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SCHWABE, WILLIAMSON & WYATT PC

By: /Lance A. Termes/
Lance A. Termes

PATENT
Attorney Docket No.: 125984-266215

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of:	Confirmation No. Unassigned
Kenneth S. Graham et al.	Examiner: Unassigned
Application No.: Unassigned	Art Unit: Unassigned
Filed: Herewith	
For: HIGH CONCENTRATION VEGF RECEPTOR FUSION PROTEIN CONTAINING FORMULATIONS	PRELIMINARY AMENDMENT
Customer No.: 147803	

Mail Stop Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Commissioner:

Prior to examination of the above-identified application, please enter the following amendments and remarks:

Amendments to the Claims are reflected in the listing of claims which begins on page 2 of this paper.

Remarks/Arguments begin on page 5 of this paper.

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Amendments to the Claims:

This listing of claims will replace all prior versions, and listings of claims in the application:

Listing of Claims:

1-29. (Canceled)

30. (Currently Amended) A method for treating an angiogenic eye disorder in a human patient~~subject~~ in need thereof comprising administering an intravitreal~~intraocular~~ injection of at least~~more than~~ about 8[[2]] mg of a VEGF receptor fusion protein comprising two polypeptides that comprise an immunoglobulin-like (Ig) domain 2 of VEGFR1, an Ig domain 3 of a VEGFR2, and a multimerizing component, to the eye of the patient~~subject~~.

31. (Currently Amended) The method of claim 30 wherein, following said intravitreal injection, the patient maintains or achieves a reduction in central retinal thickness but does not experience a significant increase in blood pressure~~comprising administering about 4 mg, about 6 mg, about 8 mg or about 10 mg of the VEGF receptor fusion protein to the eye of the subject~~.

32. (Currently Amended) The[[A]] method of claim 30 wherein, following said intravitreal injection, the patient maintains or achieves an improvement in best corrected visual acuity but does not experience a significant increase in blood pressure~~for treating an angiogenic eye disorder in a subject in need thereof, the method comprising intraocularly injecting more than about 2 mg of VEGF receptor fusion protein in a formulation of any one of claims 1-23 and 28 into an eye of the subject~~.

33-34. (Canceled)

35. (Currently Amended) The method of claim 30~~any one of claims 30-34~~, wherein the angiogenic eye disorder is age-related macular degeneration (wet), macular edema, macular edema following retinal vein occlusion, retinal vein occlusion (RVO), central retinal vein occlusion (CRVO) branch retinal vein occlusion (BRVO), diabetic macular edema (DME),

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choroidal neovascularization (CNV), iris neovascularization, neovascular glaucoma, post-surgical fibrosis in glaucoma, proliferative vitreoretinopathy (PVR), optic disc neovascularization, corneal neovascularization, retinal neovascularization, vitreal neovascularization, pannus, pterygium, vascular retinopathy, diabetic retinopathy, non-proliferative diabetic retinopathy and/or proliferative diabetic retinopathy.

36-38. (Canceled)

39. (New) The method of claim 35 wherein the angiogenic eye disorder is wet age-related macular degeneration.

40. (New) The method of claim 35 wherein the angiogenic eye disorder is diabetic macular edema.

41. (New) The method of claim 35 wherein the angiogenic eye disorder is diabetic retinopathy.

42. (New) The method of claim 35 wherein the angiogenic eye disorder is non-proliferative diabetic retinopathy.

43. (New) The method of claim 35 wherein the angiogenic eye disorder is proliferative diabetic retinopathy.

44. (New) The method of claim 35 wherein the angiogenic eye disorder is macular edema following retinal vein occlusion.

45. (New) The method of claim 30 wherein the VEGF antagonist is aflibercept.

46. (New) The method of claim 35 wherein the VEGF antagonist is aflibercept.

47. (New) The method of claim 39 wherein the VEGF antagonist is aflibercept.

48. (New) The method of claim 40 wherein the VEGF antagonist is aflibercept.

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49. (New) The method of claim 41 wherein the VEGF antagonist is aflibercept.

50. (New) The method of claim 42 wherein the VEGF antagonist is aflibercept.

51. (New) The method of claim 43 wherein the VEGF antagonist is aflibercept.

52. (New) The method of claim 44 wherein the VEGF antagonist is aflibercept.

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REMARKS/ARGUMENTS

Upon entry of the present amendment, claims 30-32, 35 and 39-52 will be pending in the application. Original claims 1-29, 33, 34 and 36-38 are hereby canceled without prejudice. Claims 30-32 and 35 are hereby amended, and new claims 39-52 are added.

Support for the amendments and new claims can be found in the specification and original claims at, *e.g.*, the following locations:

Claim 30 – original claims 33 and 34, and paragraphs 0019, 0066 and 0208;

Claims 31 and 32 – paragraphs 0068 and 0207;

Claims 39 to 44 – original claim 35; and

Claims 45 to 52 – paragraph 0019.

Claim 35 is amended to remove multiple dependencies. No new matter is added.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 541-749-4085.

Respectfully submitted,

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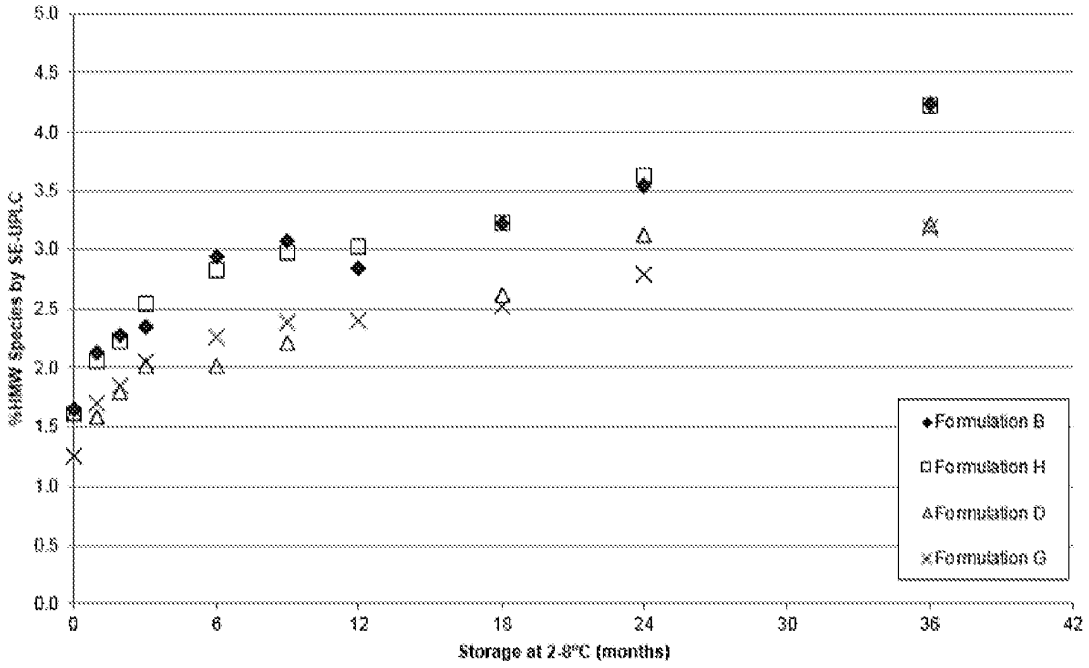

%HMW Species by SE-UPLC
Storage at 2-8°C (months)
Formulation B
Formulation H
Formulation D
Formulation G
0.0
0.5
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
0
6
12
18
24
30
36
42

FIG. 1A

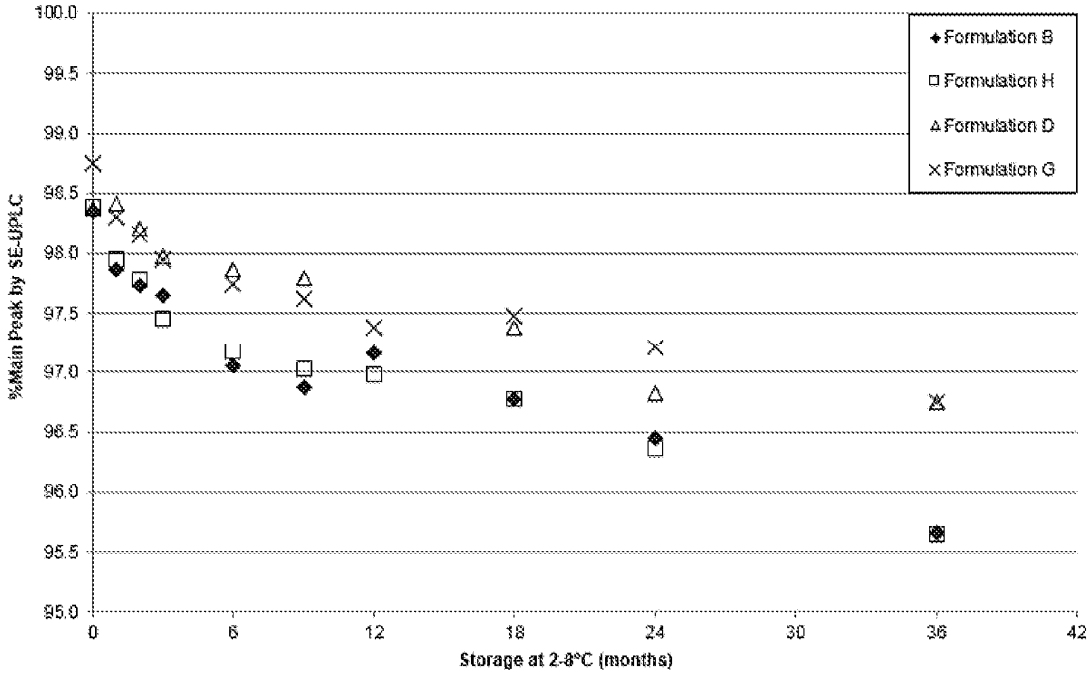

100.0
99.5
99.0
98.5
98.0
97.5
97.0
96.5
96.0
95.5
95.0
%Main Peak by SE-UPLC
0
6
12
18
24
30
36
42
Storage at 2-8°C (months)
Formulation B
Formulation H
Formulation D
Formulation G

FIG. 1B

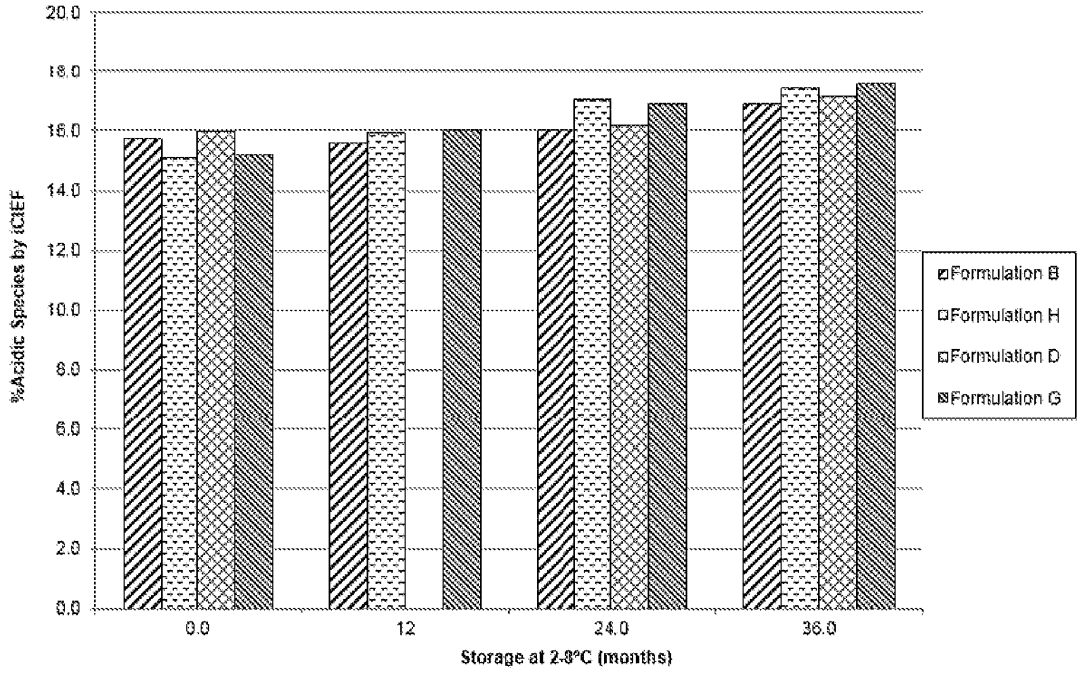

20.0
18.0
16.0
14.0
12.0
10.0
8.0
6.0
4.0
2.0
0.0
%Acidic Species by iCIEF
0.0
12
24.0
36.0
Storage at 2-8°C (months)
Formulation B
Formulation H
Formulation D
Formulation G

FIG. 1C

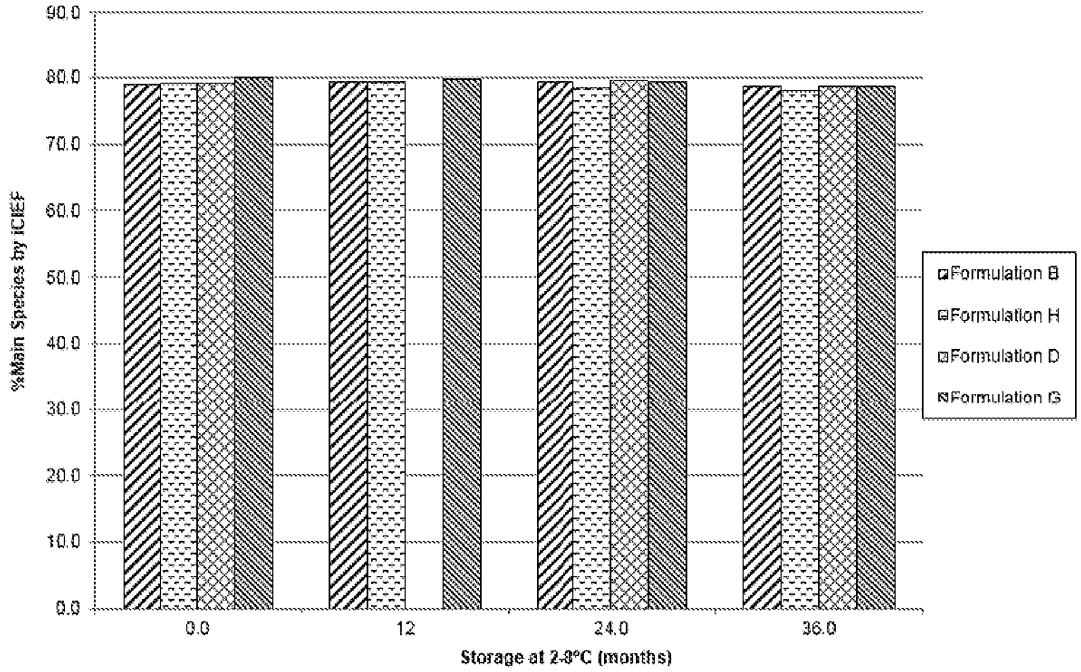

90.0
80.0
70.0
60.0
50.0
40.0
30.0
20.0
10.0
0.0
%Main Species by iCIEF
0.0
12
24.0
36.0
Storage at 2-8°C (months)
Formulation B
Formulation H
Formulation D
Formulation G

FIG. 1D

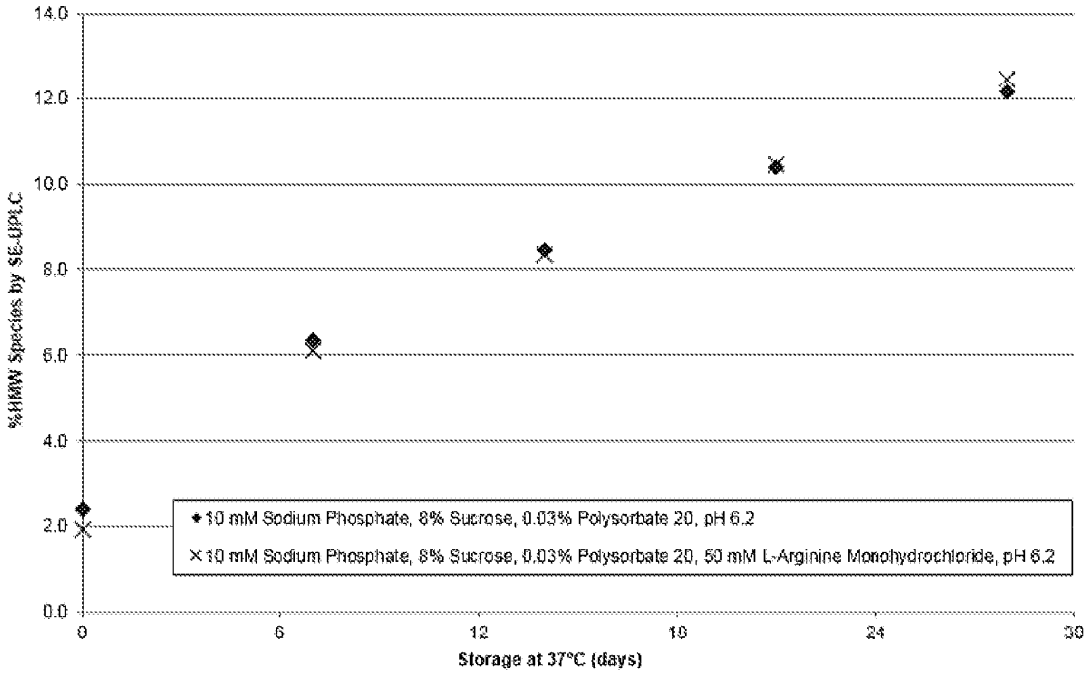

14.0
12.0
10.0
8.0
6.0
4.0
2.0
0.0
%HMW Species by SE-UPLC
0
6
12
18
24
30
Storage at 37°C (days)
10 mM Sodium Phosphate, 8% Sucrose, 0.03% Polysorbate 20, pH 6.2
10 mM Sodium Phosphate, 8% Sucrose, 0.03% Polysorbate 20, 50 mM L-Arginine Monohydrochloride, pH 6.2

FIG. 2A

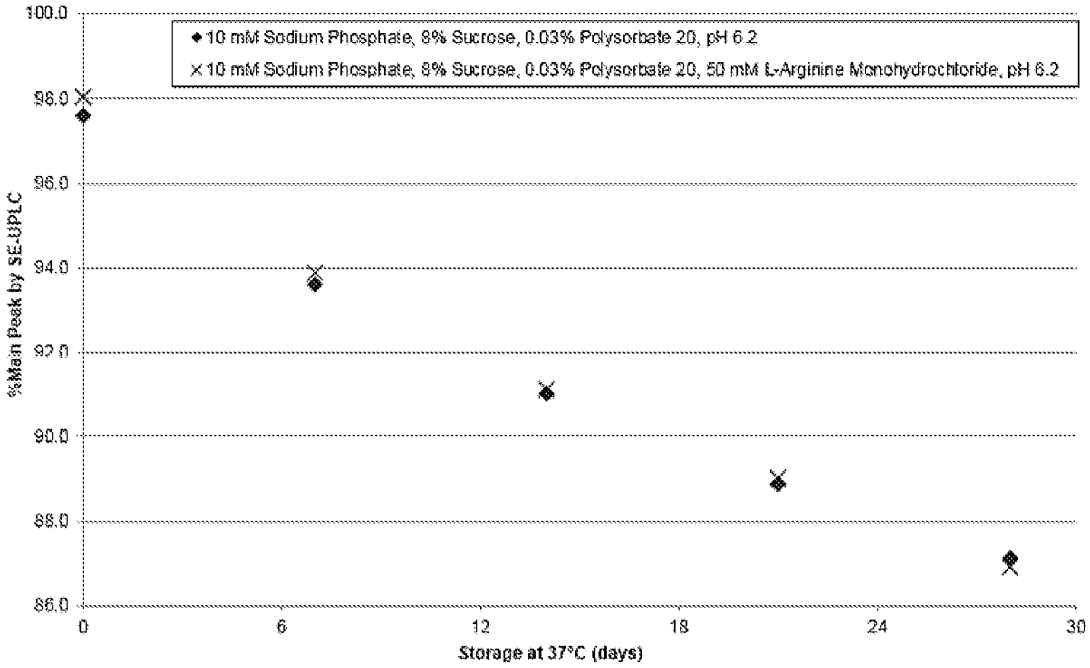

10 mM Sodium Phosphate, 8% Sucrose, 0.03% Polysorbate 20, pH 6.2
10 mM Sodium Phosphate, 8% Sucrose, 0.03% Polysorbate 20, 50 mM L-Arginine Monohydrochloride, pH 6.2
%Main Peak by SE-UPLC
100.0
98.0
96.0
94.0
92.0
90.0
88.0
86.0
0
6
12
18
24
30
Storage at 37°C (days)

FIG. 2B

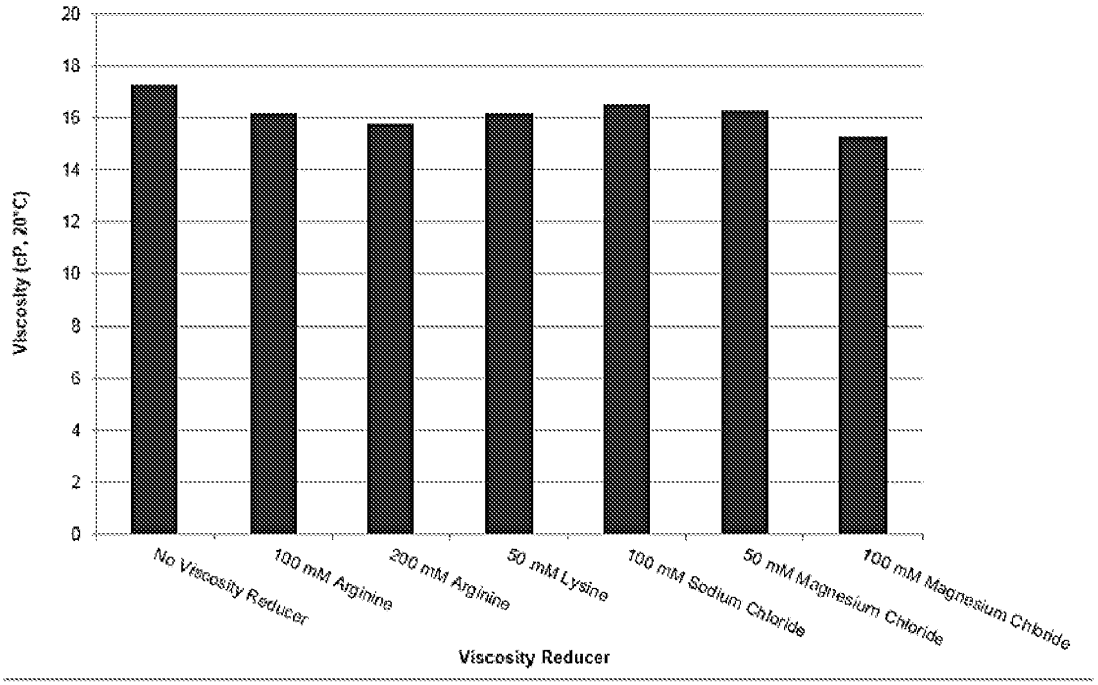

20
18
16
14
12
10
8
6
4
2
0
Viscosity (cP, 20°C)
No Viscosity Reducer
100 mM Arginine
200 mM Arginine
50 mM Lysine
100 mM Sodium Chloride
50 mM Magnesium Chloride
100 mM Magnesium Chloride
Viscosity Reducer

FIG. 3A

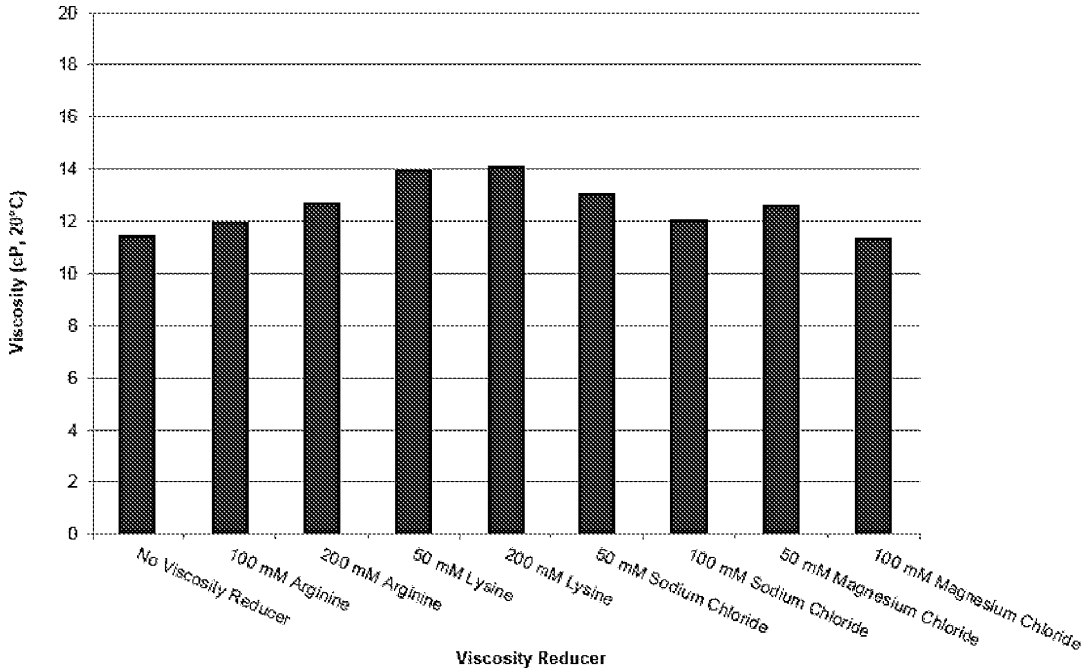

20
18
16
14
12
10
8
6
4
2
0
Viscosity (cP, 20°C)
No Viscosity Reducer
100 mM Arginine
200 mM Arginine
50 mM Lysine
200 mM Lysine
50 mM Sodium Chloride
100 mM Sodium Chloride
50 mM Magnesium Chloride
100 mM Magnesium Chloride
Viscosity Reducer

FIG. 3B

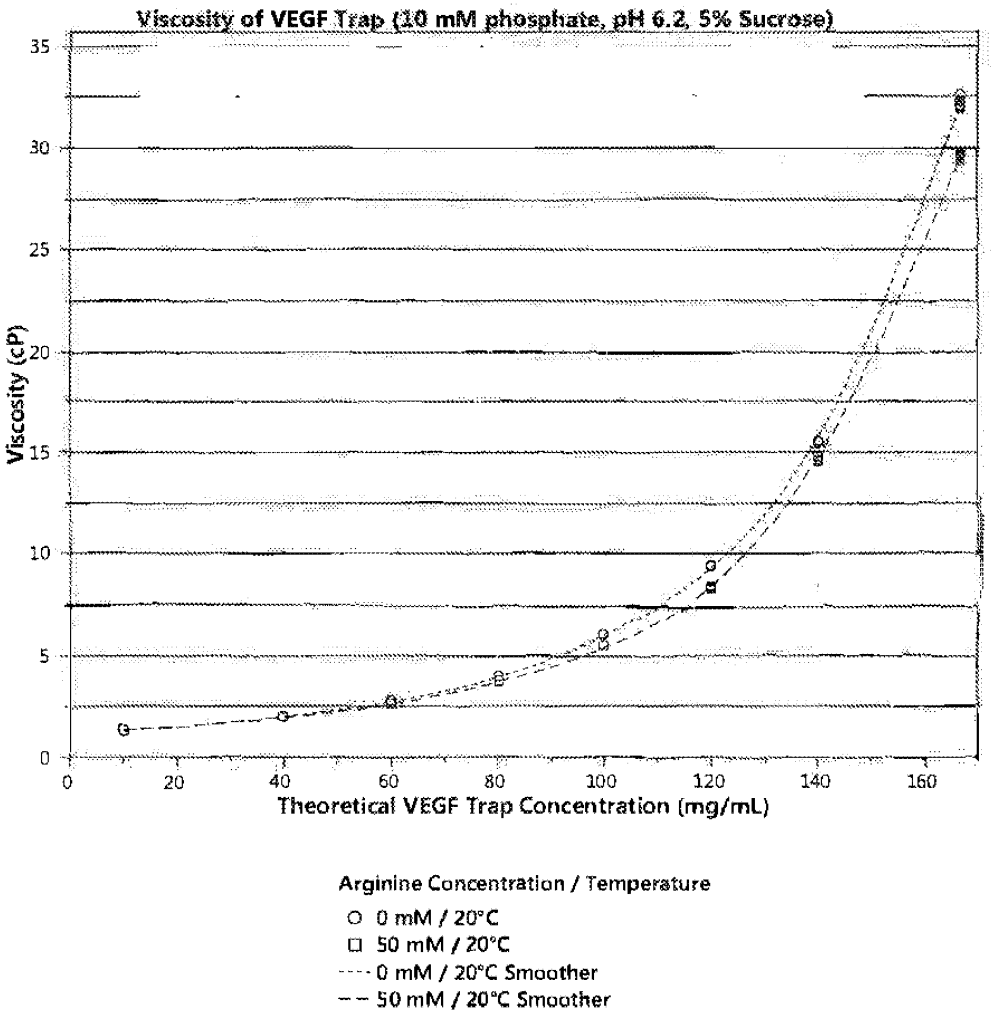

Viscosity of VEGF Trap (10 mM phosphate, pH 6.2, 5% Sucrose)
Viscosity (cP)
0
5
10
15
20
25
30
35
0
20
40
60
80
100
120
140
160
Theoretical VEGF Trap Concentration (mg/mL)
Arginine Concentration / Temperature
0 mM / 20°C
50 mM / 20°C
0 mM / 20°C Smoother
50 mM / 20°C Smoother

FIG. 3C

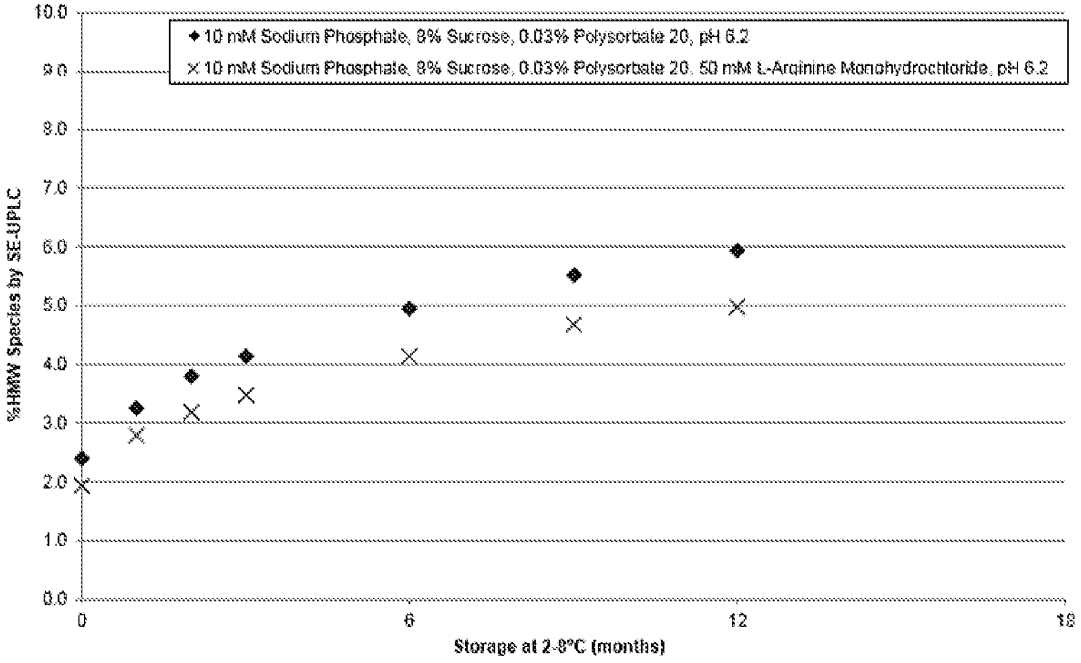

10 mM Sodium Phosphate, 8% Sucrose, 0.03% Polysorbate 20, pH 6.2
10 mM Sodium Phosphate, 8% Sucrose, 0.03% Polysorbate 20, 50 mM L-Arginine Monohydrochloride, pH 6.2
%HMW Species by SE-UPLC
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
0
6
12
18
Storage at 2-8°C (months)

FIG. 4A

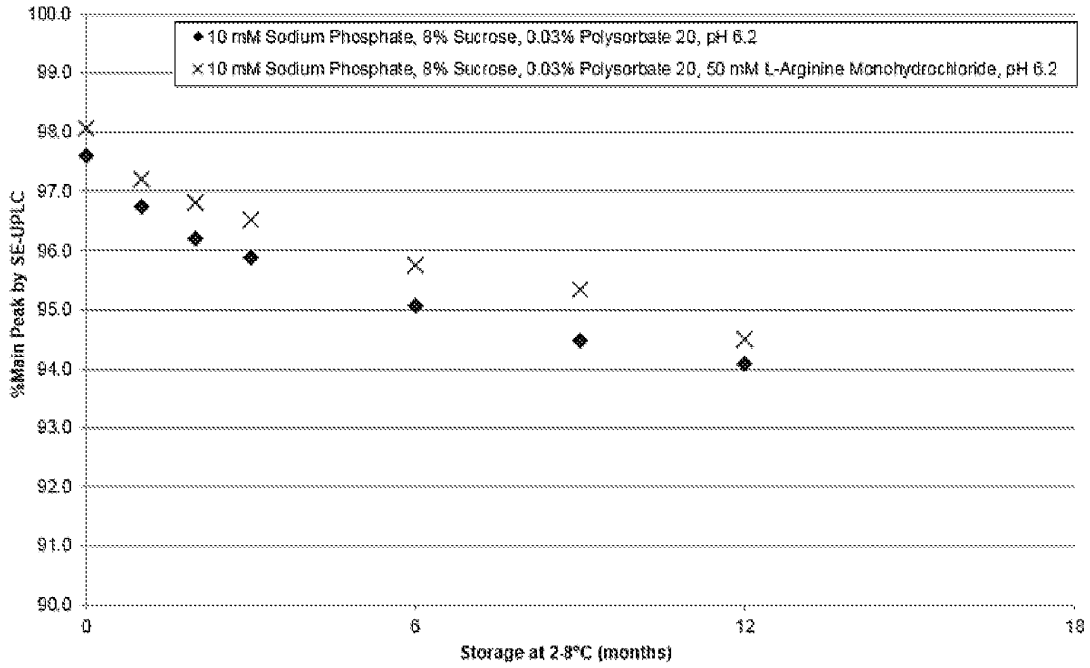

10 mM Sodium Phosphate, 8% Sucrose, 0.03% Polysorbate 20, pH 6.2
10 mM Sodium Phosphate, 8% Sucrose, 0.03% Polysorbate 20, 50 mM L-Arginine Monohydrochloride, pH 6.2
%Main Peak by SE-UPLC
100.0
99.0
98.0
97.0
96.0
95.0
94.0
93.0
92.0
91.0
90.0
0
6
12
18
Storage at 2-8°C (months)

FIG. 4B

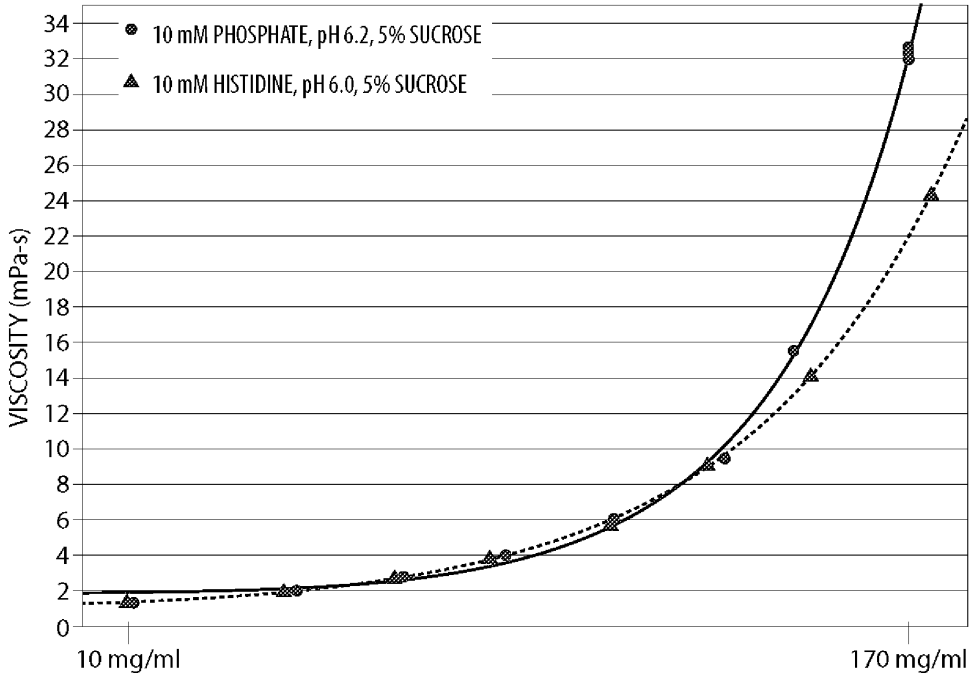


FIG. 5

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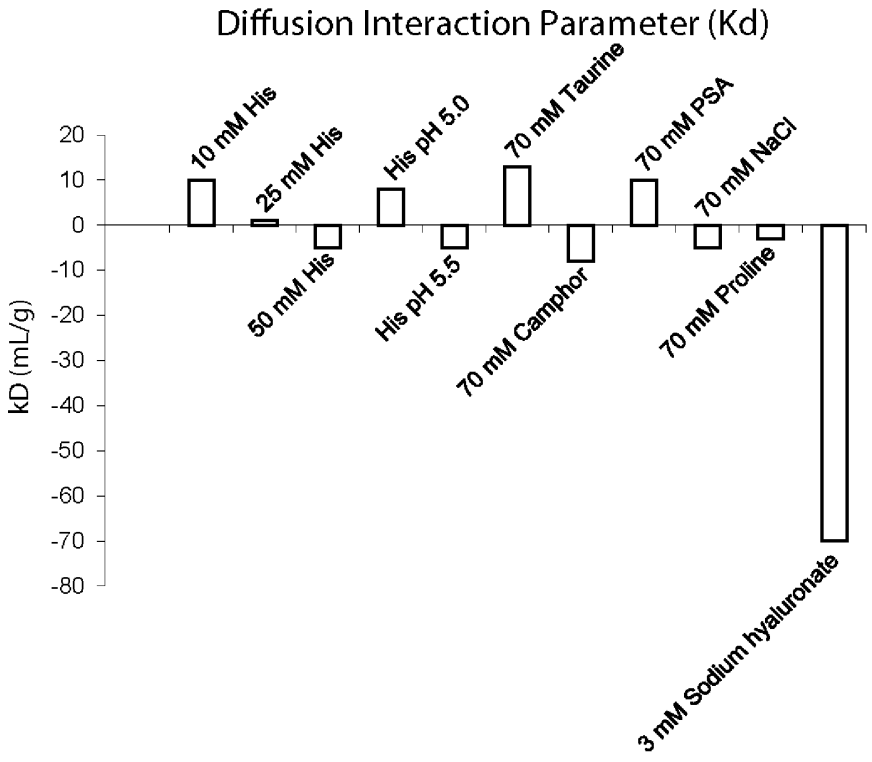

Diffusion Interaction Parameter (Kd)
kD (mL/g)
20
10
0
-10
-20
-30
-40
-50
-60
-70
-80
10 mM His
25 mM His
His pH 5.0
70 mM Taurine
70 mM PSA
70 mM NaCl
50 mM His
His pH 5.5
70 mM Camphor
70 mM Proline
3 mM Sodium hyaluronate

FIG. 6

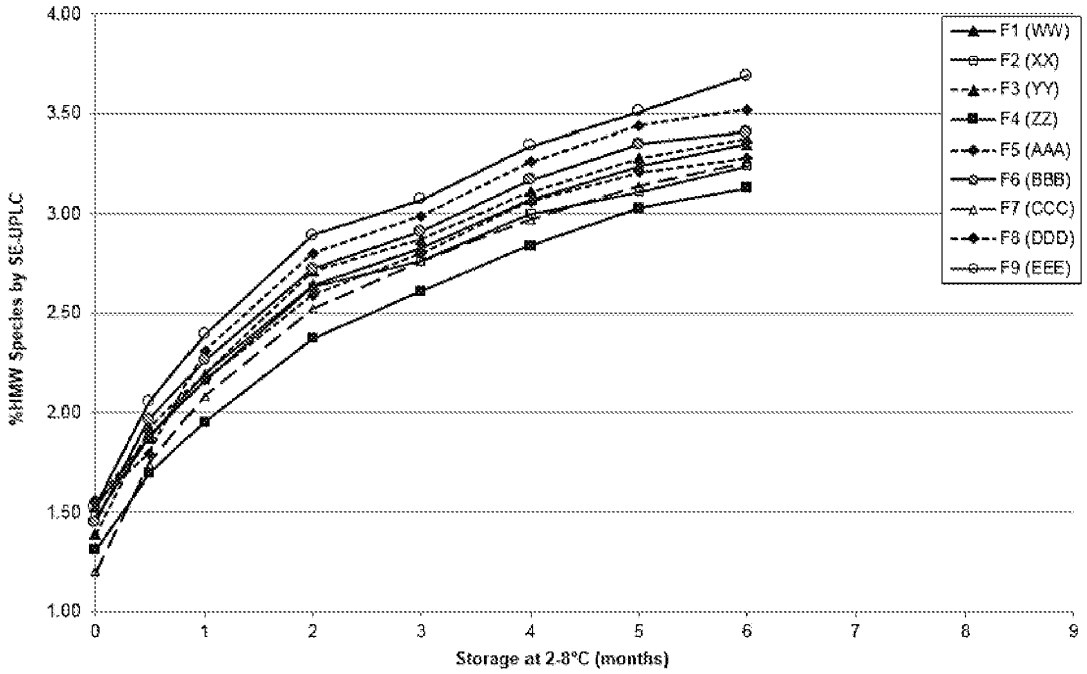

4.00
3.50
3.00
2.50
2.00
1.50
1.00
%HMW Species by SE-UPLC
0
1
2
3
4
5
6
7
8
9
Storage at 2-8°C (months)
F1 (WW)
F2 (XX)
F3 (YY)
F4 (ZZ)
F5 (AAA)
F6 (BBB)
F7 (CCC)
F8 (DDD)
F9 (EEE)

FIG. 7

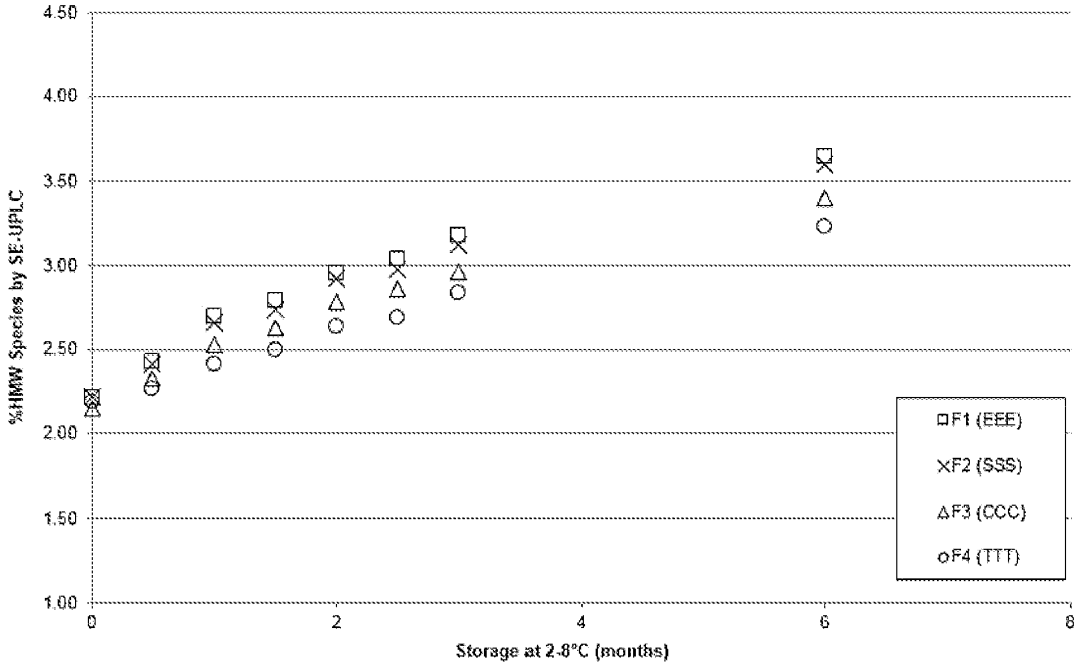

4.50
4.00
3.50
3.00
2.50
2.00
1.50
1.00
%HMW Species by SE-UPLC
0
2
4
6
8
Storage at 2-8°C (months)
□F1 (EEE)
×F2 (SSS)
△F3 (CCC)
○F4 (TTT)

FIG. 8A

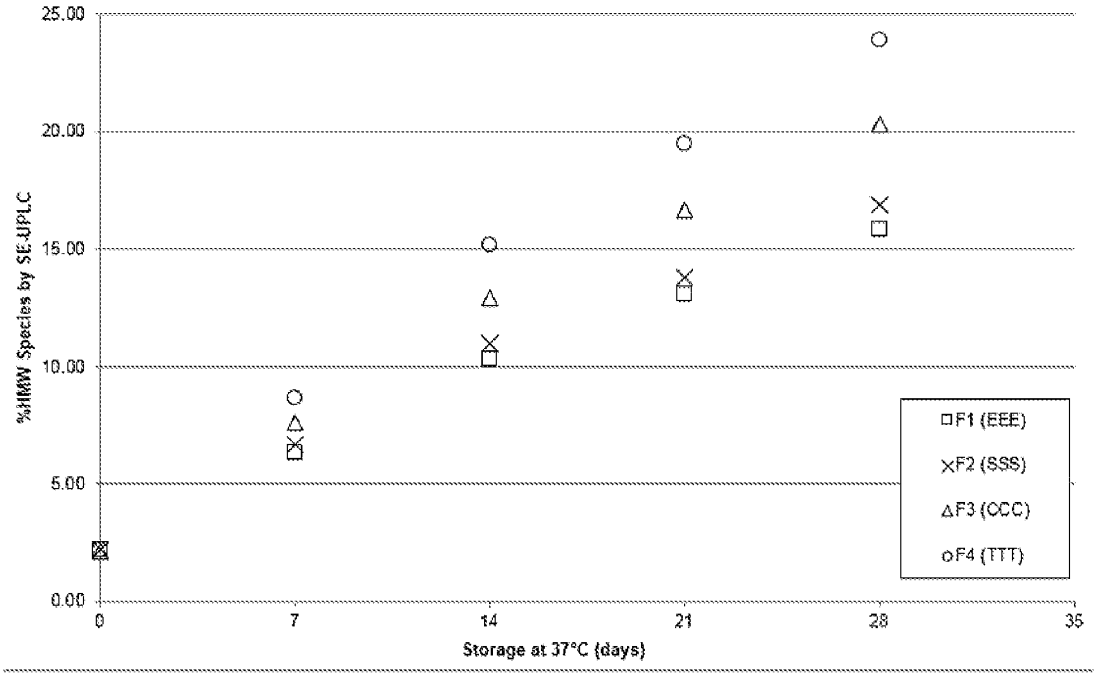

25.00
20.00
15.00
10.00
5.00
0.00
%HMW Species by SE-UPLC
0
7
14
21
28
35
Storage at 37°C (days)
□F1 (EEE)
×F2 (SSS)
△F3 (CCC)
○F4 (TTT)

FIG. 8B

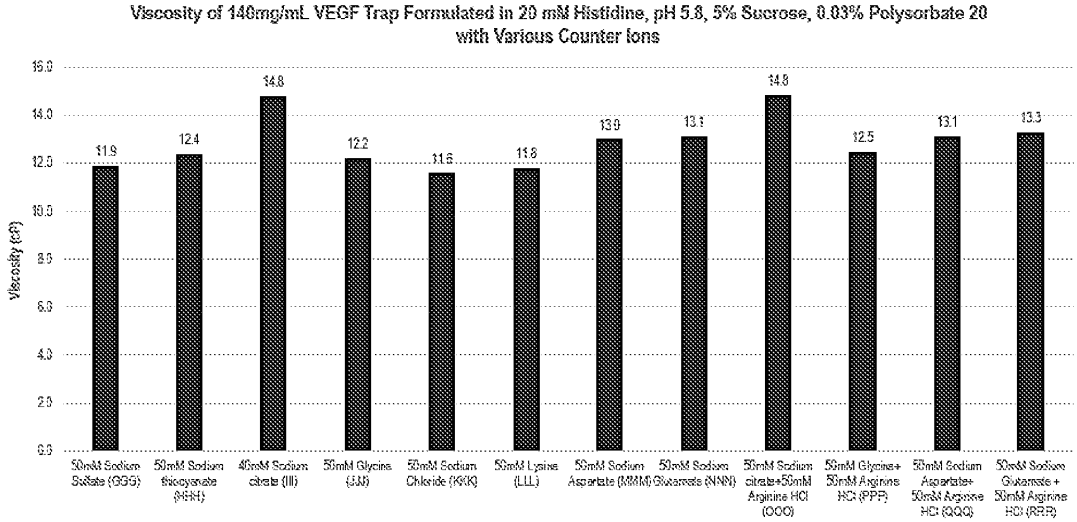

Viscosity of 140mg/mL VEGF Trap Formulated in 20 mM Histidine, pH 5.8, 5% Sucrose, 0.03% Polysorbate 20 with Various Counter Ions
Viscosity (cP)
16.0
14.0
12.0
10.0
8.0
6.0
4.0
2.0
0.0
11.9
12.4
14.8
12.2
11.6
11.8
13.0
13.1
14.8
12.5
13.1
13.3
50mM Sodium Sulfate (GGG)
50mM Sodium thiocyanate (HHH)
40mM Sodium citrate (III)
50mM Glycine (JJJ)
50mM Sodium Chloride (KKK)
50mM Lysine (LLL)
50mM Sodium Aspartate (MMM)
50mM Sodium Glutamate (NNN)
50mM Sodium citrate+50mM Arginine HCl (OOO)
50mM Glycine+ 50mM Arginine HCl (PPP)
50mM Sodium Aspartate+ 50mM Arginine HCl (QQQ)
50mM Sodium Glutamate + 50mM Arginine HCl (RRR)

FIG. 9

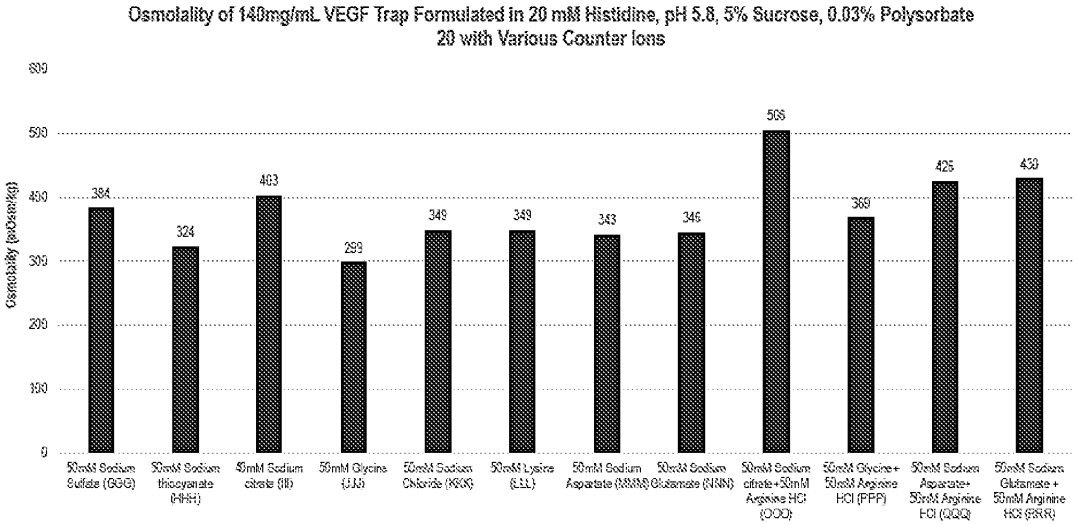

Osmolality of 140mg/mL VEGF Trap Formulated in 20 mM Histidine, pH 5.8, 5% Sucrose, 0.03% Polysorbate 20 with Various Counter Ions
Osmolality (mOsm/kg)
600
500
400
300
200
100
0
384
324
403
299
348
349
343
346
506
369
425
439
50mM Sodium Sulfate (GGG)
50mM Sodium thiocyanate (HHH)
40mM Sodium citrate (III)
50mM Glycine (JJJ)
50mM Sodium Chloride (KKK)
50mM Lysine (LLL)
50mM Sodium Aspartate (MMM)
50mM Sodium Glutamate (NNN)
50mM Sodium citrate+50mM Arginine HCl (OOO)
50mM Glycine+ 50mM Arginine HCl (PPP)
50mM Sodium Aspartate+ 50mM Arginine HCl (QQQ)
50mM Sodium Glutamate + 50mM Arginine HCl (RRR)

FIG. 10

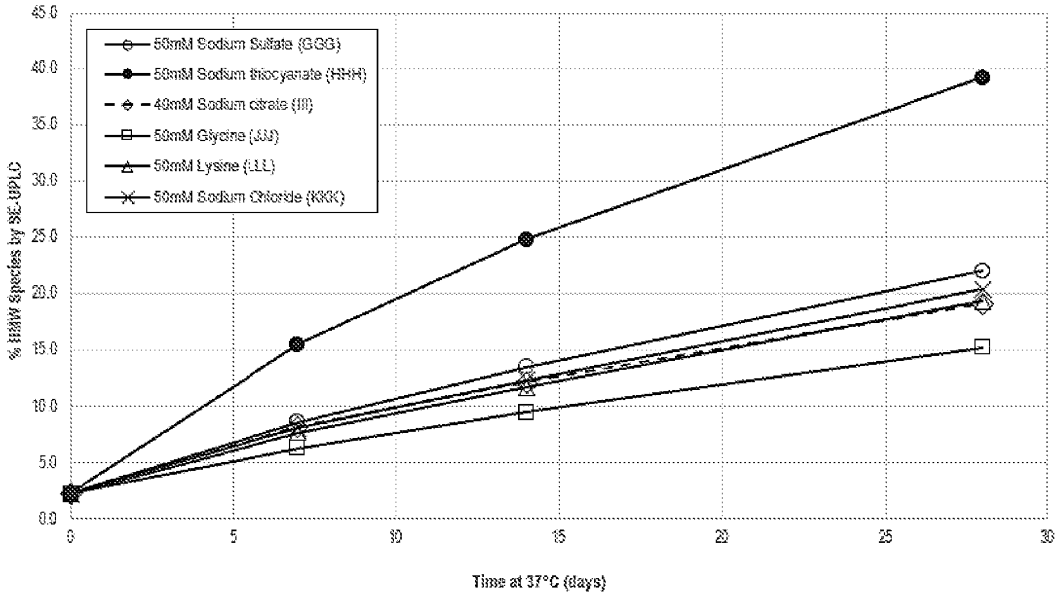


FIG. 11A

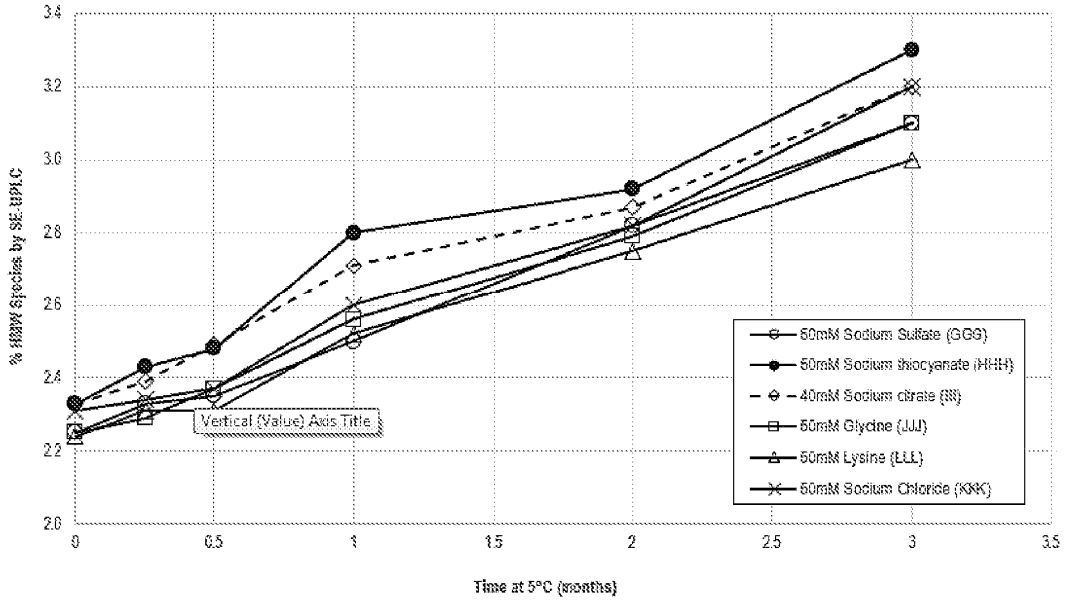


FIG. 11B

Formulations	Diffusion coefficient (cm2/sec)	Radius (nm)	% Pd
F1 (50mM Sodium Sulfate)	3.32E-07	7.4	15.3
F2(50mM Sodium thiocyanate)	2.98E-07	8.2	14.7
F3 (50mM Sodium citrate)	3.20E-07	7.7	16.3
F4 (50mM Glycine)	3.89E-07	6.3	18.9
F5 (50mM Sodium Chloride)	3.24E-07	7.6	13.8
F6 (50mM Lysine)	3.17E-07	7.7	13.5
F7 (50mM Sodium Aspartate)	3.32E-07	7.4	18.2
F8 (50mM Sodium Glutamate)	3.32E-07	7.4	15.0
F9 (50mM Sodium citrate+50mM Arginine HCl)	3.31E-07	7.4	14.4
F10 (50mM Glycine+ 50mM Arginine HCl)	3.31E-07	7.4	14.3
F11 (50mM Sodium Aspartate+ 50mM Arginine HCl)	3.24E-07	7.6	14.8
F12 (50mM Sodium Glutamate + 50mM Arginine HCl)	3.22E-07	7.6	13.3

FIG. 12

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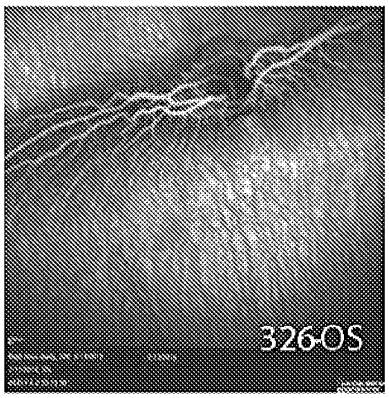


