
- Reoperation
- Ischemia or nerve injury
- Restenosis
- Pulmonary edema
- Pleural effusion
- Bleeding
- Anemia
- Abnormal lab values (including electrolyte imbalance)
- Hypertension or hypotension
- Allergic reaction to anesthesia, contrast media, or device materials
- Hematoma
- Syncope
- Pain or changes at the access site
- Exercise intolerance or weakness
- Inflammation
- Angina
- Heart murmur

- Fever

Additional potential risks associated with the use of the valve, delivery system, and/or accessories include:

- Cardiac arrest
- Cardiogenic shock
- Emergency cardiac surgery
- Cardiac failure or low cardiac output
- Coronary flow obstruction/transvalvular flow disturbance
- Device thrombosis requiring intervention
- Valve thrombosis
- Device embolization
- Device migration or malposition requiring intervention
- Left ventricular outflow tract obstruction
- Valve deployment in unintended location
- Valve stenosis
- Structural valve deterioration (wear, fracture, calcification, leaflet tear/tearing from the stent posts, leaflet retraction, suture line disruption of components of a prosthetic valve, thickening, stenosis)
- Device degeneration
- Paravalvular or transvalvular leak
- Valve regurgitation
- Hemolysis
- Injury to the mitral valve
- Device explants
- Mediastinitis
- Mediastinal bleeding
- Nonstructural dysfunction
- Mechanical failure of delivery system, and/or accessories
- Non-emergent reoperation

7.0 Directions for Use

7.1 System Compatibility

Table 6.

Product Name	20 mm System	23 mm System	26 mm System
	Model		
Edwards SAPIEN 3 Ultra Transcatheter Heart Valve	9750TFX20	9750TFX23	9750TFX26
Edwards Certitude Delivery System	9630TA20	9630TA23	9630TA26
Edwards Certitude Introducer Sheath Set	9600IS18	9600IS21	
Inflation device, Qualcrimp crimping accessory, 2-piece crimp stopper, loader and extension tubing provided by Edwards Lifesciences			
Edwards Crimper	9600CR		

Table 7.

Product Name	20 mm System	23 mm System	26 mm System	29 mm System
	Model			
Edwards SAPIEN 3 Transcatheter Heart Valve	9600TFX20	9600TFX23	9600TFX26	9600TFX29
Edwards Certitude Delivery System	9600SDS20	9600SDS23	9600SDS26	9600SDS29
Edwards Certitude Introducer Sheath Set	9600IS18			9600IS21
Inflation device, Qualcrimp crimping accessory, 2-piece crimp stopper, loader and extension tubing provided by Edwards Lifesciences				
Edwards Crimper	9600CR			

Additional Equipment:

- Balloon catheter, per the discretion of the physician
- 20 cc syringe or larger (x2)
- 50 cc syringe or larger
- Standard cardiac catheterization lab equipment
- Fluoroscopy (fixed, mobile or semi-mobile fluoroscopy systems appropriate for use in percutaneous coronary interventions)
- Transesophageal or transthoracic echocardiography capabilities
- 18 gauge Seldinger needle (for transaortic)
- 145 cm x 0.035 inch (0.89 mm) soft guidewire
- 180 cm or 260 cm x 0.035 inch (0.89 mm) & Exchange length 0.035 inch (0.89 mm) extra-stiff guidewire
- Temporary pacemaker (PM) and pacing lead
- Sterile rinsing basins, physiological saline, heparinized saline, 15% diluted radiopaque contrast medium
- Sterile table for valve and device preparation

7.2 Valve Handling and Preparation

Follow sterile technique during device preparation and implantation.

7.2.1 Valve Rinsing Procedure

Before opening the valve jar, carefully examine for evidence of damage (e.g. a cracked jar or lid, leakage, or broken or missing seals).

CAUTION: Valves from containers found to be damaged, leaking, without adequate sterilant, or missing intact seals must not be used for implantation.

Step	Procedure
1	Set up two (2) sterile bowls with at least 500 mL of sterile physiological saline to thoroughly rinse the glutaraldehyde sterilant from the valve.
2	Carefully remove the valve/holder assembly from the jar without touching the tissue. Verify the valve serial identification number with the number on the jar lid and record in the patient information documents. Inspect the valve for any signs of damage to the frame or tissue.
3	Rinse the valve as follows: Place the valve in the first bowl of sterile, physiological saline. Be sure the saline solution completely covers the valve and holder. With the valve and holder submerged, slowly agitate (to gently swirl the valve and holder) back and forth for a minimum of 1 minute. Transfer the valve and holder to the second rinsing bowl of sterile, physiological saline and gently agitate for at least one more minute. Ensure the rinse solution in the first bowl is not used. The valve should be left in the final rinse solution until needed to prevent the tissue from drying. **CAUTION: Do not allow the valve to come into contact with the bottom or sides of the rinse bowl during agitation or swirling in the rinse solution. Direct contact between the identification tag and valve is also to be avoided during the rinse procedure. No other objects should be placed in the rinse bowls. The valve should be kept hydrated to prevent the tissue from drying.**

7.2.2 Prepare the Components

Refer to the Edwards Crimper instructions for use for device preparation.

Step	Procedure
1	Visually inspect all components for damage. Ensure the Edwards Certitude delivery system is fully unflexed.
2	Prime and flush the introducer and sheath with heparinized saline. Hydrate the length of the introducer and sheath.
3	Advance the introducer fully into the sheath housing.
4	Unscrew the loader cap from the loader and flush the loader cap with heparinized saline.
5	Place the loader cap onto the delivery system with the inside of the cap oriented towards the tapered tip.
6	Flush the extension tubing and connect to the delivery system.
7	Partially fill a 50 mL or larger syringe with diluted contrast medium, and connect to the extension tubing.
8	Fill the inflation device with 20 mL of diluted contrast medium, lock the inflation device, and connect to the extension tubing. Close 3-way stopcock to inflation device.
9	De-air the delivery system using the luer lock syringe. Leave zero-pressure in the system. Close the 3-way stopcock to the luer lock syringe.
10	Remove 3 mL fluid from the delivery system by turning the knob of the locked inflation device. Keep the inflation device locked for valve crimping steps.

7.2.3 Mount and Crimp the Valve on the Delivery System

Step	Procedure
1	Set up two (2) additional sterile bowls with at least 100 mL of sterile, physiological saline to thoroughly rinse the Qualcrimp crimping accessory.
2	Completely submerge the Qualcrimp crimping accessory in the first bowl and gently compress it to ensure complete saline absorption. Slowly swirl the Qualcrimp crimping accessory for a minimum of 1 minute. Repeat this process in the second bowl.
3	Remove the valve from the holder and remove the ID tag.
4	Attach the 2-piece crimp stopper to the base of the crimper and click into place.
5	With the crimper in the open position, gently place the valve into the crimper aperture. Gradually crimp the valve (if necessary) until it fits into the Qualcrimp crimping accessory.
6	Place the Qualcrimp crimping accessory over the valve making sure the valve is parallel to the edge of the Qualcrimp crimping accessory.
7	Place the valve and Qualcrimp crimping accessory in the crimper aperture. Insert the delivery system coaxially within the valve. The orientation of the valve on the delivery system is described below: **Antegrade approach:** Inflow (outer skirt end) of the valve towards the proximal end of the delivery system. **Retrograde approach:** Inflow (outer skirt end) of the valve towards the distal end of the delivery system.
8	Crimp the valve between the two internal shoulders of the delivery system until it reaches the Qualcrimp Stop located on the 2-piece Crimp Stopper.
9	Gently remove the Qualcrimp crimping accessory from the valve. Remove the Qualcrimp Stop from the Final Stop, leaving the Final Stop in place.
10	Fully crimp the valve until it reaches the Final Stop. **NOTE: Ensure that the delivery system remains coaxial within the valve.**
11	Repeat the full crimp of the valve two more times for a total of three full crimps.
12	Flush the loader with heparinized saline. Immediately advance the valve into the loader until the tapered tip of the delivery system is exposed and the valve is within the distal end of the loader tube. **CAUTION: To prevent possible leaflet damage, the valve should not remain fully crimped and/or in the loader for over 15 minutes.**
13	Attach the loader cap to the loader and flush through the port on the loader. **CAUTION: Keep the valve hydrated until ready for implantation.** **CAUTION: The physician must verify correct orientation of the valve prior to its implantation.**
14	With 3-way stopcock still closed to the luer lock syringe, unlock the inflation device. Allow the delivery system to reach zero-pressure.

<table>
<tr><th>Step</th><th>Procedure</th></tr>
<tr><td>15</td><td>Close the 3-way stopcock to the delivery system. Use the luer lock syringe to de-air the inflation device if necessary</td></tr>
<tr><td>16</td><td>Adjust the inflation device to the inflation volume required to deploy the valve, per the following:
<table>
<tr><th>Delivery System</th><th>Valve</th><th>Inflation Volume</th></tr>
<tr><td>Model
9630TA20
9600SDS20</td><td>20 mm</td><td>12 mL</td></tr>
<tr><td>Model
9630TA23
9600SDS23</td><td>23 mm</td><td>17 mL</td></tr>
<tr><td>Model
9630TA26
9600SDS26</td><td>26 mm</td><td>23 mL</td></tr>
<tr><td>Model
9630TA29
9600SDS29</td><td>29 mm</td><td>30 mL</td></tr>
</table>
Re-lock the inflation device. Close the 3-way stopcock to the luer lock syringe and remove syringe.
CAUTION: Maintain the inflation device in a locked position until valve deployment.</td></tr>
<tr><td>17</td><td>Remove the stylet and flush the guidewire lumen of the delivery system.</td></tr>
</table>

7.3 Valvuloplasty and Valve Delivery

Valvuloplasty and valve delivery should be performed under conscious sedation and/or general anesthesia with hemodynamic monitoring in a catheterization lab/hybrid operating room with fluoroscopic and echocardiographic imaging capabilities.

The following table shows the minimum required distances from the valvular plane to the distal tip of the sheath to allow the Edwards Certitude delivery system balloon to inflate properly during valve deployment. These distances do not include sheath insertion depth, which should be considered during the transaortic approach when selecting the access site on the ascending aorta.

Delivery System	Valve	Minimum Required Distance From Sheath Tip to Valvular Plane
9630TA20 9600SDS20	20 mm	3.5 cm
9630TA23 9600SDS23	23 mm	3.5 cm
9630TA26 9600SDS26	26 mm	3.5 cm
9630TA29 9600SDS29	29 mm	4.0 cm

Administer heparin to maintain the ACT at ≥ 250 sec during the procedure.

Balloon valvuloplasty should be avoided in the treatment of failing bioprostheses as this may result in embolization of bioprosthesis material and mechanical disruption of the valve leaflets.

CAUTION: Use of excessive contrast media may lead to renal failure. Measure the patient's creatinine level prior to the procedure. Contrast media usage should be monitored.

CAUTION: Care should be taken to avoid damage to soft tissue, chordae, aorta, native leaflet or ventricular wall during insertion, positioning and removal of devices.

7.3.1 Baseline Parameters

Step	Procedure
1	Perform an angiogram with fluoroscopic view perpendicular to the valve.
2	Evaluate the distance of the left and right coronary ostia from the aortic annulus in relation to the valve frame height.
3	Introduce a pacemaker (PM) lead and position appropriately.
4	Set the stimulation parameters to obtain 1:1 capture, and test pacing.

7.3.2 Access

Step	Procedure
1	Gain access using standard catheterization techniques.
2	Using the sheath depth markers, advance the introducer and sheath over the guidewire to the desired depth while following its progression on fluoroscopy.
3	Withdraw the introducer slowly, keeping the sheath in place. Maintain guidewire position across the valve.

7.3.3 Valvuloplasty

Pre-dilate the native aortic valve, per the discretion of the physician, according to the instructions for use for the selected balloon aortic valvuloplasty catheter.

CAUTION: Valve implantation should not be carried out if the balloon cannot be fully inflated during valvuloplasty.

7.3.4 Valve Delivery

Step	Procedure
1	Confirm that the valve is oriented properly and the volume in the inflation device matches the indicated volume.
2	Advance the valve/balloon assembly with the loader over the guidewire.
3	Engage loader into sheath housing while maintaining a firm grip.
4	Advance the valve out of the loader into the large section of the sheath. Tap on the sheath housing to release air bubbles to the proximal end of the loader. Depress button valve on loader to de-air.
5	Advance the valve/balloon assembly through the sheath and position within the target valve. If needed, rotate the flex wheel on the handle to articulate the valve/balloon assembly into position. **CAUTION: To prevent possible leaflet damage, the valve should not remain in the sheath for over 5 minutes.**
6	Ensure that the valve is correctly positioned between the two internal shoulders of the delivery system.
7	Begin valve deployment: • Unlock the Inflation device provided by Edwards Lifesciences. • Begin rapid pacing; once systolic blood pressure has decreased to 50 mmHg or below, balloon inflation can commence. • Deploy the valve by inflating the balloon with the entire volume in the Inflation device provided by Edwards Lifesciences, hold for 3 seconds and confirm that the barrel of the inflation device is empty to ensure complete inflation of the balloon. • Deflate the balloon. When the balloon has been completely deflated, turn off the pacemaker.

7.3.5 System Removal

Step	Procedure
1	If articulation was used, completely unflex the delivery system. Retract the delivery system and guidewire into the sheath. Remove the loader and delivery system from the sheath. **CAUTION: Properly deflate the balloon and unflex the delivery system prior to removal.**
2	Remove all devices when the ACT level is appropriate.
3	Remove the sheath from the access site, close the access site and confirm hemostasis.

8.0 How Supplied

STERILE: The valve is supplied sterilized with glutaraldehyde solution. The delivery system is supplied sterilized with ethylene oxide gas.

8.1 Storage

The valve must be stored at 10 °C to 25 °C (50 °F to 77 °F). Each jar is shipped in an enclosure containing a temperature indicator to detect exposure of the valve to extreme temperature.

The delivery system should be stored in a cool, dry place.

9.0 MR Safety



MR Conditional

Non-clinical testing has demonstrated that the Edwards SAPIEN 3 Ultra transcatheter heart valve and the Edwards SAPIEN 3 transcatheter heart valve are MR Conditional. A patient with this device can be scanned safely, immediately after placement of this device under the following conditions:

- Static magnetic field of 1.5 tesla or 3 tesla.
- Maximum spatial gradient field of 2500 gauss/cm (25 T/m) or less.
- Maximum MR system reported, whole body averaged specific absorption rate (SAR) of 2 W/kg (Normal Operating Mode).

Under the scan conditions defined above, the transcatheter heart valve is expected to produce a maximum temperature rise of 3.0 °C after 15 minutes of continuous scanning.

In non-clinical testing, the image artifact caused by the device extends as far as 14.5 mm from the implant for spin echo images and 30 mm for gradient echo images when scanned in a 3.0 T MRI system. The artifact obscures the device lumen in gradient echo images.

The implant has not been evaluated in MR systems other than 1.5 or 3.0 T.

For valve-in-valve implantation or in the presence of other implants, please refer to the MRI safety information for the surgical valve or other devices prior to MR imaging.

10.0 Patient Information

Patient education brochures are provided to each site and should be given to the patient to inform them of the risks and benefits of the procedure and alternatives in adequate time before the procedure to be read and discussed with their physician. A copy of this brochure may also be obtained from Edwards Lifesciences by calling 1.800.822.9837. A patient implant card request form is provided with each transcatheter heart valve. After implantation, all requested information should be completed on this form. The serial number may be found on the package and on the identification tag attached to the transcatheter heart valve. The original form should be returned to the Edwards Lifesciences address indicated on the form and upon receipt, Edwards Lifesciences will provide an identification card to the patient.

11.0 Recovered Valve and Device Disposal

The explanted valve should be placed into a suitable histological fixative such as 10% formalin or 2% glutaraldehyde and returned to the company. Refrigeration is not necessary under these circumstances. Contact Edwards Lifesciences to request an Explant Kit.

Used delivery system may be disposed of in the same manner that hospital waste and biohazardous materials are handled. There are no special risks related to the disposal of these devices.

12.0 Clinical Studies

SUMMARY OF PRIMARY CLINICAL STUDY

The PARTNER II Trial Overview, SAPIEN 3 Valve

SAPIEN 3 High Risk and Inoperable Cohort: The SAPIEN 3 High Risk and Inoperable Cohort of the PARTNER II trial (PIIS3HR) was a single arm, non-randomized, historical-controlled study to compare the third generation Edwards SAPIEN 3 system with the first generation Edwards SAPIEN system in patients who either have high risk for surgery or cannot undergo surgery (inoperable). The valve sizes used in the PIIS3HR trial included only the 23, 26 and 29 mm sizes. The 20 mm valve size was introduced into the trial after enrollment was completed with the three larger sizes, thus a separate nested registry, NR7, with identical inclusion/exclusion criteria as the PIIS3HR Cohort except for the aortic annulus diameter, was created to collect data for the 20 mm valve. Data from the PIIS3HR cohort and NR7 are pooled for the statistical analyses. For convenience, this combined cohort is referred to as “PIIS3HR” hereafter.

The database included 583 eligible patients enrolled at 29 investigational sites in the U.S.

The PIIS3HR study used an independent Data Safety Monitoring Board (DSMB) that was instructed to notify Edwards Lifesciences of any safety or compliance issues, a Clinical Events Committee (CEC) that was responsible for adjudicating endpoint related events reported during the trial per *a priori* established VARC 2 definitions[2], an ECG core laboratory for independent analysis of rhythm, and an echocardiographic core laboratory for independently analyzing all echocardiograms.

SAPIEN 3 Intermediate Risk Cohort: The PIIS3i Cohort of the PARTNER II trial was a single arm, non-randomized, historical-controlled study to compare TAVR with the Edwards SAPIEN 3 system to the surgical aortic valve replacement (SAVR) arm from the previous PARTNER II trial Cohort A (PIIA-SAVR) in patients who were judged by a heart team to be at intermediate risk for open surgical therapy. The valve sizes used in the PIIS3i study included the 20, 23, 26, and 29 mm sizes.

Patients in PIIS3i were treated between February 2014 and September 2014. Patients in PIIA-SAVR were treated between January 2012 and November 2013. The database reflected data collected through December 10, 2015 and included 1,078 patients in PIIS3i enrolled at 51 investigational sites in the U.S. and 1,021 patients in PIIA-SAVR enrolled at 57 investigational sites in the U.S.

The PIIS3i study used an independent Data Safety Monitoring Board (DSMB) that was instructed to notify Edwards Lifesciences of any safety or compliance issues and a Clinical Events Committee (CEC) that was responsible for adjudicating endpoint related events reported during the trial. The CEC adjudicated the events per pre-established definitions, which were primarily Valve Academic Research Consortium-1 VARC-2 definitions[2], with the following exceptions:

- Prosthetic valve dysfunction was adjudicated per VARC-1
- Aortic valve reintervention was adjudicated per protocol definition
- Rehospitalization for symptoms of aortic stenosis and/or complications of the valve procedure were adjudicated using the protocol and VARC-2 definitions as guidelines

The events in the PIIA-SAVR cohort were adjudicated by the CEC in accordance with the pre-specified, primarily VARC-1 definitions, with the following exceptions:

- Acute Kidney Injury (AKI) was adjudicated with a modified VARC-1 definition in which the CEC applied the 72-hour staging window to any AKI event that occurred within 30-days
- Aortic valve reintervention were adjudicated per the protocol definition
- Rehospitalization for symptoms of AS and/or complications of the valve procedure were adjudicated using the protocol and VARC-1 as guidelines
- Bleeding events were adjudicated irrespective of whether there was an identifiable, overt source of bleeding

An electrocardiogram (ECG) core laboratory was used for independent analysis of rhythm, an echocardiographic core laboratory for echocardiograms, and a computerized tomography (CT) core laboratory for baseline CTs for annulus dimensions.

The PARTNER 3 Trial Overview, SAPIEN 3 Valve

Patients were enrolled between March 2016 and June 2018. The database reflected data collected through December 21, 2018 and included 1000 patients. There were 71 investigational sites in the U.S, Australia, Canada, New Zealand, and Japan.

The PARTNER 3 trial was a prospective, randomized (1:1), controlled, multicenter study to compare TAVR with the Edwards SAPIEN 3 THV to SAVR. A subset of patients were enrolled in a computed tomography (CT) substudy to investigate the prevalence of Hypoattenuated Leaflet Thickening (HALT) and reduced leaflet mobility.

The PARTNER 3 trial used an independent Data Safety Monitoring Board (DSMB) that was instructed to notify the applicant of any safety or compliance issues and a Clinical Events Committee (CEC) that was responsible for adjudicating endpoint-related events reported during the trial. The CEC adjudicated the events per Valve Academic Research Consortium-2 (VARC-2) definitions[2].A CT core laboratory was used for assessment of baseline CTs for annulus dimensions and the CT images acquired in the CT substudy.

Clinical Inclusion and Exclusion Criteria

Patients in the database extract received a commercially available SAPIEN 3 transcatheter heart valve and surgical valves for symptomatic heart disease due to severe native calcific aortic stenosis who were deemed to be at low risk for surgical aortic valve replacement.

Clinical Endpoints

The endpoints analyzed in this application included: death rate, adjudicated adverse events (stroke, TIA, and aortic valve reinterventions, rehospitalization), key site reported adverse events, atrial fibrillation, length of index hospitalization, valve performance based on echocardiographic data, New York Heart Association (NYHA) classification, 6-minute walk test, and the Kansas City Cardiomyopathy Questionnaire (KCCQ) score. The analyses in the application focused on the 30-day and/or one-year time points.

SAPIEN 3 THV IN BICUSPID AORTIC VALVE FOR PATIENTS AT INTERMEDIATE OR GREATER SURGICAL RISK– STS/ACC TRANSCATHETER VALVE THERAPY REGISTRY (TVTR) ANALYSIS

A database extract was performed on November 15, 2017, which yielded 545 patients with bicuspid aortic valves that had been treated with an Edwards SAPIEN 3 transcatheter heart valve. The patients were treated between July 14, 2015 and August 15, 2016. The procedure was performed in 225 participating hospitals.

Adjudications were completed per the TVT Registry Coder's Data Dictionary by the Duke Clinical Research Institute (DCRI) for three adverse events: stroke, transient ischemic attack (TIA), and aortic valve reinterventions.

Clinical Inclusion and Exclusion Criteria

Patients in the database extract received a commercially available SAPIEN 3 transcatheter heart valve for symptomatic heart disease associated with a bicuspid aortic valve. The patients were treated based on clinical judgement of their treating physicians.

Follow-up Schedule

All patients were followed post implantation according to their local standards of care. The TVT Registry collects follow-up data at discharge, 30 days, and 1 year.

Clinical Endpoints

Data entered into the TVT Registry were collected through standardized data collection forms. The endpoints analyzed in this application included: death rate, adjudicated adverse events (stroke, TIA, and aortic valve reinterventions), key site reported adverse events, valve performance based on echocardiographic data, New York Heart Association (NYHA) classification, 5-meter walk test, and the Kansas City Cardiomyopathy Questionnaire (KCCQ) score. The analyses in the application focused on the 30-day and one-year time points.

SAPIEN 3 THV Valve-in-Valve – STS/ACC Transcatheter Valve Therapy Registry (TVTR) Analysis

A database extract was performed on August 4, 2016, which yielded 314 patients that had been treated with an Edwards SAPIEN 3 transcatheter heart valve placed in a failed surgical aortic bioprosthesis (i.e., aortic valve-in-valve) and 311 patients that had been treated with an Edwards SAPIEN XT transcatheter heart valve (N = 241) or SAPIEN 3 transcatheter heart valve (N = 70) placed in a failed surgical mitral bioprosthesis (i.e., mitral valve-in-valve). Patients who presented with an existing valve-in-valve that was failing were excluded from the database extract. The SAPIEN XT transcatheter heart valve was included in the database extract for the mitral valve-in-valve uses because there were fewer SAPIEN 3 transcatheter heart valve cases in the registry due to its relatively shorter commercial use history and the SAPIEN XT transcatheter heart valve data were considered to be generally applicable to the SAPIEN 3 transcatheter heart valve due to their similarities in design. The aortic valve-in-valve patients were treated between July 23rd, 2015 and June 29th, 2016 at 130 participating hospitals; the mitral valve-in-valve patients were treated at 112 participating hospitals between July 10th, 2014 and June 27th, 2016 for the SAPIEN XT transcatheter heart valve and between June 23rd, 2015 and June 15th, 2016 for the SAPIEN 3 transcatheter heart valve.

Adjudications were completed per the TVT Registry Coder's Data Dictionary by the Duke Clinical Research Institute (DCRI) for three adverse events: readmission for heart failure, stroke/transient ischemic attack (TIA), and aortic and mitral valve reinterventions.

Clinical Inclusion and Exclusion Criteria

Patients in the database extract received a commercially available SAPIEN 3 transcatheter heart valve (for both aortic and mitral valve-in-valve) or SAPIEN XT transcatheter heart valve (for mitral valve-in-valve only) for symptomatic heart disease associated with a failed (stenosed, insufficient, or combined) surgical bioprosthetic aortic or mitral valve. They were deemed to be at high or greater risk for open surgical therapy and were treated off-label based on the clinical judgement of their treating physicians.

Follow-up Schedule

All patients were followed post implantation according to their local standards of care. The TVT Registry collects follow-up data at discharge, 30 days, and 1 year.

Clinical Endpoints

Data entered into the TVT Registry were collected through standardized data collection forms. The endpoints analyzed in this application included: death rate, adjudicated adverse events (readmission for heart failure, stroke/TIA, and valve reinterventions), key site reported adverse events, valve performance based on echocardiographic data, New York Heart Association (NYHA) classification, 6-minute or 5-meter walk test, and the Kansas City Cardiomyopathy Questionnaire (KCCQ) score. The analyses in the application focused on the discharge and 30-day time points.

SAPIEN 3 Ultra Confirmatory Study Overview

A prospective, single-arm, multicenter clinical study was conducted to confirm the procedural safety and effectiveness of the SAPIEN 3 Ultra system in patients with severe, calcific aortic stenosis (AS) who are at intermediate operative risk for surgical aortic valve replacement (SAVR).

The study enrolled 40 patients in Canada and United Kingdom.

It utilized an echocardiographic core laboratory for echocardiograms.

Follow-up Schedule

All patients were followed post implantation at discharge and 30 days, and will continue to be followed at 6 months, 1 year and annually thereafter for a minimum of 5 years.

Clinical Endpoints

The endpoints analyzed were procedure success (defined as freedom from mortality, conversion to surgery and moderate or severe paravalvular regurgitation at exit from the procedure room), key site reported adverse events, valve performance, and New York Heart Association (NYHA) classification.

PARTNER II SAPIEN 3 HIGH-RISK/INOPERABLE COHORT

Patient Accountability

All 583 eligible patients were successfully implanted with a SAPIEN 3 valve, which constitutes the Valve Implant (VI) population. Among the VI population, 491 patients were implanted via the transfemoral (TF) access route, and 92 patients via the transapical (TA) or transaortic (TAo) access route.

Table 8:
Patient Accountability

	SAPIEN 3 Valve Overall	SAPIEN 3 Valve Transfemoral Access	SAPIEN 3 Valve Non-Transfemoral Access
Eligible Patient Population (EPP)	583	491	92
Valve Implant (VI) Population	583	491	92

Eligible Patient Population (EPP) consists of all enrolled patients who received treatment assignment from the database and entered into the catheterization laboratory/hybrid suite and who remained eligible to receive the implant.

Valve Implant (VI) Population consists of all enrolled patients who received a SAPIEN 3 valve, and retained the valve upon leaving the catheterization laboratory/hybrid suite.

Study Population Demographics and Baseline Parameters

The demographics of the study population are summarized in Table 9, which are typical of a TAVR study performed in the U.S.

Table 9:
Patient Demographics and Baseline Characteristics –
PIIS3HR VI Population

Characteristic	SAPIEN 3 Valve Overall (N = 583)	SAPIEN 3 Valve Transfemoral Access (N = 491)	SAPIEN 3 Valve Non-Transfemoral Access (N = 92)
Age, yr	82.6 ± 8.1	82.8 ± 8.2	81.7 ± 7.5
Male sex, no. (%)	338 (58.0%)	277 (56.4%)	61 (66.3%)
STS score	8.6 ± 3.7	8.4 ± 3.5	10.0 ± 4.3
New York Heart Association (NYHA) class, no. (%):			
I/II	58 (9.9%)	51 (10.4%)	7 (7.6%)
III/IV	525 (90.1%)	440 (89.6%)	85 (92.4%)
Coronary artery disease, no. (%)	444 (76.2%)	360 (73.3%)	84 (91.3%)
Previous myocardial infarction, no. (%)	117 (20.1%)	87 (17.7%)	30 (32.6%)
Previous intervention, no. (%)			
Coronary-artery bypass grafting (CABG)	193 (33.1%)	145 (29.5%)	48 (52.2%)
Percutaneous coronary intervention (PCI)	199 (34.1%)	163 (33.2%)	36 (39.1%)
Prior aortic valvuloplasty	62 (10.6%)	49 (10.0%)	13 (14.1%)
Cerebral vascular accident (CVA), no. (%)	64 (11.0%)	53 (10.8%)	11 (12.0%)
Peripheral vascular disease, no. (%)	205 (35.2%)	155 (31.6%)	50 (54.3%)
Chronic obstructive pulmonary disease (COPD), no. (%):			
Any	259 (44.6%)	216 (44.1%)	43 (47.3%)
Oxygen-dependent	68 (11.8%)	58 (11.9%)	10 (11.0%)
Atrial fibrillation, no. (%)	255 (43.7%)	212 (43.2%)	43 (46.7%)
Permanent pacemaker, no. (%)	95 (16.3%)	78 (15.9%)	17 (18.5%)
Severe pulmonary hypertension, no. (%)	30 (5.1%)	24 (4.9%)	6 (6.5%)
Frailty, no. (%)	180 (30.9%)	162 (33.0%)	18 (19.6%)
Chest deformities that preclude an open chest procedure, no. (%)	4 (0.7%)	3 (0.6%)	1 (1.1%)
Cirrhosis, no. (%)	11 (1.9%)	9 (1.8%)	2 (2.2%)
Echocardiographic findings			
Effective Orifice Area (EOA), cm^2	0.7 ± 0.2	0.7 ± 0.2	0.7 ± 0.1
Mean aortic-valve gradient, mmHg	45.5 ± 14.3	45.7 ± 14.4	44.0 ± 13.2
Mean left ventricular ejection fraction (LVEF), %	56.4 ± 14.8	57.0 ± 14.5	53.2 ± 15.9
Moderate or severe mitral regurgitation, no./total no. (%)	69/541 (12.8%)	63/461 (13.7%)	6/80 (7.5%)

Safety and Effectiveness Results

Primary Endpoint

The composite rate of all-cause mortality, all stroke, and AI ≥ moderate at 30 days was 6.7% in the SAPIEN 3 cohort and 15.6% in the SAPIEN cohort, as shown in Table 10. The resulting proportion difference in the average treatment effect on the treated (ATT; [3]) was -6.9% (90% CI: [-13.3%, -0.5%]). Since the upper limit of the CI was < 7.5%, the non–inferiority was met.

Table 10:
Primary Endpoint Analysis –
Non-Inferiority Test SAPIEN 3 Valve (PIIS3HR VI Population) vs. SAPIEN Valve

Event at 30 days	SAPIEN 3 Valve (N = 583)	SAPIEN Valve (N = 326)	Weighted Proportion Difference in Average Treatment Effect on the Treated (ATT)
Composite of Death, Stroke and AI ≥ Moderate	6.7% [5.1%, 8.6%][1]	15.6% [12.6%, 19.5%][1]	-6.9% [-13.3%, -0.5%][2]

[1] For each individual study, the two-sided 90% stratified Wilson confidence interval was provided.
[2] The Wald-type two-sided 90% confidence interval using weighted mean and SD is provided.

The Kaplan-Meier (K-M) estimates for all-cause mortality, cardiac mortality, and all stroke at 30 days for the SAPIEN 3 cohort and the SAPIEN cohort are provided in Table 11.

Table 11:
Death and Stroke at 30 Days –
SAPIEN 3 Valve vs. SAPIEN Valve (VI Population)

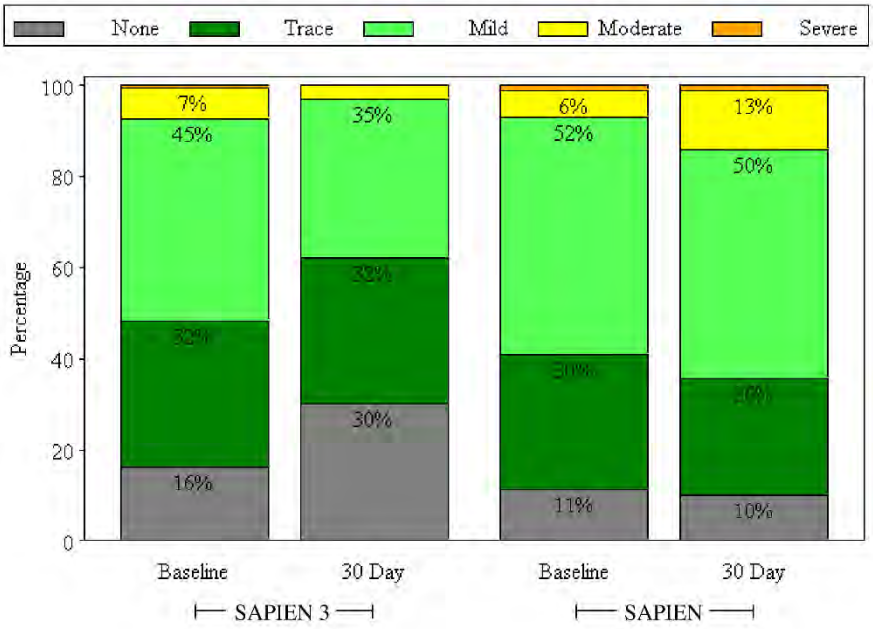
	SAPIEN 3 Valve (N = 583)			SAPIEN Valve (N = 326)		
Event at 30 Days	No. Events	No. Pts with Events	K-M Estimated Event Rate[1] (95% CI)	No. Events	No. Pts with Events	K-M Estimated Event Rate (95% CI)
Death	13	13	2.2% ([1.3%, 3.8%])	15	15	4.6% ([2.8%, 7.5%])
Cardiac Death	8	8	1.4% ([0.7%, 2.7%])	10	10	3.1% ([1.7%, 5.7%])
All Stroke	9	9	1.6% ([0.8%, 3.0%])	14	14	4.3% ([2.6%, 7.2%])

[1] Kaplan-Meier (K-M) estimates at 30 days used time to first event for each patient. Events occurring after 30 days were not included in this analysis.

Secondary Endpoints

Aortic insufficiency by visit is provided in Figure 8.

Figure 8:
Aortic Insufficiency by Visit –
SAPIEN 3 Valve (PIIS3HR VI Population) vs. SAPIEN Valve



The proportion of patients with AI ≥ moderate at 30 days was 3.0% in the SAPIEN 3 cohort and 14.3% in the SAPIEN cohort, which were found to be statistically significantly different (p=0.0051; Table 12).

Table 12:
Aortic Insufficiency at 30 Days
(SAPIEN 3 Valve vs. SAPIEN Valve VI Population)

Event at 30 Days	SAPIEN 3 Valve (N = 583)	SAPIEN Valve (N = 326)	Weighted Proportion Difference in Average Treatment Effect on the Treated (ATT)	P-value
AI ≥ Moderate, n/Total no. (%) [95% CI]	16/532 (3.0%) [1.7%, 4.8%][1]	40/280 (14.3%) [10.4%, 18.9%][1]	-13.1% [-22.2%, -3.9%][2]	0.0051

[1] 95% Clopper-Pearson Exact confidence interval.
[2] The Wald-type two-sided 90% confidence interval using weighted mean and SD is provided.

The rate of major vascular complications at 30 days post implantation is shown in Figure 9. The rate was 5.0% for the SAPIEN 3 cohort and 10.1% for the SAPIEN cohort, which were found to be not statistically significantly different (p=0.0578; Table 13).

Figure 9:
Major Vascular Complications at 30 Days –
SAPIEN 3 Valve vs. SAPIEN Valve (VI Population)

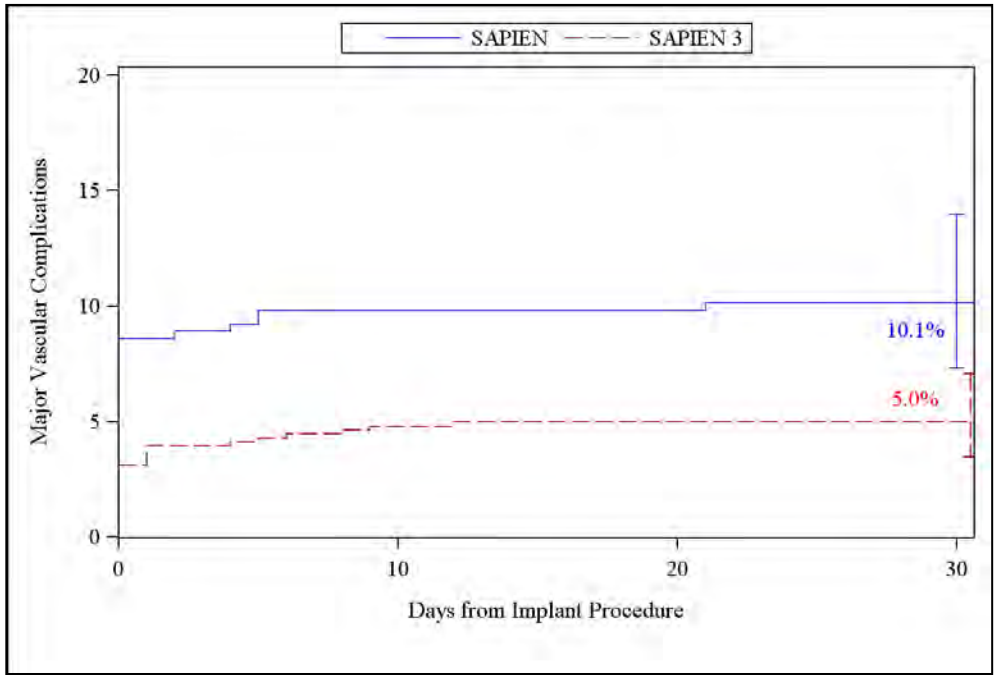


Table 13:
Major Vascular Complications at 30 Days –
SAPIEN 3 Valve vs. SAPIEN Valve (VI Population)

Event at 30 Day	SAPIEN 3 Valve (N = 583)	SAPIEN Valve (N = 326)	Weighted Proportion Difference in Average Treatment Effect on the Treated (ATT)	P-value
Major Vascular Complications, n/Total no. (%) [95% CI]	29/583 (5.0%) [3.4%, 7.1%]	33/326 (10.1%) [7.1%, 13.9%][1]	-8.0% [-16.2%, 0.3%][2]	0.0578

[1] 95% Clopper-Pearson Exact confidence interval.
[2] The Wald-type two-sided 90% confidence interval using weighted mean and SD is provided.

Table 14 lists the hypothesis testing of the two secondary endpoints conducted with p-values in descending order for the Hochberg multiplicity adjustment steps. The largest p-value (p=0.0578 from major vascular complications) was greater than 0.05. As such, the null hypothesis was not rejected for the testing of major vascular complications at 30 days. The subsequent testing of AI ≥ moderate at 30 days had a p-value of 0.0051, which was less than 0.025. As such, the null hypothesis was rejected for AI ≥ moderate at 30 days, indicating that the SAPIEN 3 cohort was superior over the SAPIEN cohort in regards to AI ≥ moderate at 30 days.

Table 14:
Secondary Endpoints for Labeling –
SAPIEN 3 Valve vs. SAPIEN Valve (VI Population)

Endpoints	Original p-value	Inference
Major Vascular Complications at 30 Days	0.0578	> 0.05; reject the alternative hypothesis. Proceed to the rest of testing
AI at 30 Days	0.0051	< 0.025; claim superiority

Adverse Events

The key CEC adjudicated adverse events at 30 days are presented in Table 15.

Table 15:
CEC Adjudicated Adverse Events at 30 Days
(PIIS3HR VI Population)

30 Day Adverse Events	SAPIEN 3 Valve Overall	SAPIEN 3 Valve Transfemoral Access TF	SAPIEN 3 Valve Non-Transfemoral Access
Composite Event Rate of Death, All Stroke and AI ≥ Moderate, n/N (%)	37/545 (6.8%)	27/463 (5.8%)	10/82 (12.2%)
Death			
From any cause, n/N (%)	13/583 (2.2%)	8/491 (1.6%)	5/92 (5.4%)
From cardiovascular cause, n/N (%)	8/583 (1.4%)	5/491 (1.0%)	3/92 (3.3%)
Stroke, n/N (%)	9/583 (1.5%)	8/491 (1.6%)	1/92 (1.1%)
AI ≥ moderate, n/N (%)	16/532 (3.0%)	12/455 (2.6%)	4/77 (5.2%)
Myocardial Infarction, n/N (%)	3/583 (0.5%)	2/491 (0.4%)	1/92 (1.1%)
Major Vascular Complications, n/N (%)	29/583 (5.0%)	26/491 (5.3%)	3/92 (3.3%)
Acute Kidney Injury, Stage III, n/N (%)	6/583 (1.0%)	4/491 (0.8%)	2/92 (2.2%)
Disabling Bleeding Event, n/N (%)	37/583 (6.3%)	27/491 (5.5%)	10/92 (10.9%)
Aortic Valve Re-Intervention, n/N (%)	6/583 (1.0%)	4/491 (0.8%)	2/92 (2.2%)
Endocarditis, n/N (%)	1/583 (0.2%)	1/491 (0.2%)	0/92 (0.0%)
Conduction Disturbance Requiring Permanent Pacemaker, n/N (%)	76/583 (13.0%)	65/491 (13.2%)	11/92 (12.0%)

Other Results

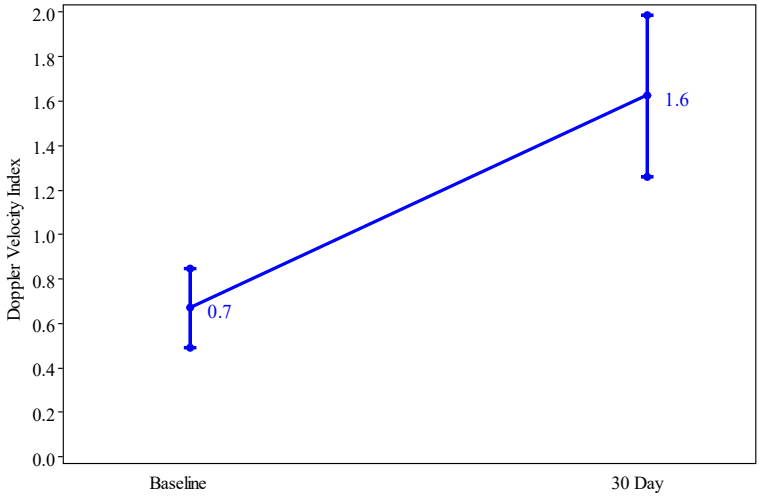
Procedural Information

Overall, the mean duration in the catheterization laboratory/hybrid suite was 192.8 ± 59.3 min, the mean total procedure time was 86.3 ± 44.2 min, and the mean total anesthesia time was 193.7 ± 62.9 min. These duration times were slightly shorter in the TF patients. General anesthesia was used in the vast majority of cases; 15.9% of the TF patients had conscious sedation. Correct positioning of the valve was achieved in 99.1% of the patients. Five patients (0.9%; including 3 TF patients) were implanted with a second valve. One patient (0.2%) experienced valve embolization following rupture of the delivery balloon on annular calcium. This patient was converted to surgical aortic valve replacement and later died from aortic dissection.

Valve Performance

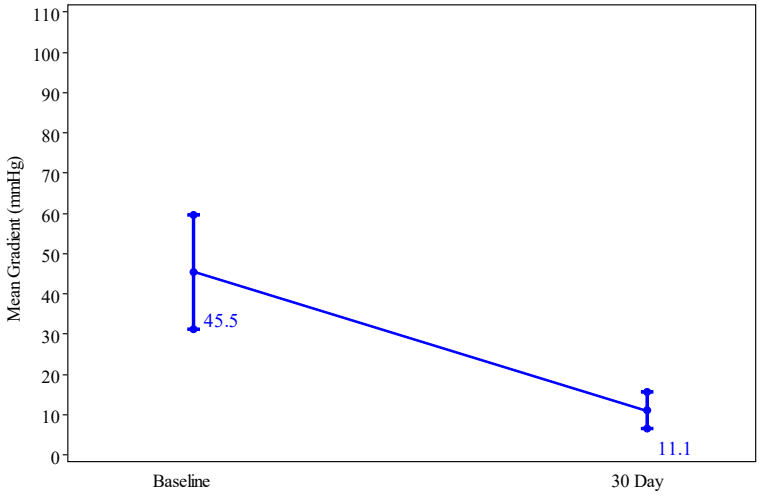
The mean EOA increased from 0.7 ± 0.2 cm^2 at baseline to 1.6 ± 0.4 cm^2 at 30 days, as shown in Figure 10.

Figure 10:
Effective Orifice Area
(PIIS3HR VI Population)



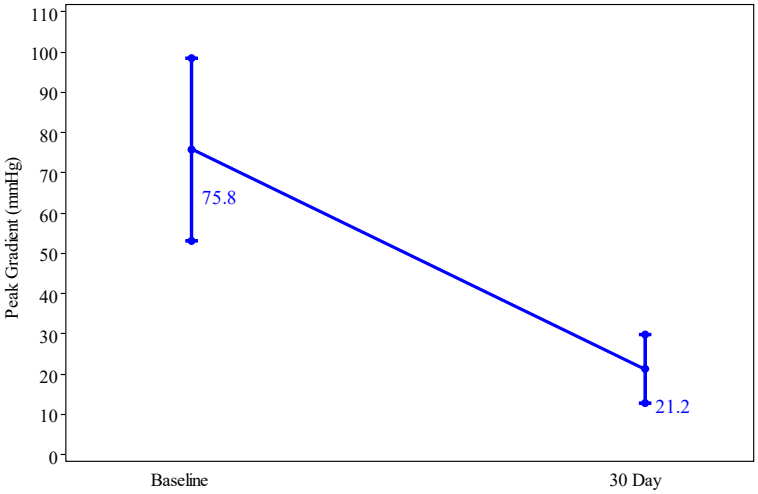
The average mean gradient decreased from 45.5 ± 14.3 mmHg at baseline to 11.1 ± 4.5 mmHg at 30 days, as shown in Figure 11.

Figure 11:
Mean Gradient
(PIIS3HR VI Population)



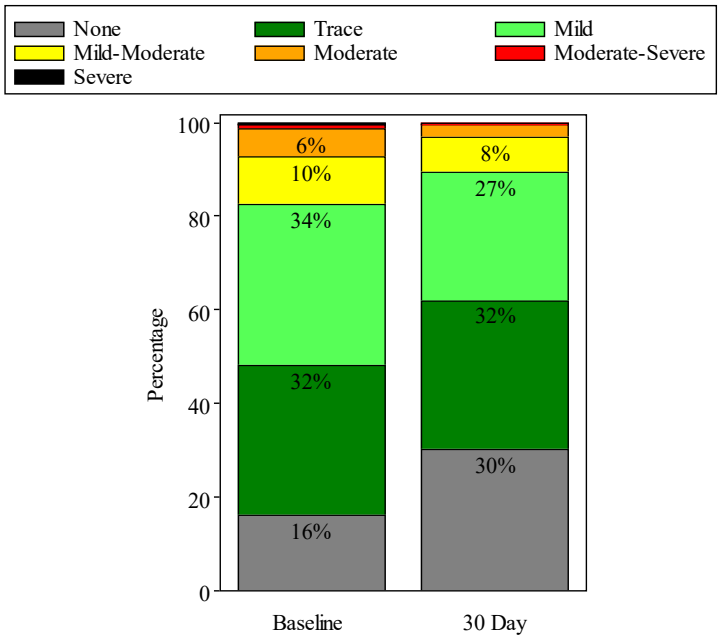
The mean peak gradient decreased from 75.8 ± 22.6 mmHg at baseline to 21.2 ± 8.5 mmHg at 30 days, as shown in Figure 12.

Figure 12:
Peak Gradient
(PIIS3HR VI Population)



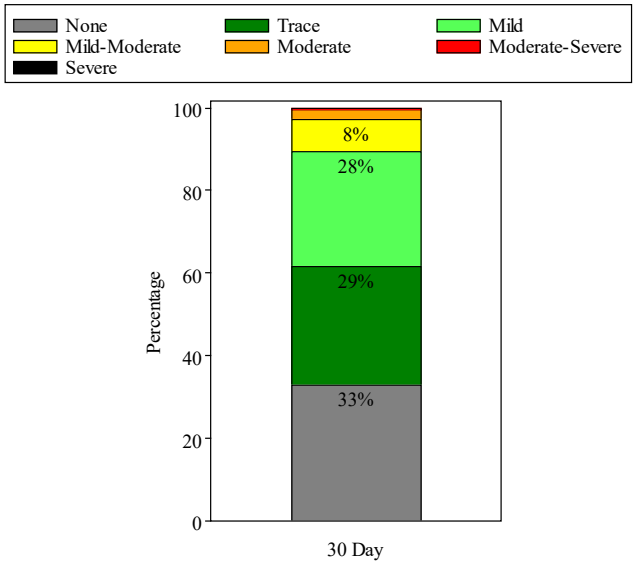
The proportion of patients with AI ≥ moderate was 7.3% at baseline and 3.0% at 30 days, as shown in Figure 13.

Figure 13:
Aortic Insufficiency
(PIIS3HR VI Population)



The proportion of patients with aortic paravalvular leak (PVL) ≥ moderate was 2.9% at 30 days, as shown in Figure 14.

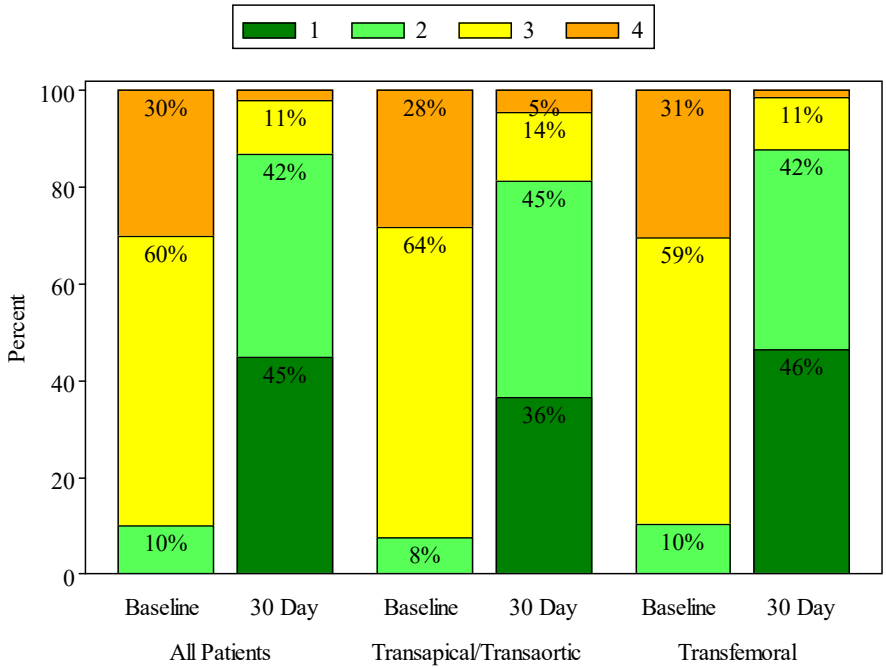
Figure 14:
Aortic Paravalvular Leak
(PIIS3HR VI Population)



NYHA

The NYHA class by visit is shown in Figure 15. For all patients, the mean NYHA class was 3.2 ± 0.6 at baseline and 1.7 ± 0.7 at 30 days.

Figure 15:
NYHA Class by Visit
(PIIS3HR VI Population)



Six Minute Walk Test (6MWT)

The improvement in mean 6MWT distance was 38.5 ± 110.2 meters from baseline to 30 days for all patients, 42.6 ± 107.8 meters for all TF patients, and 15.9 ± 121.2 meters for all TA/TAo patients.

Length of Stay (LoS)

The overall mean LoS was 6.8 ± 4.8 days, which included 3.0 ± 2.7 days in the ICU. The mean LoS was 6.1 ± 4.3 days (including 2.7 ± 2.3 days in the ICU) for the TF patients and 10.4 ± 5.4 days (including 4.8 ± 3.9 days in the ICU) for the TA/TAo patients.

Quality of Life (QoL)

QoL was measured using the visual analog scale (VAS) of the EuroQoL (EQ-5D) measure. The VAS is a self-assessment in which patients rate their well-being on a scale from 0 to 100 where 0 is the worst state they can imagine and 100 is the best state. During the trial, the mean improvement in VAS scale from baseline to 30 days was 14.6 ± 22.2 for all patients, 15.1 ± 21.5 for the TF patients, and 11.5 ± 25.7 for the TA/TAo patients.

Additional QoL instruments

The mean overall Kansas City Cardiomyopathy Questionnaire (KCCQ) summary score was 46.9 ± 22.6 at baseline, and 67.5 ± 22.6 at 30 days for the entire VI population. Except for self-efficacy which showed a small improvement, moderate to large improvements were observed in all other subscores at 30 days. In general, improvements in the TF patients were slightly larger compared to those observed in the TA/TAo patients.

Using the SF-36 norm based questionnaire, the physical component score for all patients improved from 32.0 ± 8.9 at baseline to 37.1 ± 9.7 at 30 days, and the mental component score improved from 46.9 ± 12.8 at baseline to 50.0 ± 12.5 at 30 days. In the TF patients, the physical component score improved from 31.8 ± 8.7 at baseline to 37.3 ± 9.8 at 30 days, and the mental component score improved from 46.8 ± 13.1 at baseline to 50.5 ± 12.2 at 30 days. In the TA/TAo patients, the physical component score improved from 32.9 ± 10.0 at baseline to 35.9 ± 9.4 at 30 days, and the mental component scores were 47.2 ± 11.1 at baseline and 47.2 ± 14.0 at 30 days.

SUMMARY OF SUPPLEMENTAL CLINICAL INFORMATION

Supplemental Clinical Study Design

Supplemental clinical data came from a study (referred to as “S3OUS” hereafter) conducted in Europe and Canada.

The S3OUS study was a non-randomized, prospective, multi-center study in inoperable, high surgical risk, and intermediate surgical risk patients who underwent implantation of the 23, 26, or 29 mm SAPIEN 3 valve.

Except the intermediate surgical risk patients, the inclusion/exclusion criteria of the S3OUS trial were largely similar to those of the PIIS3HR trial. The S3OUS study had a minimum age requirement (≥ 75 years) and the upper limit for AVA was higher (< 1 cm^2 instead of ≤ 0.80 cm^2). Additionally, the S3OUS study included BAV within 30 days of the procedure (unless BAV was a bridge to procedure), patients with planned concomitant surgical or transcatheter ablation for atrial fibrillation, hemodynamic or respiratory instability requiring inotropic support, mechanical ventilation or mechanical heart assistance within 30 days of screening; and the need for emergency surgery for any reason. Furthermore, the exclusion criteria in the S3OUS study excluded senile dementia and any neurologic disease which severely affected the ability to walk or perform everyday activities, and shortened the time interval regarding confirmed stroke or TIA (within 3 months instead of 6 month of the procedure). The follow-up periods were discharge or 7 days, whichever comes first, 30 days, 1 year, and annually thereafter to a minimum of 5 years post procedure.

Patient Accountability

Patients were treated at 14 investigational sites. Note that the intermediate risk patients enrolled in the S3OUS study were excluded from the analysis presented herein. The database included 102 "all treated" (AT) inoperable and high surgical risk patients. "All treated" population is defined to include all patients who were enrolled in the trial and for whom the study valve implantation procedures were started (i.e., the anesthesia was started).

One patient was excluded from the VI population. This patient experienced an aortic root rupture caused by displacement of a large lump of calcium with sharp edges through the native aortic annulus following balloon expansion of the SAPIEN 3 valve. The patient was subsequently converted to SAVR. After the patient was weaned off cardio-pulmonary bypass, bleeding in the region of the dorsal root occurred, and the patient died on the operating table.

A total of 56 patients were successfully implanted with a SAPIEN 3 valve via the transfemoral access route, and 45 via the transapical/transaortic access route, as shown in Table 16.

Table 16:
Patient Accountability (S3OUS)

SAPIEN 3 Valve Overall		SAPIEN 3 Valve Transfemoral Access		SAPIEN 3 Valve Non-Transfemoral Access	
All Treated (AT) Population	**Valve Implant (VI) Population**	**All Treated (AT) Population**	**Valve Implant (VI) Population**	**All Treated (AT) Population**	**Valve Implant (VI) Population**
102	101	57	56	45	45

All Treated (AT) Population consists of all patients who were enrolled in the trial and for whom the study valve implantation procedures were started (i.e., anesthesia was started).

Valve Implant (VI) Population consists of all enrolled patients who received a SAPIEN 3 valve, and retained the valve upon leaving the catheterization laboratory/hybrid suite.

Study Population Demographics and Baseline Parameters

The demographics of the S3OUS study population are shown in Table 17.

Table 17:
Patient Demographics and Baseline Characteristics
(S3OUS AT Population)

Demographics and Baseline Characteristics	SAPIEN 3 Valve Overall (N = 102)	SAPIEN 3 Valve Transfemoral Access (N = 57)	SAPIEN 3 Valve Non-Transfemoral Access (N = 45)
Age, yr	84.1 ± 5.0	85.1 ± 4.6	83.0 ± 5.3
Male sex, no.(%)	40 (39.2%)	23 (40.4%)	17 (37.8%)
STS score	8.0 ± 4.7	8.2 ± 4.2	7.9 ± 5.2
Logistic EuroSCORE	24.1 ± 13.0	22.3 ± 11.3	26.4 ± 14.7
New York Heart Association (NYHA) class, no.(%):			
I/II	11 (10.8%)	6 (10.5%)	5 (11.1%)
III/IV	91 (89.2%)	51 (89.5%)	40 (88.9%)
Coronary artery disease, no.(%)	68 (66.7%)	36 (63.2%)	32 (71.1%)
Previous myocardial infarction, no.(%)	20 (19.6%)	7 (12.3%)	13 (28.9%)
Previous intervention, no.(%)			
Coronary-artery bypass grafting (CABG)	24 (23.5%)	10 (17.5%)	14 (31.1%)
Percutaneous coronary intervention (PCI)	34 (33.3%)	16 (28.1%)	18 (40.0%)
Prior aortic valvuloplasty	10 (9.8%)	8 (14.0%)	2 (4.4%)
Stroke, no.(%)	7 (6.9%)	4 (7.0%)	3 (6.7%)
Peripheral vascular disease, no.(%)	27 (26.5%)	10 (17.5%)	17 (37.8%)
Chronic obstructive pulmonary disease (COPD), no.(%):			
Any	25 (24.5%)	13 (22.8%)	12 (26.7%)
Oxygen-dependent	1 (1.0%)	1 (1.8%)	0 (0%)
Atrial fibrillation, no.(%)	48 (47.1%)	22 (38.6%)	26 (57.8%)
Permanent pacemaker, no.(%)	15 (14.7%)	7 (12.3%)	8 (17.8%)
Severe pulmonary hypertension, no.(%)	10 (9.8%)	6 (10.5%)	4 (8.9%)
Severe liver disease / Cirrhosis, no.(%)	1 (1.0%)	1 (1.8%)	0 (0%)
Echocardiographic findings			
Effective Orifice Area (EOA), cm^2	0.6 ± 0.2	0.6 ± 0.2	0.6 ± 0.1
Mean aortic-valve gradient, mmHg	44.8 ± 15.3	45.2 ± 14.7	44.2 ± 16.1
Mean left ventricular ejection fraction (LVEF), %	56.7 ± 9.1	57.7 ± 9.3	55.3 ± 8.7
Moderate or severe mitral regurgitation, no./total no. (%)	23/85 (27.1%)	9/48 (18.8%)	14/37 (37.8%)

Plus–minus values are means ± SD.

Safety and Effectiveness Results

Key Adverse Events

Key adverse events as adjudicated by the CEC are presented in Table 18.

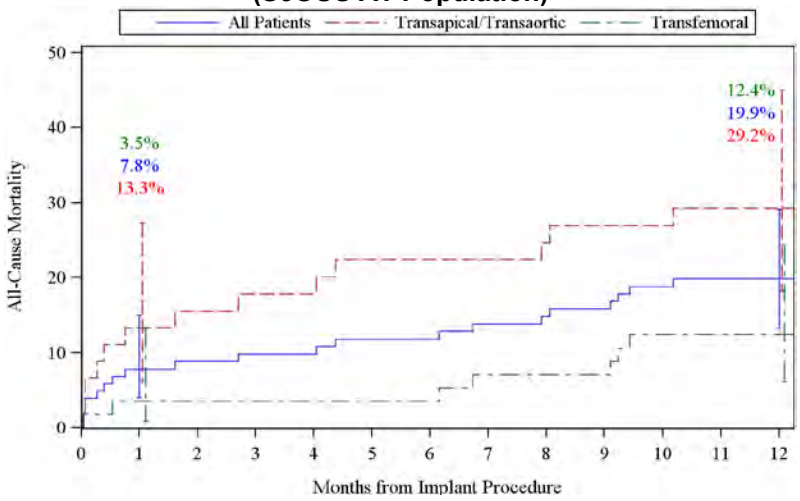
Table 18:
CEC Adjudicated Adverse Events at 1 Year
(S3OUS AT Population)

	30 Day			1 Year		
Outcomes	**SAPIEN 3 Valve Overall**	**SAPIEN 3 Valve Transfemoral Access**	**SAPIEN 3 Valve Non-Transfemoral Access**	**SAPIEN 3 Valve Overall**	**SAPIEN 3 Valve Transfemoral Access**	**SAPIEN 3 Valve Non-Transfemoral Access**
Composite Event Rate of Death, All Stroke and AI ≥ Moderate, n/N (%)	13/88 (14.8%)	3/50 (6.0%)	10/38 (26.3%)	25/82 (30.5%)	9/47 (19.1%)	16/35 (45.7%)
Death						
From any death, n/N (%)	8/102 (7.8%)	2/57 (3.5%)	6/45 (13.3%)	20/102 (19.6%)	7/57 (12.3%)	13/45 (28.9%)
From cardiovascular cause, n/N (%)	7/102 (6.9%)	2/57 (3.5%)	5/45 (11.1%)	9/102 (8.8%)	2/57 (3.5%)	7/45 (15.6%)
Stroke, n/N (%)	3/102 (2.9%)	1/57 (1.8%)	2/45 (4.4%)	5/102 (4.9%)	2/57 (3.5%)	3/45 (6.7%)
Aortic Insufficiency (AI) ≥ Moderate, n/N (%)	3/81 (3.7%)	1/49 (2.0%)	2/32 (6.3%)	1/62 (1.6%)	1/40 (2.5%)	0/22 (0.0%)
Disabling Stroke, n/N (%)	0/102 (0.0%)	0/57 (0.0%)	0/45 (0.0%)	1/102 (1.0%)	1/57 (1.8%)	0/45 (0.0%)
Myocardial Infarction, n/N (%)	2/102 (2.0%)	2/57 (3.5%)	0/45 (0.0%)	3/102 (2.9%)	2/57 (3.5%)	1/45 (2.2%)
Major Vascular Complications, n/N (%)	5/102 (4.9%)	1/57 (1.8%)	4/45 (8.9%)	N/A	N/A	N/A
Acute Kidney Injury - Stage III, n/N (%)	0/102 (0.0%)	0/57 (0.0%)	0/45 (0.0%)	N/A	N/A	N/A
Disabling Bleeding Event, n/N (%)	6/102 (5.9%)	3/57 (5.3%)	3/45 (6.7%)	N/A	N/A	N/A
Valve Dysfunction Requiring Intervention, n/N (%)	0/102 (0.0%)	0/57 (0.0%)	0/45 (0.0%)	N/A	N/A	N/A
Prosthetic Valve Endocarditis, n/N (%)	0/102 (0.0%)	0/57 (0.0%)	0/45 (0.0%)	1/102 (1.0%)	0/57 (0.0%)	1/45 (2.2%)
Conduction Abnormality Requiring Pacemaker, n/N (%)	14/102 (13.7%)	7/57 (12.3%)	7/45 (15.6%)	14/102 (13.7%)	7/57 (12.3%)	7/45 (15.6%)

The composite adverse event rate involving all-cause mortality, all stroke, and AI ≥ moderate at 30 days for all patients is higher in the S3OUS cohort than PIIS3HR cohort (14.8% vs. 6.8%). This disparity is due to the composition of the study populations, specifically the S3OUS cohort comprises 44.1% TA/TAo patients vs. 15.8% TA/TAo patients in the PIIS3HR cohort. Note, the composite adverse event rate at 30 days for TF patients was similar, specifically, 6.0% in the S3OUS cohort and 5.8% in the PIIS3HR cohort.

The K-M estimates for all-cause mortality for all patients, the TF patients, and the TA/TAo patients are shown in Figure 16.

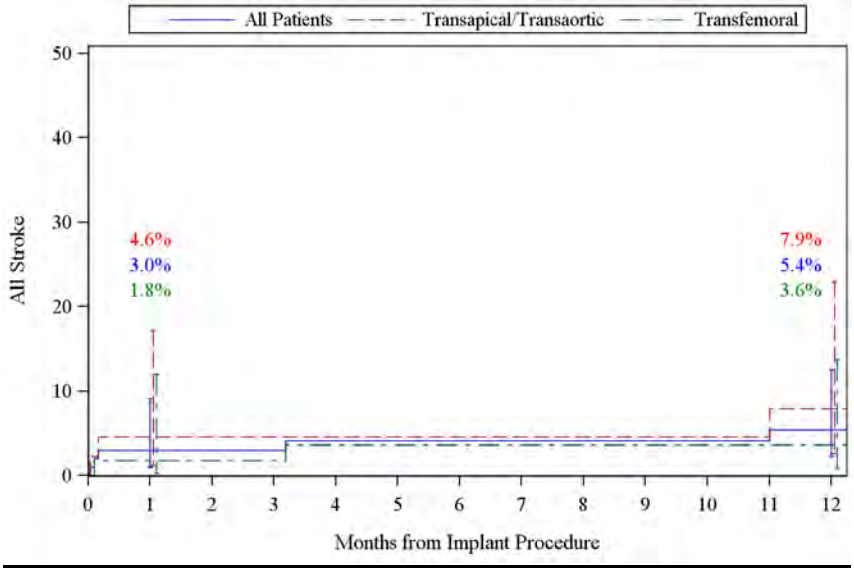
Figure 16:
All-Cause Mortality at 1 Year
(S3OUS AT Population)



Note: The confidence intervals are calculated without multiplicity adjustment. The adjusted confidence intervals could be wider than presented here. As such, confidence intervals are provided to illustrate the variability only and should not be used to draw any statistical conclusion.

The K-M estimates for the stroke rate for all patients, the TF patients, and the TA/TAo patients are shown in Figure 17.

Figure 17:
All Stroke at 1 Year
(S3OUS AT Population)

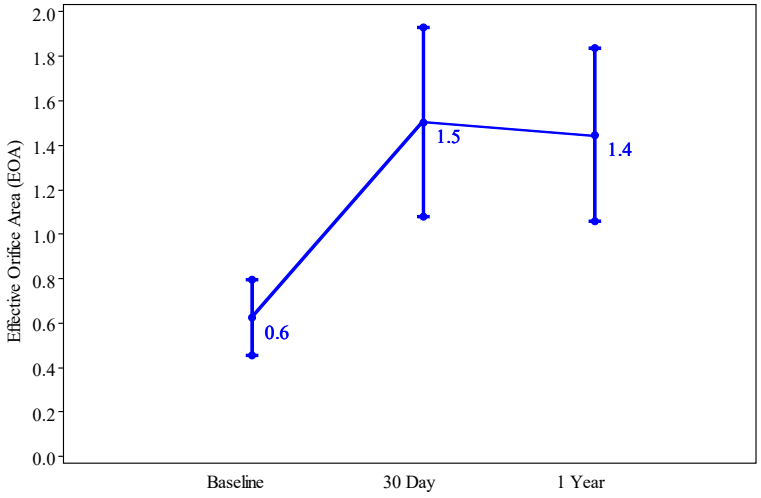


Note: The confidence intervals are calculated without multiplicity adjustment. The adjusted confidence intervals could be wider than presented here. As such, confidence intervals are provided to illustrate the variability only and should not be used to draw any statistical conclusion.

Valve Performance

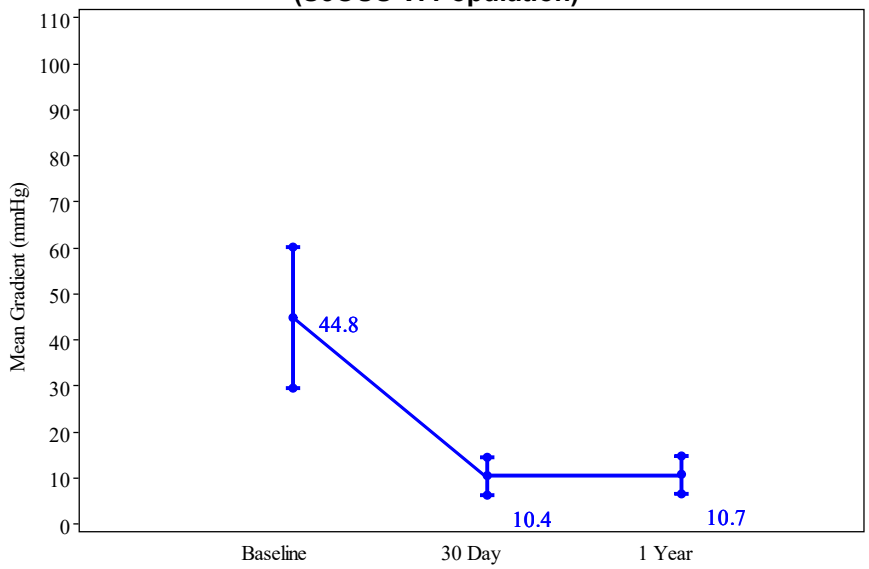
The mean EOA increased from 0.6 ± 0.2 cm^2 at baseline to 1.5 ± 0.4 cm^2 at 30 days and 1.4 ± 0.4 cm^2 at 1 year, as shown in Figure 18.

Figure 18:
Effective Orifice Area
(S3OUS VI Population)



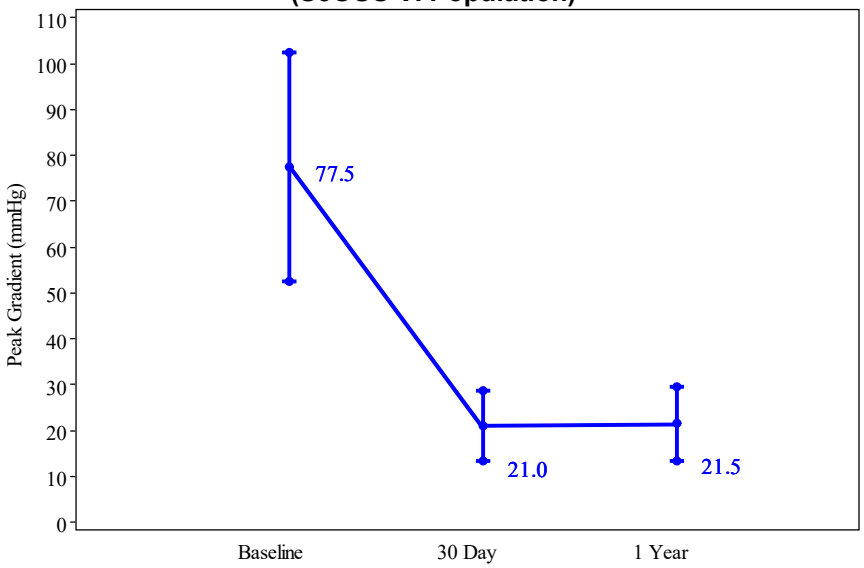
The average mean gradient decreased from 44.8 ± 15.4 mmHg at baseline to 10.4 ± 4.1 mmHg at 30 days and maintained at 10.7 ± 4.1 mmHg at 1 year, as shown in Figure 19.

Figure 19:
Mean Gradient
(S3OUS VI Population)



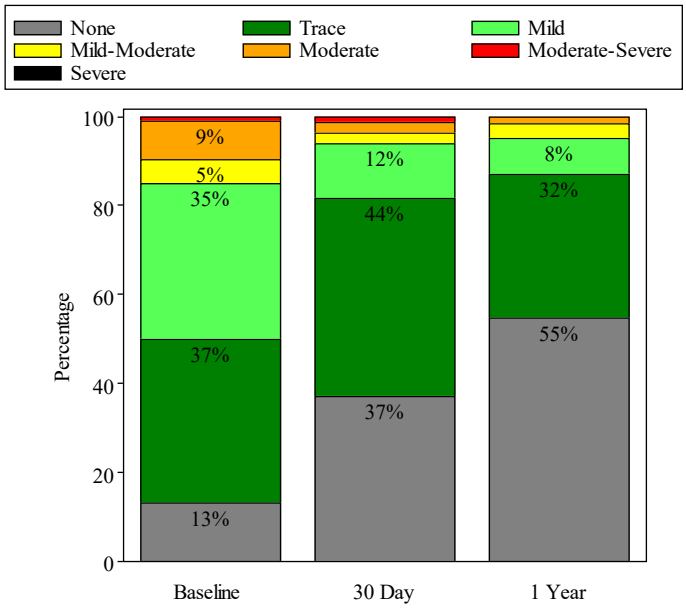
The mean peak gradient decreased from 77.5 ± 24.9 mmHg at baseline to 21.0 ± 7.7 mmHg at 30 days, and maintained at 21.5 ± 8.2 mmHg at 1 year, as shown in Figure 20.

