Tofacitinib in patients with ankylosing spondylitis: a Phase 2, 16-week, randomised, placebo-controlled, dose-ranging study

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Supplementary Section 1. Exclusion criteria

Patients were ineligible to participate in this study if any of the following criteria were met:

1. Patients who were investigational site staff members or relatives of those site staff members, or subjects who were Pfizer employees directly involved in the conduct of the trial.

2. Participation in other interventional studies within 4 weeks before the current study began and/or during study participation (excluding non-interventional follow-up during the screening period).

3. Patients receiving any other disease-modifying antirheumatic drugs (other than those allowed), thalidomide (including previous use) and other prohibited concomitant medications.

4. Patients who were currently receiving, or previous use of a tumour necrosis factor inhibitor or other biological agent.

5. Blood dyscrasias at screening or within 3 months prior to the first dose of study drug, including confirmed:

a. Haemoglobin <10 g/dL.

b. Absolute white blood cell count <3.0 x 10^9/L (<3000 mm^3).

c. Absolute neutrophil count <1.2 x 10^9/L (<1200 mm^3).

d. Absolute lymphocyte count <1.0 x 10^9/L (<1000/mm^3).

e. Platelet count <100 x 10^9/L (<100 000/mm^3).

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One re-testing of a laboratory acceptable specimen was allowed of any of these parameters if the abnormal result was considered uncharacteristic. Documentation was required in the source of the typical results to allow a repeat test and the re-test must have been completed within the screening period.

6. Estimated Creatinine Clearance <40 mL/min based on Cockcroft Gault equation at screening visit.

7. Total bilirubin, aspartate aminotransferase or alanine aminotransferase more than 1.5 times the upper limit of normal at screening visit. One re-testing with an uncompromised sample was allowed if the abnormal result was considered uncharacteristic and must have been completed within the screening period. Documentation was required in the source of the typical results to allow a repeat test.

8. History of any other autoimmune rheumatic disease (eg, systemic lupus erythematosus, mixed connective tissue disease, scleroderma, polymositis) or known diagnosis of fibromyalgia, without approval by sponsor.

9. History of an infected joint prosthesis at any time, with the prosthesis still in situ.

10. History of any lymphoproliferative disorder, such as Epstein Barr Virus-related lymphoproliferative disorder, history of lymphoma, leukaemia, or signs and symptoms suggestive of current lymphatic disease.

11. History of recurrent (more than 1 episode) herpes zoster or disseminated/multi-dermatomal (a single episode) herpes zoster or disseminated (a single episode) herpes simplex.

12. History of infection requiring hospitalisation, parenteral antimicrobial therapy, or as otherwise judged clinically significant by the investigator, within the 6 months prior to the first dose of study drug.

13. History of infection requiring antimicrobial therapy within 2 weeks prior to the first dose of study drug.

14. Any prior treatment with alkylating agents (eg, cyclophosphamide or chlorambucil), total lymphoid irradiation, etc.

15. Any patient who had been vaccinated with live or attenuated vaccines within the 6 weeks prior to the first dose of study drug or was to be vaccinated with these vaccines at any time during treatment or within 6 weeks after last dose of study drug.

16. A patient with any condition possibly affecting oral drug absorption, eg, gastrectomy, clinically significant diabetic gastroenteropathy or certain types of bariatric surgery such as gastric bypass. Procedures such as gastric banding, that simply divide the stomach into separate chambers, were NOT exclusionary.

17. History of alcohol or drug abuse unless in full remission for greater than 6 months prior to first dose of study drug.

18. Body weight or body habitus greater than what could be accommodated by the site's magnetic resonance imaging (MRI) scanner table weight limits or MRI scanner bore.

19. Any contraindication to MRI that in the judgement of the investigator and MRI centre posed a safety risk to the subject such as, but not limited to, cardiac pacemaker, implanted cardiac defibrillator, aneurysm clips, carotid artery vascular clamp, neurostimulator, insulin or infusion pumps, bone growth/fusion stimulator and cochlear, otologic and ear implants.