FIG. 13A

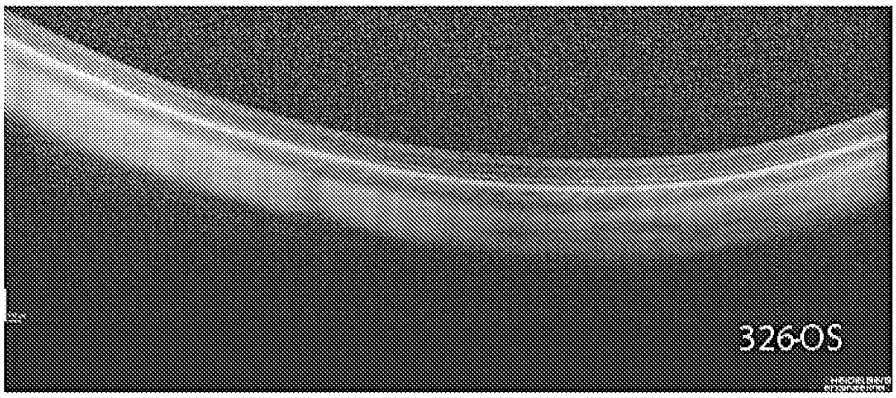


FIG. 13B

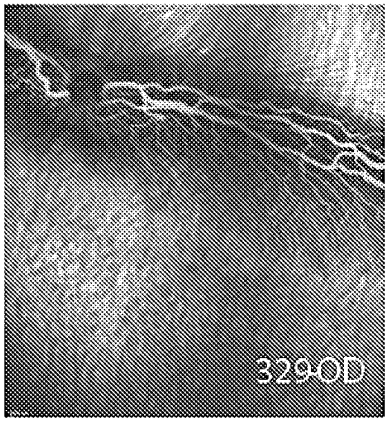


FIG. 13C

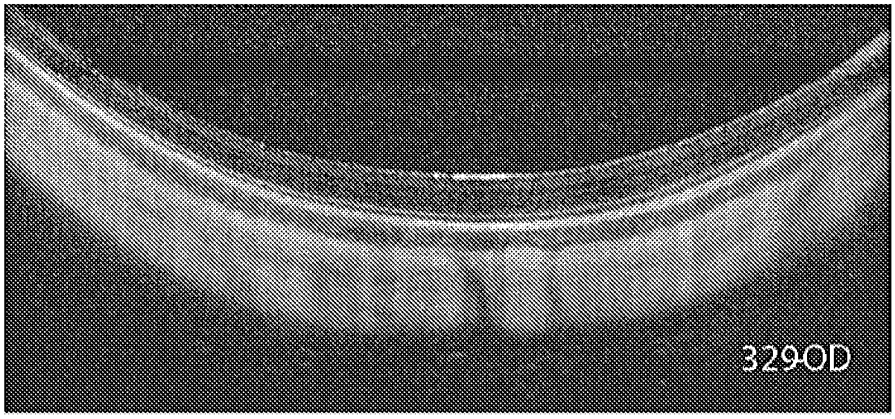


FIG. 13D

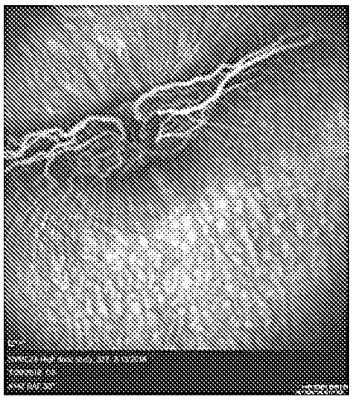


FIG. 14A

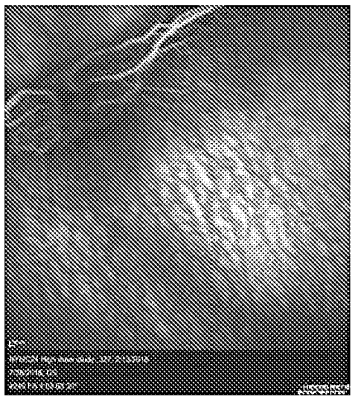


FIG. 14B

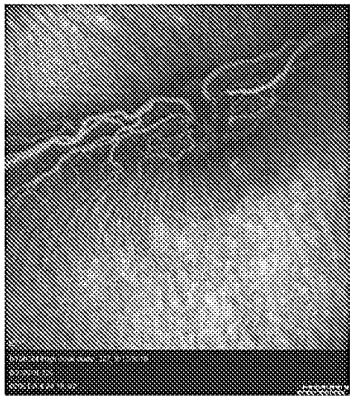


FIG. 14C

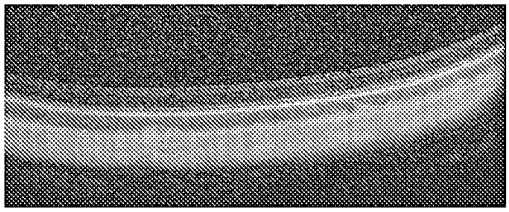


FIG. 14D

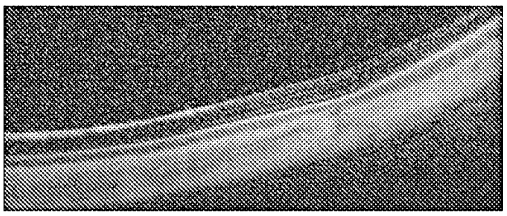


FIG. 14E

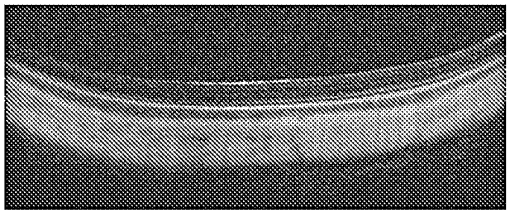


FIG. 14F

FA

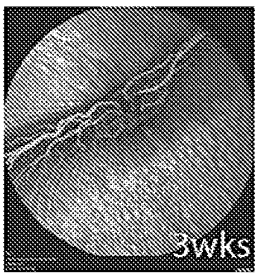


FIG. 15A

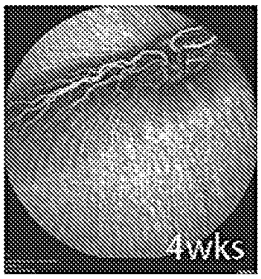


FIG. 15B

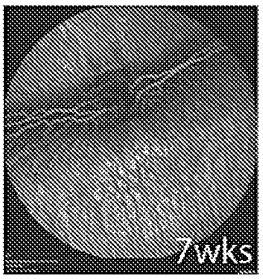


FIG. 15C

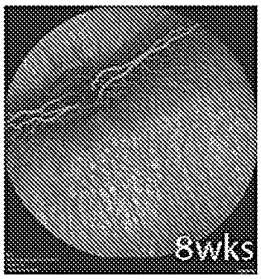


FIG. 15D

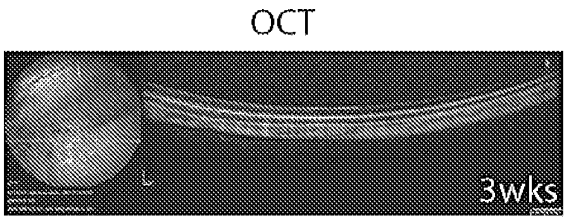


FIG. 15E

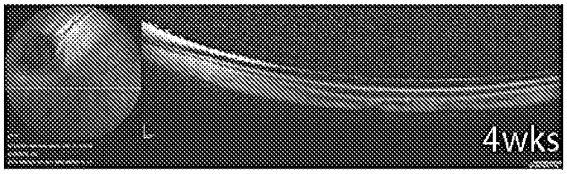


FIG. 15F

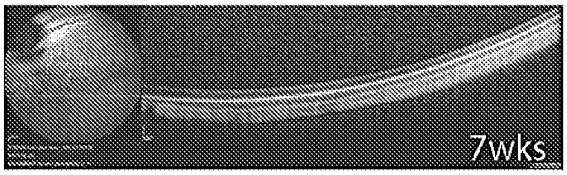


FIG. 15G

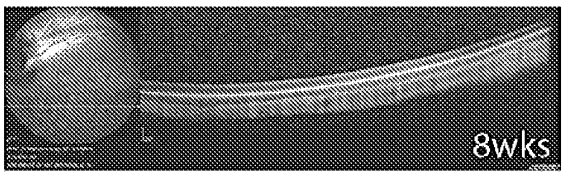


FIG. 15H

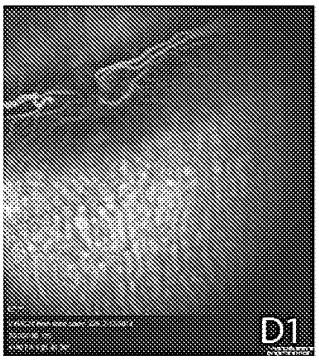


FIG. 16A

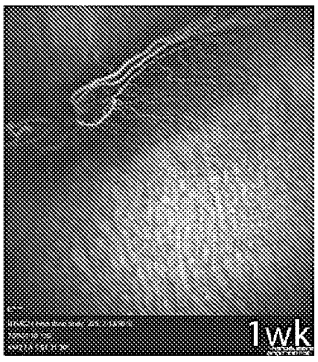


FIG. 16B

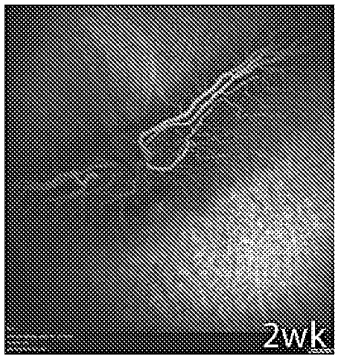


FIG. 16C

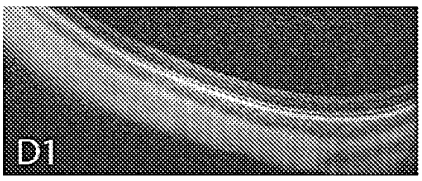


FIG. 16D

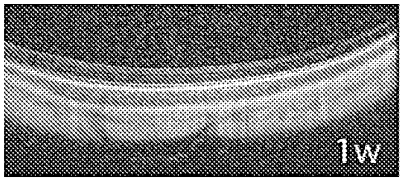


FIG. 16E

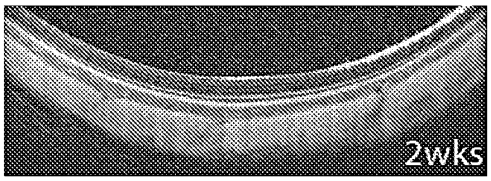


FIG. 16F

FA

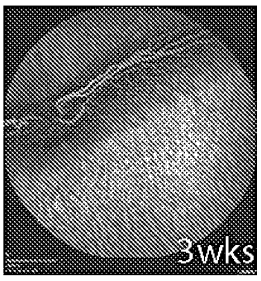


FIG. 17A

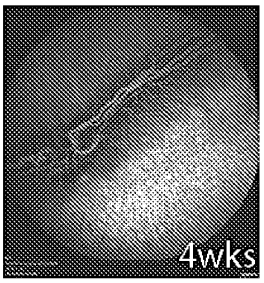


FIG. 17B

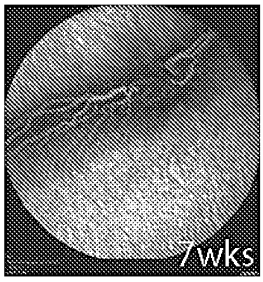


FIG. 17C

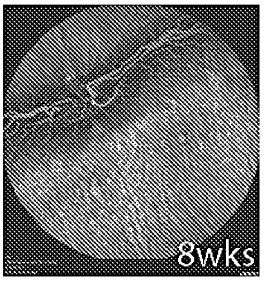


FIG. 17D

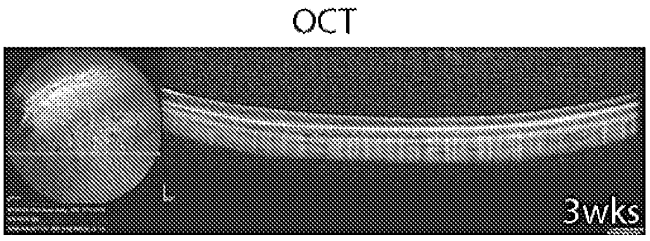


FIG. 17E

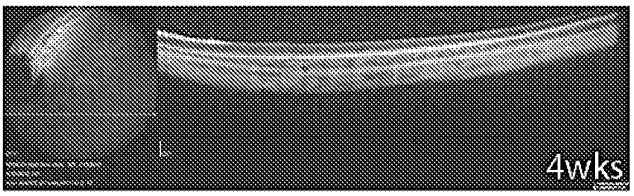


FIG. 17F

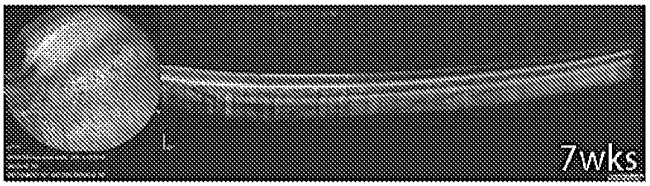


FIG. 17G

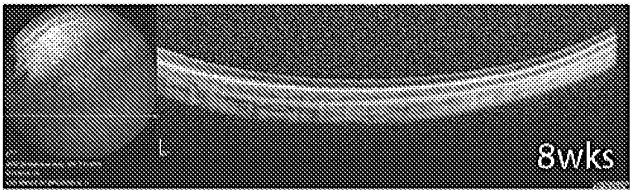


FIG. 17H

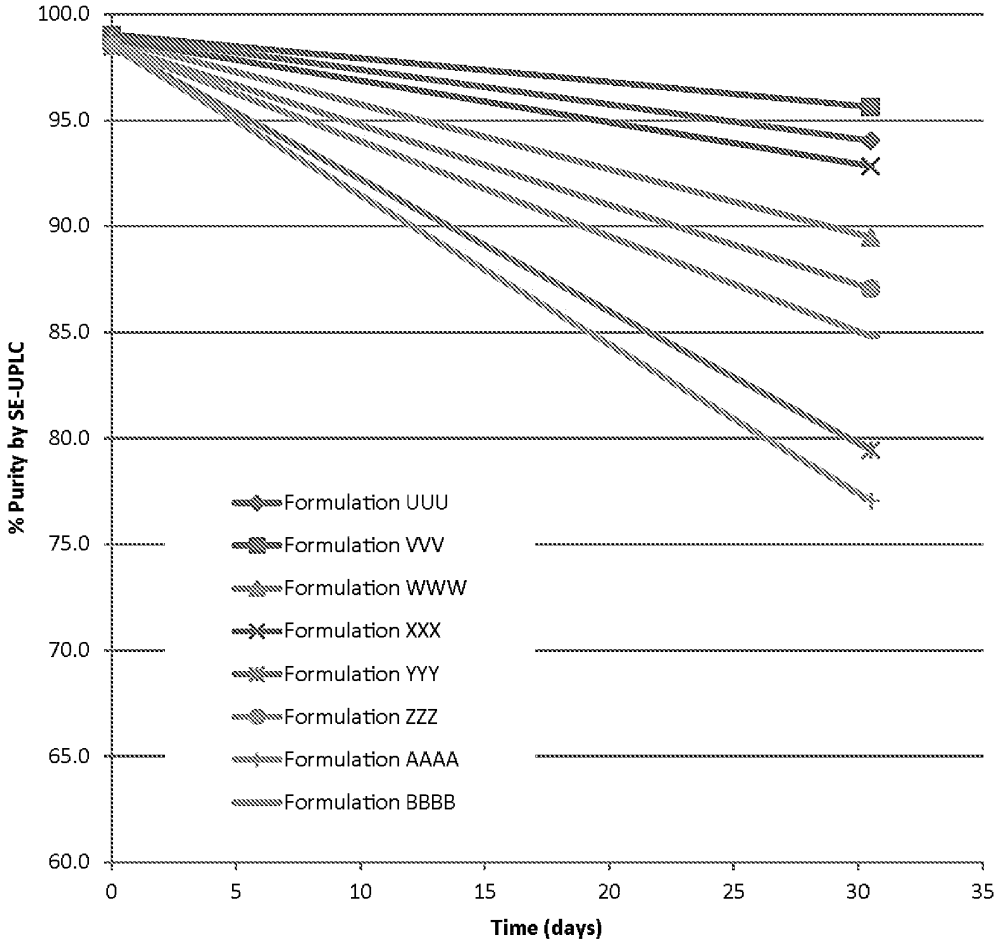

100.0
95.0
90.0
85.0
80.0
75.0
70.0
65.0
60.0
% Purity by SE-UPLC
0
5
10
15
20
25
30
35
Time (days)
Formulation UUU
Formulation VVV
Formulation WWW
Formulation XXX
Formulation YYY
Formulation ZZZ
Formulation AAAA
Formulation BBBB

FIG. 18A

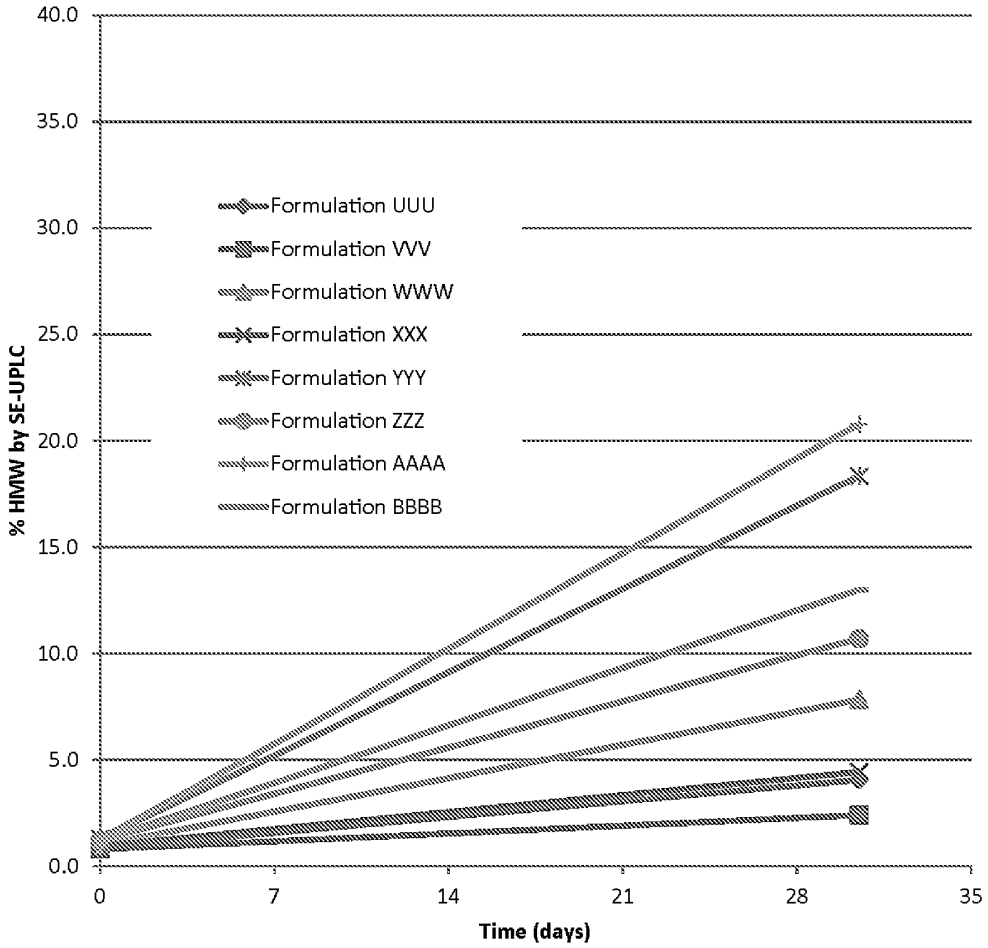

40.0
35.0
30.0
25.0
20.0
15.0
10.0
5.0
0.0
% HMW by SE-UPLC
0
7
14
21
28
35
Time (days)
Formulation UUU
Formulation VVV
Formulation WWW
Formulation XXX
Formulation YYY
Formulation ZZZ
Formulation AAAA
Formulation BBBB

FIG. 18B

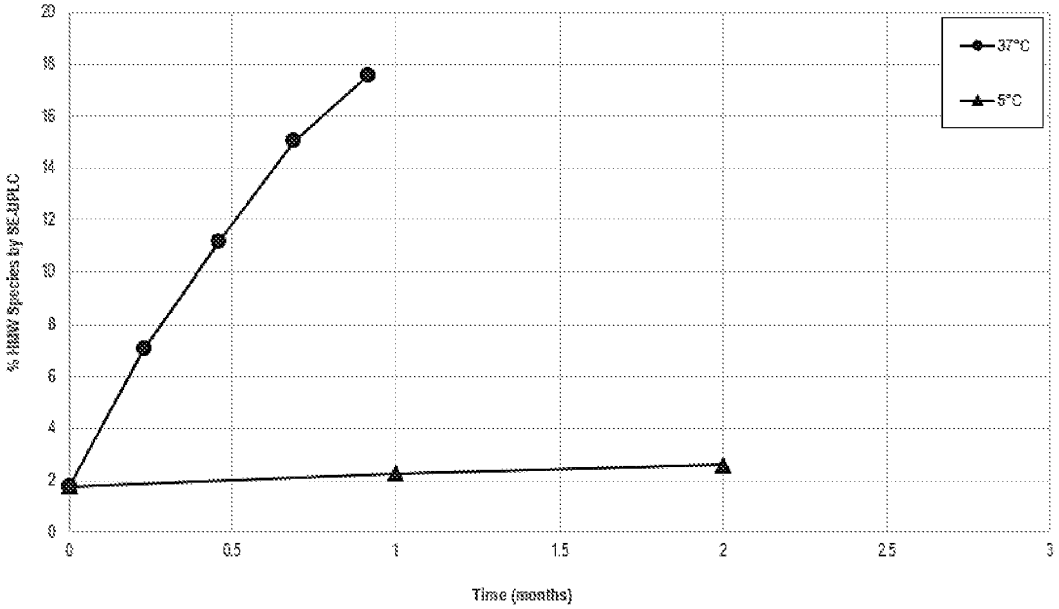


FIG. 19A

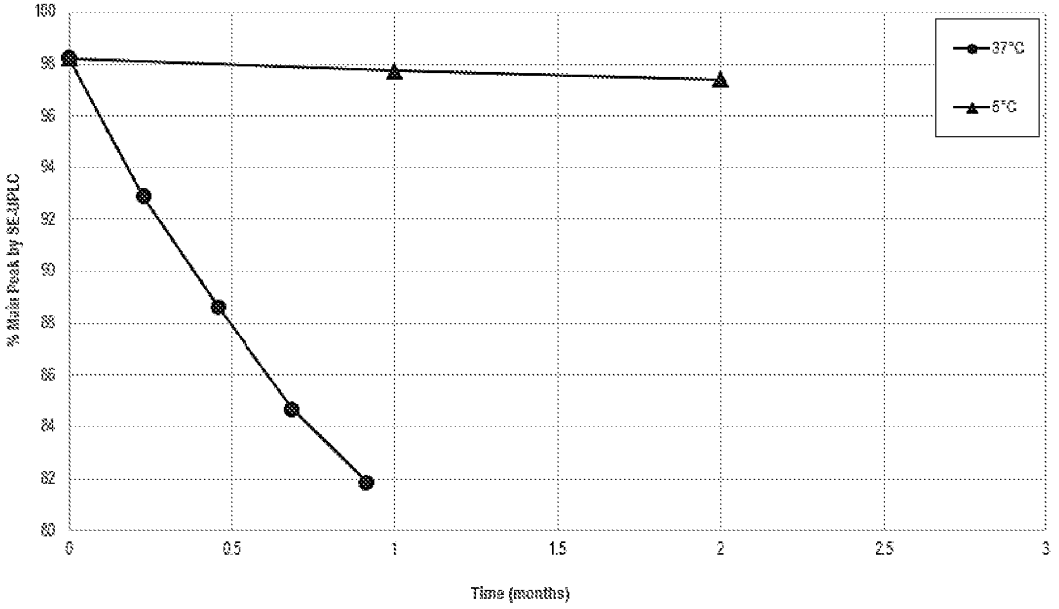


FIG. 19B

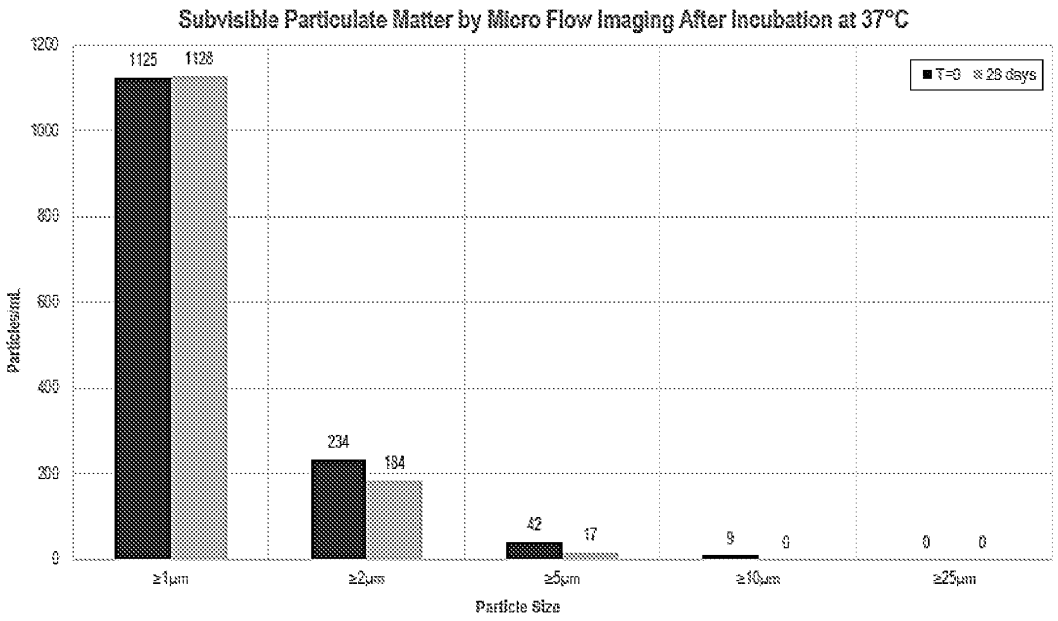


FIG. 19C

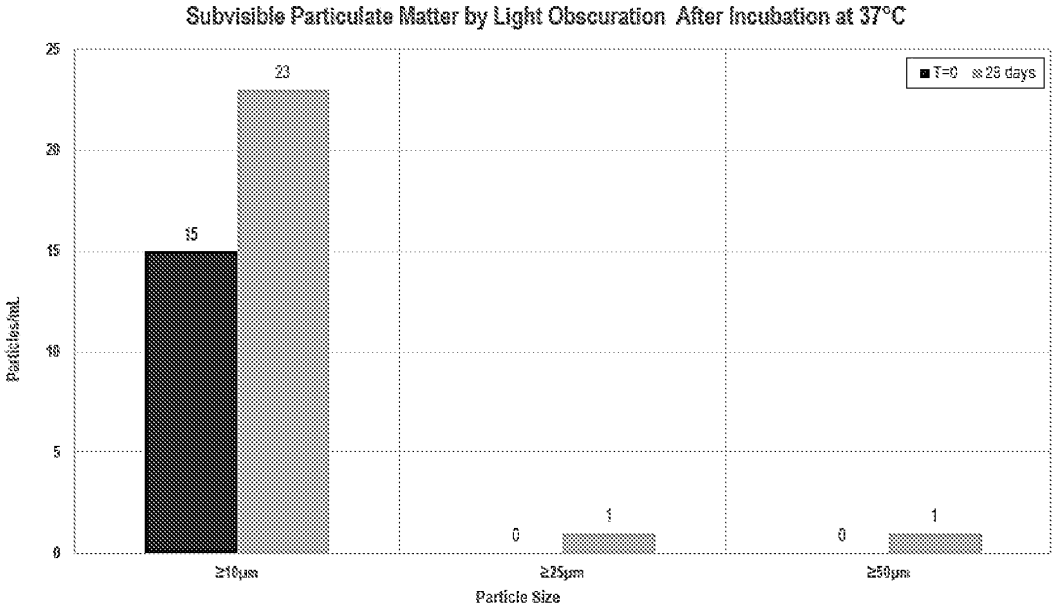


FIG. 19D

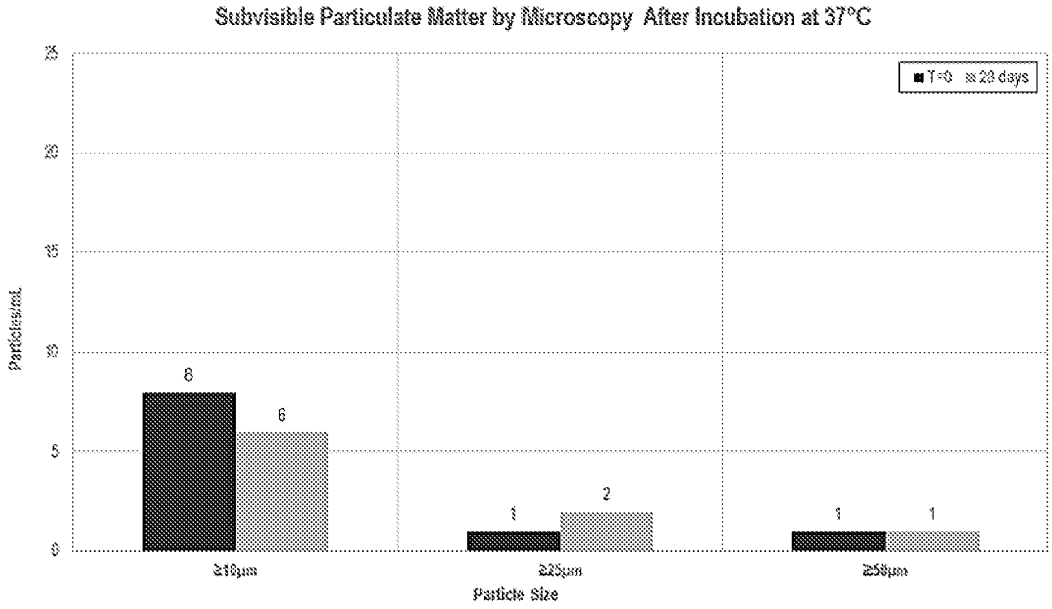

Subvisible Particulate Matter by Microscopy After Incubation at 37°C
T=0
≥ 28 days
Particles/mL
25
20
15
10
5
0
8
6
1
2
1
1
≥10µm
≥25µm
≥50µm
Particle Size

FIG. 19E

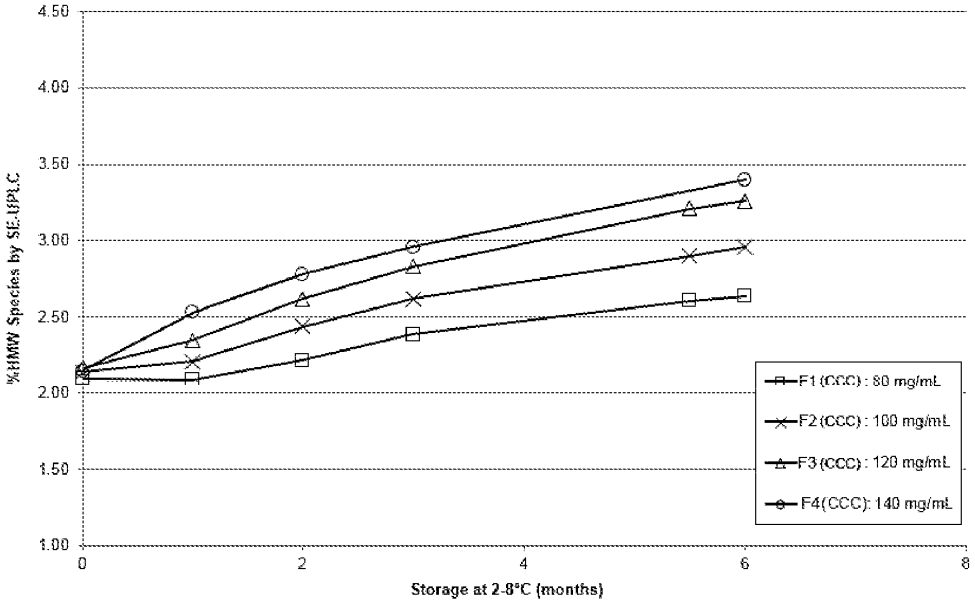

4.50
4.00
3.50
3.00
2.50
2.00
1.50
1.00
%HMW Species by SE-HPLC
0
2
4
6
8
Storage at 2-8°C (months)
F1 (CCC) : 80 mg/mL
F2 (CCC) : 100 mg/mL
F3 (CCC) : 120 mg/mL
F4 (CCC): 140 mg/mL

FIG. 20A

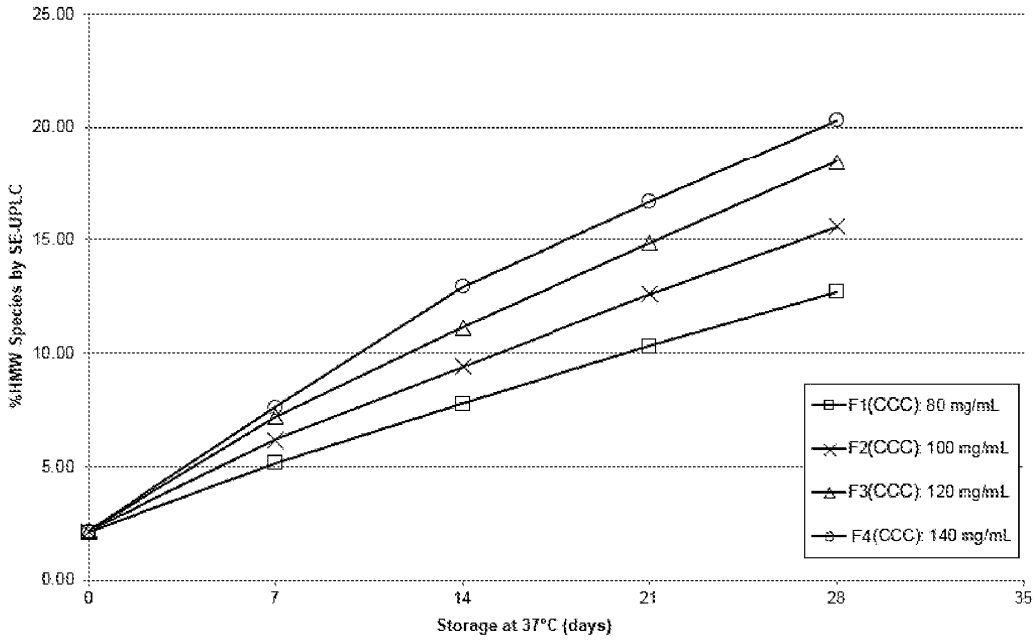

25.00
20.00
15.00
10.00
5.00
0.00
%HMW Species by SE-UPLC
0
7
14
21
28
35
Storage at 37°C (days)
F1(CCC): 80 mg/mL
F2(CCC): 100 mg/mL
F3(CCC): 120 mg/mL
F4(CCC): 140 mg/mL

FIG. 20B

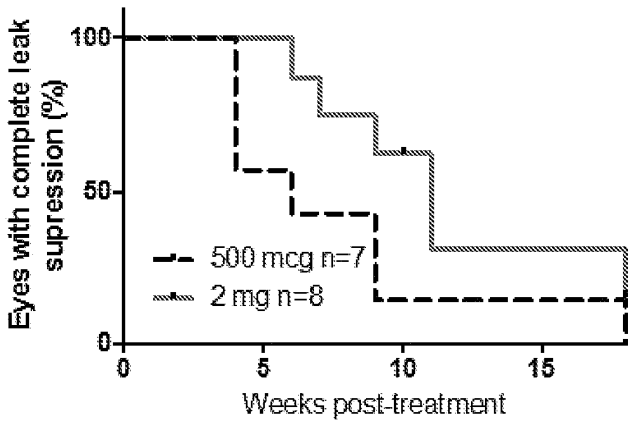

Eyes with complete leak supression (%)
100
50
0
0
5
10
15
Weeks post-treatment
500 mcg n=7
2 mg n=8

FIG. 21

Electronic Patent Application Fee Transmittal	
Application Number:	
Filing Date:	
Title of Invention:	High Concentration VEGF Receptor Fusion Protein Containing Formulations
First Named Inventor/Applicant Name:	Kenneth S. Graham
Filer:	Lance A. Termes
Attorney Docket Number:	125984-266215
Filed as Large Entity	
Filing Fees for Utility under 35 USC 111(a)	

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
UTILITY APPLICATION FILING	1011	1	320	320
UTILITY SEARCH FEE	1111	1	700	700
UTILITY EXAMINATION FEE	1311	1	800	800
Pages:				
Claims:				
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Post-Allowance-and-Post-Issuance:				
Extension-of-Time:				
Miscellaneous:				
		Total in USD ($)		**1820**

Electronic Acknowledgement Receipt	
EFS ID:	43331918
Application Number:	17384070
International Application Number:	
Confirmation Number:	1061
Title of Invention:	High Concentration VEGF Receptor Fusion Protein Containing Formulations
First Named Inventor/Applicant Name:	Kenneth S. Graham
Customer Number:	147803
Filer:	Lance A. Termes
Filer Authorized By:	
Attorney Docket Number:	125984-266215
Receipt Date:	23-JUL-2021
Filing Date:	
Time Stamp:	15:14:52
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	DA
Payment was successfully received in RAM	$1820
RAM confirmation Number	E20217MF15330215
Deposit Account	
Authorized User	
The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows:	

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Application Data Sheet	10430US02-ADS.pdf	132849 ef37349a9660ad0960aff636b599641bcb4bf297	no	6
Warnings:					
Information:					
This is not an USPTO supplied ADS fillable form					
2		10430US02-Application.pdf	566297 06f130b41da5e1c4bdd24f1a7bd30a44751519ae	yes	89

	Multipart Description/PDF files in .zip description		
	Document Description	**Start**	**End**
	Specification	1	76
	Claims	77	88
	Abstract	89	89

Warnings:					
Information:					
3	Oath or Declaration filed	10430US02-Declarations_Copy.pdf	222653 6a1f35681c36dd4c2f31c9dedd8aadbe2fa89f79	no	2
Warnings:					
Information:					
4		10430US02-Preliminary_Amendment.pdf	106052 94c315756a1aee30fd6b188a9623d5b51edcc04f	yes	5

	Multipart Description/PDF files in .zip description		
	Document Description	**Start**	**End**
	Preliminary Amendment	1	1

	Claims		2	4	
	Applicant Arguments/Remarks Made in an Amendment		5	5	
Warnings:					
Information:					
5	Drawings-only black and white line drawings	10430US02-Figures.pdf	4552789 12a8b0a5b65aad7164ae9ccce7587f4dcb2f4511	no	37
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Information:					
6	Sequence Listing (Text File)	10430US02-Sequence.txt	6385	no	-
Warnings:					
Information:					
7	Fee Worksheet (SB06)	fee-info.pdf	35202 b24699be058056e373943ed68f2e7a1d5e20b243	no	2
Warnings:					
Information:					
		Total Files Size (in bytes):	5622227		

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New Applications Under 35 U.S.C. 111
If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.
National Stage of an International Application under 35 U.S.C. 371
If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.
New International Application Filed with the USPTO as a Receiving Office
If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

Application Data Sheet

Application Information

Application number:	Unassigned
Filing Date (YYYY-MM-DD):	Herewith
Application Type:	Nonprovisional
Subject Matter:	Utility
Suggested classification:	
Suggested Group Art Unit:	
CD-ROM or CD-R??:	
Number of CD disks:	
Number of copies of CDs:	
Sequence Submission:	Yes
Computer Readable Form (CRF)?:	Yes
Number of copies of CRF:	1
Title:	High Concentration VEGF Receptor Fusion Protein Containing Formulations
Attorney Docket Number:	125984-266215
Request for Early Publication:	No
Request for Non-Publication:	No
Suggested Drawing Figure:	
Total Drawing Sheets:	37
Small Entity?:	No
Latin name:	
Variety denomination name:	
Petition included?:	No
Petition Type:	
Licensed US Govt. Agency:	
Contract or Grant Numbers One:	
Secrecy Order in Parent Appl.:	No

Regeneron Ex. 2001
Alvotech v. Regeneron
PGR2025-00085
Page 48 of 531

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Postal or Zip Code of mailing address:	10591

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State or Province of mailing address:	NY

Country of mailing address: US

Postal or Zip Code of mailing address: 10591

Correspondence Information

Correspondence Customer Number: 147803
Email Address:

Publication Information

☐ Request Early Publication:
(Fee required at time of Request 37 CFR 1.219)

☐ Request Not to Publish:
I hereby request that the attached application not be published under 35 U.S.C. 122(b) and certify that the invention disclosed in the attached application **has not and will not** be the subject of an application filed in another country, or under a multilateral international agreement, that requires publication at eighteen months after filing.

Representative Information

Representative Customer Number: 147803

Domestic Benefit/National Stage Information

Application:	Continuity Type:	Prior Application No.:	Filing Date (YYYY-MM-DD):
This Application	Continuation of	16/409,631	2019-05-10
16/409,631	An application claiming the benefit under 35 USC 119(e)	62/669,506	2018-05-10
16/409,631	An application claiming the benefit under 35 USC 119(e)	62/752,127	2018-10-29
16/409,631	An application claiming the benefit under 35 USC 119(e)	62/769,876	2018-11-20
16/409,631	An application claiming the benefit under 35 USC 119(e)	62/813,882	2019-03-05

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Foreign Priority Information

Application Number:	Country:	Filing Date (YYYY-MM-DD):	Access Code (if applicable)

Statement under 37 CFR 1.55 or 1.78 for AIA (First Inventor to File) Transition Applications

☐ This application (1) claims priority to or the benefit of an application filed before March 16, 2013 and (2) also contains, or contained at any time, a claim to a claimed invention that has an effective filing date on or after March 16, 2013.

NOTE: By providing this statement under 37 CFR 1.55 or 1.78, this application, with a filing date on or after March 16, 2013, will be examined under the first inventor to file provisions of the AIA.

Authorization or Opt-Out of Authorization to Permit Access:

When this Application Data Sheet is properly signed and filed with the application, applicant has provided written authority to permit a participating foreign intellectual property (IP) office access to the instant application-as-filed (see paragraph A in subsection 1 below) and the European Patent Office (EPO) access to any search results from the instant application (see paragraph B in subsection 1 below).

Should applicant choose not to provide an authorization identified in subsection 1 below, applicant **must opt-out** of the authorization by checking the corresponding box A or B or both in subsection 2 below.

NOTE: This section of the Application Data Sheet is **ONLY** reviewed and processed with the **INITIAL** filing of an application. After the initial filing of an application, an Application Data Sheet cannot be used to provide or rescind authorization for access by a foreign IP office(s). Instead, Form PTO/SB/39 or PTO/SB/69 must be used as appropriate.

1. Authorization to Permit Access by a Foreign Intellectual Property Office(s)

A. Priority Document Exchange (PDX) - Unless box A in subsection 2 (opt-out of authorization) is checked, the undersigned hereby **grants the USPTO authority** to provide the European Patent Office (EPO), the Japan Patent Office (JPO), the Korean Intellectual Property Office (KIPO), the State Intellectual Property Office of the People's Republic of China (SIPO), the World Intellectual Property Organization (WIPO), and any other foreign intellectual property office participating with the USPTO in a bilateral or multilateral priority document exchange agreement in which a foreign application claiming priority to the instant patent application is filed, access to: (1) the instant patent application-as-filed and its related bibliographic data, (2) any foreign or domestic application to which priority or benefit is claimed by the instant application and its related bibliographic data, and (3) the date of filing of this Authorization. See 37 CFR 1.14(h)(1).

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B. Search Results from U.S. Application to EPO - Unless box B in subsection 2 (opt-out of authorization) is checked, the undersigned hereby **grants the USPTO authority** to provide the EPO access to the bibliographic data and search results from the instant patent application when a European patent application claiming priority to the instant patent application is filed. See 37 CFR 1.14(h)(2).

The applicant is reminded that the EPO's Rule 141(1) EPC (European Patent Convention) requires applicants to submit a copy of search results from the instant application without delay in a European patent application that claims priority to the instant application.

2. Opt-Out of Authorizations to Permit Access by a Foreign Intellectual Property Office(s)

☐ A. Applicant **DOES NOT** authorize the USPTO to permit a participating foreign IP office access to the instant application-as-filed. If this box is checked, the USPTO will not be providing a participating foreign IP office with any documents and information identified in subsection 1A above.

☐ B. Applicant **DOES NOT** authorize the USPTO to transmit to the EPO any search results from the instant patent application. If this box is checked, the USPTO will not be providing the EPO with search results from the instant application.

NOTE: Once the application has published or is otherwise publicly available, the USPTO may provide access to the application in accordance with 37 CFR 1.14.

Applicant Information

Applicant 1

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Legal Representative under 35 USC 117:	
Joint Inventor:	
Person to whom the inventor is obligated to assign:	
Person who shows sufficient proprietary interest:	
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Name of the Deceased or Legally Incapacitated Inventor:	
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If the Applicant is an Organization check here: ☐

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HIGH CONCENTRATION VEGF RECEPTOR FUSION PROTEIN CONTAINING FORMULATIONS

CROSS-REFERENCE TO RELATED APPLICATIONS

[001] This application is a continuation of U.S. Application No. 16/409,631, filed May 10, 2019, which claims the benefit of U.S. Provisional Patent Application No. 62/813,882, filed March 5, 2019; U.S. Provisional Patent Application No. 62/769,876, filed November 20, 2018; U.S. Provisional Patent Application No. 62/752,127, filed October 29, 2018; and U.S. Provisional Patent Application No. 62/669,506, filed May 10, 2018; each of which is herein incorporated by reference in its entirety.

TECHNICAL FIELD

[002] Embodiments herein relate generally to high concentration VEGF receptor fusion protein containing formulations suitable for ocular administration. More particularly, embodiments herein provide liquid pharmaceutical formulations for intravitreal administration, where the formulations include more than 40 mg/ml VEGF receptor fusion protein, and show pharmaceutically acceptable potency, stability, viscosity and pH.

SEQUENCE LISTING

[003] An official copy of the sequence listing is submitted concurrently with the specification electronically via EFS-Web as an ASCII formatted sequence listing with a file name of "10430US02-Sequence.txt", a creation date of July 23, 2021, and a size of 6,385 bytes. The sequence listing contained in this ASCII formatted document is part of the specification and is herein incorporated by reference in its entirety.

BACKGROUND OF THE INVENTION

[004] The development of a therapeutically useful liquid formulation requires a combination of ingredients, at differing amounts, to provide a functional and stable delivery vehicle for a drug of interest. This is particularly true where the drug is a protein, and furthermore, an antibody. Antibody formulations have long presented challenges to drug developers and manufacturers, as antibody activity and administration typically require a pharmaceutically acceptable potency, osmolality, protein stability, viscosity, and proper pH.

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These challenges are exacerbated when the antibody is at higher concentrations in the formulation, for example, beyond 20 to 40 mg/ml, the concentration of most pharmaceutically sold antibodies.

[005] Higher concentration antibody formulations allow for shorter injection times, smaller injection volumes, lower frequency of antibody administration, and more efficient manufacturing and storage utility. However, as noted above, the higher the antibody or protein concentration, the more difficult it is to maintain the proper activity and delivery parameters for the formulation. In particular, high concentration antibody and protein formulations often contend with increased protein aggregation and viscosity, which results in lower overall antibody or protein potency, and lower manufacturing and poorer storage stability. Because of the issues related to high concentration protein or antibody formulations, few such pharmaceutically acceptable formulations have been developed. There is a need in the art for preparing high concentration, high stability, antibody and protein formulations that include the proper potency, stability, viscosity, osmolality and pH.

[006] One such protein in need of high concentration formulations is the vascular endothelial growth factor (VEGF) receptor fusion protein. VEGF receptor fusion proteins are used to block VEGF function in a number of ophthalmic formulations, for example, EYLEA® (Regeneron Pharmaceuticals, Inc.). High concentration VEGF receptor fusion protein containing formulations could allow for shorter ocular injection times, smaller injection volumes, fewer possible injections per administration cycle, and more efficient manufacturing and storage.

[007] The present invention is directed toward overcoming one or more of the problems discussed above.

SUMMARY OF THE INVENTION

[008] Various embodiments described herein encompass high concentration protein containing formulations (*e.g.*, which are suitable for intravitreal administration), and in particular, high concentration vascular endothelial growth factor (VEGF) receptor fusion protein containing formulations. High concentration VEGF receptor fusion protein containing formulations provide a number of therapeutic and economic benefits, including, pharmaceutically acceptable potency, long term manufacturing and storage stability, and a viscosity and pH compatible with ocular injection. High concentration VEGF receptor fusion

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protein containing formulations also allow for reduced ocular administration volumes, a benefit for avoiding undesired effects on the limited volume of the eye.

[009] Embodiments herein provide formulations having a VEGF receptor fusion protein, a buffer, a thermal stabilizer, a viscosity reducing agent, and a surfactant. In other embodiments, the formulations do not include a viscosity reducing agent. Formulations of the present invention have a pH and viscosity suitable for injection, and in particular, for therapeutic ocular injection.

[0010] In an embodiment of the invention, a pharmaceutical formulation of the present invention is provided having a VEGF receptor fusion protein at a concentration of at least 41 mg/ml or a concentration that contains a single dose of VEGF receptor fusion protein (which is discussed herein) in less than about 100 µl, less than about 50 µl, about 50 µl, about 57 µl, about 60 µl, about 70 µl, or about 75 µl, a buffer, optionally a thermal stabilizer and/or a viscosity reducing agent, and a surfactant, where the formulation has a pH of from about 5.0 to about 6.8 (*e.g.*, 5.8).

[0011] In an embodiment of the invention, the VEGF receptor fusion protein concentration is about 30 mg/ml, 60 mg/ml, 114 mg/ml, 120 mg/ml or 140 mg/ml.

[0012] In an embodiment of the invention, the surfactant can be a non-ionic surfactant (*e.g.*, about 0.02% to about 0.1%; or about 0.03% (w/v)). In an embodiment of the invention, the surfactant is a non-ionic surfactant having a polyoxyethylene moiety, for example, polysorbate 20 (PS20), polysorbate 80 (PS80), poloxamer 188, polyethylene glycol 3350 or mixtures thereof.

[0013] In an embodiment of the invention, the buffer is a histidine-based buffer (*e.g.*, 10 mM or 20 mM), such as histidine, histidine HCl or histidine acetate; a phosphate-based buffer, such as sodium phosphate (*e.g.*, 10 mM); an acetate-based buffer, such as sodium acetate and acetic acid, or a citrate-based buffer, such as sodium citrate or citric acid. In an embodiment of the invention, if the buffer is phosphate buffer, the pH is from about 5.7 to about 8.0, about 5.8 to about 8.0, about 5.7 to about 7.0, about 5.8 to about 7.0, about 5.9 to about 7.0 or about 6.0 to about 7.0; if the buffer is histidine buffer, the pH is from about 5.5 to about 6.5; if the buffer is citrate buffer, the pH is from about 3.0 to about 6.2 or about 5.0 to about 6.0; and if the buffer is acetate buffer, the pH is from about 3.7 to about 5.6 or about 5.0 to about 6.0.

[0014] In an embodiment of the invention, the thermal stabilizer is a sugar, such as sucrose (*e.g.*, about 2.5%, 5% or 8%, 10% or 20% (w/v), *e.g.*, about 2-20%), mannitol, sorbitol,

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or trehalose; L-proline (*e.g.*, about 2%, 3% or 4% (w/v)); glycine (*e.g.*, about 50 mM), glycerol, taurine (*e.g.*, about 50 mM) or propane sulfonic acid (*e.g.*, about 50 mM) or any combination of the above.

[0015] In some embodiments of the invention, the pharmaceutical formulations of the present invention include a viscosity reducing agent, for example, arginine hydrochloride (*e.g.*, L-arginine monohydrochloride) (*e.g.*, 50 mM), lysine, sodium chloride (*e.g.*, 40 mM or 50 mM), or magnesium chloride. Alternatively, in other embodiments, the formulations of the present invention specifically exclude substantially all, if not all, viscosity reducing agents.

[0016] In an embodiment of the invention, the pharmaceutical formulations of the present invention comprise, consists of or consists essentially of the constituents in any one of formulations A-KKKK as set forth herein.

[0017] In aspects herein, the pharmaceutical formulations of the present invention may include a VEGF receptor fusion protein (*e.g.*, aflibercept or conbercept) at a concentration of from about 41 mg/ml to about 275 mg/ml, from about 80 mg/ml to about 275 mg/ml, about 140 mg/ml to about 150 mg/ml, about 140 mg/ml to about 159 or 160 mg/ml; including about 60 mg/ml, about 80 mg/ml, about 100 mg/ml, about 113.3 mg/ml, about 114.3 mg/ml, about 120 mg/ml, about 133.3 mg/ml, about 140 mg/ml, about 150 mg/ml, about 200 mg/ml or about 250 mg/ml. In an embodiment of the invention, the formulation comprises about 40 mg/ml of the VEGF receptor fusion protein.

[0018] Some aspects of the pharmaceutical formulations of the present invention include a thermal stabilizer at a concentration of from about 2% (w/v) to about 9% (w/v) or from about 4% (w/v) to about 9% (w/v), with the proviso, that when the thermal stabilizer is taurine or propane sulfonic acid, the stabilizer is at a concentration of from about 25 mM to about 100 mM, surfactant is at a concentration of from about 0.02% (w/v) to about 0.1% (w/v) (*e.g.*, about 0.03%), and buffer is of from about 5 mM to about 15 mM.

[0019] The VEGF receptor fusion protein can, for example:

- be encoded by the nucleic acid sequence of SEQ ID NO:1 or nucleotides 79-1374 or 79-1371 of SEQ ID NO: 1;
- comprise amino acids of SEQ ID NO: 2 or amino acids 27-457 or 27-458 of SEQ ID NO: 2;
- comprise:

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(1) a VEGFR1 component comprising amino acids 27 to 129 of SEQ ID NO:2;

(2) a VEGFR2 component comprising amino acids 130 to 231 of SEQ ID NO:2;

(3) a multimerization component ("FcΔC1(a)") comprising amino acids 232 to 457 or 458 of SEQ ID NO:2 (the C-terminal amino acids of SEQ ID NO:2, *i.e.*, K458, may or may not be included in the VEGF receptor fusion proteins). Note that amino acids 1 to 26 of SEQ ID NO:2 are the signal sequence;

- comprise an immunoglobin-like (Ig) domain 2 of a first VEGF receptor (*e.g.*, VEGFR1) and Ig domain 3 of a second VEGF receptor (*e.g.*, VEGFR2), optionally further including an Ig domain 4 of the second VEGF receptor (*e.g.*, VEGFR2) and a multimerizing component (*e.g.*, Fc domain of IgG);
- be conbercept; or
- be aflibercept.

VEGF Trap

atggtcagctactgggacaccggggtcctgctgtgcgcgctgctcagctgtctgcttctc
acaggatctagttccggaagtgataccggtagacctttcgtagagatgtacagtgaaatc
cccgaaattatacacatgactgaaggaagggagctcgtcattccctgccgggttacgtca
cctaacatcactgttactttaaaaaagtttccacttgacactttgatccctgatggaaaa
cgcataatctgggacagtagaaagggcttcatcatatcaaatgcaacgtacaaagaaata
gggcttctgacctgtgaagcaacagtcaatgggcatttgtataagacaaactatctcaca
catcgacaaaccaatacaatcatagatgtggttctgagtccgtctcatggaattgaacta
tctgttggagaaaagcttgtcttaaattgtacagcaagaactgaactaaatgtggggatt
gacttcaactgggaataccttcttcgaagcatcagcataagaaacttgtaaaccgagac
ctaaaaacccagtctgggagtgagatgaagaaatttttgagcaccttaactatagatggt
gtaacccggagtgaccaaggattgtacacctgtgcagcatccagtgggctgatgaccaag
aagaacagcacatttgtcagggtccatgaaaaggacaaaactcacacatgcccaccgtgc
ccagcacctgaactcctgggggggaccgtcagtcttcctcttcccccaaaacccaaggac
accctcatgatctcccggaccccctgaggtcacatgcgtggtggtggacgtgagccacgaa
gaccctgaggtcaagttcaactggtacgtggacggcgtggaggtgcataatgccaagaca
aagccgcgggaggagcagtacaacagcacgtaccgtgtggtcagcgtcctcaccgtcctg
caccaggactggctgaatggcaaggagtacaagtgcaaggtctccaacaaagccctccca
gcccccatcgagaaaaccatctccaaagccaaagggcagccccgagaaccacaggtgtac
accctgcccccatcccgggatgagctgaccaagaaccaggtcagcctgacctgcctggtc
aaaggcttctatcccagcgacatcgccgtggagtgggagagcaatgggcagccggagaac
aactacaagaccacgcctcccgtgctggactccgacggctccttcttcctctacagcaag

ctcaccgtggacaagagcaggtggcagcaggggaacgtcttctcatgctccgtgatgcat
gaggctctgcacaaccactacacgcagaagagcctctccctgtctccgggtaaatga

(SEQ ID NO: 1)

MVSYWDTGVLLCALLSCLLLTGSSSGSDTGRPFVEMYSEIPEIIHMTEGRELVIPCRVTSPNITVTLKKFPLDTLIP
DGKRIIWDSRKGFIISNATYKEIGLLTCEATVNGHLYKTNYLTHRQTNTIIDVVLSPSHGIELSVGEKLVLNCTART
ELNVGIDFNWEYPSSKHQHKKLVNRDLKTQSGSEMKKFLSTLTIDGVTRSDQGLYTCAASSGLMTKKNSTFVRVHEK
DKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYN
STYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYP
SDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK

(SEQ ID NO: 2)

AAs 1-26 = Signal Sequence

AAs 27-129 = Flt1-D2 (VEGFR1-D2)

AAs 130-231 = Flk1-D3 (VEGFR2-D3)

AAs 232-458 = FcΔC1

[0020] In another embodiment of the present invention, a container containing an aqueous solution of from about 5 mM to about 25 mM pharmaceutically acceptable buffer, from about 4% (w/v) to about 9% (w/v) of a pharmaceutically acceptable thermal stabilizer, from about 0.02% (w/v) to about 0.1% (w/v) of a pharmaceutically acceptable surfactant, and from about 41 mg/ml to about 275 mg/ml VEGF receptor fusion protein, is provided. When the thermal stabilizer includes either taurine or propane sulfonic acid, the taurine or propane sulfonic acid is at a concentration of from about 25 mM to about 100 mM. The aqueous solution has a pH of from about 5.0 to about 6.8, and can be from about 5.5 to about 6.2 (*e.g.*, 5.8). In some aspects, the container is a vial or syringe. In other aspects, the aqueous solution does not include an inorganic salt. When the thermal stabilizer is a sugar it can be sucrose, mannitol, sorbitol or trehalose, and can be present at between about 4% (w/v) and 9% (w/v); the surfactant can be a non-ionic surfactant, and can include a polyoxyethylene moiety, such as polysorbate 20, polysorbate 80, poloxamer 188, or polyethylene glycol 3350, at a concentration of from about 0.02% to about 0.1% weight per volume (w/v), and more typically, 0.02% to about 0.04% (w/v). In an embodiment of the invention, the VEGF receptor fusion protein is encoded by the nucleic acid sequence of SEQ ID NO:1 or nucleotides 79-1374 or 79-1371 of SEQ ID NO: 1; comprises

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amino acids of SEQ ID NO: 2 or amino acids 27-457 or 27-458 of SEQ ID NO: 2; comprises (1) a VEGFR1 component comprising amino acids 27 to 129 of SEQ ID NO:2; (2) a VEGFR2 component comprising amino acids 130 to 231 of SEQ ID NO:2; and (3) a multimerization component ("FcΔC1(a)") comprising amino acids 232 to 457 of SEQ ID NO:2 (the C-terminal amino acids of SEQ ID NO:2, *i.e.*, K458, may or may not be included in the VEGF receptor fusion proteins); comprises an immunoglobin-like (Ig) domain 2 of a first VEGF receptor (*e.g.*, VEGFR1) and Ig domain 3 of a second VEGF receptor (*e.g.*, VEGFR2), optionally further including an Ig domain 4 of the second VEGF receptor (*e.g.*, VEGFR2) and a multimerizing component (*e.g.*, Fc domain of IgG); is conbercept or is aflibercept.