Figure 20:
Peak Gradient
(S3OUS VI Population)



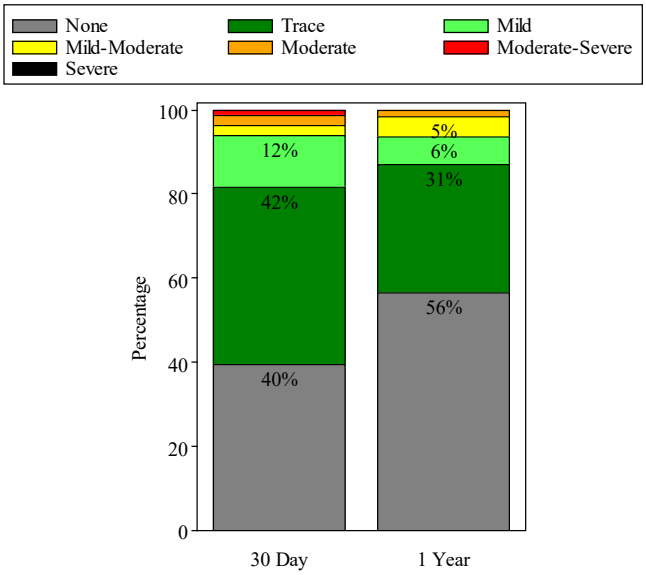
The proportion of patients with aortic insufficiency ≥ moderate was 9.8% at baseline, 3.7% at 30 days, and 1.6% at 1 year, as shown in Figure 21.

Figure 21:
Aortic Insufficiency
(S3OUS VI Population)



The proportion of patients with aortic PVL ≥ moderate was 3.7% at 30 days, and 1.6% at 1 year, as shown in Figure 22.

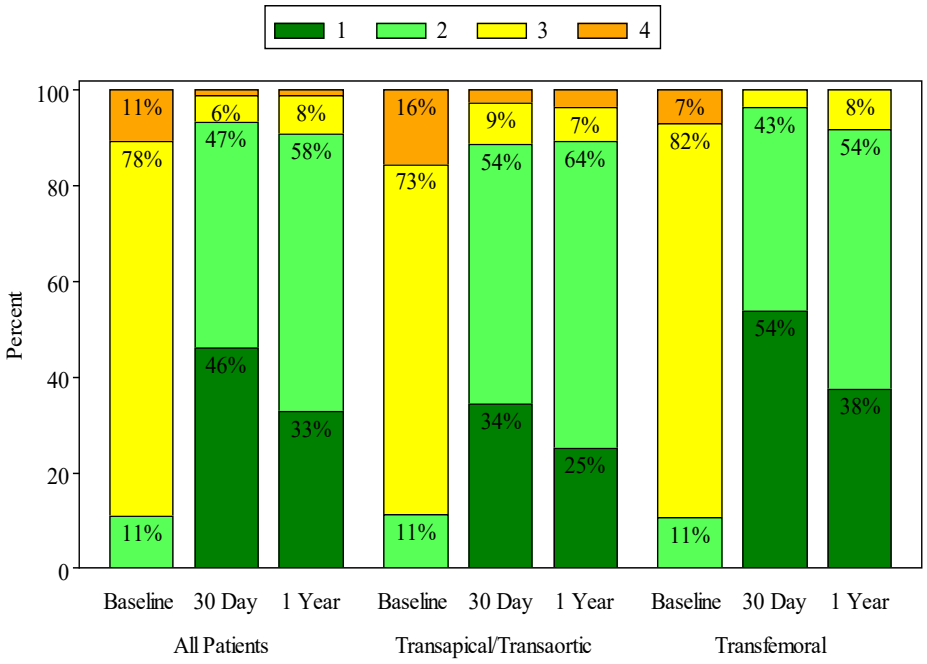
Figure 22:
Aortic Paravalvular Leak
(S3OUS VI Population)



NYHA

The NYHA class by visit is shown in Figure 23. For all patients, the mean NYHA class decreased from 3.0 ± 0.5 at baseline to 1.6 ± 0.7 at 30 days and 1.8 ± 0.6 at 1 year.

Figure 23:
NYHA Class by Visit
(S3OUS AT Population)



PARTNER II SAPIEN 3 INTERMEDIATE RISK COHORT

Patient Accountability

At the time of database lock, of the 1078 patients enrolled in the PMA study (PIIS3i), 99.2% (1069) patients are available for analysis at the completion of the study, the 1-year post-operative visit. Table 19 presents patient accountability in the PIIS3i and PIIA-SAVR cohorts. Of the 1,074 eligible patients (Eligible Patient or EP Population) in PIIS3i, 1,069 were successfully implanted with a SAPIEN 3 valve and constitute the PIIS3i Valve Implant (VI) population. Among the VI population, 943 patients were implanted via the transfemoral (TF) access route, and 126 patients via a non-transfemoral (non-TF; mainly transapical and transaortic) access route. Of the 938 eligible patients in the PIIA-SAVR cohort, 936 were successfully implanted with a surgical valve and constitute the PIIA-SAVR VI population.

Table 19:
Patient Accountability

	All Enrolled Patients	Eligible Patient (EP) Population*	Valve Implant (VI) Population†
SAPIEN 3 Cohort	1078	1074	1069
TF	952	948	943
Non-TF	126	126	126
PIIA SAVR	1021	938	936

* Eligible Patient (EP) Population consists of all enrolled patients who were determined eligible after screening, entered into the catheterization laboratory and remained eligible to receive the assigned implant.
† Valve Implant (VI) Population is a subset of the EP Population who received the assigned valve, and retained the valve upon leaving the catheterization laboratory.

Study Population Demographics and Baseline Parameters

The demographics of the study population are typical for an aortic stenosis valve replacement study performed in the US, as summarized in Table 20 for the PIIS3i and PIIA-SAVR EP populations.

Table 20:
Patient Demographics and Baseline Characteristics of the EP Population

Demographics & Characteristics*	SAPIEN 3 Valve			PIIA-SAVR (N = 938)
	Overall (N = 1074)	TF Only (N = 948)	Non-TF Only (N = 126)	
Age – years	81.9 ± 6.60	82.1 ± 6.57	80.7 ± 6.69	81.6 ± 6.73
Male sex	662/1074 (61.6%)	577/948 (60.9%)	85/126 (67.5%)	514/938 (54.8%)
Society of Thoracic Surgeons (STS) score	5.3 ± 1.29	5.3 ± 1.29	5.6 ± 1.28	5.8 ± 1.92
New York Heart Association (NYHA) class				
I/II	294/1074 (27.4%)	262/948 (27.6%)	32/126 (25.4%)	225/937 (24.0%)
III/IV	780/1074 (72.6%)	686/948 (72.4%)	94/126 (74.6%)	712/937 (76.0%)
Coronary artery disease	748/1074 (69.6%)	652/948 (68.8%)	96/126 (76.2%)	623/938 (66.4%)
Previous myocardial infarction	172/1074 (16.0%)	133/948 (14.0%)	39/126 (31.0%)	166/938 (17.7%)
Previous intervention				
Coronary artery bypass grafting (CABG)	301/1074 (28.0%)	248/948 (26.2%)	53/126 (42.1%)	241/938 (25.7%)
Percutaneous coronary intervention (PCI)	344/1074 (32.0%)	299/948 (31.5%)	45/126 (35.7%)	254/938 (27.1%)

Demographics & Characteristics*	SAPIEN 3 Valve			PIIA-SAVR (N = 938)
	Overall (N = 1074)	TF Only (N = 948)	Non-TF Only (N = 126)	
Prior aortic valvuloplasty	55/1074 (5.1%)	51/948 (5.4%)	4/126 (3.2%)	45/938 (4.8%)
Cerebral vascular accident (CVA)	97/1074 (9.0%)	81/948 (8.5%)	16/126 (12.7%)	96/938 (10.2%)
Peripheral vascular disease	304/1074 (28.3%)	231/948 (24.4%)	73/126 (57.9%)	301/938 (32.1%)
Chronic obstructive pulmonary disease (COPD)				
Any	321/1072 (29.9%)	270/946 (28.5%)	51/126 (40.5%)	279/932 (29.9%)
Oxygen-dependent	53/1067 (5.0%)	46/942 (4.9%)	7/125 (5.6%)	26/925 (2.8%)
Atrial fibrillation	385/1074 (35.8%)	342/948 (36.1%)	43/126 (34.1%)	326/938 (34.8%)
Permanent pacemaker	142/1074 (13.2%)	121/948 (12.8%)	21/126 (16.7%)	113/938 (12.0%)
Severe pulmonary hypertension	25/1074 (2.3%)	19/948 (2.0%)	6/126 (4.8%)	N/A
Frailty	92/1074 (8.6%)	86/948 (9.1%)	6/126 (4.8%)	15/938 (1.6%)
Porcelain aorta	1/1074 (0.1%)	1/948 (0.1%)	0/126 (0.0%)	0/938 (0.0%)
Chest deformities that preclude an open chest procedure	1/1074 (0.1%)	1/948 (0.1%)	0/126 (0.0%)	0/938 (0.0%)
Cirrhosis	4/1074 (0.4%)	4/948 (0.4%)	0/126 (0.0%)	4/938 (0.4%)
Echocardiographic findings (Valve Implant Population)				
Effective orifice area (EOA) - cm^2	0.7 ± 0.17	0.7 ± 0.16	0.7 ± 0.18	0.7 ± 0.20
Mean aortic-valve gradient – mmHg	46.1 ± 12.63	46.1 ± 12.66	45.8 ± 12.47	44.7 ± 12.55
Mean left ventricular ejection fraction (LVEF) %	58.5 ± 13.36	58.8 ± 13.24	56.0 ± 14.05	55.4 ± 11.75
Moderate or severe mitral regurgitation	91/1033 (8.8%)	87/909 (9.6%)	4/124 (3.2%)	153/841 (18.2%)

*Continuous measures - Mean ± SD; Categorical measures – n/total no. (%)

Safety and Effectiveness Results

Primary Endpoints

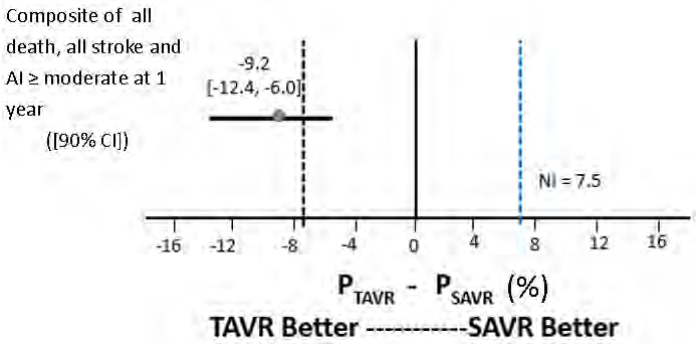
The primary endpoint was a composite of all-cause death, stroke, and AI ≥ moderate at 1 year. The weighted proportion difference of the primary endpoint was -9.2% (90% CI: [-12.4%, -6.0%]) using the average treatment effect on the treated (ATT) method[3], as shown in Table 21 and Figure 24. Since the upper limit of the CI was < 7.5%, non–inferiority was met.

Table 21:
Primary Endpoint Non-Inferiority Test
(VI Population)

	Observed Event rate		Propensity Score Quintile Pooled Proportion Difference (ATT Method*) [90% CI]†	Margin	Conclusion for Non-Inferiority Test
	SAPIEN 3 (N = 1069)	PIIA-SAVR (N = 936)			
Composite of all-cause death, all stroke, and aortic insufficiency (AI) ≥ moderate at 1 year	13.0%	23.2%	-9.2% [-12.4%, -6.0%]	7.5%	Pass

* ATT: average treatment effect on the treated
† Two-sided 90% Wald-type confidence interval

Figure 24:
Forest Plot – Composite of All Death, All Stroke and AI ≥ Moderate
(VI Population)



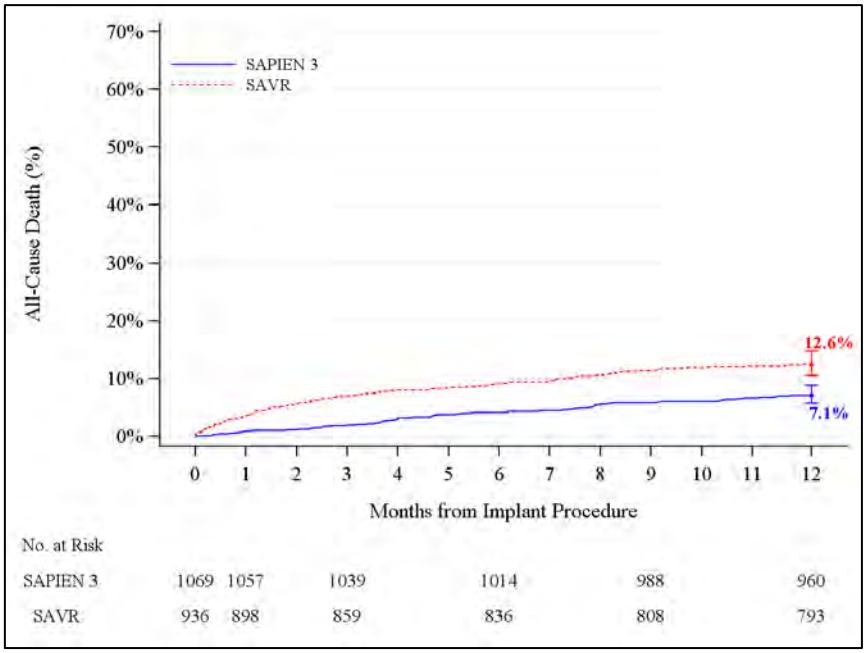
The Kaplan-Meier (KM) estimates for all-cause death and all stroke at 1 year for the PIIS3i cohort and the PIIA-SAVR cohort are provided in Table 22, as well as Figures 25 and 26, respectively.

Table 22:
All-Cause Death and All Stroke at 1 Year
(VI Population)

	SAPIEN 3 Valve (N = 1069)			PIIA-SAVR (N = 936)			Propensity Score Quintile Pooled Proportion Difference (ATT Method†)
Endpoints	Observed Event Rate	Kaplan-Meier Event Rate* Point Estimate	Kaplan-Meier Event Rate* Standard Error	Observed Event Rate	Kaplan-Meier Event Rate* Point Estimate	Kaplan-Meier Event Rate* Standard Error	
All-cause death at 1 year	7.0%	7.1%	0.79%	12.4%	12.6%	1.09%	-5.2%
All stroke at 1 year	4.5%	4.6%	0.65%	7.9%	8.1%	0.91%	-3.5%

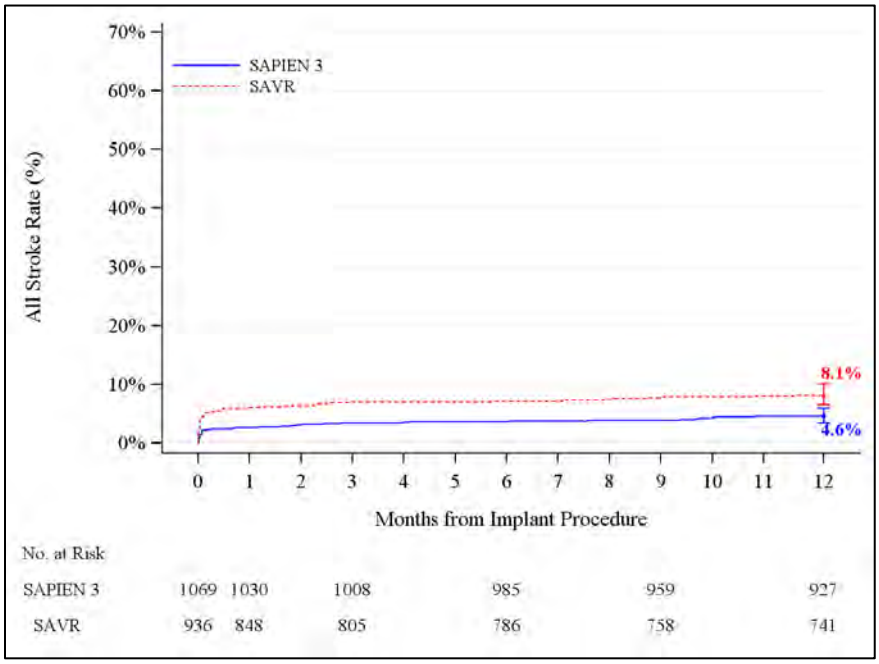
* Kaplan-Meier estimates were calculated at 365 days and included only the first event for each patient. Events occurring after 365 days were not included in this analysis.
† ATT: average treatment effect on the treated

Figure 25:
All-Cause Death through 1 Year
(VI Population)



Note: The confidence intervals were calculated without multiplicity adjustment. The adjusted confidence intervals could be wider than presented here. As such, the confidence intervals are provided to illustrate the variability only and should not be used to draw any statistical conclusion.

Figure 26:
All Stroke through 1 Year
(VI Population)



Note: The confidence intervals were calculated without multiplicity adjustment. The adjusted confidence intervals could be wider than presented here. As such, the confidence intervals are provided to illustrate the variability only and should not be used to draw any statistical conclusion.

The proportion of patients with AI ≥ moderate at 1 year was 1.6% for the PIIS3i cohort and 0.3% for the PIIA-SAVR cohort, as shown in Table 23.

Table 23:
Aortic Insufficiency (AI) ≥ Moderate at 1 Year (VI Population)

	Observed Event Rate		Propensity Score Quintile Pooled Proportion Difference (ATT Method*)
	SAPIEN 3 Valve (N = 1069)	SAVR (N = 936)	
Aortic insufficiency (AI) ≥ moderate	1.6%	0.3%	1.2%

* ATT: average treatment effect on the treated

Secondary Endpoints

The secondary endpoints were examined in a pre-specified order adjusted for the propensity quintiles using the ATT method. Table 24 summarizes the statistical conclusions on the non-inferiority hypothesis testing of the five secondary endpoints for labeling that were evaluated using a gatekeeping/hierarchical multiplicity adjustment procedure to control the overall type I error to 0.05. For each secondary endpoint, the upper limit of the confidence interval was less than the respective non-inferiority margin. Therefore, for each of the secondary endpoints for labeling, the SAPIEN 3 valve was non-inferior to SAVR.

Table 24:
Secondary Endpoints for Labeling – Gatekeeping/Hierarchical Method
(VI Population)

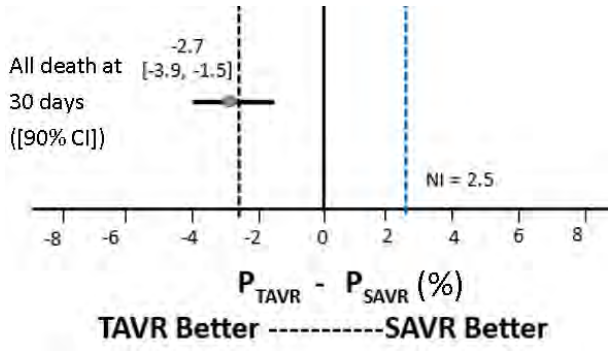
Pre-Specified Order for Gatekeeping/ Hierarchical Method	Endpoints	Observed Event Rate		Weighted Proportion Difference in Average Treatment Effect on the Treated [90% CI]†	Margin	Conclusion for Non-Inferiority Test
		SAPIEN 3 Valve (N = 1069)	PIIA-SAVR (N = 936)			
No. 1	Composite of all death, all strokes, life threatening (disabling)/ major bleeding and major vascular complication at 30 days	18.3%	79.4%	-60.5% [-63.5%, -57.4%]	7.5%	Pass
No. 2	Major vascular and access complications through 30 days	5.8%	5.3%	0.3% [-1.5%, 2.0%]	5.0%	Pass
No. 3	Life threatening (disabling)/ major bleeding through 30 days	14.6%	78.2%	-63.2% [-66.2%, -60.2%]	5.0%	Pass
No. 4	All-cause death through 30 days	0.9%	3.7%	-2.7% [-3.9%, -1.5%]	2.5%	Pass

Pre-Specified Order for Gatekeeping/ Hierarchical Method	Endpoints	Observed Event Rate		Weighted Proportion Difference in Average Treatment Effect on the Treated [90% CI]†	Margin	Conclusion for Non-Inferiority Test
		SAPIEN 3 Valve (N = 1069)	PIIA-SAVR (N = 936)			
No. 5	All stroke through 30 days	2.6%	6.1%	-3.2% [-4.7%, -1.6%]	2.5%	Pass

† Two-sided 90% Wald-type confidence interval.

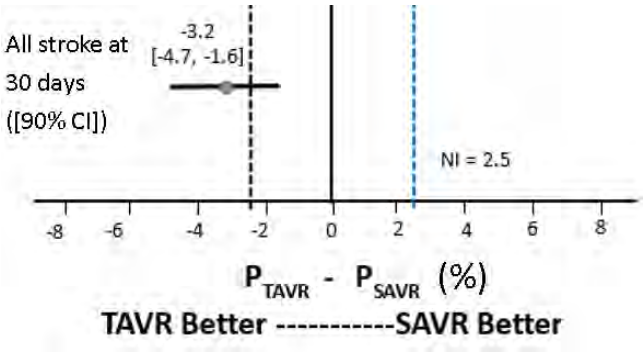
The forest plots for all-cause death and all stroke at 30 days are provided in Figures 27 and 28, respectively.

Figure 27:
Forest Plot – All-Cause Death at 30 Days (VI Population)



Note: As part of a pre-specified hierarchy, the hypothesis for this endpoint was tested using a hierarchical gatekeeping approach. The confidence interval shown here was not adjusted for multiplicity per the gatekeeping approach.

Figure 28:
Forest Plot – All Stroke at 30 Days (VI Population)



Note: As part of a pre-specified hierarchy, the hypothesis for this endpoint was tested using a hierarchical gatekeeping approach. The confidence interval shown here was not adjusted for multiplicity per the gatekeeping approach.

Adverse Events

The key CEC-adjudicated adverse events through 1 year for the EP population are presented in Table 25.

Table 25:
CEC-Adjudicated Adverse Events through 1 Year
(EP Population)

Event*	SAPIEN 3 Valve			PIIA-SAVR
	Overall	TF Only	Non-TF Only	
7 Days				
Acute kidney injury: Stage III	5/1074 (0.5%)	3/948 (0.3%)	2/126 (1.6%)	N/A
30 Days				
Death	12/1074 (1.1%)	10/948 (1.1%)	2/126 (1.6%)	35/938 (3.7%)
Cardiac death	10/1074 (0.9%)	9/948 (0.9%)	1/126 (0.8%)	26/938 (2.8%)
Non-cardiac death	2/1074 (0.2%)	1/948 (0.1%)	1/126 (0.8%)	9/938 (1.0%)
Stroke	29/1074 (2.7%)	24/948 (2.5%)	5/126 (4.0%)	57/938 (6.1%)
Major (disabling) stroke	11/1074 (1.0%)	7/948 (0.7%)	4/126 (3.2%)	41/938 (4.4%)
Minor (non-disabling) stroke	18/1074 (1.7%)	17/948 (1.8%)	1/126 (0.8%)	16/938 (1.7%)
Myocardial infarction	3/1074 (0.3%)	3/948 (0.3%)	0/126 (0.0%)	17/938 (1.8%)
Major vascular complication	65/1074 (6.1%)	60/948 (6.3%)	5/126 (4.0%)	50/938 (5.3%)
Life threatening (disabling) or major bleeding	159/1074 (14.8%)	112/948 (11.8%)	47/126 (37.3%)	733/938 (78.1%)
Aortic valve re-intervention	1/1074 (0.1%)	1/948 (0.1%)	0/126 (0.0%)	0/938 (0.0%)
Any endocarditis	2/1074 (0.2%)	2/948 (0.2%)	0/126 (0.0%)	0/938 (0.0%)
Rhythm disturbance requiring permanent pacemaker	108/1074 (10.1%)	99/948 (10.4%)	9/126 (7.1%)	68/938 (7.2%)
1 Year				
Death	79/1074 (7.4%)	61/948 (6.4%)	18/126 (14.3%)	117/938 (12.5%)
Cardiac death	47/1074 (4.4%)	37/948 (3.9%)	10/126 (7.9%)	70/938 (7.5%)
Non-cardiac death	32/1074 (3.0%)	24/948 (2.5%)	8/126 (6.3%)	47/938 (5.0%)
Stroke	49/1074 (4.6%)	40/948 (4.2%)	9/126 (7.1%)	74/938 (7.9%)
Major (disabling) stroke	24/1074 (2.2%)	16/948 (1.7%)	8/126 (6.3%)	53/938 (5.7%)
Minor (non-disabling) stroke	25/1074 (2.3%)	24/948 (2.5%)	1/126 (0.8%)	22/938 (2.3%)
Aortic valve re-intervention	6/1074 (0.6%)	6/948 (0.6%)	0/126 (0.0%)	4/938 (0.4%)
Any endocarditis	8/1074 (0.7%)	7/948 (0.7%)	1/126 (0.8%)	6/938 (0.6%)

*Categorical measures - n. / total no. (%).

In addition, site-reported new-onset atrial fibrillation was 5.9% in the PIIS3i EP population and 29.2% in the PIIA-SAVR EP population.

Bleeding Rate

The bleeding rates utilizing the number of units transfused are presented in Table 26.

Table 26:
Bleeding Rate Using Site-Reported Units Transfused (EP Population)

Event*	SAPIEN 3 Valve (N = 1074)	PIIA-SAVR (N = 938)
Transfusion units ≥ 2 and < 4	47/1074 (4.4%)	184/938 (19.6%)
Transfusion units ≥ 4	18/1074 (1.7%)	218/938 (23.2%)

*Site-reported Transfusion at Day 0 or Day 1; Categorical measures - n. / total no. (%)

Other Results

Procedural Information

In the PIIS3i EP population the mean duration in the catheterization laboratory was 187.3 ± 53.2 minutes, the mean total procedure time was 84.2 ± 40.7 minutes, and the mean total anesthesia time was 186.9 ± 61.1 minutes, all of which were slightly shorter in the TF group. General anesthesia was used in the vast majority of cases; 18.9% of the TF patients had conscious sedation. Correct positioning of the valve was achieved in 99.3% of the patients. Four (4) patients (0.4%, all TF patients) were implanted with a second valve. One (1) patient (0.1%) experienced valve embolization and two (2) patients (0.2%) experienced annular rupture.

In the PIIA-SAVR EP population, the mean duration in the operating room was 333.2 ± 96.4 min, the mean total procedure time was 237.5 ± 86.58 min, and the mean anesthesia time was 333.5 ± 108.42 min. General anesthesia was used in all patients.

Valve Performance

The measurements of EOA, mean gradient, peak gradient, total aortic regurgitation (AR), and aortic paravalvular leak (PVL) are presented in Figures 29-33. The increase in EOA and decrease in gradient were sustained at 1 year. In PIIS3i, the proportion of patients with total AR ≥ moderate was 6.2% at baseline, 3.9% at 30 days, and 1.6% at 1 year, while in PIIA-SAVR, the proportion of patients with total AR ≥ moderate was 12.0% at baseline, 0.7% at 30 days, and 0.3% at 1 year. The proportion of patients with aortic PVL ≥ moderate was 3.8% at 30 days and 1.5% at 1 year in PIIS3i, as compared to 0.5% at 30 days and 0.3% at 1 year in PIIA-SAVR.

Figure 29:
Effective Orifice Area
(VI Population)

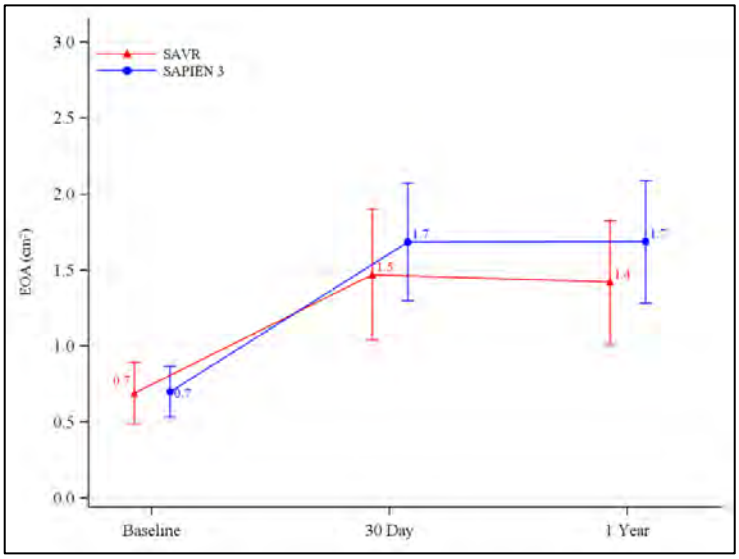


Figure 30:
Mean Gradient
(VI Population)

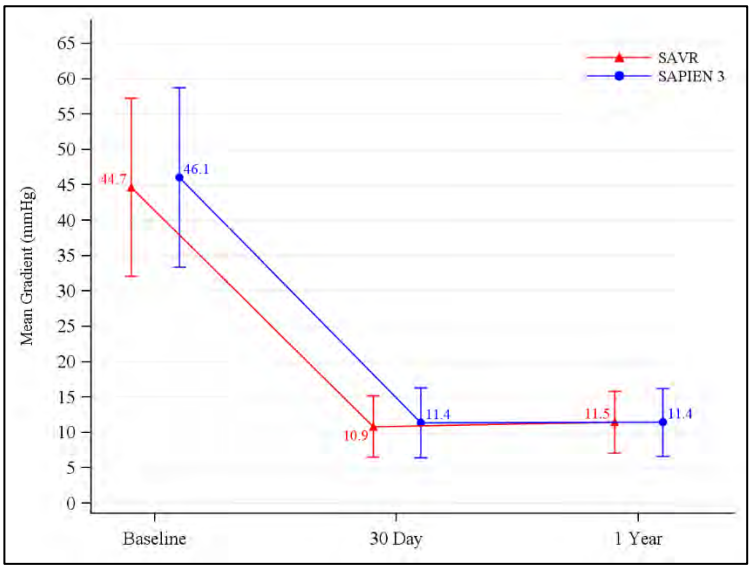


Figure 31:
Peak Gradient
(VI Population)

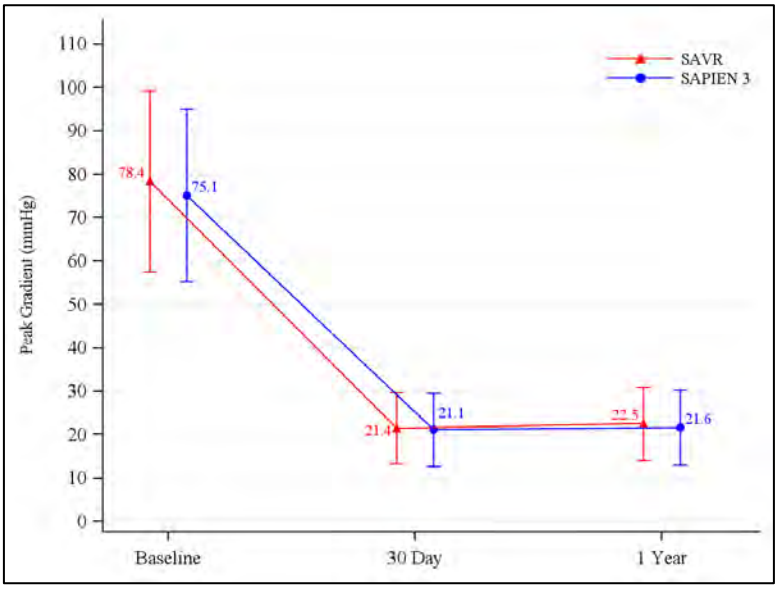


Figure 32:
Total Aortic Regurgitation
(VI Population)

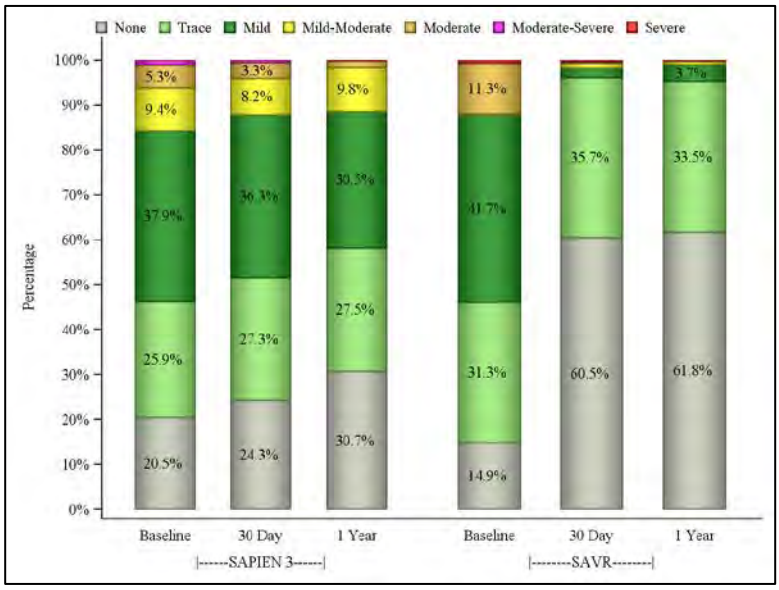
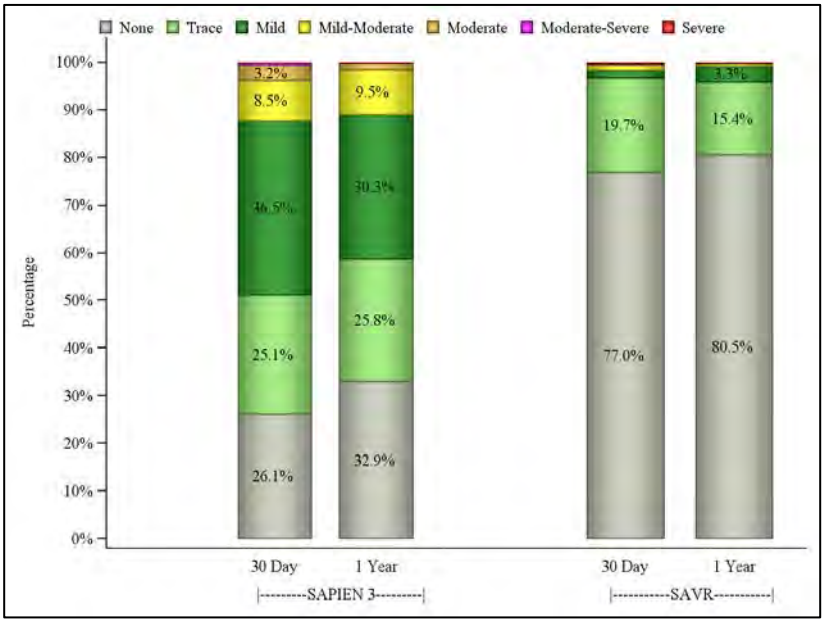


Figure 33:
Aortic Paravalvular Leak
(VI Population)



NYHA

The NYHA classifications by visit are presented in Figure 34. In PIIS3i, 72.6% of the patients were in NYHA Class III or IV at baseline, which reduced to 6.3% at 30 days and 6.7% at 1 year, while in PIIA-SAVR, the percentage of patients in NYHA Class III or IV was 76.0% at baseline, 13.6% at 30 days, and 6.7% at 1 year. A side-by-side comparison of the results by access approach is presented in Figure 35.

Figure 34:
NYHA Class by Visit
(EP Population)

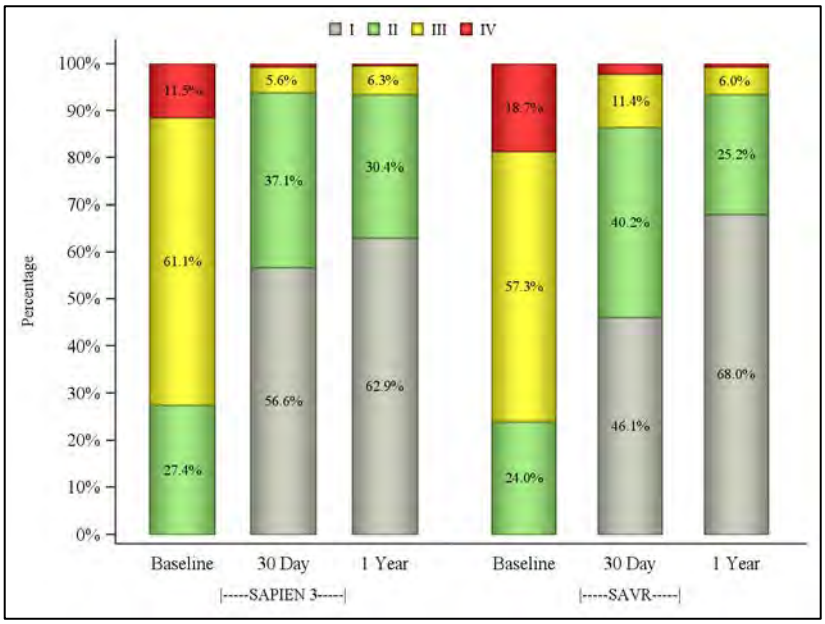
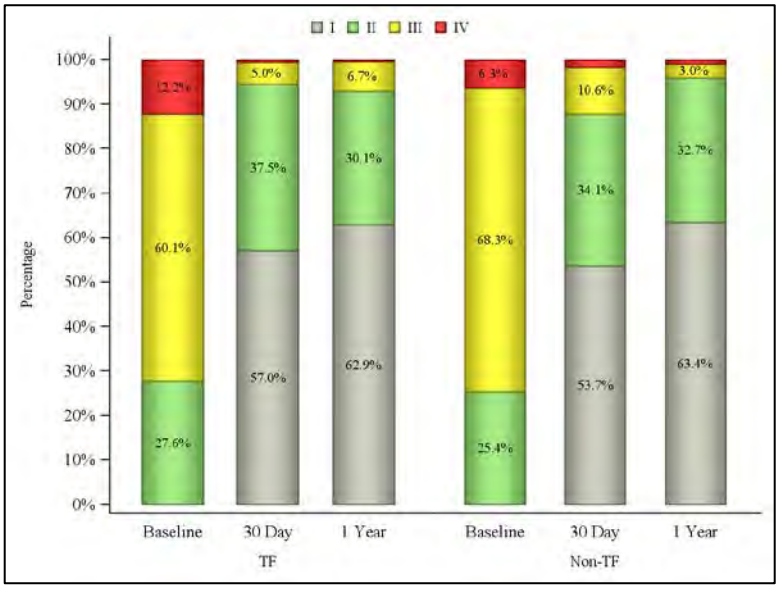


Figure 35:
NYHA Class by Visit – TF versus non-TF Access
(EP Population)



Six-Minute Walk Test (6MWT)

The improvements in mean 6MWT distance are presented in Table 27. The SAPIEN 3 valve patients had a similar increase in mean 6MWT distance from baseline to 1 year as the PIIA-SAVR patients.

Table 27:
6MWT Distance (EP Population)

6MWT Distance (m)*	SAPIEN 3 Valve			PIIA-SAVR
	All	TF	Non-TF	
Baseline	193.9 ± 118.1	194.1 ± 117.2	192.5 ± 125.5	179.3 ± 123.2
30 days	230.6 ± 126.1	234.6 ± 123.6	199.0 ± 140.6	166.7 ± 126.4

1 year	227.7 ± 134.7	230.6 ± 133.6	202.8 ± 142.1	219.2 ± 133.8

*Plus–minus values are means ± SD.

Length of Stay (LoS)

The results for LoS are presented in Table 28. Overall, the SAPIEN 3 valve patients had shorter LoS than the PIIA-SAVR patients.

Table 28:
Length of Stay (EP Population)

Length of Stay (days)*	SAPIEN 3 Valve			PIIA-SAVR
	All	TF	Non-TF	
Overall	5.5 ± 5.7	5.0 ± 5.2	9.3 ± 7.7	11.9 ± 7.6
ICU	2.7 ± 3.0	2.5 ± 2.6	4.2 ± 4.9	5.6 ± 6.1

*Plus–minus values are means ± SD.

QoL

The QoL measurements using the Kansas City Cardiomyopathy Questionnaire (KCCQ) clinical summary score are presented in Figure 36. Except for self-efficacy which showed a small improvement, moderate to large improvements were observed in all other subscores at 30 days and were sustained at 1 year in the PIIS3i EP population. A side-by-side comparison of the results by access approach is presented in Figure 37. In general, improvements in the TF group were slightly larger as compared to those observed in the Non-TF group.

Figure 36:
KCCQ Clinical Summary Score (EP Population)

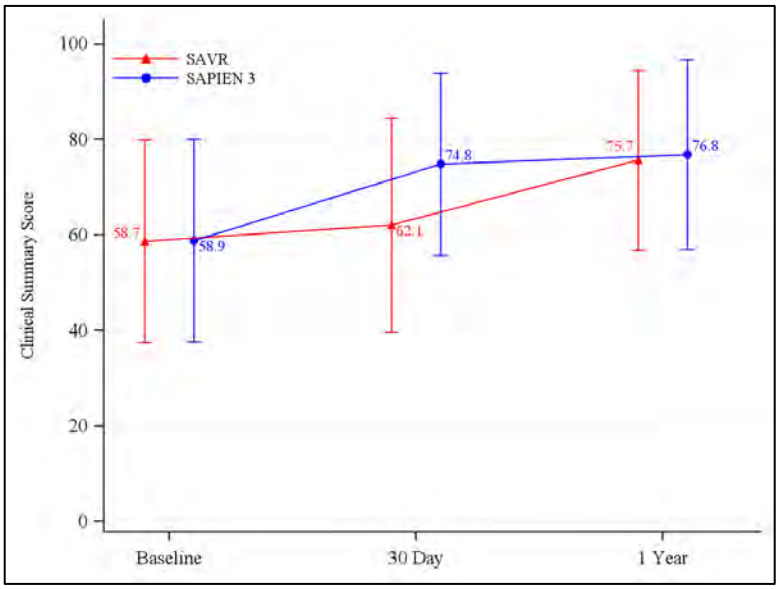
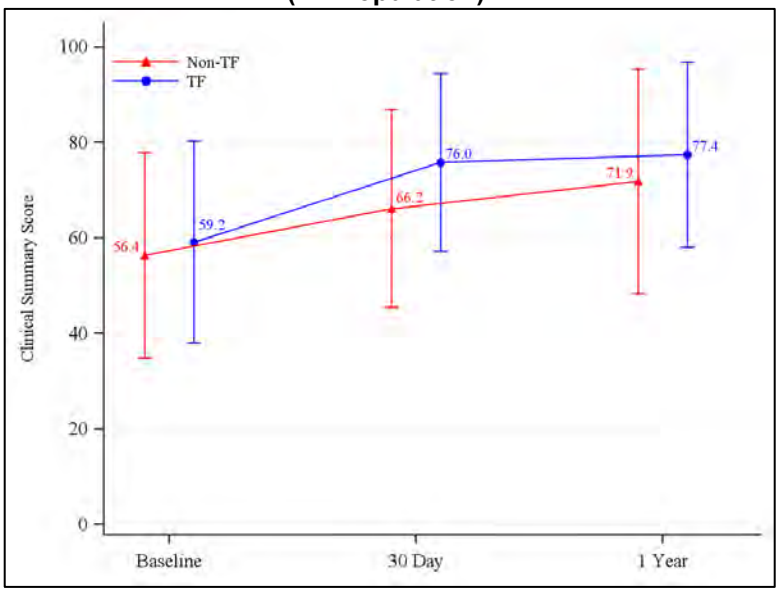


Figure 37:
KCCQ Clinical Summary Score - TF versus non-TF Access (EP Population)



Additional QoL instruments

QoL was also measured using the visual analog scale (VAS) of the EuroQoL (EQ-5D) measure and the SF-36 Health Status Questionnaire. The VAS is a self-assessment in which patients rate their well-being on a scale from 0 to 100 where 0 is the worst state they can imagine and 100 is the best state. SF-36 uses 36 questions to measure functional health and well-being from the patient's point of view and is generally reported in two (2) summary scores on a scale from 0 to 100 which evaluate physical (the Physical Summary Score) and mental (the Mental Summary Score) health, with higher scores representing better functional health and well-being. The results of the VAS and SF-36 measures are presented in Tables 29 and 30, respectively.

Table 29:
EQ-5D Visual Analog Scale
(EP Population)

EQ-5D Visual Analog Scale*	SAPIEN 3 Valve			PIIA-SAVR
	All	TF	Non-TF	
Baseline	60.3 ± 20.0	61.0 ± 19.8	55.1 ± 20.7	59.5 ± 20.5
30 days	74.0 ± 16.6	74.8 ± 16.6	68.5 ± 16.2	67.2 ± 19.5
1 year	74.4 ± 17.2	74.7 ± 17.1	71.8 ± 17.8	74.3 ± 16.7

*Plus–minus values are means ± SD.

Table 30:
SF-36 Health Status Questionnaire Score
(EP Population)

SF-36 Health Status Questionnaire Score*	SAPIEN 3 Valve			PIIA-SAVR
	All	TF	Non-TF	
Physical Component Score				
Baseline	34.7 ± 9.1	35.0 ± 9.1	33.1 ± 8.5	34.3 ± 9.0
30 days	39.7 ± 9.8	40.3 ± 9.7	34.8 ± 9.2	34.5 ± 8.4
1 year	40.0 ± 10.3	40.4 ± 10.2	37.0 ± 10.8	39.5 ± 10.4
Mental Component Score				
Baseline	48.0 ± 11.8	48.1 ± 11.8	47.0 ± 12.3	48.0 ± 12.3
30 days	51.8 ± 10.6	52.3 ± 10.4	47.8 ± 11.3	45.5 ± 13.3
1 year	52.5 ± 10.7	52.7 ± 10.8	50.7 ± 10.1	52.0 ± 11.3

*Plus–minus values are means ± SD.

PARTNER 3 SAPIEN 3 Low Risk Cohort

A. Accountability of the PMA Cohort

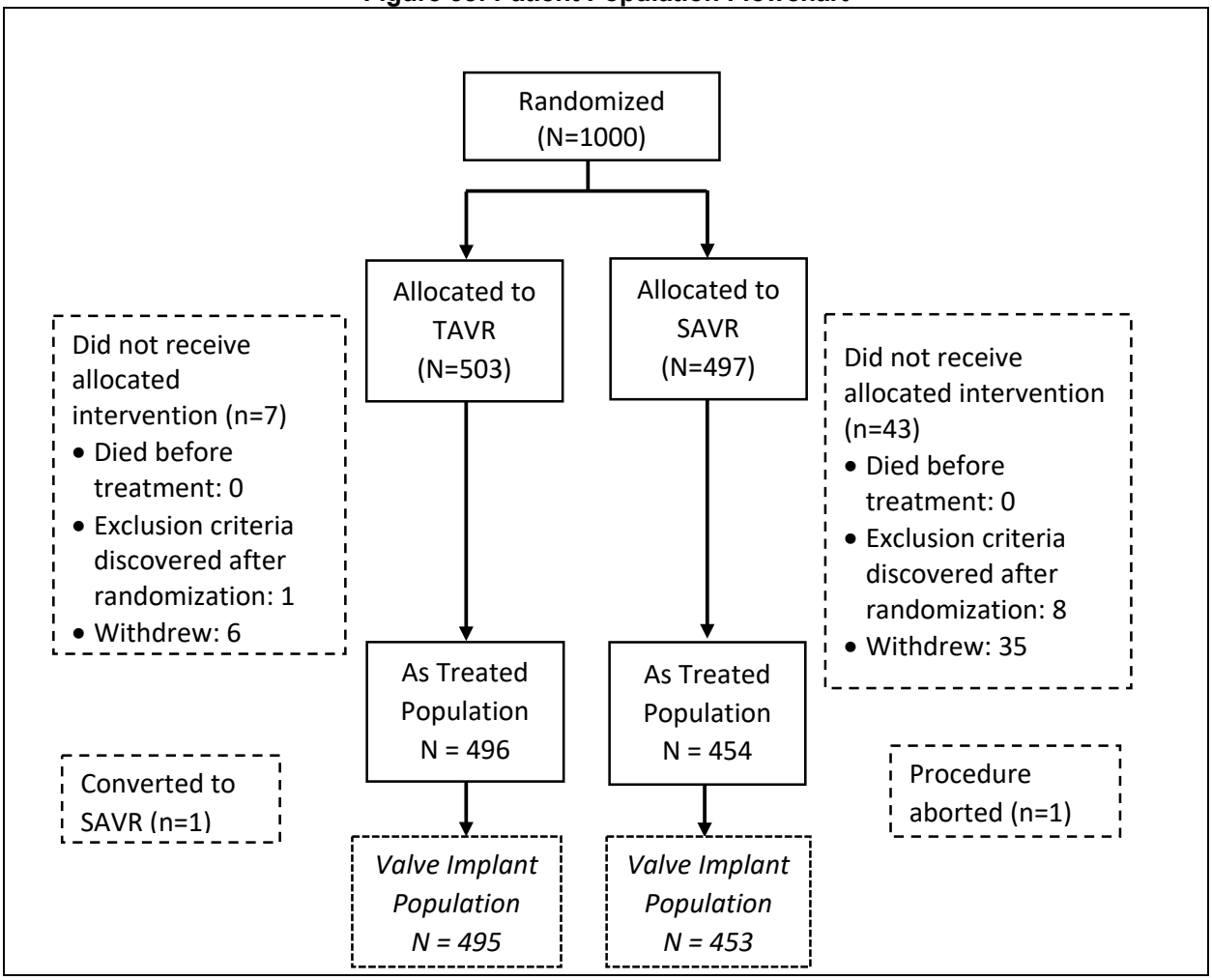
At the time of database lock, a total of 1000 subjects were randomized in the study, including 503 TAVR patients and 497 SAVR patients.

There were three different analysis populations defined in the protocol: Intention-to-Treat (ITT), As Treated (AT), and Valve Implant (VI), as summarized in Table 31 and Figure 38. The primary analysis was the AT analysis.

Table 31: Analysis Populations

Analysis Population	Definition	Number of Patients	
		TAVR	SAVR
Intention-To-Treat (ITT)	All randomized patients.	503	497
As Treated (AT)	All ITT patients for whom the index procedure was begun, whether or not the index procedure was completed.	496	454
Valve Implant (VI)	All AT patients who received and retained the intended valve during the index procedure.	495	453

Figure 38: Patient Population Flowchart



The overall follow-up compliance of the trial is summarized in Table 32.

Table 32: Overall Study Compliance (AT Population)

Patient Accountability	30-day Visit		1 Year Visit	
	TAVR (N=496)	SAVR (N=454)	TAVR (N=496)	SAVR (N=454)
Total patients	496	454	496	454
Non-eligible	2	11	6	30
Death	2	6	5	11
Withdrawal	0	3	0	12
Lost to follow-up	0	0	0	1
Exit with other reason	0	2	1	6
Visit not yet due	0	0	0	0
Eligible	494	443	490	424
Follow-up visit completed	96.5% (493)	96.5% (438)	97.8% (485)	91.2% (414)
Missed visit	0.2% (1)	1.1% (5)	1.0% (5)	2.2% (10)

.

B. Study Population Demographics and Baseline Characteristics

The demographics and baseline characteristics of the study population are typical for a TAVR study performed in the U.S., as shown in Table 33. The treatment cohorts were generally well balanced with respect to age, gender, and STS risk score.

Table 33:
Patient Demographics and Baseline Characteristics
(AT Population)

Demographics and Baseline Characteristics	Summary Statistics*	
	TAVR (N = 496)	SAVR (N = 454)
Age - years	73.3 ± 5.8	73.6 ± 6.1
Male sex	67.5% (335/496)	71.1% (323/454)
Society of Thoracic Surgeons (STS) score	1.9 ± 0.7	1.9 ± 0.6
New York Heart Association (NYHA) class		
I/II	68.8% (341/496)	76.2% (346/454)
III/IV	31.1% (155/496)	23.8% (108/454)
Previous myocardial infarction	5.7% (28/495)	5.8% (26/452)
Previous intervention		
Coronary artery bypass grafting (CABG)	3.0% (15/494)	1.8% (8/451)
Percutaneous coronary intervention (PCI)	18.8% (93/494)	16.2% (73/452)
Stroke or cerebrovascular accident (CVA)	3.4% (17/496)	5.1% (23/453)
Peripheral vascular disease (PVD)	6.9% (34/494)	7.3% (33/453)
Atrial fibrillation	15.7% (78/496)	18.8% (85/453)
Atrial flutter	3.0% (15/496)	2.4% (11/452)
Permanent pacemaker or defibrillator	2.4% (12/496)	2.9% (13/454)
Hostile chest	0.0% (0/496)	0.0% (0/454)
Echocardiographic findings (Valve Implant Population)		
Valve area (cm^2)	0.8 ± 0.2 (459)	0.8 ± 0.2 (424)
Mean gradient (mmHg)	49.4 ± 12.8 (484)	48.3 ± 11.8 (442)
Mean left ventricular ejection fraction (LVEF) %	65.7 9.0 (472)	66.2 ± 8.6 (436)
Moderate or severe aortic regurgitation	3.9% (19/484)	2.5% (11/446)
Moderate or severe mitral regurgitation	1.3% (6/477)	3.2% (14/437)

* Continuous measures - Mean ± SD (Total no.); Categorical measures % (no./Total no.)

C. Safety and Effectiveness Results

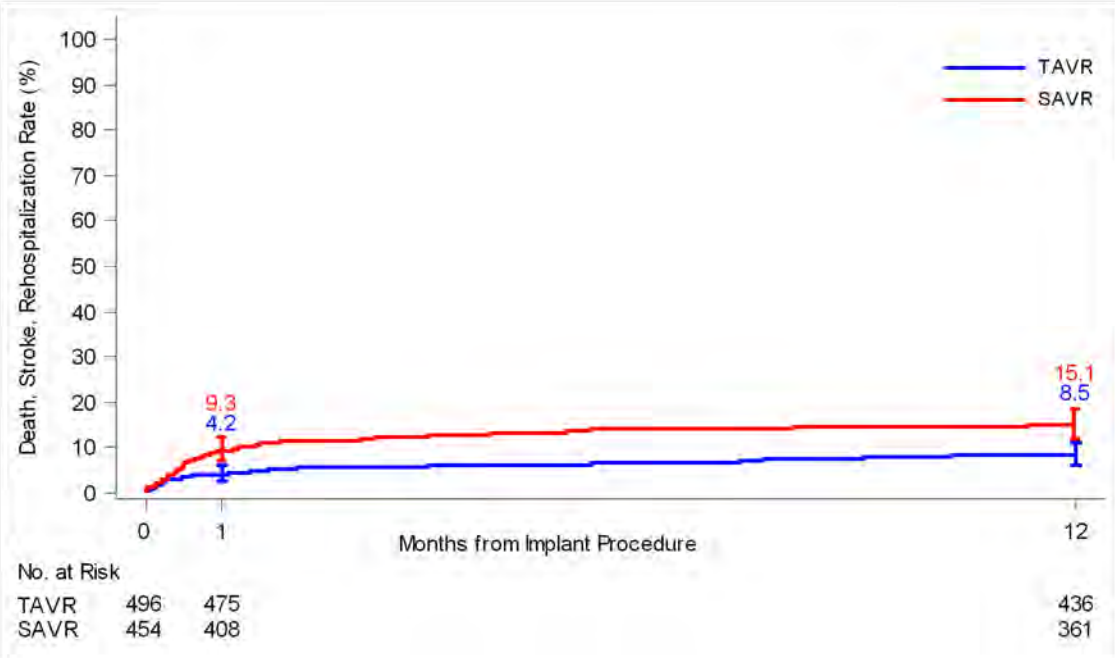
1. Primary Endpoint

The primary endpoint results are presented in Table 34 and Figure 39. The rate of all-cause death, all stroke, or rehospitalization (valve-related or procedure-related and including heart failure) at 1-year was 8.5% in the TAVR group and 15.1% in the SAVR group. Since the upper limit of the 95% confidence interval for the difference in the primary endpoint event rate was < 6.0%, non–inferiority was achieved.

Table 34:
Primary Endpoint Analysis
(AT Population)

Event	Kaplan-Meier Rate*		Difference of KM Estimate (TAVR – SAVR)	95% CI* for the Difference	Non-inferiority Criterion
	TAVR (N=496)	SAVR (N=454)			
All-cause death, all stroke, or rehospitalization	8.5% (42)	15.1% (68)	-6.65%	[-10.77%,-2.52%]	Pass
All-cause death	1.0% (5)	2.5% (11)	-1.44%	[-3.13%, 0.24%]	
All stroke	1.2% (6)	3.1% (14)	-1.90%	[-3.77%, -0.02%]	
Rehospitalization	7.3% (36)	11.0% (49)	-3.74%	[-7.45%, -0.02%]	
*Kaplan-Meier estimate - % (no. of subjects with the event)					

Figure 39: All-Cause Death, All Stroke, and Rehospitalization through 1 Year (AT Population)



Note: The confidence intervals were calculated without multiplicity adjustment. The adjusted confidence intervals could be wider than presented here. As such, confidence intervals are provided to illustrate the variability only and should not be used to draw any statistical conclusion.

2. Secondary Endpoints

Hypothesis testing:

Since the primary endpoint passed the non-inferiority testing, the prespecified superiority testing was carried out on the six select secondary endpoints sequentially. TAVR with SAPIEN 3 was found to be superior to SAVR in all six secondary endpoints, as shown in Table 35.

Table 35:
Superiority Testing of Select Secondary Endpoints (AT Population)

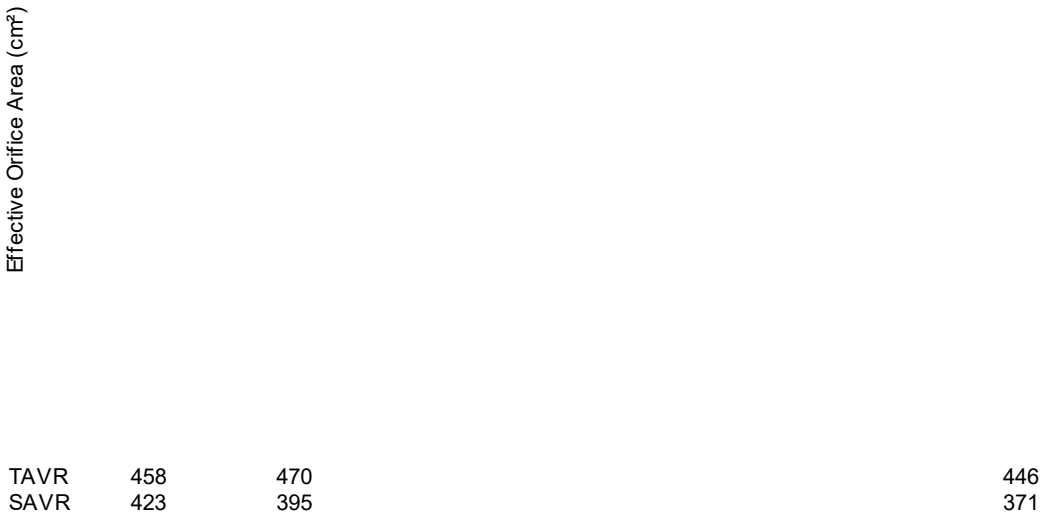
No.	Endpoint	Summary Statistics*		Difference (TAVR – SAVR)	95% CI for the Difference	p-value (Superiority Test Result)
		TAVR (N=496)	SAVR (N=454)			
1	New onset atrial fibrillation at 30 days†	5.0% (21/417)	39.3% (145/369)	-34.3%	[-39.7%, -28.9%]	<.0001 (pass)
2	Length of index hospitalization (days)	2.9 ± 0.1 (496)	7.4 ± 0.2 (454)	-4.5	[-4.8, -4.1]	<.0001 (pass)
3	All-cause death, all stroke, or rehospitalization at 1 year	8.5% (42)	15.1% (68)	-6.6%	[-10.8%, -2.5%]	0.0016 (pass)
4	Death, KCCQ < 45 or KCCQ decrease from baseline ≥ 10 points at 30 days	3.9% (19/492)	30.6% (133/435)	-26.7%	[-31.4%, -22.1%]	<.0001 (pass)
5	Death or all stroke at 30 days	1.0% (5/496)	3.3% (15/454)	-2.3%	[-4.2%, -0.4%]	0.0214 (pass)
6	All stroke at 30 days	0.6% (3/496)	2.4% (11/454)	-1.8%	[-3.4%, -0.2%]	0.0284 (pass)

*Continuous measures - Mean ± SE (Total no.); Categorical measures – observed rate, % (no./Total no.), except No. 3 - Kaplan-Meier rate, % (Total no.).
†Patients with pre-procedural atrial fibrillation were excluded from the analysis.

Valve Performance

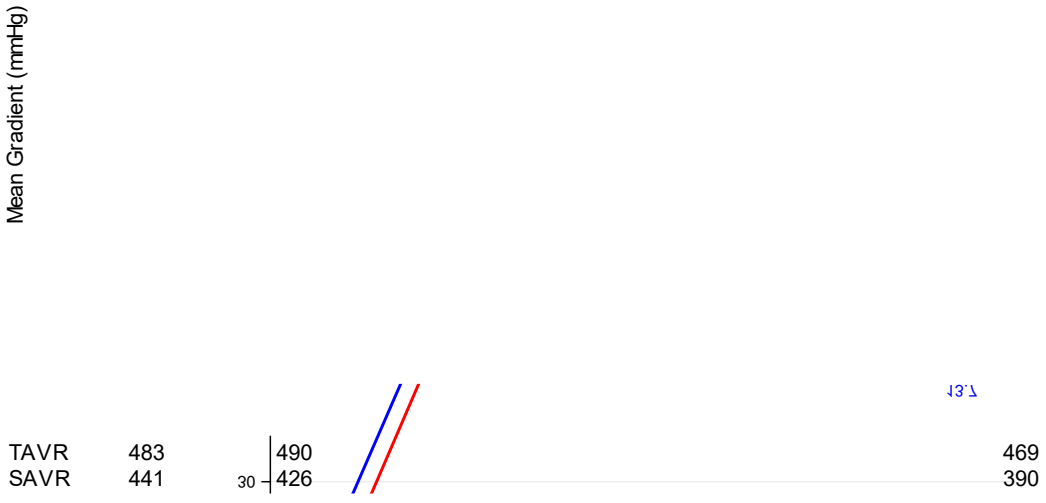
The effective orifice area (EOA), mean aortic gradient, total aortic regurgitation (AR), and paravalvular regurgitation values obtained over time for the TAVR and SAVR patients are shown in Figure 40 through Figure 43, respectively. The increase in EOA and decrease in gradient were sustained through 1 year in both cohorts. In the TAVR cohort, the proportion of patients with total AR ≥ moderate was 0.8% at 30 days and 1.1% at 1 year, while in the SAVR cohort, the corresponding proportion was 0.4% at 30 days and 0.6% at 1 year. The proportion of patients with paravalvular regurgitation ≥ moderate was 0.8% at 30 days and 0.6% at 1 year in the TAVR cohort, as compared to 0.0% at 30 days and 0.8% at 1 year in the SAVR cohort.

Figure 40: Effective Orifice Area (VI Population)



Note: Line plot with mean and standard error. The total number of patients at each visit time point only counted the patients with valid values.

Figure 41: Mean Aortic Gradient (VI Population)



Note: Line plot with mean and standard error. The total number of patients at each visit time point only counted the patients with valid values.

Figure 42: Total Aortic Regurgitation (VI Population)

|----TAVR----| |----SAVR----|

Figure 43: Paravalvular Regurgitation (VI Population)

|----TAVR----| |----SAVR----|

New York Heart Association (NYHA) Functional Class

The NYHA classifications by visit are presented in Figure 44. At baseline, 31.3% of TAVR patients and 23.6% of SAVR patients were in NYHA III/IV. At 1 year the majority (~99%) of TAVR and SAVR patients were in NYHA Class I/II.

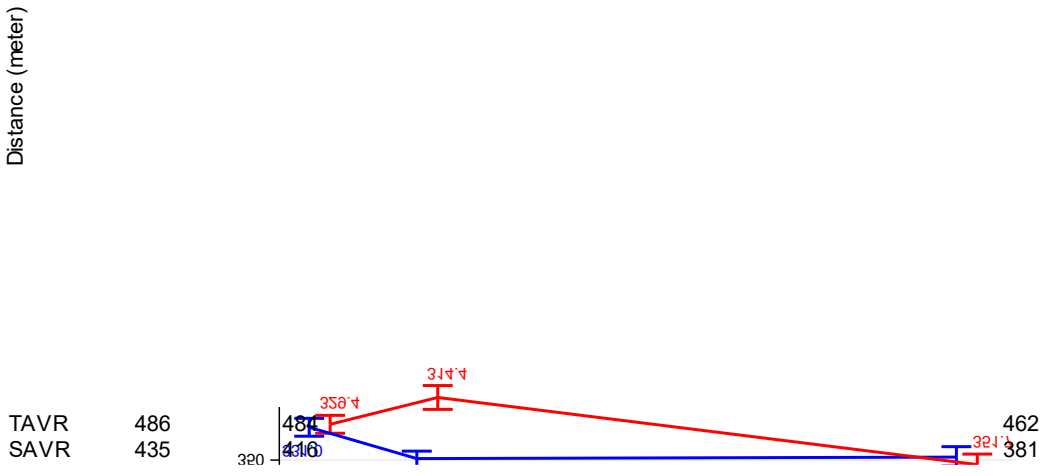
Figure 44: NYHA Class by Visit (VI Population)

|----TAVR----| |----SAVR----|

Six-Minute Walk Test (6MWT)

The results for the 6MWT distance are presented in Figure 45. The TAVR patients showed an increase in mean 6MWT distance from 331.0 m at baseline to 349.1 m at 30 days, while SAVR patients showed a decrease from 329.4 m at baseline to 314.4 m at 30 days. The two cohorts had similar values at 1 year (347.6 m for TAVR and 351.7 m for SAVR).

Figure 45: 6MWT Distance (VI Population)



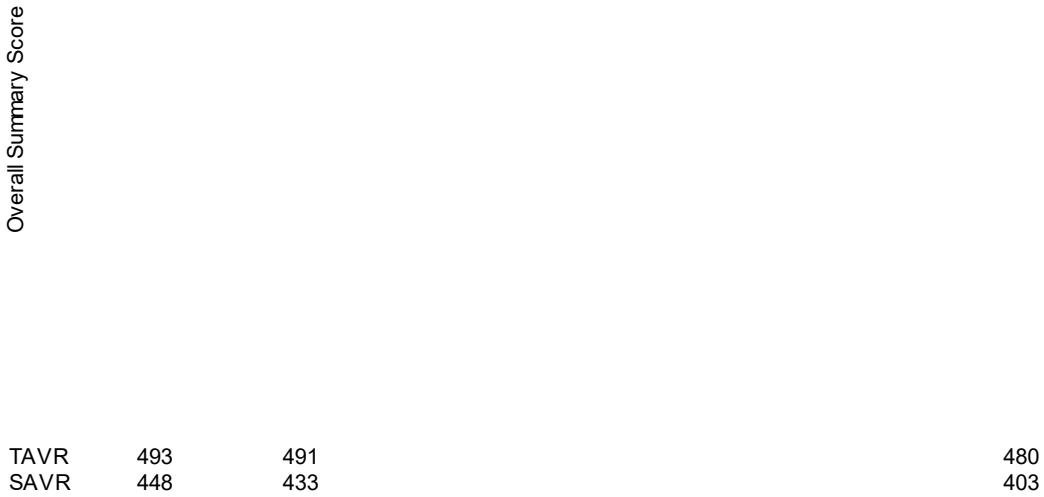
Note: Line plot with mean and standard error. The total number of patients at each visit time point only counted the patients with valid values.

Quality of Life (QoL)

KCCQ

The results for the KCCQ overall summary score are presented in Figure 46. The mean score increased from 70.3 at baseline to 88.9 at 30 days and 89.9 at 1 year in TAVR patients and from 70.1 at baseline to 72.8 at 30 days and 88.1 at 1 year in SAVR patients.

Figure 46: KCCQ Overall Summary Score (VI Population)

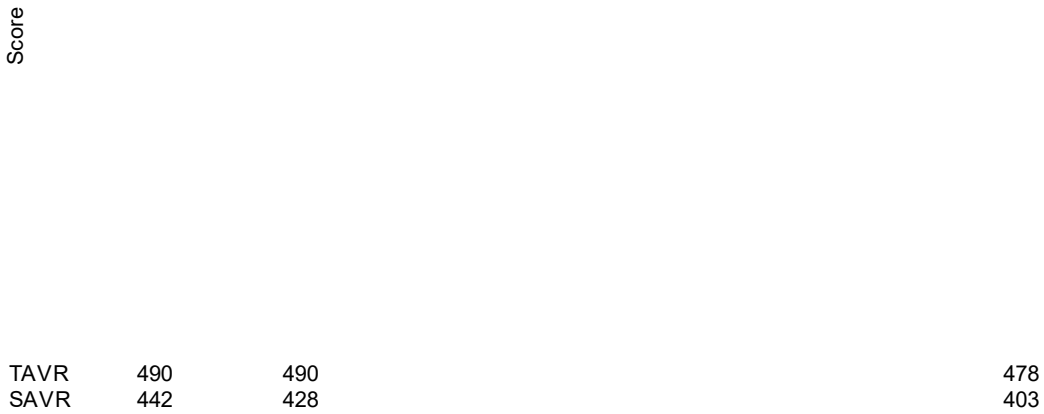


Note: Line plot with mean and standard error. The total number of patients at each visit time point only counted the patients with valid values.

EuroQol (EQ-5D)

The results for the EQ-5D visual analog score (VAS) are presented in Figure 47. The mean score was 74.2 at baseline, 85.2 at 30 days, and 84.4 at 1 year in TAVR patients as compared to 75.2 at baseline, 76.5 at 30 days, and 84.7 at 1 year in SAVR patients.

Figure 47: EQ-5D Visual Analog Score (VI Population)



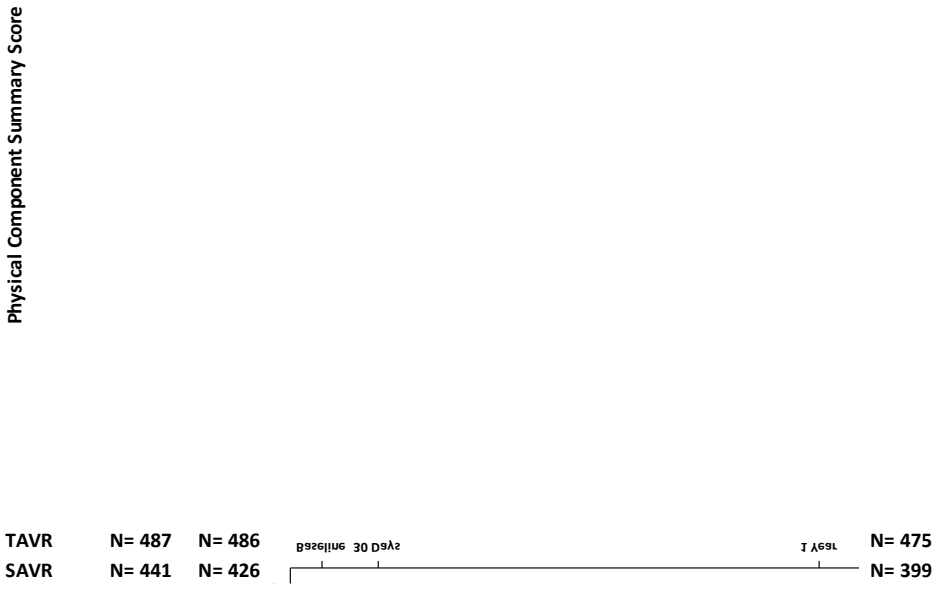
TAVR	490	490	478
SAVR	442	428	403

Note: Line plot with mean and standard error. The total number of patients at each visit time point only counted the patients with valid values.

Short Form (SF)-36

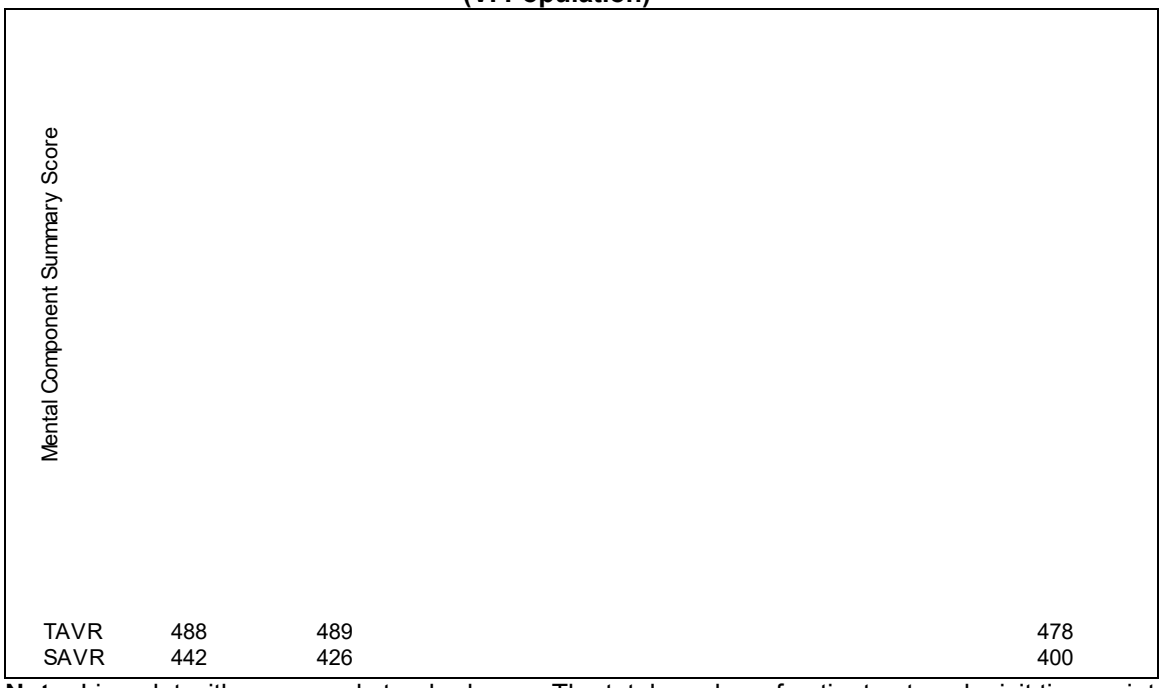
The results for the SF-36 physical component summary score and mental component summary score are presented in Figure 48 and Figure 49, respectively.