20. Patients with passive implants that may have been weakly ferromagnetic in the vicinity of the radio frequency coil that may have caused image artefacts in the spine and sacroiliac joints.

21. Severe claustrophobia that would interfere with the ability to undergo an MRI.

22. Screening 12-lead ECG that demonstrated clinically relevant abnormalities which may have affected subject safety (eg, pattern of acute myocardial infarction, acute ischaemia or serious arrhythmia) or interpretation of study results (eg, continuously paced ventricular rhythm or complete left bundle branch block).

23. A patient with a known immunodeficiency disorder or a first-degree relative with a hereditary immunodeficiency.

24. A patient with a malignancy or with a history of malignancy, with the exception of adequately treated or excised non-metastatic basal cell or squamous cell cancer of the skin or cervical carcinoma in situ.

25. Significant trauma or surgery procedure within 1 month prior to first dose of study drug, or any planned elective surgery during the study period.

26. A patient who required prohibited concomitant medications.

27. A patient known to be infected with human immunodeficiency virus, hepatitis B virus or hepatitis C virus (HCV) or any chronic infection.

- Hepatitis B surface antigen (HBsAg)+ was exclusionary; patients who were HBsAg+ but hepatitis B core antibody (HBcAb)+ must have undergone further testing for hepatitis B surface antibody (HBsAb) to be considered for enrolment. If HBsAb+, subject could enrol; if HBsAb-, the patient was to be excluded.

- Patients who were hepatitis C virus antibody (HCV Ab)+ must have undergone further testing for HCV ribonucleic acid (RNA). Patients who were HCV RNA– could enrol.

28. A patient who had previously participated in any study of tofacitinib.

29. Pregnant or lactating females, or females planning pregnancy; females of childbearing potential not using highly effective contraception or not agreeing to continue highly effective contraception for at least 1 ovulatory cycle after last dose of assigned treatment. A patient was of childbearing potential if, in the opinion of the investigator, he/she was biologically capable of having children and was sexually active.

30. Other severe acute or chronic medical or psychiatric condition or laboratory abnormality that may have increased the risk associated with study participation or study drug administration or may have interfered with the interpretation of study results and, in the judgement of the investigator, would have made the patient inappropriate for entry into this study.

31. A patient who, in the opinion of the investigator or Pfizer (or designee), would be uncooperative or unable to comply with study procedures.

Supplementary Section 2. Names of study investigators who screened patients for entry into the trial

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Supplementary Section 3. Overview of the 3-parameter Bayesian Emax model.

The Emax model is a non-linear model frequently used in dose-response analyses and can be justified based on drug-receptor interaction[1] and has been used to characterise tofacitinib dose-response in other indications.[2-4]

The model was:

$$\log\left\{\frac{\pi}{1-\pi}\right\} = E_0 + \frac{E_{max} * dose}{ED_{50} + dose}$$

Where π is the probability of an ASAS20 response at Week 12, dose is half the total daily dose in mg, E_0 is the log odds of the placebo response, E_{max} is the additive increase over placebo in the log odds due to the test drug at a theoretically infinite dose, and ED_{50} is half the total daily dose in mg that provides an effect of $\frac{E_0 + E_{max}}{2}$ on the logit scale. Bayesian methods were used to fit the model. Posterior distributions were estimated using the Markov Chain Monte Carlo methods.

Supplementary Section 4. Details of the post-hoc subanalyses.

Patients were classified by CRP ≥0.287 mg/dL (high) or CRP <0.287 mg/dL (low). Patients were defined as having positive MRI if they had SPARCC SI joint cut-off ≥2 at baseline. Patients were also analysed by composite MRI/CRP status: high CRP/positive MRI, high CRP/negative MRI, low CRP/positive MRI, low CRP/negative MRI.

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Supplementary Section 5. Narrative for herpes zoster cases

One patient (tofacitinib 2 mg BID) reported mild single-dermatome herpes zoster on Day 23, which resolved on Day 29 without treatment; causality was related to study drug. One patient (tofacitinib 10 mg BID) reported moderate herpes zoster in two adjacent dermatomes on Day 43, which resolved on Day 69 with treatment; causality was related to study drug.