[0021] In still other embodiments, pharmaceutical formulations of the present invention are provided having a VEGF receptor fusion protein in an aqueous vehicle, where the aqueous vehicle has a viscosity of from about 10 cP to about 15 cP at 20°C, more typically about 10 cP to about 13 cP at 20°C, and most typically from about 11 cP to about 12 cP at 20°C (*e.g.*, about 6.0, 7.3, 11.5 or 12.0 cP at 20°C). In an embodiment of the invention, the viscosity is about 12 cP to about 15 cP at 20°C. The pH of the formulation can be from about 5.8 to about 6.5 (*e.g.*, about 5.8). In some cases, the formulations do not include a viscosity reducing agent, for example, do not include arginine hydrochloride, lysine, sodium chloride, or magnesium chloride. In other cases, the formulations include 10 mM histidine hydrochloride or 10 mM histidine-acetate. The sugar can be sucrose, mannitol, sorbitol or trehalose, and can be present at between about 4% (w/v) and 9% (w/v) (*e.g.*, about 5%); the surfactant can be a non-ionic surfactant, and can include a polyoxyethylene moiety, such as polysorbate 20, polysorbate 80, poloxamer 188, or polyethylene glycol 3350, at a concentration of from about 0.02% to about 0.1% weight per volume (w/v), and more typically, 0.02% to about 0.04% (w/v) (*e.g.*, 0.03%). In addition, the formulation can additionally include a thermal stabilizer selected from either taurine or propane sulfonic acid at a concentration of between about 25 mM to about 100 mM, and more typically about, 50 mM to about 70 mM. In an embodiment of the invention, a formulation comprises VEGF receptor fusion protein, such as aflibercept, (*e.g.*, at a concentration of about 41-275 mg/ml, about 50 mg/ml, about 100 mg/ml, about 115 mg/ml, about 125 mg/ml, about 150 mg/ml, about 200 mg/ml or any of the "high" concentrations discussed herein), about 10 mM histidine-based buffer, about 5% (w/v) sucrose, about 0.03% (w/v) non-ionic surfactant such as polysorbate *e.g.*, polysorbate 20, and about 50 mM arginine, L-arginine or L-arginine

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monohydrochloride, with a pH of about 5.8. In an embodiment of the invention, the VEGF receptor fusion protein is encoded by the nucleic acid sequence of SEQ ID NO:1 or nucleotides 79-1374 or 79-1371 of SEQ ID NO: 1; comprises amino acids of SEQ ID NO: 2 or amino acids 27-457 or 27-458 of SEQ ID NO: 2; comprises (1) a VEGFR1 component comprising amino acids 27 to 129 of SEQ ID NO:2; (2) a VEGFR2 component comprising amino acids 130 to 231 of SEQ ID NO:2; and (3) a multimerization component ("FcΔC1(a)") comprising amino acids 232 to 457 of SEQ ID NO:2 (the C-terminal amino acids of SEQ ID NO:2, *i.e.*, K458, may or may not be included in the VEGF receptor fusion proteins); comprises an immunoglobin-like (Ig) domain 2 of a first VEGF receptor (*e.g.*, VEGFR1) and Ig domain 3 of a second VEGF receptor (*e.g.*, VEGFR2), optionally further including an Ig domain 4 of the second VEGF receptor (*e.g.*, VEGFR2) and a multimerizing component (*e.g.*, Fc domain of IgG); is conbercept or is aflibercept.

[0022] In yet another embodiment, a pharmaceutical formulation of the present invention is provided that includes a VEGF receptor fusion protein at a concentration of from about 80 mg/ml to about 275 mg/ml in a pharmaceutically acceptable buffer. In some cases, the stable pharmaceutical formulations can also include taurine or propane sulfonic acid. The formulations can be stable at a temperature of about 2°C to about 8°C for about 24-36 months. In some cases, the VEGF receptor fusion protein shows less than about a 5% increase in high molecular weight species, and more typically, less than about 4.5% increase in high molecular weight species, less than about 4.0% increase in high molecular weight species, less than about 3.5% increase in high molecular weight species, less than about 3.0% increase in high molecular weight species, less than about 2.5% increase in high molecular weight species, less than about 2.0 increase in high molecular weight species and/or less than about 1.5% increase in high molecular weight species, when stored at these temperatures and for this amount of time. In other cases, the VEGF receptor fusion protein shows less than a 2.0% to 3.0% increase in high molecular weight species when the formulations are stored at these temperatures and for this amount of time.

[0023] Embodiments herein can also include pharmaceutical formulations of the present invention that include aflibercept, a pH buffered solution, a sugar and a surfactant, where the aflibercept is at a concentration of 41 mg/ml to about 275 mg/ml. Alternatively, embodiments can be stable liquid pharmaceutical formulations that include conbercept, a pH buffered solution, a sugar and a surfactant, where the conbercept is at a concentration of 41 mg/ml to about 275

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mg/ml. Stable liquid pharmaceutical formulations can also include taurine or propane sulfonic acid. In some aspects, the aflibercept or conbercept is at a concentration of either 80 mg/ml or 150 mg/ml. In other aspects, the formulations do not include an inorganic salt, sodium chloride for example.

[0024] Some embodiments are directed to sterile syringes such that the syringes are pre-filled with an aqueous solution having 80 mg/ml aflibercept, conbercept, 10 mM histidine hydrochloride, histidine acetate or sodium phosphate, 5% (w/v) sucrose, mannitol, sorbitol or trehalose , 0.03% (w/v) polysorbate 20, polysorbate 80, poloxamer 188, or polyethylene glycol 3350, and 40 mM sodium chloride. Aspects herein include the further addition of about 25 mM to about 100 mM, and more typically about 50 mM to about 70 mM, of either taurine or propane sulfonic acid. In some aspects, the syringes are pre-filled with an aqueous solution having 80 mg/ml aflibercept, conbercept, 10 mM histidine HCl, histidine acetate or sodium phosphate, 8% (w/v) sucrose, mannitol, sorbitol or trehalose, and 0.03% (w/v) polysorbate 20, polysorbate 80, poloxamer 188, or polyethylene glycol 3350. Aspects herein include the further addition of about 25 mM to about 100 mM, and more typically about 50 mM to about 70 mM, of either taurine or propane sulfonic acid. In still other aspects, the syringes are pre-filled with an aqueous solution having 150 mg/ml aflibercept, conbercept, 10 mM histidine hydrochloride, histidine acetate, or sodium phosphate, 5% (w/v) sucrose, mannitol, sorbitol or trehalose, 0.03% (w/v) polysorbate 20, polysorbate 80, poloxamer 188, or polyethylene glycol 3350 and 40 mM sodium chloride, with a pH of about 6.2. Aspects herein can include the further addition of either taurine or propane sulfonic acid. In yet still other aspects, the syringes are pre-filled with an aqueous solution having 150 mg/ml aflibercept, conbercept, 10 mM histidine hydrochloride, histidine acetate, or sodium phosphate, 8% (w/v) sucrose, mannitol, sorbitol or trehalose, and 0.03% (w/v) polysorbate 20, polysorbate 80, poloxamer 188, or polyethylene glycol 3350, with a pH of about 6.2 and the aqueous solution does not include an inorganic salt. Aspects can further include about 25 mM to about 100 mM, and more typically, about 50 mM to about 70 mM, of either taurine or propane sulfonic acid. In yet still other aspects, the syringes are pre-filled with an aqueous solution having 150 mg/ml aflibercept or conbercept, 10 mM sodium acetate or acetic acid, 5% (w/v) glycerol and 0.03% (w/v) polysorbate 20, polysorbate 80, poloxamer 188, or polyethylene glycol 3350 and 40 mM sodium chloride, with a pH of about 6.2. In yet still other aspects, the syringes are pre-filled with an aqueous solution having 150 mg/ml aflibercept or

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conbercept, 10 mM sodium acetate or acetic acid, 8% (w/v) glycerol , and 0.03% (w/v) polysorbate 20, polysorbate 80, poloxamer 188, or polyethylene glycol 3350 and 40 mM sodium chloride, with a pH of about 6.2.

[0025] The present invention also provides a method for making any formulation set forth herein comprising the step of combining each component of the formulation into a single composition. Such a method may include the step of adding the resulting formulation into a vial or injection device. Any composition that is the product of such a method also forms part of the present invention. For example, embodiments herein also include methods for preparing a formulation by combining a histidine-based, citrate-based, acetate-based or phosphate-based buffer, with sucrose, polysorbate 20 and a VEGF receptor fusion protein; and, optionally, one or more additional components, *e.g.*, as discussed herein. In some cases, the formulation is prepared to also include taurine or propane sulfonic acid, but where it does not include taurine or propane sulfonic acid, it may also not include an inorganic salt. In aspects herein, the sucrose is at a weight per volume of from about 4% to about 10%, the polysorbate 20 has a weight per volume of about 0.02% to about 0.1%, and the receptor fusion protein is at a concentration of from about 41 mg/ml to about 275 mg/ml. Where the formulation includes taurine or propane sulfonic acid, it is present at, for example, about 25 mM to about 100 mM, but may also be included at 50 mM to 70 mM. The method can include loading a predetermined volume of prepared formulation into a sterile syringe, such that the volume has a 0.1 mg to 10 mg dose of the VEGF receptor fusion protein.

[0026] The present invention also provides a method for administering a formulation of the present invention to a subject (*e.g.*, a human) comprising intraocularly injecting (*e.g.*, intravitreal injection) the formulation into the eye of the subject. The present invention also provides a method for administering a formulation of the present invention to a subject (*e.g.*, a human) comprising implanting an intravitreal implant that contains a formulation of the present invention into the vitreous of the subject.

[0027] Embodiments herein also include methods for treating an angiogenic eye disorder, *e.g.*, age-related macular degeneration (wet), macular edema following retinal vein occlusion, retinal vein occlusion (RVO), central retinal vein occlusion (CRVO) branch retinal vein occlusion (BRVO), diabetic macular edema (DME), choroidal neovascularization (CNV), iris neovascularization, neovascular glaucoma, post-surgical fibrosis in glaucoma, proliferative

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vitreoretinopathy (PVR), optic disc neovascularization, corneal neovascularization, retinal neovascularization, vitreal neovascularization, pannus, pterygium, vascular retinopathy or diabetic retinopathy (*e.g.*, non-proliferative diabetic retinopathy and/or proliferative diabetic retinopathy) in a subject in need thereof by intraocularly injecting at least about 2 mg (*e.g.*, 4 mg, 6 mg or 8 mg) of VEGF receptor fusion protein (*e.g.*, aflibercept or conbercept) into the eye of a subject in need thereof, for example, any formulation set forth herein. In an embodiment of the invention, the injection volume is 100 microliters or less (*e.g.*, 100 microliters, 50 microliters or 57 microliters). The method comprises an intravitreal injection of a pre-mixed aqueous solution having a VEGF receptor fusion protein at a concentration of from 41 mg/ml to about 275 mg/ml, a pharmaceutically acceptable sugar, a pharmaceutically acceptable buffer, and a pharmaceutically acceptable surfactant. Treatment methods using the pre-mixed aqueous solution do not require dilution. In aspects herein, the pre-mixed aqueous solution has a pH from about 6.0 and about 6.5, and has a viscosity of between about 10 cP and 13 cP.

[0028] In aspects of the treatment method, the VEGF receptor fusion protein comprises VEGFR1R2-FcΔC1(a) encoded by the nucleic acid sequence of SEQ ID NO:1, amino acids 27 to 129 of SEQ ID NO:2, a VEGFR2 component comprising amino acids 130 to 231 of SEQ ID NO:2, or a multimerization component comprising amino acids 232 to 457 of SEQ ID NO:2, or any combination thereof. In an embodiment of the invention, the VEGF receptor fusion protein is aflibercept or conbercept.

[0029] Other embodiments in accordance with the disclosure herein will become apparent from a review of the ensuing detailed description.

BRIEF DESCRIPTION OF THE DRAWINGS

[0030] The above and other aspects, features and advantages of embodiments disclosed herein will become more apparent to those of ordinary skill in the art with reference to the accompanying drawings.

[0031] **Figure 1A** is a graph determining VEGF receptor fusion protein (aflibercept) stability in four different formulations (B, H, D and G) over the course of 36 months at 2°C to 8°C. VEGF receptor fusion protein stability was tested using size-exclusion ultra-performance liquid chromatography (SE-UPLC) to identify formation of high molecular weight (HMW) species (a sign of protein degradation).

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[0032] **Figure 1B** is also a graph determining VEGF receptor fusion protein (aflibercept) stability in four formulations (B, H, D and G) over the course of 36 months at 2°C to 8°C. VEGF receptor fusion protein stability was tested using SE-UPLC to identify the percent of the main species in each formulation.

[0033] **Figure 1C** is a bar graph showing formation of VEGF receptor fusion protein charge variants in four formulations (B, H, D and G) over the course of 36 months at 2°C to 8°C. The level of acidic species was tested at manufacture (0.0), 12 months, 24 months and 36 months using imaged capillary isoelectric focusing (iCIEF).

[0034] **Figure 1D** is a bar graph showing formation of VEGF receptor fusion protein charge variants in four formulations (B, H, D and G) over the course of 36 months at 2°C to 8°C. Identification of the main species was tested at manufacture (0.0), 12 months, 24 months and 36 months using iCIEF.

[0035] **Figure 2A** is a graph showing 150 mg/ml VEGF receptor fusion protein (aflibercept) stability in a 10 mM sodium phosphate, 8% (w/v) sucrose and 0.03% polysorbate 20 (w/v) formulation pH6.2 with and without L-arginine monohydrochloride over the course of 28 days at 37°C. VEGF receptor fusion protein stability was tested using SE-UPLC to identify formation of HMW species.

[0036] **Figure 2B** is a graph showing 150 mg/ml VEGF receptor fusion protein stability in a 10 mM sodium phosphate, 8% sucrose (w/v) and 0.03% polysorbate 20 (w/v) formulation pH6.2 with and without L-arginine monohydrochloride over the course of 28 days at 37°C. VEGF receptor fusion protein stability was tested using SE-UPLC to identify the percent of the main species in each formulation.

[0037] **Figure 3A** is a bar graph showing viscosity of 10 mM sodium phosphate buffered formulations having 155 mg/ml VEGF receptor fusion protein and no salt, 100 mM arginine, 200 mM arginine, 50 mM lysine, 200 mM lysine, 50 mM sodium chloride or 100 mM sodium chloride. Viscosity was measured in cP at 20°C.

[0038] **Figure 3B** is a bar graph showing viscosity of 10 mM histidine buffered formulations having 155 mg/ml VEGF receptor fusion protein and no salt, 100 mM arginine, 200 mM arginine, 50 mM lysine, 200 mM lysine, 50 mM sodium chloride or 100 mM sodium chloride. Viscosity was measured in cP at 20°C.

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[0039] **Figure 3C** is a graph showing viscosity of various concentrations of VEGF receptor fusion protein under different formulation conditions (with or without 50 mM arginine hydrochloride). Viscosity was measured in cP at 20°C.

[0040] **Figure 4A** is a graph showing 150 mg/ml VEGF receptor fusion protein stability in 10 mM sodium phosphate, 8% (w/v) sucrose, and 0.03% (w/v) polysorbate 20, pH6.2 with and without 50 mM L-arginine monohydrochloride over 12 months at 5°C. The VEGF receptor fusion protein was at 150 mg/ml. VEGF receptor fusion protein stability was tested using SE-UPLC to identify formation of HMW species.

[0041] **Figure 4B** is a graph showing 150 mg/ml VEGF receptor fusion protein stability in 10 mM sodium phosphate, 8% (w/v) sucrose, and 0.03% (w/v) polysorbate 20, pH6.2 with and without 50 mM L-arginine monohydrochloride over 12 months at 5°C. The VEGF receptor fusion protein was at 150 mg/ml. VEGF receptor fusion protein stability was tested using SE-UPLC to identify the percent of the main species in each formulation.

[0042] **Figure 5** is a graph that shows viscosity of formulations under two buffer conditions at 20°C, 10 mM phosphate buffer or 10 mM histidine buffer. The VEGF receptor fusion protein concentration is varied from 10 mg/ml to 170 mg/ml. Viscosity was measured in mPa-S.

[0043] **Figure 6** shows a dynamic light scattering screen for a number of different formulation conditions, each having from 2 to 10 mg/ml protein. The diffusion interaction parameter indicated that taurine and PSA (propane sulfonic acid) improved Kd.

[0044] **Figure 7** is a graph monitoring the percentage of high molecular weight (HMW) species in formulations F1-F9 (formulations WW-EEE) over time as measured by size-exclusion ultra-performance liquid chromatography (SE-UPLC) after storage at 5°C for 6 months. Formulations F1-F9 are set forth in Table 7-1 herein.

[0045] **Figures 8A and 8B** measure the percentage of high molecular weight species, by SE-UPLC, after storage at 5°C for 3 months (Fig. 8A) or incubation at 37°C for 28 days (Fig. 8B). Formulations F1-F4 (EEE, SSS, CCC (140 mg/ml) and TTT) are set forth in Table 8-1 below.

[0046] **Figure 9** shows the viscosity (cp) for Formulations F1-F12, at 20°C, at the initial time point. Formulations F1-F12 are set forth in Table A below.

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Table A. Formulations F1-F12.

Formulation #	VEGF Trap (mg/mL)	Buffer	Other Excipients	Screening Excipients (mM)
F1 (GGG)	140	20 mM Histidine, pH 5.8	5% Sucrose, 0.03% Polysorbate 20	50mM Sodium sulfate
F2 (HHH)	140	20 mM Histidine, pH 5.8	5% Sucrose, 0.03% Polysorbate 20	50mM Sodium thiocyanate
F3 (III)	140	20 mM Histidine, pH 5.8	5% Sucrose, 0.03% Polysorbate 20	40mM Sodium citrate
F4 (JJJ)	140	20 mM Histidine, pH 5.8	5% Sucrose, 0.03% Polysorbate 20	50mM Glycine
F5 (KKK)	140	20 mM Histidine, pH 5.8	5% Sucrose, 0.03% Polysorbate 20	50mM Sodium chloride
F6 (LLL)	140	20 mM Histidine, pH 5.8	5% Sucrose, 0.03% Polysorbate 20	50mM Lysine
F7 (MMM)	140	20 mM Histidine, pH 5.8	5% Sucrose, 0.03% Polysorbate 20	50mM Sodium aspartate
F8 (NNN)	140	20 mM Histidine, pH 5.8	5% Sucrose, 0.03% Polysorbate 20	50mM Sodium glutamate
F9 (OOO)	140	20 mM Histidine, pH 5.8	5% Sucrose, 0.03% Polysorbate 20	50mM Sodium Citrate + 50mM Arginine hydrochloride
F10 (PPP)	140	20 mM Histidine, pH 5.8	5% Sucrose, 0.03% Polysorbate 20	50mM Glycine + 50mM Arginine hydrochloride
F11 (QQQ)	140	20 mM Histidine, pH 5.8	5% Sucrose, 0.03% Polysorbate 20	50mM Sodium aspartate + 50mM Arginine hydrochloride
F12 (RRR)	140	20 mM Histidine, pH 5.8	5% Sucrose, 0.03% Polysorbate 20	50mM Sodium glutamate + 50mM Arginine hydrochloride

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[0047] **Figure 10** shows the osmolality (mmol/Kg) of Formulations F1-F12 (set forth in Table A herein).

[0048] **Figures 11A and 11B** measure the percentage of high molecular weight species in formulations F1-F6 (Formulations GGG, HHH, III, JJJ, LLL and KKK) over time, by SE-UPLC, after storage at 37ºC for up to 28 days (Fig. 11A) or 5ºC for up to 3 months (Fig. 11B) over time.

[0049] **Figure 12** shows the dynamic light scattering (diffusion coefficient (cm^2/second), radius (nm) and %Pd) at the initial time point of the formulations shown in Table 9-3 (GGG-RRR).

[0050] **Figures 13A, 13B, 13C and 13D** show the baseline FA images and OCT (30 degree lens) for two different rabbits (326-OS and 329-OD) before administration of aflibercept (OD=*oculus dexter* (right eye); OS=*oculus sinister* (left eye)). (Fig. 13A) FA image for rabbit 326, left eye; (Fig. 13B) OCT image for rabbit 326, left eye; (Fig. 13C) FA image for rabbit 329, right eye; (Fig. 13D) OCT image for rabbit 329, right eye.

[0051] **Figures 14A, 14B, 14C, 14D, 14E and 14F** show a time course of rabbit FA images at days 1 (Fig. 14A), 7 (Fig. 14B) and 14 (Fig. 14C) and the OCT at days 1 (Fig. 14D), 7 (Fig. 14E) and 14 (Fig. 14F) for one rabbit (326-OS) administered the histidine buffer formulation (30 degree lens) (7 mg/eye).

[0052] **Figures 15A, 15B, 15C, 15D, 15E, 15F, 15G and 15H** show a time course of rabbit FA images at 3 weeks (Fig. 15A), 4 weeks (Fig. 15B), 7 weeks (Fig. 15C) and 8 weeks (Fig. 15D); and the OCT at 3 weeks (Fig. 15E), 4 weeks (Fig. 15F), 7 weeks (Fig. 15G) and 8 weeks (Fig. 15H) for one rabbit (326-OS) administered the histidine buffer formulation (55 degree lens) (7 mg/eye).

[0053] **Figures 16A, 16B, 16C, 16D, 16E and 16F** show a time course of rabbit FA images at day 1 (Fig. 16A), week 1 (Fig. 16B) and week 2 (Fig. 16C) and the OCT at day 1 (Fig. 16D), week 1 (Fig. 16E) and week 2 (Fig. 16F) for one rabbit (329-OS) administered the phosphate buffer formulation (30 degree lens) (7 mg/eye).

[0054] **Figures 17A, 17B, 17C, 17D, 17E, 17F, 17G and 17H** show a time course of rabbit FA images at week 3 (Fig. 17A), week 4 (Fig. 17B), week 7 (Fig. 17C) and week 8 (Fig. 17D) and the OCT at week 3 (Fig. 17E), week 4 (Fig. 17F), week 7 (Fig. 17G) and week 8 (Fig.

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17H) for one rabbit (329-OS) administered the phosphate buffer formulation (55 degree lens) (7 mg/eye).

[0055] **Figures 18A and 18B** show the purity (percentage of native species) (Fig. 18A) and percentage of high molecular weight (HMW) species (Fig. 18B) in formulations UUU-BBBB over time at 37°C (up to one month) (see Table 11-1) as analyzed by SE-UPLC.

[0056] **Figures 19A, 19B, 19C, 19D and 19E** show stability and purity analysis of a formulation having 114.3 mg/mL VEGF Trap (aflibercept) formulated in 10 mM Histidine, pH 5.8, 5% Sucrose, 0.03% Polysorbate 20, 50 mM Arginine Monohydrochloride by size exclusion chromatographic determination of the percentage of (i) high molecular weight species (HMW) after incubation at 5°C or 37°C for up to 2 months (Fig. 19A) and (ii) main species (Main peak) after incubation at 5°C or 37°C for up to 2 months (Fig. 19B); as well as by microflow imaging to determine the presence of subvisible particulate matter after incubation at 37°C for up to 28 days (Fig. 19C), by particle light obscuration analysis to determine the presence of subvisible particulate matter after incubation at 37°C for up to 28 days (Fig. 19D), and by microscopic determination of subvisible particulate matter after incubation at 37°C for up to 28 days (Fig. 19E).

[0057] **Figures 20A and 20B** show stability and purity analysis of formulation CCC, having 80, 100, 120 or 140 mg/ml aflibercept, by SE-UPLC determination of the percentage of high molecular weight species (HMW) after incubation at 2-8°C for up to 6 months (Fig. 20A) or 37°C for up to 28 days (Fig. 20B).

[0058] **Figure 21** shows the percentage of eyes in rabbits tested with complete leak suppression over time, when administered 500 micrograms or 2 mg aflibercept, over time (Gehan-Breslow-Wilcoxon test (P 0.0453)).

DETAILED DESCRIPTION

[0059] The present invention provides formulations having high concentrations of VEGF receptor fusion proteins (*e.g.*, aflibercept), showing excellent functional and storage properties which were developed in spite of significant technical hurdles. For example, a common method for identifying suitable excipients for a formulation that includes a polypeptide drug (such as a VEGF receptor fusion protein) is by assessment of polypeptide stability under accelerated stress conditions, such as high temperature (*e.g.*, 37°C). Excipients, which are not suitable under non-

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stress conditions (*e.g.*, a low temperature such as 5°C), will typically cause an undesired effect, within a short period of time, while under stress, *e.g.*, protein aggregation. This approach is common in the biotechnology and pharmaceutical industry insofar as it expedites the elimination of excipients unlikely to stabilize the drug product. See *e.g.*, Magari, *Assessing Shelf Life Using Real-Time and Accelerated Stability Tests*, Biopharm Intl. 16(11): 36-48 (2003). In some cases, a product may be released based on accelerated stability data, but this must be done in parallel with real-time shelf-life analysis (non-accelerated). Magari (2003) and FDA, *Guidelines for Submitting Documentation for the Stability of Human Drugs and Biologics*, Rockville, MD (1987). Here, however, at 5°C, the presence of arginine in histidine formulations was stabilizing, though arginine, it appeared, tended to decrease stability when under temperature stress (37°C). See Figure 8 (A-B). This property of the formulations set forth herein would have presented a technical difficulty guiding a practitioner away from choosing arginine; thus, making it unlikely that a practitioner would have chosen arginine as an excipient. Nevertheless, the formulations set forth herein resulted from the overcoming of technical hurdles such as this to achieve a formulation with high stability. Formulation of VEGF trap in histidine buffer also led to a beneficial decrease in viscosity relative to that observed with a phosphate buffer formulation. Since small needle bores are preferred for performing intravitreal injections (due to decreased patient discomfort and eye trauma), a relative low viscosity is desirable. A lower viscosity formulation requires less force to push the formulation through the needle, thus making injection of the formulation through the needle easier for the treating physician. In addition, histidine and arginine containing formulation were well tolerated in rabbit eyes.

[0060] Reference will now be made in detail to representative embodiments. It should be understood that the following descriptions are not intended to limit the embodiments to one preferred embodiment. To the contrary, they are intended to cover alternatives, modifications, and equivalents as can be included within the spirit and scope of the described embodiments as defined in the appended claims.

[0061] Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which the disclosure pertains. As used herein, the term "about," when used in reference to a particular recited numerical value, means that the value may vary from the recited value by no more than 1%. So

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for example, as used herein, the expression "about 100" includes 99 and 101 and all values in between (*e.g.*, 99.1%, 99.2%, 99.3%, 99.4%, *etc.*).

[0062] In an embodiment of the invention, a pharmaceutical formulation of the present invention is compliant with USP<789> for small volume injection (SVP) of ophthalmic solutions, *e.g.*, contains less than about 50 particles ≥10 μm in diameter per ml; contains less than about 5 particles ≥25 μm in diameter per ml; or contains less than about 2 particles ≥50 μm in diameter per ml.

[0063] Note that for purposes herein, "intravitreal injection" refers to injection into the vitreous of the eye (near the retina at the back of the eye). The expressions “suitable for intravitreal administration,” “suitable for intravitreal injection,” and the like mean that the formulation in question can be safely injected into the vitreous of a subject’s eye without causing any adverse reactions beyond those known to be associated with intravitreal injection of EYLEA.

[0064] The term "pharmaceutical formulation" herein refers to formulations including pharmaceutically acceptable carriers, *e.g.*, used to administer VEGF receptor fusion proteins (*e.g.*, aflibercept or conbercept) to a subject for a therapeutic/medicinal use.

[0065] The term "pharmaceutically acceptable" refers to a formulation that within the scope of sound medical judgement is suitable for administration with the eye.

[0066] The term "subject" herein refers to any mammalian (*e.g.*, rabbit, mouse, rat or monkey) subject, particularly a human, *e.g.*, for whom diagnosis, prognosis or therapy is desired with the formulations as described herein.

[0067] The term “aqueous” formulation refers to a formulation which includes water.

[0068] The term "treat" or "treatment" refers to a therapeutic measure that reverses, stabilizes or eliminates an undesired disease or disorder (*e.g.*, an angiogenic eye disorder or cancer), for example, by causing the regression, stabilization or elimination of one or more symptoms or indicia of such disease or disorder by any clinically measurable degree, *e.g.*, with regard to an angiogenic eye disorder, by causing a reduction in or maintenance of diabetic retinopathy severity score (DRSS), by improving or maintaining vision (*e.g.*, in best corrected visual acuity *e.g.*, as measured by an increase in ETDRS letters), increasing or maintaining visual field and/or reducing or maintaining central retinal thickness and, with respect to cancer, stopping or reversing the growth, survival and/or metastasis of cancer cells in the subject.

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Typically, the therapeutic measure is administration of one or more doses of a therapeutically effective amount of VEGF receptor fusion protein to the subject with the disease or disorder.

[0069] "Prevent" or "prevention" refer to a prophylactic measure to cease the development of an undesired disease or disorder (*e.g.*, an angiogenic eye disorder).

[0070] SE-UPLC can be used in the present invention to quantitate the presence of high molecular weight species in a formulation. SE refers to size exclusion chromatography. UPLC refers to ultra-performance liquid chromatography. Suitable SE columns, which may be used in a UPLC system, to characterize such HMW species of VEGF receptor fusion proteins (*e.g.*, aflibercept or conbercept) in a formulation, are capable of resolving molecules in the molecular weight range of about 10,000–450,000 Daltons. See for example, the ACQUITY UPLC Protein BEH SEC 200Å Column. In an embodiment of the invention, two of such columns are connected in tandem when quantitating HMW species in a formulation. UPLC brings improvements over HPLC (high performance liquid chromatography) in sensitivity and resolution. UPLC uses instrumentation that operates at high pressures and uses finer particles (typically less than about 2.5μm) than that used in HPLC. Moreover, the UPLC mobile phases operate at high linear velocities than HPLC.

[0071] Embodiments herein include formulations that comprise a high concentration (*e.g.*, about 60 mg/ml, about 80 mg/ml, about 90 mg/ml, about 100 mg/ml, about 113.3 mg/ml, about 114.3 mg/ml, about 120 mg/ml, about 133.3 mg/ml, about 140 mg/ml, about 150 mg/ml, about 200 mg/ml or about 250 mg/ml) of VEGF receptor fusion protein (*e.g.*, aflibercept or conbercept). Suitable formulations included herein comprise a high concentration of VEGF receptor fusion protein, a buffer, a thermal stabilizer and a surfactant. In some aspects, a suitable formulation further includes a viscosity reducing agent. In other aspects, the suitable formulation substantially excludes all viscosity reducing agents. Typical formulations have a pH of from about 5.0 to about 6.8 (*e.g.*, 5.8), but can include any pH useful for administration of the VEGF receptor fusion protein to the eye of a subject.

[0072] The present invention includes formulations that include a VEGF receptor fusion protein (*e.g.*, aflibercept or conbercept) in association with one or more further therapeutic agents (*e.g.*, an Ang-2 inhibitor (*e.g.*, an anti-ANG2 antibody or antigen-binding fragment thereof or nesvacumab), a Tie-2 receptor activator, an anti-PDGF, PDGF receptor or PDGF receptor beta antibody or antigen-binding fragment thereof and/or an additional VEGF antagonist such as

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bevacizumab, ranibizumab, pegaptanib or a soluble form of human vascular endothelial growth factor receptor-3 (VEGFR-3) comprising extracellular domains 1-3, expressed as an Fc-fusion protein) as well as methods of prevention or treatment comprising administering such formulations as discussed herein. In an embodiment of the invention, a formulation of the present invention includes a VEGF receptor fusion protein, such as aflibercept, but excludes any further therapeutic agent (*e.g.*, which is an antibody or antigen-binding fragment thereof).

[0073] The term "in association with" indicates that a formulation and a further therapeutic agent can be formulated into a single composition, *e.g.*, for simultaneous delivery, or formulated separately into two or more compositions (*e.g.*, a kit). The further therapeutic agent may, itself, be formulated in its own pharmaceutical formulation. Each can be administered to a subject at the same time as the other or at a different time than when the other is administered; for example, each administration may be given non-simultaneously (*e.g.*, separately or sequentially) at intervals over a given period of time. Moreover, the formulation and the further therapeutic agent may be administered to a subject by the same or by a different route.

[0074] In an embodiment of the invention, a formulation of the present invention includes any one or more of sodium sulfate (*e.g.*, 50 mM); sodium thiocyanate (*e.g.*, 50 mM); sodium citrate (*e.g.*, 40 mM); glycine (*e.g.*, 50 mM); sodium chloride (*e.g.*, 50 mM); lysine (*e.g.*, 50 mM); sodium aspartate (*e.g.*, 50 mM); and/or sodium glutamate (*e.g.*, 50 mM). For example, in an embodiment the formulation comprises a combination of sodium citrate (*e.g.*, 50 mM) and arginine hydrochloride (*e.g.*, 50 mM); glycine (*e.g.*, 50 mM) and arginine hydrochloride (*e.g.*, 50 mM); sodium aspartate (*e.g.*, 50 mM) and arginine hydrochloride (*e.g.*, 50 mM); or sodium glutamate (*e.g.*, 50 mM) and arginine hydrochloride (*e.g.*, 50 mM).

VEGF Receptor Fusion Proteins and Other VEGF inhibitors

[0075] For purposes herein, a “VEGF receptor fusion protein” refers to a molecule that comprises one or more VEGF receptors or domains thereof, fused to another polypeptide, which interferes with the interaction between VEGF and a natural VEGF receptor, *e.g.*, wherein two of such fusion polypeptides are associated thereby forming a homodimer or other multimer. Such VEGF receptor fusion proteins may be referred to as a "VEGF-Trap" or “VEGF Trap”. VEGF receptor fusion proteins within the context of the present disclosure that fall within this definition include, chimeric polypeptides which comprise two or more immunoglobulin (Ig)-like domains

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of a VEGF receptor such as VEGFR1 (also known as Flt1) and/or VEGFR2 (also known as Flk1 or KDR), and may also contain a multimerizing domain (for example, an Fc domain).

[0076] An exemplary VEGF receptor fusion protein is a molecule referred to as VEGF1R2-FcΔC1(a) which is encoded by the nucleic acid sequence of SEQ ID NO:1 or nucleotides 79-1374 or 79-1371 thereof.

[0077] VEGF1R2-FcΔC1(a) comprises three components:

(1) a VEGFR1 component comprising amino acids 27 to 129 of SEQ ID NO:2;

(2) a VEGFR2 component comprising amino acids 130 to 231 of SEQ ID NO:2; and

(3) a multimerization component ("FcΔC1(a)") comprising amino acids 232 to 457 of SEQ ID NO:2 (the C-terminal amino acids of SEQ ID NO:2, *i.e.*, K458, may or may not be included in the VEGF receptor fusion proteins, see U.S. Patent No. 7,396,664 or 7,354,579, incorporated herein for all purposes). Note that amino acids 1 to 26 of SEQ ID NO:2 are the signal sequence. In an embodiment of the invention, the VEGF receptor fusion protein comprises amino acids 27-458 or 27-457 of SEQ ID NO: 2.

[0078] In an embodiment of the invention, the VEGF receptor fusion protein comprises

(1) an immunoglobin-like (Ig) domain 2 of a first VEGF receptor (*e.g.*, VEGFR1), and

(2) an Ig domain 3 of a second VEGF receptor (*e.g.*, VEGFR2),

(3) and, optionally, further including an Ig domain 4 of the second VEGF receptor (*e.g.*, VEGFR2) and

(4) a multimerizing component (*e.g.*, Fc domain of IgG).

For example, in an embodiment of the invention, the VEGF receptor fusion protein has the following arrangement of said domains:

- [VEGFR1 Ig domain 2]-[VEGFR2 Ig domain 3]-[MC] (*e.g.*, a homodimer thereof) or
- [VEGFR1 Ig domain 2]-[VEGFR2 Ig domain 3]-[VEGFR2 Ig domain 4]-[MC] (*e.g.*, a homodimer thereof).

[0079] In an embodiment of the invention, the VEGF receptor fusion protein is a VEGF mini-trap which is a VEGF trap molecule with a truncated multimerizing component (*e.g.*, Fc), *e.g.*, wherein the mini-trap still includes an Fc hinge region. See *e.g.*, WO2005/00895 or U.S. Patent No. 7,396,664.

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[0080] Note that the present disclosure also includes, within its scope, high concentration formulations including, instead of a VEGF receptor fusion proteins, VEGF binding molecules and anti-VEGF antibodies and antigen-binding fragments thereof,

- bevacizumab (*e.g.*, at a concentration of about 80-90 or 88 mg/ml),
- ranibizumab (*e.g.*, at a concentration of about 20-40 mg/ml, *e.g.*, 21-35, 21 or 35 mg/ml),
- an anti-VEGF aptamer such as pegaptanib (*e.g.*, pegaptanib sodium),
- a single chain (*e.g.*, V_L-V_H) anti-VEGF antibody such as brolucizumab (*e.g.*, at a concentration of about 200-400 or 200, 210, 400 or 420 mg/ml),
- an anti-VEGF DARPin such as the Abicipar Pegol DARPin (*e.g.*, at a concentration of about 70-140, 70 or 140 mg/ml), or
- a bispecific anti-VEGF antibody, *e.g.*, which also binds to ANG2, such as RG7716 (*e.g.*, at a concentration of about 100-400, 100, 105, 400 or 420 mg/ml).

In order to minimize the repetitiveness of the embodiments discussed herein, it is contemplated that the scope of the present invention includes embodiments wherein any of the formulations discussed herein include, in place of a VEGF receptor fusion protein, an anti-VEGF antibody or antibody fragment or other VEGF binding molecule as discussed herein (*e.g.*, substituted with an anti-VEGF DARPin) at any of the concentrations discussed herein. For example, the present invention includes a formulation having 35 or 80 mg/ml ranibizumab, a buffer, a thermal stabilizer, a viscosity reducing agent and a surfactant.

[0081] DARPins are Designed Ankyrin Repeat Proteins. DARPins generally contain three to four tightly packed repeats of approximately 33 amino acid residues, with each repeat containing a β-turn and two anti-parallel α-helices. This rigid framework provides protein stability whilst enabling the presentation of variable regions, normally comprising six amino acid residues per repeat, for target recognition.

[0082] An "anti-VEGF" antibody or antigen-binding fragment of an antibody refers to an antibody or fragment that specifically binds to VEGF.

[0083] Illustrative VEGF receptor fusion proteins include aflibercept (EYLEA®, Regeneron Pharmaceuticals, Inc.) or conbercept (sold commercially by Chengdu Kanghong Biotechnology Co., Ltd.). See International patent application publication no. WO2005/121176 or WO2007/112675. The terms "aflibercept" and "conbercept" include biosimilar versions thereof. A biosimilar version of a reference product (*e.g.*, aflibercept) generally refers to a

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product comprising the identical amino acid sequence, but includes products which are biosimilar under the U.S. Biologics Price Competition and Innovation Act.

[0084] Pharmaceutical formulations of the present invention are “high concentration”. High concentration pharmaceutical formulations of the present invention include VEGF receptor fusion protein at a concentration of at least 41 mg/ml, of at least 80 mg/ml, of at least 100 mg/ml, of at least 125 mg/ml, of at least 140 mg/ml, of at least 150 mg/ml, of at least 175 mg/ml, of at least 200 mg/ml, of at least 225 mg/ml, of at least 250 mg/ml, or of at least 275 mg/ml. Alternatively, "high concentration” can refer to formulations that include a concentration of VEGF receptor fusion protein of from about 140 mg/ml to about 160 mg/ml, at least about 140 mg/ml but less than 160 mg/ml, from about 41 mg/ml to about 275 mg/ml, from about 70 mg/ml to about 75 mg/ml or from about 80 mg/ml to about 250 mg/ml. In some aspects, the VEGF receptor fusion protein concentration in the formulation is about any of the following concentrations: 41 mg/ml; 42 mg/ml; 43 mg/ml; 44 mg/ml; 45 mg/ml; 46 mg/ml; 47 mg/ml; 48 mg/ml; 49 mg/ml; 50mg/ml; 51 mg/ml; 52 mg/ml; 53 mg/ml; 54 mg/ml; 55 mg/ml; 56 mg/ml; 57 mg/ml; 58 mg/ml; 59 mg/ml; 60 mg/ml; 61 mg/ml; 62 mg/ml; 63 mg/ml; 64 mg/ml; 65 mg/ml; 66 mg/ml; 67 mg/ml; 68 mg/ml; 69 mg/ml; 70 mg/ml; 71 mg/ml; 72 mg/ml; 73 mg/ml; 74 mg/ml; 75 mg/ml; 76 mg/ml; 77 mg/ml; 78 mg/ml; 79 mg/ml; 80 mg/ml; 81 mg/ml; 82mg/ml; 83 mg/ml; 84 mg/ml; 85 mg/ml; 86 mg/ml; 87mg/ml; 88 mg/ml; 89 mg/ml; 90 mg/ml; 91 mg/ml; 92 mg/ml; 93 mg/ml; 94 mg/ml; 95mg/ml; 96 mg/ml; 97 mg/ml; 98 mg/ml; 99 mg/ml; 100 mg/ml; 101 mg/ml; 102 mg/ml; 103 mg/ml; 104 mg/ml; 105 mg/ml; 106mg/ml; 107 mg/ml; 108 mg/ml; 109 mg/ml; 110 mg/ml; 111 mg/ml; 112 mg/ml; 113 mg/ml; 113.3 mg/ml; 114 mg/ml; 114.1 mg/ml; 114.2 mg/ml; 114.3 mg/ml; 114.4 mg/ml; 114.5 mg/ml; 114.6 mg/ml, 114.7 mg/ml, 114.8 mg/ml; 114.9 mg/ml; 115 mg/ml; 116 mg/ml; 117 mg/ml; 118 mg/ml; 119 mg/ml; 120 mg/ml; 121 mg/ml; 122 mg/ml; 123 mg/ml; 124 mg/ml; 125 mg/ml; 126 mg/ml; 127mg/ml; 128 mg/ml; 129 mg/ml; 130 mg/ml; 131 mg/ml; 132 mg/ml; 133 mg/ml; 133.3 mg/ml; 133.4 mg/ml, 134 mg/ml; 135 mg/ml; 136 mg/ml; 137 mg/ml; 138 mg/ml; 139 mg/ml; 140 mg/ml; 141 mg/ml; 142 mg/ml; 143 mg/ml; 144 mg/ml; 145 mg/ml; 146 mg/ml; 147 mg/ml; 148 mg/ml; 149 mg/ml; 150 mg/ml; 151 mg/ml; 152 mg/ml; 153 mg/ml; 154mg/ml; 155 mg/ml; 156 mg/ml; 157mg/ml; 158 mg/ml; 159 mg/ml; 160 mg/ml; 161 mg/ml; 162 mg/ml; 163 mg/ml; 164 mg/ml; 165 mg/ml; 166 mg/ml; 167 mg/ml; 168 mg/ml; 169 mg/ml; 170 mg/ml; 171 mg/ml; 172 mg/ml;

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173 mg/ml; 174 mg/ml; 175 mg/ml; 176 mg/ml; 177 mg/ml; 178 mg/ml; 179 mg/ml; 180 mg/ml; 181 mg/ml; 182 mg/ml; 183 mg/ml; 184 mg/ml; 185 mg/ml; 186 mg/ml; 187 mg/ml; 188 mg/ml; 189 mg/ml; 190 mg/ml; 191 mg/ml; 192 mg/ml; 193 mg/ml; 194 mg/ml; 195 mg/ml; 196 mg/ml; 197 mg/ml; 198 mg/ml; 199 mg/ml; 200 mg/ml; 201 mg/ml; 202 mg/ml; 203 mg/ml; 204 mg/ml; 205 mg/ml; 206 mg/ml; 207 mg/ml; 208 mg/ml; 209 mg/ml; 210 mg/ml; 211 mg/ml; 212 mg/ml; 213 mg/ml; 214 mg/ml; 215 mg/ml; 216 mg/ml; 217 mg/ml; 218 mg/ml; 219 mg/ml; 220 mg/ml; 221 mg/ml; 222 mg/ml; 223 mg/ml; 224 mg/ml; 225 mg/ml; 226 mg/ml; 227 mg/ml; 228 mg/ml; 229 mg/ml; 230 mg/ml; 231 mg/ml; 232 mg/ml; 233 mg/ml; 234 mg/ml; 235 mg/ml; 236 mg/ml; 237mg/ml; 238 mg/ml; 239 mg/ml; 240 mg/ml; 241 mg/ml; 242 mg/ml; 243 mg/ml; 244 mg/ml; 245 mg/ml; 246 mg/ml; 247 mg/ml; 248 mg/ml; 249 mg/ml; 250 mg/ml; 251 mg/ml; 252 mg/ml; 253 mg/ml; 254 mg/ml; 255 mg/ml; 256 mg/ml; 257 mg/ml; 258 mg/ml; 259 mg/ml; 260 mg/ml; 261 mg/ml; 262 mg/ml; 263 mg/ml; 264 mg/ml; 265 mg/ml; 266 mg/ml; 267 mg/ml; 268 mg/ml; 269 mg/ml; 270 mg/ml; 271 mg/ml; 272 mg/ml; 273 mg/ml; 274 mg/ml; or 275 mg/ml. Other VEGF receptor fusion protein concentrations are contemplated herein, as long as the concentration functions in accordance with embodiments herein.

[0085] In an embodiment of the invention, a pharmaceutical formulation of the present invention is of such a concentration as to contain about 4, 6, 8, 10, 12, 14, 16, 18 or 20 mg VEGF receptor fusion protein (*e.g.*, aflibercept), or the amount of such protein in any of the acceptable doses thereof which are discussed herein, in about 100 µl or less, about 75 µl or less or about 70 µl or less, *e.g.*, about 50 µl; 51 µl; 52 µl; 53 µl; 54 µl; 55 µl; 56 µl; 57 µl; 58 µl; 59 µl; 60 µl; 61 µl; 62 µl; 63 µl; 64 µl; 65 µl; 66 µl; 67 µl; 68 µl; 69 µl; 70 µl; 71 µl; 72 µl; 73 µl; 74 µl; 75 µl; 76 µl; 77 µl; 78 µl; 79 µl; 80 µl; 81 µl; 82 µl; 83 µl; 84 µl; 85 µl; 86 µl; 87 µl; 88 µl; 89 µl; 90 µl; 91 µl; 92 µl; 93 µl; 94 µl; 95 µl; 96 µl; 97 µl; 98 µl; 99 µl; or 100 µl.

[0086] The present invention includes any of the formulations set forth under "*Illustrative Formulations*" herein, but wherein the concentration of the VEGF receptor fusion protein (*e.g.*, aflibercept) is substituted with a concentration which is set forth in this section ("VEGF Receptor Fusion Proteins and Other VEGF inhibitors").

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Buffers

[0087] Buffers for use herein refer to solutions that resist pH change by use of acid-base conjugates. Buffers are capable of maintaining pH in the range of from about 5.0 to about 6.8, and more typically, from about 5.8 to about 6.5, and most typically, from about 6.0 to about 6.5. In some cases, the pH of the formulation of the present invention is about 5.0, about 5.1, about 5.2, about 5.3, about 5.4, about 5.5, about 5.6, about 5.7, about 5.8, about 5.9, about 6.0, about 6.1, about 6.2, about 6.3, about 6.4, about 6.5, about 6.6, about 6.7, or about 6.8. Example buffers for inclusion in formulations herein include histidine-based buffers, for example, histidine, histidine hydrochloride, and histidine acetate. Buffers for inclusion in formulations herein can alternatively be phosphate-based buffers, for example, sodium phosphate, acetate-based buffers, for example, sodium acetate or acetic acid, or can be citrate-based, for example, sodium citrate or citric acid. It is also recognized that buffers can be a mix of the above, as long as the buffer functions to buffer the formulations in the above described pH ranges. In some cases, the buffer is from about 5 mM to about 25 mM, or more typically, about 5 mM to about 15 mM. Buffers can be about 5 mM, about 6 mM, about 7 mM, about 8 mM, about 9 mM, about 10 mM, about 11 mM, about 12 mM, about 13 mM, about 14 mM, about 15 mM, about 16 mM, about 17 mM, about 18 mM, about 19 mM, about 20 mM, about 21 mM, about 22 mM, about 23 mM, about 24 mM, or about 25 mM.

[0088] In an embodiment of the invention, a histidine-based buffer is prepared using histidine and histidine monohydrochloride.

Surfactants

[0089] Surfactant for use herein refers to ingredients that protect the higher concentration of VEGF receptor fusion protein from various surface and interfacial induced stresses. As such, surfactants can be used to limit or minimize VEGF receptor fusion protein aggregation, and promote protein solubility. Suitable surfactants herein have been shown to be non-ionic, and can include surfactants that have a polyoxyethylene moiety. Illustrative surfactants in this category include: polysorbate 20, polysorbate 80, poloxamer 188, polyethylene glycol 3350, and mixtures thereof. Surfactants in the formulations can be present at from about 0.02% to about 0.1% weight per volume (w/v), and more typically, about 0.02% to about 0.04% (w/v). In some cases, the surfactant is about 0.02% (w/v), about 0.03% (w/v), about 0.04% (w/v), about 0.05%

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(w/v), about 0.06% (w/v), about 0.07% (w/v), about 0.08% (w/v), about 0.09% (w/v), or about 0.1% (w/v).

Thermal Stabilizers

[0090] Thermal stabilizers for use herein refers to ingredients that provide thermal stability against thermal denaturation of the VEGF receptor fusion protein, as well as protect against loss of VEGF receptor fusion protein potency or activity. Suitable thermal stabilizers include sugars, and can be sucrose, trehalose, sorbitol or mannitol, or can be amino acids, for example L-proline, L-arginine (*e.g.*, L-arginine monohydrochloride), or taurine. Additionally, thermal stabilizers may also include substituted acrylamides or propane sulfonic acid, or may be compounds like glycerol.

[0091] In some cases, the formulations herein include both a sugar and taurine, a sugar and an amino acid, a sugar and propane sulfonic acid, a sugar and taurine, glycerol and taurine, glycerol and propane sulfonic acid, an amino acid and taurine, or an amino acid and propane sulfonic acid. In addition, formulations can include a sugar, taurine and propane sulfonic acid, glycerol, taurine and propane sulfonic acid, as well as L-proline, taurine and propane sulfonic acid.

[0092] Embodiments herein typically have thermal stabilizers present alone, each independently present at a concentration of, or present in combination at a total concentration of, from about 2% (w/v) to about 10% (w/v) or 4% (w/v) to about 10% (w/v), or about 4% (w/v) to about 9% (w/v), or about 5% (w/v) to about 8% (w/v). Thermal stabilizers in the formulation can be at a concentration of about 2% (w/v), about 2.5% (w/v), about 3% (w/v), about 4% (w/v), about 5% (w/v), about 6% (w/v), about 7% (w/v), about 8% (w/v), about 9% (w/v), about 10% (w/v) or about 20% (w/v).

[0093] With respect to taurine and propane sulfonic acid, in an embodiment of the invention, these thermal stabilizers can be present in the formulations at about from 25 mM to about 100 mM, and more typically from about 50 mM to about 75 mM (as compared to the other thermal stabilizers).

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Viscosity Reducing Agents

[0094] Viscosity reducing agents typically are used to reduce or prevent protein aggregation. Viscosity reducing agents for inclusion herein include: sodium chloride, magnesium chloride, D- or L-arginine (*e.g.*, L-arginine monohydrochloride), lysine, or mixtures thereof. When present herein, viscosity reducing agents can be present at from about 10 mM to about 100 mM, and more typically from about 30 mM to about 75 mM, and even more typically from about 40 mM to about 70 mM. In some cases the viscosity reducing agent is present at about 10 mM, about 15 mM, about 20 mM, about 25 mM, about 30 mM, about 35 mM, about 40 mM, about 45 mM, about 50 mM, about 55 mM, about 60 mM, about 65 mM, about 70 mM, about 75 mM, about 80 mM, about 85 mM, about 90 mM, about 95 mM or about 100 mM.

Formulation Viscosity

[0095] Formulations in accordance with embodiments herein can also have a pharmaceutically acceptable viscosity for ocular administration, for example, intravitreal injection. Viscosity generally refers to the measure of resistance of a fluid which is being deformed by either shear stress or tensile stress (typically measured by techniques known in the art, viscometer or rheometer, for example). Typical viscosities of formulations in accordance with embodiments herein are from about 5.0 cP (centipoise) to about 15 cP, from about 11 cP to about 14 cP, from about 12 cP to about 15 cP or from about 11 cP to about 12 cP. As such, formulation viscosity herein can be about 5.0 cP, about 6.0, about 7.1 cP, about 7.2 cP, about 7.3 cP, about 7.4 cP, about 7.5 cP, about 7.6 cP, about 10 cP, about 10.5 cP, about 11.0 cP, about 11.5 cP, about 12.0 cP, about 12.5 cP, about 13.0 cP, about 13.5 cP, about 14.0 cP, about 14.5 cP, or about 15.0 cP (*e.g.*, when measured at 20°C).

[0096] Various embodiments herein do not require inclusion of an inorganic salt, or other viscosity reducing agent, to maintain these highly useful viscosities. Typically, high concentration protein solutions require viscosity reducing agents to avoid protein aggregation and higher viscosity, making the formulations difficult for intravitreal injection and reducing the potency of the VEGF receptor fusion protein. As such, embodiments herein include formulations that have had substantially no, or no added, sodium chloride (NaCl), magnesium chloride ($MgCl_2$), D- or L-arginine hydrochloride, lysine or other viscosity reducing agent.

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Formulation osmolality

[0097] Osmolality is a critical attribute for injectable formulations. It is desirable to have products match physiological osmotic conditions. Furthermore, osmolality provides confirmation of soluble content in solution. In an embodiment of the invention, the osmolality of a formulation of the present invention is less than or equal to about 506 mmol/Kg or from about 250 to about 506 mmol/Kg., *e.g.*, about 250, 260, 270, 280, 290, 299, 300, 310, 314, 315, 316, 324, 343, 346, 349, 369, 384, 403, 426, 430 or 506 mmol/Kg. In an embodiment of the invention, the osmolality is lower than about 250 mmol/Kg.

Purity and Stability of Formulations

[0098] High concentration VEGF receptor fusion protein containing formulations described herein are stable during manufacture and storage. The term "stable" herein refers to formulations that include VEGF receptor proteins that retain both chemical and physical stability over the period of formulation manufacturing and storage, *e.g.*, that maintains integrity and has minimal degradation, denaturation, or unfolding. VEGF receptor protein stability can be determined using analytical techniques available in the art at different temperatures and over different periods of time. In particular, VEGF receptor chemical stability (potency) can be determined using various bioassays (for example, a BAF/3 VEGFR1/EPOR cell line used to determine $VEGF_{165}$ binding by the VEGF receptor fusion proteins herein), and physical stability, by size exclusion (SE) chromatographic analysis, UPLC (ultra-performance liquid chromatography) size exclusion (SE) chromatography, visual appearance, OD, pH, charge variant formation, and rate of high molecular weight (HMW) species formation. A stable VEGF receptor fusion protein is one that shows limited change in its OD, pH, formation of charge variants, and formation of HMW species.

[0099] A “high molecular weight” (HMW) species as used herein, with reference to a formulation containing a given VEGF Trap (*e.g.*, aflibercept), refers to any species of polypeptide or polypeptide complex in the formulation which elutes from a size exclusion column (*e.g.*, SE-UPLC) ahead of (*e.g.*, with a higher molecular weight than) VEGF Trap polypeptide and/or a homodimer thereof. The percentage of HMW species refers to the percentage of such species relative to the overall quantity of polypeptides in the formulation, *e.g.*, by SE-UPLC analysis.

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[00100] In an embodiment of the invention, as discussed more fully in the Examples below, stable formulations show significant VEGF receptor fusion protein potency and physical stability for a period of up to 12 months, up to 24 months, and/or up to 36 months when stored at about 2°C to about 8°C.

[00101] In an embodiment of the invention, formulation of the present invention is one that:

- After about 28 days at about 37°C has about a 3, 5, 10, 11, 12, 13, 14, 15, 16, 17, 18, 20, 30, 35 or 37% (or 10-15% or 15-20% or 10-20%) increase in high molecular weight species (*e.g.*, as measured by SE-UPLC or SEC)
- After about 28 days at about 37°C has about a 5, 6, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21 or 22% (or 5-20% or 5-10% or 10-15% or 15-20%) decrease in main species (*e.g.*, as measured by SE-UPLC or SEC)
- After about 28 days at about 37°C, has about 80, 81, 82, 83, 84, 85, 86 or 87% (or about 80-85%) or more protein as main species (*e.g.*, as measured by SE-UPLC or SEC)
- After about 28 days at about 37°C has about a 1 or 1.5 or 2% (or 1-2%) increase in low molecular weight species (*e.g.*, as measured by SE-UPLC or SEC)
- After about one month at about 37°C has about a 16% increase in high molecular weight species; and/or about a 17% decrease in main species and/or about a 0.5% or <1% increase in low molecular weight species; and/or after about two months at about 5°C, has about a 1% decrease in main species, and/or about a 1% increase in high molecular weight species and/or no significant or detectable amounts low molecular weight (LMW) species; and/or after about 2 months at about 5°C, has about 97% main species (*e.g.*, as measured by SE-UPLC or SEC)
- After about 12 months at about 2-8°C has about a 3-3.5% increase in high molecular weight species (*e.g.*, as measured by SE-UPLC or SEC)
- After about 12 months at about 2-8°C has less than about a 1% or a 1, 2, 3 or 4% (*e.g.*, 1-4% or 3-4%) decrease in main species (*e.g.*, as measured by SE-UPLC or SEC)
- After about 12 months at about 2-8°C, has about 94 or 95% or more protein as main species (*e.g.*, as measured by SE-UPLC or SEC)
- After about 3 months at about 2-8°C has about a 1 or 2% increase in high molecular weight species (*e.g.*, as measured by SE-UPLC or SEC)

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- After about 6 months at about 2-8°C has about a <1, 1 or 2% increase in high molecular weight species (*e.g.*, as measured by SE-UPLC or SEC)
- After about 5$^1/_2$ or 6 months at about 5°C has about 2.5, 3.0 or 3.5 (or about 2.5-3.5%) total high molecular weight species (*e.g.*, as measured by SE-UPLC or SEC).
- After about 6 months at about 2-8°C has less than about a 1% or 1 or 2% (or about 0.5-2% or 1-2%) decrease in main species (*e.g.*, as measured by SE-UPLC or SEC)
- After about 6 months at about 2-8°C, has about 96 or 97 or 98% (or 96-98%) or more protein as main species (*e.g.*, as measured by SE-UPLC or SEC)
- After about 24 months or 36 months at about 2-8°C, had less than about 5 or 6 or 7% (*e.g.*, about 1.5, 2, 3, 4 or 5%) (or 1.5-5% or 1.5-2.5%) increase in high molecular weight species; and/or has about 3.0, 3.25, 3.5, 4.0, 4.5 or 5% total high molecular weight species; and/or a decrease of about 2 or 3% (or 2-3%) main species; and/or a total amount of main species of about 95 or 96% or more (or 95-96%) (*e.g.*, as measured by SE-UPLC or SEC)
- After about 1 month at about 37°C, has about 97, 98, 99 or 100% (or 97-100%) of aflibercept in the formulation which is recoverable by RP-HPLC
- Immediately after manufacture and purification, has less than about 1.5, 2, 2.5, 3.0 or 3.5% high molecular weight species (*e.g.*, as measured by SE-UPLC or SEC)
- After about 6 months at about 37°C, has at least about 70% or 75% (*e.g.*, 70-75%) of aflibercept as main species/main peak (*e.g.*, as measured by capillary isoelectric focusing (cIEF) or imaged capillary isoelectric focusing) (non-acidic and non-basic species)
- After about 36 months at about 2-8°C, has about a 1 or 2% (or 1-2%) increase in acidic species (*e.g.*, as measured by capillary isoelectric focusing (cIEF) or imaged capillary isoelectric focusing)
- After about 36 months at about 2-8°C, has about a 1% or less decrease in main species/main peak (*e.g.*, as measured by capillary isoelectric focusing (cIEF) or imaged capillary isoelectric focusing)
- After about 36 months at about 2-8°C, has about 78-79% main species/main peak (*e.g.*, as measured by capillary isoelectric focusing (cIEF) or imaged capillary isoelectric focusing)

and/or

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- When administered intravitreally to a mammal, such as a human or rabbit or mouse (*e.g.*, with an angiogenic eye disorder such as wet AMD), does not cause any adverse events that are clinically different from those observed for EYLEA (*e.g.*, when EYLEA is dosed intravitreally at 0.5 or 2.0 mg); or does not cause clinically significant inflammation in the eye, prolonged intraocular pressure (IOP) increases, prolonged increases in blood pressure or decreases and/or retinal detachment.