Figure 48: SF-36 Physical Component Summary Score (VI Population)



Note: Line plot with mean and standard error. The total number of patients at each visit time point only counted the patients with valid values.

Figure 49: SF-36 Mental Component Summary
(VI Population)



Note: Line plot with mean and standard error. The total number of patients at each visit time point only counted the patients with valid values.

3. Adverse Events

The Kaplan-Meier estimates of the CEC-adjudicated adverse events through 1 year are presented in Table 36.

Table 36: CEC-Adjudicated Adverse Events through 1 Year (AT Population)

Event	Kaplan-Meier Rate*			
	30 Days		1 Year	
	TAVR (N=496)	SAVR (N=454)	TAVR (N=496)	SAVR (N=454)
All cause death	0.4% (2, 2)	1.1% (5, 5)	1.0% (5, 5)	2.5% (11, 11)
Cardiovascular death	0.4% (2, 2)	0.9% (4, 4)	0.8% (4, 4)	2.0% (9, 9)
All stroke	0.6% (3, 3)	2.4% (11, 11)	1.2% (6, 6)	3.1% (14, 14)
Disabling stroke	0.0% (0, 0)	0.4% (2, 2)	0.2% (1, 1)	0.9% (4, 4)
Non-disabling stroke	0.6% (3, 3)	2.0% (9, 9)	1.0% (5, 5)	2.2% (10, 10)
Death or stroke	1.0% (5, 5)	3.3% (16, 15)	1.8% (11, 9)	4.9% (25, 22)
Death or disabling stroke	0.4% (2, 2)	1.3% (7, 6)	1.0% (6, 5)	2.9% (15, 13)
Major vascular complications	2.2% (12, 11)	1.5% (8, 7)	2.8% (15, 14)	1.5% (8, 7)
Life-threatening / disabling, or major bleeding	3.6% (22, 18)	24.5% (123, 111)	7.7% (45, 38)	25.9% (132, 117)
Life-threatening / disabling bleeding	1.2% (9, 6)	11.9% (58, 54)	2.8% (17, 14)	12.8% (63, 58)
Major bleeding	2.6% (13, 13)	13.5% (65, 61)	5.3% (28, 26)	14.2% (69, 64)
Myocardial infarction	1.0% (5, 5)	1.3% (6, 6)	1.2% (6, 6)	2.2% (10, 10)
Requirement for renal replacement†	0.2% (1, 1)	0.7% (3, 3)	0.2% (1, 1)	0.7% (3, 3)
New permanent pacemaker implantation resulting from new or worsened conduction disturbances‡	6.5% (32, 32)	4.0% (18, 18)	7.3% (36, 36)	5.4% (24, 24)
Coronary obstruction requiring intervention	0.2% (1, 1)	0.7% (3, 3)	0.2% (1, 1)	0.7% (3, 3)
New onset atrial fibrillation	5.0% (21, 21)	39.5% (145, 145)	7.0% (29, 29)	40.9% (150, 150)
Rehospitalization‖	3.4% (18, 17)	6.5% (30, 29)	7.3% (39, 36)	11.0% (59, 49)

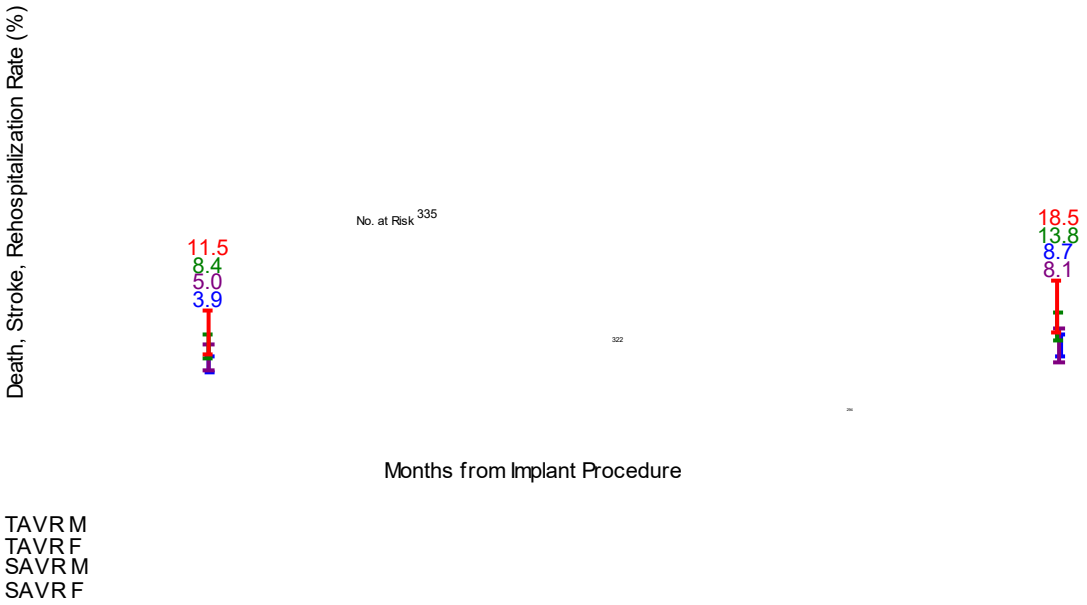
*Kaplan-Meier rate (no. of events, no. of patients with the event).
†Requirement for renal replacement was based on the site-reported event. All the other events were based on the CEC-adjudicated results.
‡Patients with pacemaker or ICD at baseline were not counted as new events.
‖Rehospitalization (valve-related or procedure-related and including heart failure).

4. Subgroup Analysis

Gender Analysis

The protocol specified a subgroup analysis on gender. The primary endpoint result stratified by gender is presented in Figure 50.

Figure 50: All-Cause Death, All Stroke, and Rehospitalization through 1 Year Stratified by Gender (AT Population)



Note: The confidence intervals were calculated without multiplicity adjustment. The adjusted confidence intervals could be wider than presented here. As such, confidence intervals are provided to illustrate the variability only and should not be used to draw any statistical conclusion.

5. Other Study Observations

Procedural Information

The general procedural data are summarized in Table 37. Conscious sedation was used in the majority of TAVR patients (65.1%). The mean procedure time was significantly lower for TAVR compared to SAVR (58.6 minutes vs. 208.3 minutes). There were less concomitant (planned) procedures performed for TAVR patients compared to SAVR patients (6.9% vs. 26.4%). Additional TAVR and SAVR specific procedural data are presented in Table 38 and 39, respectively.

Table 37:
General Procedural Data
(AT Population)

Variable	Summary Statistics*	
	TAVR (N=496)	SAVR (N=454)
Subject treated according to their treatment assignment	99.8% (495/496)	99.8% (453/454)
Procedure aborted	0	1
Subject was assigned to TAVR but received SAVR	1	0
Procedure time (min)	58.6 ± 1.6 (496)	208.3 ± 2.9 (454)
Anesthesia type		
General	33.3% (165/496)	100.0% (454/454)
Conscious sedation	65.1% (323/496)	NA
Conversion from conscious sedation to general anesthesia during the procedure	1.6% (8/496)	NA
Anesthesia time (min)	138.7 ± 2.20 (496)	309.7 ± 3.7 (454)
Concomitant procedures	6.9% (34/496)	26.4% (120/454)
Annular area (mm^2)	473.5 ± 83.3 (486)	479.6 ± 87.6 (441)

*Continuous measures – mean ± SE (n) for procedure and anesthesia time, mean ± SD (n) for annular area; Categorical measures - % (no./Total no.)

Table 38:
TAVR Procedure Data
(AT Population)

Variable	Summary Statistics*
	TAVR (N=496)
Valve size	
20 mm	2.2% (11/496)
23 mm	29.2% (145/496)
26 mm	47.6% (236/496)
29 mm	21.0% (104/496)
Successful access, delivery and retrieval of the device delivery system	99.8% (494/495)
Arterial access method	
Left percutaneous	22.2% (109/490)
Right percutaneous	76.7% (376/490)
Left surgical cutdown	0.0% (0/490)
Right surgical cutdown	1.0% (5/490)
Total fluoroscopy time (min)	13.9 ± 0.3 (487)
BAV performed	57.8% (286/495)
Post dilatation performed	20.9% (103/494)
Number of post dilatations	
1	89.3% (92/103)
2	8.7% (9/103)
3	1.9% (2/103)
More than one SAPIEN 3 THV implanted	0.2% (1/495)

*Continuous measures - mean ± SE (n); categorical measures - % (no./Total no.).
For patients in whom the procedure was aborted or who were converted to surgery, the rest of the procedure data except valve size were not collected.

Table 39:
SAVR Procedure Data
(AT Population)

Variable	Summary Statistics*
	SAVR (N=454)
Procedure aborted†	0.2% (1/454)
Valve size	
19 mm	2.9% (13/453)
21 mm	17.2% (78/453)
23 mm	36.6% (166/453)
25 mm	35.5% (161/453)
27 mm	6.8% (31/453)
29 mm	0.9% (4/453)
Total aortic cross clamp time (min)	74.3 ± 1.3 (453)
Total pump time (min)	97.7 ± 1.6 (453)
SAVR approach	
Sternotomy	95.4% (432/453)
Thoracotomy	0.9% (4/453)
Mini right upper thoracotomy	2.9% (13/453)
Port access	0.2% (1/453)
Other	0.7% (3/453)
Successful implantation of the surgical valve	100.0% (453/453)

*Continuous measures - mean ± SE (n); categorical measures - % (no./Total no.).
†For patients in whom the procedure was aborted, the rest of the procedure data were not collected.

Computed Tomography (CT) Sub-Study

There were 184 TAVR and 162 SAVR patients at 30 days and 160 and 134 patients at 1 year, respectively, who had at least one adequate CT for leaflet assessments. The HALT and leaflet mobility imaging findings are summarized in Table 40, along with the associated mean aortic pressure gradients. The mean aortic pressure gradients at 1 year stratified by HALT and leaflet mobility at 30 days are summarized in Table 41 and Table 42, respectively. The rate of death, stroke or TIA at 1 year stratified by HALT and leaflet mobility at 30 days are summarized in Table 43 and Table 44, respectively. The CT substudy was not powered to compare the relative incidence or the severity of HALT or reduced leaflet mobility between the TAVR and SAVR cohorts, or to determine whether late clinical outcomes were affected by the presence of HALT or reduced leaflet mobility.

Table 40: HALT and Leaflet Mobility Findings and Associated Mean Gradients

Findings	Summary Statistics*			
	30 Days		1 Year	
	TAVR (N=184)	SAVR (N=162)	TAVR (N=160)	SAVR (N=134)
Proportion of patients on oral anticoagulants at time of scan	6.0% (11/184)	21.0% (34/162)	8.1% (13/160)	18/134 (13.4%)
HALT†				
No thickening	84.8% (156/184)	95.7% (155/162)	74.4% (119/160)	82.1% (110/134)
Mean gradient (mmHg)	12.5 ± 0.3 (156)	10.8 ± 0.3 (155)	13.7 ± 0.4 (115)	11.7 ± 0.4 (106)
<25% leaflet length thickened	4.9% (9/184)	1.2% (2/162)	11.3% (18/160)	7.5% (10/134)
Mean gradient (mmHg)	11.4 ± 0.9 (9)	16.5 ± NA (1)	12.9 ± 0.7 (18)	9.3 ± 1.8 (8)
25%-50% leaflet length thickened	3.3% (6/184)	1.9% (3/162)	6.3% (10/160)	5.2% (7/134)
Mean gradient (mmHg)	13.7 ± 1.7 (6)	9.4 ± 1.4 (3)	13.2 ± 1.8 (10)	15.1 ± 2.4 (7)
50%-75% leaflet length thickened	6.5% (12/184)	0.6% (1/162)	5.0% (8/160)	3.7% (5/134)
Mean gradient (mmHg)	15.2 ± 1.9 (12)	9.8 ± NA (1)	16.9 ± 3.3 (8)	16.1 ± 4.0 (5)
>75% leaflet length thickened	0.5% (1/184)	0.6% (1/162)	3.1% (5/160)	1.5% (2/134)
Mean gradient (mmHg)	10.2 ± NA (1)	16.8 ± NA (1)	20.2 ± 6.2 (5)	9.0 ± 4.2 (2)
Number of leaflets with HALT	6.7% (37/552)	2.3% (11/486)	12.7% (61/480)	8.2% (33/402)
0 leaflets thickening	156	155	119	110
1 leaflet thickening	21	4	26	15
2 leaflets thickening	5	2	10	9
3 leaflets thickening	2	1	5	0
Leaflet mobility‡				
Unrestricted	85.3% (145/170)	96.8% (149/154)	77.6% (118/152)	83.% (108/129)
Mean gradient (mmHg)	12.2 ± 0.3 (145)	10.7 ± 0.3 (148)	13.3 ± 0.4 (114)	12.0 ± 0.5 (105)
Partially restricted, restriction limited to base	5.3% (9/170)	1.3% (2/154)	11.8% (18/152)	8.5% (11/129)
Mean gradient (mmHg)	11.4 ± 0.9 (9)	14.6 ± 1.9 (2)	12.5 ± 0.6 (18)	9.9 ± 1.6 (9)
Partially restricted (<50%)	5.3% (9/170)	1.3% (2/154)	3.9% (6/152)	3.1% (4/129)
Mean gradient (mmHg)	15.5 ± 2.4 (9)	10.3 ± 0.5 (2)	14.0 ± 2.8 (6)	15.6 ± 3.0 (4)
Partially restricted (50%-75%)	3.5% (6/170)	0.0% (0/154)	4.6% (7/152)	3.9% (5/129)
Mean gradient (mmHg)	12.8 ± 1.7 (6)	NA	21.8 ± 3.9 (7)	11.3 ± 3.6 (5)
Largely immobile	0.6% (1/170)	0.6% (1/154)	2.0% (3/152)	0.8% (1/129)
Mean gradient (mmHg)	13.3 ± NA (1)	16.8 ± NA (1)	19.5 ± 8.1 (3)	13.1 ± NA (1)
Number of leaflets partially restricted or largely immobile				
0 leaflet	145	149	118	108
1 leaflet	21	2	22	13
2 leaflets	4	2	8	8
3 leaflets	0	1	4	0

*Continuous measures - mean ± SE (n); categorical measures - % (no./Total no.). The analysis population included all the patients enrolled in the CT substudy and had at least one adequate CT for leaflet assessments.

†HALT was defined as: the presence of any hypoattenuated leaflet thickening in any singular leaflet as identified by an independent CT core laboratory. The extent of the hypoattenuated leaflet thickening was graded with regards to the entire leaflet as: None, <25%, 25-50%, 50-75%, or >75%. If more than one leaflet had the appearance of HALT, the thickening measure of the most impacted leaflet was used. Presence of any degree of HALT on any one leaflet rendered a finding.

‡Leaflet mobility was determined by an independent CT core laboratory and included: unrestricted, partially restricted mobility limited to the base of a leaflet, partially restricted mobility involving more than the base of the leaflet but less than 50% of the leaflet, partially restricted mobility involving more than 50% of the leaflet but less than 75% of the leaflet, and/or a largely immobile leaflet. Presence of any degree of restriction or immobility on any one leaflet rendered a finding.

Table 41: Mean Aortic Gradient at 1 Year Stratified by HALT at 30 Days

	Summary Statistics*			
	HALT at 30 Days		No HALT at 30 Days	
	TAVR (N=28)	SAVR (N=7)	TAVR (N=156)	SAVR (N=155)
Mean gradient	13.6 ± 1.2 (24)	13.7 ± 2.7 (5)	13.6 ± 0.4 (137)	11.8 ± 0.4 (125)

*Mean ± SE (n). The analysis population included all the patients enrolled in the CT substudy and had an adequate CT for leaflet assessments at 30 days.

Table 42: Mean Aortic Gradient at 1 Year Stratified by Leaflet Mobility at 30 Days

	Summary Statistics*			
	Reduced Leaflet Mobility at 30 Days		Unrestricted at 30 Days	
	TAVR (N=25)	SAVR (N=5)	TAVR (N=145)	SAVR (N=149)
Mean gradient	13.7 ± 1.28 (23)	14.2 ± 3.48 (4)	13.3 ± 0.4 (124)	11.7 ± 0.4 (119)

*Mean ± SE (n). The analysis population included all the patients enrolled in the CT substudy and had an adequate CT for leaflet assessments at 30 days.

Table 43: All-Cause Mortality, All Stroke or TIA at 1 Year Stratified by HALT at 30 Days

1-Year Endpoint	Kaplan-Meier Rate*			
	HALT at 30 Days		No HALT at 30 Days	
	TAVR (N=28)	SAVR (N=7)	TAVR (N=156)	SAVR (N=155)
All-cause mortality	0.0% (0)	0.0% (0)	1.3% (2)	1.4% (2)
All stroke	0.0% (0)	0.0% (0)	0.7% (1)	0.0% (0)
TIA	5.6% (1)	0.0% (0)	1.3% (2)	0.0% (0)
All-cause mortality or all stroke or TIA	5.6% (1)	0.0% (0)	3.3% (5)	1.4% (2)

*Kaplan-Meier rate (no. of patients with event). The analysis population included all the patients enrolled in the CT substudy and had an adequate CT for leaflet assessments at 30 days.. The Kaplan-Meier analysis used the CT test date as the start date in determining time to event. Presence of any degree of HALT on any one leaflet rendered a finding and inclusion in the HALT cohort.

Table 44: All-Cause Mortality, All Stroke or TIA at 1 Year Stratified by Leaflet Mobility at 30 Days

1-Year Endpoint	Kaplan-Meier Rate*			
	Reduced Leaflet Mobility at 30 Days		Unrestricted at 30 Days	
	TAVR (N=25)	SAVR (N=5)	TAVR (N=145)	SAVR (N=149)
All-cause mortality	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)
All stroke	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)
TIA	6.3% (1)	0.0% (0)	6.3% (1)	0.0% (0)
All-cause mortality or all stroke or TIA	6.3% (1)	0.0% (0)	3.6% (5)	1.4% (2)

*Kaplan-Meier rate (no. of patients with event). The analysis population included all the patients enrolled in the CT substudy and had an adequate CT for leaflet assessments at 30 days.. The Kaplan-Meier analysis used the CT test date as the start date in determining time to event. Reduced leaflet mobility included any of the following assessments: partially restricted limited to base, partially restricted involving more than the base but less than 50% of the leaflet, partially restricted involving more than 50% but less than 75% of the leaflet, and/or largely immobile. Presence of any degree of restriction or immobility on any one leaflet rendered a finding and inclusion in the reduced leaflet mobility cohort.

SAPIEN 3 THV IN BICUSPID AORTIC VALVE FOR PATIENTS AT INTERMEDIATE OR GREATER SURGICAL RISK– STS/ACC TRANSCATHETER VALVE THERAPY REGISTRY (TVTR) ANALYSIS

Patient Accountability

At the time of database extract, of the 545 patients in the bicuspid aortic valve cohort, 527 patients were eligible for the 30-day visit, and 486 (92.2%) patients paid a visit within the 30-day follow-up window defined as the period between 21 and 75 days post-procedure. Of the 465 patients eligible for the 1 year visit, 309 (66.5%) paid a visit within the 1 year follow-up window defined as the period between 305 and 425 days post-procedure. A detailed summary of the patient accountability at 30 days and 1 year is shown in Table 45.

Table 45:
Patient Visit Accountability

	30-day Visit	1-year Visit
Total patients	545	545
Non-eligible*	18	80
-Death	14	43
-Withdrawal	2	8
-Lost to follow-up	2	29
-Visit not yet due‡	0	0
Eligible	527	465
-Follow-up visit completed	486 (92.2%)	309 (66.5%)
-Missed visit†	41 (7.8%)	156 (33.5%)

* This includes all patients who exited the study prior to the end of the follow-up visit window and those who have not had the visit.
‡ Patients have not reached the end of the visit window and have not completed the follow-up visit yet.
† Data extract date has exceeded the end of the visit window and the patients have not reported the visit data.

The “Attempted Implant” population consisted of all patients entered into the registry with a bicuspid aortic valve. The “Valve Implant” population consisted of those patients for whom the valve implant procedure has started and a “No” was indicated for both “procedure aborted” and “conversion to open heart surgery.” The “Valve Implant” population consists of 540 patients as 5 patients were converted to open heart surgery and did not receive the SAPIEN 3 transcatheter heart valve.

Patient Demographics and Baseline Characteristics

The demographics and baseline characteristics of bicuspid aortic valve patients, as shown in Table 46, present a multimorbid cohort of patients with a mean STS score of 5.5 ± 4.0.

Table 46:
Patient Demographics and Baseline Characteristics - Bicuspid Population
(Attempted Implant Population)

Demographics and Baseline Characteristics	Summary Statistics*
Age - years	73.4 ± 11.1 (545)
Male sex	349 / 545
Society of Thoracic Surgeons (STS) score	5.5 ± 4.0 (538)
New York Heart Association (NYHA) class	
I/II	106 / 535 (19.8%)
III/IV	429 / 535 (80.2%)
Previous myocardial infarction	119 / 544 (21.9%)
Previous intervention	
Coronary artery bypass grafting (CABG)	101 / 543 (18.6%)
Percutaneous coronary intervention (PCI)	138 / 545 (25.3%)
Prior aortic valvuloplasty	34 / 545 (6.2%)
Cerebrovascular accident (CVA)	56 / 545 (10.3%)
Peripheral vascular disease	128 / 544 (23.5%)
Atrial fibrillation	183 / 545 (33.6%)
Permanent pacemaker	54 / 545 (9.9%)
Porcelain aorta	12 / 545 (2.2%)
Hostile chest	44 / 545 (8.1%)
Echocardiographic findings (Valve Implant Population)	
Valve area - cm^2	0.7 ± 0.2 (524)
Mean aortic valve gradient - mmHg	44.9 ± 15.5 (535)
Mean left ventricular ejection fraction (LVEF) %	52.9 ± 15.5 (534)
Moderate or severe aortic regurgitation	91 / 536 (17.0%)
Moderate or severe mitral regurgitation	101 / 438 (23.1%)

*Continuous measures - Mean ± SD (Total no.); categorical measures - n. / Total no. (%).

Safety and Effectiveness Results

Safety Endpoints

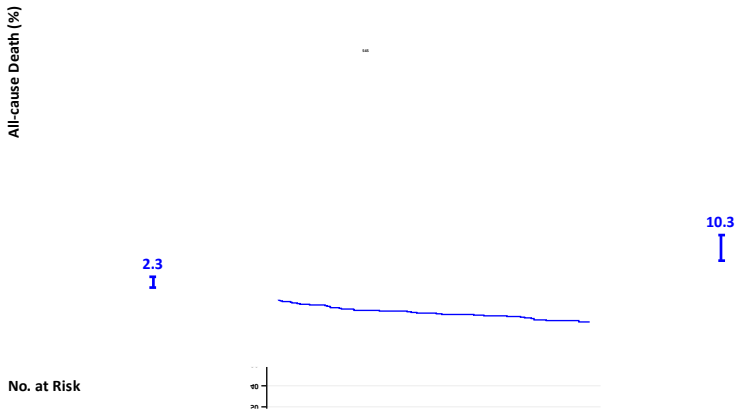
The mortality rates at discharge, 30 days, one-year and the Kaplan-Meier curve for all-cause mortality are shown in Table 47 and Figure 51, respectively. There were a total of 12 deaths reported at 30 days and 43 deaths reported at one year.

Table 47:
Death Rate - Bicuspid Population (Attempted Implant Population)

	Discharge*	30 Days†	1 Year†
All-cause death‡	1.8% (10)	2.3% (12)	10.3% (43)
Cardiac death	1.1% (6)	1.3% (7)	3.0% (13)

*Observed rate - % (n).
† Kaplan-Meier estimate - % (n)
‡ Includes all deaths reported in TVTR and identified through CMS linkage.

Figure 51:
All-Cause Death Rate - Bicuspid Population
(Attempted Implant Population)



The DCRI adjudicated events, including all strokes, TIAs and aortic valve reinterventions at discharge, 30 days and one year are shown in Table 48.

Table 48:
Duke Clinical Research Institute Adjudicated Events - Bicuspid Population
(Attempted Implant Population)

Events	Discharge*	30 Days†	1 Year†
All strokes	1.5% (8, 8)	1.9% (10, 10)	2.7% (13, 13)
Ischemic stroke	1.5% (8, 8)	1.9% (10, 10)	2.7% (13, 13)
Hemorrhagic stroke	0.0% (0, 0)	0.0% (0, 0)	0.0% (0, 0)
Transient ischemic attack (TIA)	0.2% (1, 1)	0.2% (1, 1)	0.2% (1, 1)
Aortic valve reintervention	0.2% (1, 1)	0.2% (1, 1)	0.8% (3, 3)

*Observed rate - % (no. of events, no. of subjects with the event)
†Kaplan-Meier estimate - % (no. of events, no. of subjects with the event)
Note: At the time of this extract, there is one stroke and one aortic valve reintervention that are pending adjudication.

Site Reported Adverse Events

The site reported adverse events at discharge, 30 days and one year for the bicuspid population are shown in Table 49.

Table 49:
Site Reported Adverse Events - Bicuspid Population
(Attempted Implant Population)

Events	Discharge*	30 Days†	1 Year†
Non-valve related readmission	N/A‡	8.7% (50, 45)	26.8% (164, 110)
Conduction/native pacer disturbance req pacer	7.3% (40, 40)	8.6% (46, 46)	9.7% (50, 50)
Minor vascular complication	4.6% (25, 25)	5.0% (28, 27)	5.0% (28, 27)
Unplanned vascular surgery or intervention	3.5% (19, 19)	3.5% (19, 19)	3.8% (20, 20)
Cardiac arrest	2.9% (16, 16)	3.0% (16, 16)	3.0% (16, 16)
Atrial fibrillation	2.4% (13, 13)	2.4% (13, 13)	2.4% (13, 13)
Hematoma at access site	2.2% (12, 12)	2.2% (12, 12)	2.2% (12, 12)
Ischemic Stroke	1.5% (8, 8)	2.0% (11, 11)	2.6% (13, 13)
Other bleed	2.0% (12, 11)	2.0% (12, 11)	2.0% (12, 11)
Unplanned other cardiac surgery or intervention	1.3% (7, 7)	1.9% (10, 10)	3.3% (16, 15)
Bleeding at access site	1.8% (10, 10)	1.8% (10, 10)	1.8% (10, 10)
Major vascular complication	1.1% (6, 6)	1.1% (6, 6)	1.1% (6, 6)
Perforation with or w/o tamponade	1.1% (6, 6)	1.1% (6, 6)	1.1% (6, 6)
Myocardial infarction	0.7% (4, 4)	0.9% (5, 5)	1.5% (7, 7)
Percutaneous coronary intervention (PCI)	0.7% (5, 4)	0.9% (6, 5)	1.2% (7, 6)
Valve Related Readmission	N/A‡	0.8% (5, 4)	2.1% (12, 9)
Coronary Compression or Obstruction	0.7% (4, 4)	0.7% (4, 4)	0.7% (4, 4)
New requirement for dialysis	0.4% (2, 2)	0.6% (3, 3)	0.9% (4, 4)
Major Bleeding Event	N/A‡	0.4% (2, 2)	1.3% (6, 5)
Conduction/native pacer disturbance requiring implantable cardioverter defibrillator (ICD)	0.2% (1, 1)	0.4% (2, 2)	1.6% (6, 6)
Genitourinary (GU) Bleed	0.4% (2, 2)	0.4% (2, 2)	0.4% (2, 2)
Annular Dissection	0.4% (2, 2)	0.4% (2, 2)	0.4% (2, 2)
Aortic Valve Reintervention	0.2% (1, 1)	0.2% (1, 1)	1.0% (4, 4)
Transient Ischemic Attack	0.2% (1, 1)	0.2% (1, 1)	0.2% (1, 1)
Aortic Dissection	0.2% (1, 1)	0.2% (1, 1)	0.2% (1, 1)
Device recapture or retrieval	0.2% (1, 1)	0.2% (1, 1)	0.2% (1, 1)
Retroperitoneal bleeding	0.2% (1, 1)	0.2% (1, 1)	0.2% (1, 1)
Endocarditis	0.0% (0, 0)	0.0% (0, 0)	0.6% (2, 2)
Device Thrombosis	0.0% (0, 0)	0.0% (0, 0)	0.2% (1, 1)
Undetermined Stroke	0.0% (0, 0)	0.0% (0, 0)	0.3% (1, 1)

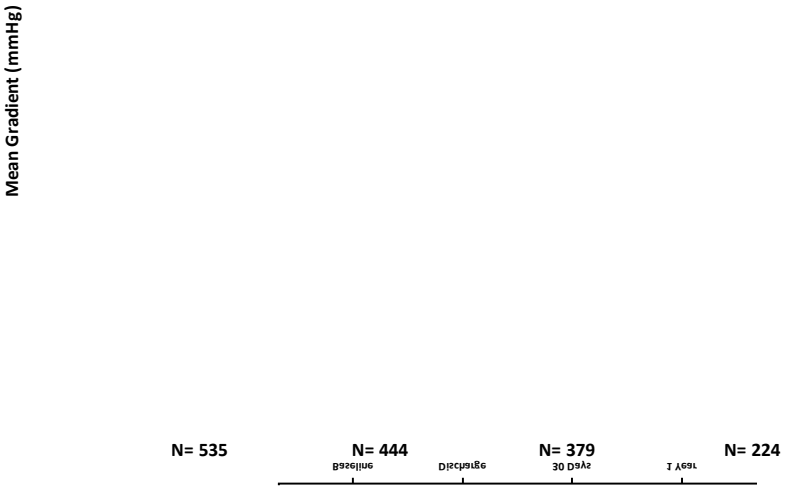
*Observed rate - % (no. of events, no. of subjects with the event)
† Kaplan-Meier estimate - % (no. of events, no. of subjects with the event)
‡ N/A = Event not collected on case report form at the time period. % (no. of events, no. of subjects with the event)

Effectiveness Endpoints

Valve Performance

The bicuspid aortic valve echocardiographic performance data are summarized in Figures 52-54. The mean gradients 44.9 ± 15.5 mmHg at baseline to 12.0 ± 5.2 mmHg at 30 days and 13.4 ± 9.6 mmHg at one year. Moderate/severe PVL was observed in 4.8% of the patients at 30 days and 5.1% of the patients at one year.

Figure 52:
Aortic Mean Gradient - Bicuspid Population
(Valve Implant Population)

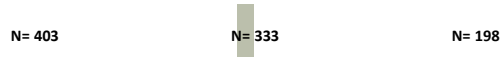


Note: Line plot with mean and standard deviation. The total number of patients at each time point only counted the patients with valid values.

Figure 53:
Aortic Regurgitation - Bicuspid Population
(Valve Implant Population)

Note: The total number of patients at each time point only counted the patients with valid values.

Figure 54:
Aortic Paravalvular Leak - Bicuspid Population
(Valve Implant Population)

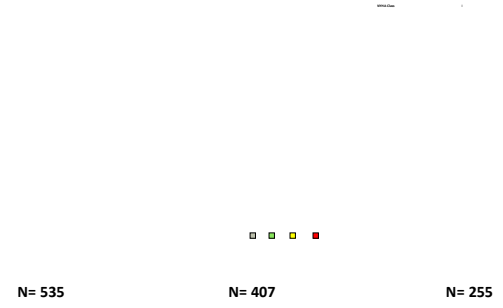


Note: The total number of patients at each time point only counted the patients with valid values.

NYHA Class

The NYHA class distributions at baseline, 30-day visit and one-year visit and the NYHA class changes from baseline to the 30-day visit and to one-year visit are shown in Figure 55 and Table 50, respectively. The majority (84.0% and 82.5%) of the patients had an improved NYHA class at the 30-day visit and one year visit, respectively.

Figure 55:
NHYA Functional Class - Bicuspid Population
(Valve Implant Population)



Note: The total number of patients at each time point only counted the patients with valid values.

Table 50:
NHYA Changes - Bicuspid Population
(Valve Implant Population)

	NYHA Class Change*		
	Improved	**Same**	**Worsened**
Baseline to 30-day visit	340/405 (84.0%)	54/405 (13.3%)	11/405 (2.7%)
Baseline to 1-year visit	208/252 (82.5%)	32/252 (12.7%)	12/252 (4.8%)

*n/Total no. (%); the total no. only counted the patients with valid values.

Five Meter Walk Test

The results of the five-meter walk test are summarized in Table 51.

Table 51:
Five-Meter Walk Test - Bicuspid Population
(Valve Implant Population)

Visit	Five Meter Walk Time (seconds)*
Baseline	8.0 ± 4.8 (411)
30-day visit	6.7 ± 2.8 (119)
Change from baseline to 30-day visit	-1.2 ± 3.5 (101)
1-year visit	6.2 ± 2.4 (43)
Change from baseline to 1-year visit	-1.6 ± 3.6 (35)

*Mean ± SD (Total no.). The total number of patients at each time point only counted the patients with valid values.

Length of Stay

The mean index hospitalization stay was 4.7 days, which included an average of 1.6 days in the intensive care unit (ICU), as summarized in Table 52.

Table 52:
Index Hospitalization Stay - Bicuspid Population
(Attempted Implant Population)

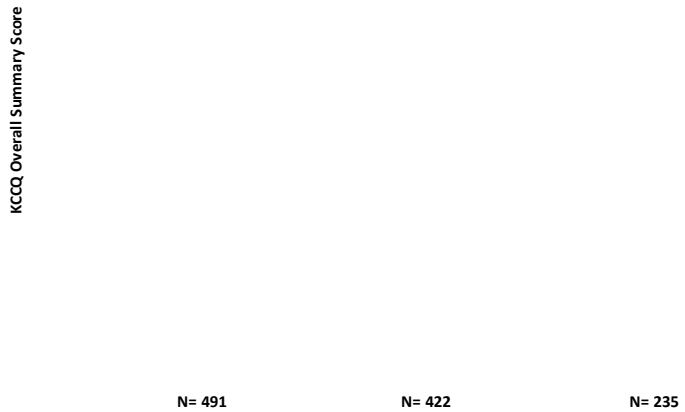
	Length (days)*
Index hospitalization duration (day)	4.7 ± 3.8 (545)
Intensive care stay (day)	1.6 ± 2.6 (537)

*Mean ± SD (Total no.).

Quality of Life (QoL)

The QoL at baseline, 30 days and one year as measured by the KCCQ overall summary score, is shown in Figure 56. The mean KCCQ summary score improved from 44.0 at baseline to 77.7 at one year.

Figure 56:
KCCQ Overall Summary - Bicuspid Population
(Valve Implant Population)



Note: Line plot with mean and standard deviation. The total number of patients at each time point only counted the patients with valid values.

Procedural Information

The procedure information is presented in Table 53. The most common delivery approach for the bicuspid population was the transfemoral approach, which was used in 94.7% (516/545) of cases, followed by the transapical and transaortic in 1.3% (7/545) and 1.3% (7/545) of cases, respectively, and other alternative approaches (subclavian, transcarotid, and other) in 2.8% (15/545). The device was successfully implanted in 539/544 (99.1%) of patients; five patients were converted to open heart surgery 0.9% (5/545) due to ventricular rupture (1 patient), annulus rupture (1 patient), coronary occlusion (1 patient) and other (2 patients). There were no cases of valve embolization. Device implant success is defined as correct positioning of a single prosthetic heart valve in the proper anatomical location.

Table 53:
Procedural Data Summary - Bicuspid Population
(Attempted Implant Population)

	Summary Statistics*
Operator reason for procedure	
Inoperable/Extreme risk	115/545 (21.1%)
High risk	394/545 (72.3%)
Intermediate risk	24/545 (4.4%)
Low risk	12/545 (2.2%)
Implant approach	
Transfemoral	516/545 (94.7%)
Transapical	7/545 (1.3%)
Transaortic	7/545 (1.3%)
Subclavian/axillary	9/545 (1.7%)
Transcarotid	3/545 (0.6%)
Other	3/545 (0.6%)
Procedure status	
Elective	497/545 (91.2%)
Urgent	47/545 (8.6%)
Emergency	1/545 (0.2%)
Valve size	
20 mm	16/545 (2.9%)
23 mm	95/545 (17.4%)
26 mm	220/545 (40.4%)
29 mm	214/545 (39.3%)
Primary procedure indication	
Aortic stenosis (Primary)	535/545 (98.2%)
Aortic insufficiency (Primary)	1/545 (0.2%)
Mixed aortic stenosis/aortic insufficiency	9/545 (1.7%)
Cardiopulmonary bypass (CPB)	5/545 (0.9%)
CPB status	
Elective	2/5 (40.0%)
Emergent	3/5 (60.0%)
CPB time (min)	52.2 ± 24.2 (5)
Type of anesthesia	
General anesthesia	389/545 (71.4%)
Moderate sedation	151/545 (27.7%)
Epidural	1/545 (0.2%)
Combination	4/545 (0.7%)

	Summary Statistics*
Total procedure time (min)	109.3 ± 49.5 (545)
Fluoroscopy time (min)	19.9 ± 10.4 (528)
Device implanted successfully	539/544 (99.1%)
Procedure aborted	0/545 (0.0%)
Conversion to open heart surgery	5/545 (0.9%)
Ventricular rupture	1/5 (20.0%)
Annulus rupture	1/5 (20.0%)
Coronary occlusion	1/5 (20.0%)
Other	2/5 (40.0%)
Mechanical assist device in place at start of procedure	5/545 (0.9%)
Intra-aortic balloon pump (IABP)	3/5 (60.0%)
Catheter based assist device	2/5 (40.0%)

*Categorical measures – no./Total no. (%); continuous measures - mean ± SD (Total no.). The total no. only counted the patients with valid values at the time point.

SAPIEN 3 THV VALVE-IN-VALVE – STS/ACC TRANSCATHETER VALVE THERAPY REGISTRY (TVTR) ANALYSIS

Patient Accountability

At the time of database extract, of the 314 patients in the aortic valve-in-valve cohort, 299 patients were eligible for the 30-day visit, and 252 (84.3%) patients paid a visit within the 30-day follow-up window defined as the period between the discharge + 1 day or 21 days post-procedure (whichever occurred first) and 75 days post-procedure; of the 311 patients (SAPIEN XT and SAPIEN 3 valve patients combined) in the mitral valve-in-valve cohort, 290 patients were eligible for the 30-day visit, and 244 (84.1%) patients paid a visit within the 30-day follow-up window. A detailed summary of the patient accountability at 30 days for the two cohorts is shown in Table 54.

Table 54:
Patient Accountability at 30-Day Follow-Up Visit

	Aortic Valve-in-Valve	Mitral Valve-in-Valve		
		SAPIEN XT	SAPIEN 3	All
Total patients	314	241	70	311
Non-eligible	15	15	6	21
-Death	11	15	4	19
-Withdrawal	0	0	0	0
-Lost to follow-up	1	0	2	2
-Visit not yet due	3	0	0	0
Eligible	299	226	64	290
-Follow-up visit completed	252 (84.3%)	196 (86.7%)	48 (75.0%)	244 (84.1%)
-Missed Visit	47 (15.7%)	30 (13.3%)	16 (25.0%)	46 (15.9%)

The “Attempted Implant” population consisted of all patients for whom the first vascular access was attempted. The “Valve Implant” population consisted of those patients for whom the valve implant procedure has started and a “No” was indicated for both “procedure aborted” and “conversion to open heart surgery.” The number of patients in each analysis population of the aortic valve-in-valve and mitral valve-in-valve cohorts is shown in Table 55.

Table 55:
Analysis Populations

Analysis Population	Aortic Valve-in-Valve	Mitral Valve-in-Valve		
		SAPIEN XT	SAPIEN 3	All
All Enrolled population	314	241	70	311
Attempted Implant population	314	241	70	311
Valve Implant population	314	236	69	305

Study Population Demographics and Baseline Characteristics

The demographics and baseline characteristics of both the aortic and mitral valve-in-valve patients, as shown in Tables 56 and 57, present an elderly, multimorbid cohort of patients, consistent with the high operative risk of the populations.

Table 56:
Patient Demographics and Baseline Characteristics - Aortic Valve-in-Valve
(Attempted Implant Population)

Demographics and Baseline Characteristics	Summary Statistics*
Age – years	74.3 ± 12.10 (313)
Male sex	188/314
Society of Thoracic Surgeons (STS) score	9.0 ± 8.0 (304)
New York Heart Association (NYHA) class	
I/II	45/312 (14.4%)
III/IV	267/312 (85.6%)
Previous myocardial infarction	62/313 (19.8%)
Previous intervention	
Coronary artery bypass grafting (CABG)	119/314 (37.9%)
Percutaneous coronary intervention (PCI)	56/314 (17.8%)
Prior aortic valvuloplasty	10/306 (3.3%)
Cerebrovascular accident (CVA)	46/313 (14.7%)
Peripheral vascular disease	79/314 (25.2%)
Atrial fibrillation	126/314 (40.1%)
Permanent pacemaker	53/314 (16.9%)
Porcelain aorta	19/314 (6.1%)
Hostile chest	58/314 (18.5%)
Echocardiographic findings (Valve Implant Population)	
Valve area - cm^2	0.8 ± 0.4 (230)
Mean aortic-valve gradient – mmHg	39.3 ± 15.8 (251)
Mean left ventricular ejection fraction (LVEF)%	52.2 ± 13.1 (308)
Moderate or severe aortic regurgitation	168/310 (54.2%)
Moderate or severe mitral regurgitation	126/261 (48.3%)

*Continuous measures - Mean ± SD (Total no.); Categorical measures - n. / Total no. (%)

Table 57:
Patient Demographics and Baseline Characteristics - Mitral Valve-in-Valve (Attempted Implant Population)

Demographics and Baseline Characteristics	Summary Statistics*		
	SAPIEN XT	SAPIEN 3	All
Age - years	73.9 ± 12.4 (241)	71.5 ± 15.0 (70)	73.4 ± 13.1 (311)
Male sex	88/241 (36.5%)	32/70 (45.7%)	120/311 (38.6%)
Society of Thoracic Surgeons (STS) score	13.2 ± 9.1 (237)	12.2 ± 8.7 (65)	13.0 ± 8.98 (302)
New York Heart Association (NYHA) class			
I/II	30/238 (12.6%)	3/70 (4.3%)	33/308 (10.7%)
III/IV	208/238 (87.4%)	67/70 (95.7%)	275/308 (89.3%)
Previous myocardial infarction	47/239 (19.7%)	18/70 (25.7%)	65/309 (21.0%)
Previous intervention			
Coronary artery bypass grafting (CABG)	93/236 (39.4%)	28/69 (40.6%)	121/305 (39.7%)
Percutaneous coronary intervention (PCI)	32/238 (13.4%)	9/69 (13.0%)	41/307 (13.4%)
Cerebrovascular accident (CVA)	45/241 (18.7%)	15/70 (21.4%)	60/311 (19.3%)
Peripheral vascular disease	42/239 (17.6%)	6/70 (8.6%)	48/309 (15.5%)
Atrial fibrillation/flutter	155/241 (64.3%)	50/70 (71.4%)	205/311 (65.9%)
Permanent pacemaker	74/240 (30.8%)	20/69 (29.0%)	94/309 (30.4%)
Porcelain aorta	6/240 (2.5%)	1/69 (1.4%)	7/309 (2.3%)
Hostile chest	41/241 (17.0%)	6/70 (8.6%)	47/311 (15.1%)
Echocardiographic findings (Valve Implant Population)			
Mitral valve area - cm^2	1.5 ± 0.9 (153)	1.4 ± 1.0 (46)	1.5 ± 0.88 (199)
Mean mitral-valve gradient - mmHg	12.7 ± 5.5 (215)	13.7 ± 6.2 (65)	12.9 ± 5.65 (280)
Mean left ventricular ejection fraction (LVEF), %	54.4 ± 11.7 (230)	53.8 ± 13.9 (67)	54.3 ± 12.2 (297)
Moderate or severe aortic regurgitation	35/231 (15.2%)	7/67 (10.5%)	42/298 (14.1%)
Moderate or severe mitral regurgitation	149/233 (63.9%)	39/68 (57.4%)	188/301 (62.5%)

*Continuous measures - Mean ± SD (Total no.); categorical measures - n. / Total no. (%). The total no. only counted the patients with valid values.

Safety and Effectiveness Results

Aortic Valve-in-Valve

Safety Endpoints

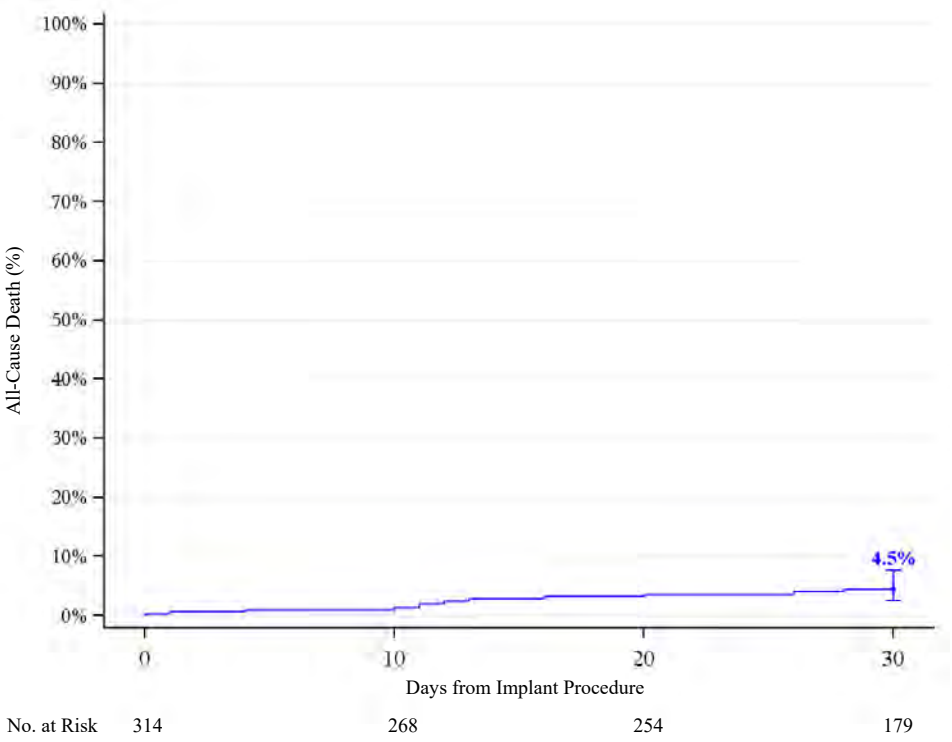
The mortality rates at discharge and 30 days and the Kaplan-Meier curve for all-cause mortality for the aortic valve-in-valve cohort are shown in Table 58 and Figure 57, respectively. There were a total of 12 deaths reported at 30 days.

Table 58:
Death Rate - Aortic Valve-in-Valve (Attempted Implant Population)

	Discharge*	30 Days†
All-cause death	2.5% (8)	4.5% (12)
Cardiac death	1.3% (4)	2.2% (6)

*Observed rate - % (n)
†Kaplan-Meier estimate - % (n)

Figure 57:
All-Cause Death Rate - Aortic Valve-in-Valve
(Attempted Implant Population)



The DCRI adjudicated events, including all strokes/TIAs and aortic valve reinterventions at discharge and 30 days for the aortic valve-in-valve cohort, are shown in Table 59.

Table 59:
Duke Clinical Research Institute Adjudicated Events - Aortic Valve-in-Valve
(Attempted Implant Population)

Events	Discharge*	30 Days†
All stroke	1.0% (3, 3)	1.0% (3, 3)
Ischemic stroke	1.0% (3, 3)	1.0% (3, 3)
Hemorrhagic stroke	0.0% (0, 0)	0.0% (0, 0)
Transient ischemic attack (TIA)	0.0% (0, 0)	0.0% (0, 0)
Aortic valve reintervention	0.3% (1, 1)	0.3% (1, 1)

*Observed rate - % (no. of events, no. of subjects with the event)
†Kaplan-Meier estimate - % (no. of events, no. of subjects with the event)

Site Reported Adverse Events

The site reported adverse events at discharge and 30 days for the aortic valve-in-valve cohort is shown in Table 60.

Table 60:
Site Reported Adverse Events - Aortic Valve-in-Valve
(Attempted Implant Population)

Events	Discharge*	30 Days†
Non-valve related readmission	N/A	5.9% (15, 15)
Minor vascular complication	3.8% (12, 12)	4.3% (13, 13)
Conduction/native pacer disturbance requiring pacer	2.9% (9, 9)	3.0% (9, 9)
Hematoma at access site	2.9% (9, 9)	2.9% (9, 9)
Atrial fibrillation	2.5% (8, 8)	2.6% (8, 8)
Bleeding at access site	2.5% (8, 8)	2.5% (8, 8)
Cardiac arrest	2.5% (8, 8)	2.5% (8, 8)
Unplanned vascular surgery or intervention	1.6% (5, 5)	2.0% (7, 6)
Percutaneous coronary intervention (PCI)	1.3% (4, 4)	1.7% (5, 5)
Other bleed	1.3% (4, 4)	1.3% (4, 4)
Coronary compression or obstruction	1.0% (3, 3)	1.0% (3, 3)
Hemorrhagic stroke	0.6% (2, 2)	1.1% (3, 3)
Life threatening bleeding	N/A	1.1% (3, 3)
Unplanned other cardiac surgery or intervention	1.0% (3, 3)	1.0% (3, 3)
Major bleeding event	N/A	0.8% (2, 2)
Major vascular complication	0.6% (2, 2)	0.6% (3, 2)
Myocardial infarction	0.3% (1, 1)	0.7% (2, 2)
New requirement for dialysis	0.6% (2, 2)	0.8% (2, 2)
Other device related event	0.6% (2, 2)	0.6% (2, 2)
Aortic valve re-intervention	0.0% (0, 0)	0.4% (1, 1)
Conduction/native pacer disturbance requiring implantable cardioverter defibrillator (ICD)	0.3% (1, 1)	0.3% (1, 1)
Device migration	0.3% (1, 1)	0.3% (1, 1)
Gastrointestinal bleeding (GI) bleed	0.3% (1, 1)	0.3% (1, 1)
Transapical related event	0.3% (1, 1)	0.3% (1, 1)
Valve related readmission	N/A	0.4% (1, 1)
Device thrombosis	0.0% (0, 0)	0.0% (0, 0)

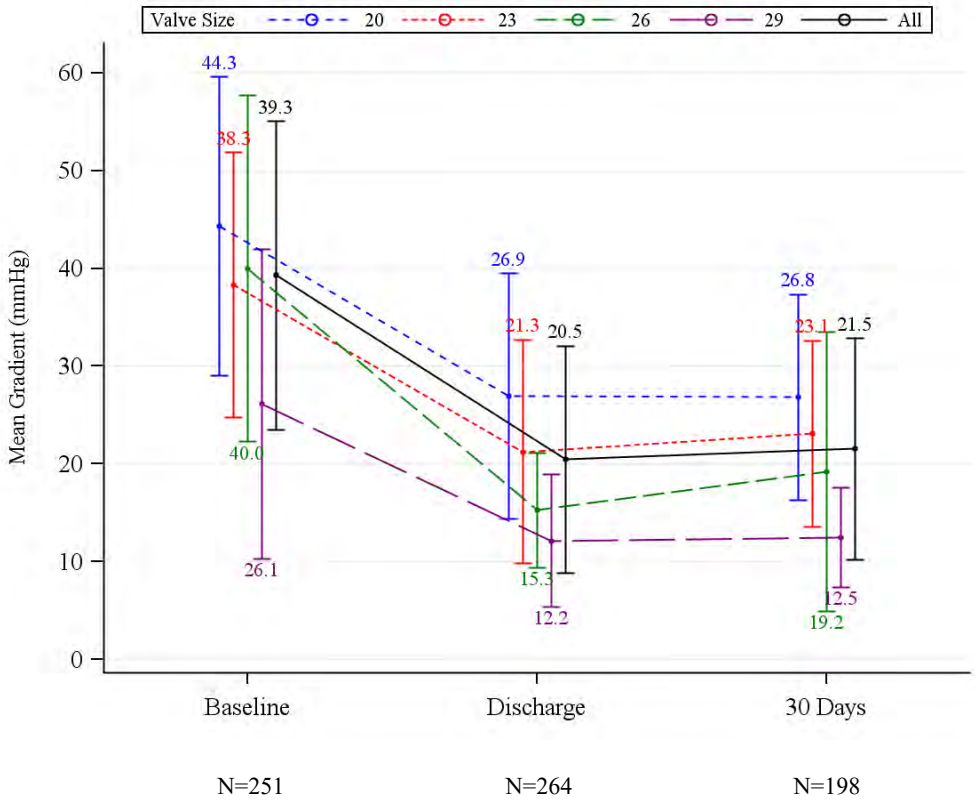
*Observed rate - % (no. of events, no. of subjects with the event)
†Kaplan-Meier estimate - % (no. of events, no. of subjects with the event)

Effectiveness Endpoints

Valve Performance

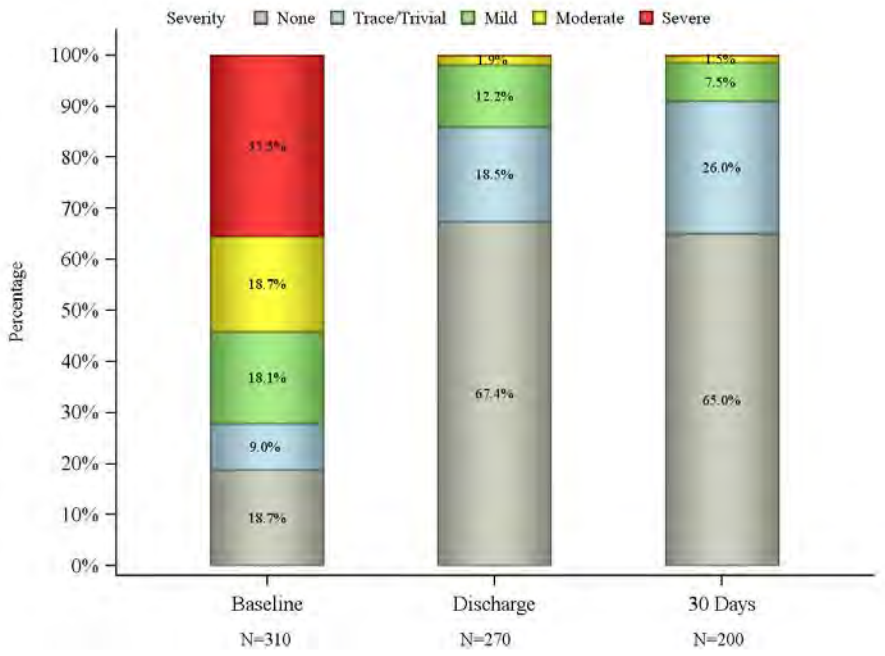
The aortic valve-in-valve echocardiographic performance data are summarized in Figures 58-60. The mean gradients improved from 39.3 ± 15.8 mmHg at baseline to 21.5 ± 11.3 mmHg at 30 days. Moderate/severe aortic regurgitation was observed in 54.2% of the patients at baseline, which decreased to 1.5% of the patients at 30 days.

Figure 58:
Mean Gradient by Visit - Aortic Valve-in-Valve
(Valve Implant Population)



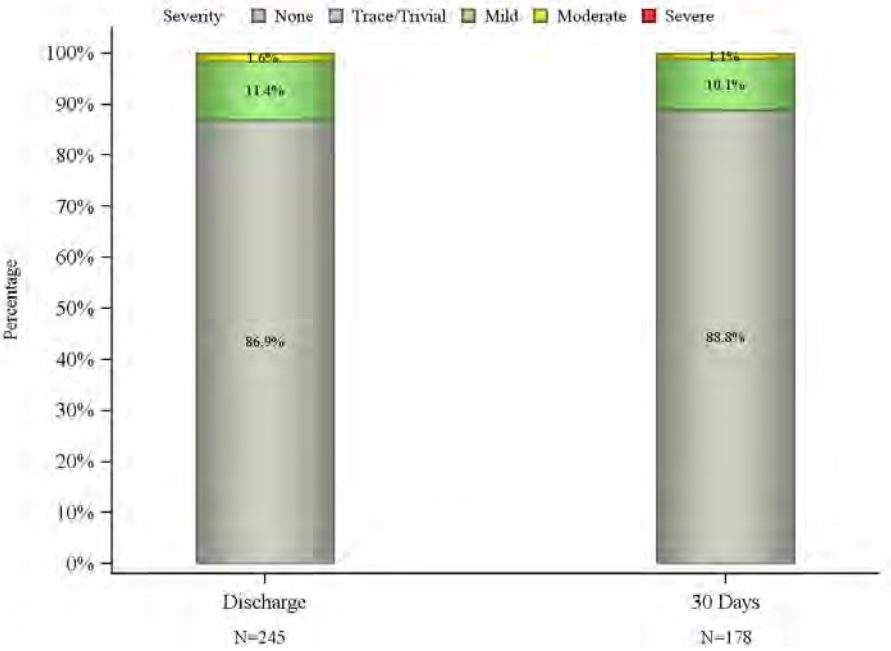
Note: Line plot with mean and standard deviation. The total number of patients at each time point only counted the patients with valid values.

Figure 59:
Aortic Regurgitation by Visit - Aortic Valve-in-Valve
(Valve Implant Population)



Note: The total number of patients at each time point only counted the patients with valid values.

Figure 60:
Paravalvular Regurgitation by Visit - Aortic Valve-in-Valve
(Valve Implant Population)

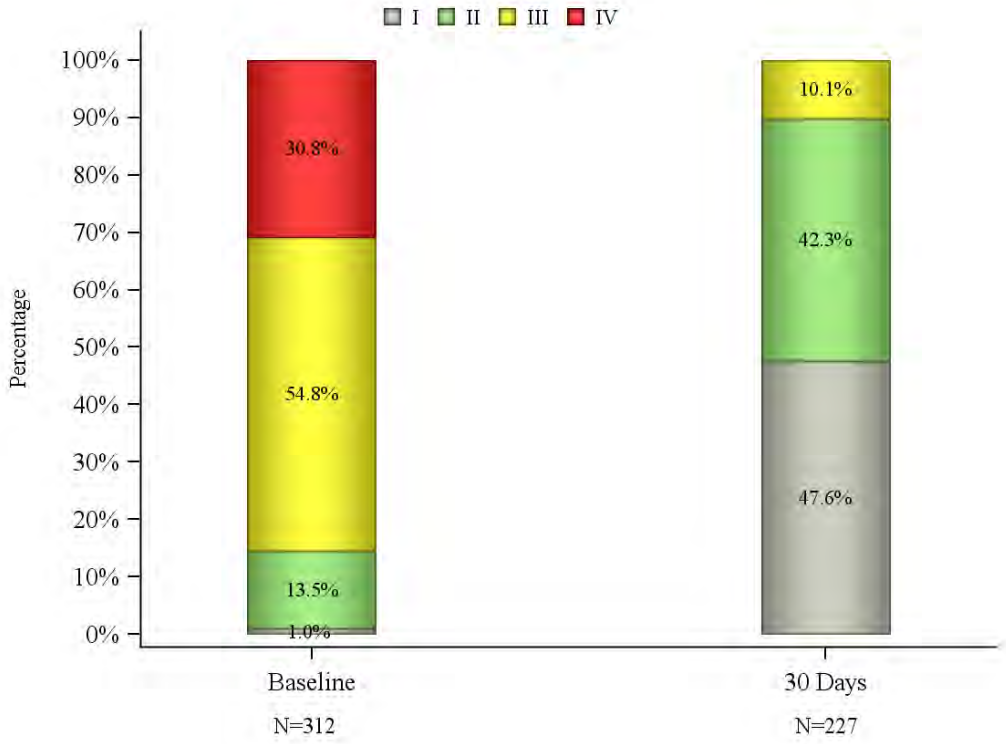


Note: The total number of patients at each time point only counted the patients with valid values.

NYHA Class

The NYHA class distributions at baseline and the 30-day visit and the NYHA class changes from baseline to the 30-day visit are shown in Figure 61 and Table 61, respectively. The majority (85.4%) of the patients had an improved NYHA class at the 30-day visit.

Figure 61:
NYHA Functional Class - Aortic Valve-in-Valve
(Valve Implant Population)



Note: The total number of patients at each time point only counted the patients with valid values.

Table 61:
NYHA Class Change - Aortic Valve-in-Valve
(Valve Implant Population)

	NYHA Class Change*		
	Improved	**Same**	**Worsened**
Baseline to 30-day visit	193/226 (85.4%)	31/226 (13.7%)	2/226 (0.9%)

*n/Total no. (%); the total no. only counted the patients with valid values.

Five-Meter Walk Test

The results of the five-meter walk test are summarized in Table 62.

Table 62:
Five-Meter Walk Test - Aortic Valve-in-Valve (Valve Implant Population)

Visit*	Five Meter Walk Time (seconds)†
Baseline	7.6 ± 3.9 (209)
30-day visit	5.9 ± 2.4 (68)
Change from baseline to 30 day visit	-1.4 ± 2.9 (51)

*There were up to 3 five-meter walk tests for each patient at each visit, and the results were averaged.
†Mean ± SD (Total no.). The total number of patients at each time point only counted the patients with valid values.

Length of Stay

The mean index hospitalization stay was 4.9 days, which included an average of 1.8 days in the intensive care unit (ICU), as summarized in Table 63.

Table 63:
Index Hospitalization Stay - Aortic Valve-in-Valve
(Attempted Implant Population)

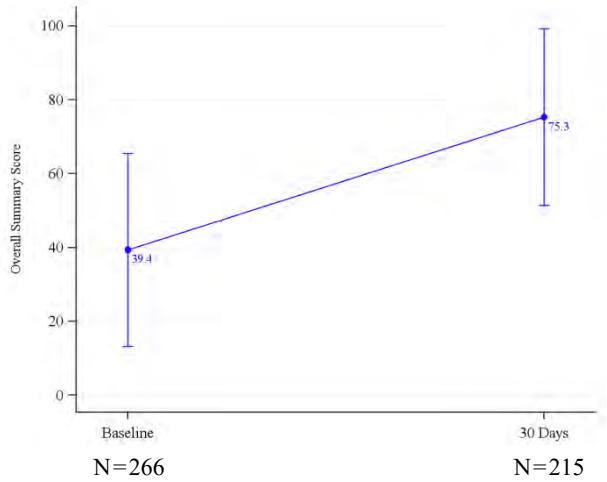
	Length (days)*
Index Hospitalization Stay	4.9 ± 3.9 (314)
Intensive Care Stay	1.8 ± 2.6 (311)

*Mean ± SD (Total no.).

Quality of Life (QoL)

The QoL at baseline and 30 days as measured by the KCCQ clinical summary score is shown in Figure 62. The mean KCCQ summary score improved from 39.4 at baseline to 75.3 at 30 days.

Figure 62:
KCCQ Overall Summary Score - Aortic Valve-in-Valve
(Valve Implant Population)



Note: Line plot with mean and standard deviation. The total number of patients at each time point only counted the patients with valid values.

Procedural Information

The procedure information is presented in Table 64. The most common delivery approach for the aortic valve-in-valve implantation was the transfemoral approach, which was used in 93.0% (292/314) of cases, followed by the transapical approach in 4.1% (13/314) of cases, and other alternative approaches (transaortic, subclavian, and other) in 2.9% (9/314) of cases. There were no aborted procedures or conversions to open heart surgery. The overall device success rate was 88.9% (272/306), which was defined as the following:

- Successful vascular access, delivery, and deployment of the device and successful retrieval of the delivery system, and
- Correct position of the device in the proper anatomical location, and
- Intended performance of the prosthetic heart valve (aortic valve area > 1.2 cm^2 and mean aortic valve gradient < 20 mmHg or peak velocity < 3 m/s, without moderate or severe prosthetic valve regurgitation), and
- Only one valve implanted in the proper anatomical location.

Table 64:
Procedural Data Summary - Aortic Valve-in-Valve
(Attempted Implant Population)

Procedural Data	Summary Statistics*
Operator Reason for Procedure	
Inoperable/extreme risk	80/313 (25.6%)
High risk	219/313 (70.0%)
Intermediate risk	10/313 (3.2%)
Low risk	4/313 (1.3%)
Implant Approach	
Transfemoral	292/314 (93.0%)
Transapical	13/314 (4.1%)
Transaortic	1/314 (0.3%)
Subclavian/axillary	6/314 (1.9%)
Other†	2/314 (0.6%)
Prior Valve Type	
Bioprosthetic stented	159/308 (51.6%)
Bioprosthetic stentless	79/308 (25.6%)
Procedure Status	
Elective	231/314 (73.6%)
Urgent	74/314 (23.6%)
Emergency	8/314 (2.5%)
Salvage	1/314 (0.3%)
Valve Size	
20 mm	83/314 (26.4%)
23 mm	130/314 (41.4%)
26 mm	57/314 (18.2%)
29 mm	44/314 (14.0%)
Primary Procedure Indication	
Aortic stenosis (Primary)	95/313 (30.4%)
Aortic insufficiency (Primary)	19/313 (6.1%)
Mixed aortic stenosis/aortic insufficiency	10/313 (3.2%)
Failed bioprosthetic valve	189/313 (60.4%)
Cardiopulmonary Bypass (CPB)	5/314 (1.6%)
CPB status	
Elective	4/5 (80.0%)
Emergent	1/5 (20.0%)
CPB time (min)	90.5 ± 140.9 (4)
Type of Anesthesia	
General anesthesia	240/314 (76.4%)
Moderate sedation	72/314 (22.9%)
Epidural	0/314 (0.0%)
Combination	2/314 (0.6%)
Total procedure time (min)	110.7 ± 63.0 (314)
Fluoroscopy time (min)	21.2 ± 16.1 (304)
Device success	272/306 (88.9%)
Procedure aborted	0/314 (0.0%)
Conversion to open heart surgery	0/314 (0.0%)
Mechanical assist device in place at start of procedure	5/313 (1.6%)

Procedural Data	Summary Statistics*
Intra-aortic balloon pump (IABP)	2/5 (40.0%)
Catheter based assist device	3/5 (60.0%)

*Categorical measures – no./Total no. (%); continuous measures - mean ± SD (Total no.). The total no. only counted the patients with valid values at the time point.

†The data collection form was changed in February 2013 to specify non-transfemoral (non-TF), non-transapical (non-TA) approaches rather than "other"; hence, "other" likely included the non-TF and non-TA approaches.

Mitral Valve-in-Valve

Safety Endpoints

The mortality rates at discharge and 30 days and the Kaplan-Meier curve for all-cause mortality for the mitral valve-in-valve cohort are shown in Table 65 and Figure 63, respectively. There were 16 reported deaths in the SAPIEN XT valve patients and 4 in the SAPIEN 3 valve patients at 30 days.

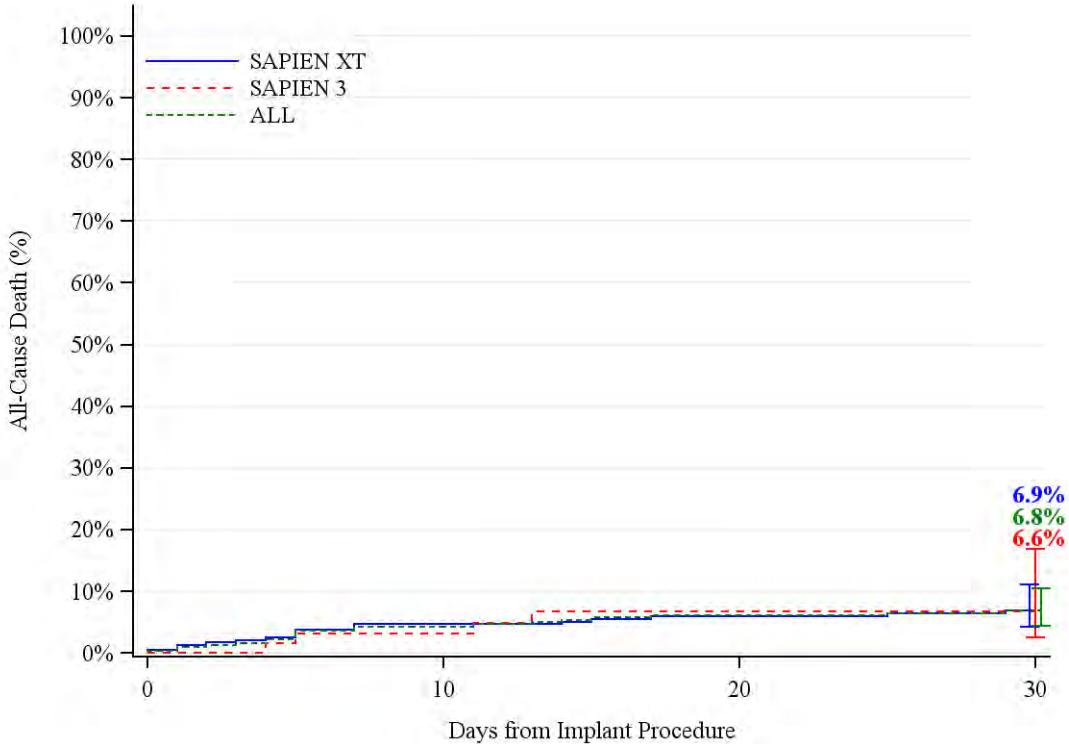
Table 65:
Death Rate - Mitral Valve-in-Valve (Attempted Implant Population)

Event	Discharge*			30 Days†		
	SAPIEN XT	SAPIEN 3	All	SAPIEN XT	SAPIEN 3	All
All-cause death	5.0% (12)	5.7% (4)	5.1% (16)	6.9% (16)	6.6% (4)	6.8% (20)
Cardiac death	3.7% (9)	4.3% (3)	3.9% (12)	4.2% (10)	4.9% (3)	4.3% (13)

*Observed rate - % (n)

†Kaplan-Meier estimate - % (n)

Figure 63:
All-Cause Death Rate - Mitral Valve-in-Valve
(Attempted Implant Population)



No. at Risk				
SAPIEN XT	241	216	209	186
SAPIEN 3	70	56	52	45
ALL	311	272	261	231

The DCRI-adjudicated events, including all strokes/TIAs, heart failure readmissions, and mitral valve reinterventions at discharge and 30 days, for the mitral valve-in-valve cohort are shown in Table 66.

Table 66:
Duke Clinical Research Institute Adjudicated Events - Mitral Valve-in-Valve
(Attempted Implant Population)

Events	Discharge*			30 Day†		
	SAPIEN XT	SAPIEN 3	All	SAPIEN XT	SAPIEN 3	All
All stroke	0.4% (1, 1)	1.4% (1, 1)	0.6% (2, 2)	0.4% (1, 1)	1.5% (1, 1)	0.7% (2, 2)
Ischemic stroke	0.4% (1, 1)	1.4% (1, 1)	0.6% (2, 2)	0.4% (1, 1)	1.5% (1, 1)	0.7% (2, 2)
Hemorrhagic stroke	0.0% (0, 0)	0.0% (0, 0)	0.0% (0, 0)	0.0% (0, 0)	0.0% (0, 0)	0.0% (0, 0)
Transient ischemic attack (TIA)	0.0% (0, 0)	0.0% (0, 0)	0.0% (0, 0)	0.0% (0, 0)	0.0% (0, 0)	0.0% (0, 0)
Readmission - heart failure	N/A	N/A	N/A	1.0% (2, 2)	0.0% (0, 0)	0.8% (2, 2)
Mitral valve reintervention	0.0% (0, 0)	0.0% (0, 0)	0.0% (0, 0)	0.5% (1, 1)	0.0% (0, 0)	0.4% (1, 1)

*Observed rate - % (no. of events, no. of subjects with the event)
†Kaplan-Meier estimate - % (no. of events, no. of subjects with the event)

Site Reported Adverse Events

The site reported adverse events at discharge and 30 days for the mitral valve-in-valve cohort are shown in Table 67.