Ex. 2112-012

Table S1. Secondary and other efficacy endpoints by study visit

	Placebo	**Tofacitinib**	**Tofacitinib**	**Tofacitinib**
		2 mg BID	**5 mg BID**	**10 mg BID**
	N=46	**N=50**	**N=50**	**N=48**
Week 2				
ASAS40 response rate, %	15.7	13.5	13.5	17.3
BASDAI50 response rate, %	15.7	11.5	21.2	13.5
ASAS5/6 response rate, %	7.8	23.1*	13.5	21.2
ASDAS clinically important improvement, response rate, %	15.7	26.9	48.1***	40.4**
ASDAS inactive disease, response rate, %	0	1.9	1.9	1.9
CRP mg/dL, LS mean (SE)	-1.6 (1.0)	-4.2 (1.0)	-8.9 (1.0)***	-9.7 (1.0)***
Week 4				
ASAS40 response rate, %	15.7	28.9	32.7*	21.2

Ex. 2112-013

BASDAI50 response rate, %	21.6	28.9	23.1	28.9
ASAS5/6 response rate, %	7.8	19.2	30.8**	28.9**
ASDAS clinically important improvement, response rate, %	19.6	42.3**	57.7***	51.9***
ASDAS inactive disease, response rate, %	2.0	1.9	5.8	7.7
CRP mg/dL, LS mean (SE)	0.7 (1.5)	-6.8 (1.5)***	-9.0 (1.5)***	-9.9 (1.5)***
Week 8				
ASAS40 response rate, %	27.5	28.9	34.6	36.5
BASDAI50 response rate, %	27.5	34.6	32.7	40.4
ASAS5/6 response rate, %	9.8	21.2**	42.3***	28.9
ASDAS clinically important	29.4	44.2	59.6***	59.6***

improvement, response rate, %				
ASDAS inactive disease, response rate, %	2.0	5.8	1.9	9.6
CRP mg/dL, LS mean (SE)	-2.0 (1.0)	-6.8 (1.0)***	-9.0 (1.0)***	-8.7 (1.0)***

*p≤0.05, **p≤0.01, ***p≤0.001 vs placebo

ASAS40 and BASDAI50 used NRI/LOCF for missing values

ASDAS clinical improvement = improvement ≥1.1 units

ASAS, Assessment of SpondyloArthritis international Society; ASDAS, Ankylosing Spondylitis Disease Activity Score; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; BID, twice daily; CRP, C-reactive protein; LOCF, last observation carried forward; LS, least squares; NRI, non-responder imputation; SD, standard deviation; SE, standard error

Ex. 2112-015

Table S2. Change from baseline to Week 12 in swollen joint count and chest expansion

	Placebo	**Tofacitinib**	**Tofacitinib**	**Tofacitinib**
		2 mg BID	**5 mg BID**	**10 mg BID**
	N=46	**N=50**	**N=50**	**N=48**
Swollen joint count				
LS mean (SE)	-1.0 (0.4)	-0.9 (0.4)	-0.8 (0.4)	-1.4 (0.4)
p value vs placebo		0.820	0.711	0.424
Chest expansion				
LS mean (SE)	0.3 (0.2)	0.7 (0.2)	0.5 (0.2)	0.1 (0.2)
p value vs placebo		0.155	0.491	0.515

BID, twice daily; LS, least squares; SE, standard error

Ex. 2112-016

Table S3. LS mean (SE) change from baseline to Week 12 in patient-reported outcomes