[00102] Further, in an embodiment of the invention, high concentration VEGF receptor fusion proteins are stable as they show little or no formation of acidic charge variants over the course of manufacture and storage, for example, little or no formation of charge variants as tested by Imaged Capillary Isoelectric Focusing, for example.

[00103] In an embodiment of the invention, a formulation of the present invention exhibits less than or equal to about 8% low molecular weight (LMW) species.

[00104] In an embodiment of the invention, a formulation of the present invention has less than about 0.2, 0.4 or 0.5 EU (endotoxin units)/ml of endotoxin;

[00105] In an embodiment of the invention, a formulation of the present invention is essentially free of particulate matter or particulate matter of about 1, 2, 5, 10, 25 or 50 micrometers (or more) in size.

[00106] In an embodiment of the invention, when a formulation of the present invention is analyzed by non-reduced CE-SDS (SDS capillary gel electrophoresis), at least 97% of the total peak area is the main peak.

[00107] In an embodiment of the invention, when a formulation of the present invention is analyzed by size-exclusion UPLC (SE-UPLC), at least 93, 94 or 95% of the total peak area is the main peak and less than or equal to 3.5, 4, 5 or 6% is aggregate.

[00108] In an embodiment of the invention, a formulation of the present invention is at about 2°C, 3°C, 4°C, 5°C, 6°C, 7°C or 8°C, 2-8°C (*e.g.*, an average temperature of 5°C), 23°C, 25°C, 30°C or 37°C.

Illustrative Formulations

[00109] Illustrative high concentration VEGF receptor fusion protein containing formulations include the following:

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[00110] Formulation A: 80 mg/ml aflibercept, 10 mM histidine-based buffer, 5 % (w/v) sucrose, 0.03% (w/v) polysorbate 20, and 40 mM sodium chloride, with a pH of 5.8 to 6.2.

[00111] Formulation B: 80 mg/ml aflibercept, 10 mM phosphate-based buffer, 5 % (w/v) sucrose, 0.03% (w/v) polysorbate 20, and 40 mM sodium chloride, with a pH of 5.8 to 6.2.

[00112] Formulation C: 80 mg/ml aflibercept, 10 mM citrate-based buffer, 5 % (w/v) sucrose, 0.03% (w/v) polysorbate 20, and 40 mM sodium chloride, with a pH of 5.8 to 6.2.

[00113] Formulation D: 80 mg/ml aflibercept, 10 mM histidine-based buffer, 5 % (w/v) sucrose, 0.03 % (w/v) polysorbate 80, and 40 mM sodium chloride, with a pH of 6.2.

[00114] Formulation E: 80 mg/ml aflibercept, 10 mM phosphate-based buffer, 5 % (w/v) sucrose, 0.03 % (w/v) polysorbate 80, and 40 mM sodium chloride, with a pH of 5.8 to 6.2.

[00115] Formulation F: 80 mg/ml aflibercept, 10 mM citrate-based buffer, 5 % (w/v) sucrose, 0.03 % (w/v) polysorbate 80, and 40 mM sodium chloride, with a pH of 5.8 to 6.2.

[00116] Formulation G: 80 mg/ml aflibercept, 10 mM histidine-based buffer, 8 % (w/v) sucrose, and 0.03 % (w/v) polysorbate 20, with a pH of 5.8 to 6.2, and, optionally, specifically excluding a viscosity reducing agent.

[00117] Formulation H: 80 mg/ml aflibercept, 10 mM phosphate-based buffer, 8 % (w/v) sucrose, and 0.03 % (w/v) polysorbate 20, with a pH of 5.8 to 6.2, and, optionally, specifically excluding a viscosity reducing agent.

[00118] Formulation I: 80 mg/ml aflibercept, 10 mM citrate-based buffer, 8 % (w/v) sucrose, and 0.0 3% (w/v) polysorbate 20, with a pH of 5.8 to 6.2, and, optionally, specifically excluding a viscosity reducing agent.

[00119] Formulation J: 80 mg/ml aflibercept, 10 mM histidine-based buffer, 8 % (w/v) sucrose, and 0.03 % (w/v) polysorbate 80, with a pH of 5.8 to 6.2, and, optionally, specifically excluding a viscosity reducing agent.

[00120] Formulation K: 80 mg/ml aflibercept, 10 mM phosphate-based buffer, 8 % (w/v) sucrose, and 0.03 % (w/v) polysorbate 80, with a pH of 5.8 to 6.2, and, optionally, specifically excluding a viscosity reducing agent.

[00121] Formulation L: 80 mg/ml aflibercept, 10 mM citrate-based buffer, 8 % (w/v) sucrose, and 0.03 % (w/v) polysorbate 80, with a pH of 5.8 to 6.2, and, optionally, specifically excluding a viscosity reducing agent.

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[00122] Formulation M: 150 mg/ml aflibercept, 10 mM histidine-based buffer, 5 % (w/v) sucrose, 0.03 % (w/v) polysorbate 20, and 40 mM sodium chloride, with a pH of 5.8 to 6.2.

[00123] Formulation N: 150 mg/ml aflibercept, 10 mM phosphate-based buffer, 5 % (w/v) sucrose, 0.03 % (w/v) polysorbate 20, and 40 mM sodium chloride, with a pH of 5.8 to 6.2.

[00124] Formulation O: 150 mg/ml aflibercept, 10 mM citrate-based buffer, 5 % (w/v) sucrose, 0.03 % (w/v) polysorbate 20, and 40 mM sodium chloride, with a pH of 5.8 to 6.2.

[00125] Formulation P: 150 mg/ml aflibercept, 10 mM histidine-based buffer, 5 % (w/v) sucrose, 0.03 % (w/v) polysorbate 80, and 40 mM sodium chloride, with a pH of 6.2.

[00126] Formulation Q: 150 mg/ml aflibercept, 10 mM phosphate-based buffer, 5 % (w/v) sucrose, 0.03 % (w/v) polysorbate 80, and 40 mM sodium chloride, with a pH of 5.8 to 6.2.

[00127] Formulation R: 150 mg/ml aflibercept, 10 mM citrate-based buffer, 5 % (w/v) sucrose, 0.03 % (w/v) polysorbate 80, and 40 mM sodium chloride, with a pH of 5.8 to 6.2.

[00128] Formulation S: 150 mg/ml aflibercept, 10 mM histidine-based buffer, 8 % (w/v) sucrose, and 0.03 % (w/v) polysorbate 20, with a pH of 5.8 to 6.2, and, optionally, specifically excluding a viscosity reducing agent.

[00129] Formulation T: 150 mg/ml aflibercept, 10 mM phosphate-based buffer, 8 % (w/v) sucrose, and 0.03 % (w/v) polysorbate 20, with a pH of 5.8 to 6.2 (*e.g.*, 6.2), and, optionally, specifically excluding a viscosity reducing agent.

[00130] Formulation U: 150 mg/ml aflibercept, 10 mM citrate-based buffer, 8 % (w/v) sucrose, and 0.03 % (w/v) polysorbate 20, with a pH of 5.8 to 6.2, and, optionally, specifically excluding a viscosity reducing agent.

[00131] Formulation V: 150 mg/ml aflibercept, 10 mM histidine-based buffer, 8 % (w/v) sucrose, and 0.03 % (w/v) polysorbate 80, with a pH of 5.8 to 6.2, and, optionally, specifically excluding a viscosity reducing agent.

[00132] Formulation W: 150 mg/ml aflibercept, 10 mM phosphate-based buffer, 8 % (w/v) sucrose, and 0.03 % (w/v) polysorbate 80, with a pH of 5.8 to 6.2, and, optionally, specifically excluding a viscosity reducing agent.

[00133] Formulation X: 150 mg/ml aflibercept, 10 mM citrate-based buffer, 8 % (w/v) sucrose, and 0.03 % (w/v) polysorbate 80, with a pH of 5.8 to 6.2, and, optionally, specifically excluding a viscosity reducing agent.

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[00134] Formulation Y: 80 mg/ml conbercept, 10 mM histidine-based buffer, 5 % (w/v) sucrose, 0.03 % (w/v) polysorbate 20, and 40 mM sodium chloride, with a pH of 5.8 to 6.2.

[00135] Formulation Z: 80 mg/ml conbercept, 10 mM phosphate-based buffer, 5 % (w/v) sucrose, 0.03 % (w/v) polysorbate 20, and 40 mM sodium chloride, with a pH of 5.8 to 6.2.

[00136] Formulation AA: 80 mg/ml conbercept, 10 mM citrate-based buffer, 5 % (w/v) sucrose, 0.03 % (w/v) polysorbate 20, and 40 mM sodium chloride, with a pH of 5.8 to 6.2.

[00137] Formulation BB: 80 mg/ml conbercept, 10 mM histidine-based buffer, 5 % (w/v) sucrose, 0.03 % (w/v) polysorbate 80, and 40 mM sodium chloride, with a pH of 6.2.

[00138] Formulation CC: 80 mg/ml conbercept, 10 mM phosphate-based buffer, 5 % (w/v) sucrose, 0.03 % (w/v) polysorbate 80, and 40 mM sodium chloride, with a pH of 5.8 to 6.2.

[00139] Formulation DD: 80 mg/ml conbercept, 10 mM citrate-based buffer, 5 % (w/v) sucrose, 0.03 % (w/v) polysorbate 80, and 40 mM sodium chloride, with a pH of 5.8 to 6.2.

[00140] Formulation EE: 80 mg/ml conbercept, 10 mM histidine-based buffer, 8 % (w/v) sucrose, and 0.03 % (w/v) polysorbate 20, with a pH of 5.8 to 6.2, and, optionally, specifically excluding a viscosity reducing agent.

[00141] Formulation FF: 80 mg/ml conbercept, 10 mM phosphate-based buffer, 8 % (w/v) sucrose, and 0.03 % (w/v) polysorbate 20, with a pH of 5.8 to 6.2, and, optionally, specifically excluding a viscosity reducing agent.

[00142] Formulation GG: 80 mg/ml conbercept, 10 mM citrate-based buffer, 8 % (w/v) sucrose, and 0.03 % (w/v) polysorbate 20, with a pH of 5.8 to 6.2, and, optionally, specifically excluding a viscosity reducing agent.

[00143] Formulation HH: 80 mg/ml conbercept, 10 mM histidine-based buffer, 8 % (w/v) sucrose, and 0.03 % (w/v) polysorbate 80, with a pH of 5.8 to 6.2, and, optionally, specifically excluding a viscosity reducing agent.

[00144] Formulation II: 80 mg/ml conbercept, 10 mM phosphate-based buffer, 8 % (w/v) sucrose, and 0.03 % (w/v) polysorbate 80, with a pH of 5.8 to 6.2, and, optionally, specifically excluding a viscosity reducing agent.

[00145] Formulation JJ: 80 mg/ml conbercept, 10 mM citrate-based buffer, 8 % (w/v) sucrose, and 0.03 % (w/v) polysorbate 80, with a pH of 5.8 to 6.2, and, optionally, specifically excluding a viscosity reducing agent.

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[00146] Formulation KK: 150 mg/ml conbercept, 10 mM histidine-based buffer, 5 % (w/v) sucrose, 0.03 % (w/v) polysorbate 20, and 40 mM sodium chloride, with a pH of 5.8 to 6.2.

[00147] Formulation LL: 150 mg/ml conbercept, 10 mM phosphate-based buffer, 5 % (w/v) sucrose, 0.03 % (w/v) polysorbate 20, and 40 mM sodium chloride, with a pH of 5.8 to 6.2.

[00148] Formulation MM: 150 mg/ml conbercept, 10 mM citrate-based buffer, 5 % (w/v) sucrose, 0.03 % (w/v) polysorbate 20, and 40 mM sodium chloride, with a pH of 5.8 to 6.2.

[00149] Formulation NN: 150 mg/ml conbercept, 10 mM histidine-based buffer, 5 % (w/v) sucrose, 0.03 % (w/v) polysorbate 80, and 40 mM sodium chloride, with a pH of 6.2.

[00150] Formulation OO: 150 mg/ml conbercept, 10 mM phosphate-based buffer, 5 % (w/v) sucrose, 0.03 % (w/v) polysorbate 80, and 40 mM sodium chloride, with a pH of 5.8 to 6.2.

[00151] Formulation PP: 150 mg/ml conbercept, 10 mM citrate-based buffer, 5 % (w/v) sucrose, 0.03 % (w/v) polysorbate 80, and 40 mM sodium chloride, with a pH of 5.8 to 6.2.

[00152] Formulation QQ: 150 mg/ml conbercept, 10 mM histidine-based buffer, 8 % (w/v) sucrose, and 0.03 % (w/v) polysorbate 20, with a pH of 5.8 to 6.2, and, optionally, specifically excluding a viscosity reducing agent.

[00153] Formulation RR: 150 mg/ml conbercept, 10 mM phosphate-based buffer, 8 % (w/v) sucrose, and 0.03 % (w/v) polysorbate 20, with a pH of 5.8 to 6.2, and, optionally, specifically excluding a viscosity reducing agent.

[00154] Formulation SS: 150 mg/ml conbercept, 10 mM citrate-based buffer, 8 % (w/v) sucrose, and 0.03 % (w/v) polysorbate 20, with a pH of 5.8 to 6.2, and, optionally, specifically excluding a viscosity reducing agent.

[00155] Formulation TT: 150 mg/ml conbercept, 10 mM histidine-based buffer, 8 % (w/v) sucrose, and 0.03 % (w/v) polysorbate 80, with a pH of 5.8 to 6.2, and, optionally, specifically excluding a viscosity reducing agent.

[00156] Formulation UU: 150 mg/ml conbercept, 10 mM phosphate-based buffer, 8 % (w/v) sucrose, and 0.03 % (w/v) polysorbate 80, with a pH of 5.8 to 6.2, and, optionally, specifically excluding a viscosity reducing agent.

[00157] Formulation VV: 150 mg/ml conbercept, 10 mM citrate-based buffer, 8 % (w/v) sucrose, and 0.03 % (w/v) polysorbate 80, with a pH of 5.8 to 6.2, and, optionally, specifically excluding a viscosity reducing agent.

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[00158] Formulation WW: 140 mg/ml VEGF receptor fusion protein (*e.g.*, aflibercept), 10 mM histidine-based buffer, 5 % (w/v) sucrose, 0.03 % (w/v) polysorbate 20, and 50 mM taurine, with a pH of 5.8.

[00159] Formulation XX: 140 mg/ml VEGF receptor fusion protein (*e.g.*, aflibercept), 20 mM histidine-based buffer, 4 % (w/v) proline, 0.03 % (w/v) polysorbate 20, and 50 mM arginine hydrochloride, with a pH of 5.8.

[00160] Formulation YY: 140 mg/ml VEGF receptor fusion protein (*e.g.*, aflibercept), 20 mM histidine-based buffer, 2.5 % (w/v) sucrose, 2.0 % (w/v) proline, 0.03 % (w/v) polysorbate 20, and 50 mM taurine, with a pH of 5.8.

[00161] Formulation ZZ: 140 mg/ml VEGF receptor fusion protein (*e.g.*, aflibercept), 10 mM histidine-based buffer, 2.5 % (w/v) sucrose, 2.0 % (w/v) proline, 0.03 % (w/v) polysorbate 20, and 50 mM arginine hydrochloride, with a pH of 5.8.

[00162] Formulation AAA: 140 mg/ml VEGF receptor fusion protein (*e.g.*, aflibercept), 20 mM histidine-based buffer, 5 % (w/v) sucrose, 0.03% (w/v) polysorbate 20, and 50 mM PSA, with a pH of 5.8.

[00163] Formulation BBB: 140 mg/ml VEGF receptor fusion protein (*e.g.*, aflibercept), 20 mM histidine-based buffer, 2.5 % (w/v) sucrose, 2.0 % (w/v) proline, 0.03 % (w/v) polysorbate 20, and 50 mM PSA, with a pH of 5.8.

[00164] Formulation CCC: 80, 100, 120 or 140 mg/ml VEGF receptor fusion protein (*e.g.*, aflibercept), 20 mM histidine-based buffer, 5 % (w/v) sucrose, 0.03 % (w/v) polysorbate 20, and 50 mM arginine hydrochloride, with a pH of 5.8.

[00165] Formulation DDD: 140 mg/ml VEGF receptor fusion protein (*e.g.*, aflibercept), 10 mM histidine-based buffer, 4 % (w/v) proline, 0.03 % (w/v) polysorbate 20, and 50 mM PSA, with a pH of 5.8.

[00166] Formulation EEE: 140 mg/ml VEGF receptor fusion protein (*e.g.*, aflibercept), 20 mM histidine-based buffer, 5 % (w/v) sucrose, and 0.03 % (w/v) polysorbate 20 and, optionally, no thermal stabilizer, with a pH of 5.8.

[00167] Formulation FFF: 140 mg/ml VEGF receptor fusion protein (*e.g.*, aflibercept), 10mM sodium phosphate, 5 % (w/v) sucrose and 0.03 % polysorbate 20 with a pH of 6.2.

[00168] Formulation GGG: 140 mg/ml VEGF receptor fusion protein (*e.g.*, aflibercept); 20 mM histidine, pH 5.8; 5% sucrose; 0.03 % polysorbate 20; 50 mM sodium sulfate

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[00169] Formulation HHH: 140 mg/ml VEGF receptor fusion protein (*e.g.*, aflibercept); 20 mM histidine, pH 5.8; 5% sucrose; 0.03 % polysorbate 20; 50 mM sodium thiocyanate

[00170] Formulation III: 140 mg/ml VEGF receptor fusion protein (*e.g.*, aflibercept); 20 mM histidine, pH 5.8; 5 % sucrose, 0.03 % polysorbate 20; 40 mM sodium citrate

[00171] Formulation JJJ: 140 mg/ml VEGF receptor fusion protein (*e.g.*, aflibercept); 20 mM histidine, pH 5.8; 5% Sucrose, 0.03 % polysorbate 20; 50 mM glycine

[00172] Formulation KKK: 140 mg/ml VEGF receptor fusion protein (*e.g.*, aflibercept); 20 mM histidine, pH 5.8; 5 % sucrose, 0.03 % polysorbate 20; 50 mM sodium chloride

[00173] Formulation LLL: 140 mg/ml VEGF receptor fusion protein (*e.g.*, aflibercept); 20 mM histidine, pH 5.8; 5 % sucrose; 0.03 % polysorbate 20; 50 mM lysine

[00174] Formulation MMM: 140 mg/ml VEGF receptor fusion protein (*e.g.*, aflibercept); 20 mM histidine, pH 5.8; 5 % sucrose; 0.03% polysorbate 20; 50 mM sodium aspartate

[00175] Formulation NNN: 140 mg/ml VEGF receptor fusion protein (*e.g.*, aflibercept); 20 mM histidine, pH 5.8; 5 % sucrose; 0.03 % polysorbate 20; 50 mM sodium glutamate

[00176] Formulation OOO: 140 mg/ml VEGF receptor fusion protein (*e.g.*, aflibercept); 20 mM histidine, pH 5.8; 5 % sucrose; 0.03% polysorbate 20; 50 mM sodium citrate; 50 mM arginine hydrochloride

[00177] Formulation PPP: 140 mg/ml VEGF receptor fusion protein (*e.g.*, aflibercept); 20 mM histidine, pH 5.8; 5 % sucrose; 0.03% polysorbate 20; 50 mM glycine; 50 mM arginine hydrochloride

[00178] Formulation QQQ: 140 mg/ml VEGF receptor fusion protein (*e.g.*, aflibercept); 20 mM histidine, pH 5.8; 5 % sucrose; 0.03% polysorbate 20; 50 mM sodium aspartate; 50 mM arginine hydrochloride

[00179] Formulation RRR: 140 mg/ml VEGF receptor fusion protein (*e.g.*, aflibercept); 20 mM histidine, pH 5.8; 5 % sucrose; 0.03% polysorbate 20; 50 mM sodium glutamate; 50 mM arginine hydrochloride

[00180] Formulation SSS: 140 mg/ml VEGF receptor fusion protein (*e.g.*, aflibercept); 20 mM His, pH 5.8; 5 % sucrose; 0.03 % polysorbate 20; 10 mM L-arginine hydrochloride

[00181] Formulation TTT: 140 mg/ml VEGF receptor fusion protein (*e.g.*, aflibercept); 20 mM His, pH 5.8; 5 % sucrose; 0.03 % polysorbate 20; 100 mM L-arginine hydrochloride

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[00182] Formulation UUU: 30 mg/ml VEGF receptor fusion protein (*e.g.*, aflibercept), 10 % sucrose, 10 mM phosphate, 0.03 % polysorbate 20, pH 6.2

[00183] Formulation VVV: 30 mg/ml VEGF receptor fusion protein (*e.g.*, aflibercept), 20 % sucrose, 10 mM phosphate, 0.03 % polysorbate 20, pH 6.2

[00184] Formulation WWW: 60 mg/ml VEGF receptor fusion protein (*e.g.*, aflibercept), 10 % sucrose, 10 mM phosphate, 0.03 % polysorbate 20, pH 6.2

[00185] Formulation XXX: 60 mg/ml VEGF receptor fusion protein (*e.g.*, aflibercept), 20 % sucrose, 10 mM phosphate, 0.03 % polysorbate 20, pH 6.2

[00186] Formulation YYY: 120 mg/ml VEGF receptor fusion protein (*e.g.*, aflibercept), 10 % sucrose, 10 mM phosphate, 0.03 % polysorbate 20, pH 6.2

[00187] Formulation ZZZ: 120 mg/ml VEGF receptor fusion protein (*e.g.*, aflibercept), 20 % sucrose, 10 mM phosphate, 0.03 % polysorbate 20, pH 6.2

[00188] Formulation AAAA: 120 mg/ml VEGF receptor fusion protein (*e.g.*, aflibercept), 10 % sucrose, 10 mM phosphate, 0.03 % polysorbate 20, 50 mM NaCl, pH 6.2

[00189] Formulation BBBB: 120 mg/ml VEGF receptor fusion protein (*e.g.*, aflibercept), 20 % sucrose, 10 mM phosphate, 0.03 % polysorbate 20, 50 mM NaCl, pH 6.2

[00190] Formulation CCCC: 140 mg/ml VEGF receptor fusion protein (*e.g.*, aflibercept), 10 mM sodium phosphate, 5 % sucrose, 40 mM sodium chloride, 0.03 % PS20, pH 6.2

[00191] Formulation DDDD: 80 mg/ml VEGF receptor fusion protein (*e.g.*, aflibercept), 20 mM histidine-based buffer, 5 % (w/v) sucrose, 0.03 % (w/v) polysorbate 20, and 50 mM L-arginine monohydrochloride, with a pH of 5.8.

[00192] Formulation EEEE: 120.0 mg/ml VEGF receptor fusion protein (*e.g.*, aflibercept) (*e.g.*, $\pm$ 12 mg/ml), 20 mM histidine-based buffer (*e.g.*, $\pm$ 2 mM), 5 % (w/v) sucrose (*e.g.*, $\pm$ 0.5%), 0.03 % (w/v) polysorbate 20 (*e.g.*, 0.02-0.04%), and 50 mM L-arginine monohydrochloride (*e.g.*, $\pm$ 5 mM), with a pH of 5.8 (*e.g.*, 5.6-6.0 or 5.5-6.1).

[00193] Formulation FFFF: 113.3 mg/ml VEGF receptor fusion protein (*e.g.*, aflibercept) (*e.g.*, 102-125 mg/ml), 20 mM histidine-based buffer (*e.g.*, $\pm$ 2 mM), 5 % (w/v) sucrose (*e.g.*, $\pm$ 0.5%), 0.03 % (w/v) polysorbate 20 (*e.g.*, 0.02-0.04%), and 50 mM L-arginine monohydrochloride (*e.g.*, $\pm$ 5 mM), with a pH of 5.8 (*e.g.*, 5.6-6.0 or 5.5-6.1).

[00194] Formulation GGGG: 114.3 mg/ml VEGF receptor fusion protein (*e.g.*, aflibercept) (*e.g.*, 103-126 mg/ml), 10 mM histidine-based buffer (*e.g.*, $\pm$ 1 mM), 5 % (w/v)

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sucrose (*e.g.*, ± 0.5%), 0.03 % (w/v) polysorbate 20 (*e.g.*, 0.02-0.04%), and 50 mM L-arginine monohydrochloride (*e.g.*, ± 5 mM), with a pH of 5.8 (*e.g.*, 5.6-6.0 or 5.5-6.1).

[00195] Formulation HHHH: 100.0 mg/ml VEGF receptor fusion protein (*e.g.*, aflibercept) (*e.g.*, ± 10 mg/ml), 20 mM histidine-based buffer (*e.g.*, ± 2 mM), 5 % (w/v) sucrose (*e.g.*, ± 0.5%), 0.03 % (w/v) polysorbate 20 (*e.g.*, 0.02-0.04%), and 50 mM L-arginine monohydrochloride (*e.g.*, ± 5 mM), with a pH of 5.8 (*e.g.*, 5.6-6.0 or 5.5-6.1).

[00196] Formulation IIII: 133.3 mg/ml VEGF receptor fusion protein (*e.g.*, aflibercept) (*e.g.*, ± 13 mg/ml), 20 mM histidine-based buffer (*e.g.*, ± 2 mM), 5 % (w/v) sucrose (*e.g.*, ± 0.5%), 0.03 % (w/v) polysorbate 20 (*e.g.*, 0.02-0.04%), and 50 mM L-arginine monohydrochloride (*e.g.*, ± 5 mM), with a pH of 5.8 (*e.g.*, 5.6-6.0 or 5.5-6.1).

[00197] Formulation JJJJ: 150 mg/ml aflibercept (*e.g.*, aflibercept) (*e.g.*, ± 15 mg/ml), 10 mM sodium phosphate, 8% (w/v) sucrose (*e.g.*, ± 0.8%), 0.03% (w/v) polysorbate 20 (*e.g.*, 0.02-0.04%) and 50 mM L-arginine hydrochloride, pH 6.2 (*e.g.*, 6.0-6.4 or 5.9-6.5).

[00198] Formulation KKKK: 114.3 mg/ml VEGF receptor fusion protein (*e.g.*, aflibercept) (*e.g.*, ± 14 mg/ml), 20 mM histidine-based buffer (*e.g.*, ± 2 mM), 5% (w/v) sucrose (*e.g.*, ± 0.5%), 0.03% (w/v) polysorbate 20 (*e.g.*, 0.02-0.04%), and 50 mM L-arginine monohydrochloride (*e.g.*, ± 5 mM), with a pH of 5.8 (*e.g.*, 5.6-6.0 or 5.5-6.1);

[00199] or any formulation which is set forth herein.

[00200] In an embodiment of the invention, the concentration of any formulation constituent (*e.g.*, all constituents) listed above (*e.g.*, any one of formulations A-KKKK) or which is discussed herein is ± about 3%, 5% or about 10% of the concentration specifically mentioned.

Methods of Manufacture

[00201] Embodiments herein include methods of manufacturing a pharmaceutical formulation of the present invention including a VEGF receptor fusion protein (*e.g.*, any of formulations A-KKKK as set forth herein) comprising combining the components of the formulation into a single composition, and, optionally, introducing the formulation into a vessel or device *e.g.*, a vial, or delivery device, *e.g.*, a pre-filled syringe. The formulations, vials or devices that are the product of such methods are part of the present invention.

[00202] In an embodiment of the invention, the method of manufacturing a VEGF receptor fusion protein containing pharmaceutical formulation of the present invention (*e.g.*, any

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of formulations A-KKKK as set forth herein) comprises the steps of culturing a host cell (*e.g.*, Chinese hamster ovary cell) comprising one or more polynucleotides encoding a VEGF receptor fusion protein (*e.g.*, aflibercept) in a culture medium and under conditions whereby the protein is expressed; and, purifying the protein from the host cell and/or culture medium and combining a portion of the protein with excipients of a pharmaceutical formulation as set forth herein. Again, the formulations, vials or devices that are the product of such methods are part of the present invention.

[00203] In an embodiment of the invention, a determination is made as to the amount and type of VEGF receptor fusion protein needed in the formulation to make it a high concentration and for its end-use. The same determination is made regarding the amount and type of buffer, the amount and type of surfactant, the amount and type of thermal stabilizer, and the inclusion, or specific exclusion, of a viscosity reducing agent. These components are combined and mixed, making sure that the formulation pH is at the desired value, *e.g.*, between about 5.0 and about 6.8 (*e.g.*, 5.8), and/or that the viscosity is at a desired value, *e.g.*, about 6.0, 7.3, 11.5 or 12.0 cP at 20°C. In an embodiment of the invention, high concentration VEGF receptor fusion protein containing formulations can be sterilized and stored in a stable condition, *e.g.*, for up to 24 or 36 months at 2°C to 8°C (*e.g.*, 5°C).

[00204] See, *e.g.*, Hardman, *et al.* (2001) Goodman and Gilman's The Pharmacological Basis of Therapeutics, McGraw-Hill, New York, N.Y.; Gennaro (2000) Remington: The Science and Practice of Pharmacy, Lippincott, Williams, and Wilkins, New York, N.Y.; Avis, *et al.* (eds.) (1993) Pharmaceutical Dosage Forms: Parenteral Medications, Marcel Dekker, NY; Lieberman, *et al.* (eds.) (1990) Pharmaceutical Dosage Forms: Tablets, Marcel Dekker, NY; Lieberman, *et al.* (eds.) (1990) Pharmaceutical Dosage Forms: Disperse Systems, Marcel Dekker, NY; Weiner and Kotkoskie (2000) Excipient Toxicity and Safety, Marcel Dekker, Inc., New York, N.Y.

Angiogenic Eye Disorders and Cancer

[00205] The pharmaceutical formulations of the present invention comprising VEGF receptor fusion proteins (*e.g.*, any of pharmaceutical formulations A-KKKK) can be used in the treatment or prevention of any angiogenic eye disorder by administration of a therapeutically effective amount of VEGF receptor fusion protein in a formulation of the present invention to a subject in need thereof, *e.g.*, by intravitreal injection. Angiogenic eye disorders herein refer to

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any disease of the eye which is caused by or associated with the growth or proliferation of blood vessels and/or by blood vessel leakage. Non-limiting examples of angiogenic eye disorders that are treatable or preventable using the formulations and methods herein, include:

- age-related macular degeneration (wet),
- macular edema,
- macular edema following retinal vein occlusion,
- retinal vein occlusion (RVO),
- central retinal vein occlusion (CRVO),
- branch retinal vein occlusion (BRVO),
- diabetic macular edema (DME),
- choroidal neovascularization (CNV),
- iris neovascularization,
- neovascular glaucoma,
- post-surgical fibrosis in glaucoma,
- proliferative vitreoretinopathy (PVR),
- optic disc neovascularization,
- corneal neovascularization,
- retinal neovascularization,
- vitreal neovascularization,
- pannus,
- pterygium,
- vascular retinopathy,
- diabetic retinopathies (*e.g.*, non-proliferative diabetic retinopathy (*e.g.*, characterized by a Diabetic Retinopathy Severity Scale (DRSS) level of about 47 or 53) or proliferative diabetic retinopathy; *e.g.*, in an subject that does not suffer from DME) and
- Diabetic retinopathy in a patient who has diabetic macular edema (DME).

[00206] The pharmaceutical formulations of the present invention comprising VEGF receptor fusion proteins (*e.g.*, any of pharmaceutical formulations A-KKKK) can be used in the treatment or prevention of any cancer by administration of a therapeutically effective amount of

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VEGF receptor fusion protein in a formulation of the present invention to a subject in need thereof, *e.g.*, by intramuscular, intratumoral, subcutaneous or intravenous injection. Cancers include those whose growth, proliferation, survival and/or metastasis is dependent, to a degree, on angiogenesis. In an embodiment of the invention, the cancer is colorectal cancer, lung cancer, skin cancer, breast cancer, brain cancer, stomach cancer, renal cancer, prostate cancer, liver cancer or pancreatic cancer.

[00207] Thus, the present invention provides methods for treating or preventing an angiogenic eye disorder in a subject in need thereof comprising administering a therapeutically effective amount of VEGF receptor fusion protein (*e.g.*, aflibercept) (*e.g.*, about 4, 6, or 8.0, 8.1, 8.4 or 8.5 mg), *e.g.*, in a pharmaceutical formulation according to the present invention, intraocularly, *e.g.*, into the vitreous, of an eye of the subject. In an embodiment of the invention, both eyes are administered the VEGF receptor fusion protein. In an embodiment of the invention, therapeutically effective doses of the VEGF receptor fusion protein are administered about every 2 weeks, 3 weeks, 4 weeks, 5 weeks, 6 weeks, 7 weeks, 8 weeks, 9 weeks, 10 weeks, 11 weeks, 12 weeks, 13 weeks, 14 weeks, 15 weeks, 16 weeks, 17 weeks 18 weeks, 19 weeks, 20 weeks, 21, weeks, 22 weeks, 23 weeks or 24 weeks. In an embodiment of the invention, such methods of treatment or prevention are done in the absence of significant increases in blood pressure (systolic and/or diastolic) and/or the development of hypertension (*e.g.*, Grade 1, Grade 2 or Grade 3) and/or abnormally high intraocular pressure in the subject. In an embodiment of the invention, the method includes the step of, following said administration, monitoring the subject for significant increases in blood pressure (systolic and/or diastolic) and/or the development of hypertension (*e.g.*, Grade 1, Grade 2 or Grade 3) and/or abnormally high intraocular pressure.

Modes of Administration

[00208] The pharmaceutical formulations of the present invention which include a VEGF receptor fusion protein may be administered in accordance with known medically approved delivery systems. In embodiments herein, these delivery systems may include administering the formulations to the patient by ocular, intraocular, intrachoroidal, intravitreal or subconjunctival injection. Alternatively, pharmaceutical formulations of the present invention can also be administered to the patient by topical routes, *e.g.*, eye drops, eye gels, eye ointments, and the

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like. Other possible routes of delivery for the formulations herein include intradermal, intramuscular, intraperitoneal, intravenous, subcutaneous, intranasal, epidural and oral.

[00209] In an embodiment of the invention, intravitreal injection of a pharmaceutical formulation of the present invention includes the step of piercing the eye with a syringe and needle (*e.g.*, 30-gauge injection needle) containing the formulation and injecting the formulation (*e.g.*, less than or equal to about 100 microliters; about 40, 50, 55, 56, 57, 57.1, 58, 60, 70 or 75 microliters) into the vitreous of the eye (*e.g.*, with a sufficient volume as to deliver a therapeutically effective amount of VEGF receptor fusion protein, *e.g.*, of about 4, 5, 6, 7, 8.0, 8.1, 8.2, 8.3, 8.4, 8.5, 8.6, 8.7, 8.8 or 8.9, 9, 10, 12, 14, 16, 18 or 20 mg VEGF receptor fusion protein). Optionally, the method includes the steps of administering a local anesthetic (*e.g.*, proparacaine, lidocaine or tetracaine), an antibiotic (*e.g.*, a fluoroquinolone), antiseptic (*e.g.*, povidone-iodine) and/or a pupil dilating agent to the eye being injected. In an embodiment of the invention, a sterile field around the eye to be injected is established before the injection. In an embodiment of the invention, following intravitreal injection, the subject is monitored for elevations in intraocular pressure and/or blood pressure. In an embodiment of the invention, the other eye is also injected by the same procedure.

Amounts of VEGF Receptor Fusion Protein to be Administered

[00210] Each dose of high concentration VEGF receptor fusion protein to a subject over the course of a treatment may contain the same or substantially the same amount of fusion protein. Alternatively, the quantity of any one dose may be different or variable over a treatment course.

[00211] An effective or therapeutically effective amount of VEGF receptor fusion protein for treating or preventing cancer (*e.g.*, which is mediated, at least in part, by angiogenesis) or an angiogenic eye disorder refers to the amount of the VEGF receptor fusion protein sufficient to cause the regression, stabilization or elimination of the cancer or angiogenic eye disorder, *e.g.*, by regressing, stabilizing or eliminating one or more symptoms or indicia of the cancer or angiogenic eye disorder by any clinically measurable degree, *e.g.*, with regard to an angiogenic eye disorder, by causing a reduction in or maintenance of diabetic retinopathy severity score (DRSS), by improving or maintaining vision (*e.g.*, in best corrected visual acuity *e.g.*, as measured by an increase in ETDRS letters), increasing or maintaining visual field and/or

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reducing or maintaining central retinal thickness and, with respect to cancer, stopping or reversing the growth, survival and/or metastasis of cancer cells in the subject. In an embodiment of the invention, an effective or therapeutically effective amount of VEGF receptor fusion protein for treating or preventing an angiogenic eye disorder is about 0.5 mg to about 10 mg or 0.5 mg to about 20 mg per dose, including: about 0.5 mg or more; or about 2 mg or more, *e.g.*, about 2.1 mg; 2.2 mg; 2.3 mg; 2.4 mg; 2.5 mg; 2.6 mg; 2.7 mg; 2.8 mg; 2.9 mg; 3.0 mg; 3.1 mg; 3.2 mg; 3.3 mg; 3.4 mg; 3.5 mg; 3.6 mg; 3.7 mg; 3.8 mg; 3.9 mg; 4.0 mg; 4.1 mg; 4.2 mg; 4.3 mg; 4.4 mg; 4.5 mg; 4.6 mg; 4.7 mg; 4.8 mg; 4.9 mg; 5.0 mg; 5.1 mg; 5.2 mg; 5.3 mg; 5.4 mg; 5.5 mg; 5.6 mg; 5.7 mg; 5.8 mg; 5.9 mg; 6.0 mg; 6.1 mg; 6.2 mg; 6.3 mg; 6.4 mg; 6.5 mg; 6.6 mg; 6.7 mg; 6.8 mg; 6.9 mg; 7.0 mg; 7.1 mg; 7.2 mg; 7.3 mg; 7.4 mg; 7.5 mg; 7.6 mg; 7.7 mg; 7.8 mg; 7.9 mg; 8.0 mg; 8.1 mg; 8.2 mg; 8.3 mg; 8.4 mg; 8.5 mg; 8.6 mg; 8.7 mg; 8.8 mg; 8.9 mg; 9 mg; 9.1 mg; 9.2 mg; 9.3 mg; 9.4 mg; 9.5 mg; 9.6 mg; 9.7 mg; 9.8 mg; 9.9 mg, 10.0 mg, 10.1 mg; 10.2 mg; 10.3 mg; 10.4 mg; 10.5 mg; 10.6 mg; 10.7 mg; 10.8 mg; 10.9 mg; 11 mg; 11.1 mg; 11.2 mg; 11.3 mg; 11.4 mg; 11.5 mg; 11.6 mg; 11.7 mg; 11.8 mg; 11.9 mg; 12 mg; 12.1 mg; 12.2 mg; 12.3 mg; 12.4 mg; 12.5 mg; 12.6 mg; 12.7 mg; 12.8 mg; 12.9 mg; 13 mg; 13.1 mg; 13.2 mg; 13.3 mg; 13.4 mg; 13.5 mg; 13.6 mg; 13.7 mg; 13.8 mg; 13.9 mg; 14 mg; 14.1 mg; 14.2 mg; 14.3 mg; 14.4 mg; 14.5 mg; 14.6 mg; 14.7 mg; 14.8 mg; 14.9 mg; 15 mg; 15.1 mg; 15.2 mg; 15.3 mg; 15.4 mg; 15.5 mg; 15.6 mg; 15.7 mg; 15.8 mg; 15.9 mg; 16 mg; 16.1 mg; 16.2 mg; 16.3 mg; 16.4 mg; 16.5 mg; 16.6 mg; 16.7 mg; 16.8 mg; 16.9 mg; 17 mg; 17.1 mg; 17.2 mg; 17.3 mg; 17.4 mg; 17.5 mg; 17.6 mg; 17.7 mg; 17.8 mg; 17.9 mg; 18 mg; 18.1 mg; 18.2 mg; 18.3 mg; 18.4 mg; 18.5 mg; 18.6 mg; 18.7 mg; 18.8 mg; 18.9 mg; 19 mg; 19.1 mg; 19.2 mg; 19.3 mg; 19.4 mg; 19.5 mg; 19.6 mg; 19.7 mg; 19.8 mg; 19.9 mg; or 20 mg. In an embodiment of the invention, an effective or therapeutically effective amount of VEGF receptor fusion protein for treating or preventing cancer is about 4 mg/kg (*e.g.*, intravenously). This dose may be administered, for example, every 2 weeks.

[00212] In an embodiment of the invention, a VEGF receptor fusion protein is administered in a volume sufficient to deliver the desired dose of fusion protein, *e.g.*, as discussed above. In an embodiment of the invention, the volume delivered (*e.g.*, for treating or preventing an angiogenic eye disorder, *e.g.*, by intravitreal injection) is less than or equal to about 100 microliters (*e.g.*, about any of the following volumes: 25 microliters; 26 microliters; 27 microliters; 28 microliters; 29 microliters; 30 microliters; 31 microliters; 32 microliters; 33

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microliters; 34 microliters; 35 microliters; 36 microliters; 37 microliters; 38 microliters; 39 microliters; 40 microliters; 41 microliters; 42 microliters; 43 microliters; 44 microliters; 45 microliters; 46 microliters; 47 microliters; 48 microliters; 49 microliters; 50 microliters; 51 microliters; 52 microliters; 53 microliters; 54 microliters; 55 microliters; 56 microliters; 57 microliters; 58 microliters; 59 microliters; 60 microliters; 61 microliters; 62 microliters; 63 microliters; 64 microliters; 65 microliters; 66 microliters; 67 microliters; 68 microliters; 69 microliters; 70 microliters; 71 microliters; 72 microliters; 73 microliters; 74 microliters; 75 microliters; 76 microliters; 77 microliters; 78 microliters; 79 microliters; 80 microliters; 81 microliters; 82 microliters; 83 microliters; 84 microliters; 85 microliters; 86 microliters; 87 microliters; 88 microliters; 89 microliters; 90 microliters; 91 microliters; 92 microliters; 93 microliters; 94 microliters; 95 microliters; 96 microliters; 97 microliters; 98 microliters or 99 microliters).

[00213] In an embodiment of the invention, the formulation is administered (*e.g.*, for treating or preventing an angiogenic eye disorder, *e.g.*, by intravitreal injection) in a volume which is about 60 microliters or less, about 70 microliters or less or about 75 microliters or less or about 100 microliters or less. For example, in an embodiment of the invention, about 2, 4, 6, 8.0, 8.1, 8.0-8.1, 8.2, 8.3, 8.4, 8.5, 8.6, 8.7, 8.8 or 8.9, 9.0 or 10 mg of VEGF receptor fusion protein is administered in about 50, 60, 70 or 75 microliters.

[00214] The scope of the present invention also encompasses methods for delivering 0.5 or 2 mg of VEGF receptor fusion protein (*e.g.*, for treating or preventing an angiogenic eye disorder, *e.g.*, by intravitreal injection) in pharmaceutical formulation of the present invention in a low volume such as less than 50 μl (*e.g.*, about 1, 5, 10, 17, 17.5, 18, 18.5, 20, 30, 40 or 45 μl).

[00215] The present invention also includes a composition including or consisting or consisting essentially of a "single dosage volume" of pharmaceutical formulation of the present invention, *i.e.*, a volume containing a single dose of VEGF receptor fusion protein (*e.g.*, aflibercept) in a pharmaceutical formulation of the present invention (*e.g.*, about 50 μl or 60 μl, 70 μl or 75 μl or whatever volume contains about 4, 6, 8 or 10 mg of VEGF receptor fusion protein). As discussed below, a container (*e.g.*, vial or injection device) comprising a single dosage volume, optionally including a small overfill volume of formulation, is also part of the present invention.

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Containers and Injection Devices

[00216] High concentration VEGF receptor fusion protein formulations in accordance with embodiments herein (*e.g.*, any of formulations A-KKKK) can be pre-packaged or pre-loaded in various useful containers and injection devices. Thus, the present invention includes containers and injection devices containing such formulations. In one embodiment herein, the container is a vial which may be sterile. In another embodiment herein, the container is a test tube which may be sterile. In an embodiment of the invention, an injection device (which may be sterile) is a syringe (*e.g.*, a pre-filled syringe or autoinjector). In an embodiment of the invention, the injection device is an intravitreal implant, *e.g.*, a refillable intravitreal implant.

[00217] A "pre-filled" syringe is a syringe which is filled with a formulation of the present invention prior to sale or use by the physician or patient.

[00218] "Sterile" herein refers to aseptic or free from substantially all, or all, living microorganisms and their spores.

[00219] Syringes as used herein include barrels made, for example, of glass or polymer, for example, cycloolefin as described in U.S. Patent Publication No. 2017/0232199, incorporated herein for all purposes, a plunger and a needle.

[00220] Containers and injection devices may be coated with silicone (*e.g.*, silicone oil or baked-silicone (*e.g.*, $\leq$40 μg or $\leq$100 μg)).

[00221] In an embodiment of the invention, a container or injection device is substantially metal-free or substantially tungsten-free or low-tungsten.

[00222] In an embodiment of the invention, the syringe contains one or more dose line graduations and/or is a dose metering system.

[00223] Containers in accordance with embodiments herein can hold the high concentration VEGF receptor fusion protein formulations. In some aspects, the container or injection device can include a label stating indications of use. In some instances, the container or injection device herein can include package inserts with instructions for use as described throughout this specification.

[00224] In other embodiments, a volume containing a single dose or multiple doses (*e.g.*, 2 or more than 2) of a high concentration VEGF receptor fusion protein (*e.g.*, wherein the dose is 2 mg, 4 mg, 6 mg, 8 mg or 10 mg of VEGF receptor fusion protein), as described above, can be pre-packaged into a container or injection device, *e.g.*, a sterile syringe, for example, for storage

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until use. In one example, the volume in the container includes a single dose of VEGF receptor fusion protein optionally further including a small amount of overfill volume. Sterile, pre-loaded syringes can be maintained under storage conditions (*e.g.*, 2°C-8°C), for example, for up to 12 months, 24 months or 36 months. Overfill is an excess volume that is meant to be sufficient to permit withdrawal and/or administration of the proper volume. In an embodiment of the invention, the container has a single dosage volume or multiple dosage volumes and about 5%-10% overfill volume.

[00225] Syringe sizes can be, for example, 0.3 cc, 0.5 cc or 1 cc, for example. Sterile syringes typically include a needle useful for ocular injection, typically about ½ inch, or 12.5 mm to 16 mm in length, and can be 29 gauge, 30 gauge, 31 gauge, 32 gauge or 33 gauge based on the patient and health care specialist preference. Other needle lengths and gauges can be used, as long as the needle is effective at accomplishing intravitreal injection.

[00226] While the invention has been particularly shown and described with reference to a number of embodiments, it would be understood by those skilled in the art that changes in the form and details may be made to the various embodiments disclosed herein without departing from the spirit and scope of the invention and that the various embodiments disclosed herein are not intended to act as limitations on the scope of the claims.

Additional formulations

[00227] The present invention includes the following formulations comprising greater than 40 mg/ml VEGF receptor fusion protein (*e.g.*, aflibercept or conbercept) and:

[00228] (a) a buffer including a histidine salt (*e.g.*, histidine-HCl or histidine-acetate, for example, 10 mM to 50 mM) and having pH ranging from 5.7 to 6.2; a sugar (*e.g.*, more than 6%, but not more than 10%) such as sucrose, trehalose, mannitol or glucose; a surfactant selected from the group consisting of polysorbate 20 and polysorbate 80 (*e.g.*, 0% to 0.1%);

[00229] (b) a histidine containing buffer such as L-histidine/histidine hydrochloride (*e.g.*, 10 mM); a non-ionic surfactant such as polysorbate 20 (*e.g.*, 0.03%), an inorganic salt such as NaCl (*e.g.*, 40 mM), and a carbohydrate such as sucrose (*e.g.*, 5%), *e.g.* pH 6.0-6.5 (*e.g.*, 6.2 or 6.5);

[00230] (c) citric acid (*e.g.*, 5 mM, 10 mM, 15 mM, 20 mM, 25 mM or 30 mM), sucrose (*e.g.*, 1%, 2%, 3%, 4%, 5%, 6%, 7%, 8%, 9% or 10%), arginine (*e.g.*, 5 mM, 10 mM, 15 mM, 20

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mM, 25 mM, 30 mM, 35 mM, 40 mM, 45 mM or 50 mM or 100 mM), and polysorbate 20 (*e.g.*, 0.01%, 0.02%, 0.03%, 0.04%, 0.05%, 0.06%, 0.07%, 0.08%, 0.09% or 0.10%);

[00231] (d) a buffer such as phosphate, histidine, acetate, succinate, citrate, glutamate, and/or lactate (*e.g.*, at 5-20 or 5-50 mM); a non-ionic surfactant such as a polysorbate (*e.g.*, PS20 or PS80), a polyethylene glycol dodecyl ether, a poloxamer, 4-(l,l,3,3-Tetramethylbutyl)phenyl-polyethylene glycol, an alkylsaccharide or an alkylglycoside, a tonicifying agent such as a polyol or an amino acid, for example, sucrose, trehalose, sorbitol, mannitol, glycerol, proline, arginine, methionine, glycine, or lysine, wherein the formulation has a final osmolality of about 300 mOsm/kg, and wherein the concentration of chloride anion is less than about 10 mM; pH 5.0-6.5; or

[00232] (e) 10 mM sodium phosphate, 40 mM sodium chloride, 0.03% polysorbate 20, and 5% sucrose, pH 6.2.

EXAMPLES

[00233] The following examples are provided for illustrative purposes only and are not intended to limit the scope of the invention. Efforts have been made to ensure accuracy with respect to numbers used, but some experimental errors and deviations should be accounted for. Any formulations set forth in these examples are part of the present invention.

[00234] In these examples, when an experiment is conducted at 2-8°C, the temperature is targeted to 5°C with a tolerance of ±3°C variation.

Example 1: 80 mg/ml VEGF Receptor Fusion Protein Formulations Maintain Potency, Physical Stability and Charge Over A 36 Month Period.

[00235] A series of four different formulations having 80 mg/ml VEGF receptor fusion protein (aflibercept) were tested for long term potency, physical stability and development of charge variants. The ingredient listing of each of the four formulations is shown in Table 1-1. Each formulation was evaluated for VEGF receptor fusion protein HMW species formation over the course of storage at 2°C to 8°C for 36 months, as well as for the percent main species by SE-UPLC. Each VEGF receptor fusion protein containing formulation was also evaluated using Imaged Capillary Isoelectric Focusing over the same course of time and temperature. Finally,

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each formulation's potency was tested by bioassay over the same course of time and temperature.

Table 1-1. VEGF Receptor Fusion Protein Containing Formulations

Formulation	VEGFT (mg/mL)	Sodium phosphate (mM)	Histidine (mM)	Sucrose (w/v)	Polysorbate 20 (w/v)	Sodium Chloride (mM)	pH
F1 (B)	80	10	NA	5	0.03	40	6.2
F2 (H)	80	10	NA	8	0.03	0	6.2
F3 (D)	80	NA	10	5	0.03	40	6.2
F4 (G)	80	NA	10	8	0.03	0	6.2

Table 1-2. %HMW Species

	Formulation B	Formulation H	Formulation D	Formulation G
	Formulation 1	Formulation 2	Formulation 3	Formulation 4
Months at 2-8C				
0.0	1.7	1.6	1.6	1.3
1	2.1	2.1	1.6	1.7
2.0	2.3	2.2	1.8	1.8
3.0	2.4	2.5	2.0	2.1
6.0	2.9	2.8	2.0	2.3
9.0	3.1	3.0	2.2	2.4
12.0	2.8	3.0		2.4
18.0	3.2	3.2	2.6	2.5
24.0	3.6	3.6	3.1	2.8
36.0	4.2	4.2	3.2	3.2

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Table 1-3. %Main Peak

	Formulation B	Formulation H	Formulation D	Formulation G
	Formulation 1	Formulation 2	Formulation 3	Formulation 4
Months at 2-8C				
0.0	98.4	98.4	98.4	98.8
1	97.9	98.0	98.4	98.3
2.0	97.7	97.8	98.2	98.2
3.0	97.7	97.5	98.0	98.0
6.0	97.1	97.2	97.9	97.7
9.0	96.9	97.0	97.8	97.6
12.0	97.2	97.0		97.4
18.0	96.8	96.8	97.4	97.5
24.0	96.5	96.4	96.8	97.2
36.0	95.7	95.7	96.8	96.8

Table 1-4. %Acidic Species

	Formulation B	Formulation H	Formulation D	Formulation G
	Formulation 1	Formulation 2	Formulation 3	Formulation 4
Months at 2-8C				
0.0	15.8	15.1	16.0	15.2
12	15.6	15.9	NP	16.0
24.0	16.0	17.1	16.2	16.9
36.0	16.9	17.4	17.2	17.6

Table 1-5. %Main Species

	Formulation B	Formulation H	Formulation D	Formulation G
	Formulation 1	Formulation 2	Formulation 3	Formulation 4
Months at 2-8C				
0.0	78.9	79.1	79.2	79.9
12	79.3	79.3	NP	79.7
24.0	79.3	78.5	79.5	79.3
36.0	78.6	78.1	78.7	78.6

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[00236] Data is shown in Figures 1A, 1B, 1C and 1D. Figure 1A shows the percent of VEGF receptor fusion protein HMW species formed for each of the four formulations. VEGF TRAP shows a slightly slower rate of HMW species formation when the formulation is histidine-based, as compared to sodium phosphate. As shown in Figure 1A, the %HMW species after storage at 2^0 to 8^0C for 36 months increased by 2.6% in sodium phosphate formulations (Formulations 1 and 2), as compared to the 1.6 to 1.9% increase in histidine buffers (Formulations 3 and 4). The data was confirmed, as shown in Figure 1B, where SE-UPLC was used to identify the percent of the VEGF receptor fusion protein main species present over the same time frame and temperature range. As a comparison point, assays were run on the current EYLEA® formulation (40 mg/ml) having 10 mM sodium phosphate, which showed a 1.2% increase in the %HMW species after storage at 2^0 to 8^0C for 36 months (not shown). In addition, each of the four 80 mg/ml VEGF TRAP formulations was tested for potency and compared to EYLEA® activity (not shown). Potency was maintained by bioassay for all four formulations as well as EYLEA®. These data show that formulations herein are able to maintain VEGF receptor fusion protein stability comparable to EYLEA®.

[00237] Referring to Figures 1C and 1D, the percent of VEGF TRAP charge variants formed after storage at 2° to 8^oC for 36 months was also tested. Figure 1C shows that the VEGF TRAP in Formulations 1 - 4 showed no meaningful change in percent acidic species over the course of 36 months, and Figure 1D shows the same finding for percent main species over the course of 36 months. The finding that the VEGF TRAP maintained charge variant species during storage shows that the quality of the VEGF TRAP was maintained, and processes like deamination, N-terminal pyroglutamate formation, isomerization, aggregation, *etc.* did not occur over the course of the storage parameters.

[00238] The data in Example 1 shows that formulations having double the VEGF TRAP concentration found in EYLEA®, can maintain physical stability, quality and potency over the course of 36 months at 2° to 8^oC. Further, although all four formulations showed similar potency over the period, histidine containing formulations resulted in a slightly smaller increase in HMW species formation (sign of protein degradation), showing that under some circumstances, histidine may be a buffer of choice. However, the findings for both histidine and phosphate based buffers showed excellent stability over the course of the study.

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Example 2: 150 mg/ml VEGF TRAP Stability in Sodium Phosphate Buffer/Sucrose Formulations.

[00239] Two sodium phosphate formulations were tested for physical stability of 150 mg/ml VEGF Trap (aflibercept) at 37°C for 28 days. The ingredient listing of each of the two formulations is shown in Table 2-1. Each formulation was evaluated for HMW species formation over the course of storage at 37°C for the 28 days as well as for the percent main species by SE-UPLC.

Table 2-1. VEGF Receptor Fusion Protein (aflibercept) Containing Formulations for Example 2

Formulation	VEGFT (mg/mL)	Sodium phosphate (mM)	Sucrose (w/v)	Polysorbate 20 (w/v)	Arginine-HCl (mM)	pH
F1 (T)	150	10	8%	0.03	N/A	6.2
F2 (JJJJ)	150	10	8%	0.03	50	6.2

Table 2-2. %HMW Species

	10 mM Sodium Phosphate, 8% Sucrose, 0.03% Polysorbate 20, pH 6.2	10 mM Sodium Phosphate, 8% Sucrose, 0.03% Polysorbate 20, 50 mM L-Arginine Monohydrochloride, pH 6.2
	Phosphate	Phosphate-Arginine
Days at 37C		
0.0	2.4	1.9
7	6.4	6.1
14.0	8.4	8.3
21.0	10.4	10.5
28.0	12.2	12.5

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Table 2-3. %Main Peak

	10 mM Sodium Phosphate, 8% Sucrose, 0.03% Polysorbate 20, pH 6.2	10 mM Sodium Phosphate, 8% Sucrose, 0.03% Polysorbate 20, 50 mM L-Arginine Monohydrochloride, pH 6.2
	Phosphate	Phosphate-Arginine
Days at 37C		
0.0	97.6	98.1
7	93.6	93.9
14.0	91.0	91.1
21.0	88.9	89.0
28.0	87.1	86.9

[00240] Figure 2A shows that there was no meaningful difference of %HMW species formed between the two formulations during storage at 37°C for 28 days, which as confirmed by the percent of main species by SE-UPLC (Figure 2B). There was no change in the appearance, turbidity or pH of the two formulations over the course of the 28 days (not shown).

[00241] The results were then compared to formulations that included 40 mg/ml EYLEA®, and Formulation 1 from Example 1 (80 mg/ml VEGF TRAP in sodium phosphate buffer). As expected, the 150 mg/ml VEGF TRAP formulations showed a higher percent of HMW species formation as compared to the EYLEA® formulation, and a somewhat higher percent of HMW species formation as compared to Formulation 1 of Example 1.

[00242] Further testing was performed on high concentration VEGF TRAP containing formulations, and histidine containing formulations showed better protection of these molecules than did formulations based in sodium phosphate. Further, inclusion of sodium chloride into each of the tested formulations actually caused destabilization of the VEGF TRAP at 37°C. The data in Example 2 shows that even at high concentrations of 150 mg/ml VEGF receptor fusion protein, and fairly extreme temperature storage, the formulations herein provide excellent protection for physical stability.

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Example 3: Pharmaceutically Acceptable Formulation Viscosity Can be Attained for 150 mg/ml VEGF TRAP.

[00243] A number of VEGF Trap (aflibercept) containing formulations were tested for their viscosity behavior. Formulations having from between 10 mg/ml to 160 mg/ml VEGF Trap were tested in the presence and absence of various viscosity reducing agents.

[00244] Figure 3A shows formulations having 155 mg/ml VEGF Trap in 10 mM sodium phosphate buffer, 5% sucrose and a pH of 6.2 in combination with no inorganic salt, arginine, lysine, sodium chloride and magnesium chloride showed little difference in viscosity. In each case viscosity was measured in cP at 20°C. A range of viscosity between about 17 cP (no inorganic salt) and 15 cP (100 mM magnesium chloride) was observed, with little variation between which viscosity reducing agent was used, or with the presence of a viscosity reducing agent at all. Figure 3B shows a similar series of formulations, except that the base buffer is 10 mM histidine and pH 5.8. Here, the lack of any inorganic salt provided a formulation with a viscosity of 11.5 cP , and 50 mM lysine a viscosity of 14 cP. The histidine containing buffer provided excellent viscosity, one in line with other low-concentration biologic injectables.

[00245] Figure 3C shows viscosity of VEGF Trap between the concentrations of 10 mg/ml and 160 mg/ml, with 10 mM sodium phosphate, 5% sucrose at a pH of 6.2 in the absence of arginine, and in 50 mM of arginine hydrochloride. Inclusion of the viscosity reducing agent resulted in similar viscosities for all VEGF Trap concentrations tested. As shown in Figures 3A and 3B, the viscosity reducing agent had little positive effect on the formulation viscosity, even at higher protein concentrations. This is a surprising result, as arginine and other viscosity reducing agents have previously been shown to have beneficial properties on high concentration protein viscosity.