Table 67:
Site Reported Adverse Events - Mitral Valve-in-Valve
(Attempted Implant Population)

Events	Discharge*			30 Day†		
	SAPIEN XT	SAPIEN 3	All	SAPIEN XT	SAPIEN 3	All
Other bleed	5.4% (13, 13)	4.3% (3, 3)	5.1% (16, 16)	6.1% (14, 14)	4.4% (3, 3)	5.8% (17, 17)
Readmission - not cardiac	N/A	N/A	N/A	5.8% (12, 12)	0.0% (0, 0)	4.6% (12, 12)
Atrial septal defect closure following transseptal catheterization	4.6% (11, 11)	5.7% (4, 4)	4.8% (15, 15)	4.6% (11, 11)	5.7% (4, 4)	4.9% (15, 15)
Cardiac arrest	4.1% (10, 10)	2.9% (2, 2)	3.9% (12, 12)	4.2% (10, 10)	3.2% (2, 2)	4.0% (12, 12)
Unplanned other cardiac surgery or intervention	3.3% (8, 8)	0.0% (0, 0)	2.6% (8, 8)	3.8% (9, 9)	0.0% (0, 0)	3.0% (9, 9)
Atrial fibrillation	3.3% (8, 8)	1.4% (1, 1)	2.9% (9, 9)	3.4% (8, 8)	1.5% (1, 1)	2.9% (9, 9)
New requirement for dialysis	2.9% (7, 7)	1.4% (1, 1)	2.6% (8, 8)	3.0% (7, 7)	1.6% (1, 1)	2.7% (8, 8)
Bleeding at access site	2.5% (6, 6)	1.4% (1, 1)	2.3% (7, 7)	2.5% (6, 6)	1.4% (1, 1)	2.3% (7, 7)
Unplanned vascular surgery or intervention	2.5% (6, 6)	2.9% (2, 2)	2.6% (8, 8)	2.5% (6, 6)	3.2% (2, 2)	2.6% (8, 8)
Perforation with or w/o tamponade	2.1% (5, 5)	0.0% (0, 0)	1.6% (5, 5)	2.1% (5, 5)	0.0% (0, 0)	1.6% (5, 5)
Hematoma at access site	1.2% (3, 3)	0.0% (0, 0)	1.0% (3, 3)	1.3% (3, 3)	0.0% (0, 0)	1.0% (3, 3)
Minor vascular complication	1.2% (3, 3)	1.4% (1, 1)	1.3% (4, 4)	1.2% (3, 3)	1.7% (1, 1)	1.3% (4, 4)
Transapical related event	1.2% (3, 3)	0.0% (0, 0)	1.0% (3, 3)	1.2% (3, 3)	0.0% (0, 0)	1.0% (3, 3)
Transseptal related event	1.2% (3, 3)	0.0% (0, 0)	1.0% (3, 3)	1.2% (3, 3)	0.0% (0, 0)	1.0% (3, 3)
Gastrointestinal bleed	0.8% (2, 2)	1.4% (1, 1)	1.0% (3, 3)	0.9% (2, 2)	1.4% (1, 1)	1.1% (3, 3)
Major vascular complication	0.8% (2, 2)	0.0% (0, 0)	0.6% (2, 2)	0.8% (2, 2)	0.0% (0, 0)	0.6% (2, 2)
Readmission - cardiac	N/A	N/A	N/A	0.9% (2, 2)	0.0% (0, 0)	0.8% (2, 2)
Device embolization	0.0% (0, 0)	0.0% (0, 0)	0.0% (0, 0)	0.5% (1, 1)	0.0% (0, 0)	0.4% (1, 1)
Device migration	0.0% (0, 0)	1.4% (1, 1)	0.3% (1, 1)	0.5% (1, 1)	1.4% (1, 1)	0.7% (2, 2)
Device recapture or retrieval	0.0% (0, 0)	1.4% (1, 1)	0.3% (1, 1)	0.5% (1, 1)	1.4% (1, 1)	0.7% (2, 2)
Genitourinary bleed	0.4% (1, 1)	0.0% (0, 0)	0.3% (1, 1)	0.4% (1, 1)	0.0% (0, 0)	0.3% (1, 1)
Major bleeding event	N/A	N/A	N/A	0.5% (1, 1)	0.0% (0, 0)	0.4% (1, 1)
Non-valve related readmission	N/A	N/A	N/A	0.5% (1, 1)	0.0% (0, 0)	0.4% (1, 1)

Events	Discharge*			30 Day†		
	SAPIEN XT	SAPIEN 3	All	SAPIEN XT	SAPIEN 3	All
Conduction/native pacer disturbance requiring pacer	0.0% (0, 0)	1.4% (1, 1)	0.3% (1, 1)	0.0% (0, 0)	1.5% (1, 1)	0.3% (1, 1)
Device thrombosis	0.0% (0, 0)	0.0% (0, 0)	0.0% (0, 0)	0.0% (0, 0)	0.0% (0, 0)	0.0% (0, 0)
Endocarditis	0.0% (0, 0)	0.0% (0, 0)	0.0% (0, 0)	0.0% (0, 0)	0.0% (0, 0)	0.0% (0, 0)
Life threatening bleeding	N/A	N/A	N/A	0.0% (0, 0)	0.0% (0, 0)	0.0% (0, 0)
Myocardial infarction	0.0% (0, 0)	1.4% (1, 1)	0.3% (1, 1)	0.0% (0, 0)	1.4% (1, 1)	0.3% (1, 1)
Other device related event	0.0% (0, 0)	1.4% (1, 1)	0.3% (1, 1)	0.0% (0, 0)	1.4% (1, 1)	0.3% (1, 1)
Transient ischemic attack	0.4% (1, 1)	0.0% (0, 0)	0.3% (1, 1)	0.4% (1, 1)	0.0% (0, 0)	0.3% (1, 1)
Ischemic stroke	0.4% (1, 1)	1.4% (1, 1)	0.6% (2, 2)	0.4% (1, 1)	1.5% (1, 1)	0.7% (2, 2)
Readmission - heart failure	N/A	N/A	N/A	1.0% (2, 2)	3.8% (2, 2)	1.6% (4, 4)

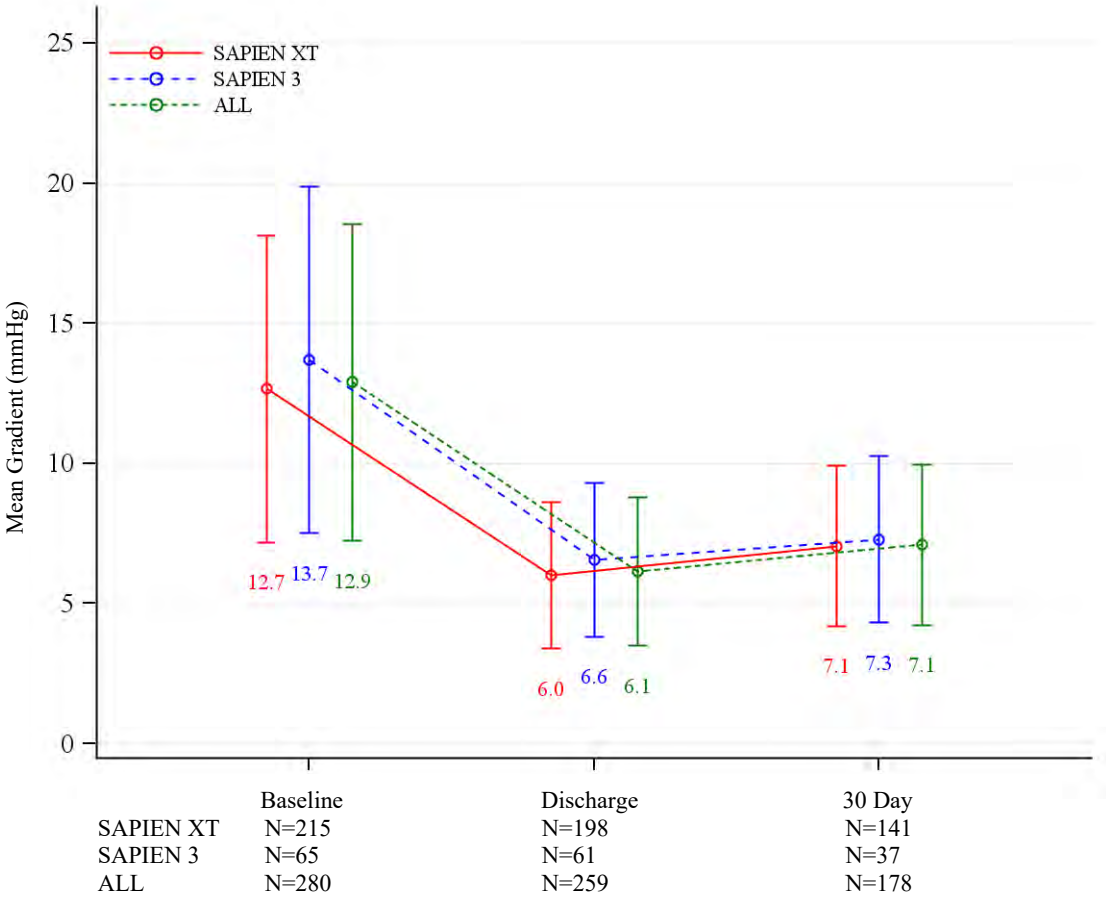
*Observed rate - % (no. of events, no. of subjects with the event)
†Kaplan-Meier estimate - % (no. of events, no. of subjects with the event)

Effectiveness Endpoints

Valve Performance

The mitral valve-in-valve echocardiographic performance data are summarized in Figures 64-66. The mean gradients improved from 12.9 mmHg at baseline to 7.1 mmHg at 30 days. Moderate/severe mitral regurgitation was observed in 62.5% of the patients at baseline, which decreased to 2.2% of the patients at 30 days.

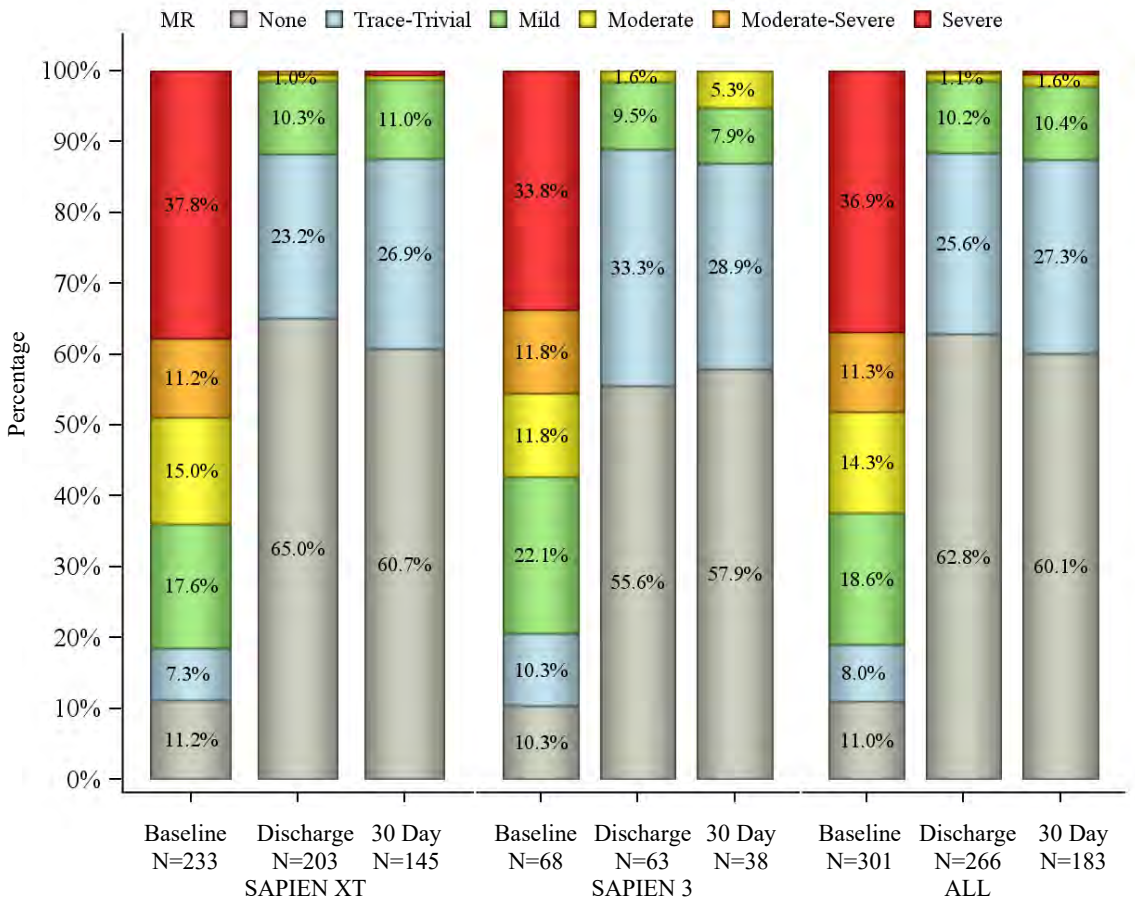
Figure 64:
Mean Gradient by Visit - Mitral Valve-in-Valve
(Valve Implant Population)



	Baseline	Discharge	30 Day
SAPIEN XT	N=215	N=198	N=141
SAPIEN 3	N=65	N=61	N=37
ALL	N=280	N=259	N=178

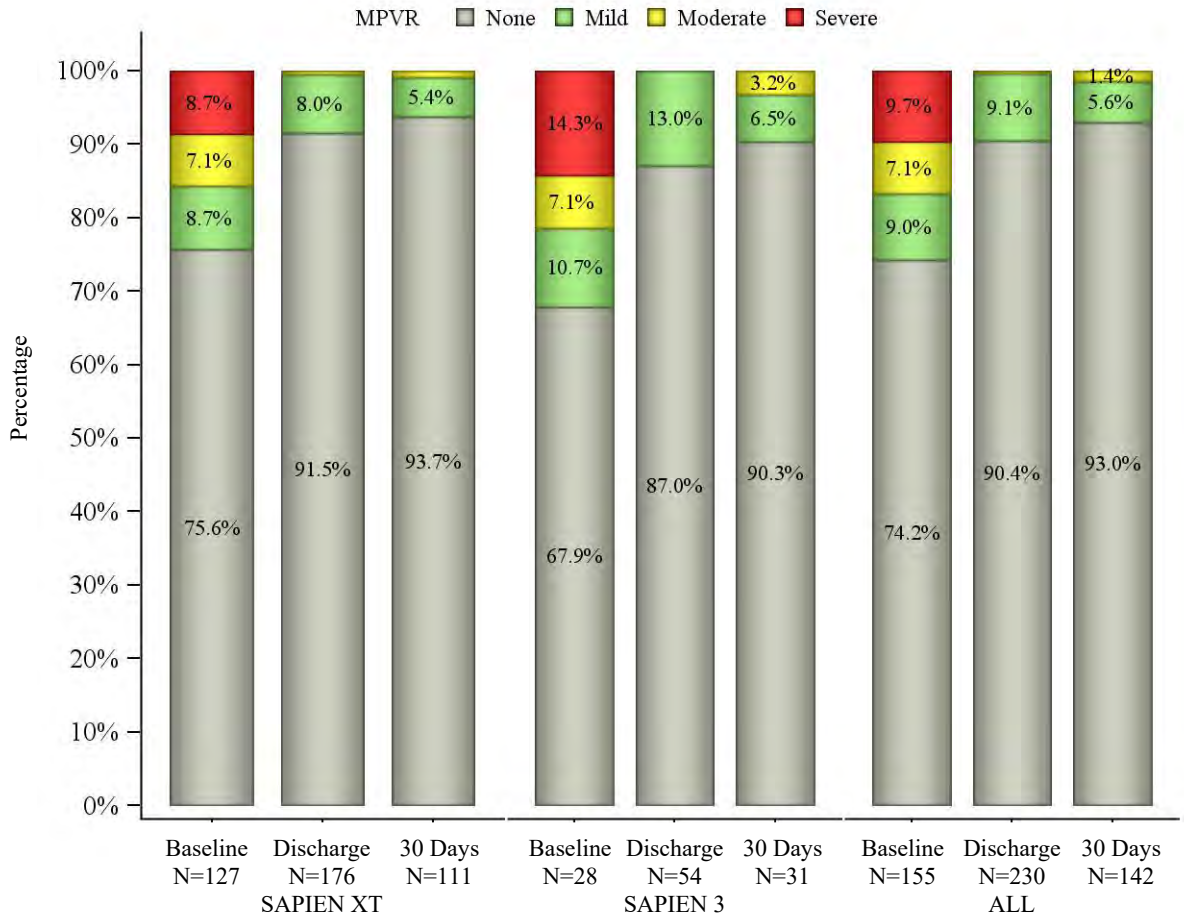
Note: Line plot with mean and standard deviation. The total number of patients at each time point only counted the patients with valid values.

Figure 65:
Mitral Regurgitation by Visit - Mitral Valve-in-Valve
(Valve Implant Population)



Note: Values that are < 1.0% are not labeled in the bar chart. The total number of patients at each time point only counted the patients with valid values.

Figure 66:
Paravalvular Regurgitation by Visit - Mitral Valve-in-Valve
(Valve Implant Population)

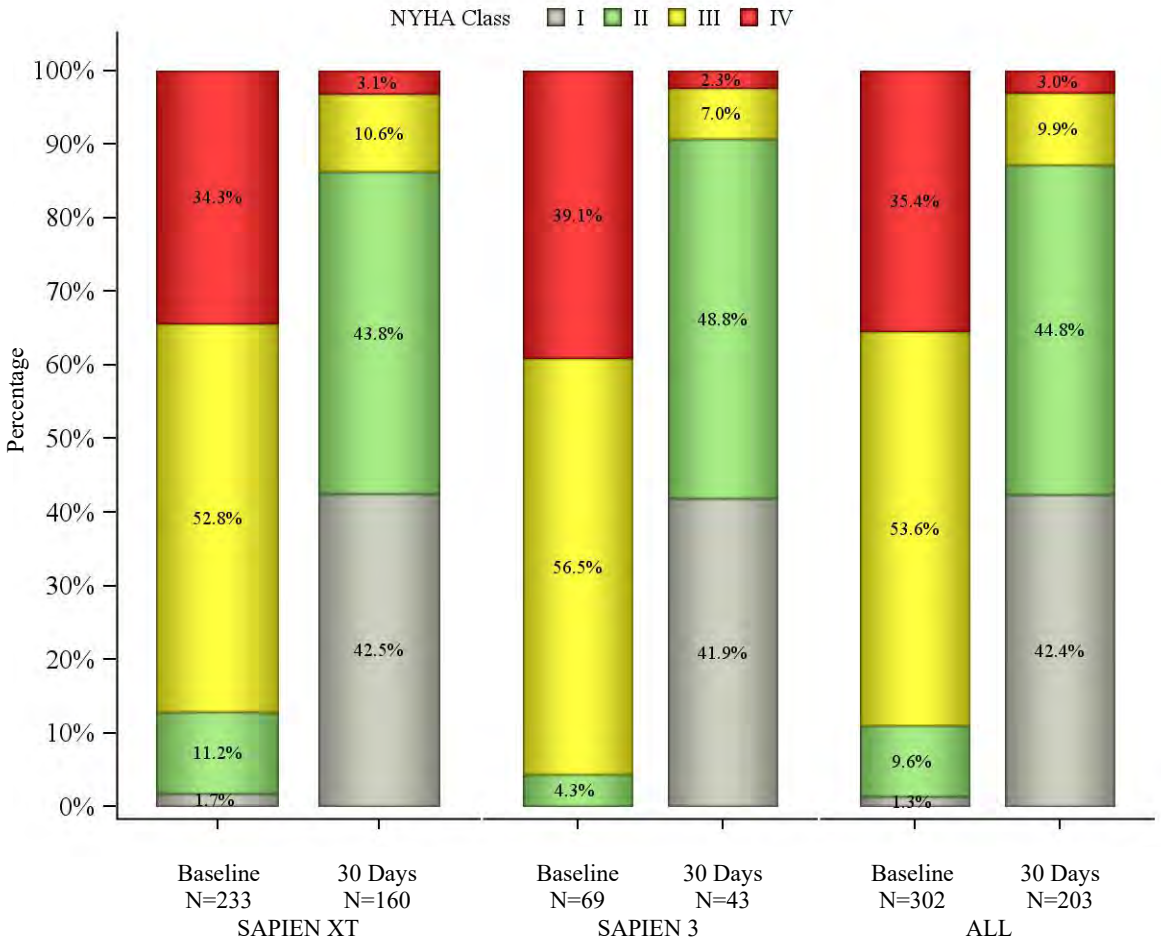


Note: Values that are < 1.0% are not labeled in the bar chart. The total number of patients at each time point only counted the patients with valid values.

NYHA Class

The NYHA class distributions at baseline and the 30-day visit and the NYHA class changes from baseline to the 30-day visit are shown in Figure 67 and Table 68, respectively. The majority (85.6%) of the patients had an improved NYHA class at the 30-day visit.

Figure 67:
NYHA Functional Class - Mitral Valve-in-Valve
(Valve Implant Population)



Note: The total number of patients at each time point only counted the patients with valid values.

Table 68:
NYHA Class Change - Mitral Valve-in-Valve
(Valve Implant Population)

		NYHA Class Change*		
		Improved	**Same**	**Worsened**
Baseline to 30-day visit	SAPIEN XT	133/159 (83.6%)	24/159 (15.1%)	2/159 (1.3%)
	SAPIEN 3	40/43 (93.0%)	3/43 (7.0%)	0/43 (0.0%)
	All	173/202 (85.6%)	27/202 (13.4%)	2/202 (1.0%)

*n/Total no. (%); the total no. only counted the patients with valid values.

Six-Minute Walk Test (6MWT)

The results of the 6MWT are summarized in Table 69.

Table 69:
Six-Minute Walk Test - Mitral Valve-in-Valve (Valve Implant Population)

Visit	6-Minute Walk Distance (feet)*		
	SAPIEN XT	SAPIEN 3	All
Baseline	240.5 ± 366.2 (77)	375.6 ± 370.4 (32)	280.2 ± 370.9 (109)
30-day visit	768.7 ± 480.6 (34)	977.5 ± 597.4 (8)	808.5 ± 503.7 (42)
Change from baseline to 30 days	479.0 ± 471.3 (20)	457.6 ± 348.1 (5)	474.7 ± 442.9 (25)

*Mean ± SD (Total no.). The total number of patients at each time point only counted the patients with valid values. The 6-minute walk distance was counted as 0 for the 6-minute walk tests not performed due to cardiac reasons.

Length of Stay

The mean index hospitalization stay was 8.5 days, which included an average of 3.4 days in the intensive care unit (ICU), as summarized in Table 70.

Table 70:
Index Hospitalization Stay - Mitral Valve-in-Valve
(Attempted Implant Population)

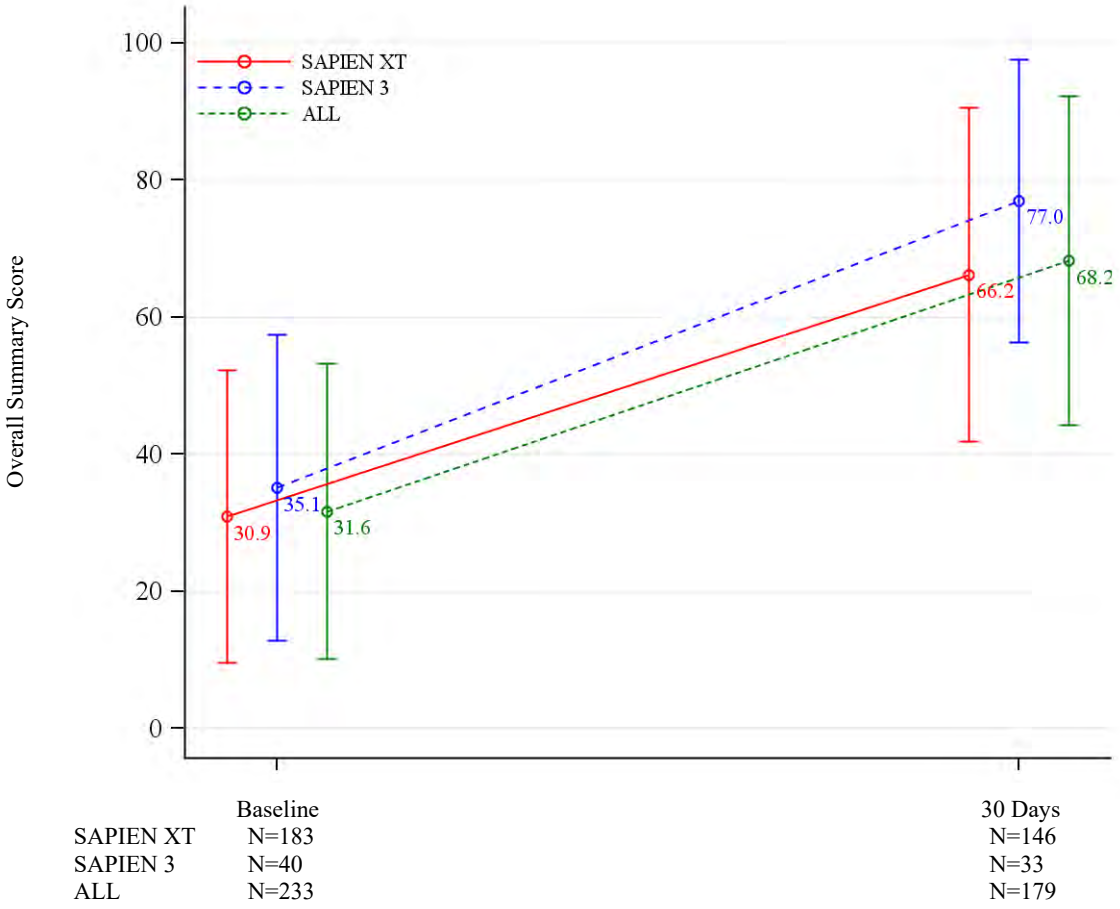
	Length (days)*		
	SAPIEN XT	SAPIEN 3	All
Index hospitalization stay	8.8 ± 7.1 (241)	7.6 ± 7.4 (70)	8.5 ± 7.1 (311)
Intensive care stay	3.3 ± 4.8 (234)	3.7 ± 7.1 (63)	3.4 ± 5.3 (297)

*Mean ± SD (Total no.).

Quality of Life (QoL)

The KCCQ clinical summary scores at baseline and 30 days are shown in Figure 68. The mean KCCQ summary score improved from 31.6 at baseline to 68.2 at 30 days.

Figure 68:
KCCQ Overall Summary Score - Mitral Valve-in-Valve (Valve Implant Population)



Note: Line plot with mean and standard deviation. The total number of patients at each time point only counted the patients with valid values.

Procedural Information

The procedure information is presented in Table 71. The most common delivery approach for the mitral valve-in-valve implantation was the transapical approach, which was used in 65.3% (203 of 311) of cases, followed by the transseptal approach in 27.0% (84 of 311) of cases, the transfemoral approach in 6.1% (19/311) of cases, and other alternative approaches in 1.6% (5 of 311) of cases. The procedures were considered elective in 71.0% (220/310) of cases, urgent in 27.7% (86/310) of cases, and emergent or salvage in 1.3% (4/310) of cases. Two (2) cases were aborted and 5 were converted to open heart surgery. Overall, the device was implanted successfully in 97.4% (303/311) of the cases, which was defined as correct positioning of a single prosthetic heart valve in the proper anatomical location.

Table 71:
Procedural Data Summary - Mitral Valve-in-Valve
(Attempted Implant Population)

Procedural Data	Summary Statistics*		
	SAPIEN XT	SAPIEN 3	All
Operator reason for procedure			
Inoperable/extreme risk	96/241 (39.8%)	11/69 (15.9%)	107/310 (34.5%)
High risk	141/241 (58.5%)	52/69 (75.4%)	193/310 (62.3%)
Intermediate risk	4/241 (1.7%)	5/69 (7.2%)	9/310 (2.9%)
Low risk	0/241 (0.0%)	1/69 (1.4%)	1/310 (0.3%)
Implant approach			
Transapical	192/241 (79.7%)	11/70 (15.7%)	203/311 (65.3%)
Transseptal	43/241 (17.8%)	41/70 (58.6%)	84/311 (27.0%)
Femoral artery	4/241 (1.7%)	15/70 (21.4%)	19/311 (6.1%)
Other	2/241 (0.8%)	3/70 (4.3%)	5/311 (1.6%)
Prior valve type			
Bioprosthetic stented	143/180 (79.4%)	35/41 (85.4%)	178/221 (80.5%)
Bioprosthetic stentless	37/180 (20.6%)	6/41 (14.6%)	43/221 (19.5%)
Procedure status			
Elective	173/241 (71.8%)	47/69 (68.1%)	220/310 (71.0%)
Urgent	64/241 (26.6%)	22/69 (31.9%)	86/310 (27.7%)
Emergency	2/241 (0.8%)	0/69 (0.0%)	2/310 (0.6%)
Salvage	2/241 (0.8%)	0/69 (0.0%)	2/310 (0.6%)
Valve size			
23 mm	22/241 (9.1%)	5/70 (7.1%)	27/311 (8.7%)
26 mm	93/241 (38.6%)	24/70 (34.3%)	117/311 (37.6%)
29 mm	126/241 (52.3%)	41/70 (58.6%)	167/311 (53.7%)
Cardiopulmonary bypass	25/241 (10.4%)	2/69 (2.9%)	27/310 (8.7%)
Status of CP Bypass			
Elective	20/25 (80.0%)	0/2 (0.0%)	20/27 (74.1%)
Emergent	5/25 (20.0%)	2/2 (100.0%)	7/27 (25.9%)
CP Bypass Time (min)	38.3 ± 51.2 (24)	148.0 ± 157.0 (2)	46.7 ± 65.4 (26)
Type of anesthesia			
General anesthesia	240/241 (99.6%)	68/69 (98.6%)	308/310 (99.4%)
Moderate sedation	0/241 (0.0%)	1/69 (1.4%)	1/310 (0.3%)
Epidural	0/241 (0.0%)	0/69 (0.0%)	0/310 (0.0%)
Combination	1/241 (0.4%)	0/69 (0.0%)	1/310 (0.3%)
Total procedure time (min)	143.6 ± 60.4 (240)	157.7 ± 107.2 (69)	146.7 ± 73.5 (309)
Fluoroscopy time (min)	23.9 ± 20.7 (223)	36.9 ± 27.3 (63)	26.8 ± 22.9 (286)
Device implanted successfully	234/241 (97.1%)	69/70 (98.6%)	303/311 (97.4%)
Procedure aborted	1/241 (0.4%)	1/70 (1.4%)	2/311 (0.6%)
Procedure aborted reason			
Navigation issue after successful access	1/1 (100.0%)	0/1 (0.0%)	1/2 (50.0%)
Other	0/1 (0.0%)	1/1 (100.0%)	1/2 (50.0%)
Procedure aborted action			
Conversion to open heart surgery	0/1 (0.0%)	1/1 (100.0%)	1/2 (50.0%)
Other	1/1 (100.0%)	0/1 (0.0%)	1/2 (50.0%)

Procedural Data	Summary Statistics*		
	SAPIEN XT	SAPIEN 3	All
Conversion to open heart surgery	4/241 (1.7%)	1/70 (1.4%)	5/311 (1.6%)
Tamponade/bleeding in the heart	4/4 (100.0%)	0/1 (0.0%)	4/5 (80.0%)
Other	0/4 (0.0%)	1/1 (100.0%)	1/5 (20.0%)
Mechanical assist device in place at start of procedure	9/241 (3.7%)	4/70 (5.7%)	13/311 (4.2%)
IABP	7/9 (77.8%)	3/4 (75.0%)	10/13 (76.9%)
Catheter-based assist device	2/9 (22.2%)	1/4 (25.0%)	3/13 (23.1%)

*Categorical measures – no./Total no. (%); continuous measures - mean ± SD (Total no.). The total no. only counted the patients with valid values at the time point.

SAPIEN 3 Ultra System

Patient Accountability

At the time of the database extract, all 40 patients enrolled were implanted, discharged and completed 30 day follow-up.

Patient Demographics and Baseline Characteristics

The demographics and baseline characteristics are shown in Table 72.

Table 72:
Patient Demographics and Baseline Characteristics

Demographics and Baseline Characteristic	Summary Statistics
Age - years	83.4 ± 5.13 (40)
Male sex	24/40 (60.0%)
Society of Thoracic Surgeons (STS) score	3.4 ± 1.27 (40)
New York Heart Association (NYHA) class	
I/II	20/40 (50.0%)
III/IV	20/40 (50.0%)
Previous myocardial infarction	1/40 (2.5%)
Previous intervention	9/40 (22.5%)
Coronary artery bypass grafting (CABG)	3/40 (7.5%)
Percutaneous bypass intervention (PCI)	8/40 (20.0%)
Prior aortic valvuloplasty	0/40 (0.0%)
Cerebrovascular accident (CVA)	1/40 (2.5%)
Peripheral vascular disease	4/40 (10.0%)
Atrial fibrillation	19/40 (47.5%)
Prior pacemaker	5/40 (12.5%)
Porcelain aorta	0/40 (0.0%)
Echocardiographic findings	
Valve area - cm^2	0.7 ± 0.16 (40)
Mean aortic-valve gradient -mmHg	51.0 ± 13.17 (40)
Mean left ventricular ejection fraction (LVEF) %	60.6 ± 7.06 (40)
Moderate or severe aortic regurgitation	1/39 (2.6%)
*Continuous measures—Mean ± SD (Total no.); Categorical measures—n./Total no. (%)	

Safety and Effectiveness Results

Primary Endpoint

The primary endpoint was procedural success, defined as freedom from mortality, conversion to surgery, and moderate or severe PVR at exit from the procedure room which was achieved in all subjects as outlined in Table 73.

Table 73:
Primary Endpoint Analysis.

Primary Endpoint	Results
Overall procedural success	40/40 (100.0%)
Freedom from mortality at exit from procedure room	40/40 (100.0%)
Freedom from conversion to surgery at exit from procedure room	40/40 (100.0%)
Freedom from moderate or severe paravalvular regurgitation at exit from procedure room	40/40 (100.0%)

Secondary Endpoints

There were no major vascular complications, valve migrations, or embolizations through discharge.

Adverse Events

There were no deaths or strokes through 30-days. The selected adverse events for the treated population are presented in Table 74.

Table 74:
Selected Adverse Events

Adverse Event	Discharge*	30 Days†
Major vascular complications	0.0% (0,0)	0.0% (0,0)
Acute kidney injury (Stage III)	0.0% (0,0)	0.0% (0,0)
Life threatening bleeding	0.0% (0,0)	0.0% (0,0)
Major bleeding	5.0% (2,2)	5.0% (2,2)
Hematoma	5.0% (2,2)	5.0% (2,2)
Bleeding at access site	15.0% (6,6)	15.0% (6,6)
Dissection	2.5% (1,1)	2.5% (1,1)
Pseudoaneurysm	2.5% (1,1)	2.5% (1,1)
Aortic-valve reintervention	0.0% (0,0)	0.0% (0,0)
Endocarditis	0.0% (0,0)	0.0% (0,0)
Device thrombosis	0.0% (0,0)	0.0% (0,0)

*Observed rate,% (no. of events, no. of subjects with the event)
†Kaplan-Meier estimate,% (no. of events, no. of subjects with the event)

The new conduction abnormalities requiring permanent pacemaker implantation through 30-days for the first 20 subjects and the last 20 subjects are presented in Table 75.

Table 75:
New Conduction Abnormalities Requiring Permanent Pacemaker Implantation

	First 20 Subjects		Last 20 Subjects	
Adverse Event	**Discharge***	**30 Days†**	**Discharge***	**30 Days†**
Conduction disturbance requiring permanent pacemaker‡	29.4% (5,5)	29.4% (5,5)	5.6% (1,1)	5.6% (1,1)

‡5 Subjects (3 from First 20 subject cohort and 2 from Last 20 subject cohort) with baseline pacemaker were excluded from the analysis.
*Observed rate,% (no. of events, no. of subjects with the event)
†Kaplan-Meier estimate,% (no. of events, no. of subjects with the event)

Other Results

Procedural Information

Overall, the mean procedure time was 56.5 ± 26.8 minutes. Conscious sedation was utilized in 95% of the patients with one patient converted to general anesthesia. The valve was placed in the intended position in all cases, there were no aborted implantation procedures or conversion to open heart surgery. Successful access, delivery and retrieval of the device and delivery system occurred in all cases. The average length of stay was 4.1 ± 2.4 days.

Valve Performance

The measurements of effective orifice area, mean gradient, total aortic regurgitation, aortic paravalvular regurgitation (PVL) are presented in Figures 69-72. Mean EOA increased and gradients decreased. PVL was trace or none in 85% of the patients.

Figure 69:
Effective Orifice Area



*Site reported. **Core lab reported.

Figure 70:
Mean Gradient by Valve Size

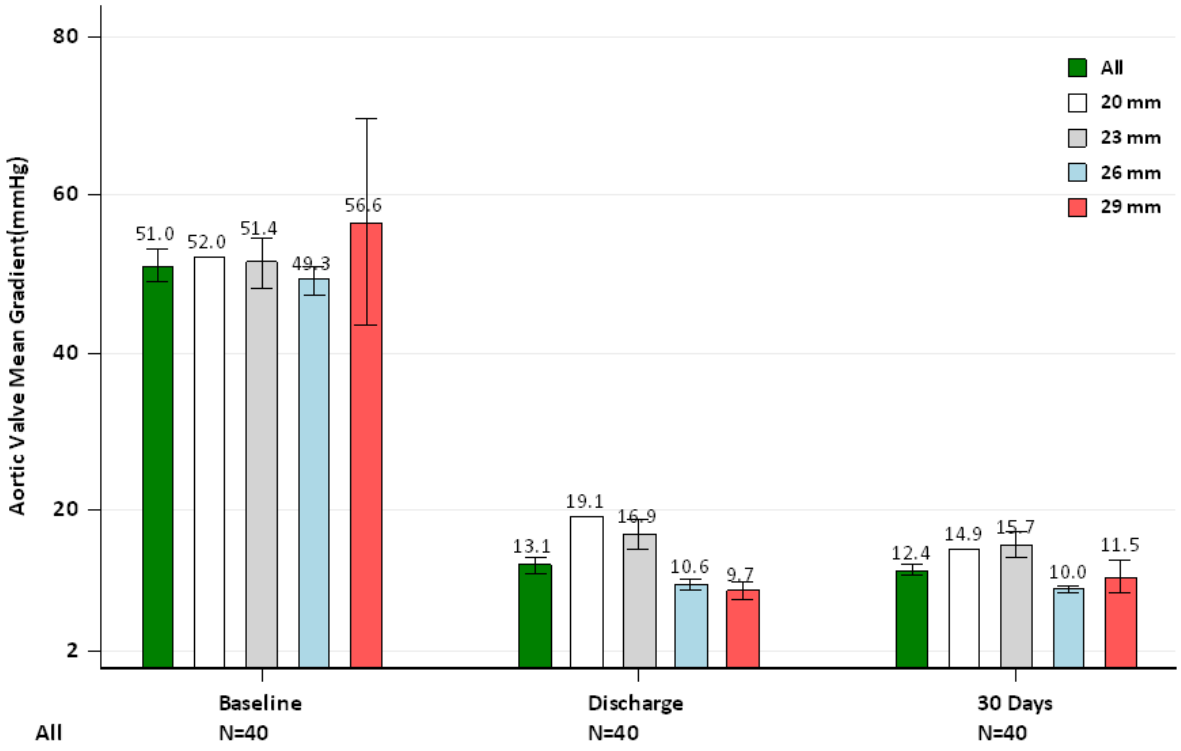


Figure 71:
Total Aortic Regurgitation

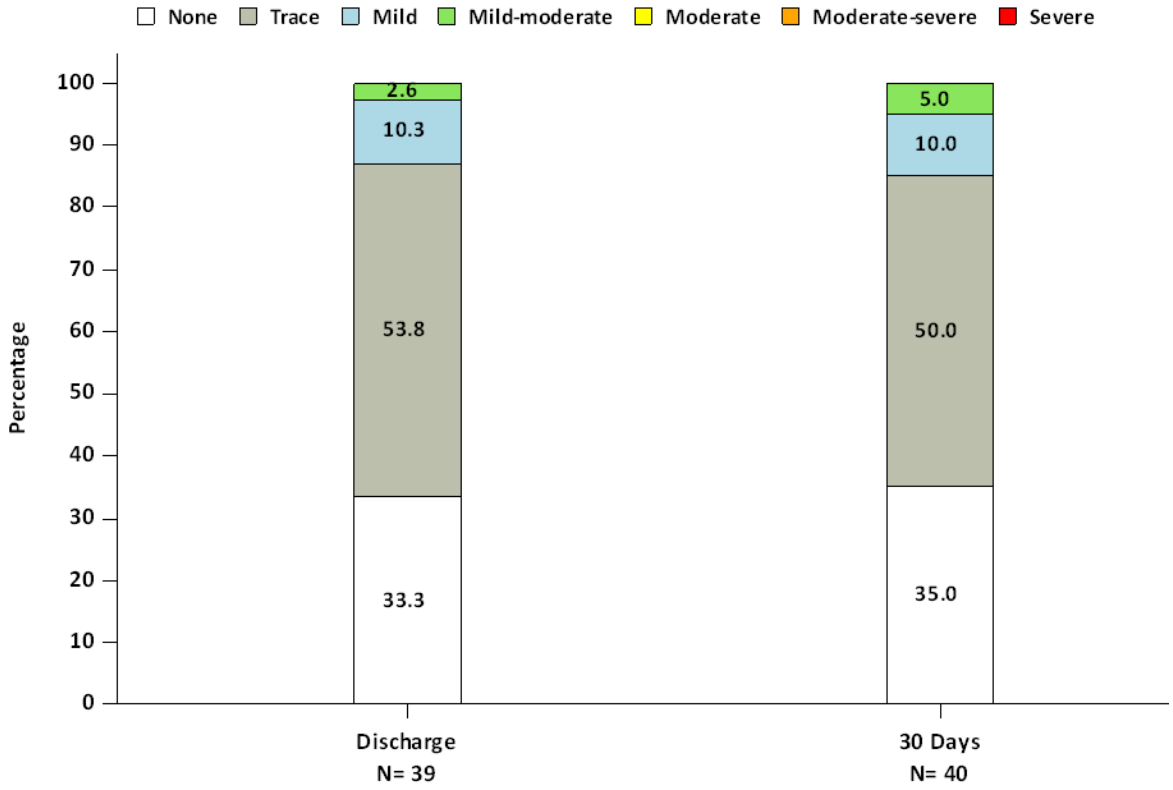
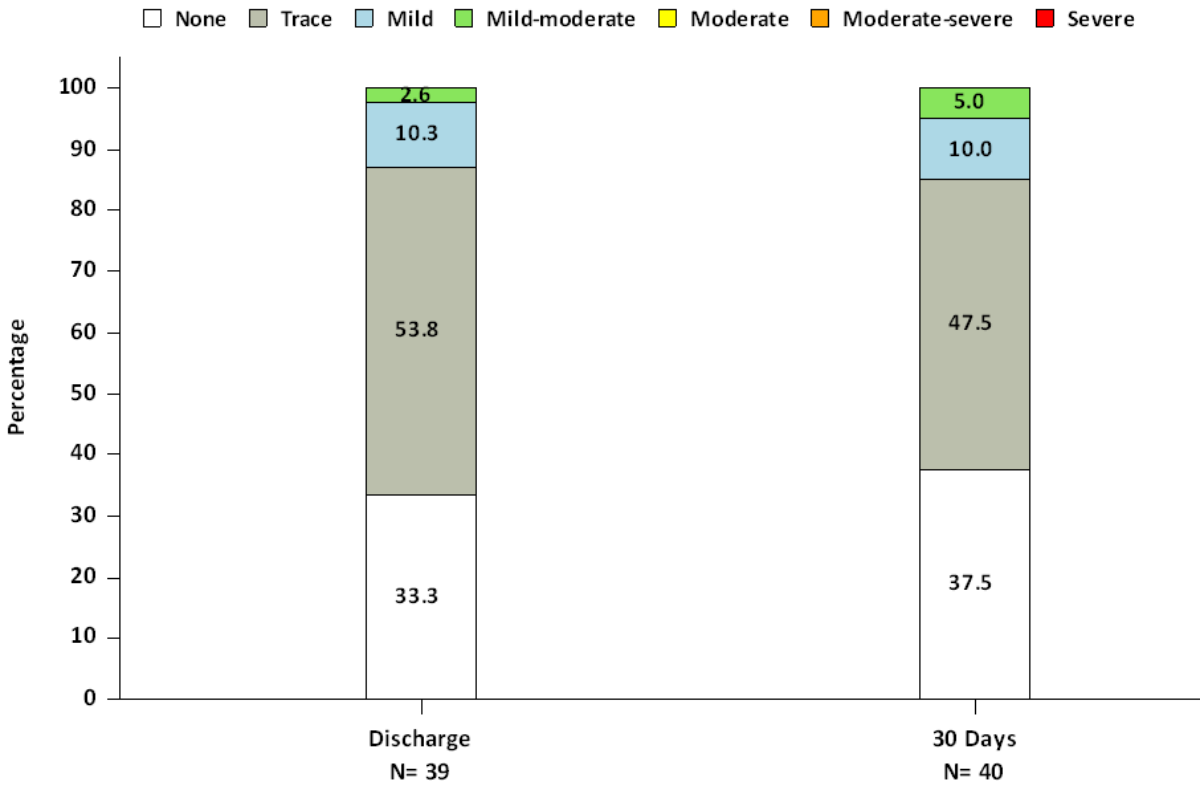


Figure 72:

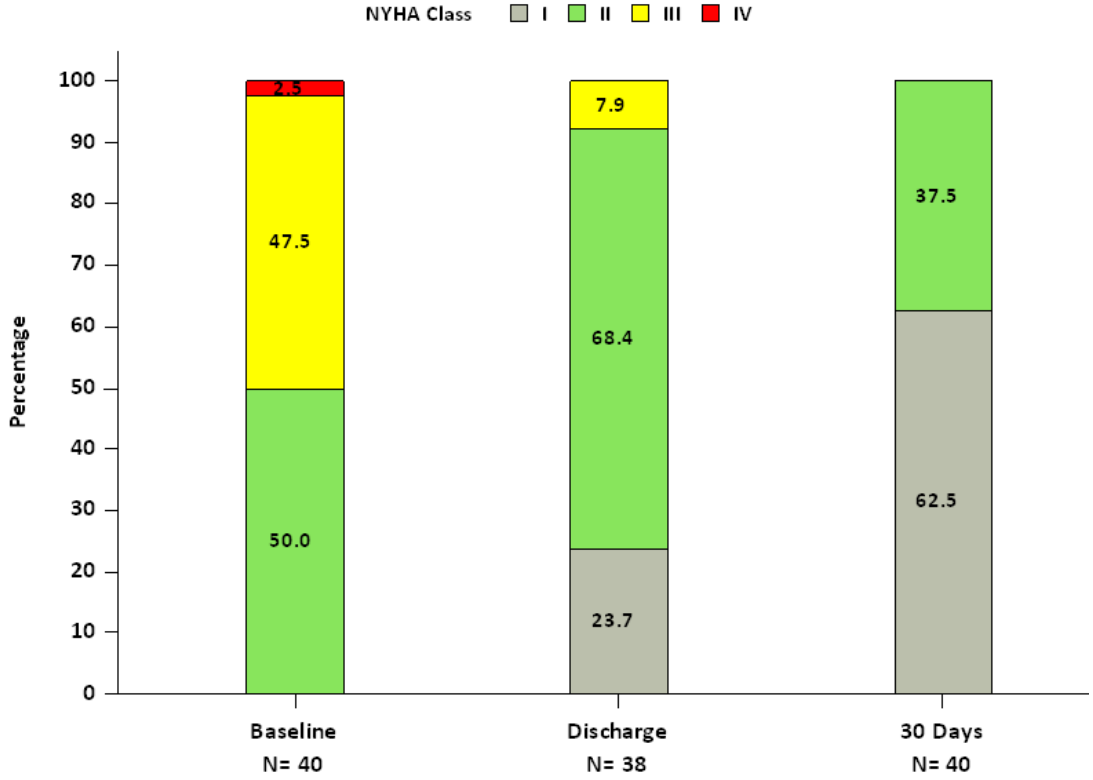
Aortic Paravalvular Regurgitation



NYHA

The NYHA Functional Class summary is shown in Figure 73**.** At 30-day follow-up, 80.0% of subjects experienced improvement in NYHA Class and all subjects were in Class I/II.

Figure 73:
NYHA Class by Visit



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[3] Imbens G. W. (2004) Nonparametric Estimation of Average Treatment Effects under Exogeneity: A Review. The Review of Economics and Statistics, February 2004, 86(1): 4–29.

These products are manufactured and sold under one or more of the following US patent(s): US Patent No. 7,530,253; 7,780,723; 7,895,876; 8,382,826; 8,591,575; 8,690,936; 8,790,387; 9,061,119; 9,301,840; 9,301,841; 9,339,384; 9,393,110; and corresponding foreign patents. Additional patents are pending.



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10033860001 A

EXHIBIT 45

SUMMARY OF SAFETY AND EFFECTIVENESS DATA

I. GENERAL INFORMATION

Device Generic Name:	Aortic valve, prosthesis, percutaneously delivered
Device Trade Name:	Edwards SAPIEN 3 Transcatheter Heart Valve System Edwards SAPIEN 3 Ultra Transcatheter Heart Valve System
Device Procode:	NPT
Applicant Name and Address:	Edwards Lifesciences LLC One Edwards Way Irvine, CA 92614
Date of Panel Recommendation:	None
Premarket Approval Application (PMA) Number:	P140031/S085
Date of FDA Notice of Approval:	August 16, 2019

The original PMA of the Edwards SAPIEN 3 Transcatheter Heart Valve (THV) System, P140031, was first approved on June 17, 2015, and the indication was later expanded in Panel Track PMA Supplement P140031/S010 on August 18, 2016, to include patients with symptomatic heart disease due to severe native calcific aortic stenosis who are judged by a heart team, including a cardiac surgeon, to be at intermediate or greater risk for open surgical therapy (i.e., predicted risk of surgical mortality ≥ 3% at 30 days, based on the Society of Thoracic Surgeons (STS) risk score and other clinical co-morbidities unmeasured by the STS risk calculator). The indication was further expanded in PMA Supplement P140031/S028 on June 5, 2017 to include patients with symptomatic heart disease due to failure (stenosed, insufficient, or combined) of a surgical bioprosthetic aortic or mitral valve who are judged by a heart team, including a cardiac surgeon, to be at high or greater risk for open surgical therapy (i.e., predicted risk of surgical mortality ≥ 8% at 30 days, based on the STS risk score and other clinical co-morbidities unmeasured by the STS risk calculator). The SSEDs to support the indication are available on the following FDA websites and are incorporated by reference herein:

- https://www.accessdata.fda.gov/cdrh_docs/pdf14/P140031b.pdf
- https://www.accessdata.fda.gov/cdrh_docs/pdf14/P140031S010b.pdf
- https://www.accessdata.fda.gov/cdrh_docs/pdf14/P140031S028b.pdf

The SAPIEN 3 Ultra THV System is a design iteration of the SAPIEN 3 THV System and was approved in P140031/S074 on December 28, 2018.

The current supplement was submitted to expand the indications for use of the Edwards SAPIEN 3 THV System and SAPIEN 3 Ultra THV System to include patients with severe symptomatic native calcific aortic stenosis who are deemed to be at low risk for surgical aortic valve replacement (SAVR).

II. INDICATIONS FOR USE

The Edwards SAPIEN 3 Transcatheter Heart Valve System and Edwards SAPIEN 3 Ultra Transcatheter Heart Valve System are indicated for relief of aortic stenosis in patients with symptomatic heart disease due to severe native calcific aortic stenosis who are judged by a heart team, including a cardiac surgeon, to be appropriate for the transcatheter heart valve replacement therapy.

III. CONTRAINDICATIONS

The Edwards SAPIEN 3 THV System and Edwards SAPIEN 3 Ultra THV System are contraindicated in patients who cannot tolerate an anticoagulation/antiplatelet regimen or who have active bacterial endocarditis or other active infections.

IV. WARNINGS AND PRECAUTIONS

The warnings and precautions can be found in the Edwards SAPIEN 3 THV System and Edwards SAPIEN 3 Ultra THV System labeling.

V. DEVICE DESCRIPTION

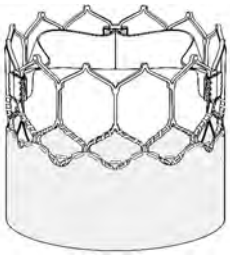
The Edwards SAPIEN 3 THV (model 9600TFX, 20, 23, 26, and 29 mm), as shown in Figure 1, is comprised of a balloon-expandable, radiopaque, cobalt-chromium (MP35N) frame, a trileaflet bovine pericardial tissue valve, a polyethylene terephthalate (PET) internal fabric skirt, and a PET external sealing skirt for reduction of paravalvular regurgitation. The leaflets are treated according to the Carpentier Edwards ThermaFix process.

Figure 1: SAPIEN 3 Transcatheter Heart Valve



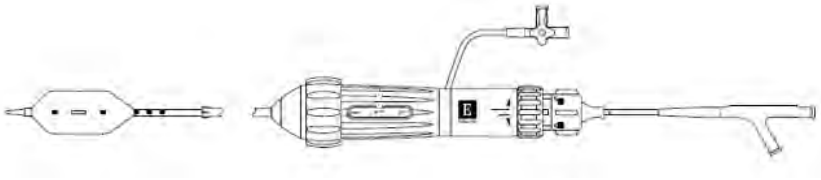
The SAPIEN 3 Ultra THV (model 9750TFX, 20, 23, and 26 mm), as shown in Figure 2, is a design iteration of the SAPIEN 3 THV, with a knitted outer skirt featuring a velour texture on one side.

Figure 2: SAPIEN 3 Ultra Transcatheter Heart Valve



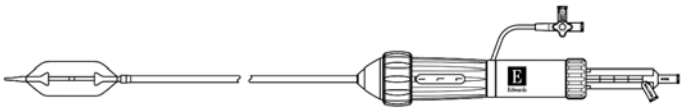
The Edwards Commander Delivery System (models 9600LDS20, 9600LDS23, 9600LDS26, and 9600LDS29), as shown in Figure 3, includes a handle that provides a flex wheel for articulation of the flex catheter, a tapered tip at the distal end of the delivery system, a balloon catheter for deployment of the THV, and radiopaque markers. It is used when a long access route is planned.

Figure 3: Edwards Commander Delivery System



The Edwards SAPIEN 3 Ultra Delivery System (models 9630TF20, 9630TF23, 9630TF26, and 9630TF29), as shown in Figure 4, includes a handle that provides a flex wheel to control flexing of the flex catheter, a fine adjustment wheel to facilitate THV positioning, a tapered tip at the distal end, and a radiopaque positioning marker in the balloon. It is also used when a long access route is planned.

Figure 4: Edwards SAPIEN 3 Ultra Delivery System



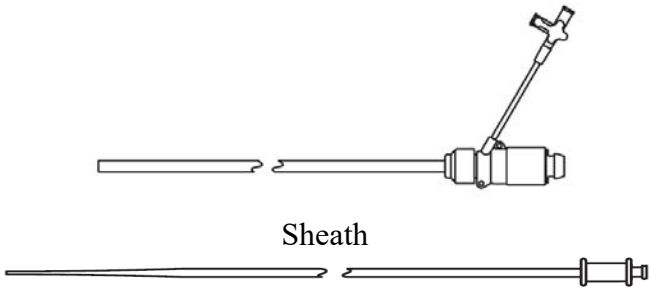
The Edwards Certitude Delivery System (models 9630TA20, 9600SDS20, 9630TA23, 9600SDS23, 9630TA26, 9600SDS26, 9630TA29, and 9600SDS29), as shown in Figure 5, includes a handle with a flex wheel for articulation of the balloon catheter and extension tubing. It is used when a short access route is planned.

Figure 5: Edwards Certitude Delivery System



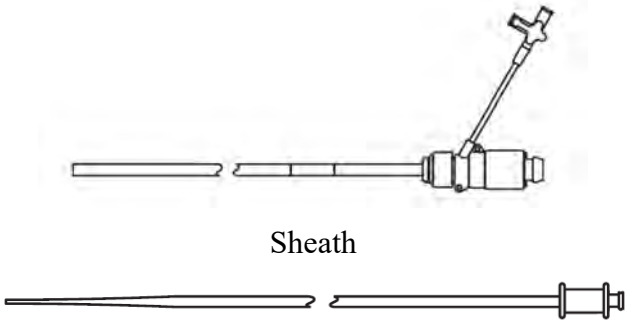
The Edwards eSheath Introducer Set (models 914ES and 916ES), as shown in Figure 6, consists of a hydrophilic coated, expandable sheath and 2 dilators. It is available in 14 and 16 Fr inner diameters.

Figure 6: Edwards eSheath Introducer Set



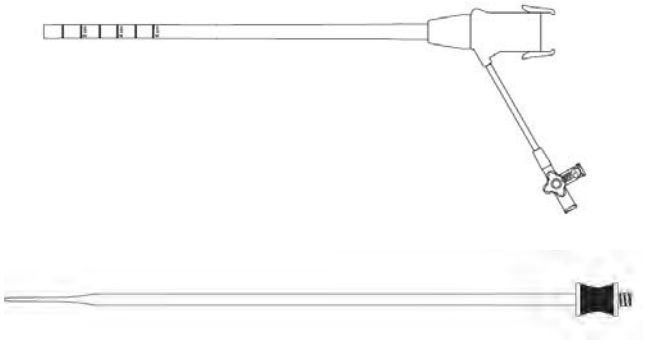
The Edwards Axela Sheath (model 9630ES14), as shown in Figure 7, also consists of a hydrophilic coated, expandable sheath and 2 dilators. It is available in 14 Fr inner diameter.

Figure 7: Edwards Axela Sheath



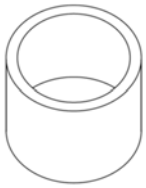
The Edwards Certitude Introducer Sheath (models 9600IS18 and 9600IS21), as shown in Figure 8, has a radiopaque marker for visualization of the sheath tip and non-radiopaque depth markings on the distal end. The proximal end of the introducer sheath includes a flush tube and three hemostasis valves.

Figure 8: Edwards Certitude Introducer Sheath



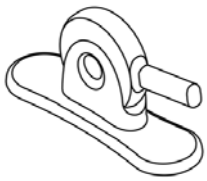
The Qualcrimp crimping accessory, as shown in Figure 9, is a non-patient contacting device that is placed around the THV to protect the leaflets during the crimping process. It is manufactured of tubular polyester polyurethane foam and laminated cylindrically on both the inner and outer surfaces with a polyether urethane material.

Figure 9: Qualcrimp Crimping Accessory



The Edwards Crimper (model 9600CR), as shown in Figure 10, is comprised of various molded plastic components which compress the valve to a controlled aperture. The aperture is created by rotating the handle until it abuts the crimp stopper. The Edwards Crimper is used with a Crimp Stopper to correctly crimp the THV.

Figure 10: Edwards Crimper



VI. ALTERNATIVE PRACTICES AND PROCEDURES

There are several other alternatives for the correction of severe native calcific aortic stenosis in patients deemed to be at low risk for open surgical therapy, including surgical aortic valve replacement (SAVR), temporary relief using balloon aortic valvuloplasty (BAV), or medical therapy (no obstruction-relieving intervention). Each alternative has its own advantages and disadvantages. A patient should fully discuss these alternatives with his/her physician to select the method that best meets his/her expectations and lifestyle.

VII. MARKETING HISTORY

The Edwards SAPIEN 3 THV System and Edwards SAPIEN 3 Ultra THV System have not been marketed in the United States or any foreign country for the "low risk" transcatheter aortic valve replacement (TAVR) indication.

VIII. POTENTIAL ADVERSE EFFECTS OF THE DEVICE ON HEALTH

Below is a list of the potential adverse effects (e.g., complications) associated with the use of the device.

- Death
- Stroke/transient ischemic attack, clusters or neurological deficit
- Paralysis
- Permanent disability
- Respiratory insufficiency or respiratory failure
- Hemorrhage requiring transfusion or intervention
- Cardiovascular injury including perforation or dissection of vessels, ventricle, myocardium or valvular structures that may require intervention
- Pericardial effusion or cardiac tamponade
- Embolization including air, calcific valve material or thrombus
- Infection including septicemia and endocarditis
- Heart failure
- Myocardial infarction
- Renal insufficiency or renal failure
- Conduction system defect which may require a permanent pacemaker
- Arrhythmia
- Retroperitoneal bleed
- Arteriovenous (AV) fistula or pseudoaneurysm
- Reoperation
- Ischemia or nerve injury
- Restenosis
- Pulmonary edema
- Pleural effusion
- Bleeding
- Anemia
- Abnormal lab values (including electrolyte imbalance)
- Hypertension or hypotension
- Allergic reaction to anesthesia, contrast media, or device materials
- Hematoma
- Syncope
- Pain or changes at the access site
- Exercise intolerance or weakness
- Inflammation

- Angina
- Heart murmur
- Fever
- Cardiac arrest
- Cardiogenic shock
- Emergency cardiac surgery
- Cardiac failure or low cardiac output
- Coronary flow obstruction/transvalvular flow disturbance
- Device thrombosis requiring intervention
- Valve thrombosis
- Device embolization
- Device migration or malposition requiring intervention
- Valve deployment in unintended location
- Valve stenosis
- Structural valve deterioration (wear, fracture, calcification, leaflet tear/tearing from the stent posts, leaflet retraction, suture line disruption of components of a prosthetic valve, thickening, stenosis)
- Device degeneration
- Paravalvular or transvalvular leak
- Valve regurgitation
- Hemolysis
- Device explants
- Nonstructural dysfunction
- Mechanical failure of delivery system, and/or accessories
- Non-emergent reoperation

For the specific adverse events that occurred in the clinical study, please see Section X.

IX. SUMMARY OF PRECLINICAL STUDIES

A summary of previously reported preclinical studies can be found in the SSED for the original PMA. No additional preclinical study was performed for the current application.

X. SUMMARY OF PRIMARY CLINICAL STUDY

The applicant performed a clinical study to establish a reasonable assurance of safety and effectiveness of TAVR with the Edwards SAPIEN 3 THV in patients with severe, native, calcific, aortic stenosis who are judged by a heart team to be at low risk for open surgical therapy under IDE G150278 (entitled the "PARTNER 3" trial). The data from this study were the basis for the PMA approval decision. A summary of the clinical study is presented below.

The Edwards SAPIEN 3 Ultra THV System was not used in the trial. However, the results obtained on the Edwards SAPIEN 3 THV System are considered applicable to the Edwards

SAPIEN 3 Ultra THV System based on prior demonstration of device comparability in application P140031/S074.

A. Study Design

Patients were enrolled between March 2016 and June 2018. The database for this Panel Track PMA Supplement reflected data collected through December 21, 2018 and included 1000 patients. There were 71 investigational sites in the U.S, Australia, Canada, New Zealand, and Japan.

The PARTNER 3 trial was a prospective, randomized (1:1), controlled, multicenter study to compare TAVR with the Edwards SAPIEN 3 THV to SAVR. A subset of patients were enrolled in a computed tomography (CT) substudy to investigate the prevalence of Hypoattenuated Leaflet Thickening (HALT) and reduced leaflet mobility.

The PARTNER 3 trial used an independent Data Safety Monitoring Board (DSMB) that was instructed to notify the applicant of any safety or compliance issues and a Clinical Events Committee (CEC) that was responsible for adjudicating endpoint-related events reported during the trial. The CEC adjudicated the events per Valve Academic Research Consortium-2 (VARC-2) definitions.[1] A CT core laboratory was used for assessment of baseline CTs for annulus dimensions and the CT images acquired in the CT substudy.

1. Clinical Inclusion and Exclusion Criteria

Enrollment in the PARTNER 3 trial was limited to patients who met the following inclusion criteria:

- Severe, calcific aortic stenosis meeting the following criteria:
  - Aortic valve area (AVA) $\leq$ 1.0 cm^2 or AVA index $\leq$ 0.6 cm^2/m^2;
  - Jet velocity $\geq$ 4.0 m/s or mean gradient $\geq$ 40 mmHg; AND
  - New York Heart Association (NYHA) Functional Class $\geq$ 2; OR Exercise tolerance test that demonstrates a limited exercise capacity, abnormal BP response, or arrhythmia; OR Asymptomatic with LVEF <50%.

  Note: Qualifying echocardiography must be within the 90 days prior to randomization.
- Heart team agrees the patient has a low risk of operative mortality and an STS score < 4%.
- The study patient has been informed of the nature of the study, agrees to its provisions and has provided written informed consent as approved by the Institutional Review Board (IRB)/Ethics Committee (EC) of the respective clinical site.

Patients were not permitted to enroll in the study if they met any of the following exclusion criteria:

- Native aortic annulus size unsuitable for sizes 20, 23, 26, or 29 mm THV based on 3D imaging analysis

- Iliofemoral vessel characteristics that would preclude safe passage of the introducer sheath
- Evidence of an acute myocardial infarction ≤ 1 month (30 days) before randomization
- Aortic valve is unicuspid, bicuspid, or non-calcified
- Severe aortic regurgitation (>3+)
- Severe mitral regurgitation (>3+) ≥ moderate stenosis
- Pre-existing mechanical or bioprosthetic valve in any position. (of note, mitral ring is not an exclusion)
- Complex coronary artery disease:
  - Unprotected left main coronary artery
  - Syntax score > 32 (in the absence of prior revascularization)
  - Heart Team assessment that optimal revascularization cannot be performed
- Symptomatic carotid or vertebral artery disease or successful treatment of carotid stenosis within 30 days of randomization
- Leukopenia (WBC < 3000 cell/mL), anemia (Hgb < 9 g/dL), Thrombocytopenia (Plt < 50,000 cell/mL), history of bleeding diathesis or coagulopathy, or hypercoagulable states
- Hemodynamic or respiratory instability requiring inotropic support, mechanical ventilation or mechanical heart assistance within 30 days of randomization
- Hypertrophic cardiomyopathy with obstruction (HOCM)
- Ventricular dysfunction with left ventricular ejection fraction (LVEF) < 30%
- Cardiac imaging (echocardiography, CT, and/or magnetic resonance imaging) evidence of intracardiac mass, thrombus or vegetation
- Inability to tolerate or condition precluding treatment with anti-thrombotic/anticoagulation therapy during or after the valve implant procedure
- Stroke or transient ischemic attack (TIA) within 90 days of randomization
- Renal insufficiency (eGFR < 30 ml/min per the Cockcroft-Gault formula) and/or renal replacement therapy at the time of screening.
- Active bacterial endocarditis within 180 days of randomization
- Severe lung disease (FEV1 < 50% predicted) or currently on home oxygen
- Severe pulmonary hypertension (e.g., pulmonary artery systolic pressure ≥ 2/3 systemic pressure)
- History of cirrhosis or any active liver disease
- Significant frailty as determined by the Heart Team (after objective assessment of frailty parameters).
- Significant abdominal or thoracic aortic disease (such as porcelain aorta, aneurysm, severe calcification, aortic coarctation, etc.) that would preclude safe passage of the delivery system or cannulation and aortotomy for SAVR
- Hostile chest or conditions or complications from prior surgery that would preclude safe reoperation (i.e., mediastinitis, radiation damage, abnormal chest wall, adhesion of aorta or internal mammary artery to sternum, etc.)
- Patient refuses blood products
- Body mass index (BMI) > 50 kg/m^2
- Estimated life expectancy < 24 months

- Absolute contraindications or allergy to iodinated contrast that cannot be adequately treated with pre-medication
- Immobility that would prevent completion of study procedures (e.g. six-minute walk tests, etc.)
- Patient is not a candidate for both arms of the study (not applicable to single-arm registries)
- Currently participating in an investigational drug or another device study. Note: Trials requiring extended follow-up for products that were investigational, but have since become commercially available, are not considered investigational trials. Observational studies are not considered exclusionary.

Patients were excluded from the CT substudy if the following was present:

- Condition requiring or planned use of anticoagulants following the valve implant procedure
- GFR < 50
- Inability to perform high-quality multiple detector CT study for any reason (e.g., atrial fibrillation with rapid ventricular response).

2. Follow-up Schedule

Follow-up periods were discharge, 30 days, 6 months, and 1 year, and will continue annually thereafter to 10 years post procedure. Preoperative and post-operative assessments included physical assessment and patient interview, laboratory measurements, imaging tests, and quality of life (QoL) questionnaires. Adverse events and complications were recorded at all visits.

3. Clinical Endpoints

The primary endpoint was a composite of all-cause mortality, all stroke, and rehospitalization (valve-related or procedure-related and including heart failure) at 1 year post procedure. The endpoint was evaluated as a non-inferiority analysis of the risk difference based on a non-inferiority margin of 6.0%. The primary hypothesis was as follows:

$$H_0: r_T - r_C \geq \Delta$$
$$H_A: r_T - r_C < \Delta$$

where r_T and r_C denote the event proportions in the test arm and control arm, respectively, and Δ denotes the non-inferiority margin. The Δ value was chosen to be 6.0%. The test was performed at a one-sided α level of 0.025. The 95% confidence interval for the difference $r_T - r_C$ was computed using the Kaplan-Meier algorithm with the standard errors being computed using the Greenwood's formula. The null hypothesis was rejected at $\alpha = 0.025$ if the upper 95% confidence limit was less than 6.0%.

Once non-inferiority was demonstrated for the primary endpoint, testing for superiority of TAVR with SAPIEN 3 as compared to SAVR was performed sequentially on six select

secondary endpoints, including the primary endpoint and five (5) additional secondary endpoints, as shown in the order below:

(1) New onset atrial fibrillation at 30 days
(2) Length of index hospitalization
(3) Composite of all-cause mortality, all stroke, and rehospitalization at 1 year
(4) Death, Kansas City Cardiomyopathy Questionnaire (KCCQ) < 45 or KCCQ decrease ≥ 10 points at 30 days
(5) Composite of death and all stroke at 30 days
(6) All stroke at 30 days

The hypothesis for each of the above superiority endpoints was as follows:

$$H_0: r_T = r_C$$
$$H_A: r_T \neq r_C$$

For endpoints (1) and (4)-(6) above, the trial arms were compared using the Fisher's exact test; for endpoint (2) above, the trial arms were compared using the Wilcoxon rank-sum test; and for endpoint (3) above, the trial arms were compared using the same statistics as the non-inferiority assessment. All tests were performed at a one-sided α level of 0.025. To keep the overall type I error of 0.05, a gatekeeping method was applied for multiplicity adjustment.[2, 3]

B. Accountability of the PMA Cohort

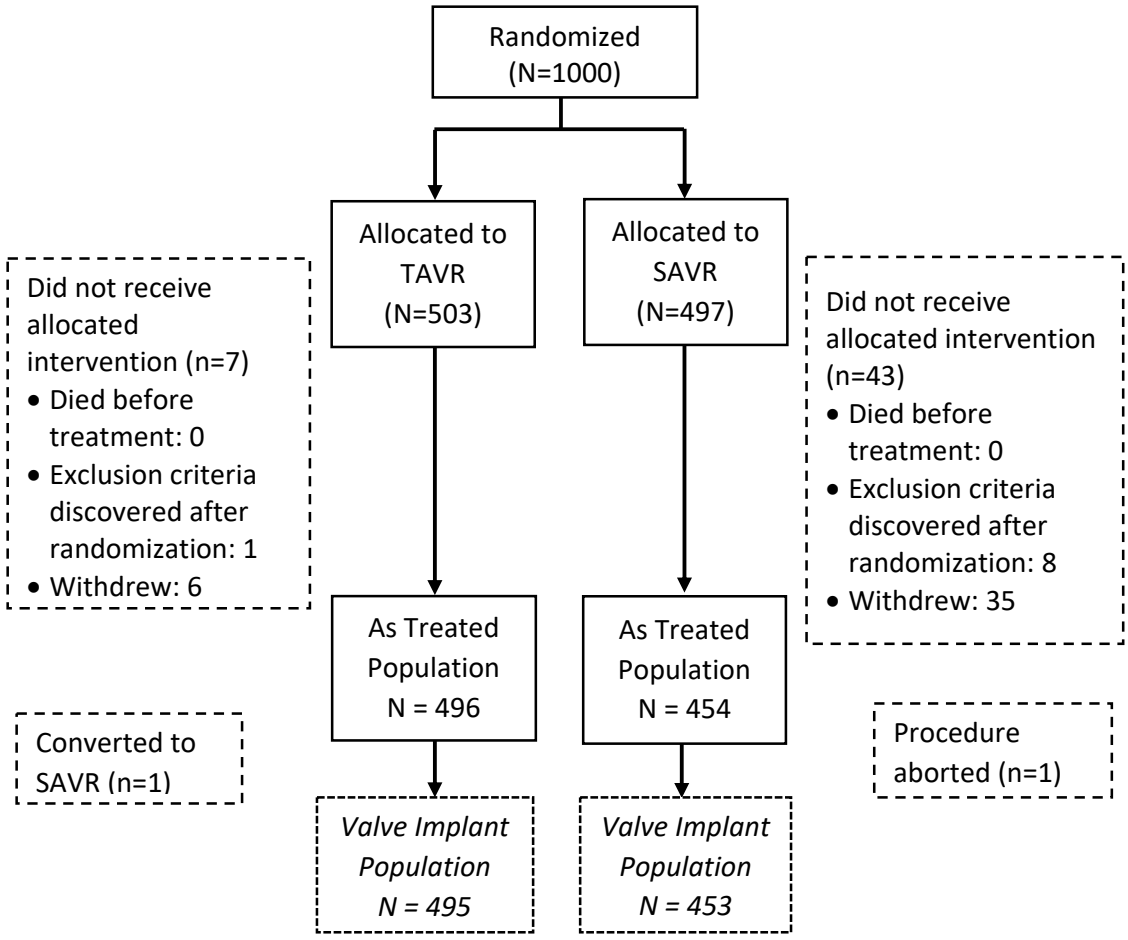
At the time of database lock, a total of 1000 patients were randomized in the study, including 503 TAVR patients and 497 SAVR patients.