	Placebo	**Tofacitinib**	**Tofacitinib**	**Tofacitinib**
		2 mg BID	**5 mg BID**	**10 mg BID**
	N=51	**N=52**	**N=52**	**N=52**
EQ-5D				
Mobility	-0.1 (0.1)	-0.3 (0.1)	-0.3 (0.1)	-0.4 (0.1)**
Self-care	-0.2 (0.1)	-0.2 (0.1)	-0.1 (0.1)	-0.2 (0.1)
Usual activities	-0.2 (0.1)	-0.3 (0.1)	-0.3 (0.1)	-0.2 (0.1)
Pain/discomfort	-0.2 (0.1)	-0.3 (0.1)	-0.3 (0.1)	-0.4 (0.1)*
Anxiety/depression	-0.0 (0.1)	-0.1 (0.1)	-0.2 (0.1)	-0.1 (0.1)
SF-36				
PCS	2.7 (0.9)	6.3 (0.9)**	6.5 (0.9)**	7.1 (0.9)**
MCS	2.4 (1.3)	2.1 (1.3)	4.2 (1.3)	3.7 (1.3)
Physical functioning	2.7 (1.1)	4.6 (1.1)	5.3 (1.1)	5.5 (1.1)
Role limitations due to physical health	2.9 (1.1)	6.1 (1.1)*	5.8 (1.1)	5.9 (1.1)
Bodily pain	3.6 (1.3)	8.6 (1.3)**	10.0 (1.2)***	8.8 (1.3)**
General health perceptions	1.4 (1.0)	1.9 (0.9)	2.2 (0.9)	5.0 (1.0)**
Vitality	3.8 (1.3)	3.8 (1.3)	6.3 (1.3)	6.6 (1.3)
Social functioning	2.5 (1.2)	5.5 (1.2)	6.9 (1.2)**	5.7 (1.2)

Ex. 2112-017

Role limitations due to emotional problems	1.6 (1.4)	3.2 (1.4)	4.1 (1.4)	4.1 (1.4)
Mental health	3.0 (1.3)	2.2 (1.3)	4.1 (1.3)	3.6 (1.3)
FACIT-F[a]	3.1 (1.2)	4.7 (1.1)	7.0 (1.1)*	7.6 (1.2)**
ASQoL	-2.5 (0.6)	-4.2 (0.6)	-4.8 (0.6)*	-3.9 (0.6)
WPAI[b]				
Work time missed due to health, %	-1.4 (1.6)	-5.9 (1.7)	-5.2 (1.5)	-4.01 (1.6)
Impairment whilst working due to health (%)	-6.1 (3.8)	-19.6 (3.8)*	-20.9 (3.4)**	-10.9 (3.8)
Overall work impairment due to health (%)	-5.4 (3.9)	-19.8 (4.0)*	-21.7 (3.6)**	-13.1 (3.9)
Activity impairment due to health (%)	-11.2 (3.3)	-20.1 (3.1)	-19.5 (3.1)	-17.4 (3.2)

*p≤0.05, **p≤0.01, ***p≤0.001 vs placebo

[a]FACIT-F patient numbers for placebo, tofacitinib 2 mg BID, tofacitinib 5 mg BID, tofacitinib 10 mg BID, respectively: 46, 50, 50, 48

[b]WPAI scores patient numbers for placebo, tofacitinib 2 mg BID, tofacitinib 5 mg BID, tofacitinib 10 mg BID, respectively: work time missed due to health, 29, 28, 35, 30; impairment whilst working due to health, 29, 29, 36, 34; overall work impairment due to health, 29, 28, 35, 30; activity impairment due to health, 46, 50, 50, 47

Ex. 2112-018

ASQoL, ankylosing spondylitis quality of life; BID, twice daily; EQ-5D, EuroQol 5 dimensions; FACIT-F, functional assessment of chronic illness therapy – fatigue; LS, least squares; MCS, mental component summary; PCS, physical component summary; SE, standard error; SF-36, short-form 36 health survey; WPAI, work productivity and activity impairment

Ex. 2112-019

Table S4. ASAS20 and ASAS40 responses at Week 12 by baseline CRP group

	Placebo	Tofacitinib 2 mg BID	Tofacitinib 5 mg BID	Tofacitinib 10 mg BID
ASAS20				
High baseline CRP[a]	37.8	56.8	78.6***	59.0
Low baseline CRP[b]	50.0	40.0	90.0*	46.2
ASAS40				
High baseline CRP[a]	16.2	48.7***	47.6***	43.6**
Low baseline CRP[b]	28.6	26.7	40.0	23.1