Table 3-1. Viscosity-Phosphate formulations (cP at 20°C)

Buffer Composition	10 mM Sodium Phosphate, 5% Sucrose, pH 6.2
No Viscosity Reducer	17.3
100 mM Arginine	16.2
200 mM Arginine	15.8
50 mM Lysine	16.2
100 mM Sodium Chloride	16.5
50 mM Magnesium Chloride	16.3
100 mM Magnesium Chloride	15.3

Table 3-2. Viscosity-Histidine formulations (cP at 20°C)

Buffer Composition	10 mM Histidine, pH 5.8
No Viscosity Reducer	11.5
100 mM Arginine	12.0
200 mM Arginine	12.7
50 mM Lysine	14.0
200 mM Lysine	14.1
50 mM Sodium Chloride	13.1
100 mM Sodium Chloride	12.1
50 mM Magnesium Chloride	12.6
100 mM Magnesium Chloride	11.4

Example 4: Arginine Hydrochloride Improves Stability of 150 mg/ml VEGF TRAP In Sodium Phosphate Buffer/Sucrose Formulations.

[00246] Two sodium phosphate formulations were tested for physical stability of 150 mg/ml VEGF Trap (aflibercept) at 2-8°C for 12 months. The ingredient listing of each of the two formulations is shown in Table 4-1. Formulation 2 further includes 50 mM arginine hydrochloride. Each formulation was evaluated for HMW species formation over the course of storage at 37°C for the 12 months as well as for the percent main species by SE-UPLC.

Table 4-1. VEGF Receptor Fusion Protein (aflibercept) Containing Formulations for Example 3

Formulation	VEGFT (mg/mL)	Sodium phosphate (mM)	Sucrose (w/v)	Polysorbate 20 (w/v)	pH	Arginine Hydrochloride (mM)
F1 (T)	150	10	8%	0.03	6.2	0
F2 (JJJJ)	150	10	8%	0.03	6.2	50

[00247] Figure 4A shows that inclusion of 50 mM arginine hydrochloride to the formulation improved the VEGF TRAP physical stability. This stabilizing attribute on the VEGF TRAP was confirmed in Figure 4B, where the percent main species remains higher for the VEGF TRAP in the presence of 50 mM arginine hydrochloride. This data shows that there are situations under which addition of arginine hydrochloride provides a stabilizing effect to the

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stored VEGF TRAP. Tabulated size-exclusion chromatography data are set forth in Table 4-2 and 4-3.

Table 4-2. %HMW Species

	10 mM Sodium Phosphate, 8% Sucrose, 0.03% Polysorbate 20, pH 6.2	10 mM Sodium Phosphate, 8% Sucrose, 0.03% Polysorbate 20, 50 mM L-Arginine Monohydrochloride, pH 6.2
Months at 2-8C		
0.0	2.4	1.9
1	3.3	2.8
2.0	3.8	3.2
3.0	4.1	3.5
6.0	4.9	4.1
9.0	5.5	4.7
12.0	5.9	5.0

Table 4-3. %Main Peak

	10 mM Sodium Phosphate, 8% Sucrose, 0.03% Polysorbate 20, pH 6.2	10 mM Sodium Phosphate, 8% Sucrose, 0.03% Polysorbate 20, 50 mM L-Arginine Monohydrochloride, pH 6.2
Months at 2-8C		
0.0	97.6	98.1
1	96.8	97.2
2.0	96.2	96.8
3.0	95.9	96.5
6.0	95.1	95.8
9.0	94.5	95.3
12.0	94.1	94.5

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Example 5: Viscosity of 10 mg/ml to 170 mg/ml VEGF TRAP in Histidine and Phosphate Buffers

[00248] Figure 5 showed that 10 mM phosphate buffer and 10 mM histidine buffer both had highly useful viscosities for a range of VEGF Trap (aflibercept) concentrations. At higher VEGF Trap concentrations, the histidine buffer showed an improvement in viscosity (relative to phosphate). Viscosity was measured at 20°C.

Example 6: Taurine and Propane Sulfonic Acid Provide Improved Stability to High Concentration VEGF Trap (aflibercept) Formulations.

[00249] An experiment was conducted to determine the effect on protein stability with a number of formulation combinations. Figure 6 shows a dynamic light scattering plot for formulations having anywhere from 2 mg/ml protein to 10 mg/ml protein (aflibercept). Formulations that included 70 mM taurine or 70 mM PSA showed reduced self-interaction at higher concentrations. These data indicate that taurine and PSA can be useful inclusions in high concentration protein formulations, like the ones at issue in this case.

Example 7: Long Term Study of Stability of Various Histidine Containing Formulations.

[00250] A total of 9 different aflibercept formulations were tested with varying buffer concentration, thermal stabilizers and hydrophobic salts. The 9 formulations, F1-F9, are summarized below in Table 7-1.

Table 7-1. Formulations F1-F9.

Formulation	VEGFT (mg/mL)	Buffer Type	Buffer Concentration (mM)	Sucrose (%w/v)	Proline (%w/v)	Polysorbate 20 (w/v)	Stabilizer (mM)	Stabilizer Concentration (mM)	pH
F1 (WW)	140	His	10	5	0	0.03	Taurine	50	5.8
F2 (XX)	140	His	20	0	4	0.03	Arginine HCl	50	5.8
F3 (YY)	140	His	20	2.5	2	0.03	Taurine	50	5.8
F4 (ZZ)	140	His	10	2.5	2	0.03	Arginine HCl	50	5.8
F5 (AAA)	140	His	20	5	0	0.03	PSA	50	5.8
F6 (BBB)	140	His	20	2.5	2	0.03	PSA	50	5.8
F7 (CCC)	140	His	20	5	0	0.03	Arginine HCl	50	5.8
F8 (DDD)	140	His	10	0	4	0.03	PSA	50	5.8
F9 (EEE)	140	His	20	5	0	0.03	NA	NA	5.8

VEGFT=VEGF Trap (aflibercept)

[00251] Fourteen (14) mL of each formulation was compounded in 15 mL Falcon tubes. The formulation was then sterile filtered using a 0.22 μM syringe filter and filled in sterile 2 mL Type 1 glass vials. Eight (8) vials were filled for each formulation with 0.4 mL volume in a laminar flow hood.

[00252] SE-UPLC (molecular weight species) was performed on all samples to determine the chemical stability of each formulation.

[00253] The percentage of HMW species over time for each of formulations F1-F9 are shown in Figure 7 (see also Table 7-2). Formulations F4 and F7 exhibited the lowest percentage of HMW species after 4 months at 5°C. The results showed that addition of excipients like arginine and proline significantly reduced the rate of %HMW species formation in VEGF Trap formulations.

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Table 7-2. SE-UPLC Analysis (2-8°C)

	F1 (WW)		F2 (XX)		F3 (YY)	
Months at 2-8C	%HMW	%Main Peak	%HMW	%Main Peak	%HMW	%Main Peak
0.0	1.53	98.46	1.48	98.52	1.39	98.61
0.5	1.87	98.13	1.87	98.13	1.92	98.08
1.0	2.19	97.81	2.16	97.84	2.19	96.15
2.0	2.64	97.36	2.63	97.37	2.71	97.29
3.0	2.83	97.17	2.76	97.24	2.87	97.13
4.0	3.07	96.93	3.00	97.00	3.11	96.89
5.0	3.24	96.76	3.11	96.89	3.28	96.72
6.0	3.35	96.65	3.24	96.76	3.38	96.62

F4 (ZZ)		F5 (AAA)		F6 (BBB)	
%HMW	%Main Peak	%HMW	%Main Peak	%HMW	%Main Peak
1.31	98.69	1.55	98.45	1.45	98.55
1.69	98.31	1.79	98.21	1.96	98.04
1.95	98.05	2.31	97.69	2.26	97.74
2.37	97.63	2.80	97.20	2.72	97.28
2.61	97.39	2.99	97.01	2.91	97.09
2.84	97.16	3.26	96.74	3.17	96.83
3.03	96.97	3.44	96.56	3.35	96.65
3.13	96.87	3.52	96.48	3.41	96.59

F7 (CCC)		F8 (DDD)		F9 (EEE)	
%HMW	%Main Peak	%HMW	%Main Peak	%HMW	%Main Peak
1.20	98.80	1.56	98.44	1.53	98.47
1.74	98.26	1.87	98.13	2.05	97.95
2.08	97.92	2.16	97.84	2.39	97.61
2.52	97.48	2.59	97.41	2.89	97.11
2.76	97.24	2.80	97.20	3.07	96.93
2.97	97.03	3.06	96.94	3.34	96.66
3.14	96.86	3.21	96.79	3.51	96.49
3.26	96.74	3.28	96.72	3.69	96.31

Example 8: Stability Study of 140 mg/mL VEGF Trap with Varying Arginine Concentrations.

[00254] The impact of varying the concentration of arginine-HCl on the stability of four 140 mg/mL VEGF Trap (aflibercept) eye drug product formulations was studied. The evaluation of stability was performed at the storage condition of 2-8°C. The drug product (DP) was also incubated under stress (37°C) conditions. The four formulations being evaluated in this stability study (F1-F4) are described in Table 8-1 set forth below.

Table 8-1. Formulations F1-F4

Formulation Number	Composition					
	VEGFT (mg/mL)	Histidine (mM)	Sucrose (w/v)	Polysorbate 20	L-Arginine-	pH
F1	140	20	5	0.03	0	5.8
F2					10	
F3					50	
F4					100	

[00255] Approximately 145 mL of 187 mg/mL VEGF Trap histidine formulations were thawed. Thirty six (36) mL of each formulation, with the exception of F3, was compounded; 39 mL of bulk F3 was compounded. Each formulation was filter sterilized within a LFH (laminar flow hood) using a 0.22 μm Durapore PVDF sterilizing filter prior to filling. Clean depyrogenated 2 mL type I Schott glass vials stoppered with 13 mm serum stoppers (S2-F451 4432/50B2-40) were used to perform stability studies.

[00256] SE-UPLC analysis of the formulations was performed as set forth above. The %HMW measurements, using SE-UPLC, in each formulation over time are set forth in Figure 8 (A-B). See also Tables 8-2 and 8-3.

[00257] When stored at 5°C, these formulations exhibited a reduction in the rate of formation of %HMW species that was proportional to the concentration of arginine-HCl. Under stress, however, this effect was reversed. The formulations, at 37°C, exhibited an apparent increase in %HMW species proportional to the concentration of arginine-HCl. This property made the discovery of arginine's beneficial effects on aflibercept in the presence of histidine buffer highly unlikely. Typically, for formulation development in the biotechnology industry, the effect of various excipients on a drug is initially screened under stress (*e.g.*, at elevated

temperature such as 37ºC) for a short period of time. The purpose of this approach it to rapidly eliminate excipients which will not likely perform well in the absence of stress (*e.g.*, at lower temperature such as 5ºC) over a longer period of time. Here, arginine was identified as a helpful excipient in spite of its effect on stability at 37ºC. Since formulated drug product is typically stored for months at 4-5ºC after manufacture, aflibercept in arginine and histidine buffer would be a highly valuable formulation for long term, stable drug product storage.

Table 8-2. SE-UPLC Analysis (2-8ºC)

	F1 (EEE)		F2 (SSS)	
Months at 2-8C	%Main Peak	%HMW	%Main Peak	%HMW
0.0	97.79	2.21	97.78	2.22
0.5	97.56	2.43	97.59	2.41
1.0	97.30	2.70	97.34	2.66
1.5	97.21	2.79	97.26	2.74
2.0	97.05	2.95	97.08	2.92
2.5	96.96	3.04	97.02	2.98
3.0	96.82	3.18	96.88	3.12
6.0	96.35	3.65	96.40	3.60

F3 (CCC)		F4 (TTT)	
%Main Peak	%HMW	%Main Peak	%HMW
97.85	2.15	97.81	2.19
97.67	2.33	97.73	2.27
97.47	2.53	97.59	2.41
97.37	2.63	97.50	2.50
97.22	2.78	97.36	2.64
97.14	2.86	97.31	2.69
97.04	2.96	97.16	2.84
96.60	3.40	96.77	3.23

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Table 8-3. SE-UPLC Analysis (37°C)

	F1 (EEE)		F2 (SSS)	
Days at 37C	%Main Peak	%HMW	%Main Peak	%HMW
0.0	97.79	2.21	97.78	2.22
7	93.66	6.34	93.32	6.68
14.0	89.48	10.35	88.79	10.98
21.0	86.64	13.08	85.69	13.82
28.0	83.90	15.85	82.66	16.90

F3 (CCC)		F4 (TTT)	
%Main Peak	%HMW	%Main Peak	%HMW
97.85	2.15	97.81	2.19
92.38	7.61	91.32	8.68
86.90	12.91	84.61	15.21
83.11	16.65	80.11	19.47
79.44	20.29	75.80	23.91

Example 9: VEGF Trap Stability in the presence of counterions from the Hofmeister Series and other Excipients.

[00258] The effect of various counterions and other excipients on stability of several formulations was determined.

A. Counterion Screening

[00259] Counter ions (*e.g.*, sulfate, thiocyanate and citrate) were tested in the form of sodium salts with high concentration VEGF Trap (aflibercept) formulations (140 mg/ml). Additionally, other amino add excipients (*e.g.*, glycine and lysine) were also tested.

[00260] Approximately 42 ml of 187 mg/ml VEGF Trap eye drug substance were thawed. 50 ml of intermediate formulated drug substance (155.56 mg/ml), having a 110% concentration of the 140 mg/ml formulated drug substance and target excipient concentration (excluding the counterions, glycine and lysine), were prepared.

[00261] The intermediate formulated drug substance was further diluted with the 0.5 M stock excipient solutions (counterions, glycine or lysine) to produce the 140 mg/ml formulated drug substance formulations listed in Table 9-1 below. Each final formulation was filter sterilized with a 0.22 μm PVDF syringe filter within a laminar flow hood prior to filling into clean

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depyrogenated 2mL type I Schott glass vials stoppered with 13 mm serum stoppers S2-F451 4432/50 82-40 (ELN item# 19700004 Wash# 0 000078949). Sixty (60) vials were filled with 0.5 ml of each formulation. Six (6) vials were filled with 1.5 ml.

Table 9-1. Formulations for Counterion Screening

Excipient (mM)	Formulation	VEGF Trap conc.
Sodium sulfate 50mM	20mM Histidine/0.03%PS20/5% Sucrose/50mM Sodium Sulfate	140
Sodium thiocyanate 50mM	20mM Histidine/0.03%PS20/5% Sucrose/50mM Sodium thiocyanate	140
Sodium Citrate 50mM	20mM Histidine/0.03%PS20/5% Sucrose/50mM Sodium Citrate	140
Glycine 50mM	20mM Histidine/0.03%PS20/5% Sucrose/50mM Glycine	140
Sodium chloride 50mM	20mM Histidine/0.03%PS20/5% Sucrose/50mM sodium chloride	140
Lysine 50mM	20mM Histidine/0.03%PS20/5% Sucrose/50mM Lysine	140

B. Glutamate And Aspartate Screening

[00262] The stability of VEGF Trap (aflibercept) high concentration formulations (140 mg/ml) in the presence of organic counter ions in combination with arginine hydrochloride was tested. In addition, two new counter ions (glutamate and asparate) were tested for compatibility with high concentration VEGF Trap (in combination and without arginine hydrochloride). The formulations tested are summarized below in Table 9-2.

[00263] Approximately 50 ml of 187 mg/ml VEGF Trap drug substance were thawed. 60 ml of intermediate formulated drug substance (155.56 mg/ml) with a 110% of the 140 mg/ml formulated drug substance and target excipient concentration (excluding the counterions, citrate, glycine, glutamate and aspartate) was prepared. The intermediate formulated drug substance was further diluted with the 1M stock excipient solutions (arginine hydrochloride, sodium citrate, glycine, sodium glutamate and sodium aspartate) to produce the 140 mg/ml formulated drug substance formulations listed in the table below. Each final formulation was filter sterilized with a 0.22 μm PVDF syringe filter within a laminar flow hood prior to filling into clean

depyrogenated 2 ml type I Schott glass vials stoppered with 13 mm serum stoppers S2-F451 4432/50 B2-40 (ELN item# 19700004 Wash# 0000078949). Sixty (60) vials were filled with 0.5 ml of each formulation. Six (6) vials were filled with 1.5 ml.

Table 9-2. Formulations for Glutamate And Aspartate Screening

Excipient (mM)	Formulation	VEGF Trap conc.
Sodium Citrate 50mM + Arginine Hydrochloride 50mM	20mM Histidine/0.03%PS20/5% Sucrose/ 50mM Sodium Citrate/50mM Arginine hydrochloride	140
Glycine 50mM + Arginine hydrochloride 50mM	20mM Histidine/0.03%PS20/5% Sucrose/ 50mM Glycine/50mM Arginine hydrochloride	140
Sodium aspartate 50mM + Arginine hydrochloride 50mM	20mM Histidine/0.03%PS20/5% Sucrose/ 50mM Sodium Aspartate/50mM Arginine hydrochloride	140
Sodium glutamate 50mM + Arginine hydrochloride 50mM	20mM Histidine/0.03%PS20/5% Sucrose/ 50mM Sodium Glutamate/50mM Arginine hydrochloride	140
Sodium aspartate 50mM	20mM Histidine/0.03%PS20/5% Sucrose/ 50mM sodium aspartate	140
Sodium glutamate 50mM	20mM Histidine/0.03%PS20/5% Sucrose/ 50mM Sodium glutamate	140

[00264] Viscosity testing was performed using a RHEOSENSE m-VROC® viscometer. Approximately, 0.5 mL of undiluted sample was loaded onto a glass syringe. The sample was equilibrated to the desired temperature and injected into a chip or measuring cell. Viscosity was calculated by measuring the pressure drop from inlet to the outlet which is correlated to the shear-stress at the wall of the chip. Results are expressed as mPas-1 or cp. See Figure 9 and Table 9-3.

[00265] Osmolality testing was performed using a VAPRO vapor pressure osmometer. Approximately, 10 µL of undiluted sample was inoculated into a paper disc. The dew point temperature depression, a function of the solution vapor pressure, was measured through a sensitive thermocouple and reported as osmolality of the solution. Results are expressed as mmol/kg or mOsm. See Figure 10 and Table 9-3.

[00266] High molecular weight species in certain formulations over time, after storage at 37°C or 5°C, was also evaluated by SE-UPLC. See Figure 11 (A-B) and Tables 9-4 and 9-5.

[00267] Dynamic light scattering experiments were performed using a DynaPro® Plate Reader II. Approximately, 100 µL of undiluted sample was loaded onto a 96-well plate. Thirty five acquisitions were obtained for each well at 25°C. Analysis of autocorrelation function using regularization was performed on the DYNAMICS v7.1 software. Radius (nm) vs %intensity plots and % mass vs radius (nm) plots were generated to derive the average molecular radius and % polydispersity values (%Pd) for each sample. See Figure 12.

Table 9-3. Viscosity and Osmolality of Various Formulations

Parameter tested	50mM Sodium Sulfate (GGG)	50mM Sodium thiocyanate (HHH)	40mM Sodium citrate (III)	50mM Glycine (JJJ)	50mM Sodium Chloride (KKK)	50mM Lysine (LLL)
viscosity (cp)	11.9	12.4	14.8	12.2	11.6	11.8
Osmolality(mOsmol/Kg)	384	324	403	299	349	349

50mM Sodium Aspartate (MMM)	50mM Sodium Glutamate (NNN)	50mM Sodium citrate+50mM Arginine HCl (OOO)	50mM Glycine+ 50mM Arginine HCl (PPP)	50mM Sodium Aspartate+ 50mM Arginine HCl (QQQ)	50mM Sodium Glutamate + 50mM Arginine HCl (RRR)
13.0	13.1	14.8	12.5	13.1	13.3
343	346	506	369	426	430

Table 9-4. SE-UPLC Analysis; %HMW (37°C)

%HMW (Days at 37C)	50mM Sodium Sulfate (GGG)	50mM Sodium thiocyanate (HHH)	40mM Sodium citrate (III)	50mM Glycine (JJJ)	50mM Sodium Chloride (KKK)	50mM Lysine (LLL)
0	2.3	2.3	2.3	2.3	2.3	2.2
7	8.6	15.5	8.2	6.3	8.1	7.7
14	13.5	24.8	12.1	9.5	12.4	11.7
28	22.0	39.2	19.1	15.3	20.4	19.3

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Table 9-5. SE-UPLC Analysis; %HMW (5°C)

%HMW (Months at 5C)	50mM Sodium Sulfate (GGG)	50mM Sodium thiocyanate (HHH)	40mM Sodium citrate (III)	50mM Glycine (JJJ)	50mM Sodium Chloride (KKK)	50mM Lysine (LLL)
0	2.3	2.3	2.3	2.3	2.3	2.2
0.25	2.3	2.4	2.4	2.3	2.3	2.3
0.5	2.4	2.5	2.5	2.4	2.4	2.3
1	2.5	2.8	2.7	2.6	2.6	2.5
2	2.8	2.9	2.9	2.8	2.8	2.8
3	3.1	3.3	3.2	3.1	3.2	3.0

Example 10: Tolerability of IVT delivery of High Dose VEGF Trap (140mg/ml) in Normal Rabbits.

[00268] Anti-VEGF therapeutics, administered via intravitreal injection, are currently the standard of care for treatment of neovascular age-related macular degeneration, diabetic macular edema, and retinal vascular occlusive disease. However, the monthly or bi-monthly intravitreal injections represent a significant treatment burden on patients, caregivers, and physicians. There is a pressing need for more effective and durable therapies in clinical practice. This study is to investigate the tolerability of stably formulated high dose VEGF Trap (140 mg/ml, equivalently 14 folds of the clinical dose) in normal New Zealand white rabbit eyes.

[00269] Two formulations of high dose VEGF-Trap (aflibercept) in histidine buffer or in phosphate buffer were tested. Three rabbits per cohort received 7mg of VEGF Trap in 50 uL by single bilateral intravitreal injection of each formulation. Ocular inflammation signs were monitored by slit lamp, optical coherence tomography (OCT) and fundus angiograph at day 1, day 4, week 1 then weekly until 12 weeks post-intravitreal administration. Intraocular pressure was measured with Tonopen before and 10 minutes and 30 minutes post intravitreal injection, then at every follow up time point. Animals were euthanized at week 12.

[00270] The rabbit eyes were dosed with either:

(1) 140 mg/ml aflibercept, 20 mM Histidine, 5% Sucrose, 50 mM Arginine HCl, 0.03% PS20, pH 5.8;

or

(2) 140 mg/ml aflibercept, 10 mM Sodium phosphate, 5% Sucrose, 40 mM Sodium Chloride, 0.03% PS20, pH 6.2.

[00271] Two of six eyes from the histidine buffer group showed dark shadows in the vitreous until 8 weeks post IVT, which were confirmed by slit-lamp examination as local cataract due to posterior lens injury, procedure related. One of 6 eyes the from phosphate buffer group showed dark shadows in the vitreous until 8 weeks post IVT, which were confirmed by slit-lamp examination as local cataract due to posterior lens injury (procedure related).

[00272] The high dose VEGF Trap (140 mg/ml) formulations tested were well tolerated in normal New Zealand White rabbit eyes within 12 weeks post-single intravitreal administration. After a single intravitreal injection of 7 mg of VEGF Trap, no signs of abnormalities or inflammation were seen in the fundus. The vitreous was clear and the retinal vascular pattern appeared normal. No retinal detachment, hemorrhage or optic nerve head changes were seen. There was no intraocular pressure change compared to baseline. The baseline fluorescein angiography (FA) and OCT images of rabbit eyes are represented in Figure 13(A-D). The time course FA and OCT images of rabbit eyes in each treatment group over 8 weeks is represented in figures 14, 15, 16 and 17. Data from the left eye (OS) or right eye (OD) of rabbits 326 and 329 are shown.

Example 11: Evaluation of Stability of Formulations UUU-BBBB

[00273] This study examined the stability of 60 mg/ml and 120 mg/ml VEGF Trap (aflibercept) in 10 mM phosphate, 10% or 20% sucrose (Suc.), 0 or 50 mM NaCl, 0.03% polysorbate 20, pH 6.2 when incubated at 37ºC for up to 6 months. The formulations for this stability study are set forth below in Table 11-1.

Table 11-1. Formulations UUU-BBBB

Formulation Designation	[VEGF Trap] mg/mL	% Sucrose	mM NaCl
F1 (UUU)	30	10	-
F2 (VVV)	30	20	-
F3 (WWW)	60	10	-
F4 (XXX)	60	20	-
F5 (YYY)	120	10	-
F6 (ZZZ)	120	20	-

F7 (AAAA)	120	10	50
F8 (BBBB)	120	20	50

Base formulation: 10 mM phosphate, 0.03% polysorbate 20, pH 6.2

VEGF Trap=aflibercept

[00274] The formulation was filter sterilized with a PVDF 0.2 µm filter in a laminar flow hood prior to dispensing.

[00275] Vials containing each formulation were stored at 37ºC for 1 month.

Table 11-2. Reverse-phase High Performance Liquid Chromatography (RP-HPLC) Results

Formulation	Storage Condition	Actual Incubation (months)	% VEGFT Recovered	[VGFT] mg/ml
30 mg/mL 10% sucrose (UUU)	37ºC	0.0	100.0	29.99
		1.0	97.9	29.37
30 mg/mL 20% sucrose (VVV)	37ºC	0.0	100.0	29.97
		1.0	98.2	29.44
60 mg/mL 10% sucrose (WWW)	37ºC	0.0	100.0	58.90
		1.0	98.3	57.89
60 mg/mL 20% sucrose (XXX)	37ºC	0.0	100.0	58.80
		1.0	98.9	58.18
120 mg/mL 10% sucrose (YYY)	37ºC	0.0	100.0	120.80
		1.0	97.4	117.63
120 mg/mL 20% sucrose (ZZZ)	37ºC	0.0	100.0	117.85
		1.0	98.9	116.51
120 mg/mL 10% sucrose 50 mM NaCl (AAAA)	37ºC	0.0	100.0	120.14
		1.0	97.9	117.64

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120 mg/mL 20% sucrose 50 mM NaCl (BBBB)	37°C	0.0	100.0	120.55
		1.0	97.0	116.94

VGFT=VEGF Trap, aflibercept

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Table 11-3. Size-exclusion Ultra Performance Liquid Chromatography (SE-UPLC) Results

Formulation	Storage Condition	Actual Incubation (months)	Total % HMW	%Native	Total % LMW
30 mg/mL VGFT 10% sucrose (UUU)	37°C	0	0.8	99.0	0.1
		1.0	4.1	94.0	1.9
30 mg/mL VGFT 20% sucrose (VVV)	37°C	0	0.8	99.0	0.2
		1.0	2.4	95.6	2.0
60 mg/mL VGFT 10% sucrose (WWW)	37°C	0	1.0	98.8	0.2
		1.0	7.8	89.5	2.7
60 mg/mL VGFT 20% sucrose (XXX)	37°C	0	1.0	98.8	0.2
		1.0	4.4	92.8	2.7
120 mg/mL VGFT 10% sucrose (YYY)	37°C	0	1.3	98.5	0.2
		1.0	18.3	79.5	2.2
120 mg/mL VGFT 20% sucrose (ZZZ)	37°C	0	1.2	98.5	0.2
		1.0	10.7	87.1	2.2
120 mg/mL VGFT 10% sucrose 50 mM NaCl (AAAA)	37°C	0	1.3	98.5	0.2
		1.0	20.8	77.1	2.2
120 mg/mL VGFT 20% sucrose 50 mM NaCl (BBBB)	37°C	0	1.2	98.5	0.3
		1.0	13.0	84.8	2.2

VGFT=VEGF Trap, aflibercept

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[00276] All of the formulations were essentially particle-free by visual inspection and optical density measurement. There was no significant protein loss in recovery by RP-HPLC after 1 month at 37°C (Table 11-2) and this trend continued out to 6 months.

[00277] The main degradation pathway for VEGF Trap was aggregation under these conditions (Figure 18 (A-B); Table 11-3). The stability of VEGF Trap was dependent on the protein and sucrose concentrations. Formulations with lower VEGF Trap concentrations and higher sucrose were more stable. Maintaining the same protein:sucrose ratio did not result in the same degradation rate. For example, F1 and F4 have the same protein:sucrose ratio of 3:1 but F4 was less stable than F1 due to its higher protein concentration. Similar trends were observed out to 6 months.

Example 12: Repeat-Dose Intravitreal Toxicology Study in Monkeys with Different Aflibercept Formulations.

[00278] The safety of various formulations in cynomolgus monkeys is assessed in this example. A total of 7 intravitreal doses are administered to both eyes approximately Q4W to Groups 1-3; a total of 3 intravitreal doses are administered to both eyes approximately Q4W to groups 4-9. A terminal necropsy is performed approximately one week after last dose (N=3/sex/group) with recovery necropsy (2/sex/group) approximately 12-week after last dose

[00279] The following assessments are performed:

- Safety assessment based on clinical signs, body weights, vital signs, electrocardiographic data (pre-dose end of treatment and end of recovery), blood pressure measurements (via tail cuff), clinical and anatomic pathology
- Comprehensive ocular exams at regular intervals during the dosing and recovery intervals including slit lamp microscopy, indirect ophthalmoscopy and intraocular pressure measurements
- Fundus photography, fluorescein angiography and electroretinography at pre-treatment, during study week 9 (all groups), week 26 (Groups 1-3 only) and end of recovery period
- Blood and vitreous samples (at termination) for bioanalytical, ADA analysis and toxicokinetic evaluation

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Table 13. Study group summary*

Group	Test Material	IVT Dose Volume (µL/dose/eye)	mg aflibercept/eye	N/sex	N/sex for terminal necropsy	N/sex for Recovery
1	20 mM Histidine, **50 mM Arginine**, 5% Sucrose, 0.03% PS20	50	0 (control)	5	3	2
2	**80 mg/mL Aflibercept** in 20 mM Histidine, **50mM Arginine**, 5% Sucrose, 0.03% PS20	50	4	5	3	2
3	**~140 mg/mL Aflibercept** in 20 mM Histidine, **50mM Arginine**, 5% Sucrose, 0.03% PS20	50	~7	5	3	2
4	20 mM Histidine, 5% Sucrose, 0.03% PS20	50	0 (control)	5	3	2
5	**80 mg/mL Aflibercept** in 20 mM Histidine, 5% Sucrose, 0.03% PS20	50	4	5	3	2
6	**~140 mg/mL Aflibercept** in 20 mM Histidine, 5% Sucrose, 0.03% PS20	50	~7	5	3	2
7	20 mM Histidine, **50 mM Glycine**, 5% Sucrose, 0.03% PS20	50	0 (control)	5	3	2
8	**80 mg/mL Aflibercept** in 20 mM Histidine, **50 mM Glycine**, 5% Sucrose, 0.03% PS20	50	4	5	3	2
9	**~140 mg/mL Aflibercept** in 20 mM Histidine, **50 mM Glycine**, 5% Sucrose, 0.03% PS20	50	~7	5	3	2

*each of said formulations are part of the present invention

[00280] It is expected that the formulations tested in any one or more of Groups 1, 2, 3, 4, 5, 6, 7, 8 and/or 9 will be determined to have a safety profile comparable to EYLEA in cynomolgous monkeys as measured in the assessments discussed above.

Example 13: Stability Study with VEGF Trap Product.

[00282] A formulation including 114.3 mg/mL VEGF Trap (aflibercept) and 10 mM Histidine, pH 5.8, 5% Sucrose, 0.03% Polysorbate 20, 50 mM Arginine Monohydrochloride was prepared within a LFH (laminar flow hood) using a 0.22 µm Durapore PVDF sterilizing filter prior to filling. Clean depyrogenated 3 mL type I Schott glass vials were filled with 0.3 mL of Drug Product and stoppered with 13 mm serum stoppers (S2-F451 4432/50B2-40). Samples were analyzed at various timepoints after storage at 37°C or 5°C for purity by size-exclusion chromatography (SEC) to determine the presence (%) of high molecular weight species (HMW), low molecular weight species (LMW) and the main peak (main); as well as microflow imaging, HIAC liquid particle counting (by light obscuration) and microscopically to determine the presence of particles of various sizes.

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[00283] Stability and purity data after storage at 37ºC, 25ºC and 2-8ºC are shown in Figure 19 (A-E). See also Tables 13-1 – 13-4.

Table 13-1. Size-Exclusion Chromatography (SEC) Purity Analysis

37°C			
Months	**%Main**	**%HMW**	**%LMW**
0	98.23	1.77	0
0.229	92.88	7.07	0.05
0.459	88.59	11.18	0.23
0.688	84.67	15.03	0.3
0.918	81.84	17.59	0.57
5°C			
Months	**%Main**	**%HMW**	**%LMW**
0	98.23	1.77	0
1	97.73	2.27	0
2	97.4	2.59	0

Table 13-2. Microflow Imaging/Subvisible Particles

37°C					
Months	**≥1µm**	**≥2µm**	**≥5µm**	**≥10µm**	**≥25µm**
T=0	1125	234	42	9	0
28 days	1128	184	17	0	0

Table 13-3. Subvisible Particulate Matter as Measured by Light Obscuration (HIAC)/Subvisible Particles

37°C			
Months	**≥10µm**	**≥25µm**	**≥50µm**
T=0	15	0	0
28 days	23	1	1

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Table 13-4. Microscopic Analysis of Subvisible Particles

37°C			
Months	**≥10µm**	**≥25µm**	**≥50µm**
T=0	8	1	1
28 days	6	2	1

Example 14: Stability Study with Varying VEGF Trap Concentrations.

[00284] The impact of varying the concentration of VEGF Trap on the stability of four VEGF Trap (aflibercept) eye drug product formulations was studied. The concentrations ranged between 80 and 140 mg/mL. The evaluation of stability was performed at the storage condition of 2-8°C. The drug product (DP) was also incubated under stress (37°C) conditions. The four formulations (each of which is named "CCC" herein) being evaluated in this stability study are described in Table 14-1 set forth below.

[00285] Approximately 27 mL of each formulation was prepared within a LFH (laminar flow hood) using a 0.22 µm Durapore PVDF sterilizing filter prior to filling. Clean depyrogenated 2 mL type I Schott glass vials were filled and stoppered with 13 mm serum stoppers (S2-F451 4432/50B2-40). Samples were analyzed at various timepoints after storage at 37°C or 2-8°C for purity by size-exclusion-ultraperformance liquid chromatography (SE-UPLC) to determine the presence (%) of high molecular weight species (HMW) and the main peak (main).

[00286] Data showing the percentage HMW after incubation at 2-8°C or 37°C for up to 6 months are set forth in Figure 20 (A-B). See also Tables 14-2 and 14-3. When stored at 37°C and 5°C, these formulations exhibited a positive correlation of the rate of HMW formation to the concentration of VEGF Trap. The 140 mg/mL formulation exhibited highest rate of %HMW species formation.

Table 14-1. Formulations tested.

Formulation Number	composition					
	L-Arginine mM	Histidine (mM)	Sucrose (w/v)	Polysorbate 20 (w/v)	VEGFT (mg/mL)	pH
F1 (CCC)	50	20	5	0.03	80	5.8
F2 (CCC)					100	
F3 (CCC)					120	
F4 (CCC)					140	

Table 14-2. SE-UPLC Analysis (2-8°C)

	F1 (CCC): 80 mg/mL		F2 (CCC): 100 mg/mL		F4 (CCC): 120 mg/mL		F3 (CCC): 140 mg/mL	
Months at 2-8C	%Main Peak	%HMW	%Main Peak	%HMW	%Main Peak	%HMW	%Main Peak	%HMW
0.0	97.90	2.10	97.86	2.14	97.83	2.17	97.85	2.15
1	97.91	2.09	97.79	2.21	97.65	2.35	97.47	2.53
2.0	97.78	2.22	97.56	2.44	97.38	2.62	97.22	2.78
3.0	97.61	2.39	97.38	2.62	97.17	2.83	97.04	2.96
5.5	97.39	2.61	97.10	2.90	96.79	3.21		
6.0	97.36	2.64	97.04	2.96	96.74	3.26	96.60	3.40

Table 14-3. SE-UPLC Analysis (37°C)

	F1 (CCC): 80 mg/mL		F2 (CCC): 100 mg/mL		F4 (CCC): 120 mg/mL		F3 (CCC): 140 mg/mL	
Days at 37C	%Main Peak	%HMW	%Main Peak	%HMW	%Main Peak	%HMW	%Main Peak	%HMW
0.0	**97.90**	**2.10**	**97.86**	**2.14**	**97.83**	**2.17**	**97.85**	**2.15**
7	**94.83**	**5.15**	**93.82**	**6.17**	**92.81**	**7.18**	**92.38**	**7.61**
14.0	**92.00**	**7.77**	**90.31**	**9.39**	**88.67**	**11.13**	**86.90**	**12.91**
21.0	**89.47**	**10.31**	**87.00**	**12.58**	**85.04**	**14.85**	**83.11**	**16.65**
28.0	**86.76**	**12.71**	**83.98**	**15.55**	**81.19**	**18.46**	**79.44**	**20.29**

Example 15: High dose Eylea has Prolonged Duration of Action in the D,L-AAA Model of Sustained Neovascular Leak.

[00287] The effect of a four-fold increase in dose on duration of action of aflibercept to inhibit chronic retinal vascular leak in the D,L-AAA model was determined in this Example.

[00288] Animals used were New Zealand White rabbits 3 months post-DL-AAA (DL-α-aminoadipic acid) disease induction. The treatment groups were:

- Placebo (formulation buffer) 50 mcl/eye; n= 6 eyes
- Aflibercept 500 mcg/eye in 50 mcl; n= 7 eyes
- Aflibercept 2 mg/eye in 50 mcl; n= 8 eyes

[00289] The formulation used in each treatment group was: 10 mM Histidine, 8% sucrose, 0.03% PS20, pH 5.8. Ophthalmic exams, which were performed at baseline and at weeks 1, 2, 4, 6, 7, 9, 10, 11, 13 and 18, were intra-ocular pressure (IOP), red-free (RF) imaging (to determine blood vessel morphology), fluorescein angiography (FA; to determine vascular leak), optical coherence tomography (OCT; to identify vitreal inflammation). Serum (ADA) and plasma (drug levels) were collected at baseline and at weeks 1, 2, 4, 6 and 9.

[00290] Data from FA exams of each group are set forth in Figure 21. These data demonstrated that vascular leak inhibition in the retinas of animals receiving higher doses of aflibercept lasted longer than that of animals receiving lower doses. The number of treated eyes in which vascular permeability was completely inhibited was significantly greater in the 2 mg dose group at all sampling times up to 18 weeks post dosing.

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What is claimed is:

1. An aqueous pharmaceutical formulation comprising:

a VEGF receptor fusion protein, anti-VEGF antibody or antigen-binding fragment or VEGF binding molecule at a concentration of at least about 100 mg/ml;

about 5% sucrose

a histidine buffer; and

about 0.03% surfactant;

optionally, in association with a further therapeutic agent;

wherein the formulation has a pH of about 5.0 to about 6.8.

2. The formulation of claim 1 which is suitable for intavitreal administration.

3. The formulation of any one of claims 1-2 further comprising sodium sulfate, sodium thiocyanate, glycine, NaCl, sodium aspartate, L-arginine and/or sodium glutamate.

4. The formulation of any one or claims 1-3, wherein the VEGF receptor fusion protein or anti-VEGF antibody or antibody fragment or VEGF binding molecule is:

(i) a VEGF receptor fusion protein comprising two polypeptides that comprise (1) a VEGFR1 component comprising amino acids 27 to 129 of SEQ ID NO:2; (2) a VEGFR2 component comprising amino acids 130-231 of SEQ ID NO:2; and (3) a multimerization component comprising amino acids 232-457 of SEQ ID NO:2;

(ii) a VEGF receptor fusion protein comprising two polypeptides that comprise immunoglobin-like (Ig) domain 2 of a first VEGF receptor and Ig domain 3 of a second VEGF receptor, and a multimerizing component;

(iii) a VEGF receptor fusion protein comprising two polypeptides that comprise an immunoglobin-like (Ig) domain 2 of a first VEGF receptor, an Ig domain 3 of a second VEGF receptor, an Ig domain 4 of said second VEGF receptor and a multimerizing component;

(iv) a VEGF receptor fusion protein comprising two polypeptides that comprise an immunoglobin-like (Ig) domain 2 of VEGFR1, an Ig domain 3 of a VEGFR2, and a multimerizing component;

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(v) a VEGF receptor fusion protein comprising two polypeptides that comprise an immunoglobin-like (Ig) domain 2 of VEGFR1, an Ig domain 3 of VEGFR2, an Ig domain 4 of VEGFR2 and a multimerizing component;

(vi) a VEGF receptor fusion protein comprising two VEGFR1R2-FcΔC1(a) polypeptides encoded by the nucleic acid sequence of SEQ ID NO:1; or

(vii) selected from the group consisting of: bevacizumab, ranibizumab, pegaptanib, brolucizumab, an anti-VEGF DARPin and a bispecific anti-VEGF/ANG2 antibody.

5. The formulation of any one or claims 1-4, wherein the VEGF receptor fusion protein or anti-VEGF antibody or antibody fragment or VEGF binding molecule is a VEGF receptor fusion protein selected from the group consisting of: aflibercept and conbercept.

6. The formulation of any one of claims 1-5 wherein the VEGF receptor fusion protein or anti-VEGF antibody or antibody fragment or VEGF binding molecule is a VEGF receptor fusion protein is a VEGF receptor fusion protein at a concentration of from about 41 to about 275 mg/ml.

7. The formulation of any one of claims 1-6, wherein the VEGF receptor fusion protein or anti-VEGF antibody or antibody fragment or VEGF binding molecule is a VEGF receptor fusion protein is a VEGF receptor fusion protein at a concentration of:

- about 100 mg/ml;
- about 111.5 mg/ml;
- about 112.0 mg/ml;
- about 113.3 mg/ml;
- about 114.3 mg/ml;
- about 115.6 mg/ml;
- about 116.3 mg/ml;
- about 120 mg/ml;
- about 133 mg/ml;
- about 140 mg/ml;
- about 150 mg/ml;
- about 200 mg/ml;

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- about 250 mg/ml;
- that which contains about 4 mg VEGF receptor fusion protein in about 100 µl or less, about 70 µl or less, about 75 µl or less, about 50 µl or less or about 60 µl or less;
- that which contains about 6 mg VEGF receptor fusion protein in about 100 µl or less, about 70 µl or less, about 75 µl or less, about 50 µl or less or about 60 µl or less;
- that which contains about 8 mg VEGF receptor fusion protein in about 100 µl or less, about 70 µl or less, about 75 µl or less, about 50 µl or less or about 60 µl or less; or
- that which contains about 10 mg VEGF receptor fusion protein in about 100 µl or less, about 70 µl or less, about 75 µl or less, about 50 µl or less or about 60 µl or less.

8. The formulation of any one of claims 1-7 wherein:
(i) the osmolality is about 299 to about 506 mmol/Kg; and/or
(ii) the viscosity is from about 6-15 cP at 20°C.

9. The formulation of any one of claims 1-8 wherein the pH is 5.8 to 6.5.

10. The formulation of claim 9 wherein the pH is about 5.8.

11. The formulation of any one of claims 1-10, wherein the surfactant is a non-ionic surfactant.

12. The formulation of claim 11, wherein the non-ionic surfactant is selected from the group consisting of polysorbate 20, polysorbate 80, poloxamer 188, polyethylene glycol 3350 and mixtures thereof.

13. The formulation of any one of claims 1-12, wherein the histidine is histidine hydrochloride.

14. The formulation of claim 13 comprising about 10 mM to 20 mM histidine hydrochloride.

15. The formulation of any one of claims 1-14, comprising a thermal stabilizer which is a sugar.

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16. The formulation of claim 15, wherein the sugar is sucrose, mannitol, sorbitol or trehalose.

17. The formulation of any one of claims 15-16 comprising about 2.5% (w/v), about 5% (w/v), about 8% (w/v), about 10% (w/v) or about 20% (w/v) sucrose.

18. The formulation of any one of claims 1-17 comprising surfactant at a concentration of about 0.03% (w/v).

19. The formulation of any one of claims 1-18, comprising L-arginine monohydrochloride.

20. The formulation of any one of claims 1-19 wherein the VEGF receptor fusion protein or anti-VEGF antibody or antibody fragment or VEGF binding molecule is a VEGF receptor fusion protein which has less than about 3.5% high molecular weight species immediately after manufacture and purification and/or less than or equal to about 6% high molecular weight species after storage for about 24 months at about 2-8ºC.

21. A formulation comprising the components in a formulation selected from the group consisting of:

Formulation A: 80 mg/ml aflibercept, 10 mM histidine-based buffer, 5% (w/v) sucrose, 0.03% (w/v) polysorbate 20, and 40 mM sodium chloride, with a pH of 5.8 to 6.2;

Formulation B: 80 mg/ml aflibercept, 10 mM phosphate-based buffer, 5% (w/v) sucrose, 0.03% (w/v) polysorbate 20, and 40 mM sodium chloride, with a pH of 5.8 to 6.2;

Formulation C: 80 mg/ml aflibercept, 10 mM citrate-based buffer, 5% (w/v) sucrose, 0.03% (w/v) polysorbate 20, and 40 mM sodium chloride, with a pH of 5.8 to 6.2;

Formulation D: 80 mg/ml aflibercept, 10 mM histidine-based buffer, 5% (w/v) sucrose, 0.03% (w/v) polysorbate 80, and 40 mM sodium chloride, with a pH of 6.2;

Formulation E: 80 mg/ml aflibercept, 10 mM phosphate-based buffer, 5% (w/v) sucrose, 0.03% (w/v) polysorbate 80, and 40 mM sodium chloride, with a pH of 5.8 to 6.2;

Formulation F: 80 mg/ml aflibercept, 10 mM citrate-based buffer, 5% (w/v) sucrose, 0.03% (w/v) polysorbate 80, and 40 mM sodium chloride, with a pH of 5.8 to 6.2.

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Formulation G: 80 mg/ml aflibercept, 10 mM histidine-based buffer, 8% (w/v) sucrose, and 0.03% (w/v) polysorbate 20, with a pH of 5.8 to 6.2;

Formulation H: 80 mg/ml aflibercept, 10 mM phosphate-based buffer, 8% (w/v) sucrose, and 0.03% (w/v) polysorbate 20, with a pH of 5.8 to 6.2;

Formulation I: 80 mg/ml aflibercept, 10 mM citrate-based buffer, 8% (w/v) sucrose, and 0.03% (w/v) polysorbate 20, with a pH of 5.8 to 6.2;

Formulation J: 80 mg/ml aflibercept, 10 mM histidine-based buffer, 8% (w/v) sucrose, and 0.03% (w/v) polysorbate 80, with a pH of 5.8 to 6.2;

Formulation K: 80 mg/ml aflibercept, 10 mM phosphate-based buffer, 8% (w/v) sucrose, and 0.03% (w/v) polysorbate 80, with a pH of 5.8 to 6.2;

Formulation L: 80 mg/ml aflibercept, 10 mM citrate-based buffer, 8% (w/v) sucrose, and 0.03% (w/v) polysorbate 80, with a pH of 5.8 to 6.2;

Formulation M: 150 mg/ml aflibercept, 10 mM histidine-based buffer, 5% (w/v) sucrose, 0.03% (w/v) polysorbate 20, and 40 mM sodium chloride, with a pH of 5.8 to 6.2;

Formulation N: 150 mg/ml aflibercept, 10 mM phosphate-based buffer, 5% (w/v) sucrose, 0.03% (w/v) polysorbate 20, and 40 mM sodium chloride, with a pH of 5.8 to 6.2;

Formulation O: 150 mg/ml aflibercept, 10 mM citrate-based buffer, 5% (w/v) sucrose, 0.03% (w/v) polysorbate 20, and 40 mM sodium chloride, with a pH of 5.8 to 6.2;

Formulation P: 150 mg/ml aflibercept, 10 mM histidine-based buffer, 5% (w/v) sucrose, 0.03% (w/v) polysorbate 80, and 40 mM sodium chloride, with a pH of 6.2;

Formulation Q: 150 mg/ml aflibercept, 10 mM phosphate-based buffer, 5% (w/v) sucrose, 0.03% (w/v) polysorbate 80, and 40 mM sodium chloride, with a pH of 5.8 to 6.2;

Formulation R: 150 mg/ml aflibercept, 10 mM citrate-based buffer, 5% (w/v) sucrose, 0.03% (w/v) polysorbate 80, and 40 mM sodium chloride, with a pH of 5.8 to 6.2;

Formulation S: 150 mg/ml aflibercept, 10 mM histidine-based buffer, 8% (w/v) sucrose, and 0.03% (w/v) polysorbate 20, with a pH of 5.8 to 6.2;

Formulation T: 150 mg/ml aflibercept, 10 mM phosphate-based buffer, 8% (w/v) sucrose, and 0.03% (w/v) polysorbate 20, with a pH of 5.8 to 6.2;

Formulation U: 150 mg/ml aflibercept, 10 mM citrate-based buffer, 8% (w/v) sucrose, and 0.03% (w/v) polysorbate 20, with a pH of 5.8 to 6.2;

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Formulation V: 150 mg/ml aflibercept, 10 mM histidine-based buffer, 8% (w/v) sucrose, and 0.03% (w/v) polysorbate 80, with a pH of 5.8 to 6.2;

Formulation W: 150 mg/ml aflibercept, 10 mM phosphate-based buffer, 8% (w/v) sucrose, and 0.03% (w/v) polysorbate 80, with a pH of 5.8 to 6.2;

Formulation X: 150 mg/ml aflibercept, 10 mM citrate-based buffer, 8% (w/v) sucrose, and 0.03% (w/v) polysorbate 80, with a pH of 5.8 to 6.2;

Formulation Y: 80 mg/ml conbercept, 10 mM histidine-based buffer, 5% (w/v) sucrose, 0.03% (w/v) polysorbate 20, and 40 mM sodium chloride, with a pH of 5.8 to 6.2;

Formulation Z: 80 mg/ml conbercept, 10 mM phosphate-based buffer, 5% (w/v) sucrose, 0.03% (w/v) polysorbate 20, and 40 mM sodium chloride, with a pH of 5.8 to 6.2;

Formulation AA: 80 mg/ml conbercept, 10 mM citrate-based buffer, 5% (w/v) sucrose, 0.03% (w/v) polysorbate 20, and 40 mM sodium chloride, with a pH of 5.8 to 6.2;

Formulation BB: 80 mg/ml conbercept, 10 mM histidine-based buffer, 5% (w/v) sucrose, 0.03% (w/v) polysorbate 80, and 40 mM sodium chloride, with a pH of 6.2;

Formulation CC: 80 mg/ml conbercept, 10 mM phosphate-based buffer, 5% (w/v) sucrose, 0.03% (w/v) polysorbate 80, and 40 mM sodium chloride, with a pH of 5.8 to 6.2;

Formulation DD: 80 mg/ml conbercept, 10 mM citrate-based buffer, 5% (w/v) sucrose, 0.03% (w/v) polysorbate 80, and 40 mM sodium chloride, with a pH of 5.8 to 6.2;

Formulation EE: 80 mg/ml conbercept, 10 mM histidine-based buffer, 8% (w/v) sucrose, and 0.03% (w/v) polysorbate 20, with a pH of 5.8 to 6.2;

Formulation FF: 80 mg/ml conbercept, 10 mM phosphate-based buffer, 8% (w/v) sucrose, and 0.03% (w/v) polysorbate 20, with a pH of 5.8 to 6.2;

Formulation GG: 80 mg/ml conbercept, 10 mM citrate-based buffer, 8% (w/v) sucrose, and 0.03% (w/v) polysorbate 20, with a pH of 5.8 to 6.2;

Formulation HH: 80 mg/ml conbercept, 10 mM histidine-based buffer, 8% (w/v) sucrose, and 0.03% (w/v) polysorbate 80, with a pH of 5.8 to 6.2;

Formulation II: 80 mg/ml conbercept, 10 mM phosphate-based buffer, 8% (w/v) sucrose, and 0.03% (w/v) polysorbate 80, with a pH of 5.8 to 6.2;

Formulation JJ: 80 mg/ml conbercept, 10 mM citrate-based buffer, 8% (w/v) sucrose, and 0.03% (w/v) polysorbate 80, with a pH of 5.8 to 6.2;

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Formulation KK: 150 mg/ml conbercept, 10 mM histidine-based buffer, 5% (w/v) sucrose, 0.03% (w/v) polysorbate 20, and 40 mM sodium chloride, with a pH of 5.8 to 6.2;

Formulation LL: 150 mg/ml conbercept, 10 mM phosphate-based buffer, 5% (w/v) sucrose, 0.03% (w/v) polysorbate 20, and 40 mM sodium chloride, with a pH of 5.8 to 6.2;

Formulation MM: 150 mg/ml conbercept, 10 mM citrate-based buffer, 5% (w/v) sucrose, 0.03% (w/v) polysorbate 20, and 40 mM sodium chloride, with a pH of 5.8 to 6.2;

Formulation NN: 150 mg/ml conbercept, 10 mM histidine-based buffer, 5% (w/v) sucrose, 0.03% (w/v) polysorbate 80, and 40 mM sodium chloride, with a pH of 6.2;

Formulation OO: 150 mg/ml conbercept, 10 mM phosphate-based buffer, 5% (w/v) sucrose, 0.03% (w/v) polysorbate 80, and 40 mM sodium chloride, with a pH of 5.8 to 6.2;

Formulation PP: 150 mg/ml conbercept, 10 mM citrate-based buffer, 5% (w/v) sucrose, 0.03% (w/v) polysorbate 80, and 40 mM sodium chloride, with a pH of 5.8 to 6.2;

Formulation QQ: 150 mg/ml conbercept, 10 mM histidine-based buffer, 8% (w/v) sucrose, and 0.03% (w/v) polysorbate 20, with a pH of 5.8 to 6.2;

Formulation RR: 150 mg/ml conbercept, 10 mM phosphate-based buffer, 8% (w/v) sucrose, and 0.03% (w/v) polysorbate 20, with a pH of 5.8 to 6.2;

Formulation SS: 150 mg/ml conbercept, 10 mM citrate-based buffer, 8% (w/v) sucrose, and 0.03% (w/v) polysorbate 20, with a pH of 5.8 to 6.2;

Formulation TT: 150 mg/ml conbercept, 10 mM histidine-based buffer, 8% (w/v) sucrose, and 0.03% (w/v) polysorbate 80, with a pH of 5.8 to 6.2;

Formulation UU: 150 mg/ml conbercept, 10 mM phosphate-based buffer, 8% (w/v) sucrose, and 0.03% (w/v) polysorbate 80, with a pH of 5.8 to 6.2;

Formulation VV: 150 mg/ml conbercept, 10 mM citrate-based buffer, 8% (w/v) sucrose, and 0.03% (w/v) polysorbate 80, with a pH of 5.8 to 6.2;

Formulation WW: 140 mg/ml VEGF receptor fusion protein, 10 mM histidine-based buffer, 5% (w/v) sucrose, 0.03% (w/v) polysorbate 20, and 50 mM taurine, with a pH of 5.8;

Formulation XX: 140 mg/ml VEGF receptor fusion protein, 20 mM histidine-based buffer, 4% (w/v) proline, 0.03% (w/v) polysorbate 20, and 50 mM arginine hydrochloride, with a pH of 5.8;

Formulation YY: 140 mg/ml VEGF receptor fusion protein, 20 mM histidine-based buffer, 2.5% (w/v) sucrose, 2.0 % (w/v) proline, 0.03% (w/v) polysorbate 20, and 50 mM taurine, with a pH of 5.8;

Formulation ZZ: 140 mg/ml VEGF receptor fusion protein, 10 mM histidine-based buffer, 2.5% (w/v) sucrose, 2.0% (w/v) proline, 0.03% (w/v) polysorbate 20, and 50 mM arginine hydrochloride, with a pH of 5.8;

Formulation AAA: 140 mg/ml VEGF receptor fusion protein, 20 mM histidine-based buffer, 5% (w/v) sucrose, 0.03% (w/v) polysorbate 20, and 50 mM PSA, with a pH of 5.8;

Formulation BBB: 140 mg/ml VEGF receptor fusion protein, 20 mM histidine-based buffer, 2.5% (w/v) sucrose, 2.0% (w/v) proline, 0.03% (w/v) polysorbate 20, and 50 mM PSA, with a pH of 5.8;

Formulation CCC: 80, 100, 120 or 140 mg/ml VEGF receptor fusion protein, 20 mM histidine-based buffer, 5% (w/v) sucrose, 0.03% (w/v) polysorbate 20, and 50 mM arginine hydrochloride, with a pH of 5.8;

Formulation DDD: 140 mg/ml VEGF receptor fusion protein, 10 mM histidine-based buffer, 4% (w/v) proline, 0.03% (w/v) polysorbate 20, and 50 mM PSA, with a pH of 5.8;

Formulation EEE: 140 mg/ml VEGF receptor fusion protein, 20 mM histidine-based buffer, 5% (w/v) sucrose, and 0.03% (w/v) polysorbate 20 and no thermal stabilizer, with a pH of 5.8;

Formulation FFF: 140 mg/ml VEGF receptor fusion protein, 10 mM sodium phosphate, 5 % (w/v) sucrose and 0.03 % polysorbate 20 with a pH of 6.2;

Formulation GGG: 140 mg/ml VEGF receptor fusion protein; 20 mM histidine, pH 5.8; 5% Sucrose; 0.03% polysorbate 20; 50 mM sodium sulfate;

Formulation HHH: 140 mg/ml VEGF receptor fusion protein; 20 mM histidine, pH 5.8; 5% sucrose; 0.03% polysorbate 20; 50 mM sodium thiocyanate;

Formulation III: 140 mg/ml VEGF receptor fusion protein; 20 mM histidine, pH 5.8; 5% sucrose, 0.03% polysorbate 20; 40 mM sodium citrate;

Formulation JJJ: 140 mg/ml VEGF receptor fusion protein; 20 mM histidine, pH 5.8; 5% Sucrose, 0.03% polysorbate 20; 50 mM glycine;

Formulation KKK: 140 mg/ml VEGF receptor fusion protein; 20 mM histidine, pH 5.8; 5% sucrose, 0.03% polysorbate 20; 50 mM sodium chloride;

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Formulation LLL: 140 mg/ml VEGF receptor fusion protein; 20 mM Histidine, pH 5.8; 5% sucrose; 0.03% polysorbate 20; 50 mM lysine;

Formulation MMM: 140 mg/ml VEGF receptor fusion protein; 20 mM histidine, pH 5.8; 5% sucrose; 0.03% polysorbate 20; 50 mM sodium aspartate;

Formulation NNN: 140 mg/ml VEGF receptor fusion protein; 20 mM histidine, pH 5.8; 5% sucrose; 0.03% polysorbate 20; 50 mM sodium glutamate;

Formulation OOO: 140 mg/ml VEGF receptor fusion protein; 20 mM histidine, pH 5.8; 5% sucrose; 0.03% polysorbate 20; 50 mM sodium Citrate; 50 mM arginine hydrochloride;

Formulation PPP: 140 mg/ml VEGF receptor fusion protein; 20 mM histidine, pH 5.8; 5% sucrose; 0.03% polysorbate 20; 50mM glycine; 50 mM arginine hydrochloride;

Formulation QQQ: 140 mg/ml VEGF receptor fusion protein; 20 mM histidine, pH 5.8; 5% sucrose; 0.03% polysorbate 20; 50 mM sodium aspartate; 50 mM arginine hydrochloride;

Formulation RRR: 140 mg/ml VEGF receptor fusion protein; 20 mM histidine, pH 5.8; 5% sucrose; 0.03% polysorbate 20; 50 mM sodium glutamate; 50 mM arginine hydrochloride;

Formulation SSS: 140 mg/ml VEGF receptor fusion protein; 20 mM His, pH 5.8; 5% sucrose; 0.03% polysorbate 20; 10 mM L-arginine hydrochloride;

Formulation TTT: 140 mg/ml VEGF receptor fusion protein; 20 mM His, pH 5.8; 5% sucrose; 0.03% polysorbate 20; 100 mM L-arginine hydrochloride;

Formulation UUU: 30 mg/ml VEGF receptor fusion protein, 10% sucrose, 10 mM phosphate, 0.03% polysorbate 20, pH 6.2;

Formulation VVV: 30 mg/ml VEGF receptor fusion protein, 20% sucrose, 10 mM phosphate, 0.03% polysorbate 20, pH 6.2;

Formulation WWW: 60 mg/ml VEGF receptor fusion protein, 10% sucrose, 10 mM phosphate, 0.03% polysorbate 20, pH 6.2;

Formulation XXX: 60 mg/ml VEGF receptor fusion protein, 20% sucrose, 10 mM phosphate, 0.03% polysorbate 20, pH 6.2;

Formulation YYY: 120 mg/ml VEGF receptor fusion protein, 10% sucrose, 10 mM phosphate, 0.03% polysorbate 20, pH 6.2;

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Formulation ZZZ: 120 mg/ml VEGF receptor fusion protein, 20% sucrose, 10 mM phosphate, 0.03% polysorbate 20, pH 6.2;

Formulation AAAA: 120 mg/ml VEGF receptor fusion protein, 10% sucrose, 10 mM phosphate, 0.03% polysorbate 20, 50 mM NaCl, pH 6.2;

Formulation BBBB: 120 mg/ml VEGF receptor fusion protein, 20% sucrose, 10 mM phosphate, 0.03% polysorbate 20, 50 mM NaCl, pH 6.2;

Formulation CCCC: 140 mg/ml VEGF receptor fusion protein, 10 mM sodium phosphate, 5% sucrose, 40 mM sodium chloride, 0.03% PS20, pH 6.2;

Formulation DDDD: 80.0 mg/ml VEGF receptor fusion protein, 20 mM histidine-based buffer, 5% (w/v) sucrose, 0.03% (w/v) polysorbate 20, and 50 mM L-arginine monohydrochloride, with a pH of 5.8;

Formulation EEEE: 120.0 mg/ml VEGF receptor fusion protein, 20 mM histidine-based buffer, 5% (w/v) sucrose, 0.03% (w/v) polysorbate 20, and 50 mM L-arginine monohydrochloride, with a pH of 5.8;

Formulation FFFF: 113.3 mg/ml VEGF receptor fusion protein, 20 mM histidine-based buffer, 5% (w/v) sucrose, 0.03% (w/v) polysorbate 20, and 50 mM L-arginine monohydrochloride, with a pH of 5.8;

Formulation GGGG: 114.3 mg/ml VEGF receptor fusion protein, 10 mM histidine-based buffer, 5% (w/v) sucrose, 0.03% (w/v) polysorbate 20, and 50 mM L-arginine monohydrochloride, with a pH of 5.8;

Formulation HHHH: 100.0 mg/ml VEGF receptor fusion protein, 20 mM histidine-based buffer, 5% (w/v) sucrose, 0.03% (w/v) polysorbate 20, and 50 mM L-arginine monohydrochloride, with a pH of 5.8; and

Formulation IIII: 133.3 mg/ml VEGF receptor fusion protein, 20 mM histidine-based buffer, 5% (w/v) sucrose, 0.03% (w/v) polysorbate 20, and 50 mM L-arginine monohydrochloride, with a pH of 5.8;

Formulation JJJJ: 150 mg/ml aflibercept, 10 mM sodium phosphate, 8% (w/v) sucrose, 0.03% (w/v) polysorbate 20 and 50 mM arginine hydrochloride, pH 6.2;

Formulation KKKK: 114.3 mg/ml VEGF receptor fusion protein, 20 mM histidine-based buffer, 5% (w/v) sucrose, 0.03% (w/v) polysorbate 20, and 50 mM L-arginine monohydrochloride, with a pH of 5.8;

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Formulation LLLL: 90 mg/ml VEGF receptor fusion protein, 10 mM histidine, 5% (w/v) sucrose, 0.03% (w/v) polysorbate 20, pH 5.75; and

Formulation MMMM: 90 mg/ml VEGF receptor fusion protein, 10 mM histidine, 7% (w/v) sucrose, 0.03% (w/v) polysorbate 20, pH 5.75.