There were three different analysis populations defined in the protocol: Intention-to-Treat (ITT), As Treated (AT), and Valve Implant (VI), as summarized in Table 1 and Figure 11. The primary analysis was the AT analysis.

Table 1: Analysis Populations

Analysis Population	Definition	Number of Patients	
		TAVR	SAVR
Intention-To-Treat (ITT)	All randomized patients.	503	497
As Treated (AT)	All ITT patients for whom the index procedure was begun, whether or not the index procedure was completed.	496	454
Valve Implant (VI)	All AT patients who received and retained the intended valve during the index procedure.	495	453

Figure 11: Patient Population Flowchart



The overall follow-up compliance of the trial is summarized in Table 2.

Table 2: Overall Study Compliance (AT Population)

Patient Accountability	30-day Visit		1 Year Visit	
	TAVR (N=496)	SAVR (N=454)	TAVR (N=496)	SAVR (N=454)
Total patients	496	454	496	454
Non-eligible	2	11	6	30
Death	2	6	5	11
Withdrawal	0	3	0	12
Lost to follow-up	0	0	0	1
Exit with other reason	0	2	1	6

Patient Accountability	30-day Visit		1 Year Visit	
	TAVR (N=496)	SAVR (N=454)	TAVR (N=496)	SAVR (N=454)
Visit not yet due	0	0	0	0
Eligible	494	443	490	424
Follow-up visit completed	96.5% (493)	96.5% (438)	97.8% (485)	91.2% (414)
Missed visit	0.2% (1)	1.1% (5)	1.0% (5)	2.2% (10)

C. Study Population Demographics and Baseline Characteristics

The demographics and baseline characteristics of the study population are typical for a TAVR study performed in the U.S., as shown in Table 3. The treatment cohorts were generally well balanced with respect to age, gender, and STS risk score.

Table 3: Patient Demographics and Baseline Characteristics (AT Population)

Demographics and Baseline Characteristics	Summary Statistics*	
	TAVR (N = 496)	SAVR (N = 454)
Age - years	73.3 ± 5.8	73.6 ± 6.1
Male sex	67.5% (335/496)	71.1% (323/454)
Society of Thoracic Surgeons (STS) score, %	1.9 ± 0.7	1.9 ± 0.6
New York Heart Association (NYHA) class		
I/II	68.8% (341/496)	76.2% (346/454)
III/IV	31.1% (155/496)	23.8% (108/454)
Previous myocardial infarction	5.7% (28/495)	5.8% (26/452)
Previous intervention		
Coronary artery bypass grafting (CABG)	3.0% (15/494)	1.8% (8/451)
Percutaneous coronary intervention (PCI)	18.8% (93/494)	16.2% (73/452)
Stroke or cerebrovascular accident (CVA)	3.4% (17/496)	5.1% (23/453)
Peripheral vascular disease (PVD)	6.9% (34/494)	7.3% (33/453)
Atrial fibrillation	15.7% (78/496)	18.8% (85/453)
Atrial flutter	3.0% (15/496)	2.4% (11/452)
Permanent pacemaker or defibrillator	2.4% (12/496)	2.9% (13/454)
Hostile chest	0.0% (0/496)	0.0% (0/454)
Echocardiographic findings (Valve Implant Population)		
Valve area (cm^2)	0.8 ± 0.2 (459)	0.8 ± 0.2 (424)

Demographics and Baseline Characteristics	Summary Statistics*	
	TAVR (N = 496)	SAVR (N = 454)
Mean gradient (mmHg)	49.4 ± 12.8 (484)	48.3 ± 11.8 (442)
Mean left ventricular ejection fraction (LVEF), %	65.7 ± 9.0 (472)	66.2 ± 8.6 (436)
Moderate or severe aortic regurgitation	3.9% (19/484)	2.5% (11/446)
Moderate or severe mitral regurgitation	1.3% (6/477)	3.2% (14/437)

*Continuous measures - Mean ± SD (Total no.); Categorical measures - % (no./Total no.)

D. Safety and Effectiveness Results

1. Primary Endpoint

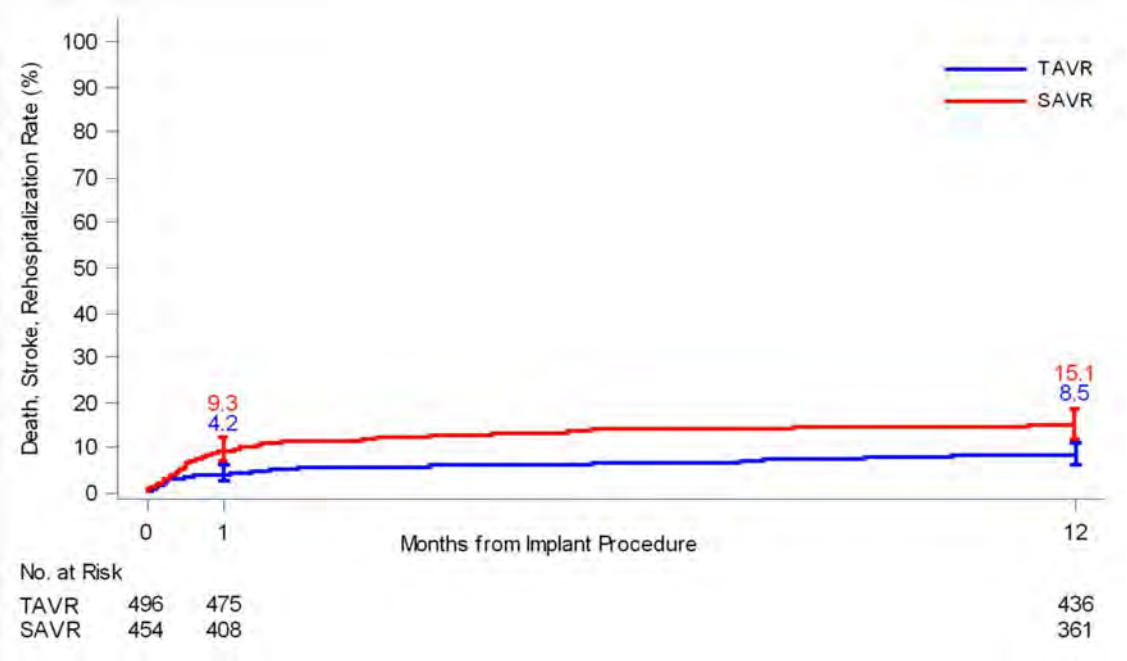
The primary endpoint results are presented in Table 4 and Figure 12. The rate of all-cause death, all stroke, or rehospitalization (valve-related or procedure-related and including heart failure) at 1 year was 8.5% in the TAVR cohort and 15.1% in the SAVR cohort. Since the upper limit of the 95% confidence interval for the difference in the primary endpoint event rate was < 6.0%, non–inferiority was achieved.

Table 4: Primary Endpoint Analysis (AT Population)

Event	Kaplan-Meier Rate*		Difference of KM Estimate (TAVR – SAVR)	95% CI for the Difference	Non-inferiority Criterion
	TAVR (N=496)	SAVR (N=454)			
All-cause death, all stroke, or rehospitalization	8.5% (42)	15.1% (68)	-6.65%	[-10.77%, -2.52%]	Pass
All-cause death	1.0% (5)	2.5% (11)	-1.44%	[-3.13%, 0.24%]	
All stroke	1.2% (6)	3.1% (14)	-1.90%	[-3.77%, -0.02%]	
Rehospitalization	7.3% (36)	11.0% (49)	-3.74%	[-7.45%, -0.02%]	

*Kaplan-Meier estimate - % (no. of patients with the event)

Figure 12: All-Cause Death, All Stroke, and Rehospitalization through 1 Year (AT Population)



Note: The confidence intervals were calculated without multiplicity adjustment. The adjusted confidence intervals could be wider than presented here. As such, confidence intervals are provided to illustrate the variability only and should not be used to draw any statistical conclusion.

2. Secondary Endpoints

Hypothesis testing

Since the primary endpoint passed the non-inferiority testing, the prespecified superiority testing was carried out on the six select secondary endpoints sequentially. TAVR with SAPIEN 3 was found to be superior to SAVR in all six secondary endpoints, as shown in Table 5.

Table 5: Superiority Testing of Select Secondary Endpoints (AT Population)

No.	Endpoint	Summary Statistics*		Difference (TAVR – SAVR)	95% CI for the Difference	p-value (Superiority Test Result)
		TAVR (N=496)	SAVR (N=454)			
1	New onset atrial fibrillation at 30 days†	5.0% (21/417)	39.3% (145/369)	-34.3%	[-39.7%, -28.9%]	<.0001 (pass)

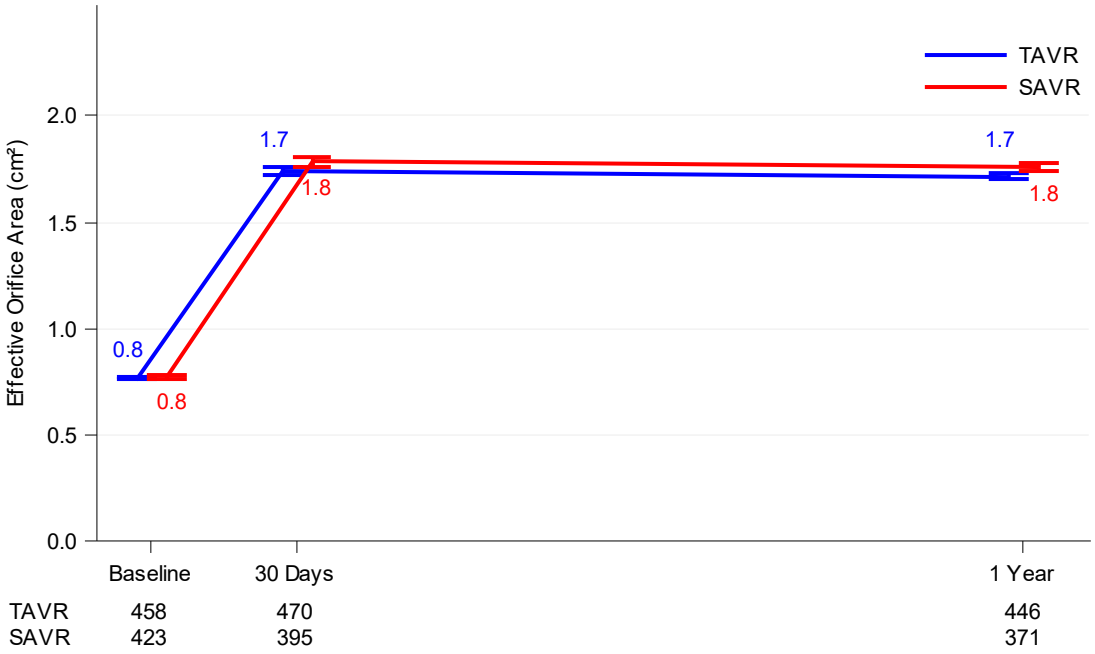
No.	Endpoint	Summary Statistics*		Difference (TAVR – SAVR)	95% CI for the Difference	p-value (Superiority Test Result)
		TAVR (N=496)	SAVR (N=454)			
2	Length of index hospitalization (days)	2.9 ± 0.1 (496)	7.4 ± 0.2 (454)	-4.5	[-4.8, -4.1]	<.0001 (pass)
3	All-cause death, all stroke, or rehospitalization at 1 year	8.5% (42)	15.1% (68)	-6.6%	[-10.8%, -2.5%]	0.0016 (pass)
4	Death, KCCQ < 45 or KCCQ decrease from baseline ≥ 10 points at 30 days	3.9% (19/492)	30.6% (133/435)	-26.7%	[-31.4%, -22.1%]	<.0001 (pass)
5	Death or all stroke at 30 days	1.0% (5/496)	3.3% (15/454)	-2.3%	[-4.2%, -0.4%]	0.0214 (pass)
6	All stroke at 30 days	0.6% (3/496)	2.4% (11/454)	-1.8%	[-3.4%, -0.2%]	0.0284 (pass)

*Continuous measures - Mean ± SE (Total no.); Categorical measures – observed rate, % (no./Total no.), except No. 3 - Kaplan-Meier rate, % (Total no.).
†Patients with pre-procedural atrial fibrillation were excluded from the analysis.

Valve Performance

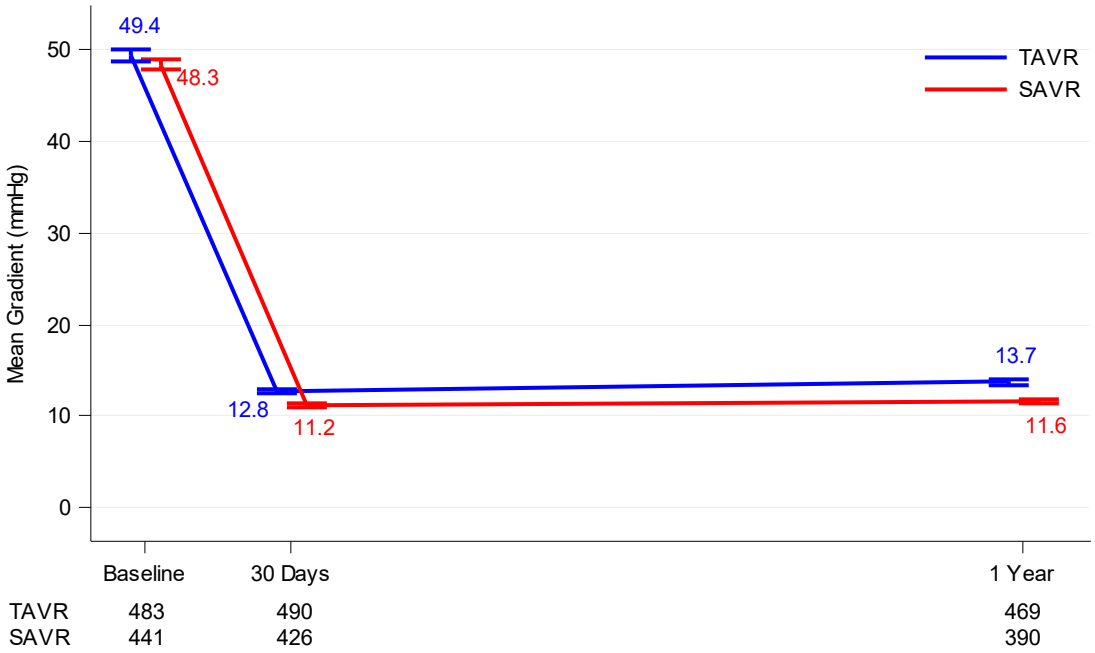
The effective orifice area (EOA), mean aortic gradient, total aortic regurgitation (AR), and paravalvular regurgitation values obtained over time for the TAVR and SAVR patients are shown in Figure 13 through Figure 16, respectively. The increase in EOA and decrease in gradient were sustained through 1 year in both cohorts. In the TAVR cohort, the proportion of patients with total AR ≥ moderate was 0.8% at 30 days and 1.1% at 1 year, while in the SAVR cohort, the corresponding proportion was 0.4% at 30 days and 0.6% at 1 year. The proportion of patients with paravalvular regurgitation ≥ moderate was 0.8% at 30 days and 0.6% at 1 year in the TAVR cohort, as compared to 0.0% at 30 days and 0.8% at 1 year in the SAVR cohort.

Figure 13: Effective Orifice Area (VI Population)



Note: Line plot with mean and standard error. The total number of patients at each visit time point only counted the patients with valid values.

Figure 14: Mean Aortic Gradient (VI Population)



Note: Line plot with mean and standard error. The total number of patients at each visit time point only counted the patients with valid values.

Figure 15: Total Aortic Regurgitation (VI Population)

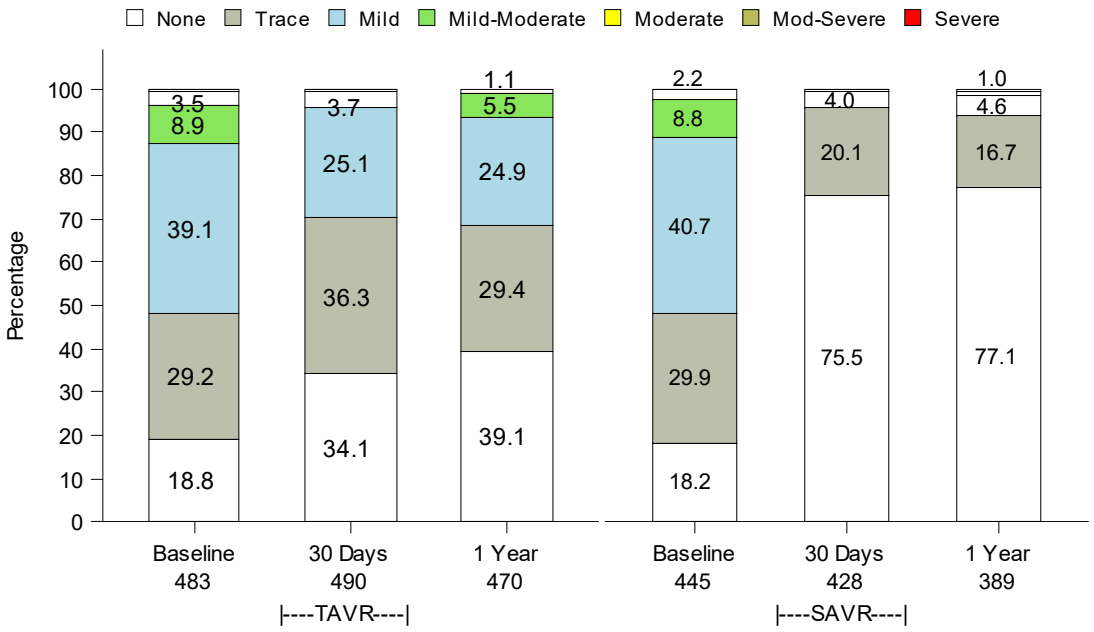
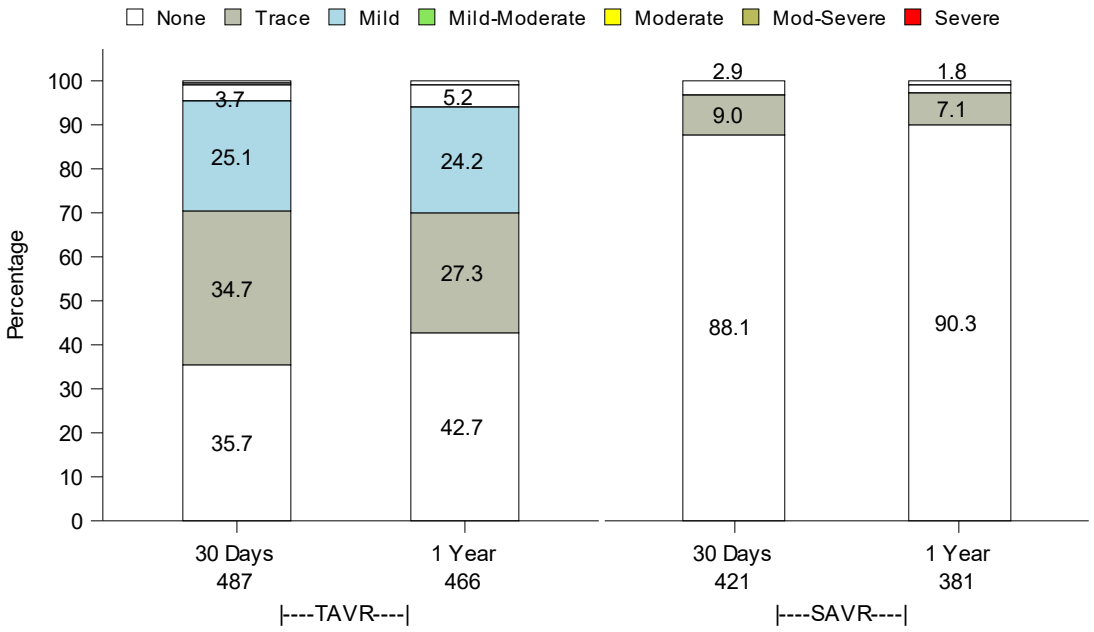


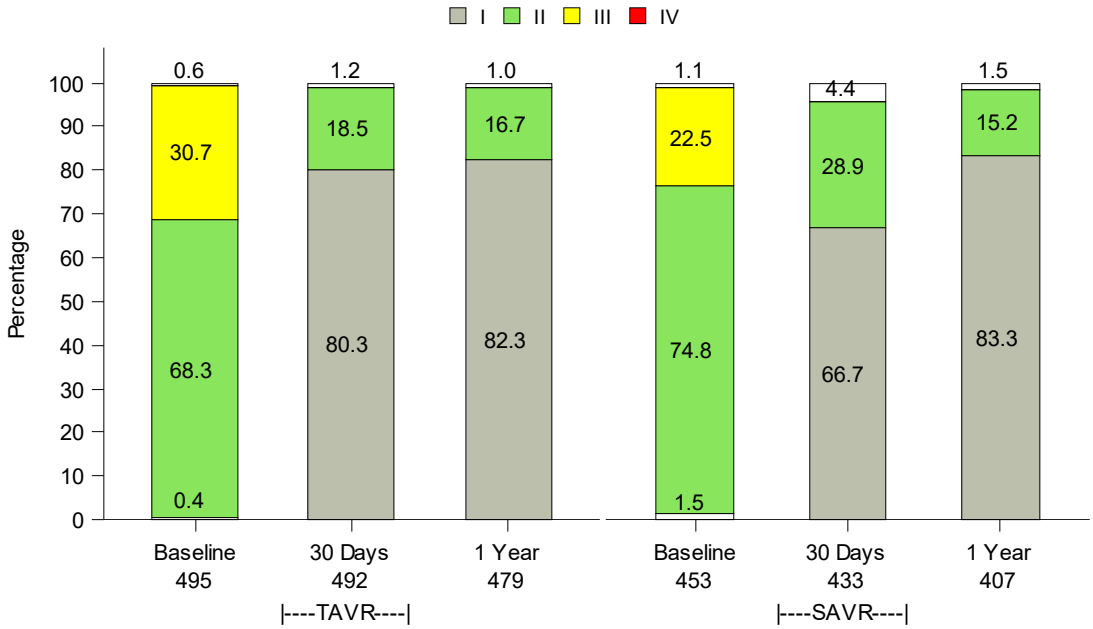
Figure 16: Paravalvular Regurgitation (VI Population)



NYHA Functional Class

The NYHA classifications by visit are presented in Figure 17. At baseline, 31.3% of TAVR patients and 23.6% of SAVR patients were in NYHA III/IV. At 1 year, the majority (~99%) of TAVR and SAVR patients were in NYHA Class I/II.

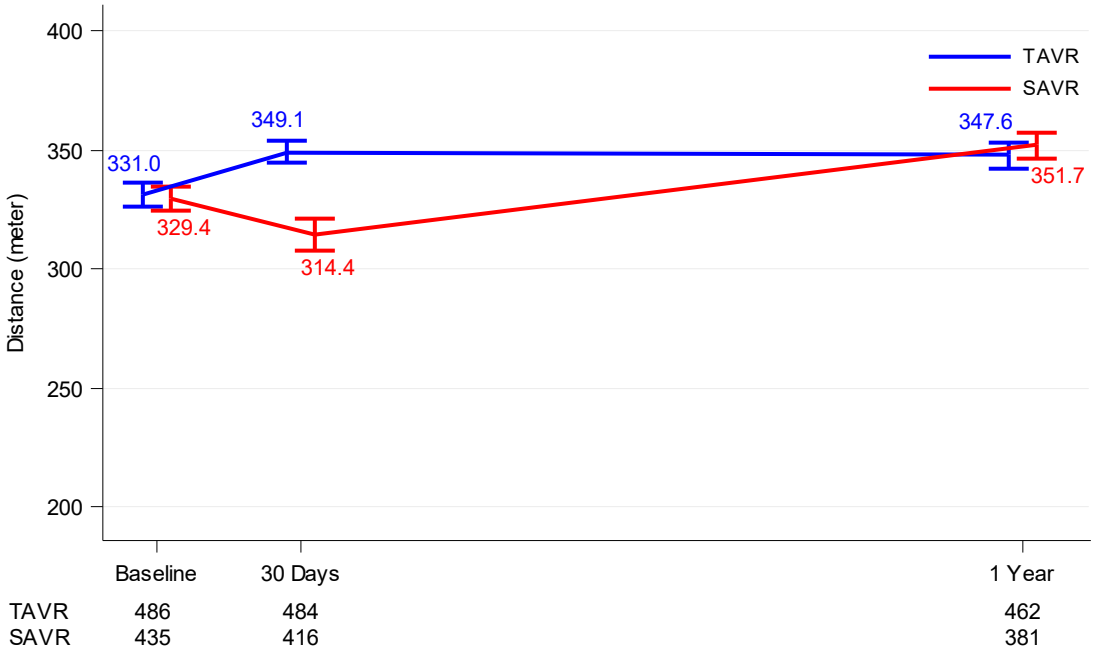
Figure 17: NYHA Class by Visit (VI Population)



Six-Minute Walk Test (6MWT)

The results for the 6MWT are presented in Figure 18. The TAVR patients showed an increase in mean 6MWT distance from 331.0 m at baseline to 349.1 m at 30 days, while SAVR patients showed a decrease from 329.4 m at baseline to 314.4 m at 30 days. The two cohorts had similar values at 1 year (347.6 m for TAVR and 351.7 m for SAVR).

Figure 18: 6MWT Distance (VI Population)



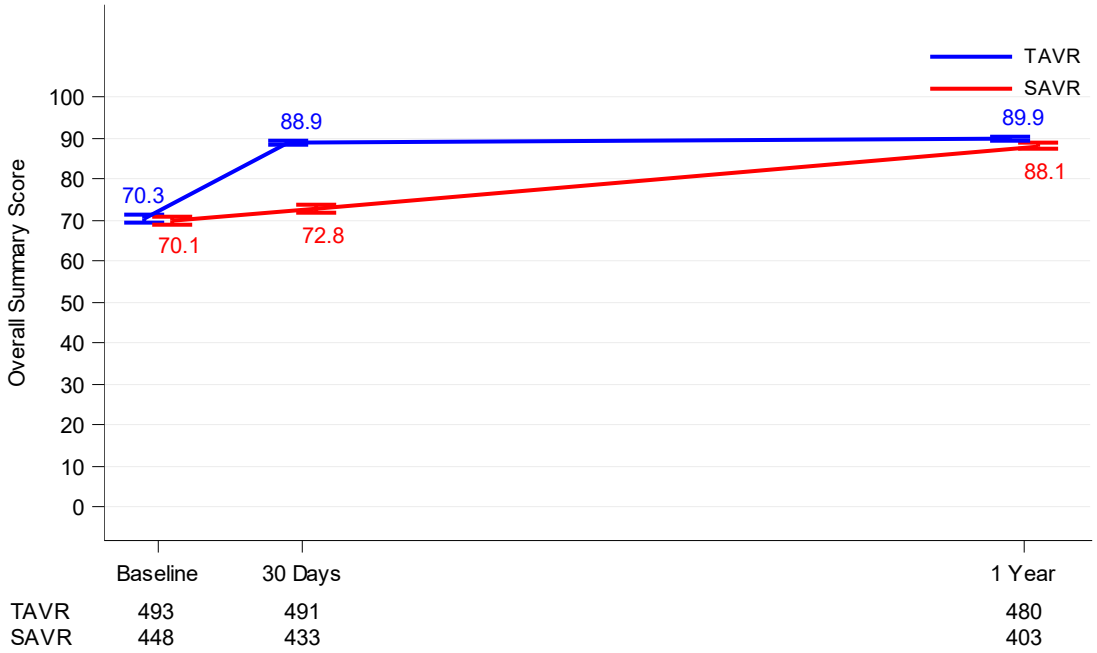
Note: Line plot with mean and standard error. The total number of patients at each visit time point only counted the patients with valid values.

QoL

KCCQ

The results for the KCCQ overall summary score are presented in Figure 19. The mean score increased from 70.3 at baseline to 88.9 at 30 days and 89.9 at 1 year in TAVR patients and from 70.1 at baseline to 72.8 at 30 days and 88.1 at 1 year in SAVR patients.

Figure 19: KCCQ Overall Summary Score (VI Population)

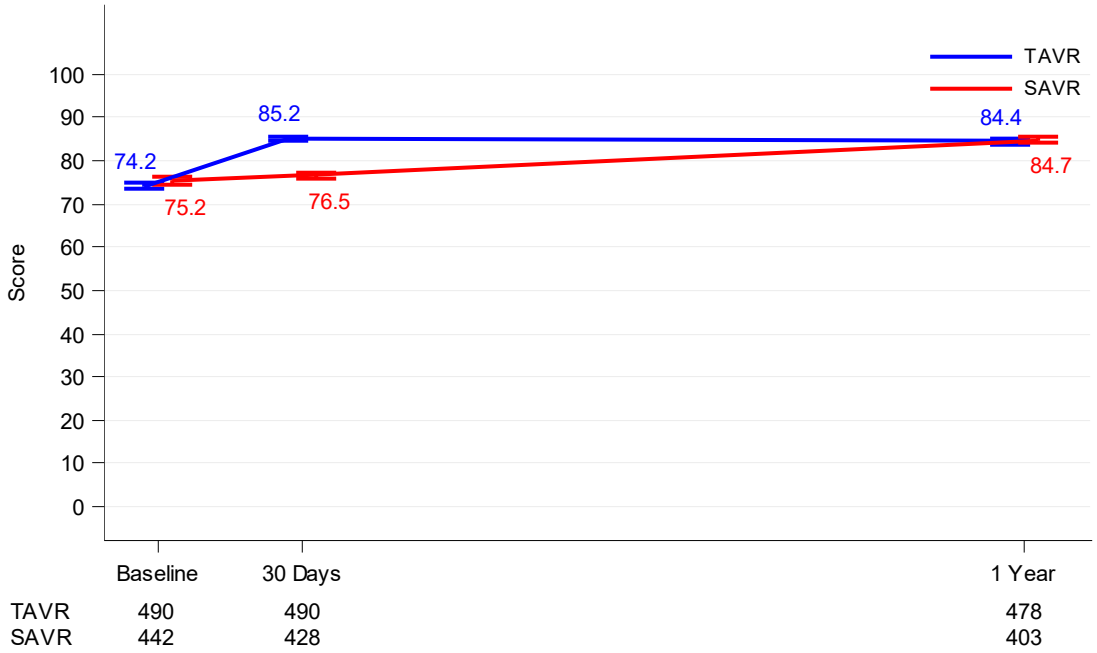


Note: Line plot with mean and standard error. The total number of patients at each visit time point only counted the patients with valid values.

EuroQol (EQ-5D)

The results for the EQ-5D visual analog score (VAS) are presented in Figure 20. The mean score was 74.2 at baseline, 85.2 at 30 days, and 84.4 at 1 year in TAVR patients, as compared to 75.2 at baseline, 76.5 at 30 days, and 84.7 at 1 year in SAVR patients.

Figure 20: EQ-5D Visual Analog Score (VI Population)

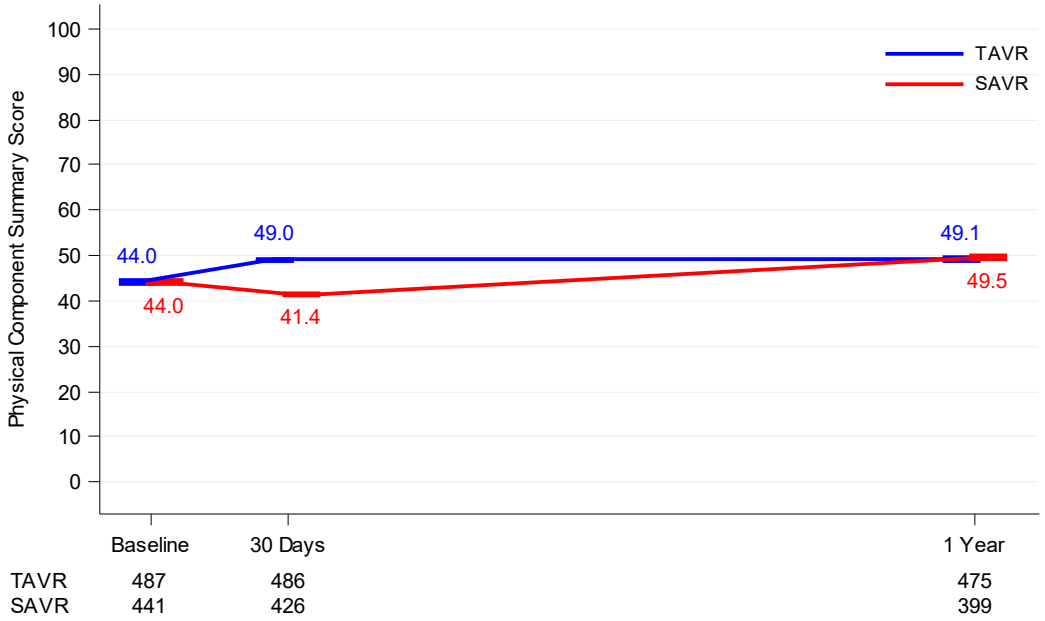


Note: Line plot with mean and standard error. The total number of patients at each visit time point only counted the patients with valid values.

Short Form (SF)-36

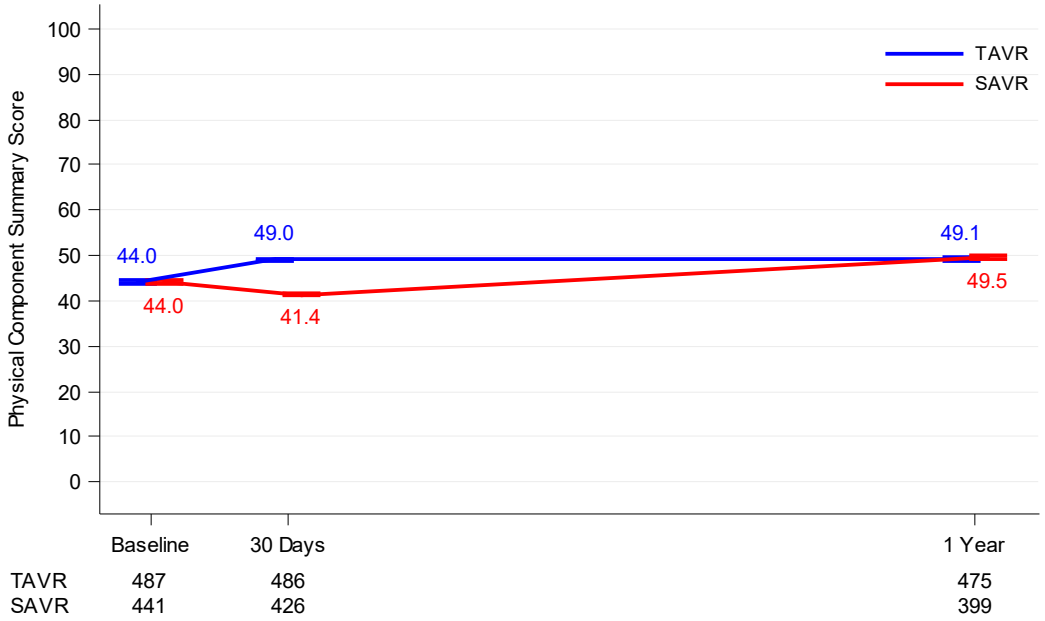
The results for the SF-36 physical component summary score and mental component summary score are presented in Figure 21 and Figure 22, respectively.

Figure 21: SF-36 Physical Component Summary Score (VI Population)



Note: Line plot with mean and standard error. The total number of patients at each visit time point only counted the patients with valid values.

Figure 22: SF-36 Mental Component Summary Score (VI Population)



Note: Line plot with mean and standard error. The total number of patients at each visit time point only counted the patients with valid values.

3. Adverse Events

The Kaplan-Meier estimates of the CEC-adjudicated adverse events through 1 year are presented in Table 6.

Table 6: CEC-Adjudicated Adverse Events through 1 Year (AT Population)

Event	Kaplan-Meier Rate*			
	30 Days		1 Year	
	TAVR (N=496)	SAVR (N=454)	TAVR (N=496)	SAVR (N=454)
All cause death	0.4% (2, 2)	1.1% (5, 5)	1.0% (5, 5)	2.5% (11, 11)
Cardiovascular death	0.4% (2, 2)	0.9% (4, 4)	0.8% (4, 4)	2.0% (9, 9)
All stroke	0.6% (3, 3)	2.4% (11, 11)	1.2% (6, 6)	3.1% (14, 14)
Disabling stroke	0.0% (0, 0)	0.4% (2, 2)	0.2% (1, 1)	0.9% (4, 4)
Non-disabling stroke	0.6% (3, 3)	2.0% (9, 9)	1.0% (5, 5)	2.2% (10, 10)
Death or stroke	1.0% (5, 5)	3.3% (16, 15)	1.8% (11, 9)	4.9% (25, 22)
Death or disabling stroke	0.4% (2, 2)	1.3% (7, 6)	1.0% (6, 5)	2.9% (15, 13)
Major vascular complications	2.2% (12, 11)	1.5% (8, 7)	2.8% (15, 14)	1.5% (8, 7)
Life-threatening / disabling, or major bleeding	3.6% (22, 18)	24.5% (123, 111)	7.7% (45, 38)	25.9% (132, 117)
Life-threatening / disabling bleeding	1.2% (9, 6)	11.9% (58, 54)	2.8% (17, 14)	12.8% (63, 58)
Major bleeding	2.6% (13, 13)	13.5% (65, 61)	5.3% (28, 26)	14.2% (69, 64)
Myocardial infarction	1.0% (5, 5)	1.3% (6, 6)	1.2% (6, 6)	2.2% (10, 10)
Requirement for renal replacement†	0.2% (1, 1)	0.7% (3, 3)	0.2% (1, 1)	0.7% (3, 3)
New permanent pacemaker implantation resulting from new or worsened conduction disturbances‡	6.5% (32, 32)	4.0% (18, 18)	7.3% (36, 36)	5.4% (24, 24)
Coronary obstruction requiring intervention	0.2% (1, 1)	0.7% (3, 3)	0.2% (1, 1)	0.7% (3, 3)
New onset atrial fibrillation	5.0% (21, 21)	39.5% (145, 145)	7.0% (29, 29)	40.9% (150, 150)
Rehospitalization‖	3.4% (18, 17)	6.5% (30, 29)	7.3% (39, 36)	11.0% (59, 49)

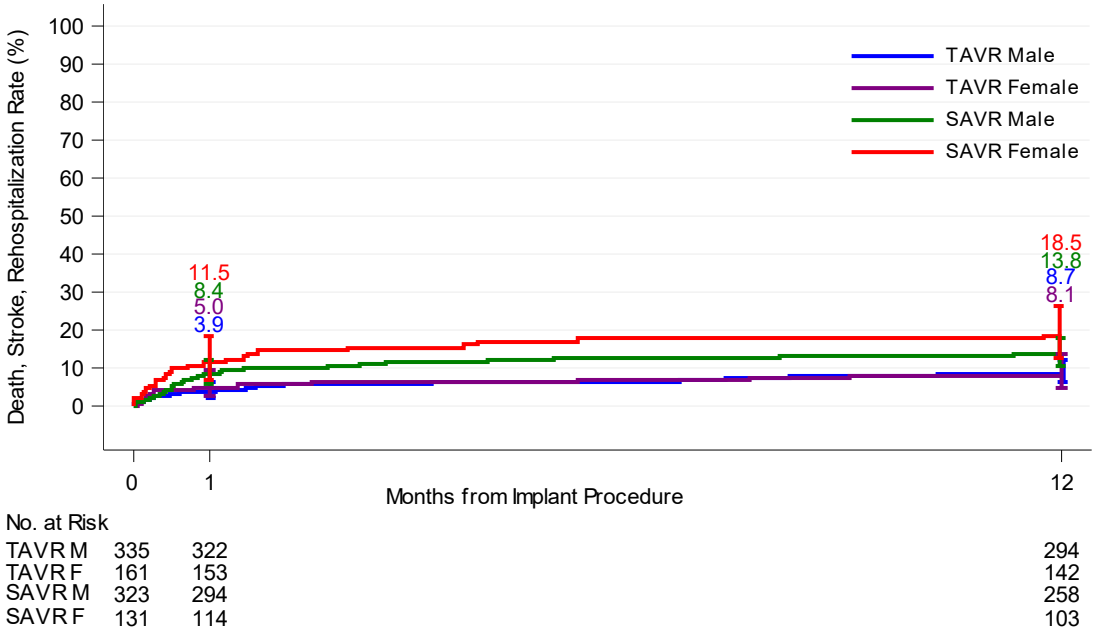
*Kaplan-Meier rate (no. of events, no. of patients with the event).
†Requirement for renal replacement was based on the site-reported event. All the other events were based on the CEC-adjudicated results.
‡Patients with pacemaker or ICD at baseline were not counted as new events.
‖Rehospitalization (valve-related or procedure-related and including heart failure).

4. Subgroup Analysis

Gender Analysis

The protocol specified a subgroup analysis on gender. The primary endpoint result stratified by gender is presented in Figure 23.

Figure 23: All-Cause Death, All Stroke, and Rehospitalization through 1 Year Stratified by Gender (AT Population)



Note: The confidence intervals were calculated without multiplicity adjustment. The adjusted confidence intervals could be wider than presented here. As such, confidence intervals are provided to illustrate the variability only and should not be used to draw any statistical conclusion.

5. Other Study Observations

Procedural Information

The general procedural data are summarized in Table 7. Conscious sedation was used in the majority of TAVR patients (65.1%). The mean procedure time was significantly lower for TAVR compared to SAVR (58.6 minutes vs. 208.3 minutes). There were less concomitant (planned) procedures performed for TAVR patients compared to SAVR patients (6.9% vs. 26.4%). Additional TAVR and SAVR specific procedural data are presented in Table 8 and 9, respectively.

Table 7: General Procedural Data (AT Population)

Variable	Summary Statistics*	
	TAVR (N=496)	SAVR (N=454)
Subject treated according to their treatment assignment	99.8% (495/496)	99.8% (453/454)
Procedure aborted	0	1
Subject was assigned to TAVR but received SAVR	1	0
Procedure time (min)	58.6 ± 1.6 (496)	208.3 ± 2.9 (454)
Anesthesia type		
General	33.3% (165/496)	100.0% (454/454)
Conscious sedation	65.1% (323/496)	NA
Conversion from conscious sedation to general anesthesia during the procedure	1.6% (8/496)	NA
Anesthesia time (min)	138.7 ± 2.20 (496)	309.7 ± 3.7 (454)
Concomitant procedures	6.9% (34/496)	26.4% (120/454)
Annular area (mm^2)	473.5 ± 83.3 (486)	479.6 ± 87.6 (441)

*Continuous measures – mean ± SE (n) for procedure and anesthesia time, mean ± SD (n) for annular area; Categorical measures - % (no./Total no.)

Table 8: TAVR Procedure Data (AT Population)

Variable	Summary Statistics*
	TAVR (N=496)
Valve size	
20 mm	2.2% (11/496)
23 mm	29.2% (145/496)
26 mm	47.6% (236/496)
29 mm	21.0% (104/496)
Successful access, delivery and retrieval of the device delivery system	99.8% (494/495)
Arterial access method	
Left percutaneous	22.2% (109/490)
Right percutaneous	76.7% (376/490)
Left surgical cutdown	0.0% (0/490)

Variable	Summary Statistics*
	TAVR (N=496)
Right surgical cutdown	1.0% (5/490)
Total fluoroscopy time (min)	13.9 ± 0.3 (487)
BAV performed	57.8% (286/495)
Post dilatation performed	20.9% (103/494)
Number of post dilatations	
1	89.3% (92/103)
2	8.7% (9/103)
3	1.9% (2/103)
More than one SAPIEN 3 THV implanted	0.2% (1/495)

*Continuous measures - mean ± SE (n); categorical measures - % (no./Total no.). For patients in whom the procedure was aborted or who were converted to surgery, the rest of the procedure data except valve size were not collected.

Table 9: SAVR Procedure Data (AT Population)

Variable	Summary Statistics*
	SAVR (N=454)
Procedure aborted†	0.2% (1/454)
Valve size	
19 mm	2.9% (13/453)
21 mm	17.2% (78/453)
23 mm	36.6% (166/453)
25 mm	35.5% (161/453)
27 mm	6.8% (31/453)
29 mm	0.9% (4/453)
Total aortic cross clamp time (min)	74.3 ± 1.3 (453)
Total pump time (min)	97.7 ± 1.6 (453)
SAVR approach	
Sternotomy	95.4% (432/453)
Thoracotomy	0.9% (4/453)
Mini right upper thoracotomy	2.9% (13/453)
Port access	0.2% (1/453)

Variable	Summary Statistics*
	SAVR (N=454)
Other	0.7% (3/453)
Successful implantation of the surgical valve	100.0% (453/453)

*Continuous measures - mean ± SE (n); categorical measures - % (no./Total no.).
†For patients in whom the procedure was aborted, the rest of the procedure data were not collected.

CT Substudy

There were 184 TAVR and 162 SAVR patients at 30 days and 160 and 134 patients at 1 year, respectively, who had at least one adequate CT for leaflet assessments. The HALT and leaflet mobility imaging findings are summarized in Table 10, along with the associated mean aortic pressure gradients. The mean aortic pressure gradients at 1 year stratified by HALT and leaflet mobility at 30 days are summarized in Table 11 and Table 12, respectively. The rate of death, stroke or TIA at 1 year stratified by HALT and leaflet mobility at 30 days are summarized in Table 13 and Table 14, respectively. The CT substudy was not powered to compare the relative incidence or the severity of HALT or reduced leaflet mobility between the TAVR and SAVR cohorts, or to determine whether late clinical outcomes were affected by the presence of HALT or reduced leaflet mobility.

Table 10: HALT and Leaflet Mobility Findings and Associated Mean Gradients

Findings	Summary Statistics*			
	30 Days		1 Year	
	TAVR (N=184)	SAVR (N=162)	TAVR (N=160)	SAVR (N=134)
Proportion of patients on oral anticoagulants at time of scan	6.0% (11/184)	21.0% (34/162)	8.1% (13/160)	18/134 (13.4%)
HALT†				
No thickening	84.8% (156/184)	95.7% (155/162)	74.4% (119/160)	82.1% (110/134)
Mean gradient (mmHg)	12.5 ± 0.3 (156)	10.8 ± 0.3 (155)	13.7 ± 0.4 (115)	11.7 ± 0.4 (106)
<25% leaflet length thickened	4.9% (9/184)	1.2% (2/162)	11.3% (18/160)	7.5% (10/134)
Mean gradient (mmHg)	11.4 ± 0.9 (9)	16.5 ± NA (1)	12.9 ± 0.7 (18)	9.3 ± 1.8 (8)
25%-50% leaflet length thickened	3.3% (6/184)	1.9% (3/162)	6.3% (10/160)	5.2% (7/134)
Mean gradient (mmHg)	13.7 ± 1.7 (6)	9.4 ± 1.4 (3)	13.2 ± 1.8 (10)	15.1 ± 2.4 (7)

Findings	Summary Statistics*			
	30 Days		1 Year	
	TAVR (N=184)	SAVR (N=162)	TAVR (N=160)	SAVR (N=134)
50%-75% leaflet length thickened	6.5% (12/184)	0.6% (1/162)	5.0% (8/160)	3.7% (5/134)
Mean gradient (mmHg)	15.2 ± 1.9 (12)	9.8 ± NA (1)	16.9 ± 3.3 (8)	16.1 ± 4.0 (5)
>75% leaflet length thickened	0.5% (1/184)	0.6% (1/162)	3.1% (5/160)	1.5% (2/134)
Mean gradient (mmHg)	10.2 ± NA (1)	16.8 ± NA (1)	20.2 ± 6.2 (5)	9.0 ± 4.2 (2)
Number of leaflets with HALT	6.7% (37/552)	2.3% (11/486)	12.7% (61/480)	8.2% (33/402)
0 leaflets thickening	156	155	119	110
1 leaflet thickening	21	4	26	15
2 leaflets thickening	5	2	10	9
3 leaflets thickening	2	1	5	0
Leaflet mobility‡				
Unrestricted	85.3% (145/170)	96.8% (149/154)	77.6% (118/152)	83.% (108/129)
Mean gradient (mmHg)	12.2 ± 0.3 (145)	10.7 ± 0.3 (148)	13.3 ± 0.4 (114)	12.0 ± 0.5 (105)
Partially restricted, restriction limited to base	5.3% (9/170)	1.3% (2/154)	11.8% (18/152)	8.5% (11/129)
Mean gradient (mmHg)	11.4 ± 0.9 (9)	14.6 ± 1.9 (2)	12.5 ± 0.6 (18)	9.9 ± 1.6 (9)
Partially restricted (<50%)	5.3% (9/170)	1.3% (2/154)	3.9% (6/152)	3.1% (4/129)
Mean gradient (mmHg)	15.5 ± 2.4 (9)	10.3 ± 0.5 (2)	14.0 ± 2.8 (6)	15.6 ± 3.0 (4)
Partially restricted (50%-75%)	3.5% (6/170)	0.0% (0/154)	4.6% (7/152)	3.9% (5/129)
Mean gradient (mmHg)	12.8 ± 1.7 (6)	NA	21.8 ± 3.9 (7)	11.3 ± 3.6 (5)
Largely immobile	0.6% (1/170)	0.6% (1/154)	2.0% (3/152)	0.8% (1/129)
Mean gradient (mmHg)	13.3 ± NA (1)	16.8 ± NA (1)	19.5 ± 8.1 (3)	13.1 ± NA (1)
Number of leaflets partially restricted or largely immobile				
0 leaflet	145	149	118	108
1 leaflet	21	2	22	13
2 leaflets	4	2	8	8
3 leaflets	0	1	4	0

Findings	Summary Statistics*			
	30 Days		1 Year	
	TAVR (N=184)	SAVR (N=162)	TAVR (N=160)	SAVR (N=134)

*Continuous measures - mean ± SE (n); categorical measures - % (no./Total no.). The analysis population included all the patients enrolled in the CT substudy and had at least one adequate CT for leaflet assessments.

†HALT was defined as: the presence of any hyopattenuated leaflet thickening in any singular leaflet as identified by an independent CT core laboratory. The extent of the hypoattenuated leaflet thickening was graded with regards to the entire leaflet as: None, <25%, 25-50%, 50-75%, or >75%. If more than one leaflet had the appearance of HALT, the thickening measure of the most impacted leaflet was used. Presence of any degree of HALT on any one leaflet rendered a finding.

‡Leaflet mobility was determined by an independent CT core laboratory and included: unrestricted, partially restricted mobility limited to the base of a leaflet, partially restricted mobility involving more than the base of the leaflet but less than 50% of the leaflet, partially restricted mobility involving more than 50% of the leaflet but less than 75% of the leaflet, and/or a largely immobile leaflet. Presence of any degree of restriction or immobility on any one leaflet rendered a finding.

Table 11: Mean Aortic Gradient at 1 Year Stratified by HALT at 30 Days

	Summary Statistics*			
	HALT at 30 Days		No HALT at 30 Days	
	TAVR (N=28)	SAVR (N=7)	TAVR (N=156)	SAVR (N=155)
Mean gradient	13.6 ± 1.2 (24)	13.7 ± 2.7 (5)	13.6 ± 0.4 (137)	11.8 ± 0.4 (125)

*Mean ± SE (n). The analysis population included all the patients enrolled in the CT substudy and had an adequate CT for leaflet assessments at 30 days.

Table 12: Mean Aortic Gradient at 1 Year Stratified by Leaflet Mobility at 30 Days

	Summary Statistics*			
	Reduced Leaflet Mobility at 30 Days		Unrestricted at 30 Days	
	TAVR (N=25)	SAVR (N=5)	TAVR (N=145)	SAVR (N=149)
Mean gradient	13.7 ± 1.28 (23)	14.2 ± 3.48 (4)	13.3 ± 0.4 (124)	11.7 ± 0.4 (119)

*Mean ± SE (n). The analysis population included all the patients enrolled in the CT substudy and had an adequate CT for leaflet assessments at 30 days.

Table 13: All-Cause Mortality, All Stroke or TIA at 1 Year Stratified by HALT at 30 Days

1-Year Endpoint	Kaplan-Meier Rate*			
	HALT at 30 Days		No HALT at 30 Days	
	TAVR (N=28)	SAVR (N=7)	TAVR (N=156)	SAVR (N=155)
All-cause mortality	0.0% (0)	0.0% (0)	1.3% (2)	1.4% (2)
All stroke	0.0% (0)	0.0% (0)	0.7% (1)	0.0% (0)
TIA	5.6% (1)	0.0% (0)	1.3% (2)	0.0% (0)
All-cause mortality or all stroke or TIA	5.6% (1)	0.0% (0)	3.3% (5)	1.4% (2)

*Kaplan-Meier rate (no. of patients with event). The analysis population included all the patients enrolled in the CT substudy and had an adequate CT for leaflet assessments at 30 days. The Kaplan-Meier analysis used the CT test date as the start date in determining time to event. Presence of any degree of HALT on any one leaflet rendered a finding and inclusion in the HALT cohort.

Table 14: All-Cause Mortality, All Stroke or TIA at 1 Year Stratified by Leaflet Mobility at 30 Days

1-Year Endpoint	Kaplan-Meier Rate*			
	Reduced Leaflet Mobility at 30 Days		Unrestricted at 30 Days	
	TAVR (N=25)	SAVR (N=5)	TAVR (N=145)	SAVR (N=149)
All-cause mortality	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)
All stroke	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)
TIA	6.3% (1)	0.0% (0)	6.3% (1)	0.0% (0)
All-cause mortality or all stroke or TIA	6.3% (1)	0.0% (0)	3.6% (5)	1.4% (2)

*Kaplan-Meier rate (no. of patients with event). The analysis population included all the patients enrolled in the CT substudy and had an adequate CT for leaflet assessments at 30 days. The Kaplan-Meier analysis used the CT test date as the start date in determining time to event. Reduced leaflet mobility included any of the following assessments: partially restricted limited to base, partially restricted involving more than the base but less than 50% of the leaflet, partially restricted involving more than 50% but less than 75% of the leaflet, and/or largely immobile. Presence of any degree of restriction or immobility on any one leaflet rendered a finding and inclusion in the reduced leaflet mobility cohort.

6. Pediatric Extrapolation

In this premarket application, existing clinical data was not leveraged to support approval of a pediatric patient population.

E. Financial Disclosure

The Financial Disclosure by Clinical Investigators regulation (21 CFR 54) requires applicants who submit a marketing application to include certain information concerning the compensation to, and financial interests and arrangement of, any clinical investigator conduction clinical studies covered by the regulation. The PARTNER 3 trial involved 588 investigators of which none were full-time or part-time employees of the sponsor and 30 investigators had disclosable financial interests/arrangements as defined in 21 CFR 54.2(a), (b), (c) and (f), as described below:

- Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: None
- Significant payment of other sorts: 29
- Proprietary interest in the product tested held by the investigator: None
- Significant equity interest held by investigator in sponsor of covered study: 1

The applicant has adequately disclosed the financial interest/arrangements with clinical investigators. Statistical analyses were conducted by FDA to determine whether the financial interests/arrangements had any impact on the clinical study outcome. The information provided does not raise any questions about the reliability of the data.

XI. PANEL MEETING RECOMMENDATION AND FDA'S POST-PANEL ACTION

In accordance with the provisions of section 515(c)(2) of the Act as amended by the Safe Medical Devices Act of 1990, this PMA was not referred to the Circulatory System Devices panel, an FDA advisory committee, for review and recommendation because the information in the PMA substantially duplicates information previously reviewed by this panel.

XII. CONCLUSIONS DRAWN FROM THE PRECLINICAL AND CLINICAL STUDIES

A. Effectiveness Conclusions

In the clinical study, patients overall demonstrated clinically significant improvement in valve hemodynamics from baseline to 1 year. On average, the EOA increased from 0.8 cm^2 at baseline to 1.7 cm^2 at 1 year, and the mean pressure gradient decreased from 49.4 mmHg at baseline to 13.7 mmHg at 1 year in the TAVR patients. These trends were consistent with those observed in the SAVR patients. In the TAVR cohort, the proportion of patients with total AR ≥ moderate was 1.1% at 1 year, while in the SAVR cohort, the proportion was 0.6% at 1 year. The proportion of patients with paravalvular AR ≥ moderate was 0.6% at 1 year, as compared to 0.8% at 1 year in the SAVR cohort.

The improvement in valve hemodynamics in the TAVR patients was further demonstrated through improvements in NYHA classification, 6MWT distance, and QoL. In the TAVR cohort, about 1% of the patients were in NYHA Class III or IV at 1 year as compared to 31.3% at baseline; similar results were seen in the SAVR cohort. The mean 6MWT distance increased from 331.0 m at baseline to 349.1 m at 30 days in the TAVR patients; this

improvement was sustained at 1 year. Similarly, clinically significant improvement in the KCCQ score was observed in the TAVR patients, which increased from 70.3 at baseline to 88.9 and 89.9 at 30 days and 1 year, respectively. In contrast, early improvements in 6MWT distance and KCCQ score at 30 days were not seen with SAVR, although the improvements at 1 year were similar to those seen with TAVR. Furthermore, the mean procedure time and index procedure hospital stay were 58.6 minutes and 2.9 days, respectively, for TAVR, and were significantly shorter compared to SAVR (208.3 minutes and 7.4 days, respectively).

B. Safety Conclusions

The risks of the device are based on nonclinical laboratory and animal studies as well as data collected in a clinical study conducted to support PMA approval as described above. The results from the nonclinical laboratory (e.g., biocompatibility, hydrodynamic performance, durability, and structural integrity) and animal studies demonstrated that this device is suitable for long-term implant.

The Kaplan-Meier estimate of the event rate of all-cause mortality, all stroke, or rehospitalization (valve-related or procedure-related and including heart failure) at 1 year (i.e., the primary endpoint) was 8.5% in the TAVR cohort and 15.1% in the SAVR cohort. TAVR with the SAPIEN 3 device was found to be non-inferior to SAVR in the primary endpoint within a non-inferiority margin of 6%. Subsequent prespecified superiority testing found that TAVR with the SAPIEN 3 device was superior to SAVR in the primary endpoint. The differences in the 1-year rates of all-cause mortality, all stroke, and rehospitalization between TAVR and SAVR patients were -1.44%, -1.90%, -3.74%, respectively. In addition, TAVR patients had significantly lower rate of new onset atrial fibrillation at 30 days than SAVR patients (5.0% vs. 39.3%).

The CT substudy revealed that 15.2% and 25.6% of TAVR patients had various degrees of leaflet thickening at 30 days and 1 year, respectively, as compared to 4.3% and 17.9% of SAVR patients. In addition, various degrees of restricted leaflet mobility were observed in 14.7% of patients at 30 days and 22.4% of patients at 1 year in the TAVR cohort, which was 3.2% and 16.3%, respectively, in the SAVR cohort. The long-term clinical sequelae of these imaging findings are presently unknown.

C. Benefit-Risk Determination

The probable benefits of TAVR with the SAPIEN 3 THV include improved valve hemodynamic performance, improved functional status as measured by the NYHA classification and 6MWT distance, and improved QoL at 1 year post-procedure.

The probable risks of TAVR with the SAPIEN 3 THV include procedure-related complications such as death, stroke, myocardial infarction, major vascular complications, bleeding, conduction disturbance, and requirement for renal replacement.

1. Patient Perspectives

   This application did not include specific information on patient perspectives for TAVR with the SAPIEN 3 THV. However, since TAVR with the SAPIEN 3 THV provides a less invasive alternative to SAVR, FDA believes that many patients would prefer the TAVR therapy. However, the long-term durability of SAPEIN THV compared to surgically implanted valves has not been established. Patients, especially younger ones, should discuss available treatment options with their heart care team to select the appropriate therapy.

In conclusion, given the available information above, the data support that for patients with severe native aortic stenosis who are at low risk for open aortic valve replacement surgery, the probable benefits of TAVR with the SAPIEN 3 THV outweigh the probable risks.

D. Overall Conclusions

The data in this application support the reasonable assurance of safety and effectiveness of the SAPIEN 3 THV System for the replacement of native aortic valves in symptomatic severe aortic stenosis patients who are deemed to be at low surgical risk. FDA has determined this conclusion is also applicable to the SAPIEN 3 Ultra THV System.

XIII. CDRH DECISION

CDRH issued an approval order on August 16, 2019. The final conditions of approval cited in the approval order are described below.

The applicant must conduct one post-approval study as well as participate in and support continued surveillance:

1. **Post-Approval Study - Continued Follow-up of the SAPIEN 3 Transcatheter Heart Valve System "Low Risk" Indication Premarket Cohort**: The study will consist of all living patients who were enrolled under the IDE. The objective of this study is to characterize the clinical outcomes annually through 10 years post-procedure. The safety and effectiveness endpoints include all-cause mortality, all stroke (disabling and non-disabling), life-threatening bleeding, requirement for renal replacement, coronary artery obstruction requiring intervention, major vascular complication, valve-related dysfunction requiring repeat procedure, new permanent pacemaker implantation, prosthetic valve endocarditis, prosthetic valve thrombosis, NYHA classification, 6MWT distance, KCCQ score, and hemodynamic performance metrics by Doppler echocardiography.

2. **Edwards SAPIEN 3 Transcatheter Heart Valve System Registry-Based Continued Access Protocol (CAP) Cohort and "Low Risk" Indication Real-World Use Surveillance**: The applicant has agreed to work with the Society of Thoracic Surgeons/American College of Cardiology Transcatheter Valve Therapy (TVT) Registry to ensure that FDA surveillance occurs for the registry-based CAP cohort per approved

protocol and for commercial uses of the SAPIEN 3 THV System and SAPIEN 3 Ultra THV System for the "low risk" indication. The surveillances will be carried out to characterize the clinical outcomes of the CAP cohort annually through 10 years post implantation and to assess the real-world use of the commercial SAPIEN 3 THV System and SAPIEN 3 Ultra THV System to ensure that the device is used in appropriate circumstances, respectively. The surveillance of the CAP cohort will consist of all living CAP patients who were enrolled at participating institutions, and the surveillance of the real-world use will involve all consecutive patients treated within the first 2 years that are entered into the TVT Registry (enrollment period). The applicant has also agreed to link the data to the Centers for Medicare and Medicaid Services (CMS) claims database for long-term surveillance of these patients through 10 years post implantation (follow-up duration). This surveillance will monitor the following: (1) device success (intra-procedure); (2) all-cause mortality, all stroke, life-threatening/major bleeding, new requirement for dialysis, peri-procedural myocardial infarction, and repeat procedure for valve-related dysfunction (surgical or interventional therapy) at 30 days and 12 months; (3) neurological (non-stroke), vascular complications, and quality of life (KCCQ) outcomes at 30 days and 12 months; and (4) all-cause mortality, all stroke, and repeat procedure for valve-related dysfunction (surgical or interventional therapy) at 2-10 year post implantation.

The applicant's manufacturing facilities have been inspected and found to be in compliance with the device Quality System (QS) regulation (21 CFR 820).

XIV. APPROVAL SPECIFICATIONS

Directions for use: See final approved labeling (Instructions for Use).

Hazards to Health from Use of the Device: See Indications, Contraindications, Warnings, Precautions, and Adverse Events in the final labeling (Instructions for Use).

Post-approval Requirements and Restrictions: See Approval Order.

XV. REFERENCES

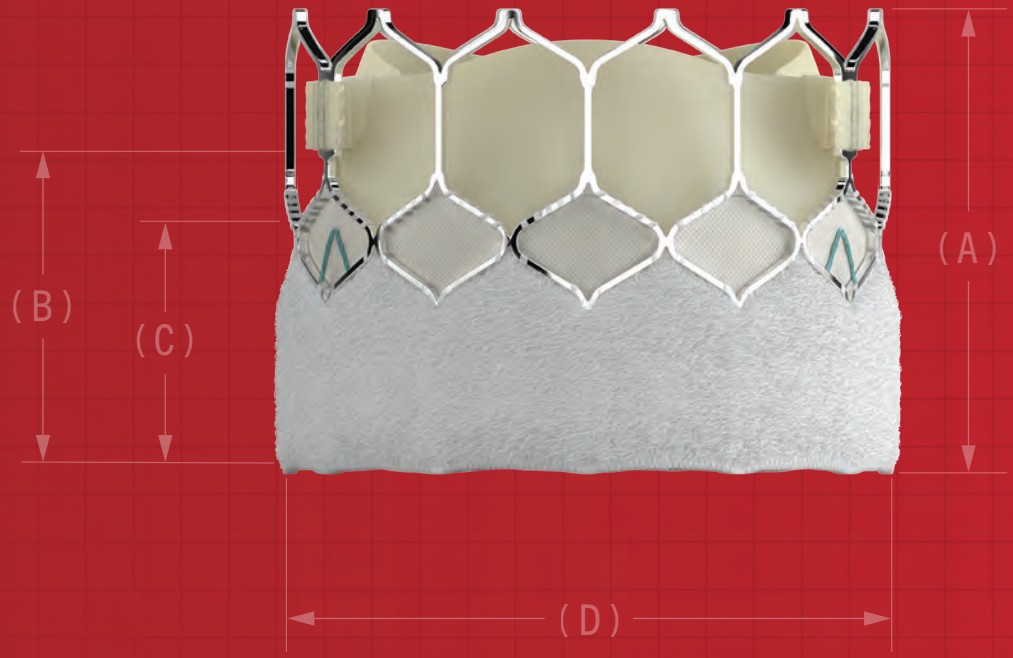
1. Kappetein AP, Head SJ, Généreux P, et al. Updated standardized endpoint definitions for transcatheter aortic valve implantation: the Valve Academic Research Consortium-2 consensus document (VARC-2). Eur J Cardiothorac Surg 2012; 42:S45-60.
2. Food and Drug Administration. FDA Guidance: Multiple Endpoints in Clinical Trials Guidance for Industry (January 2017). Retrieved from https://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm536750.pdf
3. Westfall, K. Optimally weighted, fixed sequence, and gatekeeping multiple testing procedures. J Stat Plan Inference 2001; 99:25-40.

EXHIBIT 46

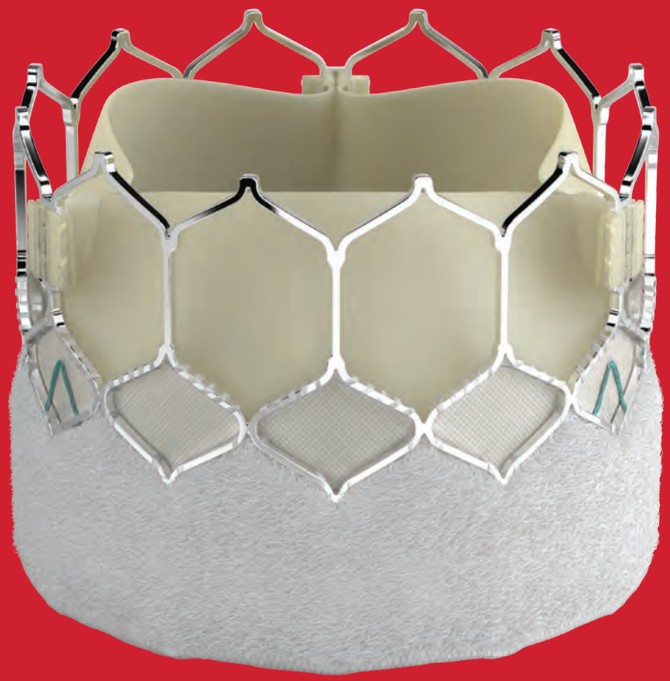
Introducing the

SAPIEN 3 Ultra valve

The next generation of Edwards SAPIEN 3 TAVR



Edwards



An evolution of the valve you know and trust

Edwards Lifesciences' commitment to innovation continues with the SAPIEN 3 Ultra valve.

Built upon the proven SAPIEN platform, the SAPIEN 3 Ultra transcatheter heart valve was designed with your patients' needs in mind.

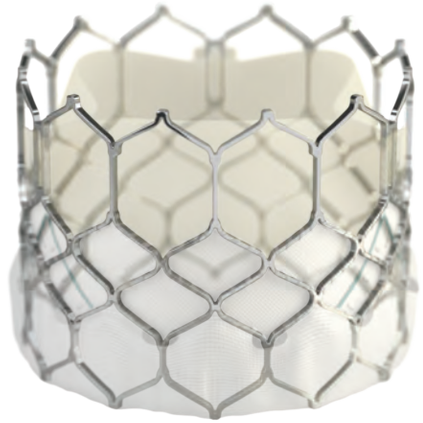


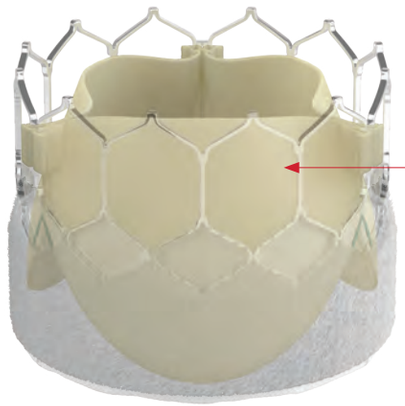
Sealing skirt technology

Built on the SAPIEN 3 valve designed to minimize paravalvular leak (PVL), the SAPIEN 3 Ultra valve now features a ~40% taller, textured polyethylene terephthalate (PET) outer skirt

Iconic geometric frame

Short frame height and open cell geometry facilitate coronary access





Valve tissue

Uses same trusted bovine pericardium tissue and process as the SAPIEN 3 valve

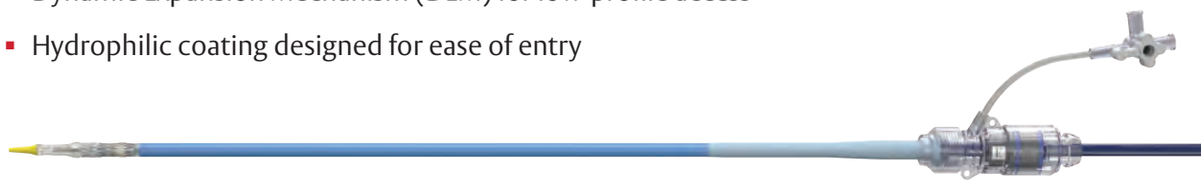
For predictable, proven results

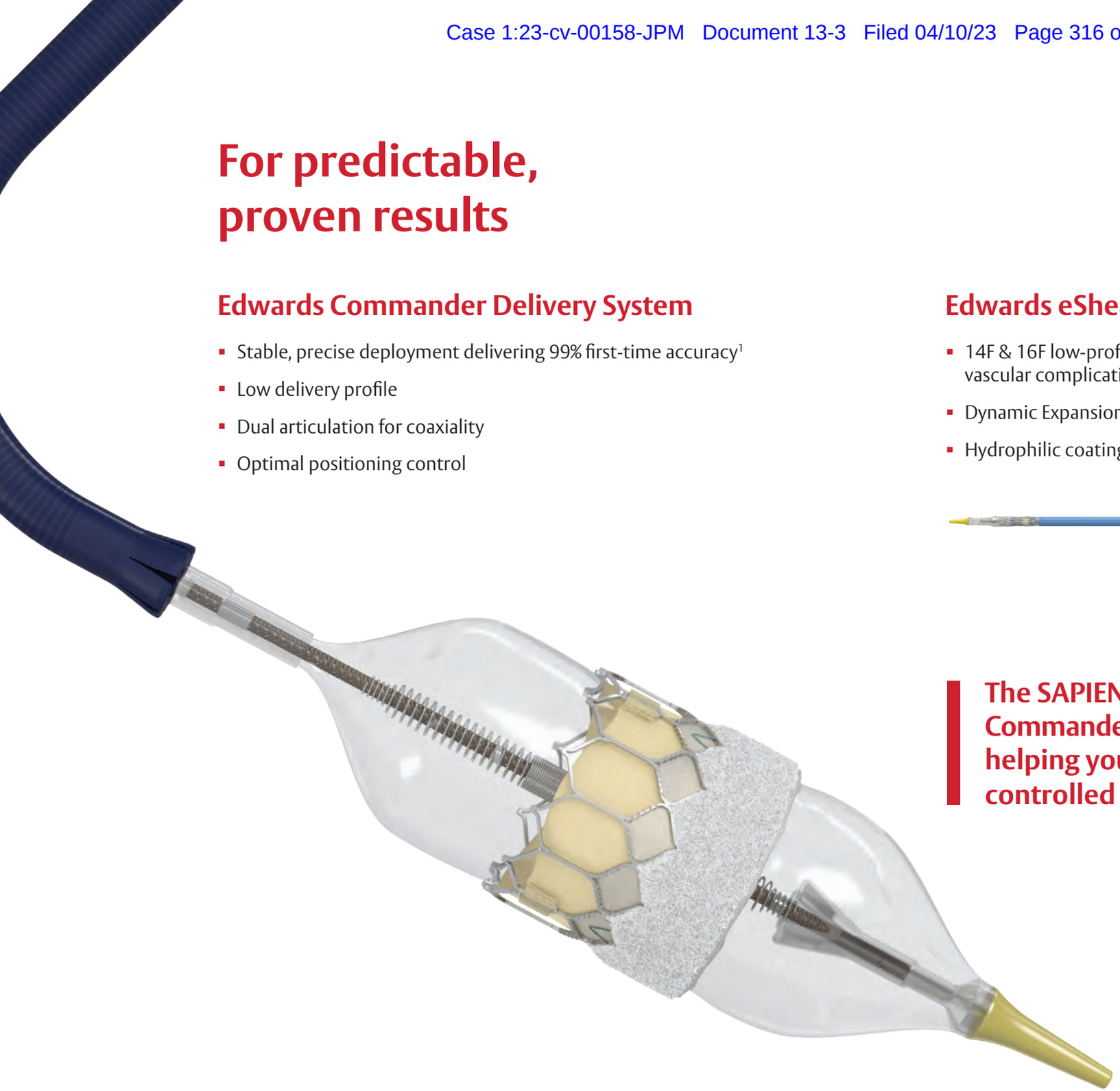
Edwards Commander Delivery System

- Stable, precise deployment delivering 99% first-time accuracy[1]
- Low delivery profile
- Dual articulation for coaxiality
- Optimal positioning control

Edwards eSheath Introducer Set

- 14F & 16F low-profile access leads to significant reduction in major vascular complications
- Dynamic Expansion Mechanism (DEM) for low-profile access
- Hydrophilic coating designed for ease of entry

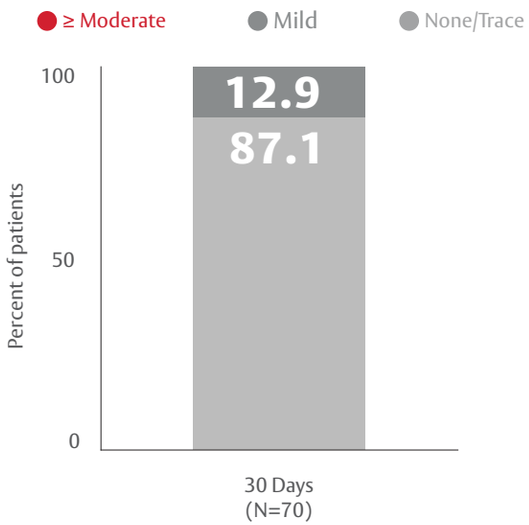




The SAPIEN 3 Ultra valve is available with the Edwards Commander Delivery System and Edwards eSheath– helping you to achieve consistent performance and controlled deployment.