*p≤0.05, **p≤0.01, ***p≤0.001 vs placebo

[a]N=37, N=37, N=42, N=39 for placebo, and tofacitinib 2, 5 and 10 mg BID, respectively

[b]N=14, N=15, N=10, N=13 for placebo, and tofacitinib 2, 5 and 10 mg BID, respectively

High baseline CRP was defined as CRP ≥0.287 mg/dL; low baseline CRP was defined as CRP <0.287 mg/dL

ASAS, Assessment of SpondyloArthritis international Society; BID, twice daily;

CRP, C-reactive protein

Ex. 2112-020

Table S5. ASAS20 and ASAS40 responses at Week 12 by positive baseline MRI

	Placebo	**Tofacitinib 2 mg BID**	**Tofacitinib 5 mg BID**	**Tofacitinib 10 mg BID**
	N=25	N=31	N=32	N=30
ASAS20	40.0	61.3	87.5***	63.3
ASAS40	20.0	48.4*	53.1**	43.3

*p≤0.05, **p≤0.01, ***p≤0.001 vs placebo

Patients were defined as having positive MRI if they had SPARCC Spine or SI joint cut-off ≥2 at baseline

ASAS, Assessment of SpondyloArthritis international Society; BID, twice daily; MRI, magnetic resonance imaging; SI, sacroiliac; SPARCC, Spondyloarthritis Research Consortium of Canada

Ex. 2112-021

Table S6. ASAS20 and ASAS40 response rates at Week 12 by composite baseline CRP and MRI

	Placebo	Tofacitinib 2 mg BID	Tofacitinib 5 mg BID	Tofacitinib 10 mg BID
High CRP/MRI+	N=19	N=24	N=27	N=19
ASAS20	36.8	70.8	88.9	68.4
ASAS40	15.8	58.3	59.3	52.6
Low CRP/MRI+	N=6	N=7	N=5	N=11
ASAS20	50.0	58.6	80.0	54.6
ASAS40	33.3	14.3	20.0	27.3
High CRP/MRI-	N=16	N=12	N=11	N=16
ASAS20	43.8	33.3	72.7	62.5
ASAS40	18.8	33.3	36.4	43.8
Low CRP/MRI-	N=6	N=6	N=5	N=1
ASAS20	66.7	66.7	100	0
ASAS40	33.3	50.0	60.0	0
High CRP or MRI+	N=43	N=44	N=47	N=50
ASAS20	39.5	52.3	78.7	58.0
ASAS40	18.6	43.2	44.7	40.0

High CRP was defined as baseline CRP ≥0.287 mg/dL; low CRP was defined as baseline CRP <0.287 mg/dL

Patients were defined as MRI+ if they had SPARCC Spine or SI joint cut-off ≥2 at baseline

Ex. 2112-022

ASAS, Assessment of SpondyloArthritis international Society; BID, twice daily; CRP, C-reactive protein; MRI, magnetic resonance imaging; SI, sacroiliac; SPARCC, Spondyloarthritis Research Consortium of Canada

Ex. 2112-023

Table S7. TEAEs by SOC in ≥2 patients in any treatment group (all causality)

Patients, n (%)	Placebo	Tofacitinib 2 mg BID	Tofacitinib 5 mg BID	Tofacitinib 10 mg BID
Evaluable for AEs	51	52	52	52
With AEs	22 (43.1)	22 (44.2)	28 (53.8)	27 (51.9)
Discontinued due to AEs	3 (5.9)	0	1 (1.9)	1 (1.9)
AEs by system organ class and MedDRA preferred terms				
Gastrointestinal disorders	**5 (9.8)**	**8 (15.4)**	**6 (11.5)**	**8 (15.4)**
Abdominal pain	1 (2.0)	3 (5.8)	0	2 (3.8)
Diarrhoea	1 (2.0)	2 (3.8)	1 (1.9)	0
Mouth ulceration	1 (2.0)	2 (3.8)	0	0
Infections and infestations	**12 (23.5)**	**12 (23.1)**	**11 (21.2)**	**9 (17.3)**
Bronchitis	2 (3.9)	0	0	1 (1.9)
Nasopharyngitis	3 (5.9)	4 (7.7)	4 (7.7)	2 (3.8)
Upper respiratory tract infection	1 (2.0)	4 (7.7)	0	3 (5.8)
Injury, poisoning and procedural complications	**2 (3.9)**	**1 (1.9)**	**2 (3.8)**	**6 (11.5)**
Ligament sprain	0	0	0	2 (3.8)
Investigations	**2 (3.9)**	**3 (5.8)**	**5 (9.6)**	**3 (5.8)**
Alanine aminotransferase increase	0	1 (1.9)	2 (3.8)	0
Blood creatine phosphokinase increased	1 (2.0)	0	2 (3.8)	1 (1.9)
Musculoskeletal and connective tissue disorders	**2 (3.9)**	**4 (7.7)**	**6 (11.5)**	**4 (7.7)**