22. The formulation of claim 21 wherein the VEGF receptor fusion protein is aflibercept or conbercept.

23. The formulation of any one of claims 21-22 wherein the VEGF receptor fusion protein has less than about 3.5% high molecular weight species immediately after manufacture and purification and/or less than or equal to about 6% high molecular weight species after storage for about 24 months at about 2-8°C.

24. A container or injection device comprising the formulation of any one of claims 1-23.

25. The container or injection device of claim 24, which is a vial, syringe, autoinjector or pre-filled syringe.

26. A method for preparing the formulation of any one of claims 1-23, comprising combining the components of said formulation into a single composition.

27. The method of claim 26, further comprising loading a volume of the formulation into a syringe.

28. A formulation which is the product of the method of any one of claims 26-27.

29. A method for administering a formulation of any one of claims 1-22 and 27 to a subject comprising intraocularly injecting the formulation into the eye of the subject.

30. A method for treating an angiogenic eye disorder in a subject in need thereof comprising administering an intraocular injection of more than about 2 mg of a VEGF receptor fusion protein to the eye of the subject.

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31. The method of claim 30 comprising administering about 4 mg, about 6 mg, about 8 mg or about 10 mg of the VEGF receptor fusion protein to the eye of the subject.

32. A method for treating an angiogenic eye disorder in a subject in need thereof, the method comprising intraocularly injecting more than about 2 mg of VEGF receptor fusion protein in a formulation of any one of claims 1-23 and 28 into an eye of the subject.

33. The method of claim 32, comprising injecting about 4 mg, about 6 mg, about 8 mg or about 10 mg of the VEGF receptor fusion protein into the eye of the subject.

34. The method of any one of claims 30-33, wherein the intraocular injection is an intravitreal injection.

35. The method of any one of claims 30-34, wherein the angiogenic eye disorder is age-related macular degeneration (wet), macular edema, macular edema following retinal vein occlusion, retinal vein occlusion (RVO), central retinal vein occlusion (CRVO) branch retinal vein occlusion (BRVO), diabetic macular edema (DME), choroidal neovascularization (CNV), iris neovascularization, neovascular glaucoma, post-surgical fibrosis in glaucoma, proliferative vitreoretinopathy (PVR), optic disc neovascularization, corneal neovascularization, retinal neovascularization, vitreal neovascularization, pannus, pterygium, vascular retinopathy, diabetic retinopathy, non-proliferative diabetic retinopathy and/or proliferative diabetic retinopathy.

36. The method of any one of claims 30-35 wherein the VEGF receptor fusion protein is administered in about 100 microliters or less, about 90 microliters, about 80 microliters, about 75 microliters, about 70 microliters, about 60 microliters or about 50 microliters.

37. The method of any one of claims 30-36, wherein the VEGF receptor fusion protein is contained within a formulation comprising: about 5% sucrose; a histidine buffer; and about 0.03% surfactant.

38. The method of any one or claims 30-37 wherein more than about 2.0 mg of the VEGF receptor fusion protein is injected once every 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23 or 24 weeks.

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ABSTRACT

The present invention provides ophthalmic formulations having high concentrations of vascular endothelial growth factor (VEGF) receptor fusion protein and high stability during storage. Methods for treating angiogenic eye disorders using the high concentration formulations are also provided.

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DECLARATION (37 CFR 1.63) FOR UTILITY OR DESIGN APPLICATION USING AN APPLICATION DATA SHEET (37 CFR 1.76)

Title of Invention	HIGH CONCENTRATION VEGF RECEPTOR FUSION PROTEIN CONTAINING FORMULATIONS

As the below named inventor, I hereby declare that:

This declaration is directed to:

☐ The attached application, or

☒ United States application or PCT international application number 16/409,631 filed on May 10, 2019.

The above-identified application was made or authorized to be made by me.

I believe that I am the original inventor or an original joint inventor of a claimed invention in the application.

I hereby acknowledge that any willful false statement made in this declaration is punishable under 18 U.S.C. 1001 by fine or imprisonment of not more than five (5) years, or both.

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LEGAL NAME OF INVENTOR

Inventor: Kenneth S. GRAHAM Date (Optional): 14 Jan 2021

Signature: Kenneth S Graham

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LEGAL NAME OF INVENTOR

Inventor: Saurabh WADHWA Date (Optional): 17 June 2021

Signature: Swadhwa

Note: An application data sheet (PTO/SB/14 or equivalent), including naming the entire inventive entity, must accompany this form or must have been previously filed. Use an additional PTO/AIA/01 form for each additional inventor.

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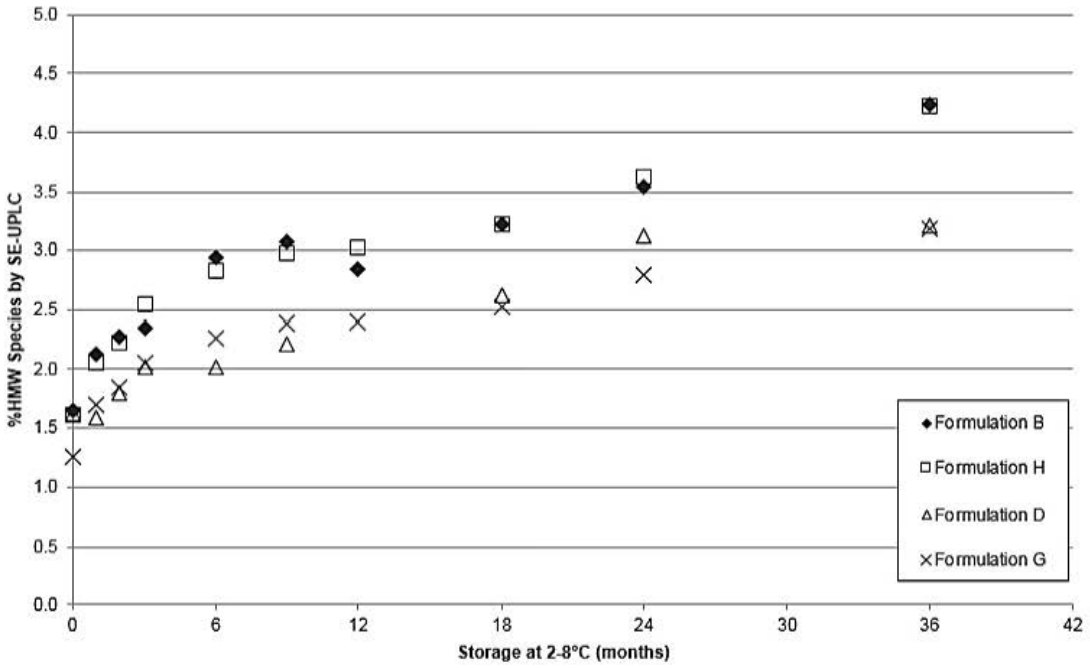

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Formulation G

FIG. 1A

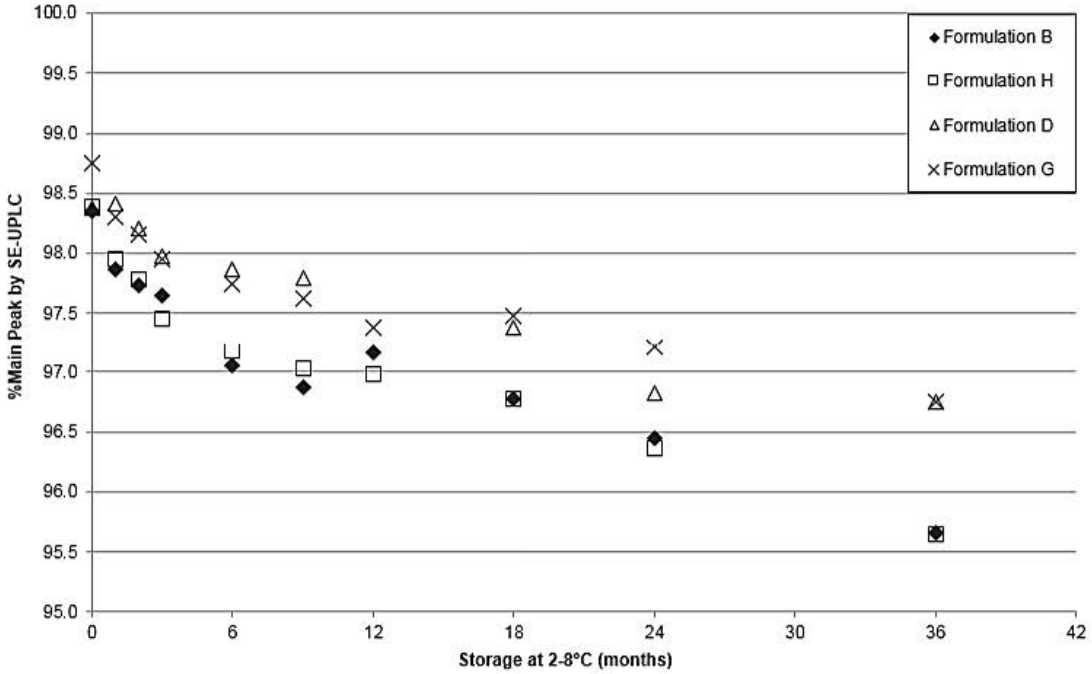

100.0
99.5
99.0
98.5
98.0
97.5
97.0
96.5
96.0
95.5
95.0
%Main Peak by SE-UPLC
0
6
12
18
24
30
36
42
Storage at 2-8°C (months)
Formulation B
Formulation H
Formulation D
Formulation G

FIG. 1B

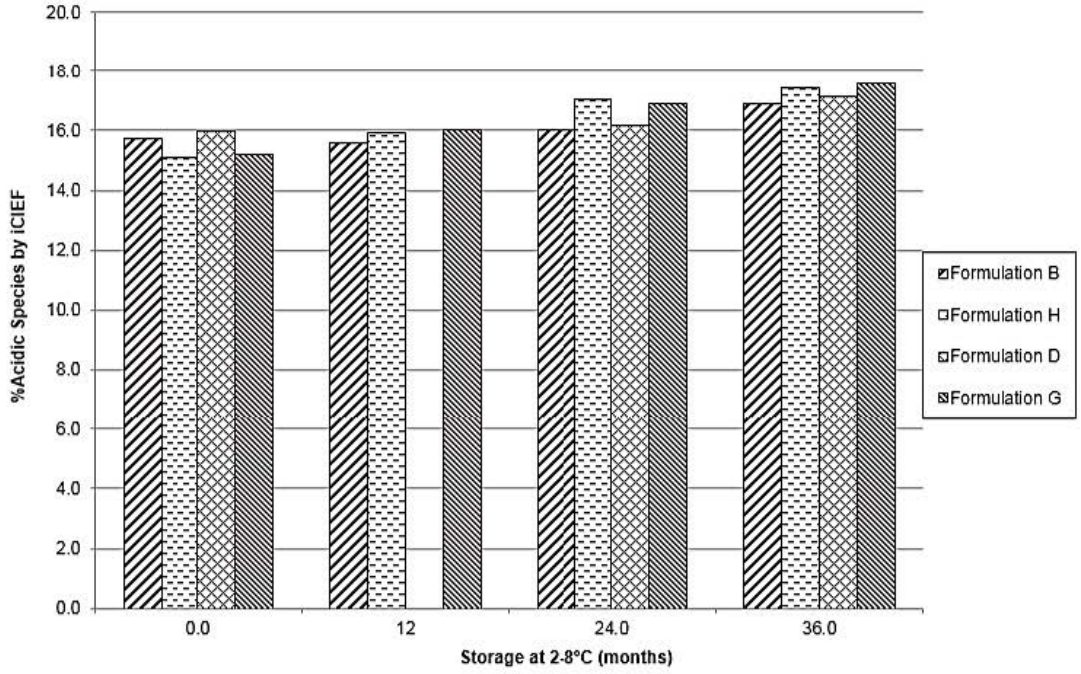

20.0
18.0
16.0
14.0
12.0
10.0
8.0
6.0
4.0
2.0
0.0
%Acidic Species by iCIEF
0.0
12
24.0
36.0
Storage at 2-8°C (months)
Formulation B
Formulation H
Formulation D
Formulation G

FIG. 1C

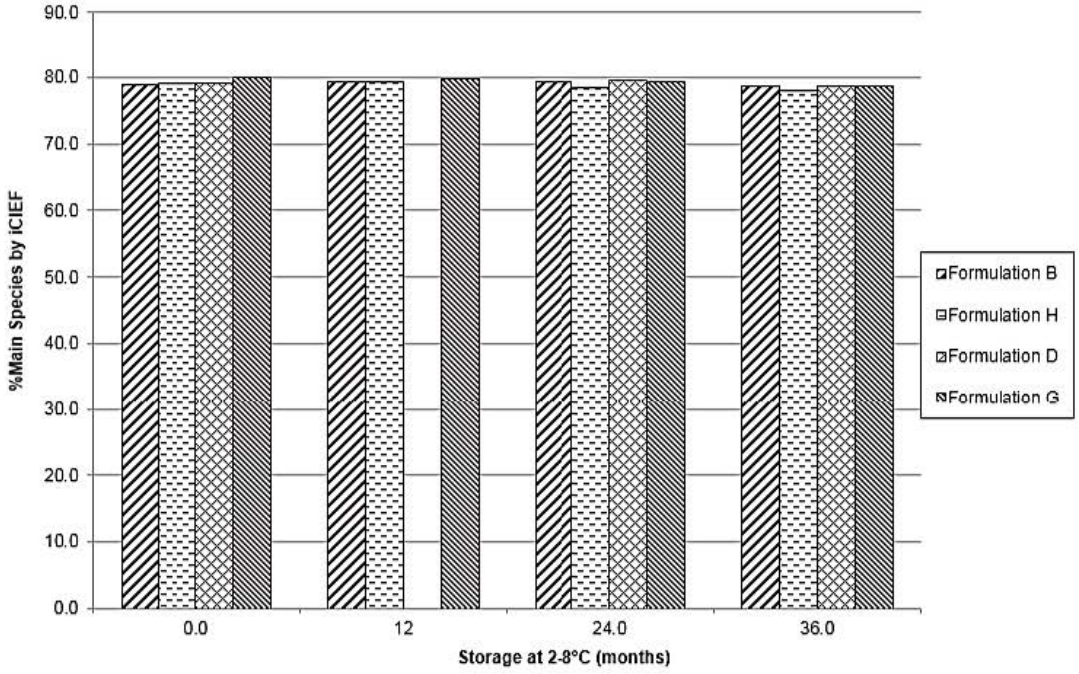

90.0
80.0
70.0
60.0
50.0
40.0
30.0
20.0
10.0
0.0
%Main Species by iCIEF
0.0
12
24.0
36.0
Storage at 2-8°C (months)
Formulation B
Formulation H
Formulation D
Formulation G

FIG. 1D

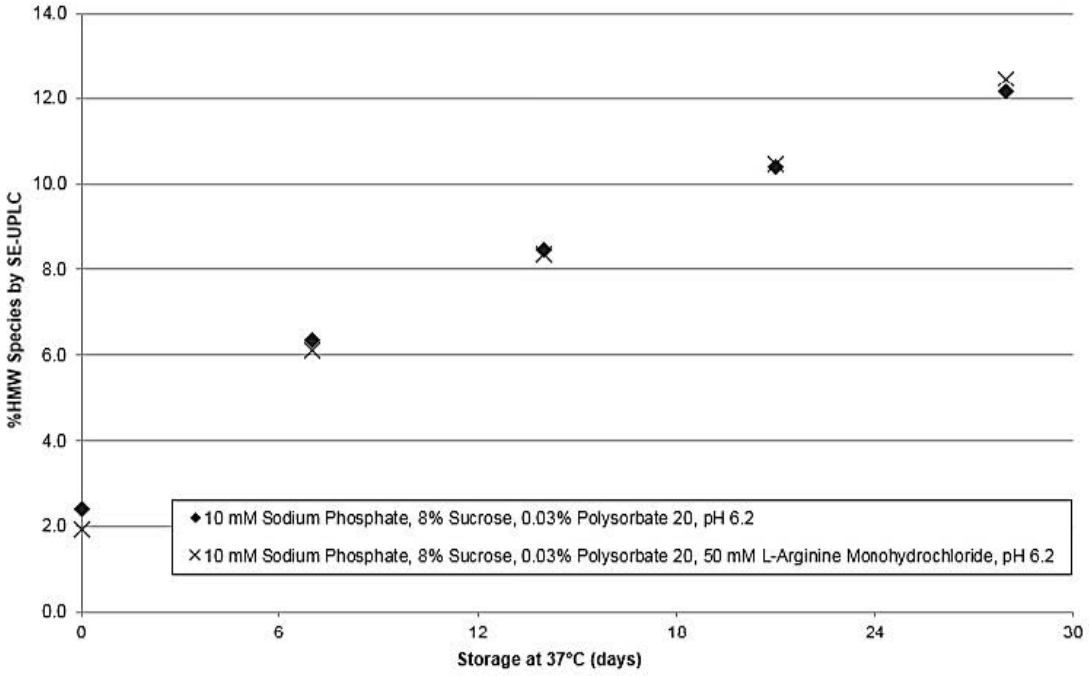

14.0
12.0
10.0
8.0
6.0
4.0
2.0
0.0
%HMW Species by SE-UPLC
0
6
12
18
24
30
Storage at 37°C (days)
10 mM Sodium Phosphate, 8% Sucrose, 0.03% Polysorbate 20, pH 6.2
10 mM Sodium Phosphate, 8% Sucrose, 0.03% Polysorbate 20, 50 mM L-Arginine Monohydrochloride, pH 6.2

FIG. 2A

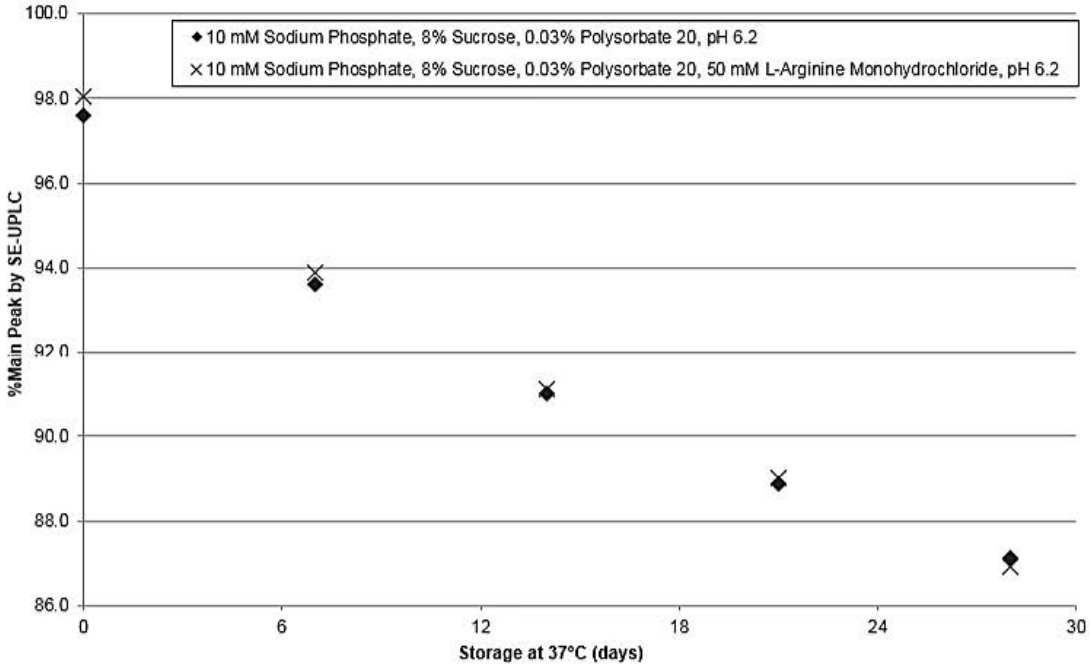

10 mM Sodium Phosphate, 8% Sucrose, 0.03% Polysorbate 20, pH 6.2
10 mM Sodium Phosphate, 8% Sucrose, 0.03% Polysorbate 20, 50 mM L-Arginine Monohydrochloride, pH 6.2
%Main Peak by SE-UPLC
100.0
98.0
96.0
94.0
92.0
90.0
88.0
86.0
0
6
12
18
24
30
Storage at 37°C (days)

FIG. 2B

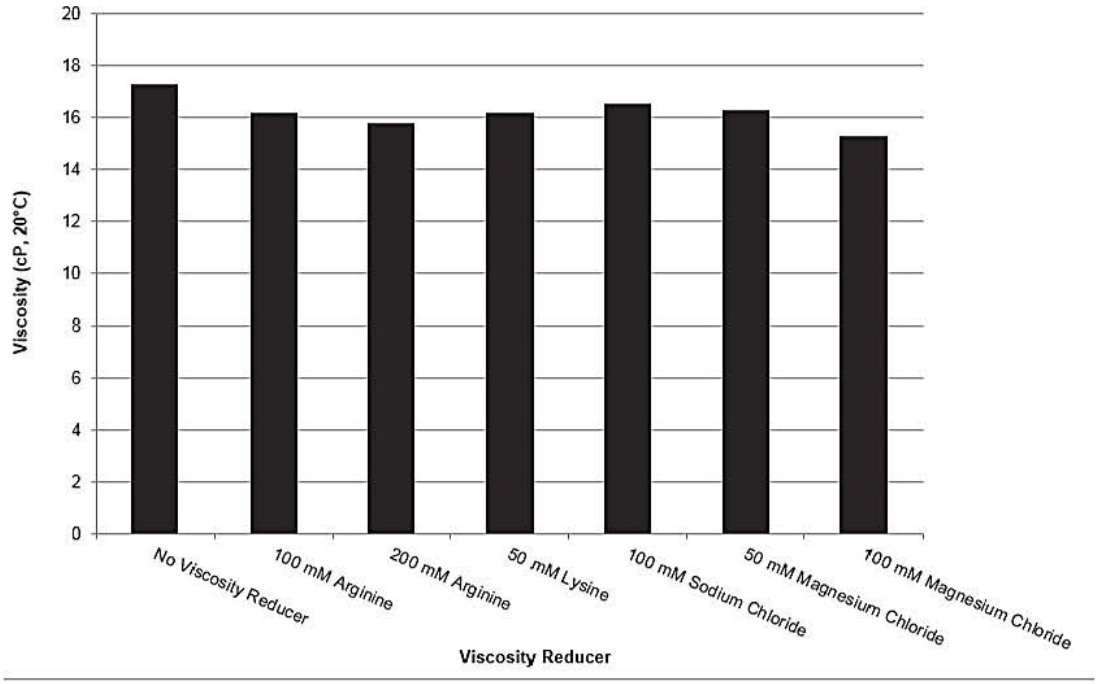

20
18
16
14
12
10
8
6
4
2
0
Viscosity (cP, 20°C)
No Viscosity Reducer
100 mM Arginine
200 mM Arginine
50 mM Lysine
100 mM Sodium Chloride
50 mM Magnesium Chloride
100 mM Magnesium Chloride
Viscosity Reducer

FIG. 3A

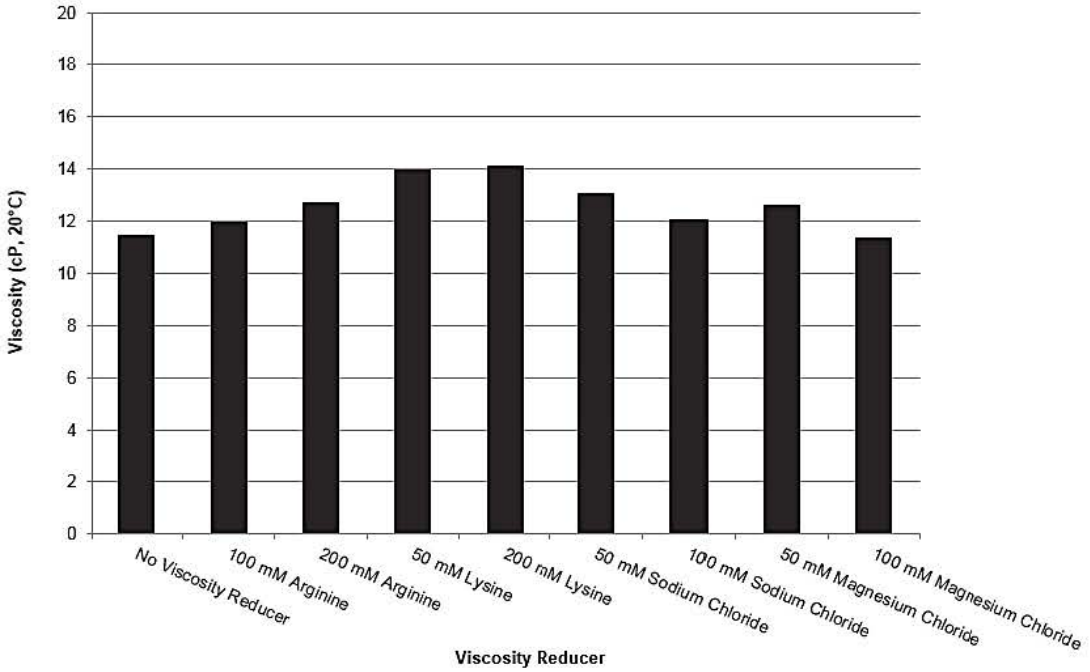

20
18
16
14
12
10
8
6
4
2
0
Viscosity (cP, 20°C)
No Viscosity Reducer
100 mM Arginine
200 mM Arginine
50 mM Lysine
200 mM Lysine
50 mM Sodium Chloride
100 mM Sodium Chloride
50 mM Magnesium Chloride
100 mM Magnesium Chloride
Viscosity Reducer

FIG. 3B

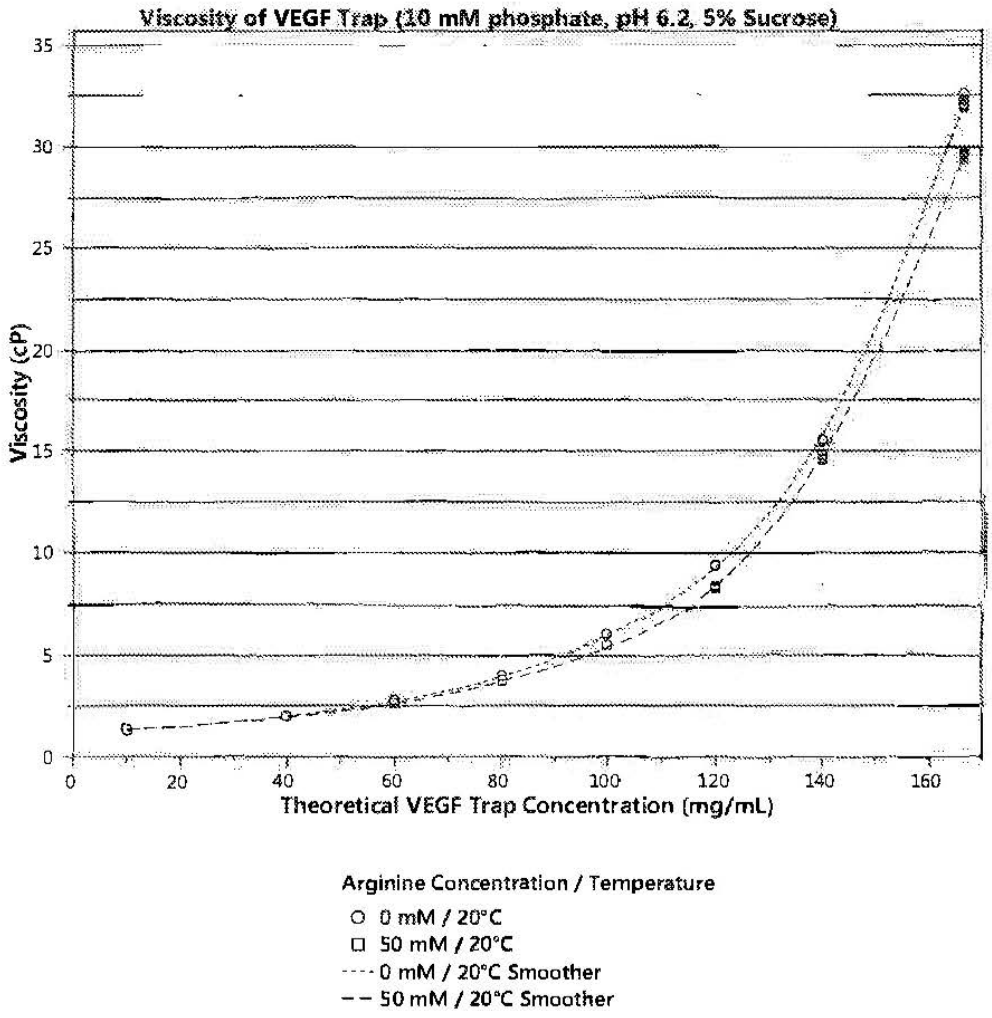

Viscosity of VEGF Trap (10 mM phosphate, pH 6.2, 5% Sucrose)
Viscosity (cP)
0
5
10
15
20
25
30
35
0
20
40
60
80
100
120
140
160
Theoretical VEGF Trap Concentration (mg/mL)
Arginine Concentration / Temperature
0 mM / 20°C
50 mM / 20°C
0 mM / 20°C Smoother
50 mM / 20°C Smoother

FIG. 3C

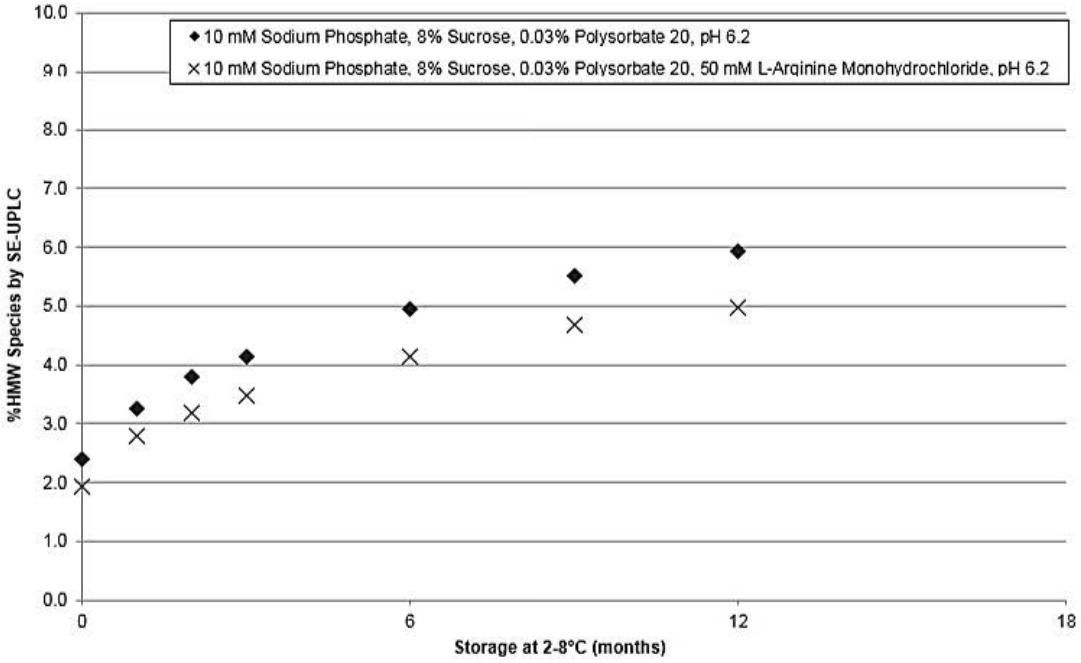

10 mM Sodium Phosphate, 8% Sucrose, 0.03% Polysorbate 20, pH 6.2
10 mM Sodium Phosphate, 8% Sucrose, 0.03% Polysorbate 20, 50 mM L-Arginine Monohydrochloride, pH 6.2
%HMW Species by SE-UPLC
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
0
6
12
18
Storage at 2-8°C (months)

FIG. 4A

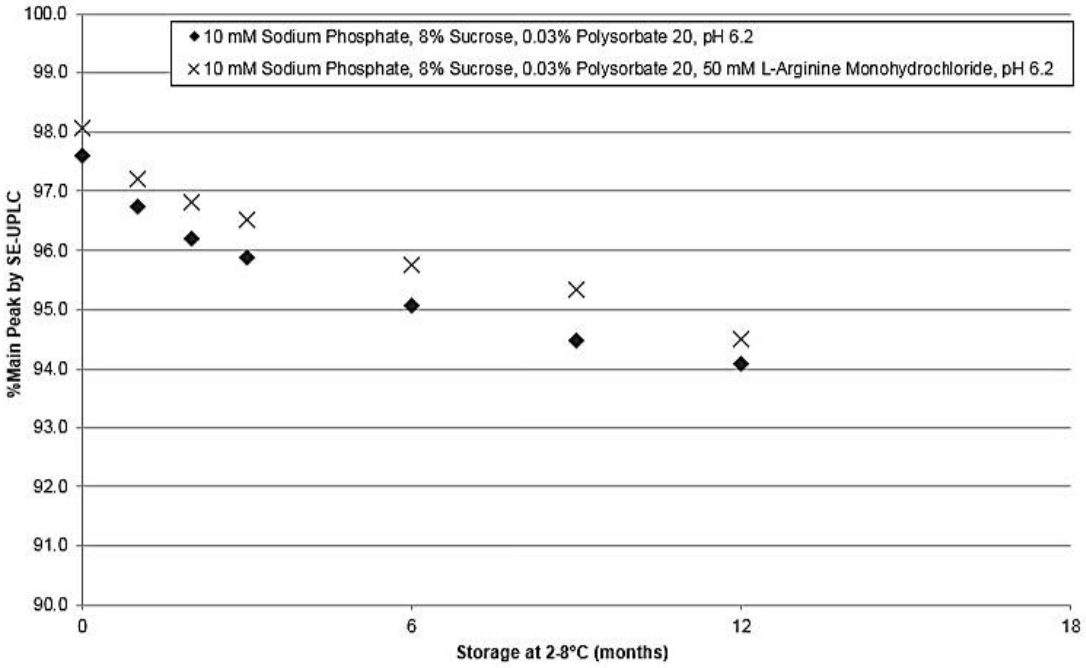

10 mM Sodium Phosphate, 8% Sucrose, 0.03% Polysorbate 20, pH 6.2
10 mM Sodium Phosphate, 8% Sucrose, 0.03% Polysorbate 20, 50 mM L-Arginine Monohydrochloride, pH 6.2
%Main Peak by SE-UPLC
100.0
99.0
98.0
97.0
96.0
95.0
94.0
93.0
92.0
91.0
90.0
0
6
12
18
Storage at 2-8°C (months)

FIG. 4B

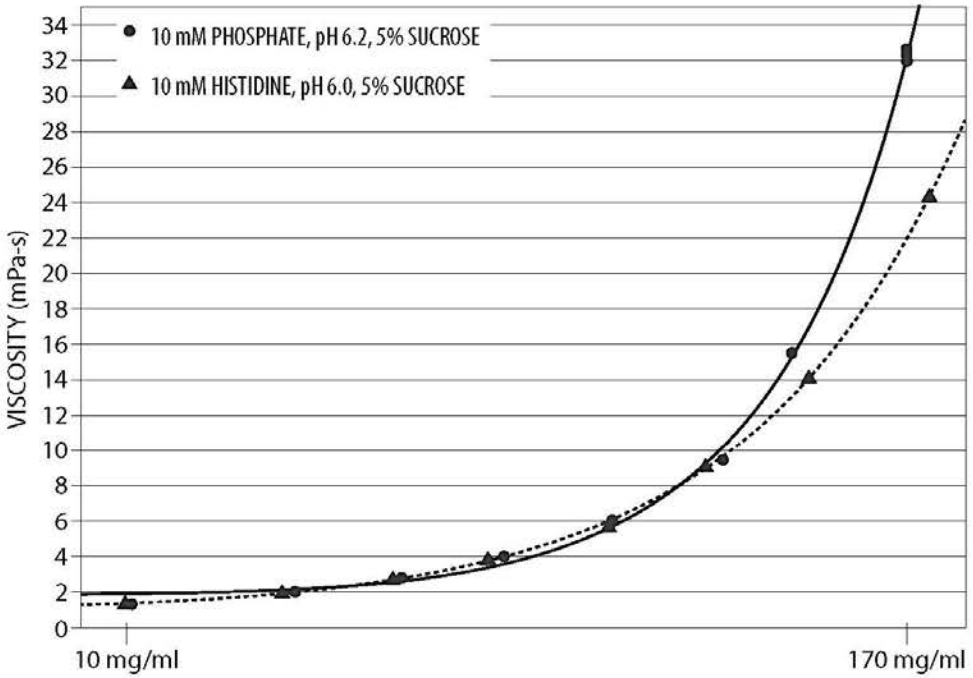

10 mM PHOSPHATE, pH 6.2, 5% SUCROSE
10 mM HISTIDINE, pH 6.0, 5% SUCROSE
VISCOSITY (mPa-s)
0
2
4
6
8
10
12
14
16
18
20
22
24
26
28
30
32
34
10 mg/ml
170 mg/ml

FIG. 5

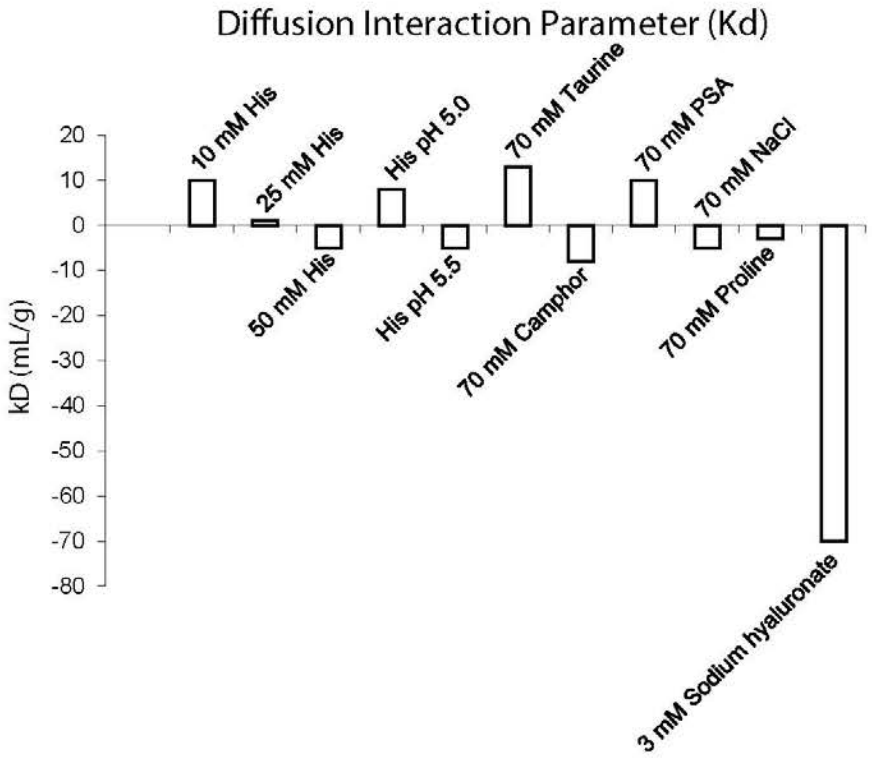

Diffusion Interaction Parameter (Kd)
kD (mL/g)
20
10
0
-10
-20
-30
-40
-50
-60
-70
-80
10 mM His
25 mM His
50 mM His
His pH 5.0
His pH 5.5
70 mM Taurine
70 mM Camphor
70 mM PSA
70 mM NaCl
70 mM Proline
3 mM Sodium hyaluronate

FIG. 6

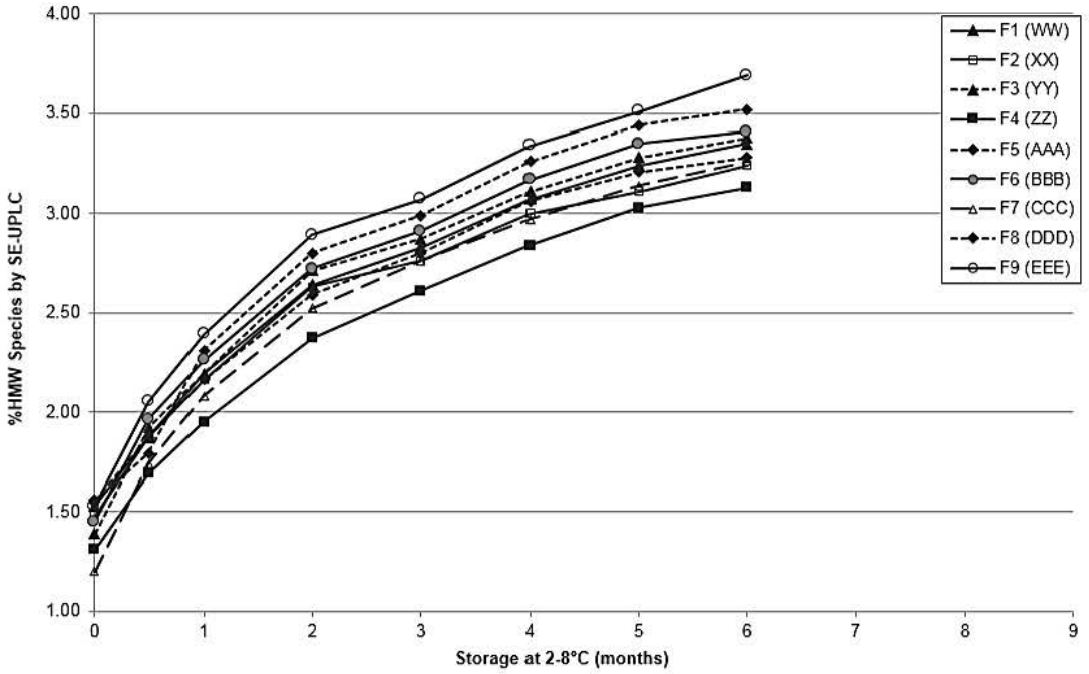

4.00
3.50
3.00
2.50
2.00
1.50
1.00
%HMW Species by SE-UPLC
0
1
2
3
4
5
6
7
8
9
Storage at 2-8°C (months)
F1 (WW)
F2 (XX)
F3 (YY)
F4 (ZZ)
F5 (AAA)
F6 (BBB)
F7 (CCC)
F8 (DDD)
F9 (EEE)

FIG. 7

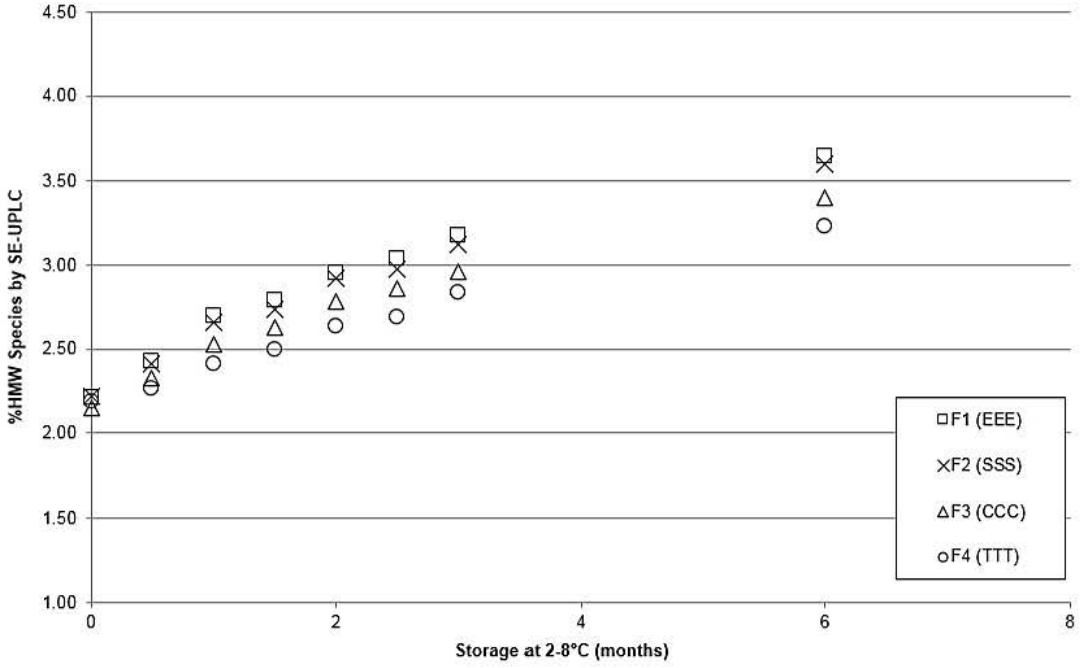

4.50
4.00
3.50
3.00
2.50
2.00
1.50
1.00
%HMW Species by SE-UPLC
0
2
4
6
8
Storage at 2-8°C (months)
F1 (EEE)
F2 (SSS)
F3 (CCC)
F4 (TTT)

FIG. 8A

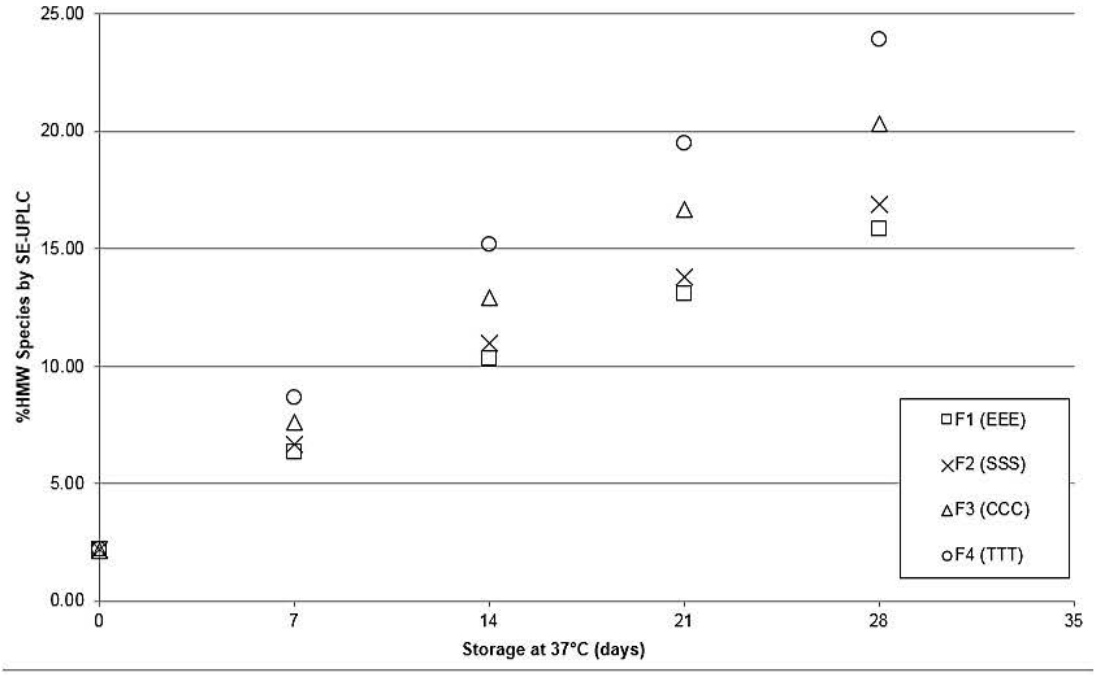

25.00
20.00
15.00
10.00
5.00
0.00
%HMW Species by SE-UPLC
0
7
14
21
28
35
Storage at 37°C (days)
F1 (EEE)
F2 (SSS)
F3 (CCC)
F4 (TTT)

FIG. 8B

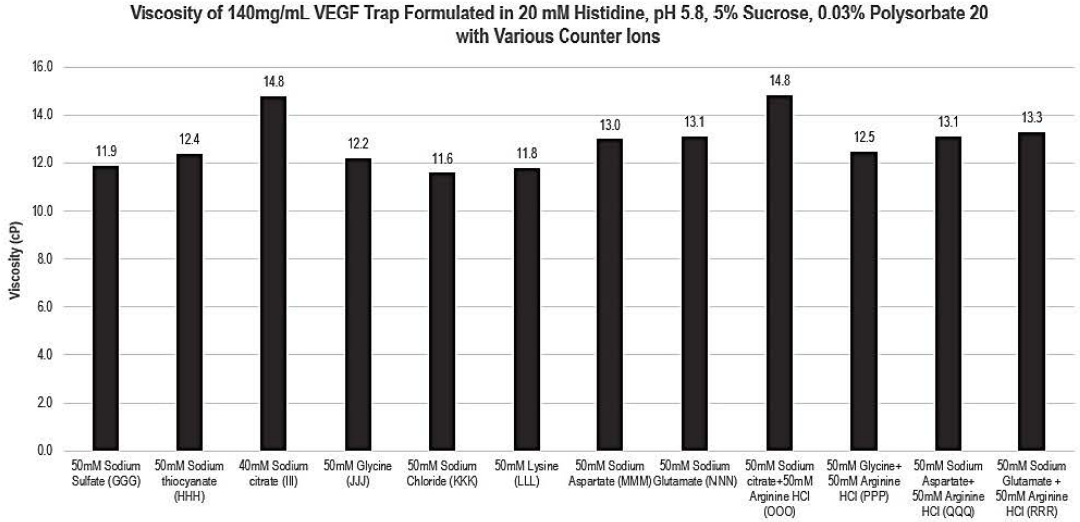

Viscosity of 140mg/mL VEGF Trap Formulated in 20 mM Histidine, pH 5.8, 5% Sucrose, 0.03% Polysorbate 20 with Various Counter Ions
Viscosity (cP)
16.0
14.0
12.0
10.0
8.0
6.0
4.0
2.0
0.0
11.9
12.4
14.8
12.2
11.6
11.8
13.0
13.1
14.8
12.5
13.1
13.3
50mM Sodium Sulfate (GGG)
50mM Sodium thiocyanate (HHH)
40mM Sodium citrate (III)
50mM Glycine (JJJ)
50mM Sodium Chloride (KKK)
50mM Lysine (LLL)
50mM Sodium Aspartate (MMM)
50mM Sodium Glutamate (NNN)
50mM Sodium citrate+50mM Arginine HCl (OOO)
50mM Glycine+ 50mM Arginine HCl (PPP)
50mM Sodium Aspartate+ 50mM Arginine HCl (QQQ)
50mM Sodium Glutamate + 50mM Arginine HCl (RRR)

FIG. 9

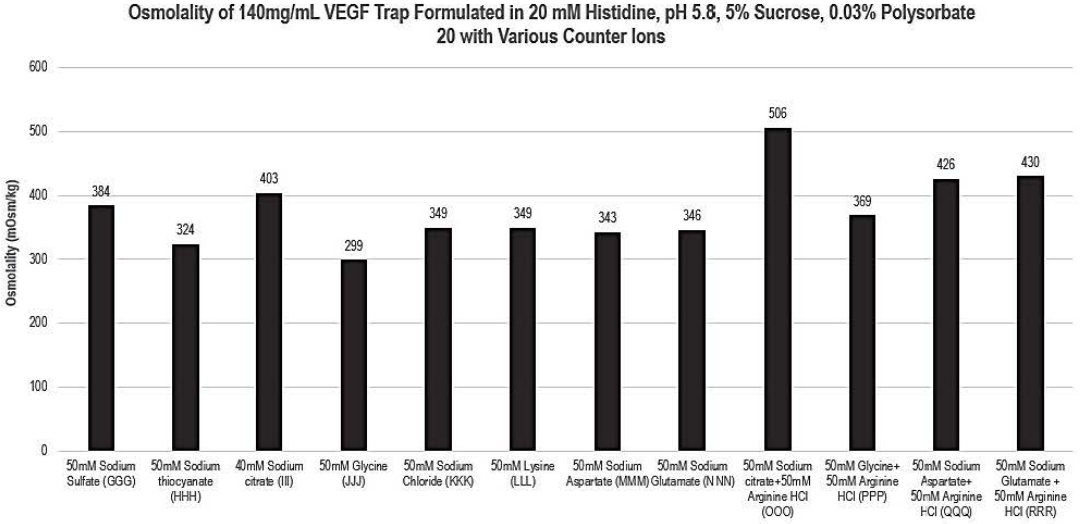

Osmolality of 140mg/mL VEGF Trap Formulated in 20 mM Histidine, pH 5.8, 5% Sucrose, 0.03% Polysorbate 20 with Various Counter Ions
Osmolality (mOsm/kg)
600
500
400
300
200
100
0
384
324
403
299
349
349
343
346
506
369
426
430
50mM Sodium Sulfate (GGG)
50mM Sodium thiocyanate (HHH)
40mM Sodium citrate (III)
50mM Glycine (JJJ)
50mM Sodium Chloride (KKK)
50mM Lysine (LLL)
50mM Sodium Aspartate (MMM)
50mM Sodium Glutamate (NNN)
50mM Sodium citrate+50mM Arginine HCl (OOO)
50mM Glycine+ 50mM Arginine HCl (PPP)
50mM Sodium Aspartate+ 50mM Arginine HCl (QQQ)
50mM Sodium Glutamate + 50mM Arginine HCl (RRR)

FIG. 10

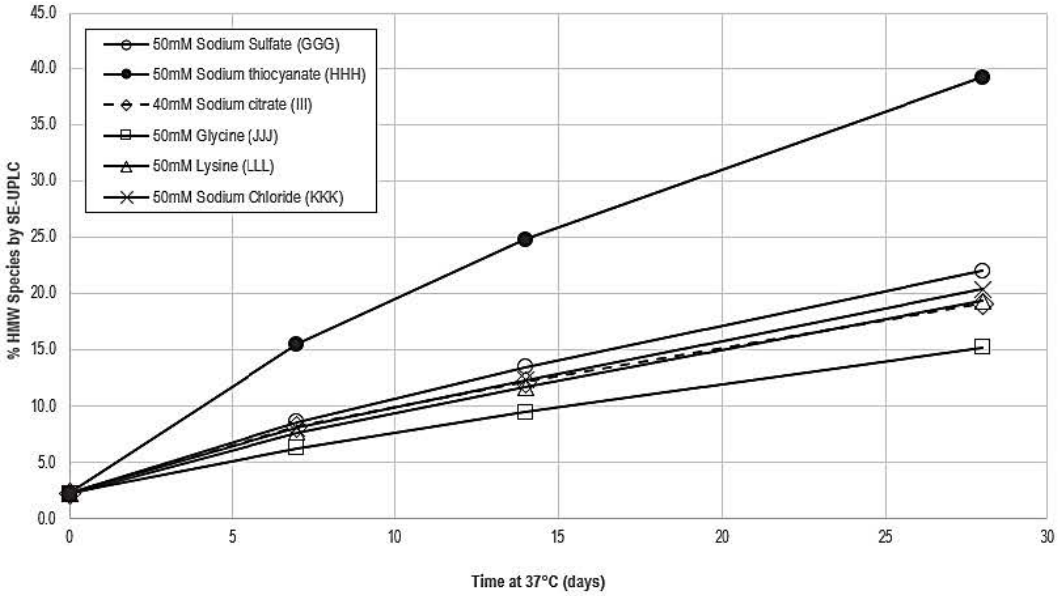


FIG. 11A

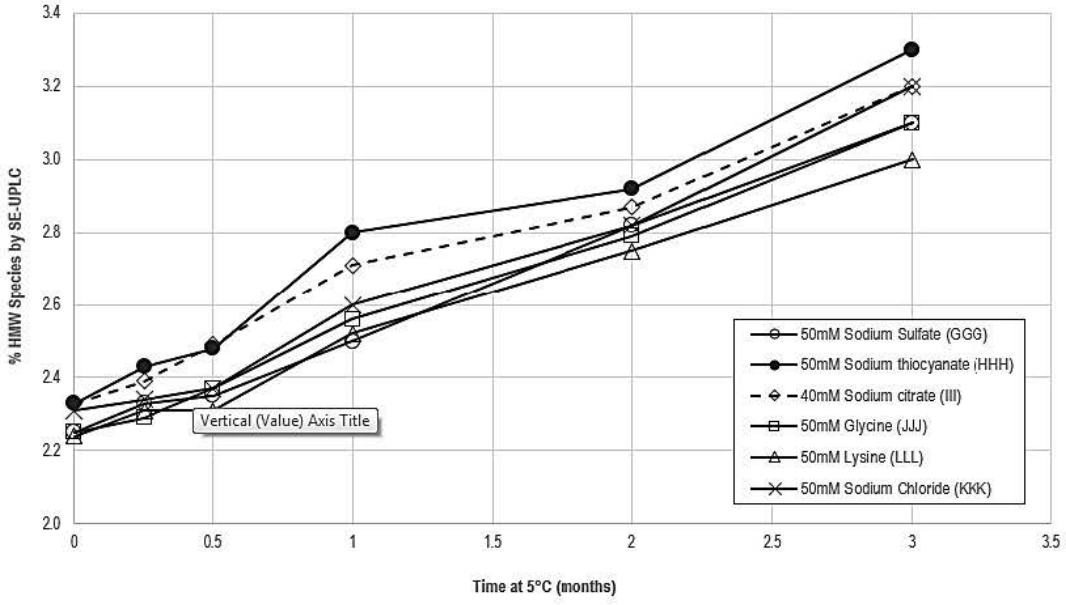


FIG. 11B

Formulations	Diffusion coefficient (cm2/sec)	Radius (nm)	% Pd
F1 (50mM Sodium Sulfate)	3.32E-07	7.4	15.3
F2(50mM Sodium thiocyanate)	2.98E-07	8.2	14.7
F3 (50mM Sodium citrate)	3.20E-07	7.7	16.3
F4 (50mM Glycine)	3.89E-07	6.3	18.9
F5 (50mM Sodium Chloride)	3.24E-07	7.6	13.8
F6 (50mM Lysine)	3.17E-07	7.7	13.5
F7 (50mM Sodium Aspartate)	3.32E-07	7.4	18.2
F8 (50mM Sodium Glutamate)	3.32E-07	7.4	15.0
F9 (50mM Sodium citrate+50mM Arginine HCl)	3.31E-07	7.4	14.4
F10 (50mM Glycine+ 50mM Arginine HCl)	3.31E-07	7.4	14.3
F11 (50mM Sodium Aspartate+ 50mM Arginine HCl)	3.24E-07	7.6	14.8
F12 (50mM Sodium Glutamate + 50mM Arginine HCl)	3.22E-07	7.6	13.3