Engineered for your patient's long-term future

- **Percentage of patients experiencing paravalvular leak at 30 Days[2]**



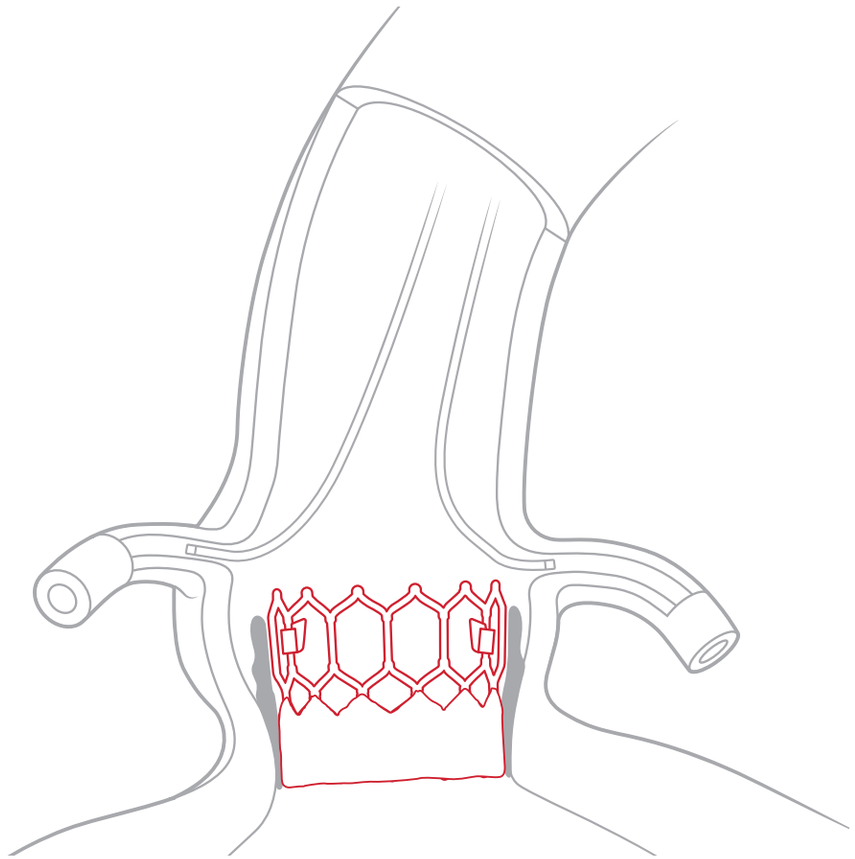
SAPIEN 3 Ultra Study

30-day findings were core lab adjudicated.

Edwards SAPIEN 3 Ultra features uniform sealing designed to minimize PVL.



- The SAPIEN 3 Ultra valve was designed with low frame height and large cell design to easily **facilitate future coronary access** should your patient require a procedure post-TAVR.



Access to the coronary arteries post-TAVR with the SAPIEN 3 Ultra valve was successful in 100% of cases (in 61 out of 61 patients).[3]

Important Safety Information

Edwards SAPIEN 3 THV System and Edwards SAPIEN 3 Ultra THV System

Indications: The Edwards SAPIEN 3 Transcatheter Heart Valve System and Edwards SAPIEN 3 Ultra Transcatheter Heart Valve System are indicated for relief of aortic stenosis in patients with symptomatic heart disease due to severe native calcific aortic stenosis who are judged by a Heart Team, including a cardiac surgeon, to be appropriate for the transcatheter heart valve replacement therapy.

The Edwards SAPIEN 3 Transcatheter Heart Valve System and Edwards SAPIEN 3 Ultra Transcatheter Heart Valve System are indicated for patients with symptomatic heart disease due to failure (stenosed, insufficient, or combined) of a surgical bioprosthetic aortic or mitral valve who are judged by a heart team, including a cardiac surgeon, to be at high or greater risk for open surgical therapy (i.e., predicted risk of surgical mortality ≥ 8% at 30 days, based on the STS risk score and other clinical co-morbidities unmeasured by the STS risk calculator).

Contraindications: The valves and delivery systems are contraindicated in patients who cannot tolerate an anticoagulation/antiplatelet regimen or who have active bacterial endocarditis or other active infections.

Warnings: Observation of the pacing lead throughout the procedure is essential to avoid the potential risk of pacing lead perforation. There may be an increased risk of stroke in transcatheter aortic valve replacement procedures, as compared to balloon aortic valvuloplasty or other standard treatments in high or greater risk patients. Incorrect sizing of the valve may lead to paravalvular leak, migration, embolization, residual gradient (patient-prosthesis mismatch), and/or annular rupture. Accelerated deterioration of the valve due to calcific degeneration may occur in children, adolescents, or young adults and in patients with an altered calcium metabolism. Prior to delivery, the valve must remain hydrated at all times and cannot be exposed to solutions other than its shipping storage solution and sterile physiologic rinsing solution. Valve leaflets mishandled or damaged during any part of the procedure will require replacement of the valve. Caution should be exercised in implanting a valve in patients with clinically significant coronary artery disease. Patients with pre-existing bioprostheses should be carefully assessed prior to implantation of the valve to ensure proper valve positioning and deployment. Do not use the valve if the tamper-evident seal is broken, the storage solution does not completely cover the valve, the temperature indicator has been activated, the valve is damaged, or the expiration date has elapsed. Do not mishandle the delivery system or use it if the packaging or any components are not sterile, have been opened or are damaged (e.g., kinked or stretched), or if the expiration date has elapsed. Use of excessive contrast media may lead to renal failure. Measure the patient's creatinine level prior to the procedure. Contrast media usage should be monitored. Patient injury could occur if the delivery system is not un-flexed prior to removal. Care should be exercised in patients with hypersensitivities to cobalt, nickel, chromium, molybdenum, titanium, manganese, silicon, and/or polymeric materials. The procedure should be conducted under fluoroscopic guidance. Some fluoroscopically guided procedures are associated with a risk of radiation injury to the skin. These injuries may be painful, disfiguring, and long-lasting. Valve recipients should be maintained on anticoagulant/antiplatelet therapy, except when contraindicated, as determined by their physician. This device has not been tested for use without anticoagulation. Do not add or apply antibiotics to the storage solution, rinse solution, or to the valve. Balloon valvuloplasty should be avoided in the treatment of failing bioprostheses as this may result in embolization of bioprosthesis material and mechanical disruption of the valve leaflets. Failure to use slow, controlled inflation and prescribed nominal inflation volumes may result in balloon rupture, and lead to patient death or serious injuries associated with difficulty retrieving the delivery system and surgical intervention.

Precautions: Safety, effectiveness, and durability have not been established for THV-in-THV procedures. Long-term durability has not been established for the valve. Regular medical follow-up is advised to evaluate valve performance. Glutaraldehyde may cause irritation of the skin, eyes, nose, and throat. Avoid prolonged or repeated exposure to, or breathing of, the solution. Use only with adequate ventilation. If skin contact occurs, immediately flush the affected area with water; in the event of contact with eyes, seek immediate medical attention. For more information about glutaraldehyde exposure, refer to the Safety Data Sheet available from Edwards Lifesciences. To maintain proper valve leaflet coaptation, do not overinflate the deployment balloon. Appropriate antibiotic prophylaxis is recommended post-procedure in patients at risk for prosthetic valve infection and endocarditis. Additional precautions for transseptal replacement of a failed mitral valve bioprosthesis include, the presence of devices or thrombus or other abnormalities in the caval vein precluding safe transvenous femoral access for transseptal approach; and the presence of an Atrial Septal Occluder Device or calcium or abnormalities in the atrial septum preventing safe transseptal access. Special care must be exercised in mitral valve replacement if chordal preservation techniques were used in the primary implantation to avoid entrapment of the subvalvular apparatus. Safety and effectiveness have not been established for patients with the following characteristics/comorbidities: non-calcified aortic annulus; severe ventricular dysfunction with ejection fraction < 20%; congenital unicuspid aortic valve; congenital bicuspid aortic valve in low surgical risk patients; mixed aortic valve disease (aortic stenosis and aortic regurgitation with predominant aortic regurgitation > 3+); pre-existing prosthetic ring in any position; severe mitral annular calcification (MAC); severe (> 3+) mitral insufficiency, or Gorlin syndrome; blood dyscrasias defined as leukopenia (WBC < 3000 cells/mL), acute anemia (Hb < 9 g/dL), thrombocytopenia (platelet count < 50,000 cells/mL), or history of bleeding diathesis or coagulopathy; hypertrophic cardiomyopathy with or without obstruction (HOCM); echocardiographic evidence of intracardiac mass, thrombus, or vegetation; a known hypersensitivity or contraindication to aspirin, heparin, ticlopidine (Ticlid), or clopidogrel (Plavix), or sensitivity to contrast media, which cannot be adequately premedicated; significant aortic disease, including abdominal aortic or thoracic aneurysm defined as maximal luminal diameter 5 cm or greater, marked tortuosity (hyperacute bend), aortic arch atheroma (especially if thick [> 5 mm], protruding, or ulcerated) or narrowing (especially with calcification and surface irregularities) of the abdominal or thoracic aorta, severe "unfolding" and tortuosity of the thoracic aorta; access characteristics that would preclude safe placement of the 14F or 16F Edwards eSheath introducer set or the 14F Axela sheath, such as severe obstructive calcification, severe tortuosity, or diameter less than 5.5 mm (14F Axela or 14F eSheath introducer set) or 6 mm (16F eSheath introducer set or 14F Axela in subclavian access); excessive calcification at access site; bulky calcified aortic valve leaflets in close proximity to coronary ostia; a concomitant paravalvular leak where the failing bioprosthesis is not securely fixed in the native annulus or is not structurally intact (e.g., wireform frame fracture); or a partially detached leaflet of the failing bioprosthesis that in the aortic position may obstruct a coronary ostium. Residual mean gradient may be higher in a "THV-in-failing bioprosthesis" configuration than that observed following implantation of the valve inside a native aortic annulus using the same size device. Patients with elevated mean gradient post procedure should be carefully followed. It is important that the manufacturer, model and size of the preexisting bioprosthetic valve be determined, so that the appropriate valve can be implanted and a prosthesis-patient mismatch be avoided. Additionally, pre-procedure imaging modalities must be employed to make as accurate a determination of the inner diameter as possible.

Potential Adverse Events: Potential risks associated with the overall procedure, including potential access complications associated with standard cardiac catheterization, balloon valvuloplasty, the potential risks of conscious sedation and/or general anesthesia, and the use of angiography: death; stroke/transient ischemic attack, clusters, or neurological deficit; paralysis; permanent disability; respiratory insufficiency or respiratory

failure; hemorrhage requiring transfusion or intervention; cardiovascular injury including perforation or dissection of vessels, ventricle, atrium, septum, myocardium, or valvular structures that may require intervention; pericardial effusion or cardiac tamponade; embolization including air, calcific valve material, or thrombus; infection including septicemia and endocarditis; heart failure; myocardial infarction; renal insufficiency or renal failure; conduction system defect which may require a permanent pacemaker; arrhythmia; retroperitoneal bleed; arteriovenous (AV) fistula or pseudoaneurysm; reoperation; ischemia or nerve injury; restenosis; pulmonary edema; pleural effusion; bleeding; anemia; abnormal lab values (including electrolyte imbalance); hypertension or hypotension; allergic reaction to anesthesia, contrast media, or device materials; hematoma; syncope; pain or changes at the access site; exercise intolerance or weakness; inflammation; angina; heart murmur; and fever. Additional potential risks associated with the use of the valve, delivery system, and/or accessories include: cardiac arrest; cardiogenic shock; emergency cardiac surgery; cardiac failure or low cardiac output; coronary flow obstruction/transvalvular flow disturbance; device thrombosis requiring intervention; valve thrombosis; device embolization; device migration or malposition requiring intervention; left ventricular outflow tract obstruction; valve deployment in unintended location; valve stenosis; structural valve deterioration (wear, fracture, calcification, leaflet tear/tearing from the stent posts, leaflet retraction, suture line disruption of components of a prosthetic valve, thickening, stenosis); device degeneration; paravalvular or transvalvular leak; valve regurgitation; hemolysis; injury to the mitral valve; device explants; mediastinitis; mediastinal bleeding; nonstructural dysfunction; mechanical failure of delivery system and/or accessories; and non-emergent reoperation.

Edwards Axela Sheath

Indications: The Edwards Axela sheath is indicated for the introduction and removal of devices used with the Edwards SAPIEN 3 Ultra delivery system.

Contraindications: There are no known contraindications.

Warnings: The devices are designed, intended, and distributed for single use only. **Do not resterilize or reuse the devices.** There are no data to support the sterility, nonpyrogenicity, and functionality of the devices after reprocessing.

Precautions: Caution should be used in vessels that have diameters less than 5.5 mm as it may preclude safe placement of the 14F Edwards Axela sheath. For subclavian/axillary vessels with the 29 mm Edwards SAPIEN 3 Ultra delivery system, caution should be used in vessels that have diameters less than 6.0 mm as it may preclude safe placement of the 14F Edwards Axela sheath. Use caution in tortuous or calcified vessels that would prevent safe entry of the sheath. Do not use the Edwards Axela sheath if the packaging sterile barriers and any components have been opened or damaged or the expiration date has elapsed. When inserting, manipulating or withdrawing a device through the sheath, always maintain sheath position. When puncturing, suturing or incising the tissue near the sheath, use caution to avoid damage to the sheath.

Potential Adverse Events: Complications associated with standard catheterization and use of angiography include, but are not limited to, injury including perforation or dissection of vessels, thrombosis and/or plaque dislodgement which may result in emboli formation, distal vessel obstruction, hemorrhage, infection, and/or death.

Edwards eSheath

Indications: The Edwards eSheath introducer set is indicated for the introduction and removal of devices used with the Edwards SAPIEN 3 and the Edwards SAPIEN 3 Ultra transcatheter heart valves.

Contraindications: There are no known contraindications.

Warnings: The devices are designed, intended, and distributed for single use only. **Do not resterilize or reuse the devices.** There is no data to support the sterility, nonpyrogenicity, and functionality of the devices after reprocessing. The Edwards eSheath introducer set must be used with a compatible 0.035" (0.89 mm) guidewire to prevent vessel injury.

Precautions: Caution should be used in vessels that have diameters less than 5.5 mm or 6 mm as it may preclude safe placement of the 14F and 16F Edwards eSheath introducer set respectively. Use caution in tortuous or calcified vessels that would prevent safe entry of the introducer set. Do not use the Edwards eSheath introducer set if the packaging sterile barriers and any components have been opened or damaged. When inserting, manipulating or withdrawing a device through the sheath, always maintain sheath position. When puncturing, suturing or incising the tissue near the sheath, use caution to avoid damage to the sheath.

Potential Adverse Events: Complications associated with standard catheterization and use of angiography include, but are not limited to, injury including perforation or dissection of vessels, thrombosis and/or plaque dislodgement which may result in emboli formation, distal vessel obstruction, hemorrhage, infection, and/or death.

Edwards Crimper

Indications: The Edwards crimper is indicated for use in preparing the Edwards SAPIEN 3 Ultra transcatheter heart valve and the Edwards SAPIEN 3 transcatheter heart valve for implantation.

Contraindications: There are no known contraindications.

Warnings: The devices are designed, intended, and distributed for single use only. **Do not resterilize or reuse the devices.** There are no data to support the sterility, nonpyrogenicity, and functionality of the devices after reprocessing.

Precautions: For special considerations associated with the use of the Edwards crimper prior to THV implantation, refer to the THV Instructions for Use.

Potential Adverse Events: There are no known potential adverse events associated with the Edwards crimper.

CAUTION: Federal (United States) law restricts these devices to sale by or on the order of a physician.

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Edwards

Experience the difference with the SAPIEN 3 Ultra valve

Learn more at **SAPIEN3Ultra.com.**

References:

1. The PARTNER II Trial intermediate-risk cohort 30-day unadjusted clinical event rates for TAVR with the SAPIEN 3 valve, AT population (n=1077).
2. Webb, John. A prospective multicenter study of the SAPIEN 3 Ultra system in intermediate-risk patients with severe aortic stenosis. Presented at: PCR London Valves 2019; November 2019; London, UK.
3. Tarantini G, Fovino LN, Leprince P, et al. Predictors, feasibility and outcomes of coronary intervention up to 3 years after TAVI with a balloon-expandable valve: results from a large European multicenter registry. Presented at: ESC Congress 2019; September 2019; Paris, France.

See enclosed Important Safety Information.

CAUTION: Federal (United States) law restricts these devices to sale by or on the order of a physician.

SAPIEN 3 and SAPIEN 3 Ultra involve serious risks, including death, stroke, major bleeding, and major vascular complications.

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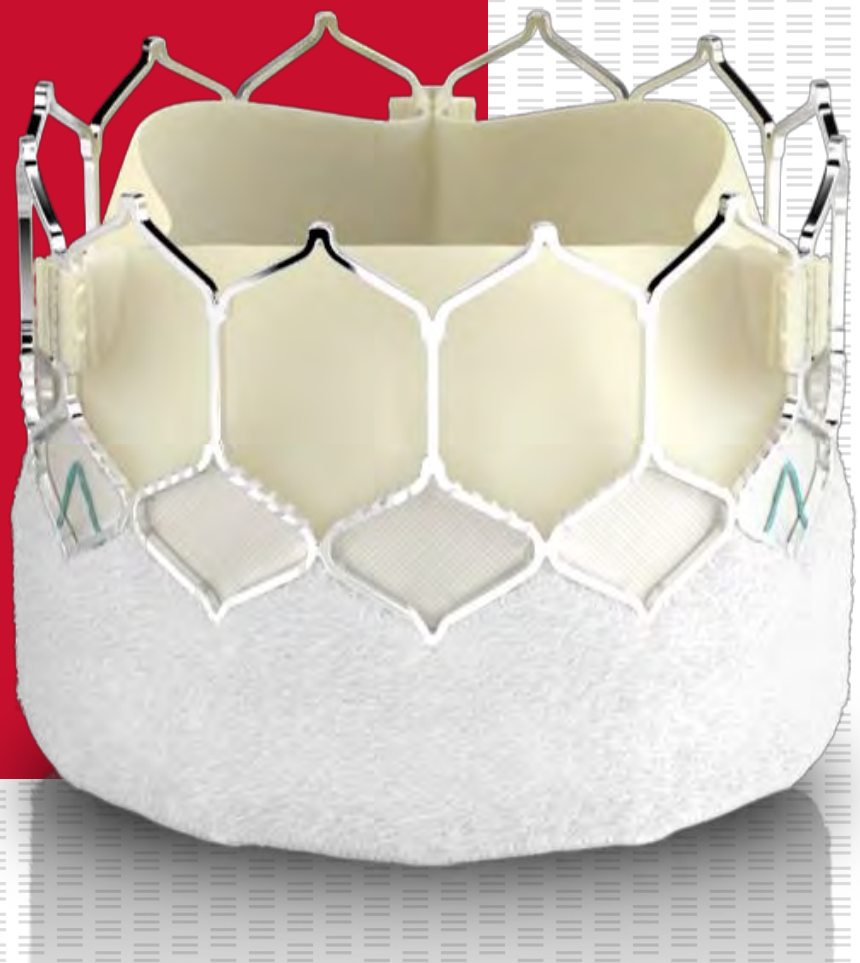
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EXHIBIT 47

SAPIEN 3 Ultra Valve First-In-Human Experience

Dr Martyn Thomas
VP of Medical Affairs
Edwards Lifesciences



Edwards

Disclosures:

Employee and stock holder: Edwards Lifesciences

Could not be more conflicted!!

Time Between Regional Approvals is Narrowing



SAPIEN valve



SAPIEN XT valve



SAPIEN 3 valve



SAPIEN 3 Ultra valve



September 2007

4 Years

November 2011

March 2010

4 Years

June 2014

January 2014

1.5 Years

June 2015

November 2018

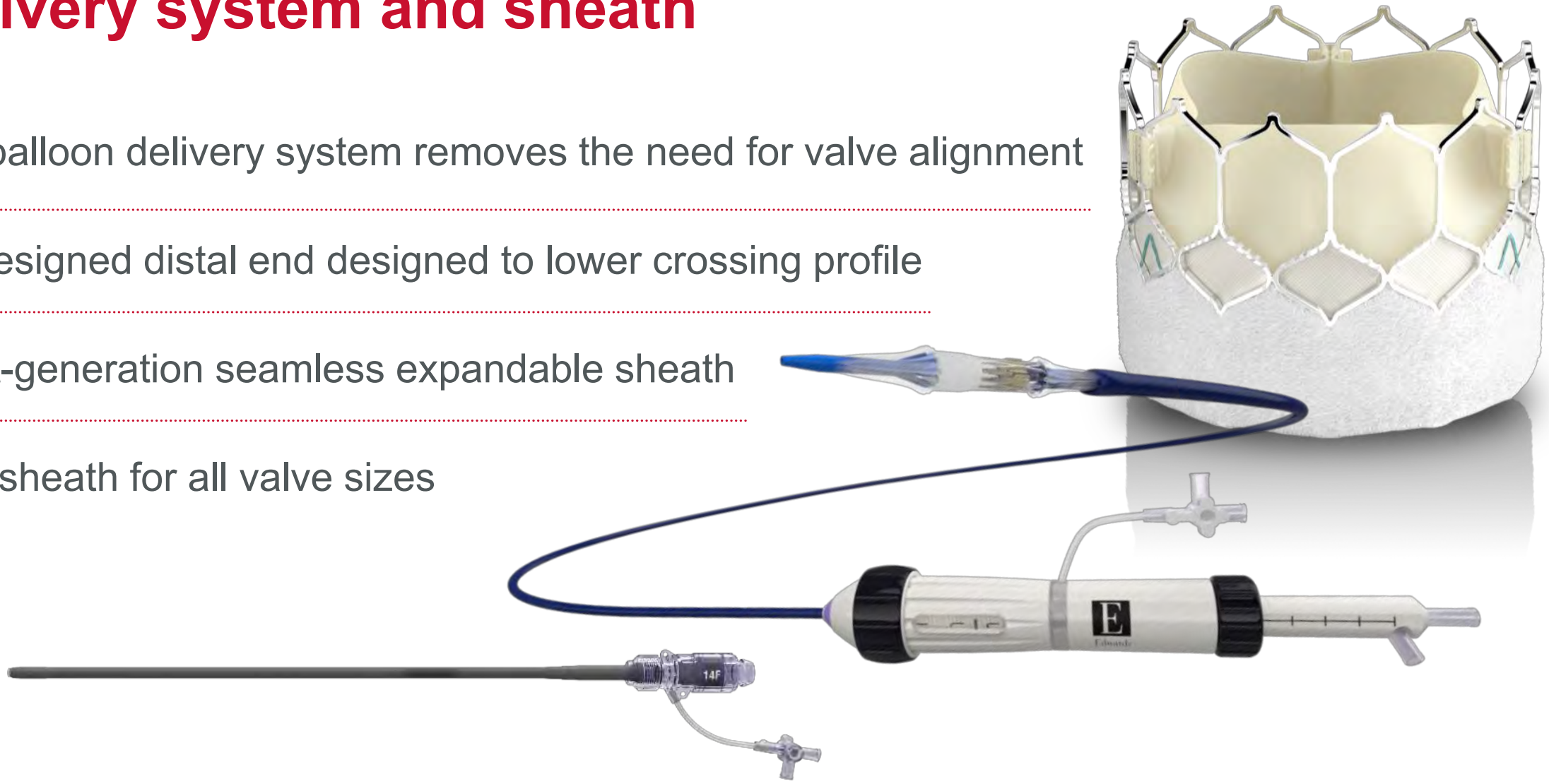
1 Month

December 2018



The Edwards SAPIEN 3 Ultra System Delivery system and sheath

- On-balloon delivery system removes the need for valve alignment
- Redesigned distal end designed to lower crossing profile
- Next-generation seamless expandable sheath
- 14F sheath for all valve sizes

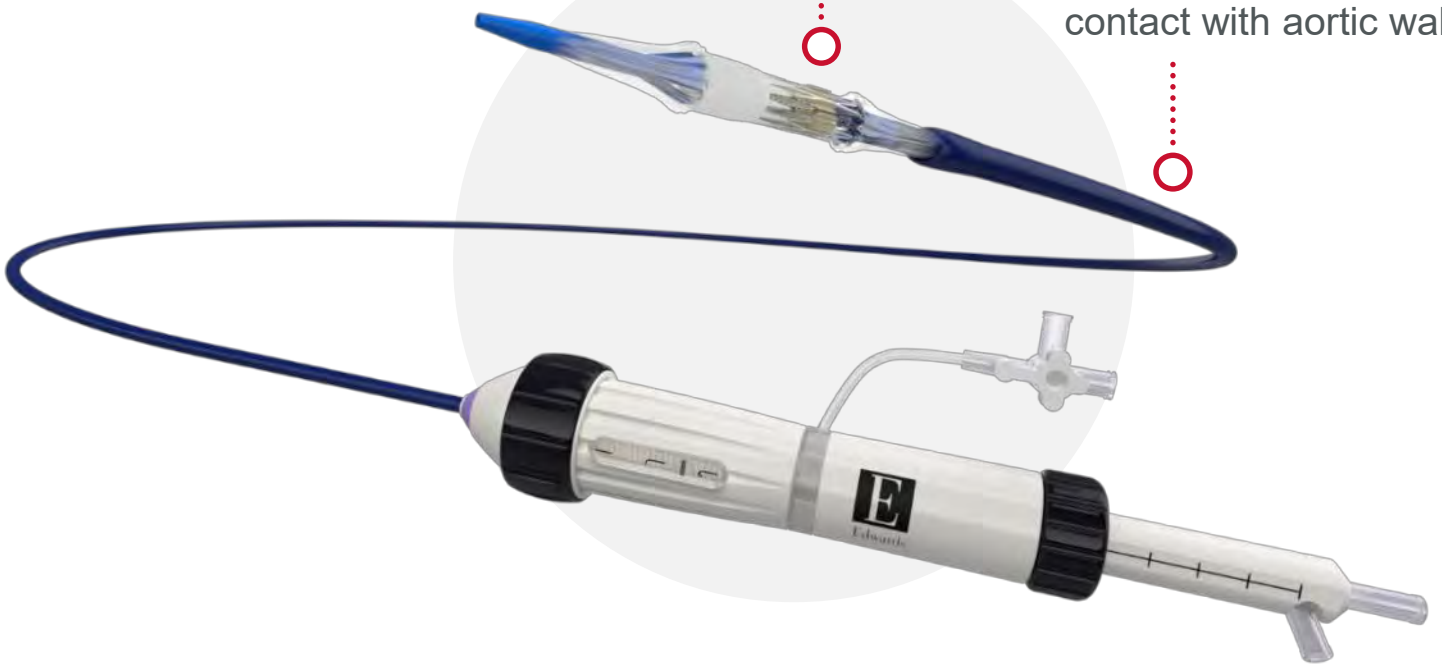


The Edwards SAPIEN 3 Ultra System

Redesigned distal end for improved crossability

On-balloon delivery system removes the need for valve alignment

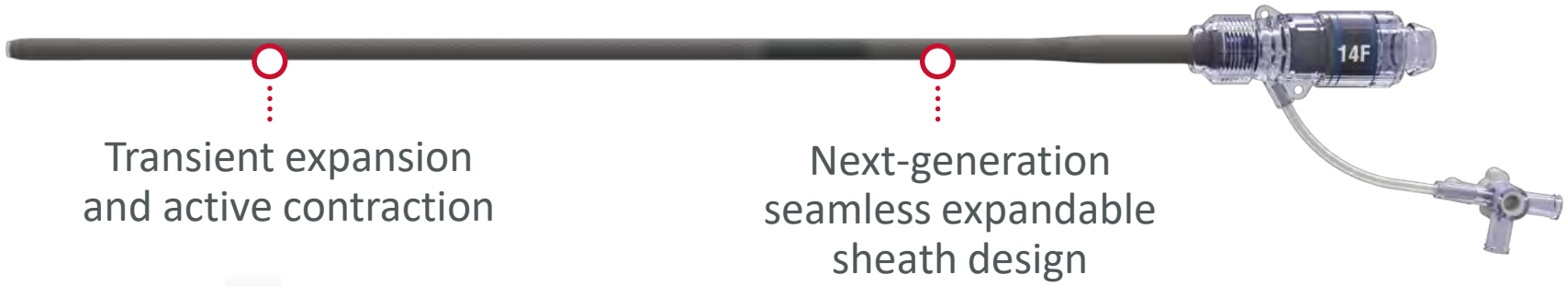
Responsive articulation avoids contact with aortic wall

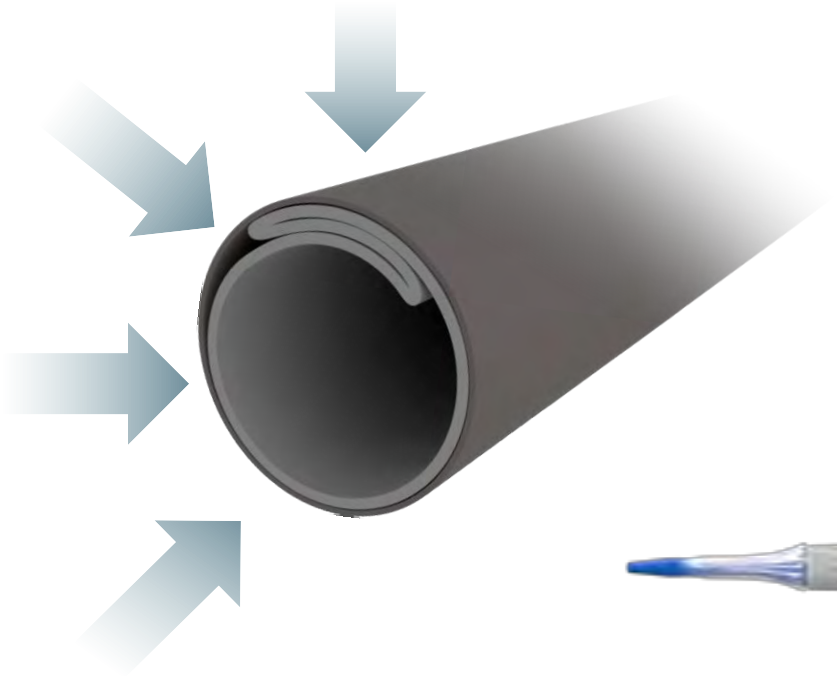


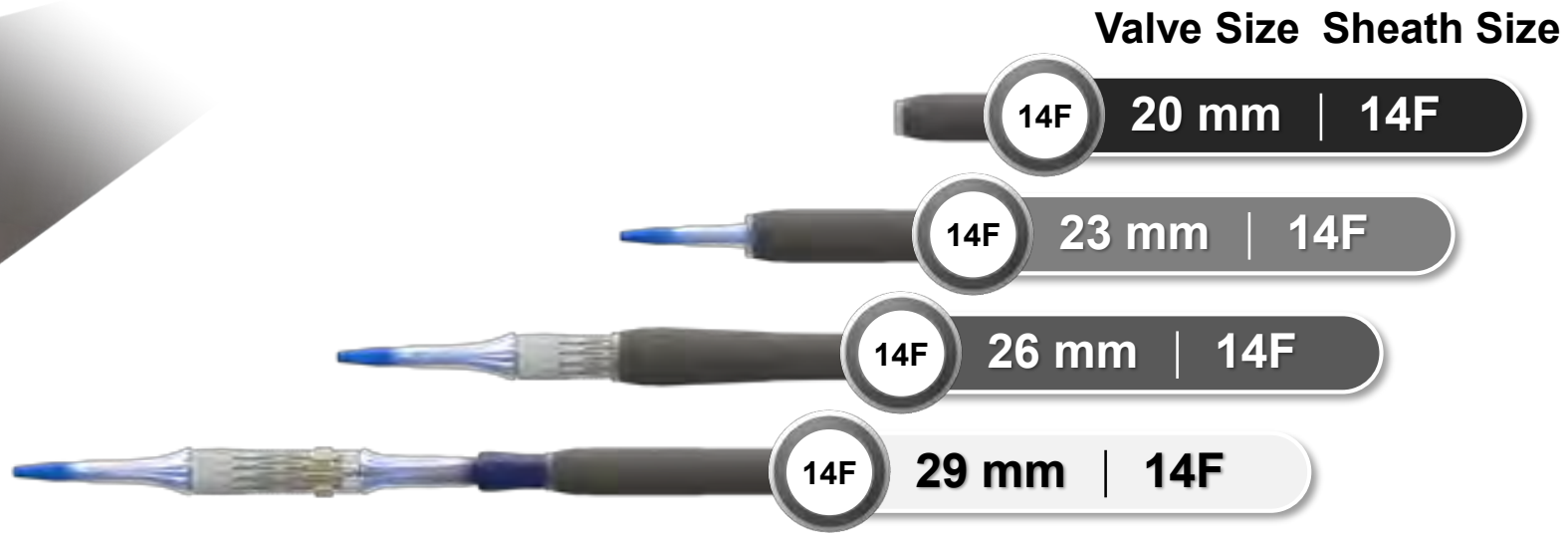


Advanced balloon technology

The Edwards SAPIEN 3 Ultra System: Axela Sheath



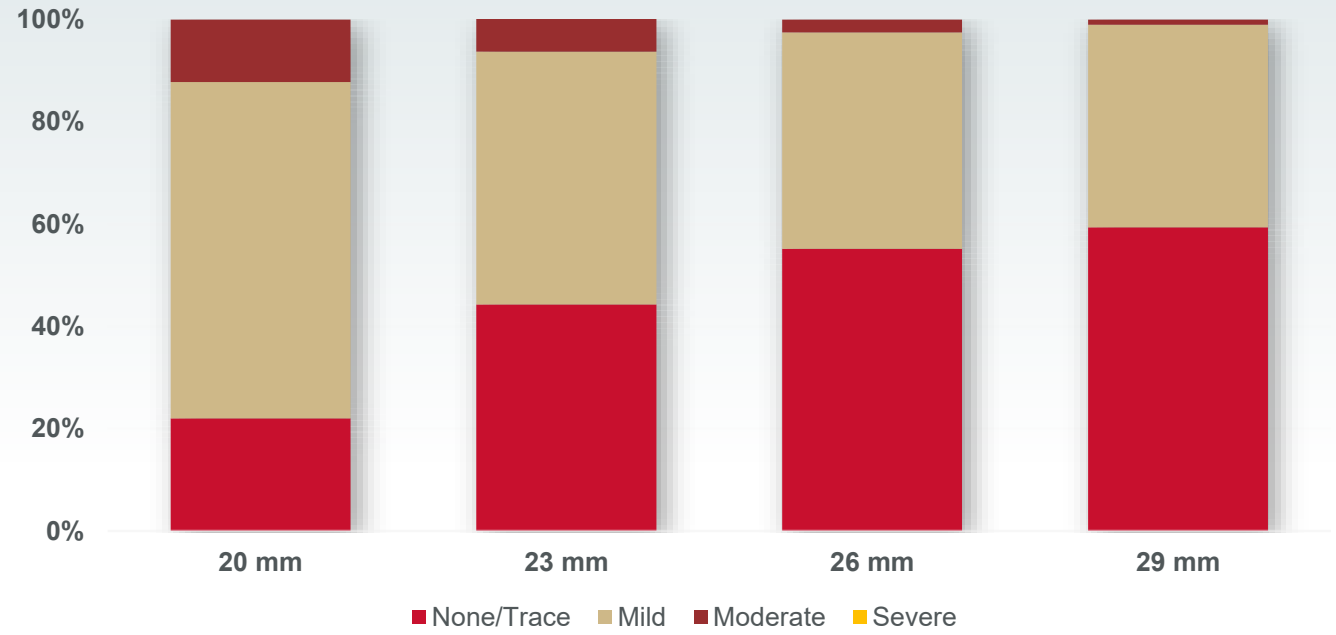




The SAPIEN 3 Ultra Valve
Inspired by the 29mm SAPIEN 3 Valve

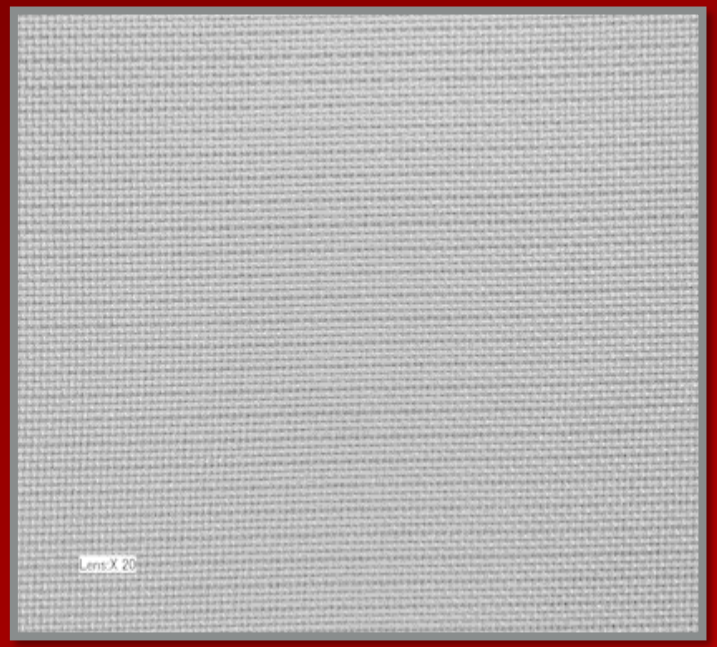


PARTNER IIA S3i PVL by Valve Size at 30 days

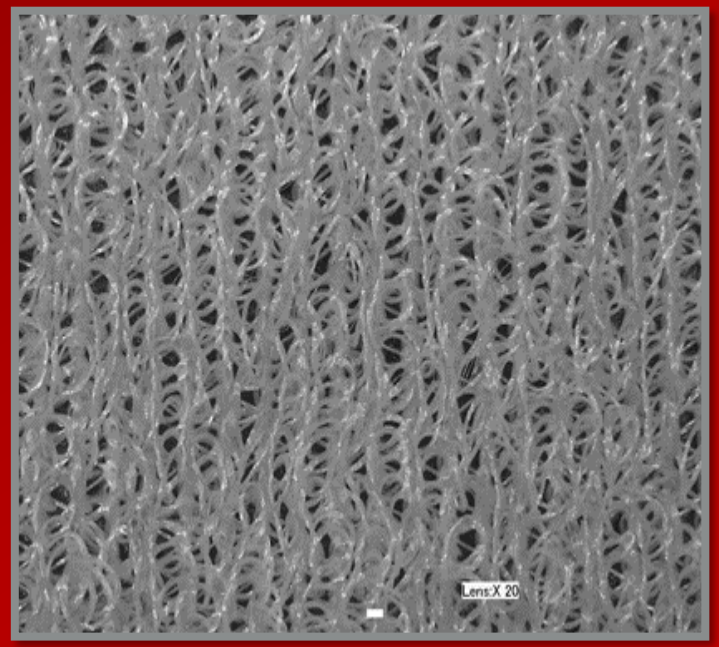


* Source: Clinical Study Report: The Placement of Aortic Transcatheter Valves (PARTNER) II Trial (Study 2012-12-US) -- SAPIEN 3, Feb 2016

Fabric Skirt



SAPIEN 3
Flat woven



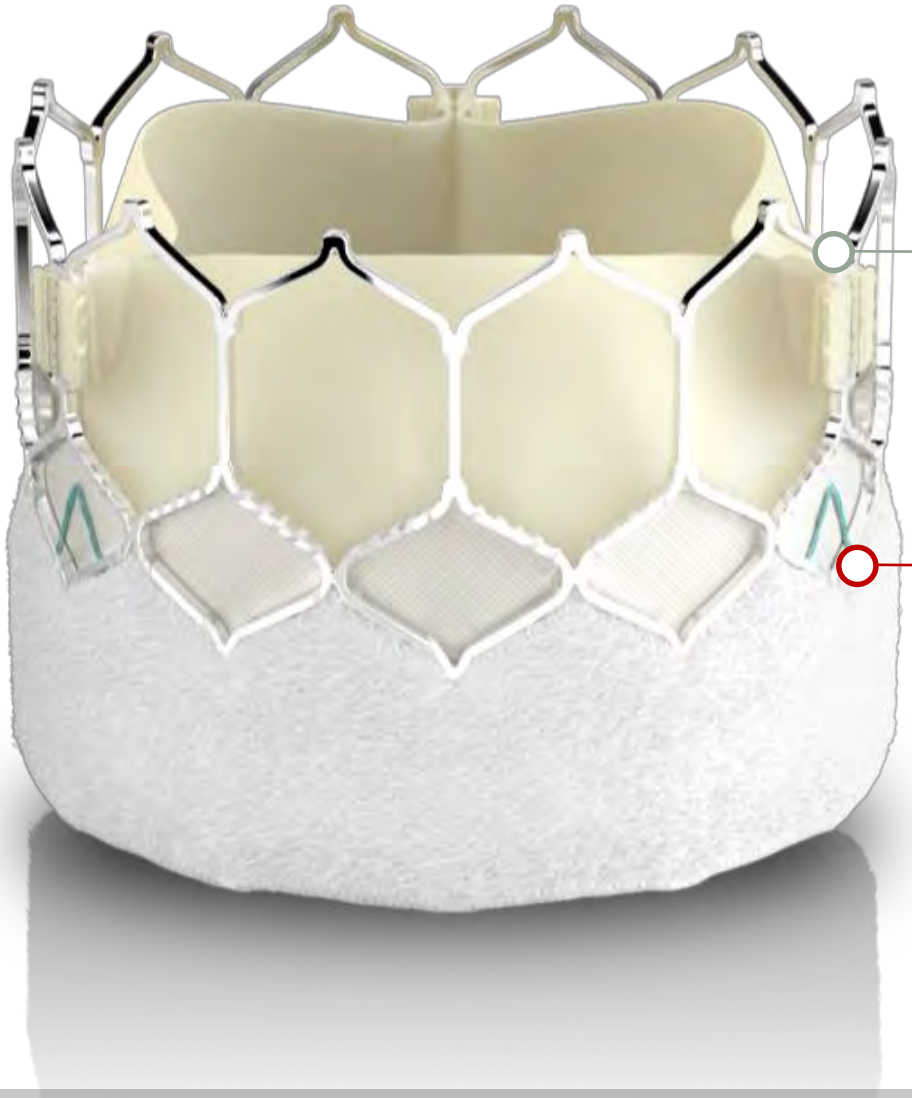
SAPIEN 3 Ultra
Textured



Proven PET Skirt Material

- Same biocompatible material as SAPIEN 3 valve
- Knitted, textured PET material

Edwards SAPIEN 3 Ultra Valve



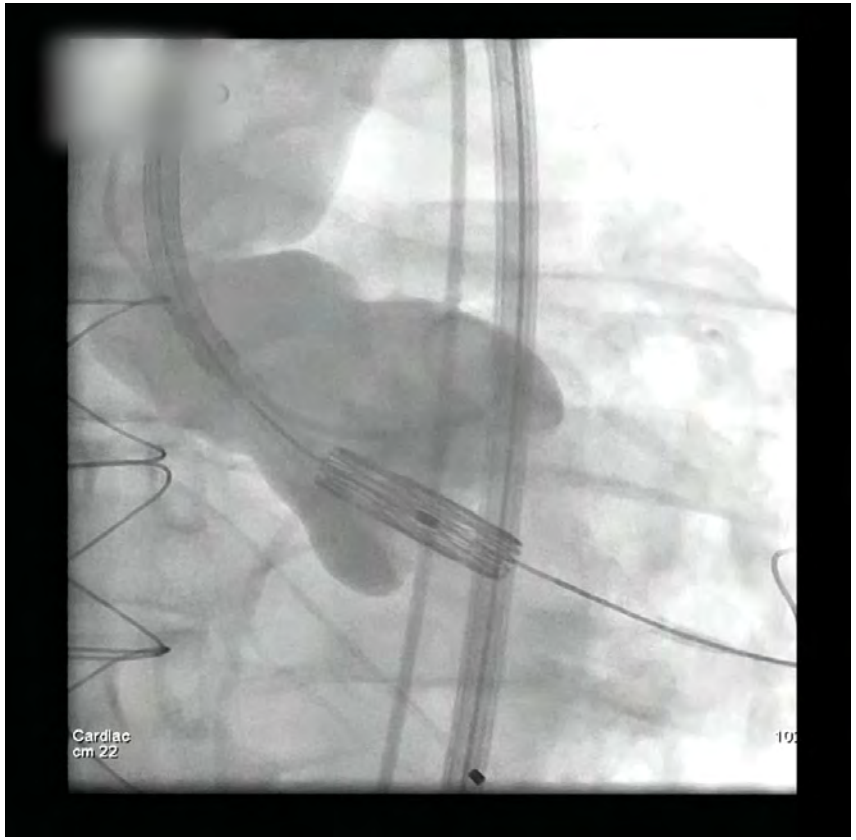
Frame and Leaflet Design

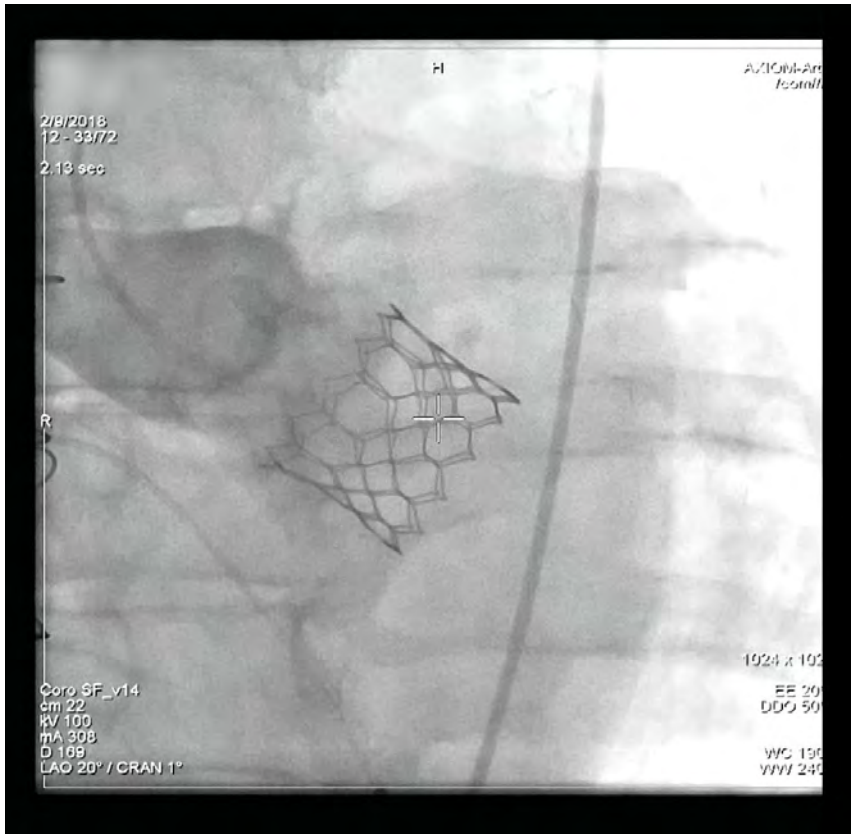
- Proven SAPIEN 3 leaflet and frame design

Outer Skirt

- Textured 3-dimensional PET skirt design
- 40% taller skirt - up to 50% more contact surface area with native anatomy
- 14F sheath compatible

SAPIEN 3 Ultra System Case Example





Courtesy Dr. John Webb

THE SAPIEN 3 ULTRA TRIAL



SAPIEN 3 Ultra Trial

Up to 4 Sites and a minimum of 20 Patients

Severe, Calcific Aortic Stenosis

Intermediate Risk Assessment by Heart Team and STS ≥ 3 to < 8

Enrollment

TAVR
(SAPIEN 3 Ultra THV and Delivery System)

Follow-up: Discharge, 30 days, 6 months, and annually through 5 years

Primary Endpoint: freedom from all of the following at exit from the procedure room:

- Mortality
- Conversion to surgery
- Moderate or severe paravalvular regurgitation

SAPIEN 3 Ultra Trial: Baseline Characteristics (n=40)

Demographics and Baseline Characteristics	Summary Statistics
Age – years	83.4 ± 5.13 (40)
Male sex	24/40 (60.0%)
Society of Thoracic Surgeons (STS) score	3.4 ± 1.27 (40)
New York Health Association (NYHA) class	
I/II	20/40 (50.0%)
III/IV	20/40 (50.0%)
Previous myocardial infarction	1/40 (2.5%)
Previous intervention	9/40 (22.5%)
Coronary artery bypass grafting (CABG)	3/40 (7.5%)
Percutaneous bypass intervention (PCI)	8/40 (20.0%)
Prior aortic valvuloplasty	0/40 (0.0%)
Cerebrovascular accident (CVA)	1/40 (2.5%)
Atrial fibrilllation	19/40 (47.5%)
Prior pacemaker	5/40 (12.5%)
Echocardiographic findings	
Valve area – cm^2	0.7 ± 0.16 (40)
Mean aortic-valve gradient –mmHg	51.0 ± 13.17 (40)
Mean left ventricular ejection fractions (LVEF) %	60.6 ± 7.06 (40)

SAPIEN 3 Ultra Trial: Primary Endpoint

Primary Endpoint	Results
Overall procedural success	40/40 (100.0%)
Freedom from mortality at exit from procedure room	40/40 (100.0%)
Freedom from conversion to surgery at exit from procedure room	40/40 (100.0%)
Freedom from moderate or severe paravalvular regurgitation at exit from procedure room	40/40 (100.0%)

SAPIEN 3 Ultra Trial: Adverse Events

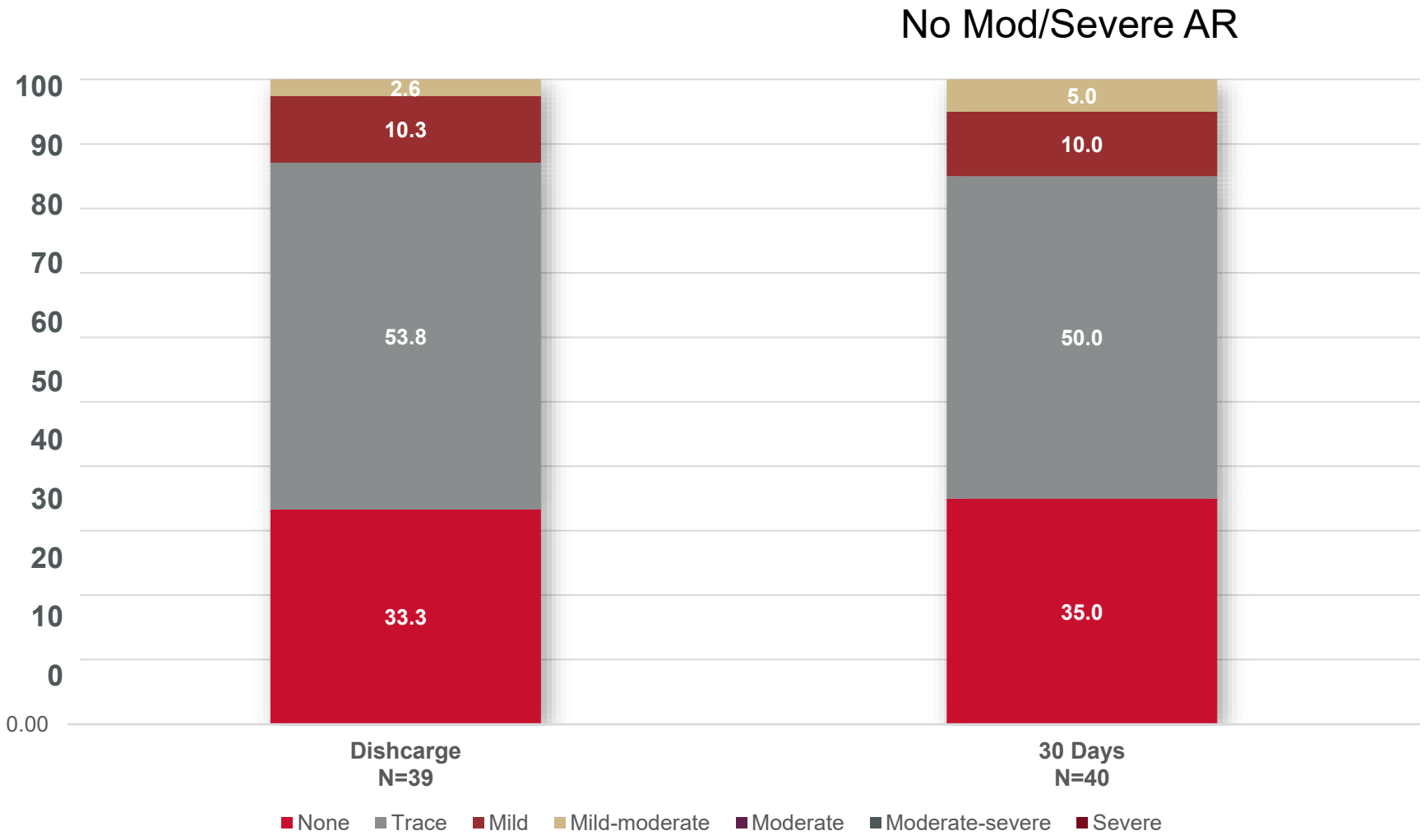
Adverse Event	Discharge*	30 Days†
Major vascular complications	0.0% (0,0)	0.0% (0,0)
Acute kidney injury (Stage III)	0.0% (0,0)	0.0% (0,0)
Life threatening bleeding	0.0% (0,0)	0.0% (0,0)
Major bleeding	5.0% (2.2)	5.0% (2.2)
Endocarditis	0.0% (0,0)	0.0% (0,0)
Device thrombosis	0.0% (0,0)	0.0% (0,0)

* Observed rate, % (no. of events, no. of subjects with the event)
† Kaplan-Meier estimate, % (no. of events, no. of subjects with the event)

	First 20 Subject		Last 20 Subjects	
Adverse Event	Discharge*	30 Days†	Discharge*	30 Days†
Conduction disturbance requiring permanent pacemaker‡	29.4% (5,5)	29.4% (5,5)	5.6% (1,1)	5.6% (1,1)

‡ 5 Subjects (3 from First 20 subject cohort and 2 from Last 20 subject cohort) with baseline pacemaker were excluded from the analysis.
* Observed rate, % (no. of events, no. of subjects with the event
† Kaplan- Meier estimate, % (no. of events, no. of subjects with the event)

SAPIEN 3 Ultra Trial: Total Aortic Regurgitation



Conclusions

- The on-balloon SAPIEN 3 Ultra system simplifies the TAVR procedure.
- Two important steps (valve alignment and pulling back the “pusher”) are no longer required.
- We believe the rates of pre deployment BAV are likely to decline.
- Initial results are encouraging in terms of hemodynamics, PVL and requirement for new permanent pacemaker.

- Further data, techniques and nuances will be gathered in the post approval setting.

EXHIBIT 48

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Dale Murdoch



Dale Murdoch
Interventional Cardiologist at The Prince Charles Hospital and St Vincent's Northside
7mo

First Australian SAPIEN 3 ULTRA case today at TPCH Congrats to all the team. Borderline annulus sizing at 540mm2 - 26mm nominal with no PVL - with Karl Poon



322 · 23 Comments

Like Comment Share



Michael Vallely 7mo
Well done. Great for Australian patients. Sapien 3 Ultra is a game changer when it comes to paravalvular leak - need the 29 (& a 31!).
Like Reply | 8 Likes



Gilbert Tang, MD, MSc, MBA, FRCSC, FACC 7mo
Great job Karl and team. 540mm2 we definitely go 26 S3 Ultra and depending on Ca severity may to +1cc. We've used it to treat area up to 580mm2 going +2cc with trivial PVL only. Bicuspid we can go up to 590mm2!
Like Reply | 1 Like



Belinda Shearer 7mo
Congrats team!
Like Reply | 2 Likes



Dr Anthony French 7mo
Legend leading legends.... karl poon
Like Reply

Maria Fernanda R. 7mo ···

Inspiring
Like Reply

Rogerio Zeimert 7mo ···
beautiful!
Like Reply

Nick Aroney 7mo ···
Great to hear Dale! I've had a great experience with them over here thus far.
Like Reply

Nicholas Dangerfield 6mo ···
Congrats Dale,Karl and team
Like Reply

John Kearney 7mo ···
Well done Murdoch!!!
Like Reply

Kannan Natarajan 7mo ···
Inspiring Dale, Karl, Chris & team.
Like Reply

See more comments

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6 Posts · 0 Articles

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Privacy Policy
Cookie Policy
Copyright Policy
Brand Policy
Guest Controls
Community Guidelines
Language

EXHIBIT 49

From: **Don Bobo** <Don_Bobo@edwards.com>
Date: Tue, Jul 20, 2021 at 5:36 PM
Subject: Re: [EXTERNAL] Aortic Innovations LLC
To: Ali Shahriari <ali.shahriari@aorticinnovations.com>
CC: Keith Newburry <Keith_Newburry@edwards.com>

Ali,
Thanks for the email and additional details, let me get to the team and take a look and we should be able to talk once we've taken a look. I've copied my admin Greta who can help with a followup time in early August.

All the Best,
Don

Sent from my iPad

On Jul 19, 2021, at 11:48 AM, Ali Shahriari <ali.shahriari@aorticinnovations.com> wrote:

EXTERNAL EMAIL - Use caution opening attachments and links

Donald Bobo

Corporate Vice President, Strategy and Development

Edwards Lifesciences Corp.

1 Edwards Way

Irvine, CA 92614

RE: Aortic Innovations Patents for Transcatheter Valve Replacement

Dear Don:

I hope all is well since we last spoke in 2017 with you and many of your team. At that time, I was focused on Ascyrus Medical, LLC, which has now been sold. During our conversations, your team indicated an interest in Aortic Innovations ("AI"). As you are aware, I invented transcatheter aortic valve replacement ("TAVR") and

transcatheter mitral valve replacement ("TMVR") devices and systems, including those covered by at least the following patents:

- United States Patent No. 10,792,172
- United States Patent No. 10,857,011
- United States Patent No. 10,881,538
- United States Patent No. 10,888,441
- United States Patent No. 10,966,846
- United States Patent No. 10,987,236
- United States Patent No. 11,026,817
- United States Patent Publication No. 2021-0212846
- United States Patent Publication No. 2021-0161688
- Related patents and patent applications in Europe, Canada, Germany, and Japan

Each of these patents is owned by AI. It appears that the Sapien 3 Ultra and/or Sapien M3 practice one or more claims from these patents. You may wish to have your patent counsel examine the above patents in order to determine whether a license is needed.

I look forward to hearing from you and welcome a discussion regarding a potential license to the AI patent portfolio, a portfolio that we think could be very valuable to Edwards going forward. If you have any questions, please feel free to reach out.

Best,

Dr. Ali Shahriari

Chief Executive Officer

Aortic Innovations, LLC

977 Hillsboro Mile

Hillsboro Beach, FL 33062

Ali.Shahriari@aorticinnovations.com

CC; Keith Newburry, Chief IP Counsel

--
Ali Shahriari
CEO
Aortic Innovations LLC.

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EXHIBIT 50

From: Greta Crook
Sent: Wednesday, July 21, 2021 12:16 PM
To: ali.shahriari@aorticinnovations.com
Cc: Keith Newburry <Keith_Newburry@edwards.com>; Don Bobo <Don_Bobo@edwards.com>
Subject: Aortic Innovations LLC

Dr. Shahriari:

Don asked me to find a time for the two of you to talk briefly (30 mins). I've listed below Don's current availability over the next several weeks. Please let me know if something matches your schedule, and I'll send a confirming invitation.

Date	Time (PDT)	Time (EDT)
8/30	1:00-1:30p	4:00-4:30p
8/31	10:00-10:30a 11:00a-12:00p 1:00-2:00p	1:00-1:30p 2:00-3:00p 4:00-5:00p
9/1	9:30a-12:00p	12:30-3:00p
9/3	8:00-10:00a	11:00a-1:00p
9/7	8:00-10:00a	11:00a-1:00p

I wanted to also mention that Don plans to attend TCT 11/4-6 in Orlando, if an in-person meeting might be preferrable (and if you plan to also attend).

Thank you,
Greta Crook

Executive Assistant to
Don Bobo

From: Don Bobo <Don_Bobo@edwards.com>
Sent: Tuesday, July 20, 2021 2:36 PM
To: Ali Shahriari <ali.shahriari@aorticinnovations.com>
Cc: Keith Newburry <Keith_Newburry@edwards.com>
Subject: Re: [EXTERNAL] Aortic Innovations LLC

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Best,

Dr. Ali Shahriari
Chief Executive Officer
Aortic Innovations, LLC
977 Hillsboro Mile
Hillsboro Beach, FL 33062
Ali.Shahriari@aorticinnovations.com

CC; Keith Newburry, Chief IP Counsel

--

Ali Shahriari

CEO

Aortic Innovations LLC.

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EXHIBIT 51

From: Ali Shahriari <ali.shahriari@aorticinnovations.com>
Sent: Monday, July 26, 2021 6:47 PM
To: Don Bobo <Don_Bobo@edwards.com>; Greta Crook <Greta_Crook@edwards.com>
Cc: Damergy, Seth-GB+ <seth.damergy@ubs.com>
Subject: [External] Re: Aortic Innovations LLC

Thank you both for the follow up. We have engaged Seth Damergy and the UBS team that worked with us on the sale of Ascyrus to assist here and he and his team will reach out to your assistant to help coordinate a call and discuss next steps. We look forward to our future discussions and the opportunity to work together.

With kind regards,

Ali

On Fri, Jul 23, 2021 at 12:22 PM Don Bobo <Don_Bobo@edwards.com> wrote:

Sending from Don's email, in case you didn't recognize mine.

Thanks,
Greta

From: Greta Crook
Sent: Wednesday, July 21, 2021 12:16 PM
To: ali.shahriari@aorticinnovations.com
Cc: Keith Newburry <Keith_Newburry@edwards.com>; Don Bobo <Don_Bobo@edwards.com>
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CC; Keith Newburry, Chief IP Counsel

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Ali Shahriari

CEO

Aortic Innovations LLC.

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--

Ali Shahriari

CEO

Aortic Innovations LLC.

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intended recipient, please contact the sender by reply email and destroy all copies of the original message.

EXHIBIT 52

Premarket Approval (PMA)

Note: This medical device record is a PMA supplement. A supplement may have changed the device description/function or indication from that approved in the original PMA. Be sure to look at the original PMA[23] record for more information.

Device	Edwards SAPIEN 3 Ultra RESILIA Transcatheter Heart Valve
Generic Name	Aortic Valve, Prosthesis, Percutaneously Delivered
Applicant	EDWARDS LIFESCIENCES, LLC. One Edwards Way Irvine, CA 92614
PMA Number	P140031
Supplement Number	S141
Date Received	05/02/2022
Decision Date	07/28/2022
Product Code	NPT[24]
Advisory Committee	Cardiovascular
Supplement Type	Normal 180 Day Track
Supplement Reason	Change Design/Components/Specifications/Material
Expedited Review Granted?	No
Combination Product	No

Approval Order Statement

Approval For The Edwards SAPIEN 3 Ultra RESILIA Transcatheter Heart Valve.

Post-Approval Study Show Report Schedule And Study Progress[25]

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Page Last Updated: 02/06/2023

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15. /scripts/cdrh/cfdocs/cfStandards/search.cfm
16. /scripts/cdrh/cfdocs/cfCFR/CFRSearch.cfm
17. /scripts/cdrh/cfdocs/cfPCD_RH/classification.cfm
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19. /scripts/cdrh/cfdocs/Medsun/searchReportText.cfm
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25. /scripts/cdrh/cfdocs/cfpma/pma_pas.cfm?tid=762598

EXHIBIT 53

UNITED STATES
SECURITIES AND EXCHANGE COMMISSION

Washington, D.C. 20549

FORM 10-K

(Mark One)

☒ **ANNUAL REPORT PURSUANT TO SECTION 13 OR 15(d) OF THE SECURITIES EXCHANGE ACT OF 1934**

For the Fiscal Year Ended December 31, 2021

OR

☐ **TRANSITION REPORT PURSUANT TO SECTION 13 OR 15(d) OF THE SECURITIES EXCHANGE ACT OF 1934**

For the Transition Period From to
Commission File Number 1-15525

EDWARDS LIFESCIENCES CORPORATION

(Exact name of registrant as specified in its charter)

Delaware	**36-4316614**
(State or other jurisdiction of incorporation or organization)	(I.R.S. Employer Identification No.)

One Edwards Way	**Irvine**	**California**	**92614**
(Address of Principal Executive Offices)			(Zip Code)

(949) 250-2500
Registrant's telephone number, including area code

Securities registered pursuant to Section 12(b) of the Act:

Title of each class	**Trading Symbol(s)**	**Name of each exchange on which registered:**
Common Stock, par value $1.00 per share	EW	New York Stock Exchange

Securities registered pursuant to Section 12(g) of the Act: None

Indicate by check mark if the registrant is a well-known seasoned issuer, as defined by Rule 405 of the Securities Act. Yes ☒ No ☐

Indicate by check mark if the registrant is not required to file reports pursuant to Section 13 or 15(d) of the Exchange Act. Yes ☐ No ☒

Indicate by check mark whether the registrant (1) has filed all reports required to be filed by Section 13 or 15(d) of the Securities Exchange Act of 1934 during the preceding 12 months (or for such shorter period that the registrant was required to file such reports), and (2) has been subject to such filing requirements for the past 90 days. Yes ☒ No ☐

Indicate by check mark whether the registrant has submitted electronically every Interactive Data File required to be submitted pursuant to Rule 405 of Regulation S-T (§232.405 of this chapter) during the preceding 12 months (or for such shorter period that the registrant was required to submit such files). Yes ☒ No ☐

Indicate by check mark whether the registrant is a large accelerated filer, an accelerated filer, a non-accelerated filer, a smaller reporting company, or an emerging growth company. See the definitions of "large accelerated filer," "accelerated filer," "smaller reporting company," and "emerging growth company" in Rule 12b-2 of the Exchange Act.

Large accelerated filer	Accelerated filer	Non-accelerated filer	Smaller reporting company	Emerging growth company
☒	☐	☐	☐	☐

If an emerging growth company, indicate by check mark if the registrant has elected not to use the extended transition period for complying with any new or revised financial accounting standards provided pursuant to Section 13(a) of the Exchange Act. ☐

Indicate by check mark whether the registrant has filed a report on and attestation to its management's assessment of the effectiveness of its internal control over financial reporting under Section 404(b) of the Sarbanes-Oxley Act (15 U.S.C. 7262(b)) by the registered public accounting firm that prepared or issued its audit report ☒.

Indicate by check mark whether the registrant is a shell company (as defined in Rule 12b-2 of the Exchange Act). Yes ☐ No ☒

The aggregate market value of the registrant's common stock held by non-affiliates as of June 30, 2021 (the last trading day of the registrant's most recently completed second quarter): $64,028,235,982 based on the closing price of the registrant's common stock on the New York Stock Exchange. This calculation does not reflect a determination that persons are affiliates for any other purpose.

The number of shares outstanding of the registrant's common stock, $1.00 par value, as of January 31, 2022, was 623,207,437.

Documents Incorporated by Reference

Portions of the registrant's proxy statement for the 2022 Annual Meeting of Stockholders (to be filed within 120 days of December 31, 2021) are incorporated by reference into Part III, as indicated herein.

Table of Contents

EDWARDS LIFESCIENCES CORPORATION
Form 10-K Annual Report—2021
Table of Contents

PART I		
Item 1.	Business	2
Item 1A.	Risk Factors	11
Item 1B.	Unresolved Staff Comments	19
Item 2.	Properties	19
Item 3.	Legal Proceedings	19
Item 4.	Mine Safety Disclosures	19
PART II		
Item 5.	Market for Registrant's Common Equity, Related Stockholder Matters and Issuer Purchases of Equity Securities	20
Item 6.	[Reserved]	21
Item 7.	Management's Discussion and Analysis of Financial Condition and Results of Operations	21
Item 7A.	Quantitative and Qualitative Disclosures About Market Risk	37
Item 8.	Financial Statements and Supplementary Data	39
Item 9.	Changes in and Disagreements With Accountants on Accounting and Financial Disclosure	89
Item 9A.	Controls and Procedures	90
Item 9B.	Other Information	90
Item 9C.	Disclosure Regarding Foreign Jurisdictions That Prevent Inspections	90
PART III		
Item 10.	Directors, Executive Officers and Corporate Governance	91
Item 11.	Executive Compensation	91
Item 12.	Security Ownership of Certain Beneficial Owners and Management and Related Stockholder Matters	91
Item 13.	Certain Relationships and Related Transactions, and Director Independence	91
Item 14.	Principal Accounting Fees and Services	91
PART IV		
Item 15.	Exhibits and Financial Statement Schedules	92
Item 16.	Form 10-K Summary	93
	Signatures	94

Table of Contents

PART I

NOTE REGARDING FORWARD-LOOKING STATEMENTS

This report contains forward-looking statements within the meaning of Section 27A of the Securities Act of 1933, as amended, and Section 21E of the Securities Exchange Act of 1934, as amended. We intend the forward-looking statements contained in this report to be covered by the safe harbor provisions of such Acts. Some statements other than statements of historical fact in this report or referred to or incorporated by reference into this report are "forward-looking statements" for purposes of these sections. These statements include, among other things, the continued impact of COVID-19 on our business, any predictions, opinions, expectations, plans, strategies, objectives and any statements of assumptions underlying any of the foregoing relating to our current and future business and operations, including, but not limited to, financial matters, development activities, clinical trials and regulatory matters, manufacturing and supply operations, and product sales and demand. These statements can sometimes be identified by the use of the forward-looking words such as "may," "believe," "will," "expect," "project," "estimate," "should," "anticipate," "plan," "goal," "continue," "seek," "pro forma," "forecast," "intend," "guidance," "optimistic," "aspire," "confident," other forms of these words or similar words or expressions or the negative thereof. Statements of past performance, efforts, or results about which inferences or assumptions may be made can also be forward-looking statements and are not indicative of future performance or results; these statements can be identified by the use of words such as "preliminary," "initial," diligence," "industry-leading," "compliant," "indications," or "early feedback" or other forms of these words or similar words or expressions or the negative thereof. These forward-looking statements are subject to substantial risks and uncertainties that could cause our results or future business, financial condition, results of operations or performance to differ materially from our historical results or experiences or those expressed or implied in any forward-looking statements contained in this report. These risks and uncertainties include, but are not limited to: uncertainties regarding the severity and duration of the COVID-19 pandemic and its impact on our business and the economy generally, clinical trial or commercial results or new product approvals and therapy adoption; inability or failure to comply with applicable regulations; unpredictability of product launches; competitive dynamics; changes to reimbursement for the company's products; the company's success in developing new products and avoiding manufacturing and quality issues; the impact of currency exchange rates; the timing or results of research and development and clinical trials; unanticipated actions by the United States Food and Drug Administration and other regulatory agencies; unexpected impacts or expenses resulting from litigation or internal or government investigations; and other risks detailed under "Risk Factors" in Part I, Item 1A below, as such risks and uncertainties may be amended, supplemented or superseded from time to time by our subsequent reports on Forms 10-Q and 8-K we file with the U.S. Securities and Exchange Commission. These forward-looking statements speak only as of the date on which they are made and we do not undertake any obligation to update any forward-looking statement to reflect events or circumstances after the date of the statement. If we do update or correct one or more of these statements, investors and others should not conclude that we will make additional updates or corrections.

Unless otherwise indicated or otherwise required by the context, the terms "we," "our," "it," "its," "Company," "Edwards," and "Edwards Lifesciences" refer to Edwards Lifesciences Corporation and its subsidiaries.