Ex. 2112-024

Arthralgia	0	1 (1.9)	2 (3.8)	0
Nervous system disorders	**3 (5.9)**	**2 (3.8)**	**3 (5.8)**	**5 (9.6)**
Dizziness	2 (3.9)	0	0	0
Headache	1 (2.0)	2 (3.8)	2 (3.8)	2 (3.8)
Renal and urinary disorders	**1 (2.0)**	**0**	**1 (1.9)**	**3 (5.8)**
Haematuria	1 (2.0)	0	1 (1.9)	2 (3.8)
Skin and subcutaneous tissue disorders	**3 (5.9)**	**1 (1.9)**	**2 (3.8)**	**0**
Rash	2 (3.9)	1 (1.9)	0	0

BID, twice daily; MedDRA, Medical Dictionary for Regulatory Activities; SOC, system organ class; TEAE, treatment-emergent adverse event

Ex. 2112-025

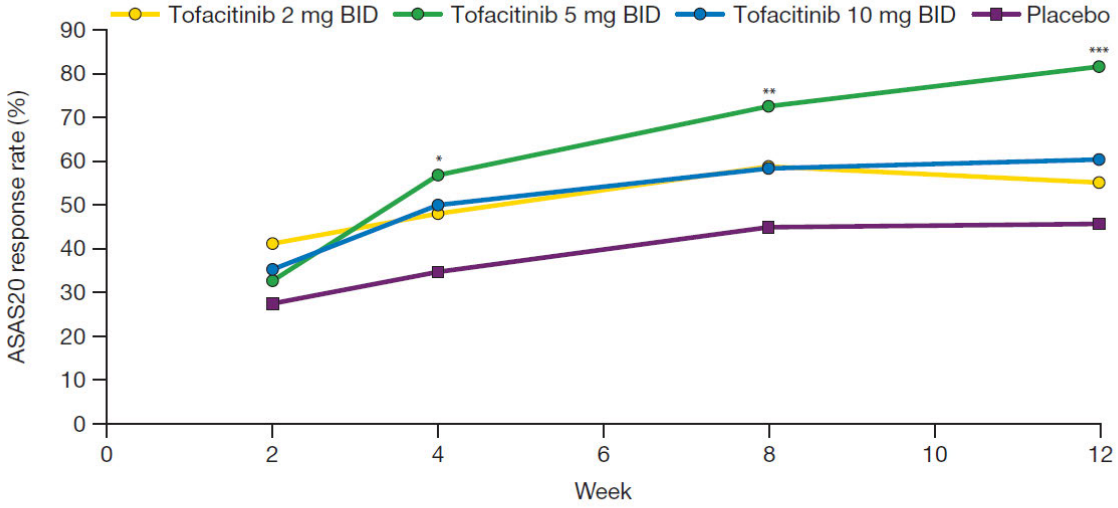
Table S8. Number (%) of patients with laboratory values meeting monitoring criteria