FIG. 12

Regeneron Ex. 2001
Alvotech v. Regeneron
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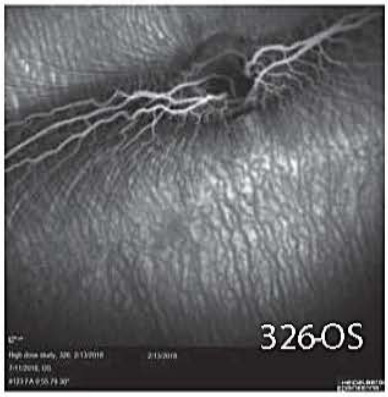


FIG. 13A



FIG. 13B

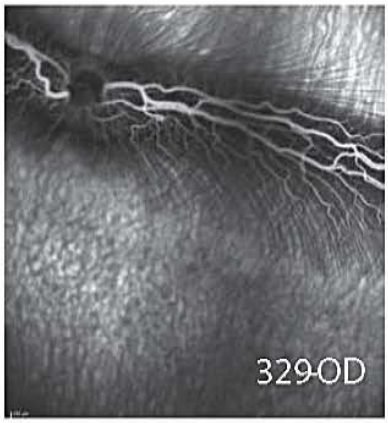


FIG. 13C

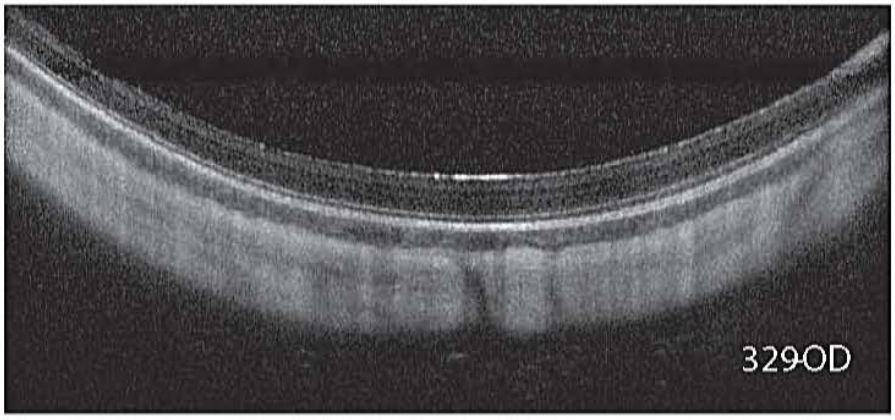


FIG. 13D

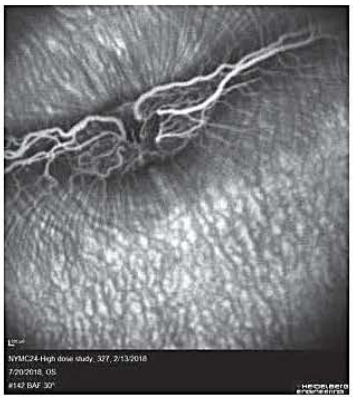


FIG. 14A



FIG. 14B

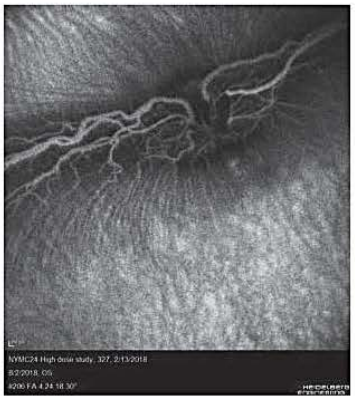


FIG. 14C

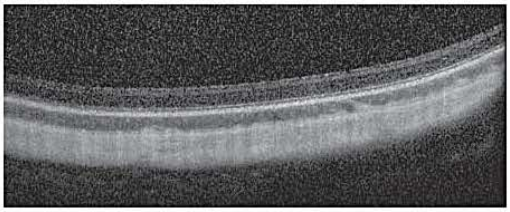


FIG. 14D

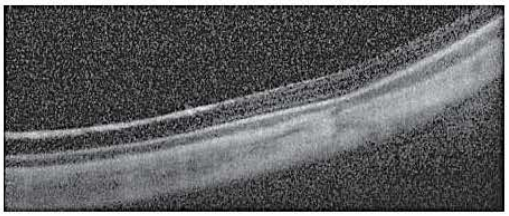


FIG. 14E

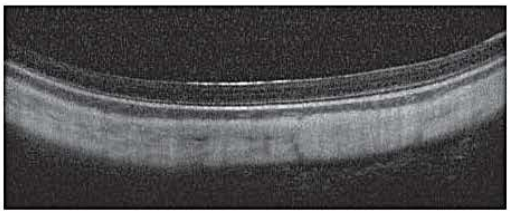


FIG. 14F

FA



FIG. 15A

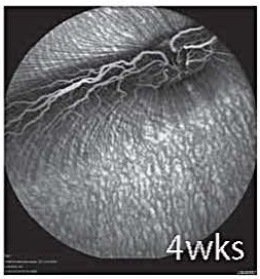


FIG. 15B

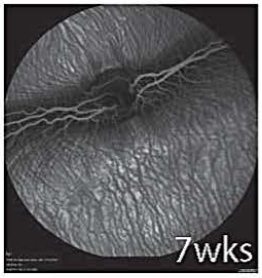


FIG. 15C

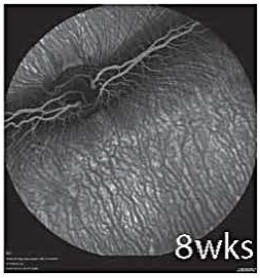


FIG. 15D

OCT

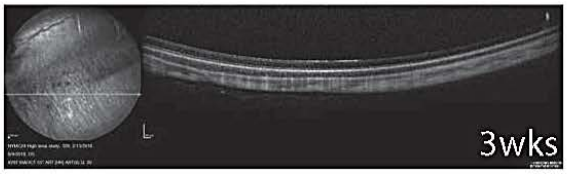


FIG. 15E



FIG. 15F

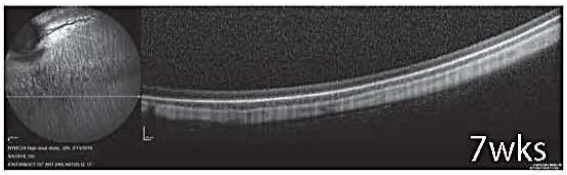


FIG. 15G

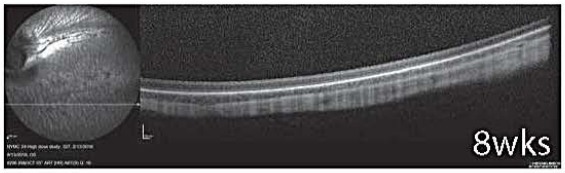


FIG. 15H



FIG. 16A

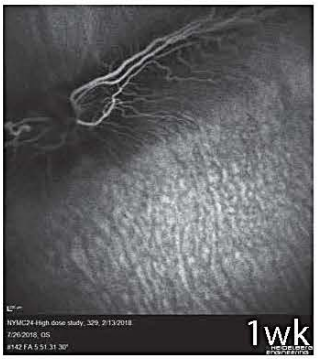


FIG. 16B

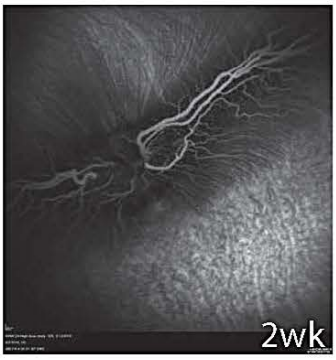


FIG. 16C



FIG. 16D

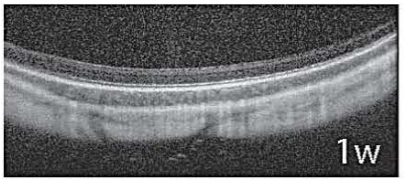


FIG. 16E



FIG. 16F

FA



FIG. 17A



FIG. 17B

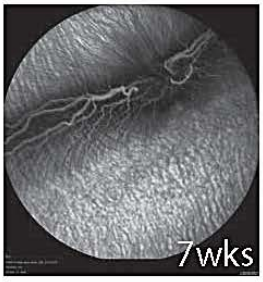


FIG. 17C



FIG. 17D

OCT



FIG. 17E

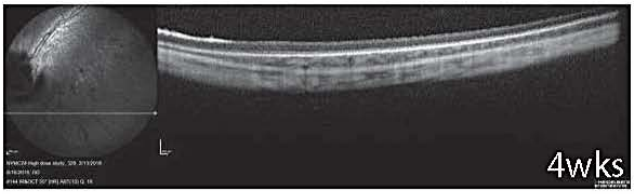


FIG. 17F

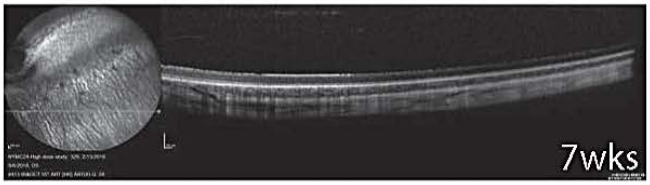


FIG. 17G

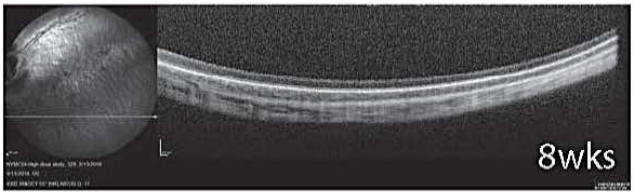


FIG. 17H

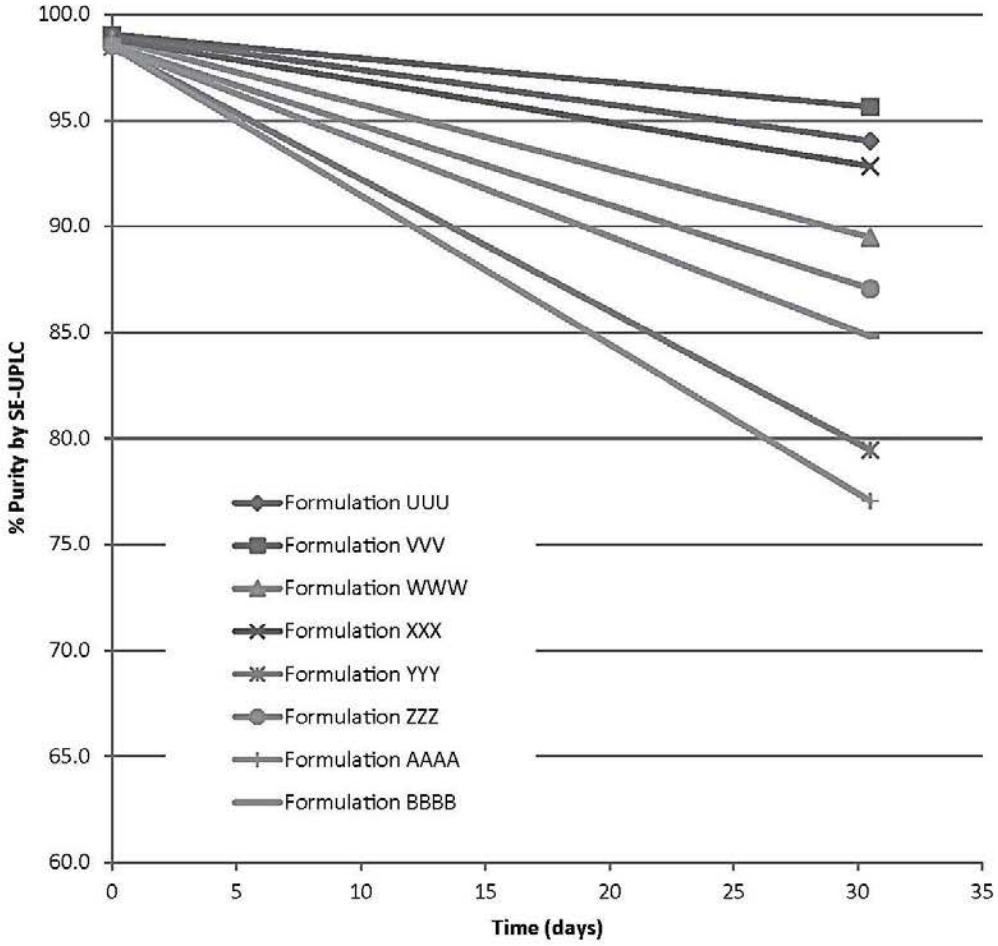

100.0
95.0
90.0
85.0
80.0
75.0
70.0
65.0
60.0
% Purity by SE-UPLC
0
5
10
15
20
25
30
35
Time (days)
Formulation UUU
Formulation VVV
Formulation WWW
Formulation XXX
Formulation YYY
Formulation ZZZ
Formulation AAAA
Formulation BBBB

FIG. 18A

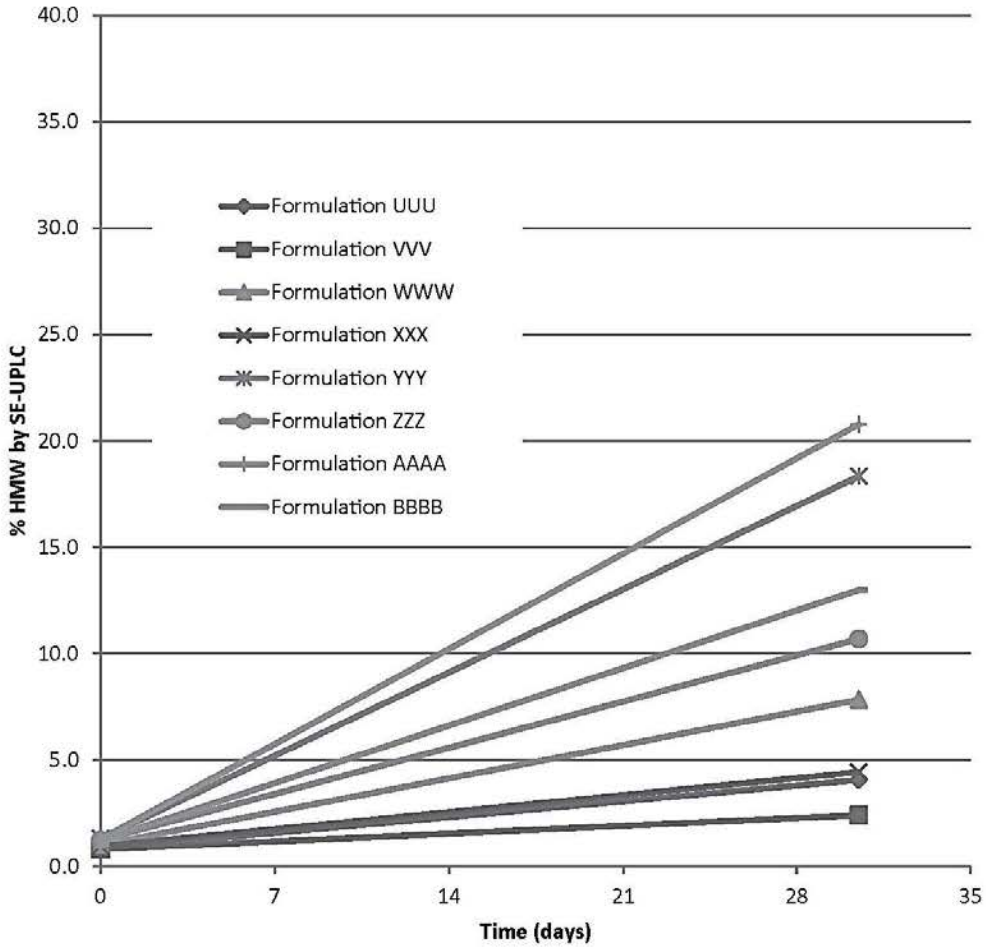

40.0
35.0
30.0
25.0
20.0
15.0
10.0
5.0
0.0
% HMW by SE-UPLC
0
7
14
21
28
35
Time (days)
Formulation UUU
Formulation VVV
Formulation WWW
Formulation XXX
Formulation YYY
Formulation ZZZ
Formulation AAAA
Formulation BBBB

FIG. 18B

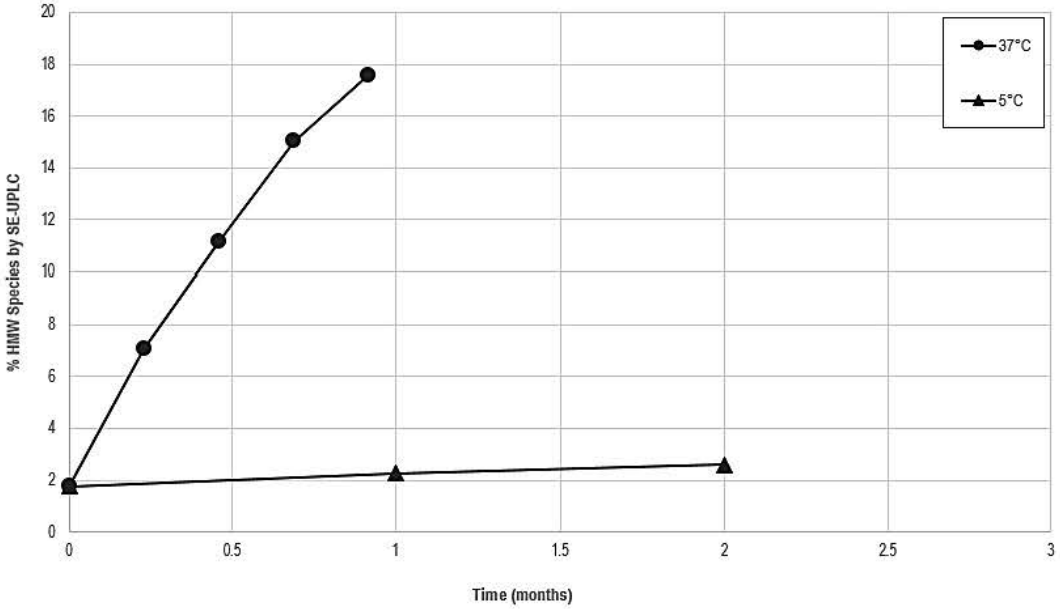


FIG. 19A

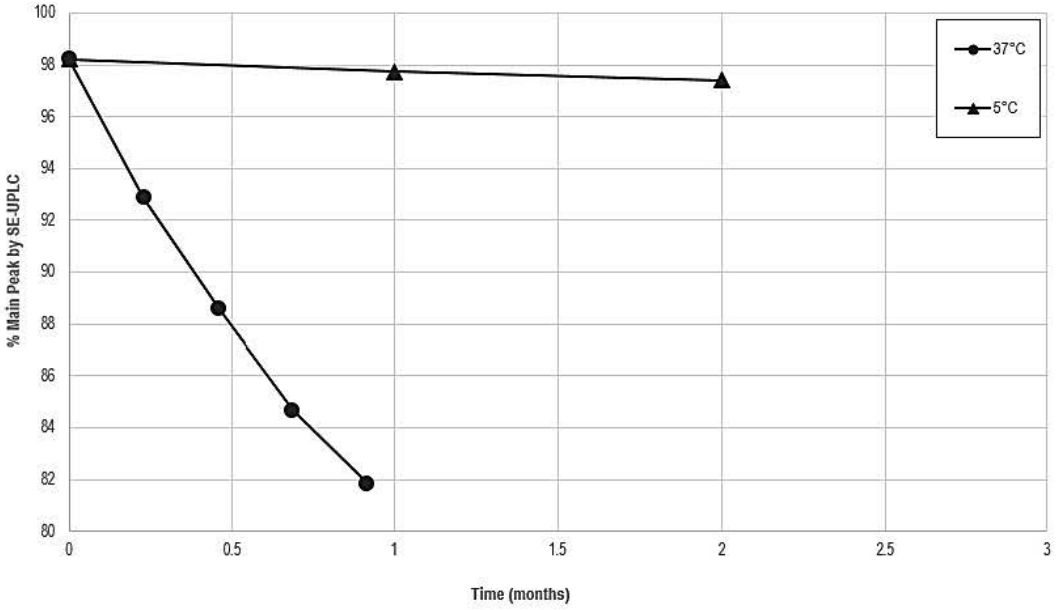


FIG. 19B

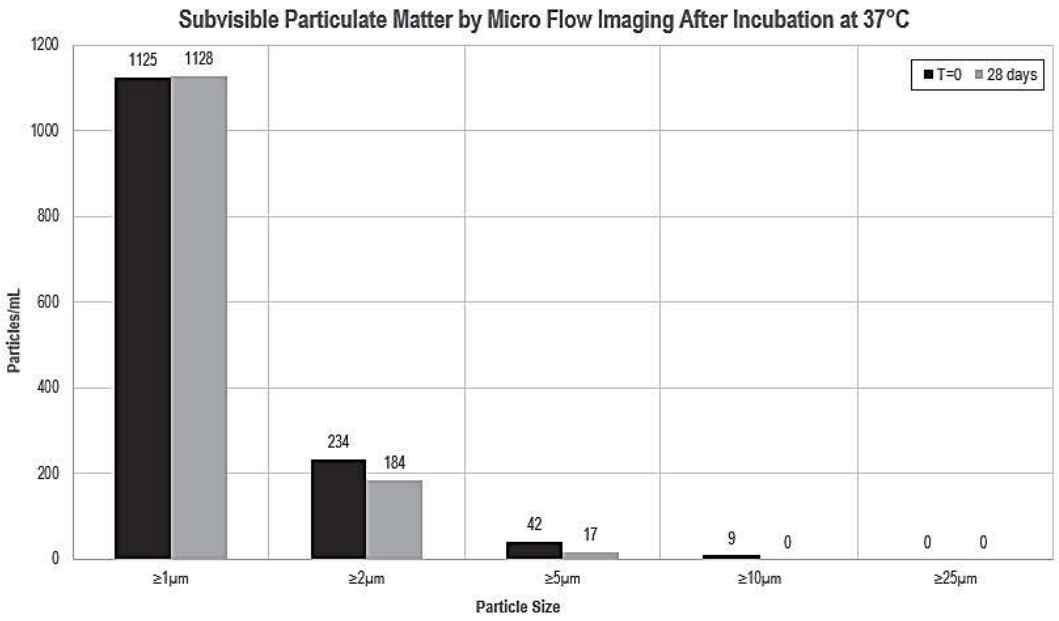


FIG. 19C

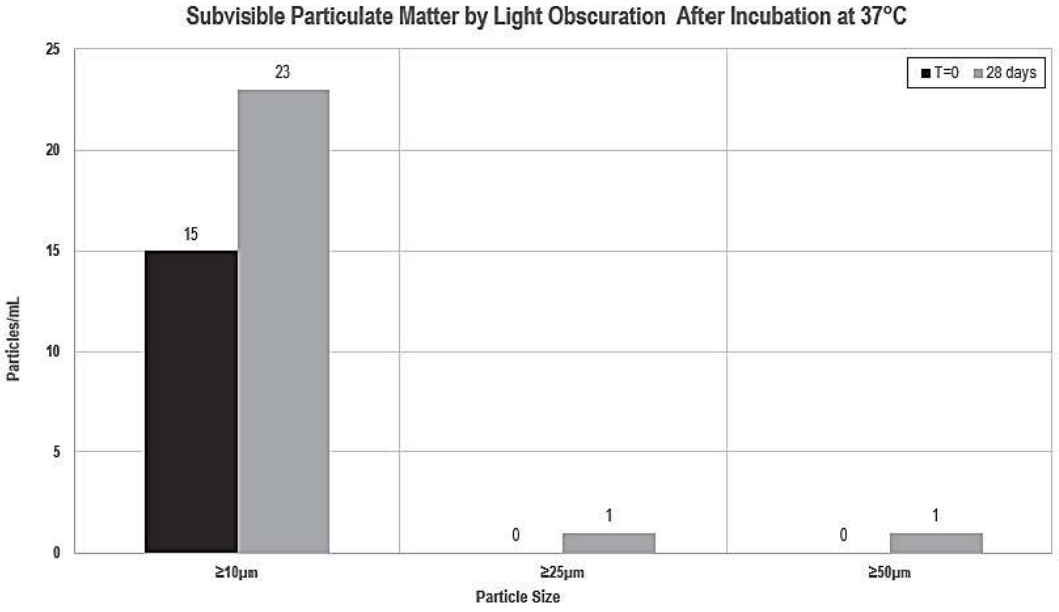


FIG. 19D

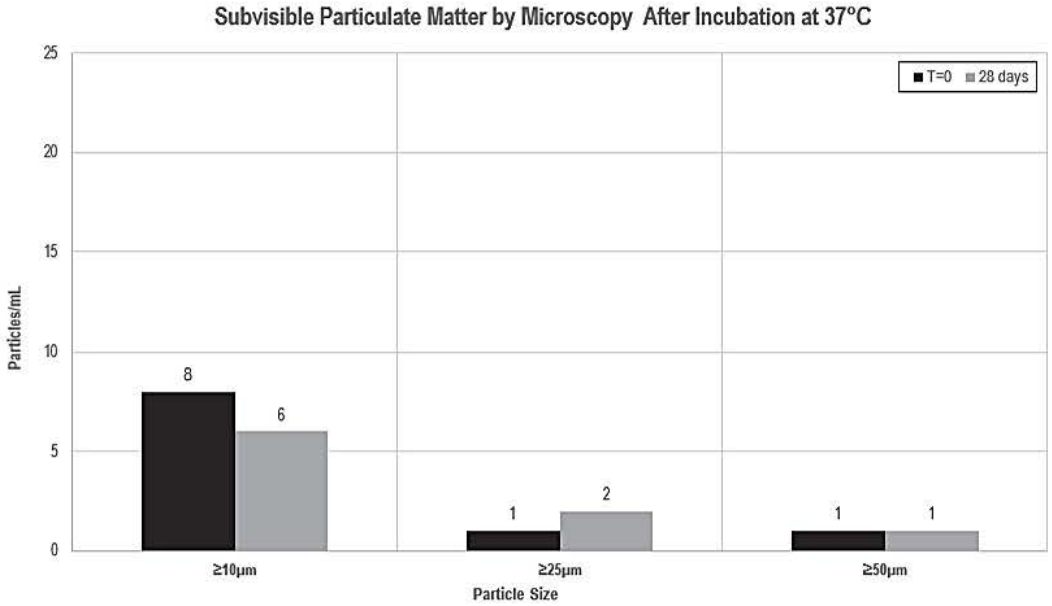

Subvisible Particulate Matter by Microscopy After Incubation at 37°C
T=0
28 days
Particles/mL
25
20
15
10
5
0
8
6
1
2
1
1
≥10µm
≥25µm
≥50µm
Particle Size

FIG. 19E

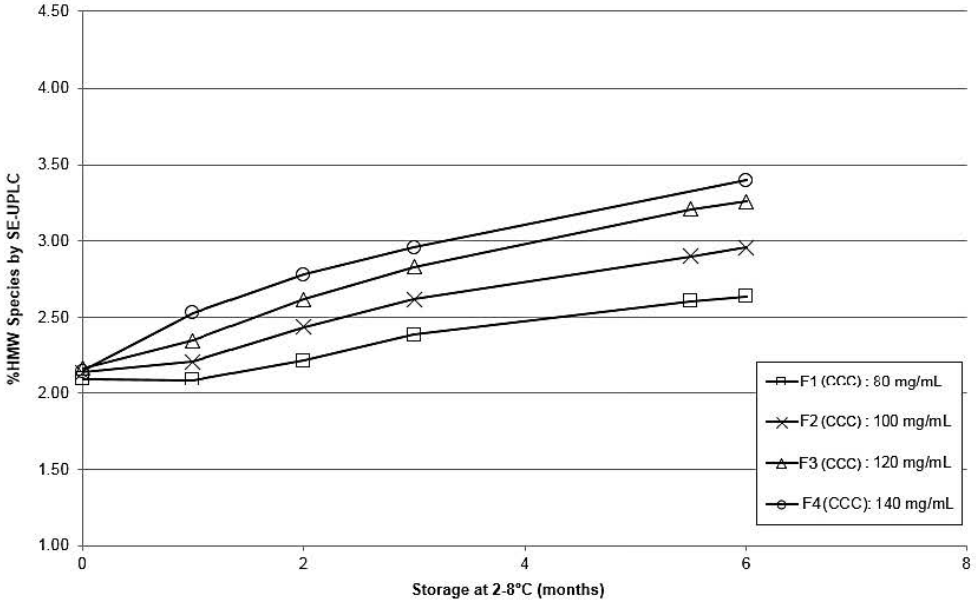

4.50
4.00
3.50
3.00
2.50
2.00
1.50
1.00
%HMW Species by SE-UPLC
0
2
4
6
8
Storage at 2-8°C (months)
F1 (CCC) : 80 mg/mL
F2 (CCC) : 100 mg/mL
F3 (CCC) : 120 mg/mL
F4 (CCC): 140 mg/mL

FIG. 20A

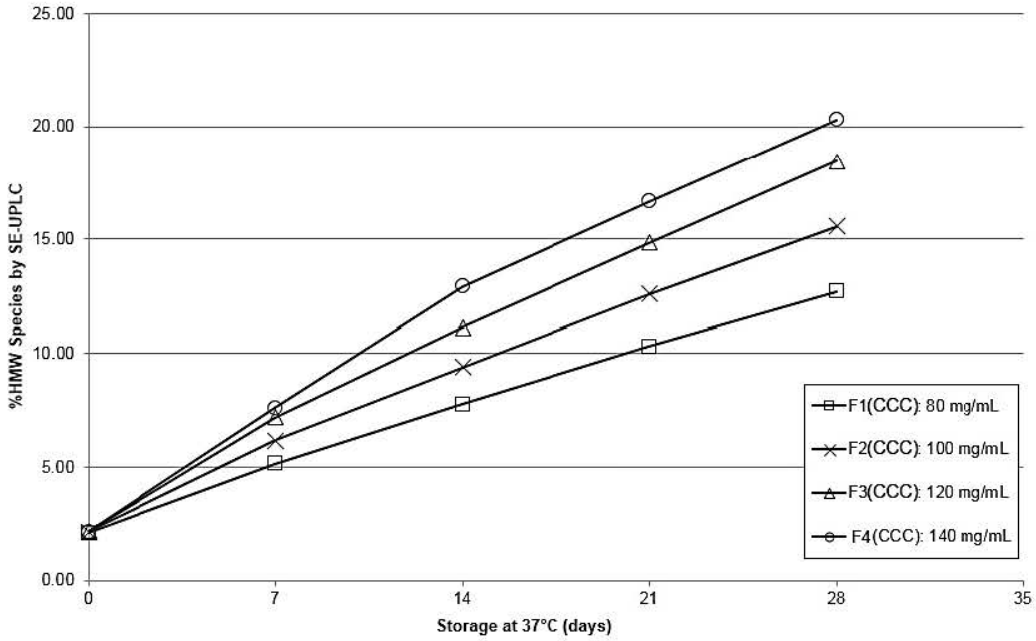

25.00
20.00
15.00
10.00
5.00
0.00
%HMW Species by SE-UPLC
0
7
14
21
28
35
Storage at 37°C (days)
F1(CCC): 80 mg/mL
F2(CCC): 100 mg/mL
F3(CCC): 120 mg/mL
F4(CCC): 140 mg/mL

FIG. 20B

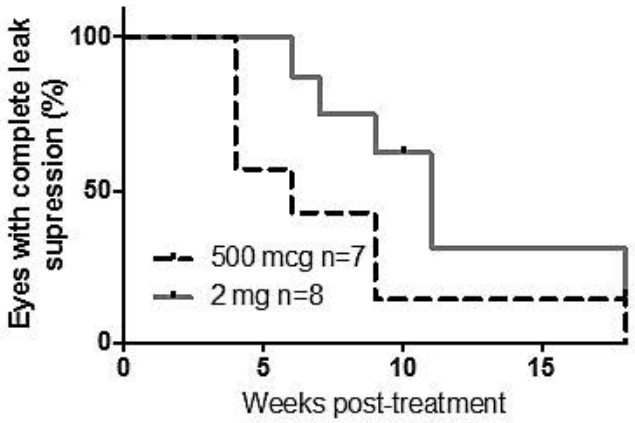

Eyes with complete leak supression (%)
100
50
0
0
5
10
15
Weeks post-treatment
500 mcg n=7
2 mg n=8

FIG. 21

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (not for submission under 37 CFR 1.99)		
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	Art Unit	Not Yet Assigned
	Confirmation Number	1061
	Examiner Name	Not Yet Assigned
	Attorney Docket Number	125984-266215 / 10430US02

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	101	6,171,586		01-09-2001	Lam et al.	
	102	6,267,958		07-31-2001	Andya et al.	
	233	6,358,530		03-19-2002	Eljamal et al.	
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	235	6,586,574		07-01-2003	Hansen	
	236	6,652,875		11-25-2003	Bannister	
	103	6,685,940		02-03-2004	Andya et al.	
	034	6,833,349		12-21-2004	Xia et al.	
	237	6,875,432		04-05-2005	Liu et al.	
	035	7,070,959		07-04-2006	Papadopoulos et al.	
	036	7,087,411		08-08-2006	Daly et al.	
	104	7,060,268		06-13-2006	Andya et al.	
	037	7,279,159		10-09-2007	Daly et al.	
	051	7,303,746		12-04-2007	Wiegand et al.	
	056	7,303,747		12-04-2007	Wiegand et al.	
	054	7,306,799		12-11-2007	Wiegand et al.	
	053	7,374,757		05-20-2008	Papadopoulos et al.	
	052	7,374,758		05-20-2008	Papadopoulos et al.	
	055	7,396,664		07-08-2008	Daly et al.	
	045	7,399,612		07-15-2008	Daly et al.	
	046	7,521,049		04-21-2009	Wiegand et al.	
	048	7,524,499		04-28-2009	Papadopoulos et al.	
	064	7,608,261		10-27-2009	Furfine et al.	
	050	7,635,474		12-22-2009	Daly et al.	
	005	7,648,702		01-19-2010	Gombotz et al.	
	105	7,682,609		03-23-2010	Andya et al.	
	047	7,704,500		04-27-2010	Papadopoulos et al.	
	239	7,956,160		06-07-2010	Krishnan et al.	
	065	7,807,164		10-05-2010	Furfine et al.	
	238	7,851,443		12-14-2010	Bissery et al.	
	040	7,964,377		06-21-2011	Papadopoulos et al.	

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	Attorney Docket Number	125984-266215 / 10430US02

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	049	8,029,791		10-04-2011	Papadopoulos et al.	
	042	8,084,234		12-27-2011	Papadopoulos et al.	
	066	8,092,803		01-10-2012	Furfine et al.	
	072	8,110,546		02-07-2012	Dix et al.	
	106	8,216,575		07-10-2012	Yu	
	107	8,372,396		02-12-2013	Andya et al.	
	043	8,343,737		01-01-2013	Papadopoulos et al.	
	073	8,404,638		03-26-2013	Dix et al.	
	067	8,481,046		07-09-2013	Furfine et al.	
	108	8,568,720		10-29-2013	Morichika et al.	
	027	8,623,395		01-07-2014	de Juan, Jr. et al.	
	044	8,647,842		02-11-2014	Papadopoulos et al.	
	074	8,710,004		04-29-2014	Dix et al.	
	068	8,802,107		08-12-2014	Furfine et al.	
	075	8,921,316		12-30-2014	Dix et al.	
	109	8,961,964		02-24-2015	Liu et al.	
	038	9,139,644		09-22-2015	Papadopoulos et al.	
	060	9,254,338		02-09-2016	Yancopoulos	
	110	9,283,273		03-15-2016	Andya et al.	
	069	9,340,594		05-17-2016	Furfine et al.	
	080	9,402,898		08-02-2016	Walsh et al.	
	076	9,416,167		08-16-2016	Dix et al.	
	018	9,474,803		10-25-2016	Park et al.	
	077	9,511,140		12-06-2016	Dix et al.	
	071	9,580,489		02-28-2017	Furfine et al.	
	078	9,636,400		05-02-2017	Dix et al.	
	061	9,669,069		06-06-2017	Yancopoulos	
	039	9,708,386		07-18-2017	Papadopoulos et al.	
	240	9,884,019		02-06-2018	Tchessalov et al.	
	070	9,914,763		03-13-2018	Furfine et al.	
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	Attorney Docket Number	125984-266215 / 10430US02

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	111	10,400,025		09-03-2019	Furfine et al.	
	112	10,406,226		09-10-2019	Dix et al.	
	242	10,413,513		09-17-2019	Fabio et al.	
	113	10,464,992		11-05-2019	Furfine et al.	
	243	10,501,523		12-10-2019	Chiron-Blondel et al.	
	244	10,576,128		03-03-2020	Sigl	
	309	10,610,600		04-07-2020	Soane et al.	
	114	10,689,438		06-23-2020	Zhang et al.	
	310	10,799,642		10-13-2020	Wong et al.	
	221	10,828,345		11-10-2020	Yancopoulos	
	222	10,857,205		12-08-2020	Yancopoulos	
	115	10,857,231		12-08-2020	Dix et al.	
	313	10,869,924		12-22-2020	Andrews et al.	
	223	10,888,601		01-12-2021	Yancopoulos	
	315	10,898,572		01-26-2021	Kameoka et al.	
	316	10,925,927		02-23-2021	Brockmeyer et al.	
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	377	11,066,458		07-20-2021	Furfine et al.	
	378	11,077,059		08-03-2021	Coffman et al	
	379	11,077,188		08-03-2021	Kauvar et al.	
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	383	11,123,411		09-21-2021	Borodic	
	384	11,135,266		10-05-2021	Kerwin et al.	

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	Attorney Docket Number	125984-266215 / 10430US02

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	033	2019-0160145		05-30-2019	IM et al.	
	280	2019-0275021		09-12-2019	JIANG et al.	
	281	2019-0290725		09-26-2019	VITTI et al.	
	282	2019-0298801		10-03-2019	Kerwin et al.	
	283	2019-0343918		11-14-2019	Graham et al.	
	284	2019-0358323		11-28-2019	LIU et al.	
	125	2020-0017572		01-16-2020	FURFINE et al.	
	285	2020-0046834		02-13-2020	Tang et al.	
	286	2020-0108064		04-09-2020	Horn et al.	
	319	2020-0114002		04-16-2020	Soane et al.	
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	Attorney Docket Number	125984-266215 / 10430US02

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	321	2020-0206028		07-02-2020	BOSCHETTI et al.	
	322	2020-0214888		07-09-2020	BRYANT et al.	
	323	2020-0230237		07-23-2020	KAUVAR et al.	
	324	2020-0237862		07-30-2020	SIGL	
	325	2020-0237997		07-30-2020	Brockmeyer et al.	
	326	2020-0246423		08-06-2020	Liu et al.	
	327	2020-0253875		08-13-2020	Coffman et al.	
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Name/Print	Lance A. Termes	Registration Number	43184

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Examiner Initial*	Cite No	Foreign Document Number[3]	Country Code[2]	Kind Code[4]	Publication Date	Name of Patentee or Applicant of cited Document	Pages, Columns, Lines where Relevant Passages or Relevant Figures Appear	T[5]

NON-PATENT LITERATURE DOCUMENTS			
Examiner Initial*	Cite No	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, pages(s), volume-issue number(s), publisher, city and/or country where published	T[5]
	411	AVERY, "What is the evidence for systemic effects of intravitreal anti-VEGF agents, and should we be concerned?," Open Access, Br J Ophthalmol, Volume (98) i7–i10, (2014). [doi:10.1136/bjophthalmol-2013-303844].	
	412	HANNA et al., "Three patients with injection of intravitreal vascular endothelial growth factor inhibitors and subsequent exacerbation of chronic proteinuria and hypertension," Clinical Kidney Journal, 2019, vol. 12, no. 1, 92–100. [doi: 10.1093/ckj/sfy060].	
	413	HAYMAN et al., "VEGF Inhibition, Hypertension, and Renal Toxicity," Curr Oncol Rep. 2012 August ; 14(4): 285–294. [doi:10.1007/s11912-012-0242-z].	
	414	RAISER et al., "The effect of intravitreal bevacizumab (avastin) administration on systemic hypertension," Macmillan Publishers Limited, Eye (2009) 23, 1714–1718. [doi:10.1038/eye.2008.360; published online 12 December 2008].	

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Alvotech v. Regeneron
PGR2025-00085
Page 217 of 531

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (not for submission under 37 CFR 1.99)		
	Application Number	17/384,070
	Filing Date	Jul-23-2021
	First Named Inventor	Kenneth S. Graham
	Art Unit	Not Yet Assigned
	Confirmation Number	1061
	Examiner Name	Not Yet Assigned
	Attorney Docket Number	125984-266215 / 10430US02

EXAMINER SIGNATURE			
Examiner Signature		Date Considered	

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[1] See Kind Codes of USPTO Patent Documents at www.USPTO.GOV or MPEP 901.04. [2] Enter office that issued the document, by the two-letter code (WIPO Standard ST.3). [3] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [4] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [5] Applicant is to place a check mark here if English language translation is attached.

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Alvotech v. Regeneron
PGR2025-00085
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	Attorney Docket Number	125984-266215 / 10430US02

CERTIFICATION STATEMENT

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OR

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☐ See attached certification statement.

☐ Fee set forth in 37 CFR 1.17 (p) has been submitted herewith.

☒ None

SIGNATURE

A signature of the applicant or representative is required in accordance with CFR 1.33, 10.18. Please see CFR 1.4(d) for the form of the signature.

Signature	/Lance A. Termes/	Date (YYYY-MM-DD)	2022-04-11
Name/Print	Lance A. Termes	Registration Number	43184

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Alvotech v. Regeneron
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U.S. PATENTS						
Examiner Initial*	Cite No	Patent Number	Kind Code[1]	Issue Date	Name of Patentee or Applicant of cited Document	Pages, Columns, Lines where Relevant Passages or Relevant Figures Appear
	415	11,160,881		11-02-2021	Rangaramanujam et al.	
	416	11,179,521		11-23-2021	Bryant et al.	
	417	11,185,635		11-30-2021	Bryant et al.	
	418	11,209,444		12-28-2021	Baldwin et al.	
	419	11,241,498		02-08-2022	Tang et al.	
	420	11,253,572		02-22-2022	Yancopoulos et al.	

U.S. PATENT APPLICATION PUBLICATIONS						
Examiner Initial*	Cite No	Publication Number	Kind Code[1]	Publication Date	Name of Patentee or Applicant of cited Document	Pages, Columns, Lines where Relevant Passages or Relevant Figures Appear
	421	2021-0340605		11-04-2021	Perlee et al.	
	422	2021-0353713		11-18-2021	WEXLER-COHEN et al.	
	423	2021-0361769		11-25-2021	KAUVAR et al.	
	424	2021-0369616		12-02-2021	TALLEY	
	425	2021-0371457		12-02-2021	Casteels et al.	
	426	2021-0379012		12-09-2021	Corson et al.	
	427	2022-0025032		01-27-2022	BIGELOW et al.	
	428	2022-0031952		02-03-2022	BRYANT et al.	
	429	2022-0054586		02-24-2022	KIM et al.	
	430	2022-0079876		03-17-2022	Blizzard et al.	
	431	2022-0087939		03-27-2022	PATEL et al.	
	432	2022-0111015		04-14-2022	CONSTABLE et al.	
	433	2022-0112278		04-14-2022	LI et al.	

FOREIGN PATENT DOCUMENTS								
Examiner Initial*	Cite No	Foreign Document Number[3]	Country Code[2]	Kind Code[4]	Publication Date	Name of Patentee or Applicant of cited Document	Pages, Columns, Lines where Relevant Passages or Relevant Figures Appear	T[5]
	434	3640643	EP	A1	12-22-2021	DREYMANN et al.		

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	435	21/252647	WO	A1	12-16-2021	ALKAHEST INC.		
	436	22/008699	WO	A1	01-13-2022	F. HOFFMANN-LA ROCHE AG		
	437	22/011323	WO	A1	01-13-2022	ICONIC THERAPEUTICS, INC.		
	438	22/013171	WO	A1	01-20-2022	MERCK PATENT GMBH		
	439	22/026510	WO	A1	02-03-2022	SEAGEN INC.		
	440	22/038038	WO	A2	02-24-2022	EPO EXPERIMENTELLE PHARMAKOLOGIE & ONKOLOGIE BERLIN-BUCH GMBH		
	441	22/056326	WO	A1	03-17-2022	ELIXIR MEDICAL CORPORATION		

NON-PATENT LITERATURE DOCUMENTS			
Examiner Initial*	Cite No	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, pages(s), volume-issue number(s), publisher, city and/or country where published	T[5]

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Examiner Signature		Date Considered	

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CERTIFICATION STATEMENT

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☐ See attached certification statement.

☐ Fee set forth in 37 CFR 1.17 (p) has been submitted herewith.

☒ None

SIGNATURE

A signature of the applicant or representative is required in accordance with CFR 1.33, 10.18. Please see CFR 1.4(d) for the form of the signature.

Signature	/Lance A. Termes/	Date (YYYY-MM-DD)	2022-05-16
Name/Print	Lance A. Termes	Registration Number	43184

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Alvotech v. Regeneron
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	Filing Date	Jul-23-2021
	First Named Inventor	Kenneth S. Graham
	Art Unit	OPAP
	Confirmation Number	1061
	Examiner Name	Not Yet Assigned
	Attorney Docket Number	125984-266215

U.S. PATENTS						
Examiner Initial*	Cite No	Patent Number	Kind Code[1]	Issue Date	Name of Patentee or Applicant of cited Document	Pages, Columns, Lines where Relevant Passages or Relevant Figures Appear
	446	11351256	B2	6-7-2022	Tang et al.	
	457	11459374	B2	10-4-2022	Tustian et al.	

U.S. PATENT APPLICATION PUBLICATIONS						
Examiner Initial*	Cite No	Publication Number	Kind Code[1]	Publication Date	Name of Patentee or Applicant of cited Document	Pages, Columns, Lines where Relevant Passages or Relevant Figures Appear
	443	2022-0143137		5-12-2022	Witt et al.	
	461	2022-0151920		5-19-2022	Shepard et al.	
	447	2022-0175883		6-9-2022	Brockmeyer et al.	
	448	2022-0226477		7-21-2022	Sloey et al.	
	458	2022-0227836		7-21-2022	Wang et al.	
	453	2022-0265740		8-25-2022	Blumenkranz et al.	
	452	2022-0273764		9-1-2022	Yancopoulos e tal.	
	456	2022-0306732		9-29-2022	Bakhle et al.	
	451	2022-0331430		10-20-2022	Rosenkranz et al.	

FOREIGN PATENT DOCUMENTS								
Examiner Initial*	Cite No	Foreign Document Number[3]	Country Code[2]	Kind Code[4]	Publication Date	Name of Patentee or Applicant of cited Document	Pages, Columns, Lines where Relevant Passages or Relevant Figures Appear	T[5]
	459	2022/089440	WO	A1	5-5-2022	Eluminex Biosciences (Suzhou) Limited		
	460	2022/094340	WO	A1	5-5-2022	Gemini Therapeutics Sub, Inc.		
	445	2022/101826	WO	A1	5-19-2022	Astrazeneca UK Limited		
	449	2022/175601	WO	A1	8-25-2022	Rebio Technologies OY		
	444	2022/195505	WO	A1	9-22-2022	Kashiv Biosciences, LLC		
	462	2022/201084	WO	A1	9-29-2022	Novartis AG		
	463	2022/217110	WO	A1	10-13-2022	Avirmax, Inc.		
	454	3503883	EP	B1	7-3-2019	Nat Institute of Biological Sciences Beijing		

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	455	3716992	EP	B1	8-10-2022	Regeneron Pharmaceuticals, Inc.		
	450	4070786	EP	A1	10-12-2022	Sichuan Honghe Biotechnology Co., Ltd.		

NON-PATENT LITERATURE DOCUMENTS			
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	442	NAOTO et al., "Arginine and lysine reduce the high viscosity of serum albumin solutions for pharmaceutical injection," Journal of bioscience and bioengineering, Volume 117 (No. 5): 539-543, (2013). [http://hdl.handle.net/2241/00121920], [doi: 10.1016/j.jbiosc.2013.10.016].	

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Examiner Signature		Date Considered	

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	Attorney Docket Number	125984-266215

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Signature	/Lance A. Termes/	Date (YYYY-MM-DD)	2022-11-16
Name/Print	Lance A. Termes	Registration Number	43184

Regeneron Ex. 2001
Alvotech v. Regeneron
PGR2025-00085
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UNITED STATES PATENT AND TRADEMARK OFFICE

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
17/384,070	07/23/2021	Kenneth S. Graham	125984-266215	1061

147803 7590 03/22/2023

Schwabe W&W, PC / Regeneron Pharmaceuticals, Inc.
PacWest Center
1211 SW Fifth Avenue, Suite 1900
Portland, OR 97204

EXAMINER	
LOCKARD, JON MCCLELLAND	

ART UNIT	PAPER NUMBER
1647	

NOTIFICATION DATE	DELIVERY MODE
03/22/2023	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

LTermes@schwabe.com
ipdocketing@schwabe.com

Office Action Summary	**Application No.** 17/384,070	**Applicant(s)** Graham et al.	
	Examiner JON M LOCKARD	**Art Unit** 1647	**AIA (FITF) Status** Yes

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTHS FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☑ Responsive to communication(s) filed on 23 July 2021.

☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on _____.

2a)☐ This action is **FINAL.** 2b) ☑ This action is non-final.

3)☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.

4)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims*

5) ☑ Claim(s) 30-32,35 and 39-52 is/are pending in the application.

5a) Of the above claim(s) _____ is/are withdrawn from consideration.

6) ☐ Claim(s) _____ is/are allowed.

7) ☑ Claim(s) 30-32,35 and 39-52 is/are rejected.

8) ☐ Claim(s) _____ is/are objected to.

9) ☐ Claim(s) _____ are subject to restriction and/or election requirement

* If any claims have been determined allowable, you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information, please see http://www.uspto.gov/patents/init_events/pph/index.jsp or send an inquiry to **PPHfeedback@uspto.gov.**

Application Papers

10)☑ The specification is objected to by the Examiner.

11)☑ The drawing(s) filed on 23 July 2021 is/are: a)☑ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

Certified copies:

a)☐ All b)☐ Some** c)☐ None of the:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

** See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)

2) ☑ Information Disclosure Statement(s) (PTO/SB/08a and/or PTO/SB/08b) Paper No(s)/Mail Date _____.

3) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date _____.

4) ☐ Other: _____.

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Notice of Pre-AIA or AIA Status

1. The present application, filed on or after March 16, 2013, is being examined under the first inventor to file provisions of the AIA.

DETAILED ACTION

Status of Application, Amendments, and/or Claims

2. The Preliminary Amendment filed on 23 July 2021 has been entered in full. Claims 1-29, 33-34 and 36-38 have been cancelled, claims 30-32 and 35 have been amended, and claims 39-52 have been added. Therefore, claims 30-32, 35 and 39-52 are pending and the subject of this Office Action.

Information Disclosure Statement

3. The information disclosure statements (IDS) filed 03 December 2021, 06 December 2021, 17 December 2021, 04 January 2022, 11 April 2022, 16 May 2022, and 16 November 2022 have been considered by the examiner.

Specification

4. The disclosure is objected to because of the following informalities:

5. An updated status of the parent nonprovisional applications should be included in the first sentence of the specification.

6. The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed.

Claim Objections

7. Claim 35 is objected to because of the following informalities: In line 4 of the claim, there should be a comma separating "(CRVO)" and "branch retinal vein". Appropriate correction is required.

Claim Rejections - 35 USC § 112

8. The following is a quotation of 35 U.S.C. 112(b):

> (b) CONCLUSION.—The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the inventor or a joint inventor regards as the invention.

The following is a quotation of 35 U.S.C. 112 (pre-AIA), second paragraph:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

9. Claims 30-32, 35 and 39-52 are rejected under 35 U.S.C. 112(b) or 35 U.S.C. 112 (pre-AIA), second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which the inventor or a joint inventor (or for applications subject to pre-AIA 35 U.S.C. 112, the applicant), regards as the invention.

10. Claim 30 is rejected as being indefinite for reciting the limitation "at least about" in line 3 of the claim. Since the specification does not provide any indication as to what range is covered by the term "at least about", the metes and bounds of the claim cannot be determined.

11. Claims 31-32, 35 and 39-52 are rejected for depending from an indefinite claim.

Claim Rejections - 35 USC § 112, 1st Paragraph (Written Description)

12. The following is a quotation of the first paragraph of 35 U.S.C. 112(a):

> (a) IN GENERAL.—The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such

> full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same, and shall set forth the best mode contemplated by the inventor or joint inventor of carrying out the invention.

The following is a quotation of the first paragraph of pre-AIA 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same, and shall set forth the best mode contemplated by the inventor of carrying out his invention.

13. Claims 30-32, 35 and 39-52 are rejected under 35 U.S.C. 112(a) or 35 U.S.C. 112 (pre-AIA), first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor or a joint inventor, or for pre-AIA the inventor(s), at the time the application was filed, had possession of the claimed invention.

14. The claims are drawn quite broadly to a method for treating an angiogenic eye disorder in a human patient in need thereof comprising administering an intravitreal injection of at least about 8 mg of a VEGF receptor fusion protein comprising two polypeptides that comprise an immunoglobulin-like (Ig) domain 2 of VEGFR1, an Ig domain 3 of VEGFR2 receptor, and a multimerizing domain.

15. The guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶1 "Written Description" Requirements make clear that the written description requirement for a claimed genus may be satisfied by disclosure of relevant, identifying characteristics, i.e., structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying

characteristics, sufficient to show the applicant was in possession of the genus (Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001, see especially page 1106 3rd column).

16. In the instant case, the claim recites a high concentration of a VEGF receptor fusion protein without any recitation of the elements of the composition that permit such a high concentration of the protein. The Specification discloses that L-arginine monohydrochloride increases the stability of high concentrations of the VEGF trap Aflibercept, a fusion protein that comprises Ig domain 2 of VEFGFR1, Ig domain 3 of VEGFR2, and an Fc (See Example 4 at pp. 55-56). Therefore, while the specification provides adequate written description for stable, high concentration formulations of a VEGF receptor fusion protein along with 5% sucrose, polysorbate, a histidine based buffer, and L-arginine, it does not provide adequate written description for the breadth of the formulation encompassed by the claims.

17. *Vas-Cath Inc. v. Mahurkar*, 19USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed*." (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See *Vas-Cath* at page 1116).

18. One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481 at 1483. In *Fiddes*, claims directed to mammalian FGF's were found to be unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence.

19. Therefore, only high concentration formulations of a VEGF receptor fusion protein along with 5% sucrose, polysorbate, a histidine-based buffer, and L-arginine, but not the full breadth of the claims, meet the written description provision of 35 U.S.C. §112, first paragraph. Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

Double Patenting

20. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory double patenting rejection is appropriate where the claims at issue are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

21. A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the reference application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope

of a joint research agreement. A terminal disclaimer must be signed in compliance with 37 CFR 1.321(b).

22. The USPTO internet Web site contains terminal disclaimer forms which may be used. Please visit http://www.uspto.gov/forms/. The filing date of the application will determine what form should be used. A web-based eTerminal Disclaimer may be filled out completely online using web-screens. An eTerminal Disclaimer that meets all requirements is auto-processed and approved immediately upon submission. For more information about eTerminal Disclaimers, refer to http://www.uspto.gov/patents/process/file/efs/guidance/eTD-info-I.jsp.

23. Claims 30-32, 35 and 39-52 are rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1-36 of U.S. Patent No. 11,103,552. Although the conflicting claims are not identical, as they recite different dosing schedules, they are not patentably distinct from each other because claims 1-26 of the '338 patent are drawn to a method for treating an angiogenic eye disorder, including age-related macular degeneration (wet), macular edema, central retinal vein occlusion (CRVO), branch retinal vein occlusion (BRVO), diabetic retinal edema, choroidal neovascularization, proliferative vitreoretinopathy, vascular retinopathy, diabetic retinopathy, and non-proliferative or proliferative diabetic retinopathy, comprising the intravitreal injection of a VEGF receptor fusion protein comprising two polypeptides that comprise an immunoglobulin-like (Ig) domain 2 of VEGFR1, Ig domain 3 of a VEGFR2 and a multimerizing component. The claims of the '552 patent also recite wherein the dosage of the VEGF receptor fusion protein is about 8 mg, and also recite wherein the VEGF receptor fusion protein is aflibercept.

Therefore, the claims are overlapping in scope.

Summary

24. No claim is allowed.

Advisory Information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to **Jon M. Lockard** whose telephone number is **(571) 272-2717**. The examiner can normally be reached on Monday through Friday, 8:00 AM to 4:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, **Joanne Hama**, can be reached on **(571) 272-2911**. The fax number for the organization where this application or proceeding is assigned is **571-273-8300**.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at **866-217-9197** (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/JON M LOCKARD/
Examiner, Art Unit 1647
March 16, 2023

Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
	17/384,070	Graham et al.
	Examiner	Art Unit
	JON M LOCKARD	1647

CPC - Searched*		
Symbol	Date	Examiner

CPC Combination Sets - Searched*		
Symbol	Date	Examiner

US Classification - Searched*			
Class	Subclass	Date	Examiner
NONE		03/16/2023	JML

* See search history printout included with this form or the SEARCH NOTES box below to determine the scope of the search.