Item 1. Business

Overview

Edwards Lifesciences Corporation is the global leader in patient-focused medical innovations for structural heart disease and critical care monitoring. Driven by a passion to help patients, we partner with the world's leading clinicians and researchers and invest in research and development to transform care for those impacted by structural heart disease or who require hemodynamic monitoring in the hospital setting. Edwards Lifesciences has been a leader in these areas for over six decades. Since our founder, Lowell Edwards, first dreamed of using engineering to address diseases of the human heart, we have steadily built a company on the premise of imagining, building, and realizing a better future for patients.

A pioneer in the development of heart valve therapies, we are the world's leading manufacturer of heart valve systems and repair products used to replace or repair a patient's diseased or defective heart valve. Our innovative work in heart valves encompasses both surgical and transcatheter therapies for heart valve replacement and repair. In addition, our robust pipeline of future technologies is focused on the less invasive repair or replacement of the mitral and tricuspid valves of the heart, which are more complex and more challenging to treat than the aortic valve that is currently the focus of many of our commercially approved valve technologies. We are also a global leader in hemodynamic and noninvasive brain and tissue oxygenation monitoring systems used to measure a patient's cardiovascular function in the hospital setting.

Cardiovascular disease is the number-one cause of death in the world and is the top disease in terms of health care spending in nearly every country. Cardiovascular disease is progressive in that it tends to worsen over time and often affects the structure of an individual's heart.

Patients undergoing treatment for cardiovascular disease can be treated with a number of our medical technologies, which are designed to address individual patient needs with respect to disease process, comorbidities, and health status. For example, an individual with a heart valve disorder may have a faulty valve that is affecting the function of his or her heart or blood flow throughout his or her body. A clinician may elect to remove the valve and replace it with one of our bioprosthetic surgical tissue heart valves or surgically re-shape and repair the faulty valve with an Edwards Lifesciences annuloplasty ring. Alternatively, a clinician may implant an Edwards Lifesciences transcatheter valve or repair system via a catheter-based approach that does not require traditional open-heart surgery and can be done while the heart continues to beat. Patients in the hospital setting, including high-risk patients in the operating room or intensive care unit, are candidates for having their cardiac function or fluid levels monitored by our Critical Care products through multiple monitoring options, including noninvasive and minimally- invasive technologies. These technologies enable proactive clinical decisions while also providing the opportunity for improving diagnoses and developing individualized therapeutic management plans for patients.

Corporate Background

Edwards Lifesciences Corporation was incorporated in Delaware on September 10, 1999.

Our principal executive offices are located at One Edwards Way, Irvine, California 92614. The telephone number at that address is (949) 250-2500. We make available, free of charge on our website located at www.edwards.com, our annual report on Form 10-K, quarterly reports on Form 10-Q, current reports on Form 8-K, and any amendments to those reports, as soon as reasonably practicable after filing such reports with the Securities and Exchange Commission ("SEC"). The contents of our website are not incorporated by reference into this report.

Edwards Lifesciences' Product and Technology Offerings

The following discussion summarizes the main areas of products and technologies we offer to treat advanced cardiovascular disease. Our products and technologies are categorized into four main areas: Transcatheter Aortic Valve Replacement, Transcatheter Mitral and Tricuspid Therapies, Surgical Structural Heart, and Critical Care. For more information on net sales from these four main areas, see *"Net Sales by Product Group*" in Part II, Item 7 "*Management's Discussion and Analysis of Financial Condition and Results of Operations*."

Transcatheter Aortic Valve Replacement

We are the global leader in transcatheter heart valve replacement technologies designed for the minimally-invasive replacement of aortic heart valves. The *Edwards SAPIEN* family of valves, including *Edwards SAPIEN XT,* the *Edwards SAPIEN 3,* and the *Edwards SAPIEN 3 Ultra* transcatheter heart valves, and their respective delivery systems, are used to treat heart valve disease using catheter-based approaches for patients who have severe symptomatic aortic stenosis and certain

patients with congenital heart disease. Delivered while the heart is beating, these valves can enable patients to experience a better quality of life sooner than patients receiving traditional surgical therapies. We began offering our transcatheter aortic heart valves to patients commercially in Europe in 2007, in the United States in 2011, and in Japan in 2013. Supported by extensive customer training and service, and a growing body of compelling clinical evidence, our *SAPIEN* family of transcatheter aortic heart valves are the most widely prescribed transcatheter heart valves in the world.

Sales of our transcatheter aortic valve replacement products represented 65%, 65%, and 63% of our net sales in 2021, 2020, and 2019, respectively.

Transcatheter Mitral and Tricuspid Therapies

We continue to make significant investments in the development of transcatheter heart valve repair and replacement technologies designed to treat mitral and tricuspid valve diseases. While many of these technologies are in development and clinical phases, the *PASCAL* and *Cardioband* transcatheter valve repair systems are commercially available in Europe for mitral and tricuspid valve repair. The *PASCAL* system provides a differentiated, minimally-invasive therapy to address the needs of patients with mitral or tricuspid regurgitation through leaflet approximation, while the *Cardioband* system enables clinicians to reduce the valve's annulus to restore a patient's mitral or tricuspid valve to a more functional state and lower regurgitation. In addition to transcatheter repair, we believe transcatheter replacement is key to unlocking the full mitral and tricuspid opportunity, given the complex and diverse patient population. Our two-platform mitral replacement strategy positions us for leadership in the mid-to-long term. *SAPIEN M3* is based on the proven *SAPIEN* valve, paired with a novel docking system. *EVOQUE Eos* is our next generation transcatheter replacement system, designed specifically for mitral patients. Both *SAPIEN M3* and *EVOQUE Eos* are implanted with transfemoral delivery systems that are sub 30-French, which has benefits for femoral puncture and septal crossing, contributing to ease of use, and patient safety. For tricuspid valve replacement, our *EVOQUE* system is also sub 30-French, and available in three valve sizes to enable treatment in a wide range of patient anatomies.

Surgical Structural Heart

We are pioneering more resilient surgical therapies that help patients and can improve the quality of their lives. Our *RESILIA* tissue, now with five years of published clinical data showing 0% structural valve deterioration through five years[1], is helping us redefine tissue durability standards. Our latest innovation, the *INSPIRIS RESILIA* aortic valve, is built on our *PERIMOUNT* platform and offers *RESILIA* tissue and *VFit* technology. *INSPIRIS* is the leading aortic surgical valve in the world. Sales of our surgical therapies in the United States also continue to gain traction with *KONECT RESILIA*, the first pre-assembled, aortic tissue valved conduit, for patients who require replacement of the valve, root, and ascending aorta. In 2021, we also received regulatory approval with reimbursement in Japan for our *MITRIS RESILIA* valve, a new mitral valve incorporating our newest tissue technology. In addition to our replacement valves, we are the worldwide leader in surgical heart valve repair therapies. Our recently launched *HARPOON Beating Heart Mitral Valve Repair System* can help transform care for many patients with degenerative mitral regurgitation. We believe the demand for surgical structural heart therapies is growing worldwide and that our innovation strategy will continue to extend our leadership and patient impact.

Sales of our surgical tissue heart valve products represented 15%, 16%, and 17% of our net sales in 2021, 2020, and 2019, respectively.

Critical Care

We are a world leader in advanced hemodynamic monitoring systems used to measure a patient's heart function and fluid status in surgical and intensive care settings. Hemodynamic monitoring plays an important role in enhancing surgical recovery. Edwards' complete hemodynamic portfolio helps clinicians make proactive clinical decisions that can improve patient outcomes. The portfolio includes the minimally invasive *FloTrac* and *Acumen IQ* sensors, the noninvasive *ClearSight* and *Acumen IQ* cuffs, and the *ForeSight* noninvasive tissue oximetry sensor. We also support clinical needs with our well-established *Swan-Ganz* line of pulmonary artery catheters and arterial pressure monitoring products. Compatible with our portfolio of sensors and catheters, the *HemoSphere* monitoring platform displays valuable physiological information in an easy to understand and actionable manner. Our first predictive algorithm, *Acumen Hypotension Prediction Index* software, alerts clinicians in advance of a patient developing dangerously low blood pressure and amplifies the clinical need for our *Acumen IQ* and *HemoSphere* monitoring solutions.

[1] Bavaria, et al. Five-year Outcomes of the COMMENCE trial investigating Aortic Valve Replacement with a Bioprosthetic Valve with a Novel Tissue. The Society of Thoracic Surgeons 2021 Annual Meeting; Bartus, et al. Final 5-year outcomes following aortic valve replacement with *RESILIA* tissue bio prosthesis. European Journal of Cardio-Thoracic Surgery, 2020.

Sales of our hemodynamic products represented 8%, 9%, and 10% of our net sales in 2021, 2020, and 2019, respectively.

Competition

The medical technology industry is highly competitive. We compete with many companies, including divisions of companies much larger than us and smaller companies that compete in specific product lines or certain geographies. Furthermore, new product development and technological change characterize the areas in which we compete. Our present or future products could be rendered obsolete or uneconomical as a result of technological advances by one or more of our present or future competitors or by other therapies, including drug therapies. We must continue to develop and commercialize new products and technologies to remain competitive in the cardiovascular medical technology industry. We believe that we are competitive primarily because we deliver superior clinical outcomes that are supported by extensive data, and innovative features that enhance patient benefit, product performance, and reliability; these superior clinical outcomes are in part due to the level of customer and clinical support we provide.

The cardiovascular segment of the medical technology industry is dynamic and subject to significant change due to cost-of-care considerations, regulatory reform, industry and customer consolidation, and evolving patient needs. The ability to provide products and technologies that demonstrate value and improve clinical outcomes is becoming increasingly important for medical technology manufacturers.

We believe that we are a leading global competitor in each of our product lines. In Transcatheter Aortic Valve Replacement, our primary competitors include Medtronic PLC and Abbott Laboratories ("Abbott"). In Transcatheter Mitral and Tricuspid Therapies, our primary competitor is Abbott, and there are a considerable number of large and small companies with development efforts in these fields. In Surgical Structural Heart, our primary competitors include Medtronic PLC, Abbott, and Artivion, Inc (formerly CryoLife). In Critical Care, we compete primarily with a variety of companies in specific product lines including ICU Medical, Inc., PULSION Medical Systems SE, a subsidiary of Getinge AB, Cheetah Medical, Inc., a subsidiary of Baxter International, and LiDCO Group PLC, a subsidiary of Masimo Corporation.

Sales and Marketing

Our portfolio includes some of the most recognizable cardiovascular device product brands in treating structural heart disease today. We have a number of product lines that require sales and marketing strategies tailored to deliver high-quality, cost-effective products and technologies to customers worldwide. Because of the diverse global needs of the population that we serve, our distribution system consists of several direct sales forces as well as independent distributors. We are not dependent on any single customer and no single customer accounted for 10% or more of our net sales in 2021.

To ensure optimal outcomes for patients, we conduct educational symposia and best practices training for our physician, hospital executive, service line leadership, nursing, and clinical-based customers. We rely extensively on our sales and field clinical specialist personnel who work closely with our customers in hospitals. Field clinical specialists routinely attend procedures where Edwards' products are being used in order to provide guidance on the use of our devices, thereby enabling physicians and staff to reach expert proficiency and deliver positive patient outcomes. Our customers include physicians, nurses, and other clinical personnel, but can also include decision makers such as service line leaders, material managers, biomedical staff, hospital administrators and executives, purchasing managers, and ministries of health. Also, for certain of our product lines and where appropriate, our corporate sales team actively pursues approval of Edwards Lifesciences as a qualified supplier for hospital group purchasing organizations ("GPOs") that negotiate contracts with suppliers of medical products. Additionally, we have contracts with a number of United States and European national and regional buying groups, including healthcare systems and Integrated Delivery Networks. Where we choose to market our products is also influenced by the existence of, or potential for, adequate reimbursement to hospitals and other providers by national healthcare systems.

United States. In the United States, we sell substantially all of our products through our direct sales forces. In 2021, 57% of our net sales were derived from sales to customers in the United States.

Outside of the United States. In 2021, 43% of our net sales were derived outside of the United States through our direct sales forces and independent distributors. Of the total sales outside of the United States, 53% were in Europe, 23% were in Japan, and 24% were in Rest of World. We sell our products in approximately 100 countries, and our major international markets include Canada, China, France, Germany, Italy, Japan, Spain, and the United Kingdom. A majority of the sales and marketing approach outside of the United States is direct sales, although it varies depending on each country's size and state of development.

Raw Materials and Manufacturing

We operate manufacturing facilities in various geographies around the world. We manufacture our Transcatheter Aortic Valve Replacement, Transcatheter Mitral and Tricuspid technologies, and Structural Surgical Heart products primarily in the United States (California and Utah), Singapore, Costa Rica, and Ireland. We manufacture our Critical Care products primarily in Puerto Rico and the Dominican Republic.

We use a diverse and broad range of raw and organic materials in the design, development, and manufacture of our products. We manufacture our non-implantable products from fabricated raw materials including resins, chemicals, electronics, and metals. Most of our replacement heart valves are manufactured from natural tissues harvested from animal tissue, as well as fabricated materials. We purchase certain materials and components used in manufacturing our products from external suppliers. In addition, we purchase certain supplies from single sources for reasons of sole source availability or constraints resulting from regulatory requirements.

We work with our suppliers to mitigate risk and seek continuity of supply while maintaining quality and reliability. Alternative supplier options are generally considered, identified, and approved for materials deemed critical to our products, although we do not typically pursue immediate regulatory qualification of alternative sources due to the strength of our existing supplier relationships and the time and expense associated with the regulatory validation process.

We comply with all current global guidelines regarding risks for products incorporating animal tissue intended to be implanted in humans. We follow rigorous sourcing and manufacturing procedures intended to safeguard humans from potential risks associated with diseases such as bovine spongiform encephalopathy ("BSE"). We obtain bovine tissue used in our pericardial tissue valve products only from sources within the United States and Australia, where strong control measures and surveillance programs exist. In addition, bovine tissue used in our pericardial tissue valve products is from tissue types considered by global health and regulatory organizations to have shown no risk of infectibility. Our manufacturing and sterilization processes are designed to render tissue biologically safe from all known infectious agents and viruses.

Quality Assurance

We are committed to providing to our patients quality products and have implemented modern quality systems and concepts throughout the organization. The quality system starts with the initial design concept, risk management, and product specification, and continues through the design of the product, packaging and labeling, and the manufacturing, sales, support, and servicing of the product. The quality system is intended to design quality into the products and utilizes continuous improvement concepts, including Lean/Six Sigma principles, throughout the product lifecycle.

Our operations are frequently inspected by the many regulators that oversee medical device manufacturing, including the United States Food and Drug Administration ("FDA"), European Notified Bodies, and other regulatory entities. The medical technology industry is highly regulated and our facilities and operations are designed to comply with all applicable quality systems standards, including the International Organization for Standardization ("ISO") 13485. These standards require, among other items, quality system controls that are applied to product design, component material, suppliers, and manufacturing operations. These regulatory approvals and ISO certifications can be obtained only after a successful audit of a company's quality system has been conducted by regulatory or independent outside auditors. Periodic reexamination by an independent outside auditor is required to maintain these certifications.

Environmental, Health, and Safety

We are committed to providing a safe and healthy workplace and complying with all relevant regulations and medical technology industry standards. Through our corporate and site level Environmental, Health, and Safety functions, we establish and monitor programs to reduce pollution, prevent injuries, and maintain compliance with applicable regulations. In order to measure performance, we monitor and report on a number of metrics, including regulated and non-regulated waste disposal, energy usage, water consumption, air toxic emissions, and injuries from our production activities. Each of our manufacturing sites is evaluated regularly with respect to a broad range of Environmental, Health, and Safety criteria.

Research and Development

In 2021, we made significant investments in research and development as we worked to develop therapies that we believe have the potential to change the practice of medicine. Research and development spending increased 19% year over year, representing 17% of 2021 sales. This increase was primarily the result of significant investments in our transcatheter structural heart programs, including an increase in clinical research for our mitral and tricuspid therapies. We are engaged in ongoing research and development to deliver clinically advanced new products, to enhance the effectiveness, ease of use, safety, and reliability of our current leading products, and to expand the applications of our products as appropriate. We focus on opportunities within specific areas of structural heart disease and critical care monitoring.

A considerable portion of our research and development investment includes clinical trials and the collection of evidence that provide data for use in regulatory submissions, and required post-market approval studies involving applications of our products. Our investment in clinical studies also includes outcomes and cost-effectiveness data for payers, clinicians, and healthcare systems.

In Transcatheter Aortic Valve Replacement, we are developing new products to further improve and streamline transcatheter aortic heart valve replacement procedures.

In Transcatheter Mitral and Tricuspid Therapies, we are making significant investments in innovation and clinical evidence to develop technologies designed to treat mitral and tricuspid valve diseases. In addition to our internally developed programs, we have made investments in several companies that are independently developing minimally-invasive technologies to treat structural heart diseases.

Our Surgical Structural Heart development programs include innovative platforms for patients who are best treated surgically, specifically active patients and patients with more complex combined procedures.

In our Critical Care product line, we are pursuing the development of a variety of decision support solutions for our clinicians. This includes next-generation noninvasive and minimally-invasive hemodynamic monitoring systems, and a next-generation monitor platform. We are also developing a decision support software suite with advanced algorithms for proactive hemodynamic management, including a semi-closed loop system for standardized management of patient fluid levels. Lastly, we are developing a connectivity platform that will offer clinicians additional clinical support, remote monitoring capability, analytics, and insights for their patients' hemodynamic status.

Our research and development activities are conducted primarily in facilities located in the United States and Israel. Our experienced research and development staff are focused on product design and development, quality, clinical research, and regulatory compliance. To pursue primary research efforts, we have developed alliances with several leading research institutions and universities, and also work with leading clinicians around the world in conducting scientific studies on our existing and developing products.

Proprietary Technology

Patents, trademarks, and other proprietary rights are important to the success of our business. We also rely upon trade secrets, know-how, continuing innovations, licensing opportunities, and non-disclosure agreements to develop and maintain our competitive position.

We own or have rights to a substantial number of patents and have patent applications pending both in the United States and in foreign countries. We continue to innovate and file new patent applications to protect our new products and technologies.

Additionally, we are a party to license agreements with various third parties pursuant to which we have obtained, for varying terms, the exclusive or non-exclusive rights to certain patents held by such third parties in consideration for cross-licensing rights and/or royalty payments. We have also licensed certain patent rights to others.

We undertake reasonable measures to protect our patent rights, including monitoring the products of our competitors for possible infringement of our patents. Litigation has been necessary to enforce certain patent rights held by us, and we plan to continue to defend and prosecute our rights with respect to such patents.

Moreover, we own certain United States registered trademarks used in our business. Many of our trademarks have also been registered for use in certain foreign countries where registration is available and where we have determined it is commercially advantageous to do so.

Government Regulation and Other Matters

Our products and facilities are subject to regulation by numerous government agencies, including the FDA, European Union Member States competent authorities, and the Japanese Pharmaceuticals and Medical Devices Agency, to confirm compliance with the various laws and regulations governing the development, testing, manufacturing, labeling, marketing, and distribution of our products.

We are also governed by federal, state, local, and international laws of general applicability, including, but not limited to, those regulating employee health and safety, labor, competition, trade secret, and the protection of the environment. Overall, the amount and scope of domestic and foreign laws and regulations applicable to our business has increased over time. Compliance with these regulations has not had a material effect on our capital expenditures, earnings, or competitive position to date, but new regulations or amendments to existing regulations to make them more stringent could have such an effect in the future. We cannot estimate the expenses we may incur to comply with potential new laws or changes to existing laws, or the other potential effects these laws may have on our business.

United States Regulation. In the United States, the FDA has responsibility for regulating medical devices. The FDA regulates design, development, testing, clinical studies, manufacturing, labeling, promotion, and record keeping for medical devices, and reporting of adverse events, recalls, or other field actions by manufacturers and users to identify potential problems with marketed medical devices. Many of the devices that we develop and market are in a category for which the FDA has implemented stringent clinical investigation and pre-market clearance or approval requirements. The process of obtaining FDA clearance or approval to market a product is resource intensive, lengthy, and costly. FDA review may involve substantial delays that adversely affect the marketing and sale of our products. A number of our products are pending regulatory clearance or approval to begin commercial sales in various markets. Ultimately, the FDA may not authorize the commercial release of a medical device if it determines the device is not safe and effective or does not meet other regulatory standards. Additionally, even if a product is cleared or approved, the FDA may impose restrictions or require testing and surveillance programs to monitor the effects of these products once commercialized.

The FDA has the authority to halt the distribution of certain medical devices, detain or seize adulterated or misbranded medical devices, order the repair, replacement, or refund of the costs of such devices, or preclude the importation of devices that are or appear violative. The FDA also conducts inspections to determine compliance with the quality system regulations concerning the manufacturing and design of devices and current medical device reporting regulations, recall regulations, clinical testing regulations, and other requirements. The FDA may withdraw product clearances or approvals due to failure to comply with regulatory standards, or the occurrence of unforeseen problems following initial approval, and require notification of health professionals and others with regard to medical devices that present unreasonable risks of substantial harm to the public health. Additionally, the failure to comply with FDA or comparable regulatory standards or the discovery of previously unknown product problems could result in fines, delays, suspensions or withdrawals of regulatory clearances or approvals, seizures, injunctions, recalls, refunds, civil money penalties, or criminal prosecution. Our compliance with applicable regulatory requirements is subject to continual review. Moreover, the FDA and several other United States agencies administer controls over the export of medical devices from the United States and the import of medical devices into the United States, which could also subject us to sanctions for noncompliance.

We are also subject to additional laws and regulations that govern our business operations, products, and technologies, including:

- federal, state, and foreign anti-kickback laws and regulations, which generally prohibit payments to anyone, including physicians as an inducement to purchase or recommend a product;
- the Stark law, which prohibits physicians from referring Medicare or Medicaid patients to a provider that bills these programs for the provision of certain designated health services if the physician (or a member of the physician's immediate family) has a financial relationship with that provider;
- federal and state laws and regulations that protect the confidentiality of certain patient health information, including patient records, and restrict the use and disclosure of such information, in particular, the Health Insurance Portability and Accountability Act of 1996;

- the Physician Payments Sunshine Act, which requires public disclosure of the financial relationships of United States physicians and teaching hospitals with applicable manufacturers, including medical device, pharmaceutical, and biologics companies;

- the False Claims Act, which prohibits the submission of false or otherwise improper claims for payment to a federally funded health care program, and health care fraud statutes that prohibit false statements and improper claims to any third-party payor; and

- the United States Foreign Corrupt Practices Act, which can be used to prosecute United States companies for arrangements with foreign government officials or other parties, or for not keeping accurate financial records or maintaining adequate internal controls to prevent and detect arrangements with foreign government officials or other parties.

Failure to comply with these laws and regulations could result in criminal liability, significant fines or penalties, negative publicity, and substantial costs and expenses associated with investigation and enforcement activities. To assist in our compliance efforts, we work to adhere to many codes of ethics and conduct regarding our business activities in the United States and other countries in which we operate. In addition, we have in place a dedicated team to improve our internal business compliance programs and policies.

Regulation Outside of the United States. Outside of the United States, the regulation of medical devices is complex. In Europe, our products are subject to extensive regulatory requirements. The regulatory regime in the European Union for medical devices became mandatory in June 1998. It requires that medical devices may only be placed on the market if they do not compromise safety and health when properly installed, maintained, and used in accordance with their intended purpose. National laws conforming to the European Union's legislation regulate our products under the medical devices regulatory system. Although the more variable national requirements under which medical devices were formerly regulated have been substantially replaced by the European Union Medical Devices Directive, individual nations can still impose unique requirements that may require supplemental submissions. The European Union medical device laws require manufacturers to declare that their products conform to the essential regulatory requirements after which the products may be placed on the market bearing the CE Mark. Manufacturers' quality systems for products in all but the lowest risk classification are also subject to certification and audit by an independent notified body. In Europe, particular emphasis is being placed on more sophisticated and faster procedures for the reporting of adverse events to the competent authorities.

In May 2017, the European Union (the "EU") implemented a new regulatory scheme for medical devices under the Medical Device Regulation ("MDR"). The MDR became fully effective on May 26, 2021 and brought significant new requirements for many medical devices, including enhanced requirements for clinical evidence and documentation, increased focus on device identification and traceability, new definitions and registration of economic operators throughout the distribution chain, and additional post-market surveillance and vigilance. Compliance with the MDR requires re-certification of many of our products to the enhanced standards, and has resulted in and will continue to result in substantial additional expense. In addition, in the EU, we import some of our devices through our offices in Switzerland. Switzerland is not a member state of the EU, but is linked to the EU through bilateral treaties; therefore, the free movement of goods, including medical devices, between the EU and Switzerland after implementation of the MDR requires a revised Mutual Recognition Agreement ("MRA"). If an MRA covering the MDR is not put in place, then non-EU manufacturers may be required to make significant changes, including replacement of Swiss economic operators with operators based in EU Member States, and changes will need to be made to our device labeling and/or packaging to satisfy MDR requirements. If these measures are unable to be taken, it may no longer be possible to place such devices on the EU market.

In Japan, pre-market approval and clinical studies are required as is governmental pricing approval for medical devices. Clinical studies are subject to a stringent Japanese "Good Clinical Practices" standard. Approval time frames from the Japanese Ministry of Health, Labour and Welfare vary from simple notifications to review periods of one or more years, depending on the complexity and risk level of the device. In addition, importation of medical devices into Japan is subject to the "Good Import Practices" regulations. As with any highly regulated market, significant changes in the regulatory environment could adversely affect future sales.

In many of the other foreign countries in which we market our products, we may be subject to regulations affecting, among other things:

- product standards and specifications;

- packaging requirements;

- labeling requirements;
- product collection and disposal requirements;
- quality system requirements;
- import restrictions;
- tariffs;
- duties; and
- tax requirements.

Many of the regulations applicable to our devices and products in these countries are similar to those of the FDA. In some regions, the level of government regulation of medical devices is increasing, which can lengthen time to market and increase registration and approval costs. In many countries, the national health or social security organizations require our products to be qualified before they can be marketed and considered eligible for reimbursement.

Health Care Initiatives. Government and private sector initiatives to limit the growth of health care costs, including price regulation and competitive pricing, coverage and payment policies, comparative effectiveness reviews, technology assessments, increasing evidentiary demands, and managed-care arrangements, are continuing in many countries where we do business, including the United States, Europe, and Japan. As a result of these changes, the marketplace has placed increased emphasis on the delivery of more cost-effective medical therapies. For example, government programs, private health care insurance, and managed-care plans have attempted to control costs by restricting coverage and limiting the level of reimbursement for procedures or treatments, and some third-party payors require their pre-approval before new or innovative devices or therapies are utilized by patients. These various initiatives have created increased price sensitivity over medical products generally and may impact demand for our products and technologies.

The delivery of our products is subject to regulation by the United States Department of Health and Human Services ("HHS") and comparable state and foreign agencies responsible for reimbursement and regulation of health care items and services. Foreign governments also impose regulations in connection with their health care reimbursement programs and the delivery of health care items and services. Reimbursement schedules regulate the amount the United States government will reimburse hospitals and doctors for the inpatient care of persons covered by Medicare. HHS' Centers for Medicare & Medicaid Services ("CMS") may also review whether and/or under what circumstances a procedure or technology is reimbursable for Medicare beneficiaries. Changes in current coverage and reimbursement levels could have an adverse effect on market demand and our pricing flexibility. The CMS National Coverage Determination for Transcatheter Aortic Valve Replacement was issued in June 2019. The modernized requirements and more streamlined patient evaluation process are meaningful enhancements that may help ensure equitable access for more patients suffering from severe aortic stenosis.

Health care cost containment efforts have also prompted domestic hospitals and other customers of medical device manufacturers to consolidate into larger purchasing groups to enhance purchasing power. The medical technology industry has also experienced some consolidation, partly in order to offer a broader range of products to large purchasers. As a result, transactions with customers are larger, more complex, and tend to involve more long-term contracts than in the past. These larger customers, due to their enhanced purchasing power, may have a material impact on product pricing.

These laws or any future legislation, including deficit reduction legislation, could impact medical procedure volumes, reimbursement for our products, and demand for our products or the prices at which we sell our products.

Seasonality

Our quarterly net sales are influenced by many factors, including new product introductions, acquisitions, regulatory approvals, patient and physician holiday schedules, and other factors. Net sales in the third quarter are typically lower than other quarters of the year due to the seasonality of the United States and European markets, where summer vacation schedules normally result in fewer medical procedures.

Human Capital Management Strategy

Human Capital Management ("HCM") Governance

Attracting, developing, and retaining talent is fundamental to our success. The primary goals of our talent management strategy are to attract and maintain a motivated, professional workforce and to ensure alignment on our patient-focused innovation strategy.

Our Board of Directors routinely engages with leadership in human capital management with time dedicated at each regularly scheduled meeting to discuss talent management, including, among other things, talent strategy, diversity, succession planning, employee development, employee health, safety, and welfare, results of employee surveys, and compensation. The Board of Directors also approves Key Operating Drivers, which are strategic milestones that include financial objectives and are tracked using a point system across our entire organization, that focus the Company and management toward short, medium, and long-term goals that align with our talent management strategy. In addition, the Chief Executive Officer ("CEO") has talent management related performance goals tied to his compensation; these Performance Management Objectives are reviewed on an annual basis, tracked, and then reported to and evaluated by our Board of Directors.

As we scale to reach more patients around the world, we have integrated our Talent & Organization (“T&O”) Strategy with our Edwards Strategic Planning process. The purpose of our T&O Strategy is to anticipate dynamic global trends related to our workforce, develop our talent to meet future organizational needs, and enable us to be well-poised for ongoing market success. The T&O Strategy enables us to explore external workforce signals, share insights, and identify and build emerging capabilities across our organization. The T&O Strategy framework takes a comprehensive approach which includes envisioning the future of our work (the "what" and "how" we deliver our patient focused strategy), planning our workforce (the "who" joining our community of trusted partners), and designing our workplace (the "where" and "when" work gets done). This consistent and scalable approach looks across all our product groups, regions, and significant functions to align and elevate priorities, critical capabilities, and organizational evolutions in line with our strategic plan. This integrated approach informs our yearly objectives and fuels our talent roadmap across the strategic horizon.

Our HCM governance includes a global talent development review ("TDR") process as well as an HCM dashboard. The purpose of our TDR process is to align our business strategy with talent strategies, assess talent against future organizational needs, evaluate critical talent populations, and enhance the strength of our succession planning. Our HCM dashboard is generated quarterly and provides insights on key metrics related to areas such as attraction and growth rates, retention trends, diversity, and employee sentiment.

Culture

Investing in our workforce means our employees can stay focused on our patient-focused innovation strategy and the development of life-saving therapies for the patients we serve. We are committed to maintaining an ethical culture where we celebrate diversity, promote good health and safety, empower employees to speak up, and ensure that employees' voices are heard. We strive to offer competitive employee benefits packages and are committed to fair and equitable pay practices. We track compensation patterns in all geographies where we operate, and we regularly look for ways to ensure fair and equitable pay.

We are committed to fostering an environment where all employees can grow and thrive. A diverse workforce results in a broader range of perspectives, helping drive our commitment to innovation. We have established a Diversity, Inclusion, and Belonging strategy that incorporates the four pillars of Business, People, Communication, and Community.

We believe in empowering our employees and providing avenues that enable their voices to be heard. We conduct a multilingual global employee survey, called *my*Voice, to pulse our employees and gain their feedback in a confidential manner. We gain insights on various topics including patient focus, diversity, inclusion and belonging, quality, innovation, and engagement. Speak-Up is a resource available to all employees to bring forth compliance related concerns; a key element of our compliance program is that each employee is accountable for maintaining ethical business practices. In addition, during each quarterly townhall meeting, our CEO has an "Ask Mike" section in which he answers questions that have been submitted to him by employees. Answers to questions that are not covered in the townhall meeting are posted online internally.

We understand that good health leads to better performance. We offer competitive employee benefits packages that include, among other things, health and welfare insurance, health savings accounts, family support services, and a variety of site-specific programs. We regularly evaluate our benefits package to make modifications that are aligned with the competitive landscape, legislative changes, and the unique needs of our population. We also provide robust wellness programs that address prevention, nutrition, mental health, physical activity, education, financial fitness, and community service. In recent years, mental wellness has become a central topic for organizations worldwide. As part of our regular evaluation and commitment to putting employees first, we launched a new program, Mind+, which offers a wide variety of mental health benefits and wellness

programs for our employees. This commitment extends to creating a work environment where employees can feel confident speaking about mental health with their managers and know how best to access the tools and resources available to support them. We believe there are strong benefits when employees are feeling their best. Employees who are mentally healthy are more innovative, resilient, better decision-makers, and able to build stronger relationships. We also believe that prioritizing and promoting Mind+ allows us to help patients around the world to live longer, healthier, and more productive lives and supports employees to be their best self at home and at work.

Talent Development

In addition to our robust TDR process and tuition reimbursement programs, we provide a variety of leadership, technical, and professional development programs around the globe.

Headcount and Labor Representation

As of December 31, 2021, we had approximately 15,700 employees worldwide, the majority of whom were located in the United States, Singapore, the Dominican Republic, and Costa Rica. None of our North American employees are represented by a labor union. In various countries outside of North America, we interact with trade unions and work councils that represent employees.

Additional details regarding diversity, talent development, compensation, and employee health and safety can be found in our Sustainability Report posted on our website at www.edwards.com under "About Us — Corporate Responsibility."

References to our website in this Annual Report on Form 10-K are provided for convenience only and the content on our website does not constitute a part of this Report.

Item 1A. Risk Factors

Our business and assets are subject to varying degrees of risk and uncertainty. An investor should carefully consider the risks described below, as well as other information contained in this Annual Report on Form 10-K and in our other filings with the SEC. Additional risks not presently known to us or that we currently deem immaterial may also adversely affect our business. If any of these events or circumstances occurs, our business, financial condition, results of operations, or prospects could be materially harmed. In that case, the value of our securities could decline and an investor could lose part or all of his or her investment. In addition, forward-looking statements within the meaning of the federal securities laws that are contained in this Annual Report on Form 10-K or in our other filings or statements may be subject to the risks described below as well as other risks and uncertainties. Please note that the headers provided below are intended to assist the reader in navigating the risk factors; however, some risks, present or future, may implicate multiple types of risks. Please read the cautionary notice regarding forward-looking statements in Part I above.

Business and Operating Risks

We are subject to risks associated with public health threats and epidemics, including the novel coronavirus ("COVID-19") and any variants of COVID-19.

We are subject to risks associated with public health threats and epidemics, including the global health concerns related to the COVID-19 pandemic. The global pandemic has adversely impacted and is likely to further adversely impact nearly all aspects of our business and markets, including our workforce and operations and the operations of our customers, suppliers, and business partners. In particular, we may experience material financial or operational impacts, including:

- Significant volatility or reductions in demand for our products;
- Impacts and delays to clinical trials, our pipeline milestones, or regulatory clearances and approvals; or
- The inability to meet our customers' needs or other obligations due to disruptions to our operations or the operations of our third-party partners, suppliers, contractors, logistics partners, or customers including disruptions to production, development, manufacturing, administrative, and supply operations and arrangements.

The extent to which the COVID-19 global pandemic and measures taken in response thereto impact our business, results of operations, and financial condition will depend on future developments, which are highly uncertain and are difficult to

predict. These developments include, but are not limited to, the duration and spread of the outbreak (including new variants of COVID-19), its severity, the actions to contain the virus or address its impact, the timing, distribution, and efficacy of vaccines and other treatments, United States and foreign government actions to respond to the reduction in global economic activity, and how quickly and to what extent normal economic and operating conditions can resume.

Failure to successfully innovate and develop new and differentiated products in a timely manner and effectively market these products could have a material effect on our prospects.

Our continued growth and success depend on our ability to innovate and develop new and differentiated products in a timely manner and effectively market these products. Without the timely innovation and development of products, our products could be rendered obsolete or less competitive by changing customer preferences or because of the introduction of a competitor's newer technologies. Innovating products requires the devotion of significant financial and other resources to research and development activities; however, there is no certainty that the products we are currently developing will complete the development process, or that we will obtain the regulatory or other approvals required to market such products in a timely manner or at all. Even if we timely innovate and develop products, our ability to market them could be constrained by a number of different factors, including barriers in patients' treatment pathway (including disease awareness, detection, and diagnosis), the need for regulatory clearance, restrictions imposed on approved indications, and uncertainty over third-party reimbursement. Failure in any of these areas could have a material effect on our prospects.

Unsuccessful clinical trials or procedures relating to products could have a material adverse effect on our prospects.

The regulatory approval process for new products and new indications for existing products requires extensive clinical trials and procedures, including early clinical feasibility and regulatory studies. Unfavorable or inconsistent clinical data from current or future clinical trials or procedures conducted by us, our competitors, or third parties, or perceptions regarding this clinical data, could adversely affect our ability to obtain necessary approvals and the market's view of our future prospects. Such clinical trials and procedures are inherently uncertain and there can be no assurance that these trials or procedures will be enrolled or completed in a timely or cost-effective manner or result in a commercially viable product or indication; failure to do so could have a material adverse effect on our prospects. Clinical trials or procedures may experience significant setbacks even after earlier trials have shown promising results. Further, preliminary results from clinical trials or procedures may be contradicted by subsequent analyses. In addition, results from our clinical trials or procedures may not be supported by actual long-term studies or clinical experience. If preliminary clinical results are later contradicted, or if initial results cannot be supported by actual long-term studies or clinical experience, our business could be adversely affected. Clinical trials or procedures may be delayed, suspended, or terminated by us, the FDA, or other regulatory authorities at any time if it is believed that the trial participants face unacceptable health risks or any other reasons, and any such delay, suspension, or termination could have a material adverse effect on our prospects or the market's view of our future prospects.

We operate in highly competitive markets, and if we do not compete effectively, our business will be harmed.

We face substantial competition and compete with companies of all sizes on the basis of cost-effectiveness, technological innovations, product performance, brand name recognition, breadth of product offerings, real or perceived product advantages, pricing and availability and rate of reimbursement. In addition, given the trend toward value-based healthcare, if we are not able to continue to demonstrate the full value of our differentiated products to healthcare providers and payors, our competitive position could be adversely affected. See "*Competition*" under "*Business*" in Part I, Item 1 included herein.

If we identify underperforming operations or products or if there are unforeseen operating difficulties and expenditures in connection with business acquisitions or strategic alliances, we may be required, from time to time, to recognize charges, which could be substantial and which could adversely affect our results of operations.

We actively manage a portfolio of research and development products, and we regularly explore potential acquisitions of complementary businesses, technologies, services, or products, as well as potential strategic alliances. From time to time, we identify operations and products that are underperforming, do not fit with our longer-term business strategy or there may be unforeseen operating difficulties and significant expenditures during the integration of an acquired business, technology, service, or product into our existing operations. We may seek to dispose of these underperforming operations or products, and we may also seek to dispose of other operations or products for strategic or other business reasons. If we cannot dispose of an operation or product on acceptable terms, we may voluntarily cease operations related to that product. In addition, we may be required to take charges or write-downs in connection with acquisitions and divestitures. In particular, acquisitions of businesses engaged in the development of new products may give rise to developed technology and/or in-process research and development assets. To the extent that the value of these assets decline, we may be required to write down the value of the assets. Also, in connection with certain asset acquisitions, we may be required to take an immediate charge related to acquired in-process research and development assets. Any of these events could result in charges, which could be substantial and which could adversely affect our results of operations.

The success of many of our products depends upon certain key physicians.

We work with leading global physicians who provide considerable knowledge and experience. These physicians may assist us as researchers, marketing consultants, product trainers and consultants, inventors, and as public speakers. If new laws, regulations, or other developments limit our ability to appropriately engage these professionals or to continue to receive their advice and input or we are otherwise unsuccessful in maintaining strong working relationships with these physicians, the development, marketing, and successful use of our products could suffer, which could have a material adverse effect on our business, financial condition, and results of operations.

If we or one of our suppliers or logistics partners encounters manufacturing, logistics, or quality problems, our business could be materially adversely affected.

The manufacture and sterilization of many of our products is highly complex due in part to rigorous regulatory requirements. Quality is extremely important due to the serious and costly consequences of a product failure. Problems can arise for a number of reasons, including disruption of facility utilities, equipment malfunction, failure to follow protocols and procedures, raw material problems, software problems, cyber incidents, or human error. Disruptions can occur at any time, including during production line transfers and expansions. Disruptions can also occur if our manufacturing and warehousing facilities are damaged by earthquakes, hurricanes, volcanoes, fires, and other natural disasters or catastrophic circumstances. As we expand into new markets and scale new products for commercial production, we may face unanticipated delays or surges in demand which could strain our production capacity and lead to other types of disruption. If any of these manufacturing, logistics, or quality problems arise or if we or one of our suppliers or logistics partners otherwise fail to meet internal quality standards or those of the FDA or other applicable regulatory body, our reputation could be damaged, we could become subject to a safety alert or a recall, we could incur product liability and other costs, product approvals and production could be delayed, and our business could otherwise be materially adversely affected.

We rely on third parties in the design, manufacture, and sterilization of our products. Any failure by or loss of a vendor could result in delays and increased costs, which may adversely affect our business.

We rely on third parties for a broad range of raw and organic materials and other items in the design, manufacture, and sterilization of our products, and we purchase certain supplies and services from single sources for reasons of quality assurance, cost-effectiveness, availability, constraints resulting from regulatory requirements, and other reasons. We may experience supply interruptions due to a variety of factors, including:

- General economic conditions that could adversely affect the financial viability of our vendors;
- Vendors' election to no longer service medical technology companies due to the burdens of applicable quality requirements and regulations;
- The limitation or ban of certain chemicals or other materials used in the manufacture of our products; and
- Delays or shortages due to trade or regulatory embargoes.

A change or addition to our vendors could require significant effort due to the rigorous regulations and requirements of the FDA and other regulatory authorities; it could be difficult to establish additional or replacement sources on a timely basis or at all, which could have a material adverse effect on our business.

Failure to protect our information technology infrastructure and our products against cyber-based attacks, network security breaches, service interruptions, or data corruption could materially disrupt our operations and adversely affect our business and operating results.

The operation of our business depends on our information technology systems. We rely on our information technology systems to, among other things, effectively manage sales and marketing data, accounting and financial functions, inventory management, product development tasks, clinical data, customer service and technical support functions. Our information technology systems are vulnerable to damage or interruption from earthquakes, fires, floods and other natural disasters, terrorist attacks, power losses, computer system or data network failures, security breaches, and data corruption.

In addition, our information technology infrastructure and products are vulnerable to cyber-based attacks. Cyber-based attacks can include, but are not limited to, computer viruses, denial-of-service attacks, phishing attacks, ransomware attacks, and other introduction of malware to computers and networks; unauthorized access through the use of compromised credentials; exploitation of design flaws, bugs, or security vulnerabilities; intentional or unintentional acts by employees or other insiders with access privileges; and intentional acts of vandalism by third parties and sabotage. In addition, United States federal and state laws and regulations, and the laws and regulations of jurisdictions outside of the United States, such as the General Data Protection Regulation adopted by the European Union and the California Consumer Privacy Act, can expose us to investigations and enforcement actions by regulatory authorities and claims from individuals potentially resulting in penalties and significant legal liability, if our information technology security efforts are inadequate. In addition, we rely upon technology suppliers, including cloud-based data management applications hosted by third-party service providers, whose security and information technology systems are subject to similar risks.

Significant disruption in either our or our service providers' or suppliers' information technology or the security of our products could impede our operations or result in decreased sales, result in liability claims or regulatory penalties, or lead to increased overhead costs, product shortages, loss or misuse of proprietary or confidential information, intellectual property, or sensitive or personal information, all of which could have a material adverse effect on our reputation, business, financial condition, and operating results.

Our business and results of operations may be adversely affected if we are unable to recruit and retain qualified management and other personnel.

Our continued success depends, in large part, on our ability to hire and retain qualified people or otherwise have access to such qualified people globally and if we are unable to do so, our business and operations may be impaired or disrupted. See "*Human Capital Management Strategy*" under "*Business*" in Part I, Item 1 included herein. Competition for highly qualified people is intense, and there is no assurance that we will be successful in attracting or retaining replacements to fill vacant positions, successors to fill retirements or employees moving to new positions, or other highly qualified personnel.

Market and Other External Risks

Because we operate globally, our business is subject to a variety of risks associated with international sales and operations.

Our extensive global operations and business activity as well as the fact that many of our manufacturing facilities and suppliers are outside of the United States are accompanied by certain financial, economic, political, and other risks, including those listed below.

Domestic and Global Economic Conditions. We cannot predict to what extent general domestic and global economic conditions may negatively impact our business. These include, but are not limited to, credit and capital markets, interest rates, tax law, including tax rate and policy changes, factors affecting global economic stability, and the political environment relating to health care. These and other conditions could also adversely affect our customers, payers, vendors and other stakeholders and may impact their ability or decision to purchase our products or make payments on a timely basis.

Health Care Legislation and Other Regulations. We are subject to various federal and foreign laws that govern our domestic and international business practices. For example, in the United States, the Affordable Care Act, the Medicare Access and CHIP Reauthorization Act of 2015, and the 21st Century Cures Act, or any future legislation, including deficit reduction legislation, could impact medical procedure volumes, reimbursement for our products, and demand for our products or the prices at which we sell our products. In addition, a Mutual Recognition Agreement still under negotiation for the Medical Device Regulation can result in a lack of free movement of medical devices between the European Union and Switzerland, can impact our access in the European Union and can, ultimately, have a material effect on our business, financial condition, and results of operations. For more information about these laws as they relate to our business, see the section entitled "*Government Regulation and Other Matters*" in Part I, Item 1, "*Business*."

In addition, the United States Foreign Corrupt Practices Act, the United Kingdom Bribery Act, and similar laws in other jurisdictions contain prohibitions against bribery and other illegal payments, and make it an offense to fail to have procedures in place that prevent such payments. Penalties resulting from any violation of these laws could adversely affect us and our business.

Taxes. We are subject to income taxes in the United States as well as other jurisdictions.

- *Provision for Income Taxes.* Our provision for income taxes and our underlying effective tax rate could fluctuate due to changes in the mix of earnings and losses in countries with differing statutory tax rates. Our income tax provision could also be impacted by changes in excess tax benefits of stock-based compensation, federal and state tax credits, non-deductible expenses, changes in the valuation of deferred tax assets and liabilities and our ability to utilize them, the applicability and creditability of withholding taxes, and effects from acquisitions.

- *Tax Reform*. Our provision for income taxes could be materially impacted by changes in accounting principles or evolving tax laws, including, but not limited to, global corporate tax reform and base-erosion and tax transparency efforts. For example, many countries are aligning their international tax rules with the Organisation for Economic Co-operation and Development's Base Erosion and Profit Shifting recommendations and action plans that aim to standardize and modernize international corporate tax policy, including changes to cross-border taxes, transfer pricing documentation rules, nexus-based tax practices, and taxation of digital activities.

- *Tax Audits*. We are subject to ongoing tax audits in the various jurisdictions in which we operate. Tax authorities may disagree with certain positions we have taken and assess additional taxes. Although we regularly assess the likely outcomes of the audits and record reserves for potential tax payments, the calculation of tax liabilities involves the application of complex tax laws, and our estimates could be different than the amounts for which we are ultimately liable.

- *Tax Incentives*. We benefit from various global tax incentives extended to encourage investment or employment. Several foreign jurisdictions have granted us tax incentives which require renewal at various times in the future. If our incentives are not renewed or we cannot or do not wish to satisfy all or part of the tax incentive conditions, we may lose the tax incentives and could be required to refund tax incentives previously realized. As a result, our provision for income taxes could be higher than it would have been had we maintained the benefits of the tax incentives.

Other economic, political, and social risks. In addition to the factors enumerated above, we are from time to time impacted by a variety of other factors associated with doing business internationally that can harm our future results, including the following:

- trade protection measures, quotas, embargoes, import or export requirements, and duties, tariffs, or surcharges;

- cultural or other local factors affecting financial terms with customers;

- differing labor regulations; and

- currency exchange rate fluctuations; that is, decreases in the value of the United States dollar to the Euro or the Japanese yen, as well as other currencies, have the effect of increasing our reported revenues even when the volume of sales outside of the United States has remained constant. Increases in the value of the United States dollar relative to the Euro or the Japanese yen, as well as other currencies, have the opposite effect. Significant increases or decreases in the value of the United States dollar could have a material adverse effect on our revenues, cost of sales, or results of operations.

If government and other third-party payors decline to reimburse our customers for our products or impose other cost containment measures to reduce reimbursement levels, our ability to profitably sell our products will be harmed.

We sell our products and technologies to hospitals and other health care providers, nearly all of which receive reimbursement for the health care services provided to patients from third-party payors, such as government programs (both domestic and outside of the United States), private insurance plans, and managed care programs. The ability of customers to obtain appropriate reimbursement for their products from private and governmental third-party payors is critical to our success. The availability of reimbursement affects which products customers purchase and the prices they are willing to pay. Reimbursement varies from country to country and can significantly impact acceptance of new products.

Government and other third-party payors are increasingly attempting to contain health care costs by limiting both coverage and the level of reimbursement for medical products and services. Reimbursement levels may be decreased in the future. Additionally, future legislation, regulation, or reimbursement policies of third-party payors may otherwise adversely affect the demand for and price levels of our products. The introduction of cost containment incentives, combined with closer scrutiny of health care expenditures by both private health insurers and employers, has resulted in increased discounts and contractual adjustments to hospital charges for services performed. Hospitals or physicians may respond to such cost-containment pressures by substituting lower cost products or other therapies.

Third-party payors may deny reimbursement if they determine that a device used in a procedure was not used in accordance with cost-effective treatment methods as determined by such third-party payors or was used for an unapproved indication. Third-party payors may also deny reimbursement for experimental procedures and devices. We believe that many of our existing products are cost-effective, even though the one-time cost may be significant, because they are intended to improve quality of life and reduce overall health care costs over a long period of time. We cannot be certain that these third-party payors will recognize these cost savings and quality of life benefits instead of merely focusing on the lower initial costs associated with competing therapies. If our products are not considered cost-effective by third-party payors, our customers may not be reimbursed for them, resulting in lower sales of our products.

Continued consolidation in the health care industry could have an adverse effect on our sales and results of operations.

The health care industry has been consolidating, and organizations such as GPOs, independent delivery networks, and large single accounts, such as the United States Veterans Administration, continue to consolidate purchasing decisions for many of our health care provider customers. As a result, transactions with customers are larger and more complex, and tend to involve more long-term contracts. The purchasing power of these larger customers has increased, and may continue to increase, causing downward pressure on product pricing. If we are not one of the providers selected by one of these organizations, we may be precluded from making sales to its members or participants. Even if we are one of the selected providers, we may be at a disadvantage relative to other selected providers that are able to offer volume discounts based on purchases of a broader range of medical equipment and supplies. Further, we may be required to commit to pricing that has a material adverse effect on our revenues, profit margins, business, financial condition, and results of operations. We expect that market demand, governmental regulation, third-party reimbursement policies, and societal pressures will continue to drive consolidation and increase pricing pressure.

Legal, Compliance, and Regulatory Risks

Our inability to protect our intellectual property or failure to maintain the confidentiality and integrity of data or other sensitive company information, by cyber-attack or other event, could have a material adverse effect on our business.

Our success and competitive position are dependent in part upon our ability to protect our proprietary intellectual property through a combination of patents and trade secrets. We cannot guarantee that the protective steps we take are adequate to protect these rights:

- Patents issued to or licensed by us in the past or in the future may be challenged and held invalid.
- As our patents expire, we may be unsuccessful in extending their protection through patent term extensions.
- Confidentiality agreements with certain employees, consultants, and other third parties intended to protect, in part, trade secrets and other proprietary information could be breached, and we may not have adequate remedies.
- Others could independently develop substantially equivalent proprietary information or gain access to our trade secrets or proprietary information, design around our technology, or develop competing technologies.
- Our intellectual property, other proprietary technology, and other sensitive company information is dependent on sophisticated information technology systems and is potentially vulnerable to cyber-attacks, loss, theft, damage, destruction from system malfunction, computer viruses, loss of data privacy, or misappropriation or misuse of it by those with permitted access, and other events.
- We may not detect infringement.
- Intellectual property protection may also be unavailable or limited in some foreign countries.

We spend significant resources to protect and enforce our intellectual property rights, sometimes resulting in expensive and time-consuming litigation that is complex and may ultimately be unsuccessful. Our inability to protect our intellectual property could have a material adverse effect on our business or prospects.

Third parties may claim we are infringing their intellectual property, and we could suffer significant litigation or licensing expenses or be prevented from selling products.

During recent years, we and our competitors have been involved in substantial litigation regarding patent and other intellectual property rights which is typically costly and time-consuming. We may be forced to defend against claims and legal actions alleging infringement of the intellectual property rights of others, and, if our defense is unsuccessful, we could have significant liabilities to third parties or face injunctions that bar the sale of our products, or could require us to seek licenses from third parties. Such licenses may not be available on commercially reasonable terms, may prevent us from manufacturing, selling, or using certain products, or may be non-exclusive, which could provide our competitors access to the same technologies.

In addition, third parties could also obtain patents that may require us to either redesign products, negotiate licenses from such third parties, which may be costly, unavailable or require us to exit a particular product offering.

We and our customers are subject to rigorous governmental regulations and we may incur significant expenses to comply with these regulations and develop products that are compatible with these regulations. In addition, failure to comply with these regulations could subject us to substantial sanctions which could adversely affect our business, results of operations, and financial condition.

The medical technologies we create, study, manufacture and market globally are subject to rigorous regulation and scrutiny by the FDA and various other federal, state, and foreign governmental authorities. Government regulation applies to nearly all aspects of our products' lifecycles, including testing, clinical study, manufacturing, transporting, sourcing, safety, labeling, storing, packaging, recordkeeping, reporting, advertising, promoting, distributing, marketing, and importing or exporting of medical devices and products. In general, unless an exemption applies, a medical device or product must receive regulatory approval or clearance before it can be marketed or sold. Modifications to existing products or the marketing of new uses for existing products also may require regulatory approvals, approval supplements, or clearances. If we are unable to obtain these required approvals, we may be required to cease manufacturing and sale, or recall or restrict the use of such modified device, pay fines, or take other action until such time as appropriate clearance or approval is obtained.

Regulatory agencies may refuse to grant approval or clearance, or review and disagree with our interpretation of approvals or clearances, or with our decision that regulatory approval is not required or has been maintained. Regulatory submissions may require the provision of additional data and may be time consuming and costly, and their outcome is uncertain. Regulatory agencies may also change policies, adopt additional regulations, or revise existing regulations, each of which could prevent or delay approval or clearance of devices, or could impact our ability to market a previously cleared, approved, or unregulated device. Our failure to comply with these regulatory requirements of the FDA or other applicable regulatory requirements in the United States or elsewhere might subject us to administratively or judicially imposed sanctions. These sanctions include, among others, warning letters, fines, civil penalties, criminal penalties, injunctions, debarment, product seizure or detention, product recalls and total or partial suspension of production, sale and/or promotion. Any of the foregoing actions could result in decreased sales including as a result of negative publicity and product liability claims, and could have a material adverse effect on our financial condition, results of operations, and prospects. In addition to the sanctions for noncompliance described above, commencement of an enforcement proceeding, inspection, or investigation could divert substantial management attention from the operation of our business and have an adverse effect on our business, results of operations, and financial condition.

We are also subject to various United States and foreign laws pertaining to health care pricing, anti-corruption, and fraud and abuse, including prohibitions on kickbacks and the submission of false claims laws and restrictions on relationships with physicians and other referral sources. These laws are broad in scope and are subject to evolving interpretation, which could require us to incur substantial costs to monitor compliance. If we are found not to be in compliance, we may be required to alter our practices or have sanctions imposed against us and our officers and employees, including substantial fines, imprisonment, and exclusion from participation in governmental health care programs.

In addition, as a global company, we are subject to global data privacy and security laws, regulations and codes of conduct that apply to our businesses. We are required to comply with increasingly complex and changing legal and regulatory requirements that govern the collection, use, storage, security, transfer, disclosure and other processing of personal data in the United States and in other countries, which may include, but are not limited to, The Health Insurance Portability and Accountability Act, as amended ("HIPAA"), The Health Information Technology for Economic and Clinical Health Act, the California Consumer Privacy Act ("CCPA"), and the European Union's General Data Protection Regulation ("GDPR"). The GDPR imposes stringent European Union data protection requirements and provides for significant penalties for noncompliance. HIPAA also imposes stringent data privacy and security requirements and the regulatory authority has imposed

significant fines and penalties on organizations found to be out of compliance. CCPA provides consumers with a private right of action against companies who have a security breach due to lack of appropriate security measures. We or our third-party providers and business partners may also be subjected to audits or investigations by one or more domestic or foreign government agencies relating to compliance with information security and privacy laws and regulations, and noncompliance with the laws and regulations could result in substantial and material fines or class action litigation.

Additional risks related to government regulation are also described under "*Health Care Legislation and Other Regulations*" in the risk factor above titled "*Because we operate globally, our business is subject to a variety of risks associated with international sales and operations.*"

We may incur losses from product liability or other claims that could adversely affect our operating results.

Our business exposes us to potential product liability risks that are inherent in the design, manufacture, and marketing of medical technologies. Our products are often used in surgical and intensive care settings with seriously ill patients. In addition, many of the devices we manufacture and sell are designed to be implanted in the human body for long periods of time. Component failures, manufacturing and assembly flaws, design defects, software defects, medical procedure errors, or inadequate disclosure of product-related risks or information could result in an unsafe condition, injury to, or death of, patients. Such problems could result in product liability, medical malpractice or other lawsuits and claims, safety alerts, or product recalls in the future. We establish reserves and may incur charges in excess of those reserves. Although we maintain product liability and other insurance with coverages we believe are adequate, product liability or other claims may exceed insurance coverage limits, fines, and penalties. In addition, regulatory sanctions may not be covered by insurance, or insurance may not continue to be available or available on commercially reasonable terms. These litigation matters and regulatory actions, recalls or other actions, regardless of outcome, could have a material adverse effect on our business, reputation, and ability to attract and retain customers.

Use of our products in unapproved circumstances could expose us to liabilities.

The marketing approval from the FDA and other regulators of certain of our products are, or are expected to be, limited to specific indications. We are prohibited from marketing or promoting any unapproved use of our products. Physicians, however, can use these products in ways or circumstances other than those strictly within the scope of the regulatory approval. Although the product training we provide to physicians and other health care professionals is conducted in compliance with applicable laws, and therefore, is mainly limited to approved uses or for clinical trials, no assurance can be given that claims might not be asserted against us if our products are used in ways or for procedures that are not approved.

Our operations are subject to environmental, health, and safety regulations that could result in substantial costs.

Our operations are subject to environmental, health, and safety laws, and regulations concerning, among other things, the generation, handling, transportation, and disposal of hazardous substances or wastes, the cleanup of hazardous substance releases, and emissions or discharges into the air or water. We have incurred and may incur in the future expenditures in connection with environmental, health and safety laws, and regulations. New laws and regulations, violations of these laws or regulations, stricter enforcement of existing requirements, or the discovery of previously unknown contamination could require us to incur costs or could become the basis for new or increased liabilities that could be material.

Climate change, or legal, regulatory or market measures to address climate change, may materially adversely affect our financial condition and business operations.

Climate change resulting from increased concentrations of carbon dioxide and other greenhouse gases in the atmosphere could present risks to our future operations from natural disasters and extreme weather conditions, such as hurricanes, tornadoes, seismic events, wildfires, or flooding. Such extreme weather conditions could pose physical risks to our facilities and disrupt operation of our supply chain and may impact operational costs. Concern over climate change could result in new legal or regulatory requirements designed to mitigate the effects of climate change on the environment. If such laws or regulations are more stringent than current legal or regulatory requirements, we may experience increased compliance burdens and costs to meet the regulatory obligations, and it may adversely affect our raw material sourcing, manufacturing operations, and the distribution of our products.

We are subject to risks arising from concerns and/or regulatory actions relating to animal borne illnesses, including "mad cow disease."

Certain of our products, including pericardial tissue valves, are manufactured using bovine tissue. Concerns relating to the potential transmission of animal borne illnesses, including BSE, commonly known as "mad cow disease," from cows to humans may result in reduced acceptance of products containing bovine materials. Certain medical device regulatory agencies have considered whether to continue to permit the sale of medical devices that incorporate bovine material. We obtain bovine tissue

only from closely controlled sources within the United States and Australia. The bovine tissue used in our pericardial tissue valves is from tissue types considered by global health and regulatory organizations to have shown no risk of infectibility for the suspected BSE infectious agent. We have not experienced any significant adverse impact on our sales as a result of concerns regarding BSE, but no assurance can be given that such an impact may not occur in the future.

Item 1B. Unresolved Staff Comments

None.

Item 2. Properties

The locations and uses of our major properties are as follows:

North America		
Irvine, California	(1)	Corporate Headquarters, Research and Development, Regulatory and Clinical Affairs, Manufacturing, Marketing, Administration
Draper, Utah	(1),(2)	Manufacturing, Administration
Haina, Dominican Republic	(1),(2)	Manufacturing
Añasco, Puerto Rico	(2)	Manufacturing
Central America		
Cartago, Costa Rica	(1),(2)	Manufacturing
Europe		
Nyon, Switzerland	(1)	Administration, Marketing
Prague, Czech Republic	(2)	Administration
Shannon, Limerick, Ireland	(1),(2)	Manufacturing
Asia		
Singapore	(1),(2)	Manufacturing, Distribution, Administration
Tokyo, Japan	(2)	Administration, Marketing, Distribution
Shanghai, China	(2)	Administration, Marketing
Caesarea, Israel	(2)	Research and Development

(1) Owned property.

(2) Leased property.

The Draper, Utah lease expires in 2031; the Dominican Republic lease expires in 2022; the Puerto Rico property has two leases that expire in 2023; the Costa Rica lease expires in 2026; the Prague, Czech Republic lease expires in 2026; the Shannon, Ireland lease expires in 2024; the Tokyo, Japan lease expires in 2024; the Shanghai, China lease expires in 2024; Singapore has one land lease that expires in 2036 and one that expires in 2041; and the Caesarea, Israel lease expires in 2030. We believe our properties have been well maintained, are in good operating condition, and are adequate for current needs. We do not anticipate difficulty in renewing existing leases as they expire or in finding alternative facilities.

Item 3. Legal Proceedings

For a description of our material pending legal proceedings, please see Note 18 to the "*Consolidated Financial Statements*" of this Annual Report on Form 10-K, which is incorporated by reference.

Item 4. Mine Safety Disclosures

Not applicable.

PART II

Item 5. Market for Registrant's Common Equity, Related Stockholder Matters and Issuer Purchases of Equity Securities

Market Information

Our common stock is traded on the New York Stock Exchange (the "NYSE") under the symbol "EW."

Number of Stockholders

On January 31, 2022, there were 8,413 stockholders of record of our common stock.

Dividends

We have never paid any cash dividends on our capital stock and have no current plans to pay any cash dividends. Our current policy is to retain any future earnings for use in our business.

Issuer Purchases of Equity Securities

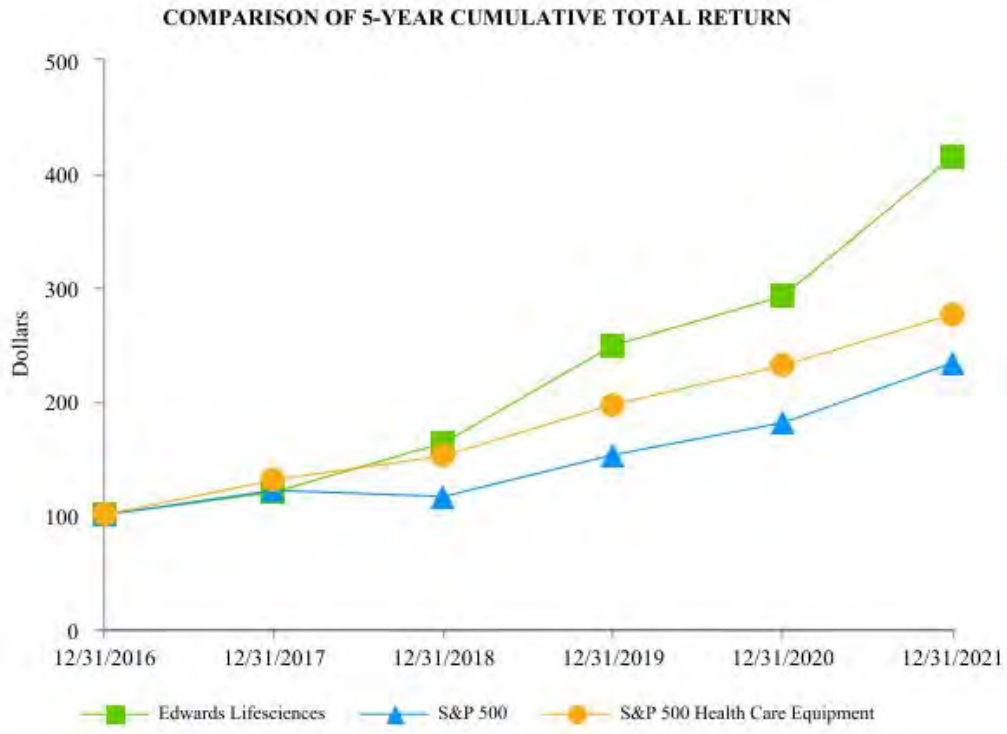
Period	Total Number of Shares (or Units) Purchased (a)	Average Price Paid per Share (or Unit)	Total Number of Shares (or Units) Purchased as Part of Publicly Announced Plans or Programs	Maximum Number (or Approximate Dollar Value) of Shares that May Yet Be Purchased Under the Plans or Programs (in millions) (b)
October 1, 2021 through October 31, 2021	—	$ —	—	$ 1,222.7
November 1, 2021 through November 30, 2021	458,862	114.46	456,745	1,170.4
December 1, 2021 through December 31, 2021	401,444	109.58	401,444	1,126.4
Total	860,306	112.18	858,189	

(a) The difference between the total number of shares (or units) purchased and the total number of shares (or units) purchased as part of publicly announced plans or programs is due to shares withheld by us to satisfy tax withholding obligations in connection with the vesting of restricted stock units issued to employees.

(b) On May 8, 2019, the Board of Directors approved a stock repurchase program authorizing us to purchase up to $1.0 billion of our common stock. On May 4, 2021, the Board of Directors approved a new stock repurchase program providing for an additional $1.0 billion of repurchases of our common stock. Repurchases under the programs may be made on the open market, including pursuant to a Rule 10b5-1 plan, and in privately negotiated transactions. These repurchase programs do not have an expiration date.

Performance Graph

The following graph compares the performance of our common stock with that of the S&P 500 Index and the S&P 500 Health Care Equipment Index. The cumulative total return listed below assumes an initial investment of $100 at the market close on December 31, 2016 and reinvestment of dividends. Stockholder returns over the indicated period should not be considered indicative of future stockholder returns.



	Total Cumulative Return				
	2017	2018	2019	2020	2021
Edwards Lifesciences	**$ 120.29**	**$ 163.47**	**$ 248.98**	**$ 292.09**	**$ 414.78**
S&P 500	**121.83**	**116.49**	**153.17**	**181.35**	**233.41**
S&P 500 Health Care Equipment	**130.90**	**152.15**	**196.77**	**231.46**	**276.26**

Item 6. [Reserved]

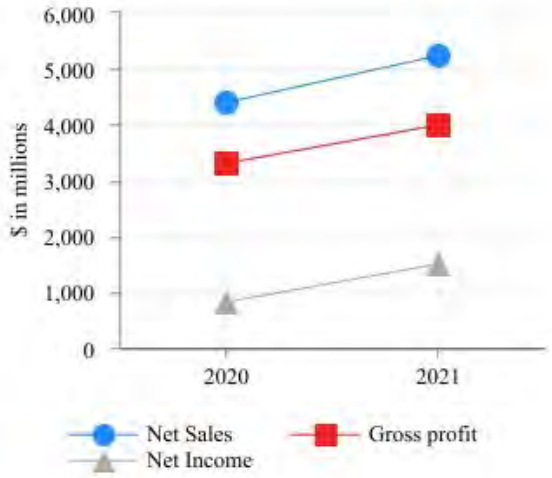
Item 7. Management's Discussion and Analysis of Financial Condition and Results of Operations

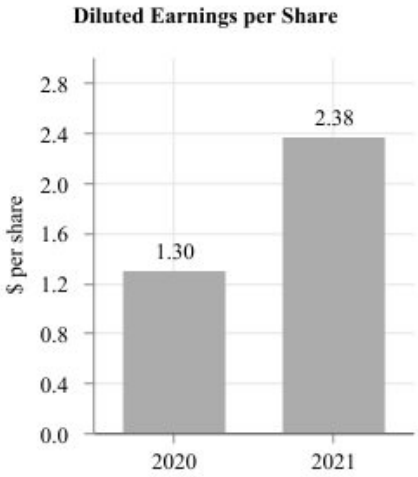
The following discussion and analysis presents the factors that had a material effect on our results of operations during the two years ended December 31, 2021. Also discussed is our financial position as of December 31, 2021. You should read this discussion in conjunction with the historical consolidated financial statements and related notes included elsewhere in this Form 10-K. For a discussion related to the results of operations for 2020 compared to 2019 and a discussion related to our consolidated cash flows for 2020 compared to 2019, refer to Part II, Item 7, "*Management's Discussion and Analysis of Financial Condition and Results of Operations*" in our 2020 Annual Report on Form 10–K filed with the Securities and Exchange Commission on February 12, 2021.

Overview

We are the global leader in patient-focused medical innovations for structural heart disease and critical care monitoring. Driven by a passion to help patients, we partner with the world's leading clinicians and researchers and invest in research and development to transform care for those impacted by structural heart disease or who require hemodynamic monitoring during surgery or in intensive care. We conduct operations worldwide and are managed in the following geographical regions: United States, Europe, Japan, and Rest of World. Our products are categorized into the following areas: Transcatheter Aortic Valve Replacement ("TAVR"), Transcatheter Mitral and Tricuspid Therapies ("TMTT"), Surgical Structural Heart ("Surgical"), and Critical Care.

Financial Highlights and COVID-19





The COVID-19 pandemic has adversely impacted, and may further adversely impact, nearly all aspects of our business and markets, including our workforce and the operations of our customers, suppliers, and business partners. Our priority has been to maintain access for patients to our life-saving technologies while providing continuous front-line support to our clinician partners, and protecting the well-being of our employees. Our manufacturing operations have continued to respond to impacts related to COVID-19, and we have been able to supply our technologies around the world. Across the organization, we are proactively managing inventory, assessing alternative logistics options, and closely monitoring the supply of components.

TAVR and Surgical procedure volumes varied greatly since the middle of March 2020 by geography, and even by hospital, as patients and their physicians analyzed the trade-off between aortic stenosis and their concern for COVID-19. In the last few weeks of the first quarter of 2020, procedure volumes related to our TAVR and Surgical products dropped significantly. Beginning in the second quarter of 2020, procedure volumes improved. In the second quarter of 2020, we also started to progressively resume patient enrollment in all clinical trials that were voluntarily paused or slowed at the end of the first quarter of 2020. While we saw improvements to pre-COVID levels when we resumed enrollment, procedure volumes and enrollment in our clinical trials were negatively impacted in late 2020 due to a resurgence of COVID-19. In Critical Care, during 2020 there was greater demand in Europe and the United States for our pressure monitoring products, but demand for

other Critical Care products began to decrease at the end of the first quarter of 2020 due to decreased hospital spending related to COVID-19, and that trend continued through the fourth quarter of 2020.

During the first quarter of 2021, COVID-19 stressed the global healthcare system during the winter months. However, we saw strong recovery beginning in the second quarter of 2021 as widespread vaccine adoption contributed to an increased number of patients. However, the Delta variant had a significant impact on hospital resources during the last two months of the third quarter of 2021, and the Omicron variant had a significant impact during December 2021, especially in the United States.

Despite the challenges associated with COVID-19, our net sales for 2021 were $5.2 billion, representing an increase of $846.2 million over 2020, driven by sales growth of our TAVR products. During the first half of 2021, United States TAVR procedures began to grow as COVID-19 hospitalizations decreased and vaccinations increased. However, TAVR sales were negatively impacted in the second half of 2021 as United States procedures declined due to the significant impact the Delta and Omicron variants had on hospital resources. Surgical sales grew during 2021 due to increased adoption of our premium high-value technologies around the world and rebounding surgical aortic treatment rates in the United States. We also saw an increased demand for our Critical Care products in 2021 as hospital capital spending continued to show signs of recovery and elevated COVID hospitalizations in the United States and Europe increased demand for our pressure monitoring devices.

Our gross profit increase in 2021 was driven by our sales growth and lower incremental costs associated with COVID-19. The increase in our diluted earnings per share in 2021 was driven by our gross profit increase and an after-tax charge of $305.1 million in 2020 to settle certain patent litigation related to transcatheter mitral and tricuspid repair products.

We are closely monitoring the impact of COVID-19 on all aspects of our business and geographies, including its impact on our customers, employees, suppliers, vendors, business partners and distribution channels. The extent to which COVID-19 and measures taken in response thereto impact our business, results of operations, and financial condition will depend on future developments, which are highly uncertain and are difficult to predict. These developments include, but are not limited to, the duration and spread of the outbreak (including new and more contagious variants of COVID-19), its severity, the actions to contain the virus or address its impact, the timing, distribution, public acceptance and efficacy of vaccines and other treatments, United States and foreign government actions to respond to the reduction in global economic activity, and how quickly and to what extent normal economic and operating conditions can resume. Even after the COVID-19 outbreak has subsided, we may continue to experience materially adverse impacts on our financial condition and results of operations.