	Placebo	**Tofacitinib 2 mg BID**	**Tofacitinib 5 mg BID**	**Tofacitinib 10 mg BID**
	N=50	**N=51**	**N=52**	**N=50**
Absolute lymphocyte count <500 cells/mm^3	0	0	1 (1.9)	0
Absolute neutrophil count <1.2 cells/mm^3	0	0	1 (1.9)	1 (2.0)
Haemoglobin >2.0 g/dL decrease from baseline	0	0	0	0
Platelets <100 000 cell/mm^3	0	0	0	0
ALT or AST ≥3 x ULN	1 (2.0)	0	1 (3.8)	1 (2.0)
Serum creatinine >50% increase over average screening and baseline values, or absolute increase >0.5 mg/dL from baseline	1 (2.0)	0	0	1 (2.0)
Creatine kinase >5 x ULN	2 (4.0)	0	2 (3.8)	1 (2.0)

ALT, alanine aminotransferase; AST, aspartate aminotransferase; BID, twice daily; ULN, upper limit of normal

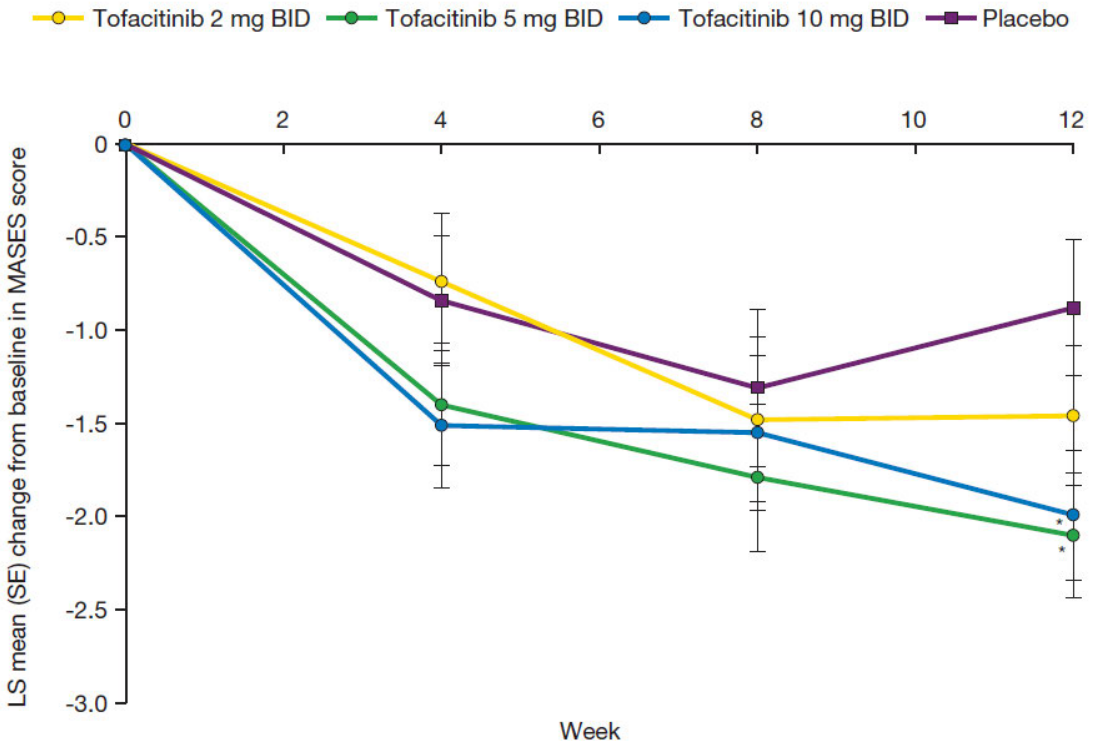
Ex. 2112-026

Figure S1. ASAS20 actual response rates over time



*p≤0.05, **p≤0.01, ***p≤0.001 vs placebo
ASAS, Assessment of SpondyloArthritis international Society; BID, twice daily; SE, standard error

Figure S2. LS mean (SE) change form baseline in MASES score for patients with enthesitis at baseline



*p≤0.05 vs placebo
BID, twice daily; LE, least squares; MASES, Maastricht Ankylosing Spondylitis Enthesitis Score; SE, standard error

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Ex. 2112-029