Healthcare Environment, Opportunities, and Challenges

The medical technology industry is highly competitive and continues to evolve. Our success is measured both by the development of innovative products and the value we bring to our stakeholders. We are committed to developing new technologies and providing innovative patient care, and we are committed to defending our intellectual property in support of those developments. Despite the challenges of the COVID-19 pandemic, our dedicated field teams found creative ways to support physicians, our engineers continued to advance innovation, and our colleagues worked diligently to keep our clinical trials on track. In 2021, we invested 17.3% of our net sales in research and development. The following is a summary of important developments during 2021:

- we received United States Food and Drug Administration ("FDA") clearance for the *Acumen Hypotension Prediction Index* software with the *Acumen IQ* finger cuff. This is the first noninvasive solution that uses machine learning to alert clinicians of the likelihood a patient is trending toward hypotension, or low blood pressure;
- we received FDA approval for the use of the *Edwards SAPIEN 3* transcatheter valve with the *Alterra* adaptive prestent for patients with severe pulmonary regurgitation;
- we completed enrollment in EARLY TAVR, a pivotal trial studying the treatment of severe aortic stenosis patients before their symptoms develop, and CLASP IID, a pivotal trial studying *Edwards PASCAL* in patients with degenerative mitral regurgitation;
- we received CE Mark approval to begin treating patients with a previously repaired or replaced valve in the pulmonic position;
- we received regulatory approval in Japan for our *MITRIS* valve, a new mitral valve incorporating *RESILIA* technology; and
- we received FDA approval for our ALLIANCE pivotal trial to study our next generation TAVR technology, *SAPIEN X4*.

We are dedicated to generating robust clinical, economic, and quality-of-life evidence increasingly expected by patients, clinicians, and payors in the current healthcare environment, with the goal of encouraging the adoption of innovative new medical therapies that demonstrate superior outcomes.

Results of Operations

Net Sales by Major Regions
(dollars in millions)

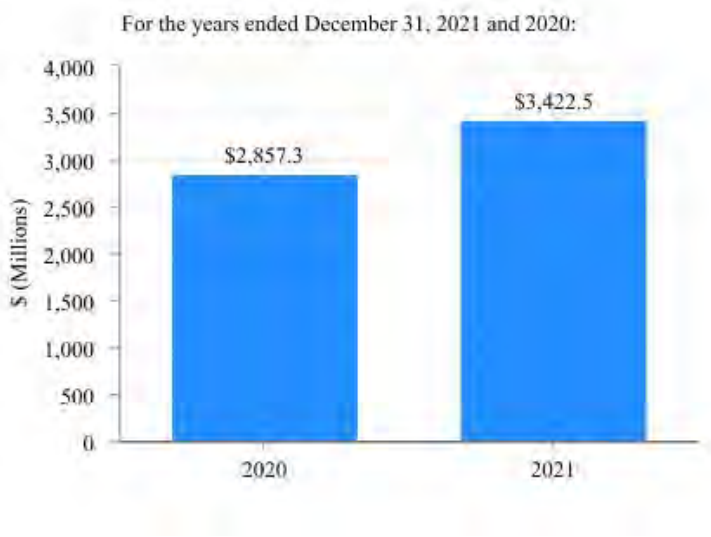
	Years Ended December 31,		Change	
	2021	2020	$	%
United States	$ 2,963.1	$ 2,516.8	$ 446.3	17.7 %
Europe	1,190.3	973.6	216.7	22.3 %
Japan	528.9	460.1	68.8	15.0 %
Rest of World	550.2	435.8	114.4	26.3 %
Outside of the United States	2,269.4	1,869.5	399.9	21.4 %
Total net sales	$ 5,232.5	$ 4,386.3	$ 846.2	19.3 %

Net sales outside of the United States include the impact of foreign currency exchange rate fluctuations. The impact of foreign currency exchange rate fluctuations on net sales is not necessarily indicative of the impact on net income due to the corresponding effect of foreign currency exchange rate fluctuations on international manufacturing and operating costs, and our hedging activities. For more information, see *"Quantitative and Qualitative Disclosures About Market Risk."*

Net Sales by Product Group
(dollars in millions)

	Years Ended December 31,		Change	
	2021	2020	$	%
Transcatheter Aortic Valve Replacement	$ 3,422.5	$ 2,857.3	$ 565.2	19.8 %
Transcatheter Mitral and Tricuspid Therapies	86.0	41.8	44.2	105.5 %
Surgical Heart Valve Therapy	889.1	761.8	127.3	16.7 %
Critical Care	834.9	725.4	109.5	15.1 %
Total net sales	$ 5,232.5	$ 4,386.3	$ 846.2	19.3 %

Transcatheter Aortic Valve Replacement



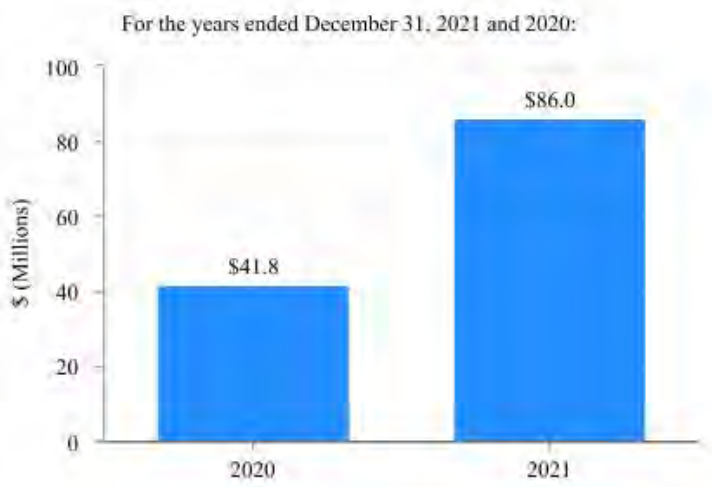
The increase in net sales of TAVR products was driven by:

- higher sales of the *Edwards SAPIEN* platform in 2021 in the United States, Europe, and Japan driven by improved COVID-19 conditions compared to 2020. Sales, however, were negatively impacted in the second half of 2021 as United States procedures declined due to the significant impact COVID had on hospital resources; and

- foreign currency exchange rate fluctuations, which increased net sales outside of the United States by $33.9 million primarily due to the strengthening of the Euro against the United States dollar.

In the second quarter of 2021, we (1) received approval for a United States pivotal trial for TAVR in moderate aortic stenosis patients, (2) received approval in Japan to begin treating low-risk patients with *SAPIEN 3*, and (3) received *SAPIEN 3* CE Mark approval to begin treating patients with a previously repaired or replaced valve in the pulmonic position. In the fourth quarter of 2021, we (1) completed enrollment of our EARLY TAVR pivotal trial, which is focused on the treatment of asymptomatic aortic stenosis patients, (2) initiated enrollment in our PROGRESS pivotal trial for moderate aortic stenosis patients, (3) received FDA approval for our ALLIANCE pivotal trial to study our next generation TAVR device, *SAPIEN X4*, and (4) received FDA approval for the use of the *Edwards SAPIEN 3* transcatheter valve with the *Alterra* adaptive prestent for congenital heart patients. The *Alterra* prestent compensates for variations in size and morphology of the right ventricular outflow tract to provide a stable landing zone for the *SAPIEN 3* valve.

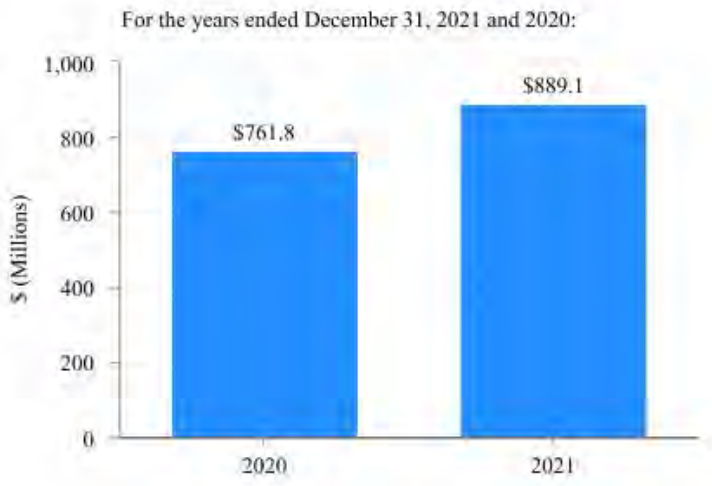
Transcatheter Mitral and Tricuspid Therapies



The increase in net sales of TMTT products was due primarily to improved COVID-19 conditions compared to 2020 and continued adoption of our *PASCAL* system in Europe.

In the fourth quarter of 2021, we completed enrollment of our CLASP IID pivotal trial studying *Edwards PASCAL* in patients with degenerative mitral regurgitation. We continued to treat patients with both of our transcatheter mitral replacement therapies through the ENCIRCLE trial for *SAPIEN M3* and the MISCEND study for *EVOQUE Eos.* The MISCEND study will evaluate the safety and performance of *EVOQUE Eos*, which is designed to advance the treatment of patients with mitral regurgitation with a low-profile valve delivered through a sub 30 French transfemoral delivery system. We also began treating patients with *EVOQUE* in the TRISCEND II pivotal trial. This study will evaluate the safety and effectiveness of the *EVOQUE* tricuspid valve replacement system for patients with severe tricuspid regurgitation.

Surgical Structural Heart

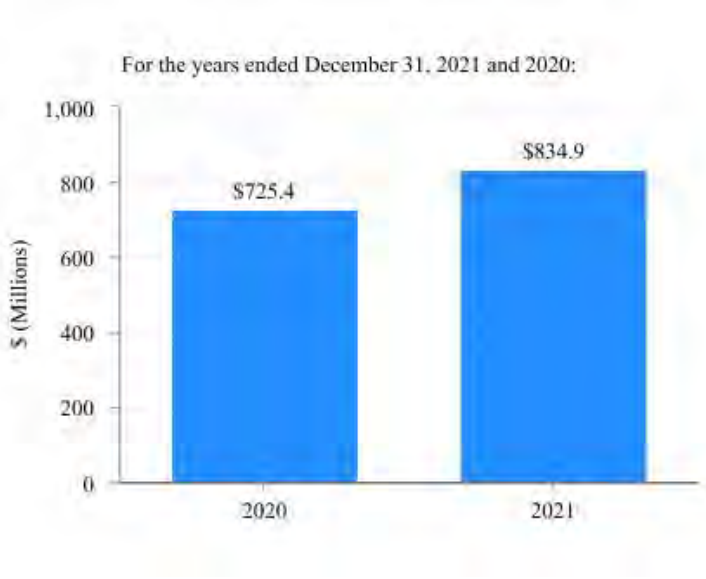


The increase in net sales of Surgical products was due primarily to improved COVID-19 conditions compared to 2020 and increased sales of the *INSPIRIS RESILIA* aortic valve and the *KONECT* aortic valved conduit, primarily in the United States. In

addition, foreign currency exchange rate fluctuations increased net sales outside of the United States by $13.1 million primarily due to the strengthening of the Euro against the United States dollar.

In January 2021, we received regulatory approval in Japan for our *MITRIS* valve, a new mitral valve incorporating *RESILIA* technology, which was launched in Japan during the second quarter of 2021.

Critical Care



The increase in net sales of Critical Care products was driven by:

- increased demand for our capital products, primarily *Hemosphere* platforms in the United States, as hospital capital spending continued to show signs of recovery;
- increased demand for our pressure monitoring products due to elevated COVID hospitalizations, primarily in the United States;
- increased demand for our enhanced surgical recovery products, primarily in the United States; and
- foreign currency exchange rate fluctuations, which increased net sales outside of the United States by $9.0 million primarily due to the strengthening of the Euro against the United States dollar.

In June 2021, we received FDA clearance for the *Acumen Hypotension Prediction Index* software with the *Acumen IQ* finger cuff. This is the first noninvasive solution that uses machine learning to alert clinicians of the likelihood a patient is trending toward hypotension, or low blood pressure.

Exhibit 23

CONSENT OF INDEPENDENT REGISTERED PUBLIC ACCOUNTING FIRM

We hereby consent to the incorporation by reference in the Registration Statements on Form S-8 (Nos. 333-33054, 333-33056, 333-40434, 333-52334, 333-52346, 333-60670, 333-98219, 333-105961, 333-127260, 333-150810, 333-154242, 333-168462, 333-183106, 333-192229, 333-195853, 333-204180, 333-211333, 333-217909, 333-255853, and 333-255854,) and Form S-3 (No. 333-232866) of Edwards Lifesciences Corporation of our report dated February 14, 2022 relating to the financial statements and the effectiveness of internal control over financial reporting, which appears in this Form 10-K.

/s/ PricewaterhouseCoopers LLP
Irvine, California
February 14, 2022

Exhibit 31.1

EDWARDS LIFESCIENCES CORPORATION
CERTIFICATIONS PURSUANT TO
SECTION 302 OF
THE SARBANES-OXLEY ACT OF 2002
CERTIFICATION

I, Michael A. Mussallem, certify that:

1. I have reviewed this annual report on Form 10-K of Edwards Lifesciences Corporation;

2. Based on my knowledge, this report does not contain any untrue statement of a material fact or omit to state a material fact necessary to make the statements made, in light of the circumstances under which such statements were made, not misleading with respect to the period covered by this report;

3. Based on my knowledge, the financial statements, and other financial information included in this report, fairly present in all material respects the financial condition, results of operations and cash flows of the registrant as of, and for, the periods presented in this report;

4. The registrant's other certifying officer(s) and I are responsible for establishing and maintaining disclosure controls and procedures (as defined in Exchange Act Rules 13a-15(e) and 15d-15(e)) and internal control over financial reporting (as defined in Exchange Act Rules 13a-15(f) and 15d-15(f)) for the registrant and have:

   (a) Designed such disclosure controls and procedures, or caused such disclosure controls and procedures to be designed under our supervision, to ensure that material information relating to the registrant, including its consolidated subsidiaries, is made known to us by others within those entities, particularly during the period in which this report is being prepared;

   (b) Designed such internal control over financial reporting, or caused such internal control over financial reporting to be designed under our supervision, to provide reasonable assurance regarding the reliability of financial reporting and the preparation of financial statements for external purposes in accordance with generally accepted accounting principles;

   (c) Evaluated the effectiveness of the registrant's disclosure controls and procedures and presented in this report our conclusions about the effectiveness of the disclosure controls and procedures, as of the end of the period covered by this report based on such evaluation; and

   (d) Disclosed in this report any change in the registrant's internal control over financial reporting that occurred during the registrant's most recent fiscal quarter (the registrant's fourth fiscal quarter in the case of an annual report) that has materially affected, or is reasonably likely to materially affect, the registrant's internal control over financial reporting; and

5. The registrant's other certifying officer(s) and I have disclosed, based on our most recent evaluation of internal control over financial reporting, to the registrant's auditors and the audit committee of the registrant's board of directors (or persons performing the equivalent functions):

   (a) All significant deficiencies and material weaknesses in the design or operation of internal control over financial reporting which are reasonably likely to adversely affect the registrant's ability to record, process, summarize and report financial information; and

   (b) Any fraud, whether or not material, that involves management or other employees who have a significant role in the registrant's internal control over financial reporting.

By: /s/ MICHAEL A. MUSSALLEM
Michael A. Mussallem
Chairman of the Board and Chief Executive Officer

February 14, 2022

Exhibit 31.2

EDWARDS LIFESCIENCES CORPORATION
CERTIFICATIONS PURSUANT TO
SECTION 302 OF
THE SARBANES-OXLEY ACT OF 2002
CERTIFICATION

I, Scott B. Ullem, certify that:

1. I have reviewed this annual report on Form 10-K of Edwards Lifesciences Corporation;

2. Based on my knowledge, this report does not contain any untrue statement of a material fact or omit to state a material fact necessary to make the statements made, in light of the circumstances under which such statements were made, not misleading with respect to the period covered by this report;

3. Based on my knowledge, the financial statements, and other financial information included in this report, fairly present in all material respects the financial condition, results of operations and cash flows of the registrant as of, and for, the periods presented in this report;

4. The registrant's other certifying officer(s) and I are responsible for establishing and maintaining disclosure controls and procedures (as defined in Exchange Act Rules 13a-15(e) and 15d-15(e)) and internal control over financial reporting (as defined in Exchange Act Rules 13a-15(f) and 15d-15(f)) for the registrant and have:

   (a) Designed such disclosure controls and procedures, or caused such disclosure controls and procedures to be designed under our supervision, to ensure that material information relating to the registrant, including its consolidated subsidiaries, is made known to us by others within those entities, particularly during the period in which this report is being prepared;

   (b) Designed such internal control over financial reporting, or caused such internal control over financial reporting to be designed under our supervision, to provide reasonable assurance regarding the reliability of financial reporting and the preparation of financial statements for external purposes in accordance with generally accepted accounting principles;

   (c) Evaluated the effectiveness of the registrant's disclosure controls and procedures and presented in this report our conclusions about the effectiveness of the disclosure controls and procedures, as of the end of the period covered by this report based on such evaluation; and

   (d) Disclosed in this report any change in the registrant's internal control over financial reporting that occurred during the registrant's most recent fiscal quarter (the registrant's fourth fiscal quarter in the case of an annual report) that has materially affected, or is reasonably likely to materially affect, the registrant's internal control over financial reporting; and

5. The registrant's other certifying officer(s) and I have disclosed, based on our most recent evaluation of internal control over financial reporting, to the registrant's auditors and the audit committee of the registrant's board of directors (or persons performing the equivalent functions):

   (a) All significant deficiencies and material weaknesses in the design or operation of internal control over financial reporting which are reasonably likely to adversely affect the registrant's ability to record, process, summarize and report financial information; and

   (b) Any fraud, whether or not material, that involves management or other employees who have a significant role in the registrant's internal control over financial reporting.

By: /s/ SCOTT B. ULLEM
Scott B. Ullem
Corporate Vice President,
Chief Financial Officer

February 14, 2022

Exhibit 32

EDWARDS LIFESCIENCES CORPORATION
CERTIFICATION PURSUANT TO
18 U.S.C. SECTION 1350,
AS ADOPTED PURSUANT TO
SECTION 906 OF THE SARBANES-OXLEY ACT OF 2002

In connection with the Annual Report of Edwards Lifesciences Corporation (the "Company") on Form 10-K for the year ended December 31, 2021 as filed with the Securities and Exchange Commission on the date hereof (the "Report"), we, Michael A. Mussallem, Chairman of the Board and Chief Executive Officer of the Company, and Scott B. Ullem, Corporate Vice President, Chief Financial Officer, certify, pursuant to 18 U.S.C. 1350, as adopted pursuant to Section 906 of the Sarbanes-Oxley Act of 2002, that:

(1) The Report fully complies with the requirements of section 13(a) or 15(d) of the Securities Exchange Act of 1934; and

(2) The information contained in the Report fairly presents, in all material respects, the financial condition and results of operations of the Company.

/s/ MICHAEL A. MUSSALLEM
Michael A. Mussallem
Chairman of the Board and Chief Executive Officer

February 14, 2022

/s/ SCOTT B. ULLEM
Scott B. Ullem
Corporate Vice President,
Chief Financial Officer

February 14, 2022

EXHIBIT 54

Transcatheter Aortic Valve Replacement

Larry L. Wood
Corporate Vice President
Transcatheter Aortic Valve Replacement

Edwards

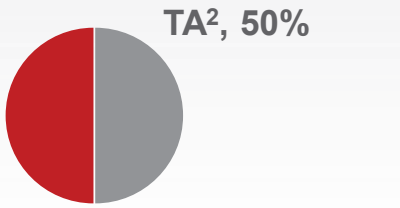
Over a decade ago, we set out to establish new frontiers in heart valve therapy

Original SAPIEN System used in PARTNER Study







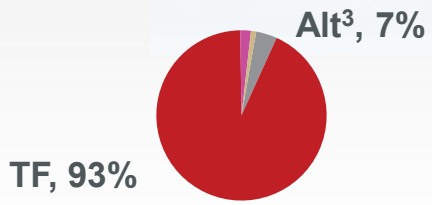


SAPIEN 3 Ultra System









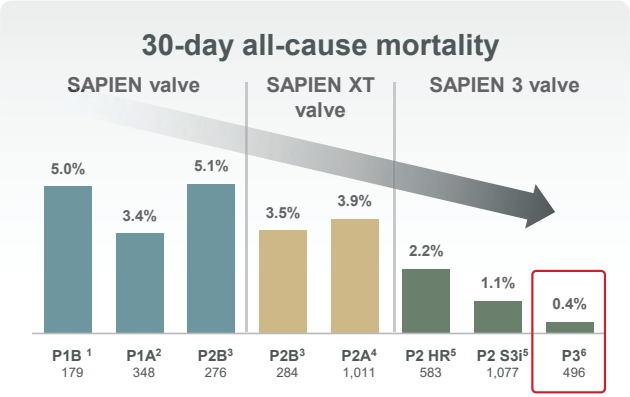
Over 600,000 patients treated with SAPIEN platform

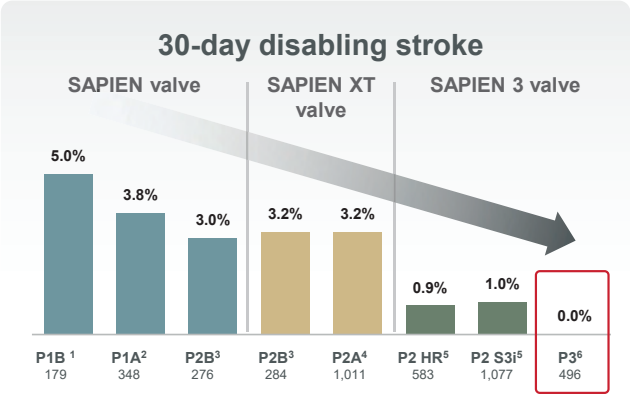
1. TF = Transfemoral; 2. TA = Transapical; 3. Alt = Alternative Access

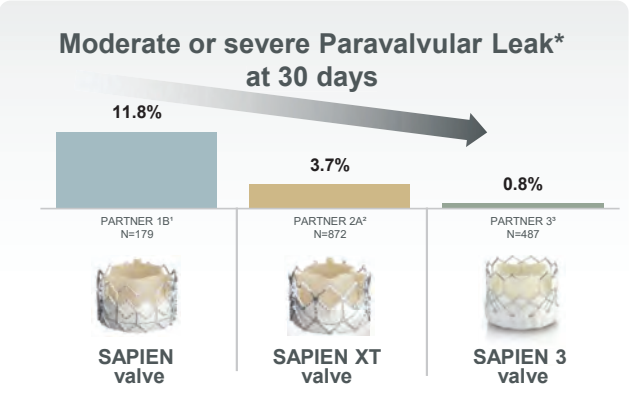
Where we are today

	THE PARTNER TRIAL 2011	THE PARTNER 3 TRIAL 2019
All-cause Death	3.4%	1%
All-Stroke	5.5%	1.2%
Major Vascular Complications	11%	2%
Index Hospitalization	8 days	3 days
	At 30-days	At 1-year

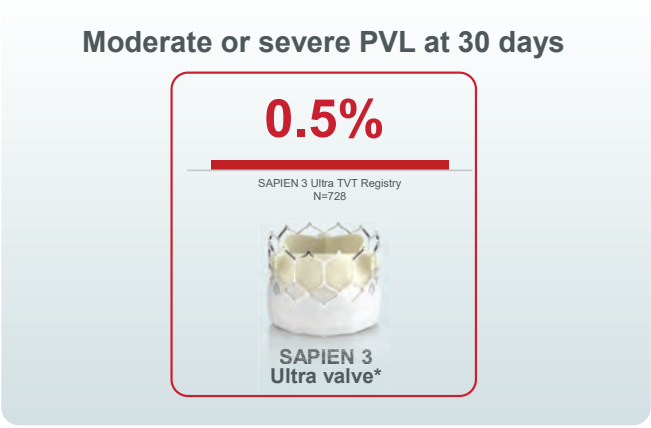
We have made significant progress







SAPIEN 3 Ultra has further elevated the benchmark of SAPIEN Platform



SAPIEN 3 Ultra now accounts for **92%** of global sales

For references 1 through 6, see supplemental slides
** Nazif T, Daniels D, McCabe J, Chehab B, et al. Real-world experience with the SAPIEN 3 Ultra TAVI: A propensity matched analysis from the United States. Presented virtually at TVT Connect 2020.*

EXHIBIT 55

Table of Contents

UNITED STATES
SECURITIES AND EXCHANGE COMMISSION
Washington, D.C. 20549

FORM 10-K

(Mark One)

☒ **ANNUAL REPORT PURSUANT TO SECTION 13 OR 15(d) OF THE SECURITIES EXCHANGE ACT OF 1934**

For the Fiscal Year Ended December 31, 2022
OR

☐ **TRANSITION REPORT PURSUANT TO SECTION 13 OR 15(d) OF THE SECURITIES EXCHANGE ACT OF 1934**

For the Transition Period From to
Commission File Number 1-15525

EDWARDS LIFESCIENCES CORPORATION
(Exact name of registrant as specified in its charter)

Delaware			**36-4316614**
(State or other jurisdiction of incorporation or organization)			(I.R.S. Employer Identification No.)
One Edwards Way	**Irvine**	**California**	**92614**
(Address of Principal Executive Offices)			(Zip Code)

(949) 250-2500
Registrant's telephone number, including area code

Securities registered pursuant to Section 12(b) of the Act:

Title of each class	**Trading Symbols(s)**	**Name of each exchange on which registered:**
Common Stock, par value $1.00 per share	EW	New York Stock Exchange

Securities registered pursuant to Section 12(g) of the Act: None

Indicate by check mark if the registrant is a well-known seasoned issuer, as defined by Rule 405 of the Securities Act. Yes ☒ No ☐

Indicate by check mark if the registrant is not required to file reports pursuant to Section 13 or 15(d) of the Exchange Act. Yes ☐ No ☒

Indicate by check mark whether the registrant (1) has filed all reports required to be filed by Section 13 or 15(d) of the Securities Exchange Act of 1934 during the preceding 12 months (or for such shorter period that the registrant was required to file such reports), and (2) has been subject to such filing requirements for the past 90 days. Yes ☒ No ☐

Indicate by check mark whether the registrant has submitted electronically every Interactive Data File required to be submitted pursuant to Rule 405 of Regulation S-T (§232.405 of this chapter) during the preceding 12 months (or for such shorter period that the registrant was required to submit such files). Yes ☒ No ☐

Indicate by check mark whether the registrant is a large accelerated filer, an accelerated filer, a non-accelerated filer, a smaller reporting company, or an emerging growth company. See the definitions of "large accelerated filer," "accelerated filer," "smaller reporting company," and "emerging growth company" in Rule 12b-2 of the Exchange Act.

Large accelerated filer	Accelerated filer	Non-accelerated filer	Smaller reporting company	Emerging growth company
☒	☐	☐	☐	☐

If an emerging growth company, indicate by check mark if the registrant has elected not to use the extended transition period for complying with any new or revised financial accounting standards provided pursuant to Section 13(a) of the Exchange Act. ☐

Indicate by check mark whether the registrant has filed a report on and attestation to its management's assessment of the effectiveness of its internal control over financial reporting under Section 404(b) of the Sarbanes-Oxley Act (15 U.S.C. 7262(b)) by the registered public accounting firm that prepared or issued its audit report ☒.

If securities are registered pursuant to Section 12(b) of the Act, indicate by check mark whether the financial statements of the registrant included in the filing reflect the correction of an error to previously issued financial statements. ☐

Indicate by check mark whether any of those error corrections are restatements that required a recover analysis of incentive-based compensation received by any of the registrant's executive officers during the relevant recovery period pursuant to §240.10D-1(b). ☐

Indicate by check mark whether the registrant is a shell company (as defined in Rule 12b-2 of the Exchange Act). Yes ☐ No ☒

The aggregate market value of the registrant's common stock held by non-affiliates as of June 30, 2022 (the last trading day of the registrant's most recently completed second quarter): $58,453,646,002 based on the closing price of the registrant's common stock on the New York Stock Exchange. This calculation does not reflect a determination that persons are affiliates for any other purpose.

The number of shares outstanding of the registrant's common stock, $1.00 par value, as of January 31, 2023, was 608,313,396.

Table of Contents

Documents Incorporated by Reference

Portions of the registrant's proxy statement for the 2023 Annual Meeting of Stockholders (to be filed within 120 days of December 31, 2022) are incorporated by reference into Part III, as indicated herein.

Table of Contents

EDWARDS LIFESCIENCES CORPORATION
Form 10-K Annual Report—2022
Table of Contents

PART I		
Item 1.	Business	2
Item 1A.	Risk Factors	11
Item 1B.	Unresolved Staff Comments	20
Item 2.	Properties	20
Item 3.	Legal Proceedings	20
Item 4.	Mine Safety Disclosures	20
PART II		
Item 5.	Market for Registrant's Common Equity, Related Stockholder Matters and Issuer Purchases of Equity Securities	21
Item 6.	[Reserved]	22
Item 7.	Management's Discussion and Analysis of Financial Condition and Results of Operations	22
Item 7A.	Quantitative and Qualitative Disclosures About Market Risk	36
Item 8.	Financial Statements and Supplementary Data	39
Item 9.	Changes in and Disagreements With Accountants on Accounting and Financial Disclosure	87
Item 9A.	Controls and Procedures	88
Item 9B.	Other Information	88
Item 9C.	Disclosure Regarding Foreign Jurisdictions That Prevent Inspections	88
PART III		
Item 10.	Directors, Executive Officers and Corporate Governance	89
Item 11.	Executive Compensation	89
Item 12.	Security Ownership of Certain Beneficial Owners and Management and Related Stockholder Matters	89
Item 13.	Certain Relationships and Related Transactions, and Director Independence	89
Item 14.	Principal Accounting Fees and Services	89
PART IV		
Item 15.	Exhibits and Financial Statement Schedules	90
Item 16.	Form 10-K Summary	91
	Signatures	92

PART I

NOTE REGARDING FORWARD-LOOKING STATEMENTS

This report contains forward-looking statements within the meaning of Section 27A of the Securities Act of 1933 and Section 21E of the Securities Exchange Act of 1934. We intend the forward-looking statements contained in this report to be covered by the safe harbor provisions of such Acts. Statements other than statements of historical or current fact in this report or referred to or incorporated by reference into this report are "forward-looking statements" for purposes of these sections. These statements include, among other things, the expected impact of COVID-19 on our business, the expected impact of macroeconomic conditions on our business, any predictions, opinions, expectations, plans, strategies, objectives and any statements of assumptions underlying any of the foregoing relating to the our current and future business and operations, including, but not limited to, financial matters, development activities, clinical trials and regulatory matters, manufacturing and supply operations, and product sales and demand. These statements can sometimes be identified by the use of the forward-looking words such as "may," "believe," "will," "expect," "project," "estimate," "should," "anticipate," "plan," "goal," "continue," "seek," "pro forma," "forecast," "intend," "guidance," "optimistic," "aspire," "confident," other forms of these words or similar words or expressions or the negative thereof. Statements of past performance, efforts, or results about which inferences or assumptions may be made can also be forward-looking statements and are not indicative of future performance or results; these statements can be identified by the use of words such as "preliminary," "initial," diligence," "industry-leading," "compliant," "indications," or "early feedback" or other forms of these words or similar words or expressions or the negative thereof. These forward-looking statements are subject to substantial risks and uncertainties that could cause our results or future business, financial condition, results of operations or performance to differ materially from our historical results or experiences or those expressed or implied in any forward-looking statements contained in this report. These risks and uncertainties include, but are not limited to: our success in developing new products and avoiding manufacturing and quality issues; clinical trial or commercial results or new product approvals and therapy adoption; the impact of public health crises, including the COVID-19 pandemic; the impact of domestic and global economic conditions; competitive dynamics in the markets in which we operate; our reliance on vendors, suppliers, and other third parties; damage, failure, or interruption of our information technology systems; consolidation in the healthcare industry; our ability to protect our intellectual property; our compliance with applicable regulations; our exposure to product liability claims; use of our products in unapproved circumstances; changes to reimbursement for our products; the impact of currency exchange rates; unanticipated actions by the United States Food and Drug Administration and other regulatory agencies; changes to tax laws; unexpected impacts or expenses of litigation or internal or government investigations; and other risks detailed under "Risk Factors" in Part I, Item 1A below, as such risks and uncertainties may be amended, supplemented or superseded from time to time by our subsequent reports on Forms 10-Q and 8-K we file with the United States Securities and Exchange Commission. These forward-looking statements speak only as of the date on which they are made and we do not undertake any obligation to update any forward-looking statement to reflect events or circumstances after the date of the statement. If we do update or correct one or more of these statements, investors and others should not conclude that we will make additional updates or corrections.

Unless otherwise indicated or otherwise required by the context, the terms "we," "our," "it," "its," "Company," "Edwards," and "Edwards Lifesciences" refer to Edwards Lifesciences Corporation and its subsidiaries.

WEBSITE REFERENCES

In this Annual Report on Form 10-K, we make references to our website at www.edwards.com. References to our website through this Form 10-K are provided for convenience only and the content of our website does not constitute a part of, and shall not be deemed incorporated by reference into, this Annual Report on Form 10-K.

Item 1. Business

Overview

Edwards Lifesciences Corporation is the global leader in patient-focused medical innovations for structural heart disease and critical care monitoring. Driven by a passion to help patients, we partner with the world's leading clinicians and researchers and invest in research and development to transform care for those impacted by structural heart disease or who require hemodynamic monitoring during surgery or in intensive care. Edwards Lifesciences has been a leader in our field for over six decades. Since our founder, Lowell Edwards, first dreamed of using engineering to address diseases of the human heart, we have steadily built a company on the premise of imagining, building, and realizing a better future for patients.

A pioneer in the development of heart valve therapies, we are the world's leading manufacturer of heart valve systems and repair products used to replace or repair a patient's diseased or defective heart valve. Our innovative work in heart valves encompasses both surgical and transcatheter therapies for heart valve replacement and repair. In addition, our robust pipeline of future technologies is focused on the less invasive repair or replacement of the mitral and tricuspid valves of the heart, which are more complex and more challenging to treat than the aortic valve that is currently the focus of many of our commercially approved valve technologies. We are also a global leader in hemodynamic and noninvasive brain and tissue oxygenation monitoring systems used to measure a patient's cardiovascular function in the hospital setting.

Cardiovascular disease is the number-one cause of death in the world and is the top disease in terms of health care spending in nearly every country. Cardiovascular disease is progressive in that it tends to worsen over time and often affects the structure of an individual's heart.

Patients undergoing treatment for cardiovascular disease can be treated with a number of our medical technologies, which are designed to address individual patient needs with respect to disease process, comorbidities, and health status. For example, an individual with a heart valve disorder may have a faulty valve that is affecting the function of his or her heart or blood flow throughout his or her body. A cardiac surgeon may elect to remove the valve and replace it with one of our bioprosthetic surgical tissue heart valves or surgically re-shape and repair the faulty valve with an Edwards Lifesciences annuloplasty ring. Alternatively, a clinician (typically an interventional cardiologist) may implant an Edwards Lifesciences transcatheter valve or repair system via a catheter-based approach that does not require traditional open-heart surgery and can be done while the heart continues to beat. Patients in the hospital setting, including high-risk patients in the operating room or intensive care unit, are candidates for having their cardiac function or fluid levels monitored by our Critical Care products through multiple monitoring options, including noninvasive and minimally-invasive technologies. These technologies enable proactive clinical decisions while also providing the opportunity for improving diagnoses and developing individualized therapeutic management plans for patients.

Corporate Background

Our principal executive offices are located at One Edwards Way, Irvine, California 92614. The telephone number at that address is (949) 250-2500. We make available, free of charge on our website located at www.edwards.com, our annual report on Form 10-K, quarterly reports on Form 10-Q, current reports on Form 8-K, and any amendments to those reports, as soon as reasonably practicable after filing such reports with the Securities and Exchange Commission ("SEC"). The contents of our website are not incorporated by reference into this report.

Edwards Lifesciences' Product and Technology Offerings

The following discussion summarizes the main areas of products and technologies we offer to treat advanced cardiovascular disease. Our products and technologies are categorized into four main areas: Transcatheter Aortic Valve Replacement, Transcatheter Mitral and Tricuspid Therapies, Surgical Structural Heart, and Critical Care. For more information on net sales from these four main areas, see *"Net Sales by Product Group*" in Part II, Item 7 "*Management's Discussion and Analysis of Financial Condition and Results of Operations*."

Transcatheter Aortic Valve Replacement

We are the global leader in transcatheter heart valve replacement technologies designed for the minimally-invasive replacement of aortic heart valves. The *Edwards SAPIEN* family of valves, including *Edwards SAPIEN XT,* the *Edwards SAPIEN 3,* the *Edwards SAPIEN 3 Ultra,* and the *Edwards SAPIEN 3 Ultra RESILIA* transcatheter heart valves, and their respective delivery systems, are used to treat heart valve disease using catheter-based approaches for patients who have severe symptomatic aortic stenosis and certain patients with congenital heart disease. Delivered while the heart is beating, these valves

can enable patients to experience a better quality of life sooner than patients receiving traditional surgical therapies. We began offering our transcatheter aortic heart valves to patients commercially in Europe in 2007, in the United States in 2011, and in Japan in 2013. Supported by extensive customer training and service, and a growing body of compelling clinical evidence, our *SAPIEN* family of transcatheter aortic heart valves are the most widely prescribed transcatheter heart valves in the world.

Sales of our transcatheter aortic valve replacement products represented 65% of our net sales in each of 2022, 2021, and 2020, respectively.

Transcatheter Mitral and Tricuspid Therapies

We continue to make significant investments in the development of transcatheter heart valve repair and replacement technologies designed to treat mitral and tricuspid valve diseases. While many of these technologies are in development and clinical phases, the *PASCAL PRECISION* and *Cardioband* transcatheter valve repair systems are commercially available in Europe for mitral and tricuspid valve repair. As of 2022, the *PASCAL PRECISION* system is also commercially available in the U.S. for degenerative mitral regurgitation patients. The *PASCAL PRECISION* system addresses the needs of patients with mitral or tricuspid regurgitation through leaflet approximation, while the *Cardioband* system enables clinicians to reduce the valve's annulus and lower regurgitation. In addition to transcatheter repair, we believe transcatheter replacement is key to unlocking the full mitral and tricuspid opportunity. We believe our two-platform mitral replacement strategy positions us for leadership in the mid-to-long term. *SAPIEN M3* is based on the proven *SAPIEN* valve while *EVOQUE Eos* is designed specifically for mitral patients. For tricuspid valve replacement, our *EVOQUE* system is also sub 30-French, and available in a variety of valve sizes to enable treatment in a wide range of patient anatomies.

Surgical Structural Heart

We are innovating in the field of cardiac surgical therapies to improve the quality of life for patients. Our *RESILIA* tissue, with published clinical data showing 0% structural valve deterioration through five years[1], is helping us redefine tissue durability standards. Our latest innovation, the *INSPIRIS RESILIA* aortic valve, is built on our *PERIMOUNT* platform, offering *RESILIA* tissue and *VFit* technology. *INSPIRIS* is the leading aortic surgical valve in the world. Sales of our surgical therapies in the United States also continue to gain traction with *KONECT RESILIA*, the first pre-assembled, aortic tissue valved conduit.

The *MITRIS RESILIA* valve, our newest mitral valve incorporating our latest tissue technology, is now commercially available in both the U.S. and Japan. We believe the demand for surgical structural heart therapies is growing worldwide, and that our innovation strategy will continue to strengthen our leadership and positive impact on patients.

Sales of our surgical tissue heart valve products represented 15%, 15%, and 16% of our net sales in 2022, 2021, and 2020, respectively.

Critical Care

We are the world leader in advanced hemodynamic monitoring systems used to measure a patient's heart function and fluid status in surgical and intensive care settings. Edwards' complete hemodynamic portfolio helps clinicians make proactive clinical decisions that can improve patient recovery. The portfolio includes the minimally-invasive *FloTrac* and *Acumen IQ* sensors, the noninvasive *ClearSight* and *Acumen IQ* cuffs, and the *ForeSight* noninvasive tissue oximetry sensor. We also support clinical needs with our well-established *Swan-Ganz* pulmonary artery catheters and arterial pressure monitoring products. Compatible with our portfolio of sensors and catheters, the *HemoSphere* monitoring platform displays valuable physiological information. Our first predictive algorithm, *Acumen Hypotension Prediction Index* software, alerts clinicians in advance of a patient developing dangerously low blood pressure. Our latest algorithm, *Acumen Assisted Fluid Management* software, provides patient-specific fluid suggestions to help keep patients in an optimal range during surgery.

[1] Bavaria, et al. Five-year Outcomes of the COMMENCE trial investigating Aortic Valve Replacement with a Bioprosthetic Valve with a Novel Tissue. The Society of Thoracic Surgeons 2021 Annual Meeting; Bartus, et al. Final 5-year outcomes following aortic valve replacement with *RESILIA* tissue bio prosthesis. European Journal of Cardio-Thoracic Surgery, 2020.

Competition

The medical technology industry is highly competitive. We compete with divisions of larger companies as well as smaller companies that offer competitive product lines in certain geographies in which we operate. We also compete with both established and newer technologies that target the patients served by our products. New product development and technological change characterize the areas in which we compete. Our present or future products could be rendered obsolete or uneconomical as a result of technological advances by one or more of our present or future competitors or by other therapies, including drug therapies. We believe we hold leadership positions because we develop and produce safe and effective therapies supported by rigorous clinical studies with extensive data and with innovative features that enhance patient benefit, product performance, and reliability; these superior clinical outcomes are in part due to the level of customer and clinical support we provide.

The cardiovascular segment of the medical technology industry is dynamic and subject to significant change due to cost-of-care considerations, regulatory reform, industry and customer consolidation, and evolving patient needs. The ability to provide products and technologies that demonstrate value and improve clinical outcomes is becoming increasingly important for medical technology manufacturers.

We believe that we are a leading global competitor in each of our product lines. In Transcatheter Aortic Valve Replacement, our primary competitors include Medtronic PLC and Abbott Laboratories ("Abbott"). In Transcatheter Mitral and Tricuspid Therapies, our primary competitor is Abbott, and there are a considerable number of large and small companies with development efforts in these fields. In Surgical Structural Heart, our primary competitors include Medtronic PLC, Abbott, and Artivion, Inc (formerly CryoLife). In Critical Care, we compete primarily with a variety of companies in specific product lines including ICU Medical, Inc., PULSION Medical Systems SE, a subsidiary of Getinge AB, Cheetah Medical, Inc., a subsidiary of Baxter International, and LiDCO Group PLC, a subsidiary of Masimo Corporation.

Sales and Marketing

Our portfolio includes some of the most recognizable cardiovascular device product brands in treating structural heart disease today. We have a number of product lines that require sales and marketing strategies tailored to deliver high-quality, cost-effective products and technologies to customers worldwide. Because of the diverse global needs of the population that we serve, our distribution system consists of several direct sales forces as well as independent distributors. We are not dependent on any single customer and no single customer accounted for 10% or more of our net sales in 2022.

To ensure optimal outcomes for patients, we conduct educational symposia and best practices training for our physician, hospital executive, service line leadership, nursing, and clinical-based customers. We rely extensively on our sales and field clinical specialist personnel who work closely with our customers in hospitals. Field clinical specialists routinely attend procedures where Edwards' products are being used in order to provide guidance on the use of our devices, thereby enabling physicians and staff to reach expert proficiency and deliver positive patient outcomes. Our customers include physicians, nurses, and other clinical personnel, but can also include decision makers such as service line leaders, material managers, biomedical staff, hospital administrators and executives, purchasing managers, and ministries of health. Also, for certain of our product lines and where appropriate, our corporate sales team actively pursues approval of Edwards Lifesciences as a qualified supplier for hospital group purchasing organizations ("GPOs") that negotiate contracts with suppliers of medical products. Additionally, we have contracts with a number of United States and European national and regional buying groups, including healthcare systems and Integrated Delivery Networks. Where we choose to market our products is also influenced by the existence of, or potential for, adequate reimbursement to hospitals and other providers by national healthcare systems.

United States. In the United States, we sell substantially all of our products through our direct sales forces. In 2022, 58% of our net sales were derived from sales to customers in the United States.

Outside of the United States. In 2022, 42% of our net sales were derived outside of the United States through our direct sales forces and independent distributors. Of the total sales outside of the United States, 52% were in Europe, 21% were in Japan, and 27% were in Rest of World. We sell our products in approximately 100 countries, including Japan, Germany, France, United Kingdom, Italy, China, and Canada. A majority of the sales and marketing approach outside of the United States is direct sales, although it varies depending on each country's size and state of development.

Raw Materials and Manufacturing

We operate manufacturing facilities in various geographies around the world. We manufacture our Transcatheter Aortic Valve Replacement, Transcatheter Mitral and Tricuspid technologies, and Structural Surgical Heart products primarily in the United States (California and Utah), Singapore, Costa Rica, and Ireland. We manufacture our Critical Care products primarily in the Dominican Republic and Puerto Rico.

We use a diverse and broad range of raw and organic materials in the design, development, and manufacture of our products. We manufacture our non-implantable products from fabricated raw materials including resins, chemicals, electronics, and metals. Most of our replacement heart valves are manufactured from natural tissues harvested from animal tissue as well as fabricated materials. We purchase certain materials and components used in manufacturing our products from external suppliers. In addition, we purchase certain supplies from single sources for reasons of sole source availability or constraints resulting from regulatory requirements.

We work with our suppliers to mitigate risk and seek continuity of supply while maintaining quality and reliability. Alternative supplier options are generally considered, identified, and approved for materials deemed critical to our products, although we do not typically pursue immediate regulatory qualification of alternative sources due to the strength of our existing supplier relationships and the time and expense associated with the regulatory validation process.

We comply with all current global guidelines regarding risks for products incorporating animal tissue intended to be implanted in humans. We follow rigorous sourcing and manufacturing procedures intended to safeguard humans from potential risks associated with diseases such as bovine spongiform encephalopathy ("BSE"). We obtain bovine tissue used in our pericardial tissue valve products only from sources within the United States and Australia, where strong control measures and surveillance programs exist. In addition, bovine tissue used in our pericardial tissue valve products is from tissue types considered by global health and regulatory organizations to have shown no risk of infectibility. Our manufacturing and sterilization processes are designed to render tissue biologically safe from all known infectious agents and viruses.

Quality Assurance

We are committed to providing quality products to our patients and have implemented modern quality systems and concepts throughout the organization. The quality system starts with the initial design concept, risk management, and product specification, and continues through the design of the product, packaging and labeling, and the manufacturing, sales, support, and servicing of the product. The quality system is intended to design quality into the products and uses continuous improvement concepts, including Lean/Six Sigma principles, throughout the product lifecycle.

Our operations are frequently inspected by the many regulators that oversee medical device manufacturing, including the United States Food and Drug Administration ("FDA"), European Notified Bodies, and other regulatory entities. The medical technology industry is highly regulated and our facilities and operations are designed to comply with all applicable quality systems standards, including the International Organization for Standardization ("ISO") 13485. These standards require, among other items, quality system controls that are applied to product design, component material, suppliers, and manufacturing operations. These regulatory approvals and ISO certifications can be obtained only after a successful audit of a company's quality system has been conducted by regulatory or independent outside auditors. Periodic reexamination by an independent outside auditor is required to maintain these certifications.

Environmental, Health, and Safety

We are committed to providing a safe and healthy workplace and complying with all relevant regulations and medical technology industry standards. Through our corporate and site level Environmental, Health, and Safety functions, we establish and monitor programs to reduce pollution, prevent injuries, and maintain compliance with applicable regulations. In order to measure performance, we monitor and report on a number of metrics, including regulated and non-regulated waste disposal, energy usage, water consumption, air toxic emissions, and injuries from our production activities. Each of our manufacturing sites is evaluated regularly with respect to a broad range of Environmental, Health, and Safety criteria.

Research and Development

In 2022, we made significant investments in research and development as we worked to develop therapies that we believe have the potential to change the practice of medicine. Research and development spending increased 5% year over year, representing 18% of 2022 sales. This increase was primarily the result of significant investments in our transcatheter structural heart programs, including an increase in clinical research for our mitral and tricuspid therapies. We are engaged in ongoing research and development to deliver clinically advanced new products, to enhance the effectiveness, ease of use, safety, and reliability of our current leading products, and to expand the applications of our products as appropriate. We focus on opportunities within specific areas of structural heart disease and critical care monitoring.

A considerable portion of our research and development investment includes clinical trials and the collection of evidence that provide data for use in regulatory submissions, and required post-market approval studies involving applications of our products. Our investment in clinical studies also includes outcomes and cost-effectiveness data for payers, clinicians, and healthcare systems.

In Transcatheter Aortic Valve Replacement, we are developing new products to further improve and streamline transcatheter aortic heart valve replacement procedures.

In Transcatheter Mitral and Tricuspid Therapies, we are making significant investments in innovation and clinical evidence to develop technologies designed to treat mitral and tricuspid valve diseases. In addition to our internally developed programs, we have made investments in several companies that are independently developing minimally-invasive technologies to treat structural heart diseases.

Our Surgical Structural Heart development programs include innovative platforms for patients who are best treated surgically, specifically active patients and patients with more complex combined procedures.

In our Critical Care product line, we are pursuing the development of a variety of decision support solutions for our clinicians. This includes next-generation noninvasive and minimally-invasive hemodynamic monitoring systems, and a next-generation monitor platform. We are also developing a decision support software suite with advanced algorithms for proactive hemodynamic management, including a semi-closed loop system for standardized management of patient fluid levels. Lastly, we are developing a connectivity platform that will offer clinicians additional clinical support, remote monitoring capability, analytics, and insights for their patients' hemodynamic status.

Our research and development activities are conducted primarily in facilities located in the United States and Israel. Our experienced research and development staff are focused on product design and development, quality, clinical research, and regulatory compliance. To pursue primary research efforts, we have developed alliances with several leading research institutions and universities, and also work with leading clinicians around the world in conducting scientific studies on our existing and developing products.

Proprietary Technology

Patents, trademarks, and other proprietary rights are important to the success of our business. We also rely upon trade secrets, know-how, continuing innovations, licensing opportunities, and non-disclosure agreements to develop and maintain our competitive position.

We own or have rights to a substantial number of patents and have patent applications pending both in the United States and in foreign countries. We continue to innovate and file new patent applications to protect our new products and technologies.

Additionally, we are a party to license agreements with various third parties pursuant to which we have obtained, for varying terms, the exclusive or non-exclusive rights to certain patents held by such third parties in consideration for cross-licensing rights and/or royalty payments. We have also licensed certain patent rights to others.

We undertake reasonable measures to protect our patent rights, including monitoring the products of our competitors for possible infringement of our patents. Litigation has been necessary to enforce certain patent rights held by us, and we plan to continue to defend and prosecute our rights with respect to such patents.

Moreover, we own certain United States registered trademarks used in our business. Many of our trademarks have also been registered for use in certain foreign countries where registration is available and where we have determined it is commercially advantageous to do so.

Government Regulation and Other Matters

Our products and facilities are subject to regulation by numerous government agencies, including the FDA, European Union member states competent authorities, and the Japanese Pharmaceuticals and Medical Devices Agency, to confirm compliance with the various laws and regulations governing the development, testing, manufacturing, labeling, marketing, and distribution of our products.

We are also governed by federal, state, local, and international laws of general applicability, including, but not limited to, those regulating employee health and safety, labor, competition, trade secret, and the protection of the environment. Overall, the amount and scope of domestic and foreign laws and regulations applicable to our business has increased over time. Compliance with these regulations has not had a material effect on our capital expenditures, earnings, or competitive position to date, but new regulations or amendments to existing regulations to make them more stringent could have such an effect in the future. We cannot estimate the expenses we may incur to comply with potential new laws or changes to existing laws, or the other potential effects these laws may have on our business.

United States Regulation. In the United States, the FDA has responsibility for regulating medical devices. The FDA regulates design, development, testing, clinical studies, manufacturing, labeling, promotion, and record keeping for medical devices, and reporting of adverse events, recalls, or other field actions by manufacturers and users to identify potential problems with marketed medical devices. Many of the devices that we develop and market are in a category for which the FDA has implemented stringent clinical investigation and pre-market clearance or approval requirements. The process of obtaining FDA clearance or approval to market a product is resource intensive, lengthy, and costly. FDA review may involve substantial delays that adversely affect the marketing and sale of our products. A number of our products are pending regulatory clearance or approval to begin commercial sales in various markets. Ultimately, the FDA may not authorize the commercial release of a medical device if it determines the device is not safe and effective or does not meet other regulatory standards. Additionally, even if a product is cleared or approved, the FDA may impose restrictions or require testing and surveillance programs to monitor the effects of these products once commercialized.

The FDA has the authority to halt the distribution of certain medical devices, detain or seize adulterated or misbranded medical devices, order the repair, replacement, or refund of the costs of such devices, or preclude the importation of devices that are or appear violative. The FDA also conducts inspections to determine compliance with the quality system regulations concerning the manufacturing and design of devices and current medical device reporting regulations, recall regulations, clinical testing regulations, and other requirements. The FDA may withdraw product clearances or approvals due to failure to comply with regulatory standards, or the occurrence of unforeseen problems following initial approval, and require notification of health professionals and others with regard to medical devices that present unreasonable risks of substantial harm to the public health. Additionally, the failure to comply with FDA or comparable regulatory standards or the discovery of previously unknown product problems could result in fines, delays, suspensions or withdrawals of regulatory clearances or approvals, seizures, injunctions, recalls, refunds, civil money penalties, or criminal prosecution. Our compliance with applicable regulatory requirements is subject to continual review. Moreover, the FDA and several other United States agencies administer controls over the export of medical devices from the United States and the import of medical devices into the United States, which could also subject us to sanctions for noncompliance.

We are also subject to additional laws and regulations that govern our business operations, products, and technologies, including:

- federal, state, and foreign anti-kickback laws and regulations, which generally prohibit payments to anyone, including physicians as an inducement to purchase or recommend a product;
- the Stark law, which prohibits physicians from referring Medicare or Medicaid patients to a provider that bills these programs for the provision of certain designated health services if the physician (or a member of the physician's immediate family) has a financial relationship with that provider;
- federal and state laws and regulations that protect the confidentiality of certain patient health information, including patient records, and restrict the use and disclosure of such information, in particular, the Health Insurance Portability and Accountability Act of 1996;

- the Physician Payments Sunshine Act, which requires public disclosure of the financial relationships of United States physicians and teaching hospitals with applicable manufacturers, including medical device, pharmaceutical, and biologics companies;

- the False Claims Act, which prohibits the submission of false or otherwise improper claims for payment to a federally funded health care program, and health care fraud statutes that prohibit false statements and improper claims to any third-party payor; and

- the United States Foreign Corrupt Practices Act, which can be used to prosecute United States companies for arrangements with foreign government officials or other parties, or for not keeping accurate financial records or maintaining adequate internal controls to prevent and detect arrangements with foreign government officials or other parties.

Failure to comply with these laws and regulations could result in criminal liability, significant fines or penalties, negative publicity, and substantial costs and expenses associated with investigation and enforcement activities. To assist in our compliance efforts, we work to adhere to many codes of ethics and conduct regarding our business activities in the United States and other countries in which we operate. In addition, we have in place a dedicated team to improve our internal business compliance programs and policies.

Regulation Outside of the United States. Outside of the United States, the regulation of medical devices is complex. In Europe, our products are subject to extensive regulatory requirements. The regulatory regime in the European Union ("EU") for medical devices became mandatory in June 1998. It requires that medical devices may only be placed on the market if they do not compromise safety and health when properly installed, maintained, and used in accordance with their intended purpose. National laws conforming to the EU's legislation regulate our products under the medical devices regulatory system. Although the more variable national requirements under which medical devices were formerly regulated have been substantially replaced by the European Union Medical Devices Directive, individual nations can still impose unique requirements that may require supplemental submissions. The EU medical device laws require manufacturers to declare that their products conform to the essential regulatory requirements after which the products may be placed on the market bearing the CE Mark. Manufacturers' quality systems for products in all but the lowest risk classification are also subject to certification and audit by an independent notified body. In Europe, particular emphasis is being placed on more sophisticated and faster procedures for the reporting of adverse events to the competent authorities.

In May 2017, the EU implemented a new regulatory scheme for medical devices under the Medical Device Regulation ("MDR"). The MDR became effective on May 26, 2021 and brought significant new requirements for many medical devices, including enhanced requirements for clinical evidence and documentation, increased focus on device identification and traceability, new definitions and registration of economic operators throughout the distribution chain, and additional post-market surveillance and vigilance. Compliance with the MDR requires re-certification of many of our products to the enhanced standards, and has resulted in and will continue to result in substantial additional expense. In addition, in the EU, we import some of our devices through our offices in Switzerland. Switzerland is not a member state of the EU, but is linked to the EU through bilateral treaties; therefore, the free movement of goods, including medical devices, between the EU and Switzerland after implementation of the MDR requires a revised Mutual Recognition Agreement ("MRA"). If an MRA covering the MDR is not put in place, then non-EU manufacturers may be required to make significant changes, including replacement of Swiss economic operators with operators based in EU member states, and changes will need to be made to our device labeling and/or packaging to satisfy MDR requirements. If these measures are unable to be taken, it may no longer be possible to place such devices on the EU market.

In Japan, pre-market approval and clinical studies are required as is governmental pricing approval for medical devices. Clinical studies are subject to a stringent Japanese "Good Clinical Practices" standard. Approval time frames from the Japanese Ministry of Health, Labour and Welfare vary from simple notifications to review periods of one or more years, depending on the complexity and risk level of the device. In addition, importation of medical devices into Japan is subject to the "Good Import Practices" regulations. As with any highly regulated market, significant changes in the regulatory environment could adversely affect future sales.

In many of the other foreign countries in which we market our products, we may be subject to regulations affecting, among other things:

- product standards and specifications;

- packaging requirements;

- labeling requirements;
- product collection and disposal requirements;
- quality system requirements;
- import restrictions;
- tariffs;
- duties; and
- tax requirements.

Many of the regulations applicable to our devices and products in these countries are similar to those of the FDA. In some regions, the level of government regulation of medical devices is increasing, which can lengthen time to market and increase registration and approval costs. In many countries, the national health or social security organizations require our products to be qualified before they can be marketed and considered eligible for reimbursement.

Health Care Initiatives. Government and private sector initiatives to limit the growth of health care costs, including price regulation and competitive pricing, coverage and payment policies, comparative effectiveness reviews, technology assessments, increasing evidentiary demands, and managed-care arrangements, are continuing in many countries where we do business, including the United States, Europe, and Japan. As a result of these changes, the marketplace has placed increased emphasis on the delivery of more cost-effective medical therapies. For example, government programs, private health care insurance, and managed-care plans have attempted to control costs by restricting coverage and limiting the level of reimbursement for procedures or treatments, and some third-party payors require their pre-approval before new or innovative devices or therapies are utilized by patients. These various initiatives have created increased price sensitivity over medical products generally and may impact demand for our products and technologies.

The delivery of our products is subject to regulation by the United States Department of Health and Human Services ("HHS") and comparable state and foreign agencies responsible for reimbursement and regulation of health care items and services. Foreign governments also impose regulations in connection with their health care reimbursement programs and the delivery of health care items and services. Reimbursement schedules regulate the amount the United States government will reimburse hospitals and doctors for the inpatient care of persons covered by Medicare. HHS' Centers for Medicare & Medicaid Services ("CMS") may also review whether and/or under what circumstances a procedure or technology is reimbursable for Medicare beneficiaries. Changes in current coverage and reimbursement levels could have an adverse effect on market demand and our pricing flexibility. The CMS National Coverage Determination for Transcatheter Aortic Valve Replacement was issued in June 2019. The modernized requirements and more streamlined patient evaluation process are meaningful enhancements that may help ensure equitable access for more patients suffering from severe aortic stenosis.

Health care cost containment efforts have also prompted domestic hospitals and other customers of medical device manufacturers to consolidate into larger purchasing groups to enhance purchasing power. The medical technology industry has also experienced some consolidation, partly in order to offer a broader range of products to large purchasers. As a result, transactions with customers are larger, more complex, and tend to involve more long-term contracts than in the past. These larger customers, due to their enhanced purchasing power, may have a material impact on product pricing.

These laws or any future legislation, including deficit reduction legislation, could impact medical procedure volumes, reimbursement for our products, and demand for our products or the prices at which we sell our products.

Seasonality

Our quarterly net sales are influenced by many factors, including new product introductions, acquisitions, regulatory approvals, patient and physician holiday schedules, and other factors. Net sales in the third quarter are typically lower than other quarters of the year due to the seasonality of the United States and European markets, where summer vacation schedules normally result in fewer medical procedures.

Human Capital Management Strategy

Human Capital Management ("HCM") Governance

The primary goals of our talent management strategy are to attract and maintain a motivated, professional workforce and to ensure alignment on our patient-focused innovation strategy.

Our Board of Directors routinely engages with leadership to review and discuss our human capital management ("HCM"), with time dedicated at each regularly scheduled meeting to discuss talent management, which include topics such as talent strategy, diversity, succession planning, employee development, employee health, safety, and welfare, results of employee surveys, and compensation. Our Board of Directors also annually approves the strategic talent imperatives that are tied to our Key Operating Drivers ("KODs"). Our KODs are tracked using a point system across our entire organization that focus the Company and management toward short-, medium-, and long-term goals. The strategic talent imperatives are developed to identify talent related initiatives that support achievement of the KODs.

In addition, the Chief Executive Officer ("CEO") and his leadership team have talent management related performance goals tied to their compensation; these Performance Management Objectives are reviewed on an annual basis, tracked, and then reported to and evaluated by our Board of Directors.

As we scale to reach more patients around the world, we have integrated our Talent & Organization (“T&O”) Strategy with our Edwards Strategic Planning process. The purpose of our T&O Strategy is to anticipate dynamic global trends related to our workforce, develop our talent to meet future organizational needs, and enable us to be well-poised to meet these needs. Our T&O Strategy enables us to explore external workforce signals, share insights, and identify and build emerging capabilities across our organization. This has enabled us to build a comprehensive succession planning process that allows us to build strong talent from within while we pursue an aggressive recruiting process to fill any gaps with highly qualified external talent. This consistent and scalable approach looks across all our product groups, regions, and significant functions to align and elevate priorities, critical capabilities, and organizational evolutions in line with our strategic plan. This integrated approach informs our yearly objectives and fuels our talent roadmap across the strategic horizon.

Our HCM governance includes a global talent development review ("TDR") process to align our business strategy with talent strategies, assess talent against future organizational needs, evaluate critical talent populations, and enhance the strength of our succession planning. We track our performance regularly.

Culture

Investing in our workforce means our employees can stay focused on our patient-focused innovation strategy and the development of life-saving therapies for the patients we serve. We are committed to maintaining an ethical culture where we celebrate diversity, promote good health and safety, empower employees to speak up, and ensure that employees' voices are heard. We strive to offer competitive employee well-being packages and are committed to fair and equitable pay practices. We track compensation patterns in all geographies where we operate, and we regularly look for ways to ensure fair and equitable pay.

Diversity, Inclusion, and Belonging

We are committed to fostering an environment where all employees can grow and thrive. A diverse workforce results in a broader range of perspectives, helping drive our commitment to innovation. We have established a Diversity, Inclusion, and Belonging strategy that includes our four focus areas of Business, People, Communication, and Community, and whose overriding priority is "The Patient." As a practice, all employees receive unconscious bias training as a foundational aspect of our culture.

Employee Listening

We believe in empowering our employees and providing avenues that enable their voices to be heard. We conduct a multilingual global employee survey, called *my*Voice, to gain employees' feedback in a confidential manner. The CEO and Executive Leadership Team hold themselves accountable to act on the results of the survey, and these results are reviewed by management with our Board of Directors. This initiative helps us gain insights on various topics including patient focus, diversity, inclusion and belonging, quality, innovation, engagement, as well as a sense of support at all levels of the organization. Speak-Up is a resource available to all employees to bring forth compliance related concerns; a key element of our compliance program is that each employee is accountable for maintaining ethical business practices. In addition, during each quarterly townhall meeting, our CEO answers questions that have been submitted to him by employees. Answers to questions that are not covered in the townhall meeting are posted online internally.

Total Well-being

We understand that good health leads to better performance. We offer competitive employee well-being packages that include, among other things, health and wellness insurance, health savings accounts, family support services, and a variety of site-specific programs. We regularly evaluate our well-being package to make modifications that are aligned with the competitive landscape, legislative changes, and the unique needs of our population. We also provide robust well-being programs that address prevention, nutrition, mental health, physical activity, financial fitness, and community service. In recent years, mental well-being has become a central topic for organizations worldwide. As part of our regular evaluation and commitment to putting employees first, we launched a new program, Mind+, which offers a wide variety of mental well-being programs for our employees. This commitment extends to creating a work environment where employees can feel confident speaking about mental well-being with their managers and know how best to access the tools and resources available to support them. We believe there are strong benefits when employees are feeling their best. Employees who are mentally healthy are more innovative, resilient, better decision-makers, and able to build stronger relationships. We also believe that prioritizing and promoting Mind+ allows us to help patients around the world to live longer, healthier, and more productive lives and supports employees to be their best self at home and at work.

Talent Development

Edwards has established a long-term aspiration to grow and develop talent significantly, centering our efforts around critical leadership and technical skills for the present and future needs of the business. Our learning and development structure and processes strive to meet the internal demand to develop our talent in such a way that demonstrates impact at scale and delivered to our workforce through optimized learning modalities. This includes leadership training programs, including our ethical decision making training program for managers.

Headcount and Labor Representation

As of December 31, 2022, we had approximately 17,300 employees worldwide, the majority of whom were located in the United States, Singapore, the Dominican Republic, and Costa Rica. None of our North American employees are represented by a labor union. In various countries outside of North America, we interact with trade unions and work councils that represent employees.

Additional details regarding diversity, talent development, compensation, and employee health and safety can be found in our Sustainability Report posted on our website at www.edwards.com under "About Us — Corporate Responsibility."

References to our website in this Annual Report on Form 10-K are provided for convenience only and the content on our website does not constitute a part of this Report.

Item 1A. Risk Factors

Our business and assets are subject to varying degrees of risk and uncertainty. An investor should carefully consider the risks described below, as well as other information contained in this Annual Report on Form 10-K and in our other filings with the SEC. Additional risks not presently known to us or that we currently deem immaterial may also adversely affect our business. If any of these events or circumstances occurs, our business, financial condition, results of operations, or prospects could be materially harmed. In that case, the value of our securities could decline and an investor could lose part or all of his or her investment. In addition, forward-looking statements within the meaning of the federal securities laws that are contained in this Annual Report on Form 10-K or in our other filings or statements may be subject to the risks described below as well as other risks and uncertainties. Please read the cautionary notice regarding forward-looking statements in Part I above. Please note that the headers and summary provided below are only intended to assist the reader in navigating the risk factors; some risks, present or future, may implicate multiple types of risks. Please read all risk factors in their entirety.

Summary of Risk Factors

We group our risk factors into three principal sections: (1) Business and Operating Risks; (2) Market and Other External Risks and (3) Legal, Compliance and Regulatory Risks. The following summarizes the principal risks and uncertainties affecting our business, financial condition, and results of operations. This summary should not be relied upon as an exhaustive summary of the material risks facing our business and you should read this summary together with the more detailed description of risks and uncertainties discussed below.

Business and Operating Risks

- Failure to successfully innovate and market products
- Unsuccessful clinical trials or procedures
- Manufacturing, logistics, or quality problems
- Public health crises, including pandemics and epidemics
- Competition
- Dependence on key physicians and research institutions
- Reliance on vendors, suppliers, and other third parties
- Damage, failure, or interruption of our information technology systems, including due to cyber-based attacks and breaches
- Failure to recruit and retain qualified talent or execute management succession plans
- Underperforming operations or unsuccessful business acquisitions or strategic alliances

Market and Other External Risks

- Risks associated with international sales and operations
- Inability to obtain government reimbursement or reductions in reimbursement levels
- Industry consolidation

Legal, Compliance and Regulatory Risks

- Inability to protect our intellectual property
- Inability to defend against intellectual property claims from third parties
- Compliance with government regulations
- Losses from product liability claims
- Use of products in unapproved circumstances
- Substantial costs from environmental, health and safety regulations
- Climate change
- Regulatory actions relating to animal borne illnesses

Business and Operating Risks

Failure to successfully innovate and develop new and differentiated products in a timely manner and effectively market these products could have a material effect on our prospects.

Our continued growth and success depend on our ability to innovate and develop new and differentiated products in a timely manner and effectively market these products. Without the timely innovation and development of products, our products could be rendered obsolete or less competitive because of the introduction of a competitor’s newer technologies or changing customer preferences. Innovating products requires the devotion of significant financial and other resources to research and development activities; however, there is no certainty that the products we are currently developing will complete the development process, or that we will obtain the regulatory or other approvals required to market such products in a timely manner or at all. Even if we timely innovate and develop products, our ability to successfully market them could be constrained by a number of different factors, including competitive products and pricing, barriers in patients' treatment pathway (including disease awareness, detection, and diagnosis), the need for regulatory clearance, restrictions imposed on approved indications, and uncertainty over third-party reimbursement. Failure in any of these areas could have a material effect on our prospects.

Unsuccessful clinical trials or procedures relating to products could have a material adverse effect on our prospects.

The regulatory approval process for new products and new indications for existing products requires extensive clinical trials and procedures, including early clinical feasibility and regulatory studies. Unfavorable or inconsistent clinical data from current or future clinical trials or procedures conducted by us, our competitors, or third parties, or perceptions regarding this clinical data, could adversely affect our ability to obtain necessary approvals and the market's view of our future prospects. Such clinical trials and procedures are inherently uncertain and there can be no assurance that these trials or procedures will be enrolled or completed in a timely or cost-effective manner or result in a commercially viable product or indication; failure to do so could have a material adverse effect on our prospects. Clinical trials or procedures may experience significant setbacks even after earlier trials have shown promising results. Further, preliminary results from clinical trials or procedures may be contradicted by subsequent analyses. In addition, results from our clinical trials or procedures may not be supported by actual long-term studies or clinical experience. If preliminary clinical results are later contradicted, or if initial results cannot be supported by actual long-term studies or clinical experience, our business could be adversely affected. Clinical trials or procedures may be delayed, suspended, or terminated by us, the FDA, or other regulatory authorities at any time if it is believed

that the trial participants face unacceptable health risks or any other reasons, and any such delay, suspension, or termination could have a material adverse effect on our prospects or the market's view of our future prospects.

If we or one of our suppliers or logistics partners encounters manufacturing, logistics, or quality problems, our business could be materially adversely affected.

The manufacture and sterilization of many of our products is highly complex due in part to rigorous regulatory requirements. Quality is extremely important due to the serious and costly consequences of a product failure. Problems can arise for a number of reasons, including disruption of facility utilities, equipment malfunction, failure to follow protocols and procedures, raw material problems, software problems, cyber incidents, or human error. Disruptions can occur at any time, including during production line transfers and expansions. Disruptions can also occur if our manufacturing and warehousing facilities are damaged by earthquakes, hurricanes, volcanoes, fires, and other natural disasters or catastrophic circumstances. As we expand into new markets and scale new products for commercial production, we may face unanticipated delays or surges in demand which could strain our production capacity and lead to other types of disruption. If any of these manufacturing, logistics, or quality problems arise or if we or one of our suppliers or logistics partners otherwise fail to meet internal quality standards or those of the FDA or other applicable regulatory body, our reputation could be damaged, we could become subject to a safety alert or a recall, we could incur product liability and other costs, product approvals and production could be delayed, and our business could otherwise be materially adversely affected.

We are subject to risks associated with public health crises, including the COVID-19 pandemic and other pandemics or epidemics.

We are subject to risks associated with public health crises, including the global health concerns related to the COVID-19 pandemic. The COVID-19 pandemic has adversely impacted and is likely to further adversely impact nearly all aspects of our business and markets, including our workforce and operations and the operations of our customers, suppliers, and business partners. Other public health crises, including any future epidemics or pandemics, could result in similar adverse impacts on our business and markets. Financial or operational impacts that we have experienced in connection with the COVID-19 pandemic and may experience as a result of future COVID-19 outbreaks or other public health crises include:

- Staffing shortages at hospitals which can add to the barriers along the patient treatment pathway;
- Impacts and delays to clinical trials, our pipeline milestones, or regulatory clearances and approvals;
- The inability to meet our customers' needs or other obligations due to disruptions to our operations or the operations of our third-party partners, suppliers, contractors, logistics partners, or customers including disruptions to production, development, manufacturing, administrative, and supply operations and arrangements; or
- Significant volatility or reductions in demand for our products.

Depending on the severity of the financial and operational impacts, our business, financial condition, and results of operations may be materially adversely impacted. The extent to which the COVID-19 pandemic or other future public health crises may impact our business, results of operations, and financial condition depends on many factors which are highly uncertain and are difficult to predict. These factors include, but are not limited to, the duration and spread of any outbreak, its severity, the actions to contain or address the impact of the outbreak, the timing, distribution, and efficacy of vaccines and other treatments, United States and foreign government actions to respond to possible reductions in global economic activity, and how quickly and to what extent normal economic and operating conditions can resume.

We operate in highly competitive markets, and if we do not compete effectively, our business will be harmed.

We face substantial competition and compete with technologies of many types and companies of all sizes on the basis of cost-effectiveness, technological innovations, product performance, brand name recognition, breadth of product offerings, real or perceived product advantages, pricing and availability and rate of reimbursement. In addition, given the trend toward value-based healthcare, if we are not able to continue to demonstrate the full value of our differentiated products to healthcare providers and payors, our competitive position could be adversely affected. See "*Competition*" under "*Business*" in Part I, Item 1 included herein.