Search Notes		
Search Notes	Date	Examiner
PE2E Search (USPAT, US-PGPUB, EPO, DERWENT): See attached search history.	03/16/2023	JML
STN (MEDLINE, SCISEARCH, EMBASE, BIOSIS): See attached search history.	03/16/2023	JML
PALM: Inventor search.	03/16/2023	JML

Interference Search			
US Class/CPC Symbol	US Subclass/CPC Group	Date	Examiner

Regeneron Ex. 2001
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Receipt date: 12/03/2021

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	Confirmation Number	1061
	Examiner Name	~~Not Yet Assigned~~ Jon Lockard
	Attorney Docket Number	125984-266215 / 10430US02

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	190	Regeneron Gets A Win With Eylea Approval In Diabetic Retinopathy Scrip Intelligence, May 13, 2019	
	189	Regeneron Pharmaceuticals Inc at J.P. Morgan 2019 Spring Biotech Conference Call – Final FD (Fair Disclosure) Wire, March 15, 2019	
	181	Regeneron Pharmaceuticals Inc at Morgan Stanley Healthcare Conference -Final FD (Fair Disclosure) Wire, September 12, 2018	
	184	Regeneron Pharmaceuticals Outlines Pipeline Progress, Shares 2019 Financial Guidance MT Newswires Live Briefs, January 7, 2019	
	183	Regeneron Provides Update on Commercial and Pipeline Progress at J.P. Morgan Healthcare Conference PR Newswire, January 7, 2019	
	185	Regeneron Provides Update on Commercial and Pipeline Progress at J.P. Morgan Healthcare Conference Plus Company Updates (PCU), January 8, 2019	
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	188	Regeneron Reports Fourth Quarter and Full Year 2018 Financial and Operating Results Plus Company Updates (PCU), February 7, 2019	
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	200	SEC Form 10-K, Regeneron, Dec. 31, 2018	
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	Art Unit	Not Yet Assigned
	Confirmation Number	1061
	Examiner Name	Not Yet Assigned
	Attorney Docket Number	125984-266215 / 10430US02

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EXAMINER SIGNATURE			
Examiner Signature	/JON M LOCKARD/	Date Considered	03/15/2023

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☒ None

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Signature	/Lance A. Termes/	Date (YYYY-MM-DD)	2021-12-03
Name/Print	Lance A. Termes	Registration Number	43184

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Regeneron Ex. 2001
Alvotech v. Regeneron
PGR2025-00085
Page 253 of 531

Receipt date: 05/16/2022

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	Art Unit	~~Not Yet Assigned~~ 1647
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	Examiner Name	~~Not Yet Assigned~~ Jon Lockard
	Attorney Docket Number	125984-266215 / 10430US02

U.S. PATENTS						
Examiner Initial*	Cite No	Patent Number	Kind Code[1]	Issue Date	Name of Patentee or Applicant of cited Document	Pages, Columns, Lines where Relevant Passages or Relevant Figures Appear
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	434	3640643	EP	A1	12-22-2021	DREYMANN et al.		

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	435	21/252647	WO	A1	12-16-2021	ALKAHEST INC.		
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	437	22/011323	WO	A1	01-13-2022	ICONIC THERAPEUTICS, INC.		
	438	22/013171	WO	A1	01-20-2022	MERCK PATENT GMBH		
	439	22/026510	WO	A1	02-03-2022	SEAGEN INC.		
	440	22/038038	WO	A2	02-24-2022	EPO EXPERIMENTELLE PHARMAKOLOGIE & ONKOLOGIE BERLIN-BUCH GMBH		
	441	22/056326	WO	A1	03-17-2022	ELIXIR MEDICAL CORPORATION		

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Name/Print	Lance A. Termes	Registration Number	43184

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Regeneron Ex. 2001
Alvotech v. Regeneron
PGR2025-00085
Page 256 of 531

PE2E SEARCH - Search History (Prior Art)

/J.L./

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	British Equivalents	Time Stamp
L1	7076	vegf ADJ trap	(US-PGPUB; USPAT; EPO; DERWENT)	OR	ON	ON	2023/03/16 01:06 PM
L2	8296	aflibercept	(US-PGPUB; USPAT; EPO; DERWENT)	OR	ON	ON	2023/03/16 01:06 PM
L3	737	eylea	(US-PGPUB; USPAT; EPO; DERWENT)	OR	ON	ON	2023/03/16 01:06 PM
L4	269	vegf ADJ trap-eye	(US-PGPUB; USPAT; EPO; DERWENT)	OR	ON	ON	2023/03/16 01:06 PM
L5	1290	(L1 L2 L3 L4) SAME formulation	(US-PGPUB; USPAT; EPO; DERWENT)	OR	ON	ON	2023/03/16 01:06 PM
L6	32	L5 SAME "high concentration"	(US-PGPUB; USPAT; EPO; DERWENT)	OR	ON	ON	2023/03/16 01:07 PM
L7	49	L5 SAME (8mg OR "8 mg")	(US-PGPUB; USPAT; EPO; DERWENT)	OR	ON	ON	2023/03/16 01:07 PM
L8	1	L5 AND "high concentration".clm.	(US-PGPUB; USPAT; EPO; DERWENT)	OR	ON	ON	2023/03/16 01:09 PM
L9	6	L5 AND (8mg OR "8 mg").clm.	(US-PGPUB; USPAT; EPO; DERWENT)	OR	ON	ON	2023/03/16 01:09 PM
L10	80	(graham-k$-s$ washawa-s$).in.	(US-PGPUB; USPAT; EPO; DERWENT)	OR	ON	ON	2023/03/16 01:10 PM
L11	16	L5 AND L10	(US-PGPUB; USPAT; EPO; DERWENT)	OR	ON	ON	2023/03/16 01:11 PM
L12	3	L6 SAME l-arginine	(US-PGPUB; USPAT; EPO; DERWENT)	OR	ON	ON	2023/03/16 02:08 PM
L13	0	L7 SAME l-arginine	(US-PGPUB; USPAT; EPO; DERWENT)	OR	ON	ON	2023/03/16 02:08 PM
L14	5	L5 SAME l-arginine	(US-PGPUB; USPAT; EPO; DERWENT)	OR	ON	ON	2023/03/16 02:09 PM

PE2E SEARCH - Search History (Interference)

There are no Interference searches to show.

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/J.L/	406	CHANG et al., "Ziv-Aflibercept as a Possible Alternative to Aflibercept," Medical Retina, Retina Today, Pages 67-68, (2014).	

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Page 260 of 531

Bibliographic Data

Application No: 17/384,070

Foreign Priority claimed: ○ Yes ◉ No

35 USC 119 (a-d) conditions met: ☐ Yes ☐ No ☐ Met After Allowance

Verified and Acknowledged: /JON M LOCKARD/ Examiner's Signature | Initials

Title: High Concentration VEGF Receptor Fusion Protein Containing Formulations

FILING or 371(c) DATE	CLASS	GROUP ART UNIT	ATTORNEY DOCKET NO.
07/23/2021	424	1647	125984-266215
RULE			

APPLICANTS

Regeneron Pharmaceuticals, Inc., Tarrytown, NY,

INVENTORS

Kenneth S. Graham, Pleasant Valley, NY, UNITED STATES

Saurabh WADHWA, Nanuet, NY, UNITED STATES

CONTINUING DATA

This application is a CON of 16409631 05/10/2019 PAT 11103552

16409631 has PRO of 62813882 03/05/2019

16409631 has PRO of 62769876 11/20/2018

16409631 has PRO of 62752127 10/29/2018

16409631 has PRO of 62669506 05/10/2018

FOREIGN APPLICATIONS

IF REQUIRED, FOREIGN LICENSE GRANTED**

08/09/2021

STATE OR COUNTRY

UNITED STATES

ADDRESS

Schwabe W&W, PC / Regeneron Pharmaceuticals, Inc.
PacWest Center
1211 SW Fifth Avenue, Suite 1900
Portland, OR 97204
UNITED STATES

FILING FEE RECEIVED

$1,820

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	446	11351256	B2	6-7-2022	Tang et al.	
	457	11459374	B2	10-4-2022	Tustian et al.	

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Examiner Initial*	Cite No	Publication Number	Kind Code[1]	Publication Date	Name of Patentee or Applicant of cited Document	Pages, Columns, Lines where Relevant Passages or Relevant Figures Appear
	443	2022-0143137		5-12-2022	Witt et al.	
	461	2022-0151920		5-19-2022	Shepard et al.	
	447	2022-0175883		6-9-2022	Brockmeyer et al.	
	448	2022-0226477		7-21-2022	Sloey et al.	
	458	2022-0227836		7-21-2022	Wang et al.	
	453	2022-0265740		8-25-2022	Blumenkranz et al.	
	452	2022-0273764		9-1-2022	Yancopoulos e tal.	
	456	2022-0306732		9-29-2022	Bakhle et al.	
	451	2022-0331430		10-20-2022	Rosenkranz et al.	

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Examiner Initial*	Cite No	Foreign Document Number[3]	Country Code[2]	Kind Code[4]	Publication Date	Name of Patentee or Applicant of cited Document	Pages, Columns, Lines where Relevant Passages or Relevant Figures Appear	T[5]
	459	2022/089440	WO	A1	5-5-2022	Eluminex Biosciences (Suzhou) Limited		
	460	2022/094340	WO	A1	5-5-2022	Gemini Therapeutics Sub, Inc.		
	445	2022/101826	WO	A1	5-19-2022	Astrazeneca UK Limited		
	449	2022/175601	WO	A1	8-25-2022	Rebio Technologies OY		
	444	2022/195505	WO	A1	9-22-2022	Kashiv Biosciences, LLC		
	462	2022/201084	WO	A1	9-29-2022	Novartis AG		
	463	2022/217110	WO	A1	10-13-2022	Avirmax, Inc.		
	454	3503883	EP	B1	7-3-2019	Nat Institute of Biological Sciences Beijing		

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /J.L/

Receipt date: 11/16/2022

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (not for submission under 37 CFR 1.99)		
	Application Number	17/384,070
	Filing Date	Jul-23-2021
	First Named Inventor	Kenneth S. Graham
	Art Unit	OPAP
	Confirmation Number	1061
	Examiner Name	Not Yet Assigned
	Attorney Docket Number	125984-266215

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	455	3716992	EP	B1	8-10-2022	Regeneron Pharmaceuticals, Inc.		
	450	4070786	EP	A1	10-12-2022	Sichuan Honghe Biotechnology Co., Ltd.		

NON-PATENT LITERATURE DOCUMENTS			
Examiner Initial*	Cite No	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, pages(s), volume-issue number(s), publisher, city and/or country where published	T[5]
	442	NAOTO et al., "Arginine and lysine reduce the high viscosity of serum albumin solutions for pharmaceutical injection," Journal of bioscience and bioengineering, Volume 117 (No. 5): 539-543, (2013). [http://hdl.handle.net/2241/00121920], [doi: 10.1016/j.jbiosc.2013.10.016].	

EXAMINER SIGNATURE			
Examiner Signature	/JON M LOCKARD/	Date Considered	03/15/2023

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☐ See attached certification statement.

☐ Fee set forth in 37 CFR 1.17 (p) has been submitted herewith.

☒ None

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Signature	/Lance A. Termes/	Date (YYYY-MM-DD)	2022-11-16
Name/Print	Lance A. Termes	Registration Number	43184

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Receipt date: 01/04/2022

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (not for submission under 37 CFR 1.99)		
	Application Number	17/384,070
	Filing Date	Jul-23-2021
	First Named Inventor	Kenneth S. Graham
	Art Unit	~~Not Yet Assigned~~ 1647
	Confirmation Number	1061
	Examiner Name	~~Not Yet Assigned~~ Jon Lockard
	Attorney Docket Number	125984-266215 / 10430US02

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	407	COORS et al., "Polysorbate 80 in medical products and nonimmunologic anaphylactoid reactions," Ann Allergy Asthma Immunol, Volume (95): 593-599, (2005).	
	408	EMA et al., "Evaluation of Developmentl neurotoxicity of polysorbate 80 in rats," Science Direct, Reproductive Toxicology, Volume (25): 89-99, (2008). [DOI: 10.1016/j.reprotox.2007.08.003]	
	409	GAJDOVA et al., "Delayed Effects of neonatal exposure to tween 80 on female reproductive organs in rats," Fd Chem.Toxic, Volume (31) No. (3): 183-190, (1993).	

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Alvotech v. Regeneron
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	410	THACKABERRY et al., "Comprehensive Investigation of Hydroxypropyl Methylcellulose, Propylene Glycol, Polysorbate 80, and Hydroxypropyl-Beta-Cyclodextrin for use in General Toxicology Studies," TOXICOLOGICAL SCIENCES, Volume (117) No. (2): 485-492, (2010). [Downloaded from https://academic.oup.com/toxsci/article/117/2/485/1641380 by Williams Connolly user on 17 December 2021].	

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Examiner Signature	/JON M LOCKARD/	Date Considered	03/15/2023

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☒ None

SIGNATURE

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Signature	/Lance A. Termes/	Date (YYYY-MM-DD)	2022-01-04
Name/Print	Lance A. Termes	Registration Number	43184

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Regeneron Ex. 2001
Alvotech v. Regeneron
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Page 267 of 531

Inventor Information for 17/384070

/J.L./

Inventor Name	City	State/Country
GRAHAM, KENNETH S.	PLEASANT VALLEY	NEW YORK
WADHWA, SAURABH	NANUET	NEW YORK

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/J.L./

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     (FILE 'HOME' ENTERED AT 14:11:25 ON 16 MAR 2023)

     FILE 'MEDLINE, SCISEARCH, EMBASE, BIOSIS' ENTERED AT 14:11:37 ON 16 MAR
     2023
L1          1917 S VEGF (W) TRAP
L2         18711 S AFLIBERCEPT
L3          1702 S EYLEA
L4           308 S VEGF (W) TRAP-EYE
L5           144 S (L1 OR L2 OR L3 OR L4) (P) FORMULATION
L6             2 S L5 AND "HIGH CONCENTRATION"
L7             2 S L5 AND (8MG OR "8 MG")
L8             4 S L6 OR L7
L9             4 DUP REM L8 (0 DUPLICATES REMOVED)
                 E GRAHAM K S/AU
L10          270 S E3-E5 OR E136 OR E142
                 E WADHWA S/AU
L11          510 S E3 OR E42
L12            1 S L5 AND (L10 OR L11)
L13           33 S (L1 OR L2 OR L3 OR L4) (P) ("HIGH CONCENTRATION" OR 8MG OR
L14           22 DUP REM L13 (11 DUPLICATES REMOVED)
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Receipt date: 12/06/2021

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (not for submission under 37 CFR 1.99)		
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	Filing Date	Jul-23-2021
	First Named Inventor	Kenneth S. Graham
	Art Unit	~~Not Yet Assigned~~ 1647
	Confirmation Number	1061
	Examiner Name	~~Not Yet Assigned~~ Jon Lockard
	Attorney Docket Number	125984-266215 / 10430US02

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	402	Fauser S, Schwabecker V, Muether PS. Suppression of intraocular vascular endothelial growth factor during aflibercept treatment of age-related macular degeneration. Am J Ophthalmol. 2014;158:532-536.	
	403	Framme C, Eter N, Hamacher T, et al. Aflibercept for patients with neovascular age-related macular degeneration in routine clinical practice in Germany: Twelve month outcomes of PERSEUS. Ophthalmology Retina. 2018;2:539-549.	
	404	Khurana RN, Rahimy E, Joseph WA, et al. Extended (every 12 weeks or longer) dosing interval with intravitreal aflibercept and ranibizumab in neovascular age-related macular degeneration: post hoc analysis of VIEW trials. Am J Ophthalmol. 2019;200:161-168.	

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	405	Krohne TU, Liu Z, Holz FG, Meyer CH. Intraocular pharmacokinetics of ranibizumab following a single intravitreal injection in humans. Am J Ophthalmol. 2012;154:682-686	

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Examiner Signature	/JON M LOCKARD/	Date Considered	03/15/2023

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Signature	/Lance A. Termes/	Date (YYYY-MM-DD)	2021-12-06
Name/Print	Lance A. Termes	Registration Number	43184

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Regeneron Ex. 2001
Alvotech v. Regeneron
PGR2025-00085
Page 272 of 531

Receipt date: 04/11/2022

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	411	AVERY, "What is the evidence for systemic effects of intravitreal anti-VEGF agents, and should we be concerned?," Open Access, Br J Ophthalmol, Volume (98) i7–i10, (2014). [doi:10.1136/bjophthalmol-2013-303844].	
	412	HANNA et al., "Three patients with injection of intravitreal vascular endothelial growth factor inhibitors and subsequent exacerbation of chronic proteinuria and hypertension," Clinical Kidney Journal, 2019, vol. 12, no. 1, 92–100. [doi: 10.1093/ckj/sfy060].	
	413	HAYMAN et al., "VEGF Inhibition, Hypertension, and Renal Toxicity," Curr Oncol Rep. 2012 August ; 14(4): 285–294. [doi:10.1007/s11912-012-0242-z].	
	414	RAISER et al., "The effect of intravitreal bevacizumab (avastin) administration on systemic hypertension," Macmillan Publishers Limited, Eye (2009) 23, 1714–1718. [doi:10.1038/eye.2008.360; published online 12 December 2008].	

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Document Description: Power of Attorney

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I hereby revoke all previous powers of attorney given in the application identified in either the attached transmittal letter or the boxes below.

Application Number	Filing Date
17/384,070	July 23, 2021

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I am the Applicant (if the Applicant is a juristic entity, list the Applicant name in the box):

Regeneron Pharmaceuticals, Inc.

☐ Inventor or Joint Inventor (title not required below)

☐ Legal Representative of a Deceased or Legally Incapacitated Inventor (title not required below)

☑ Assignee or Person to Whom the Inventor is Under an Obligation to Assign (provide signer's title if applicant is a juristic entity)

☐ Person Who Otherwise Shows Sufficient Proprietary Interest (e.g., a petition under 37 CFR 1.46(b)(2) was granted in the application or is concurrently being filed with this document) (provide signer's title if applicant is a juristic entity)

SIGNATURE of Applicant for Patent

The undersigned (whose title is supplied below) is authorized to act on behalf of the applicant (e.g., where the applicant is a juristic entity).

Signature	/Frank R. Cottingham/	Date (Optional)	
Name	Frank R. Cottingham		
Title	Vice President Intellectual Property, Regeneron Pharmaceuticals, Inc.		

NOTE: Signature - This form must be signed by the applicant in accordance with 37 CFR 1.33. See 37 CFR 1.4 for signature requirements and certifications. If more than one applicant, use multiple forms.

☑ Total of 1 forms are submitted.

This collection of information is required by 37 CFR 1.131, 1.32, and 1.33. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.11 and 1.14. This collection is estimated to take 3 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

Electronic Acknowledgement Receipt

EFS ID:	47728100
Application Number:	17384070
International Application Number:	
Confirmation Number:	1061
Title of Invention:	High Concentration VEGF Receptor Fusion Protein Containing Formulations
First Named Inventor/Applicant Name:	Kenneth S. Graham
Customer Number:	147803
Filer:	Lance A. Termes
Filer Authorized By:	
Attorney Docket Number:	125984-266215
Receipt Date:	22-MAR-2023
Filing Date:	23-JUL-2021
Time Stamp:	18:06:14
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	no

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Power of Attorney	10430US02_POA.pdf	1123774 bf312ce998e73c565d305d02b44db156688c5c30	no	1
Warnings:					

Information:	
Total Files Size (in bytes):	1123774

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (not for submission under 37 CFR 1.99)		
	Application Number	17/384,070
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	Art Unit	1647
	Confirmation Number	1061
	Examiner Name	Lockard, Jon McClelland
	Attorney Docket Number	125984-266215

U.S. PATENTS						
Examiner Initial*	Cite No	Patent Number	Kind Code[1]	Issue Date	Name of Patentee or Applicant of cited Document	Pages, Columns, Lines where Relevant Passages or Relevant Figures Appear
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	524	11,505,593		11-22-2022	Wang et al.	
	525	11,534,396		12-27-2022	Blizzard et al.	
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	530	11,667,702		06-06-2023	Liu et al.	
	531	11,692,027		07-04-2023	Kraft et al.	

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	549	2005-0032699		02-10-2005	Holash et al.	
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	534	2022-0356236		11-10-2022	Bigelow et al.	
	535	2023-0025418		01-26-2023	Wexler-Cohen et al.	
	536	2023-0063116		03-02-2023	Martin et al.	
	537	2023-0089914		03-23-2023	Kansara et al.	

FOREIGN PATENT DOCUMENTS								
Examiner Initial*	Cite No	Foreign Document Number[3]	Country Code[2]	Kind Code[4]	Publication Date	Name of Patentee or Applicant of cited Document	Pages, Columns, Lines where Relevant Passages or Relevant Figures Appear	T[5]
	491	102380096	CN	N	04-30-2014	Chengdu Kanghong Biotechnologies Co Ltd.		x
	494	2663325	EP	A1	11-20-2013	Yancopoulos		
	495	3222285	EP	A1	09-27-2017	Yancopoulos		
	496	4147709	EP	A1	03-15-2023	Doyle et al.		

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	497	4190310	EP	A1	06-07-2023	Kim et al.		
	538	2019/199476	WO	A1	10-17-2019	AMGEN INC.		
	539	2019/217927	WO	A1	11-14-2019	Regeneron Pharmaceuticals, Inc.		
	540	2022/025660	WO	A1	02-03-2022	CELLTRION INC.		x
	541	2022/229932	WO	A1	11-03-2022	Stefansson		
	542	2022/232790	WO	A1	11-03-2022	ADVERUM BIOTECHNOLOGIES, INC.		
	543	2022/245739	WO	A1	11-24-2022	Regeneron Pharmaceuticals, Inc.		
	544	2023/001288	WO	A1	01-26-2023	BIOTHERA SOLUTIONS, LTD.		x
	545	2023/023278	WO	A2	02-23-2023	UNIVERSITY OF UTAH RESEARCH FOUNDATION		
	546	2023/031478	WO	A1	03-09-2023	LEK PHARMACEUTICALS D.D.		
	547	2023/041569	WO	A1	03-23-2023	The Provost, Fellows, Foundation Scholars & the Other Members of Board, of the College of the Holy & Undiv. Trinity of Queen Elizabeth Near Dublin		
	548	2023/075506	WO	A1	05-04-2023	ALTEOGEN INC.		x

NON-PATENT LITERATURE DOCUMENTS			
Examiner Initial*	Cite No	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, pages(s), volume-issue number(s), publisher, city and/or country where published	T[5]
	466	Anonymous, Meeting Archive Titled "PA003 Eighteen-Month Results From an Extension Study of a Phase 2, Dose- and Interval-Ranging Study of VEGF Trap-Eye in Wet AMD," presented by David S Boyer, MD at Moscone Center (October 2009)	
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Regeneron Ex. 2001
Alvotech v. Regeneron
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Examiner Initial*	Cite No	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, pages(s), volume-issue number(s), publisher, city and/or country where published	T5
	468	Anonymous, Meeting Archive Titled "PO259 OCT and Fluorescein Angiography Outcomes Through 1 Year for a Phase 2 Study of Intravitreal VEGF Trap-Eye in Neovascular AMD," presented by Peter K Kaiser, MD at Moscone Center (October 2009)	
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	511	BROWN, "High-Dose Aflibercept - Rationale & Clinical Studies" Houston, TX 9 Feb 2020	
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	473	ClinicalTrials.gov Archive, History of Changes for Study: NCT00320775, "Safety and Tolerability Study of Intravitreal VEGF-Trap Administration in Patients With Neovascular AMD," Version 02 (October 3, 2006)	
	474	ClinicalTrials.gov Archive, History of Changes for Study: NCT00320775, "Safety and Tolerability Study of Intravitreal VEGF-Trap Administration in Patients With Neovascular AMD," Version 03 (July 25, 2007)	
	475	ClinicalTrials.gov Archive, History of Changes for Study: NCT00320775, "Safety and Tolerability Study of Intravitreal VEGF-Trap Administration in Patients With Neovascular AMD," Version 04 (January 23, 2009)	
	476	ClinicalTrials.gov Archive, History of Changes for Study: NCT00320775, "Safety and Tolerability Study of Intravitreal VEGF-Trap Administration in Patients With Neovascular AMD," Version 05 (April 29, 2009)	
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	480	ClinicalTrials.gov Archive, History of Changes for Study: NCT00320775, "Safety and Tolerability Study of Intravitreal VEGF-Trap Administration in Patients With Neovascular AMD," Version 09 (March 16, 2015)	
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	498	Eylea, "Wet AMD: Dosing Flexibility," https://hcp.eylea.us/about/wet-amd-dosing/ (accessed January 5, 2022)	
	499	Eylea Label (revised March 2021), https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/125387s069lbl.pdf (accessed September 26, 2022)	
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	509	Heier et al., "The 1-year Results of CLEAR-IT 2, a Phase 2 Study of Vascular Endothelial Growth Factor Trap-Eye Dosed As-needed After 12-week Fixed Dosing: Erratum," Ophthalmology, 118(9):1700 (September 2011)	
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	514	Nguyen et al., "Results of a Phase I, Dose-Escalation, Safety, Tolerability, and Bioactivity Study of Intravitreous VEGF Trap in Patients with Neovascular Age-Related Macular Degeneration," ARVO Annual Meeting Abstract (May 1, 2006)	
	464	PAUL et al., "Direct analysis of mAb aggregates in mammalian cell culture supernatant," BMC Biotechnology, Volume 14:99 (2014); 11 pages.	
	515	Regeneron Pharmaceuiticals, Inc. press release, "EYLEA (AFLIBERCEPT) INJECTION REDUCED RISK OF DEVELOPING VISION-THREATENING EVENTS BY 75% AFTER TWO YEARS IN PATIENTS WITH DIABETIC RETINOPATHY," February 8, 2020	
	516	Regeneron Pharmaceuiticals, Inc. press release, "Regeneron announces encouraging topline phase 2 data of high-dose aflibercept in wet age-related macular degeneration," Tarrytown, New York. August 24, 2021	
	517	Regeneron Pharmaceuticals, Inc., "VEGF Trap-Eye CLEAR-IT 2 Final Primary Endpoint Results," presented at the 2007 Retina Society Conference in Boston, Massachusetts (September 30, 2007)	
	518	Regeneron Pharmaceuticals, Inc., "EYLEA," https://eylea.us/ (accessed May 18, 2022)	
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	Examiner Name	Lockard, Jon McClelland
	Attorney Docket Number	125984-266215

EXAMINER SIGNATURE			
Examiner Signature		Date Considered	

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through a citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

[1] See Kind Codes of USPTO Patent Documents at www.USPTO.GOV or MPEP 901.04. [2] Enter office that issued the document, by the two-letter code (WIPO Standard ST.3). [3] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [4] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [5] Applicant is to place a check mark here if English language translation is attached.

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	Examiner Name	Lockard, Jon McClelland
	Attorney Docket Number	125984-266215

CERTIFICATION STATEMENT

Please see 37 CFR 1.97 and 1.98 to make the appropriate selection(s):

☐ That each item of information contained in the information disclosure statement was first cited in any communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(1).

OR

☐ That no item of information contained in the information disclosure statement was cited in a communication from a foreign patent office in a counterpart foreign application, and, to the knowledge of the person signing the certification after making reasonable inquiry, no item of information contained in the information disclosure statement was known to any individual designated in 37 CFR 1.56(c) more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(2).

☐ See attached certification statement.

☒ Fee set forth in 37 CFR 1.17 (p) has been submitted herewith.

☐ None

SIGNATURE

A signature of the applicant or representative is required in accordance with CFR 1.33, 10.18. Please see CFR 1.4(d) for the form of the signature.

Signature	/Lance A. Termes/	Date (YYYY-MM-DD)	2023-08-01
Name/Print	Lance A. Termes	Registration Number	43184

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I hereby certify that this correspondence is being filed via EFS-Web with the United States Patent and Trademark Office on August 1, 2023.

SCHWABE, WILLIAMSON & WYATT PC

By: /Lance A. Termes/
Lance A. Termes

PATENT
Attorney Docket No.: 125984-266215

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of:	Confirmation No. 1061
Kenneth S. Graham et al.	Examiner: Jon McClelland Lockard
Application No.: 17/384,070	Art Unit: 1647
Filed: July 23, 2021	
For: HIGH CONCENTRATION VEGF RECEPTOR FUSION PROTEIN CONTAINING FORMULATIONS	RESPONSE TO NON-FINAL OFFICE ACTION
Customer No.: 147803	

Mail Stop Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Commissioner:

This paper is submitted in response to the non-final office action mailed March 22, 2023. A petition to extend the time for reply by two months is submitted herewith. Please enter the following amendments and remarks:

Amendments to the Specification begin on page 2 of this paper.

Amendments to the Claims are reflected in the listing of claims which begins on page 3 of this paper.

Remarks/Arguments begin on page 8 of this paper.

Regeneron Ex. 2001
Alvotech v. Regeneron
PGR2025-00085
Page 287 of 531

Amendments to the Specification:

Please replace paragraph [001] with the following amended paragraph:

[001] This application is a continuation of U.S. Application No. 16/409,631, filed May 10, 2019, now U.S. Patent No. 11,103,552, which claims the benefit of U.S. Provisional Patent Application No. 62/813,882, filed March 5, 2019; U.S. Provisional Patent Application No. 62/769,876, filed November 20, 2018; U.S. Provisional Patent Application No. 62/752,127, filed October 29, 2018; and U.S. Provisional Patent Application No. 62/669,506, filed May 10, 2018; each of which is herein incorporated by reference in its entirety.

Please replace the title of the application with the following new title:

METHODS FOR TREATING ANGIOGENIC EYE DISORDERS WITH HIGH DOSES OF VEGF RECEPTOR FUSION PROTEINS

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Amendments to the Claims:

This listing of claims will replace all prior versions, and listings of claims in the application:

Listing of Claims:

1-29. (Canceled)

30. (Currently Amended) A method for treating an angiogenic eye disorder in a human subject~~patient~~ in need thereof comprising administering, intravitreally into an eye of the subject, in a volume of about 100 microliters or less, ~~an intravitreal injection of~~ at least about 8 mg of a VEGF receptor fusion protein comprising two polypeptides that comprise an immunoglobulin-like (Ig) domain 2 of VEGFR1, an Ig domain 3 of a VEGFR2, and a multimerizing component; wherein the VEGF receptor fusion protein is in an aqueous pharmaceutical formulation comprising at least 100 mg/ml of the VEGF receptor fusion protein and having a viscosity of about 5-15 centiPoise (cP) at 20°C~~, to the eye of the patient~~.

31. (Currently Amended) The method of claim 30 wherein, following said intravitreal injection, the subject~~patient~~ maintains or achieves a reduction in central retinal thickness but does not experience a significant increase in blood pressure.

32. (Currently Amended) The method of claim 30 wherein, following said intravitreal injection, the subject~~patient~~ maintains or achieves an improvement in best corrected visual acuity but does not experience a significant increase in blood pressure.

33-52. (Canceled)

53. (New) The method of claim 30, wherein the viscosity is about 10-13 cP at 20°C.

54. (New) The method of claim 30, wherein the viscosity is about 11-12 cP at 20°C.

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55. (New) The method of claim 30, wherein the viscosity is about 12-15 cP at 20°C.

56. (New) The method of claim 30, wherein the viscosity is about 5 cP at 20°C.

57. (New) The method of claim 30, wherein the viscosity is about 6 cP at 20°C.

58. (New) The method of claim 30 ,wherein the formulation comprises a sugar.

59. (New) The method of claim 30, wherein the formulation comprises sucrose, trehalose, sorbitol, mannitol, propane sulfonic acid or glycerol.

60. (New) The method of claim 30, wherein the formulation comprises an amino acid.

61. (New) The method of claim 30, wherein the angiogenic eye disorder is age-related macular degeneration (wet), macular edema, macular edema following retinal vein occlusion, retinal vein occlusion (RVO), central retinal vein occlusion (CRVO), branch retinal vein occlusion (BRVO), diabetic macular edema (DME), choroidal neovascularization (CNV), iris neovascularization, neovascular glaucoma, post-surgical fibrosis in glaucoma, proliferative vitreoretinopathy (PVR), optic disc neovascularization, corneal neovascularization, retinal neovascularization, vitreal neovascularization, pannus, pterygium, vascular retinopathy, diabetic retinopathy, non-proliferative diabetic retinopathy and/or proliferative diabetic retinopathy.

62. (New) The method of claim 61, wherein the angiogenic eye disorder is wet age-related macular degeneration.

63. (New) The method of claim 61, wherein the angiogenic eye disorder is diabetic macular edema.

64. (New) The method of claim 61, wherein the angiogenic eye disorder is diabetic retinopathy.

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65. (New) The method of claim 61, wherein the angiogenic eye disorder is non-proliferative diabetic retinopathy.

66. (New) The method of claim 61, wherein the angiogenic eye disorder is proliferative diabetic retinopathy.

67. (New) The method of claim 61, wherein the angiogenic eye disorder is macular edema following retinal vein occlusion.

68. (New) The method of claim 30, wherein the VEGF receptor fusion protein is aflibercept.

69. (New) The method of claim 61, wherein the VEGF receptor fusion protein is aflibercept.

70. (New) The method of claim 62, wherein the VEGF receptor fusion protein is aflibercept.

71. (New) The method of claim 63, wherein the VEGF receptor fusion protein is aflibercept.

72. (New) The method of claim 64, wherein the VEGF receptor fusion protein is aflibercept.

73. (New) The method of claim 65, wherein the VEGF receptor fusion protein is aflibercept.

74. (New) The method of claim 66, wherein the VEGF receptor fusion protein is aflibercept.

75. (New) The method of claim 67, wherein the VEGF receptor fusion protein is aflibercept.

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76. (New) The method of claim 30 for treating an angiogenic eye disorder in a human subject in need thereof comprising administering, intravitreally into an eye of the subject, in a volume of about 100 microliters or less, about 8 mg aflibercept; wherein the aflibercept is in an aqueous pharmaceutical formulation comprising at least 100 mg/ml of the aflibercept and having a viscosity of about 5-15 cP at 20ºC.

77. (New) The method of claim 76, wherein the angiogenic eye disorder is wet age-related macular degeneration.

78. (New) The method of claim 76, wherein the angiogenic eye disorder is diabetic macular edema.

79. (New) The method of claim 76, wherein the angiogenic eye disorder is diabetic retinopathy.

80. (New) The method of claim 30 for treating an angiogenic eye disorder in a human subject in need thereof comprising administering, intravitreally into an eye of the subject, in a volume of about 70 microliters, about 8 mg aflibercept; wherein the aflibercept is in an aqueous pharmaceutical formulation comprising about 114.3 mg/ml of the aflibercept and having a viscosity of about 5-15 cP at 20ºC.

81. (New) The method of claim 80, wherein the angiogenic eye disorder is wet age-related macular degeneration.

82. (New) The method of claim 80, wherein the angiogenic eye disorder is diabetic macular edema.

83. (New) The method of claim 80, wherein the angiogenic eye disorder is diabetic retinopathy.

84. (New) A method for treating an angiogenic eye disorder in a human subject in need thereof comprising administering, intravitreally into an eye of the subject, about 70

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microliters of an aqueous pharmaceutical formulation comprising about 103-126 mg/ml of aflibercept and having a viscosity of about 5-15 cP at 20°C.

85. (New) The method of claim 84, wherein the angiogenic eye disorder is wet age-related macular degeneration.

86. (New) The method of claim 84, wherein the angiogenic eye disorder is diabetic macular edema.

87. (New) The method of claim 84, wherein the angiogenic eye disorder is diabetic retinopathy.

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REMARKS/ARGUMENTS

Upon entry of the present amendment, claims 30-32 and 53-87 will be pending in the application. Claims 30-32 are hereby amended, former claims 35 and 39-52 are canceled, and new claims 53-87 are added.

Support for the amendments and new claims can be found in the specification at, *e.g.*, the following locations:

Claim 1 – paragraphs 0084, 0085 and 0095;

Claims 53-55 – paragraph 0021;

Claims 56 and 57 – paragraph 0095;

Claims 58 and 60 – paragraph 0090;

Claim 59 – paragraph 0091;

Claims 61-67, 77-79, 81-83 and 85-87 – paragraph 0027;

Claims 68-75 – paragraph 0019;

Claim 76 – paragraphs 0027, 0084 and 0095;

Claim 80 – paragraphs 0017, 0027, 0095 and 0213; and

Claim 84 – paragraphs 0027, 0095, 0194 and 0213.

No new matter is added.

No amendment or lack of comment on any specific remark should be construed as acquiescence to the validity of any ground of rejection or agreement therewith.

Objection to the Specification

The priority information in the specification has been updated. The title has been changed to: Methods for Treating Angiogenic Eye Disorders with High Doses of VEGF Receptor Fusion Proteins. Accordingly, Applicant respectfully requests withdrawal of this ground of objection.

Claim Objections

Claim 35 is canceled and a comma separates CRVO and branch retinal vein in new claim 61. Accordingly, Applicant respectfully requests withdrawal of this ground of objection.

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Claim Rejections – 35 USC § 112(b) - Indefiniteness

Applicant disagrees that the term "at least about" is unclear. The specification discusses the term "about" in paragraph 0061 (pages 17-18). The meaning of the term "at least" is self-explanatory - the stated value or higher. Thus, the meaning of the term would be clear to a practitioner of ordinary skill in the art.

Claim Rejections – 35 USC § 112(a) – Written Description

Claims 30-32, 35 and 39-52 stand rejected as allegedly lacking sufficient written description support. The Examiner argued that the specification provides inadequate description for the breadth of formulations encompassed by the claims alleging that the claims do not specify the components that permit such use of a high concentration of VEGF receptor fusion protein. Applicant disagrees. The amended claims are fully described.

The formulation specified in the amended claims is optimal for delivery of at least 8 mg of VEGF receptor fusion protein to the vitreum in terms of several interrelated factors: protein concentration, injection volume and viscosity.

Volume. Intravitreal injection of a liquid formulation into the eye should be done in a volume of about 100 microliters or less. The vitreous chamber is a closed system having a typical volume of about 4-5 ml. The introduction of excess volume into the eye risks damaging increases in intraocular pressure.

Protein concentration. In order to inject the target amount of VEGF receptor fusion protein (8 mg) in an acceptably low volume ($\leq$100 microliters), the concentration of the formulation must be relatively high, for example, greater than 100 mg/ml.

Viscosity. Formulations having high concentrations of VEGF receptor fusion protein, however, must have a viscosity suitable for injection via syringe. High viscosity formulations in a syringe would require excess pressure on the syringe plunger; possibly causing, for example, damaging shearing forces to the protein and difficulty for the clinician who delivers the injection. Acceptably low viscosities can be about 5-15 cP at 20ºC. A major factor affecting viscosity of VEGF receptor fusion protein formulations is protein concentration. See *e.g.*, Figures 3C and 5. Lowering protein concentration to lower viscosity, however, presents a

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challenge since delivery of ≥8 mg of VEGF receptor fusion protein to the eye would need to be done in a higher volume - thus, raising the possibility of causing an increase in intraocular pressure if 100 microliters is exceeded.

In spite of being constrained by these factors, Applicant successfully developed several formulations that meet these criteria. See for example, Figures 3B, 3C and 5 wherein the viscosities of several formulations including a variety of excipients were measured to be within the 5-15 cP range specified in the claims (Note: 1000 mPa-s=1000 cP). Thus, a representative number of species encompassed by the claims have been disclosed.

In view of the foregoing, Applicant submits that the amended claims are fully described and respectfully request withdrawal of this rejection.

Claim Rejections – Obviousness-Type Double Patenting

Claims 30-32, 35 and 39-52 stand rejected for allegedly being unpatentable on the ground of obviousness-type double patenting over claims 1-36 of US Patent No. 11,103,552.

Applicant thanks the Examiner for acknowledging that "[a] timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground. . . ." (numbered paragraph 21 of the Office Action) . Applicant submits herewith a terminal disclaimer over US Patent No. 11,103,552 in compliance with 37 C.F.R. § 1.321(c) and respectfully requests withdrawal of the double patenting rejection and allowance of the claims. Additionally, it is noted that the filing of a terminal disclaimer to obviate a rejection based on non-statutory double patenting is not an admission of the propriety of the rejection. See, e.g., *Quad Environmental Technologies Corp. v. Union Sanitary District*, 946 F.2d 870, 874 (Fed. Cir. 1991) (filing of a terminal disclaimer simply serves the statutory function of removing the rejection of double patenting, and raises neither a presumption nor estoppel on the merits of the rejection).

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 541-749-4085.

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Please charge any fees or additional fees that may be due in connection with this paper, or credit any overpayment, to the undersigned's deposit account No. 500393.

Respectfully submitted,

/Lance A. Termes/

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT (not for submission under 37 CFR 1.99)		
	Application Number	17/384,070
	Filing Date	Jul-23-2021
	First Named Inventor	Kenneth S. Graham
	Art Unit	1647
	Confirmation Number	1061
	Examiner Name	Jon Mcclelland Lockard
	Attorney Docket Number	125984-266215

U.S. PATENTS						
Examiner Initial*	Cite No	Patent Number	Kind Code[1]	Issue Date	Name of Patentee or Applicant of cited Document	Pages, Columns, Lines where Relevant Passages or Relevant Figures Appear
	553	11707506	B2	07-25-2023	Yancopoulos, George	

U.S. PATENT APPLICATION PUBLICATIONS						
Examiner Initial*	Cite No	Publication Number	Kind Code[1]	Publication Date	Name of Patentee or Applicant of cited Document	Pages, Columns, Lines where Relevant Passages or Relevant Figures Appear

FOREIGN PATENT DOCUMENTS								
Examiner Initial*	Cite No	Foreign Document Number[3]	Country Code[2]	Kind Code[4]	Publication Date	Name of Patentee or Applicant of cited Document	Pages, Columns, Lines where Relevant Passages or Relevant Figures Appear	T[5]
	552	2014/005728	WO	A1	01-09-2014	Novartis AG		

NON-PATENT LITERATURE DOCUMENTS			
Examiner Initial*	Cite No	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, pages(s), volume-issue number(s), publisher, city and/or country where published	T[5]

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT (not for submission under 37 CFR 1.99)		
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	Confirmation Number	1061
	Examiner Name	Jon Mcclelland Lockard
	Attorney Docket Number	125984-266215

EXAMINER SIGNATURE			
Examiner Signature		Date Considered	

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through a citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

[1] See Kind Codes of USPTO Patent Documents at www.USPTO.GOV or MPEP 901.04. [2] Enter office that issued the document, by the two-letter code (WIPO Standard ST.3). [3] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [4] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [5] Applicant is to place a check mark here if English language translation is attached.

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT (not for submission under 37 CFR 1.99)		
	Application Number	17/384,070
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	Examiner Name	Jon Mcclelland Lockard
	Attorney Docket Number	125984-266215

CERTIFICATION STATEMENT

Please see 37 CFR 1.97 and 1.98 to make the appropriate selection(s):

☐ That each item of information contained in the information disclosure statement was first cited in any communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(1).

OR

☐ That no item of information contained in the information disclosure statement was cited in a communication from a foreign patent office in a counterpart foreign application, and, to the knowledge of the person signing the certification after making reasonable inquiry, no item of information contained in the information disclosure statement was known to any individual designated in 37 CFR 1.56(c) more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(2).

☐ See attached certification statement.

☒ Fee set forth in 37 CFR 1.17 (p) has been submitted herewith.

☐ None

SIGNATURE

A signature of the applicant or representative is required in accordance with CFR 1.33, 10.18. Please see CFR 1.4(d) for the form of the signature.

Signature	/Lance A. Termes/	Date (YYYY-MM-DD)	2023-08-11
Name/Print	Lance A. Termes	Registration Number	43184

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UNITED STATES PATENT AND TRADEMARK OFFICE

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P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

NOTICE OF ALLOWANCE AND FEE(S) DUE

147803 7590 09/01/2023

Schwabe W&W, PC / Regeneron Pharmaceuticals, Inc.
PacWest Center
1211 SW Fifth Avenue, Suite 1900
Portland, OR 97204

EXAMINER	
LOCKARD, JON MCCLELLAND	
ART UNIT	PAPER NUMBER
1647	

DATE MAILED: 09/01/2023

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
17/384,070	07/23/2021	Kenneth S. Graham		1061

TITLE OF INVENTION: Methods for Treating Angiogenic Eye Disorders with High Doses of VEGF Receptor Fusion Proteins

APPLN. TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	UNDISCOUNTED	$1200	$0.00	$0.00	$1200	12/01/2023

THE APPLICATION IDENTIFIED ABOVE HAS BEEN EXAMINED AND IS ALLOWED FOR ISSUANCE AS A PATENT. PROSECUTION ON THE MERITS IS CLOSED. THIS NOTICE OF ALLOWANCE IS NOT A GRANT OF PATENT RIGHTS. THIS APPLICATION IS SUBJECT TO WITHDRAWAL FROM ISSUE AT THE INITIATIVE OF THE OFFICE OR UPON PETITION BY THE APPLICANT. SEE 37 CFR 1.313 AND MPEP 1308.

THE ISSUE FEE AND PUBLICATION FEE (IF REQUIRED) MUST BE PAID WITHIN THREE MONTHS FROM THE MAILING DATE OF THIS NOTICE OR THIS APPLICATION SHALL BE REGARDED AS ABANDONED. THIS STATUTORY PERIOD CANNOT BE EXTENDED. SEE 35 U.S.C. 151. THE ISSUE FEE DUE INDICATED ABOVE DOES NOT REFLECT A CREDIT FOR ANY PREVIOUSLY PAID ISSUE FEE IN THIS APPLICATION. IF AN ISSUE FEE HAS PREVIOUSLY BEEN PAID IN THIS APPLICATION (AS SHOWN ABOVE), THE RETURN OF PART B OF THIS FORM WILL BE CONSIDERED A REQUEST TO REAPPLY THE PREVIOUSLY PAID ISSUE FEE TOWARD THE ISSUE FEE NOW DUE.

HOW TO REPLY TO THIS NOTICE:

I. Review the ENTITY STATUS shown above. If the ENTITY STATUS is shown as SMALL or MICRO, verify whether entitlement to that entity status still applies.

If the ENTITY STATUS is the same as shown above, pay the TOTAL FEE(S) DUE shown above.

If the ENTITY STATUS is changed from that shown above, on PART B - FEE(S) TRANSMITTAL, complete section number 5 titled "Change in Entity Status (from status indicated above)".

For purposes of this notice, small entity fees are 40% the amount of undiscounted fees, and micro entity fees are 20% the amount of undiscounted fees.

II. PART B - FEE(S) TRANSMITTAL, or its equivalent, must be completed and returned to the United States Patent and Trademark Office (USPTO) with your ISSUE FEE and PUBLICATION FEE (if required). If you are charging the fee(s) to your deposit account, section "4b" of Part B - Fee(s) Transmittal should be completed. If an equivalent of Part B is filed, a request to reapply a previously paid issue fee must be clearly made, and delays in processing may occur due to the difficulty in recognizing the paper as an equivalent of Part B.

III. All communications regarding this application must give the application number. Please direct all communications prior to issuance to Mail Stop ISSUE FEE unless advised to the contrary.

IMPORTANT REMINDER: Maintenance fees are due in utility patents issuing on applications filed on or after Dec. 12, 1980. It is patentee's responsibility to ensure timely payment of maintenance fees when due. More information is available at www.uspto.gov/PatentMaintenanceFees.

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PART B - FEE(S) TRANSMITTAL

Complete and send this form, together with applicable fee(s), by mail or fax, or via EFS-Web.

By mail, send to: Mail Stop ISSUE FEE
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450

By fax, send to: (571)-273-2885

INSTRUCTIONS: This form should be used for transmitting the ISSUE FEE and PUBLICATION FEE (if required). Blocks 1 through 5 should be completed where appropriate. All further correspondence will be mailed to the current correspondence address as indicated unless corrected below or directed otherwise in Block 1, by (a) specifying a new correspondence address; and/or (b) indicating a separate "FEE ADDRESS" for maintenance fee notifications. **Because electronic patent issuance may occur shortly after issue fee payment, any desired continuing application should preferably be filed prior to payment of this issue fee in order not to jeopardize copendency.**

CURRENT CORRESPONDENCE ADDRESS (Note: Use Block 1 for any change of address)

147803 7590 09/01/2023
Schwabe W&W, PC / Regeneron Pharmaceuticals, Inc.
PacWest Center
1211 SW Fifth Avenue, Suite 1900
Portland, OR 97204

Note: A certificate of mailing can only be used for domestic mailings of the Fee(s) Transmittal. This certificate cannot be used for any other accompanying papers. Each additional paper, such as an assignment or formal drawing, must have its own certificate of mailing or transmission.

Certificate of Mailing or Transmission

I hereby certify that this Fee(s) Transmittal is being deposited with the United States Postal Service with sufficient postage for first class mail in an envelope addressed to the Mail Stop ISSUE FEE address above, or being transmitted to the USPTO via EFS-Web or by facsimile to (571) 273-2885, on the date below.

(Typed or printed name)
(Signature)
(Date)

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
17/384,070	07/23/2021	Kenneth S. Graham		1061

TITLE OF INVENTION: Methods for Treating Angiogenic Eye Disorders with High Doses of VEGF Receptor Fusion Proteins

APPLN. TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	UNDISCOUNTED	$1200	$0.00	$0.00	$1200	12/01/2023

EXAMINER	ART UNIT	CLASS-SUBCLASS
LOCKARD, JON MCCLELLAND	1647	424-134100

1. Change of correspondence address or indication of "Fee Address" (37 CFR 1.363).

❑ Change of correspondence address (or Change of Correspondence Address form PTO/AIA/122 or PTO/SB/122) attached.

❑ "Fee Address" indication (or "Fee Address" Indication form PTO/AIA/47 or PTO/SB/47; Rev 03-02 or more recent) attached. **Use of a Customer Number is required.**

2. For printing on the patent front page, list
(1) The names of up to 3 registered patent attorneys or agents OR, alternatively,
(2) The name of a single firm (having as a member a registered attorney or agent) and the names of up to 2 registered patent attorneys or agents. If no name is listed, no name will be printed.

1 _____
2 _____
3 _____

3. ASSIGNEE NAME AND RESIDENCE DATA TO BE PRINTED ON THE PATENT (print or type)

PLEASE NOTE: Unless an assignee is identified below, no assignee data will appear on the patent. If an assignee is identified below, the document must have been previously recorded, or filed for recordation, as set forth in 37 CFR 3.11 and 37 CFR 3.81(a). Completion of this form is NOT a substitute for filing an assignment.

(A) NAME OF ASSIGNEE (B) RESIDENCE: (CITY and STATE OR COUNTRY)

Please check the appropriate assignee category or categories (will not be printed on the patent) : ❑ Individual ❑ Corporation or other private group entity ❑ Government

4a. Fees submitted: ❑ Issue Fee ❑ Publication Fee (if required)

4b. Method of Payment: *(Please first reapply any previously paid fee shown above)*

❑ Electronic Payment via Patent Center or EFS-Web ❑ Enclosed check ❑ Non-electronic payment by credit card (Attach form PTO-2038)

❑ The Director is hereby authorized to charge the required fee(s), any deficiency, or credit any overpayment to Deposit Account No. _____

5. **Change in Entity Status** (from status indicated above)

❑ Applicant certifying micro entity status. See 37 CFR 1.29

NOTE: Absent a valid certification of Micro Entity Status (see forms PTO/SB/15A and 15B), issue fee payment in the micro entity amount will not be accepted at the risk of application abandonment.

❑ Applicant asserting small entity status. See 37 CFR 1.27

NOTE: If the application was previously under micro entity status, checking this box will be taken to be a notification of loss of entitlement to micro entity status.

❑ Applicant changing to regular undiscounted fee status.

NOTE: Checking this box will be taken to be a notification of loss of entitlement to small or micro entity status, as applicable.

NOTE: This form must be signed in accordance with 37 CFR 1.31 and 1.33. See 37 CFR 1.4 for signature requirements and certifications.

Authorized Signature _____ Date _____

Typed or printed name _____ Registration No. _____

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UNITED STATES PATENT AND TRADEMARK OFFICE

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United States Patent and Trademark Office
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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
17/384,070	07/23/2021	Kenneth S. Graham		1061

147803 7590 09/01/2023

Schwabe W&W, PC / Regeneron Pharmaceuticals, Inc.
PacWest Center
1211 SW Fifth Avenue, Suite 1900
Portland, OR 97204

EXAMINER	
LOCKARD, JON MCCLELLAND	
ART UNIT	**PAPER NUMBER**
1647	

DATE MAILED: 09/01/2023

Determination of Patent Term Adjustment under 35 U.S.C. 154 (b)
(Applications filed on or after May 29, 2000)

The Office has discontinued providing a Patent Term Adjustment (PTA) calculation with the Notice of Allowance.

Section 1(h)(2) of the AIA Technical Corrections Act amended 35 U.S.C. 154(b)(3)(B)(i) to eliminate the requirement that the Office provide a patent term adjustment determination with the notice of allowance. See Revisions to Patent Term Adjustment, 78 Fed. Reg. 19416, 19417 (Apr. 1, 2013). Therefore, the Office is no longer providing an initial patent term adjustment determination with the notice of allowance. The Office will continue to provide a patent term adjustment determination with the Issue Notification Letter that is mailed to applicant approximately three weeks prior to the issue date of the patent, and will include the patent term adjustment on the patent. Any request for reconsideration of the patent term adjustment determination (or reinstatement of patent term adjustment) should follow the process outlined in 37 CFR 1.705.

Any questions regarding the Patent Term Extension or Adjustment determination should be directed to the Office of Patent Legal Administration at (571)-272-7702. Questions relating to issue and publication fee payments should be directed to the Customer Service Center of the Office of Patent Publication at 1-(888)-786-0101 or (571)-272-4200.

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OMB Clearance and PRA Burden Statement for PTOL-85 Part B

The Paperwork Reduction Act (PRA) of 1995 requires Federal agencies to obtain Office of Management and Budget approval before requesting most types of information from the public. When OMB approves an agency request to collect information from the public, OMB (i) provides a valid OMB Control Number and expiration date for the agency to display on the instrument that will be used to collect the information and (ii) requires the agency to inform the public about the OMB Control Number's legal significance in accordance with 5 CFR 1320.5(b).

The information collected by PTOL-85 Part B is required by 37 CFR 1.311. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 30 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, Virginia 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, Virginia 22313-1450. Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

Privacy Act Statement

The Privacy Act of 1974 (P.L. 93-579) requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether disclosure of these records is required by the Freedom of Information Act.
2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.
3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.
4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).
5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.
6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).
7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.
8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspection or an issued patent.
9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

Notice of Allowability	Application No. 17/384,070	Applicant(s) Graham et al.	
	Examiner JON M LOCKARD	Art Unit 1647	AIA (FITF) Status Yes

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address--

All claims being allowable, PROSECUTION ON THE MERITS IS (OR REMAINS) CLOSED in this application. If not included herewith (or previously mailed), a Notice of Allowance (PTOL-85) or other appropriate communication will be mailed in due course. **THIS NOTICE OF ALLOWABILITY IS NOT A GRANT OF PATENT RIGHTS.** This application is subject to withdrawal from issue at the initiative of the Office or upon petition by the applicant. See 37 CFR 1.313 and MPEP 1308.

1. ☑ This communication is responsive to the Amendment filed 01 August 2023.
   ☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on _____.

2. ☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.

3. ☑ The allowed claim(s) is/are See Continuation Sheet . As a result of the allowed claim(s), you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information, please see **http://www.uspto.gov/patents/init_events/pph/index.jsp** or send an inquiry to **PPHfeedback@uspto.gov.**

4. ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

   Certified copies:

   a) ☐ All b) ☐ Some* c) ☐ None of the:

   1. ☐ Certified copies of the priority documents have been received.
   2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
   3. ☐ Copies of the certified copies of the priority documents have been received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

   * Certified copies not received: _____ .

Applicant has THREE MONTHS FROM THE "MAILING DATE" of this communication to file a reply complying with the requirements noted below. Failure to timely comply will result in ABANDONMENT of this application.
THIS THREE-MONTH PERIOD IS NOT EXTENDABLE.

5. ☐ CORRECTED DRAWINGS (as "replacement sheets") must be submitted.
   ☐ including changes required by the attached Examiner's Amendment / Comment or in the Office action of Paper No./Mail Date _____ .

   Identifying indicia such as the application number (see 37 CFR 1.84(c)) should be written on the drawings in the front (not the back) of each sheet. Replacement sheet(s) should be labeled as such in the header according to 37 CFR 1.121(d).

6. ☐ DEPOSIT OF and/or INFORMATION about the deposit of BIOLOGICAL MATERIAL must be submitted. Note the attached Examiner's comment regarding REQUIREMENT FOR THE DEPOSIT OF BIOLOGICAL MATERIAL.

Attachment(s)

1. ☐ Notice of References Cited (PTO-892)
2. ☑ Information Disclosure Statements (PTO/SB/08), Paper No./Mail Date _____.
3. ☐ Examiner's Comment Regarding Requirement for Deposit of Biological Material _____.
4. ☐ Interview Summary (PTO-413), Paper No./Mail Date. _____.
5. ☑ Examiner's Amendment/Comment
6. ☐ Examiner's Statement of Reasons for Allowance
7. ☐ Other _____.

/J.L/ Examiner, Art Unit 1647	/CHRISTINE J SAOUD/ Primary Examiner, Art Unit 1645

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Continuation of 3. The allowed claim(s) is/are: 30-32 and 53-87 (renumbered as claims 1-11,13-14,16,18,20,22,24,12,26,15,17,19,21,23,25 and 27-38, respectively)

Notice of Pre-AIA or AIA Status

1. The present application, filed on or after March 16, 2013, is being examined under the first inventor to file provisions of the AIA.

Terminal Disclaimer

2. The terminal disclaimer filed on 01 August 2023 has been reviewed and is accepted. The terminal disclaimer has been recorded.

Information Disclosure Statement

3. The information disclosure statements (IDS) submitted on 01 August 2023 and 11 August 2023 have been considered by the examiner.

Withdrawn Objections and/or Rejections

4. The objections to the Specification as set forth at pg. 2 of the previous Office action (mailed 22 March 2023) is withdrawn in view of Applicant's amendments to the Specification (filed 01 August 2023).

5. The objection to claim 35 as set forth at pg. 3 of the previous Office action (mailed 22 March 2023) is moot in view of Applicant's cancellation of said claim (filed 01 August 2023).

6. The rejection of claims 30-32, 35 and 39-52 under 35 U.S.C. 112(b) as set forth at pg. 3 of the previous Office action (mailed 22 March 2023) is withdrawn in view of Applicant's amendment to claim 30, the persuasive arguments presented at pg. 9 of the response which

points to a limiting definition in the Specification for the term "at least about", and cancellation of claims 35 and 39-52 (filed 01 August 2023).

7. The rejection of claims 30-32, 35 and 39-52 under 35 U.S.C. 112(a) as set forth at pg. 3 of the previous Office action (mailed 22 March 2023) is withdrawn in view of Applicant's amendment to claim 30, the persuasive arguments at pp. 9-10 of the Response, and cancellation of claims 35 and 39-52 (filed 01 August 2023).

8. The rejection of claims 30-32, 35 and 39-52 on the ground of nonstatutory double patenting as set forth at pp. 6-7 of the previous Office action (mailed 22 March 2023) is withdrawn in view of Applicant's submission of a terminal disclaimer (filed 01 August 2023).

Summary

9. Claims 30-32 and 53-87 are allowed.

Advisory Information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to **JON M LOCKARD** whose telephone number is **(571) 272-2717**. The examiner can normally be reached M-F 9-6 EST.

Examiner interviews are available via telephone, in-person, and video conferencing using a USPTO supplied web-based collaboration tool. To schedule an interview, applicant is encouraged to use the USPTO Automated Interview Request (AIR) at http://www.uspto.gov/interviewpractice. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, **Joanne Hama** can be reached on **(571) 272-2911**. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of published or unpublished applications may be obtained from Patent Center. Unpublished application information in Patent Center is available to registered users. To file and manage patent submissions in Patent Center, visit: https://patentcenter.uspto.gov. Visit https://www.uspto.gov/patents/apply/patent-center for more information about Patent Center and https://www.uspto.gov/patents/docx for information about filing in DOCX format. For additional questions, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Christine J Saoud/
Primary Examiner, Art Unit 1645

/J.L/
Examiner, Art Unit 1647
August 25, 2023

Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
	17/384,070	Graham et al.
	Examiner	Art Unit
	JON M LOCKARD	1647

CPC - Searched*		
Symbol	Date	Examiner

CPC Combination Sets - Searched*		
Symbol	Date	Examiner

US Classification - Searched*			
Class	Subclass	Date	Examiner
NONE		03/16/2023	JML

* See search history printout included with this form or the SEARCH NOTES box below to determine the scope of the search.

Search Notes		
Search Notes	Date	Examiner
PE2E Search (USPAT, US-PGPUB, EPO, DERWENT): See attached search history.	03/16/2023	JML
STN (MEDLINE, SCISEARCH, EMBASE, BIOSIS): See attached search history.	03/16/2023	JML
PALM: Inventor search.	03/16/2023	JML

Interference Search			
US Class/CPC Symbol	US Subclass/CPC Group	Date	Examiner
	PE2E Search (USPAT): See attached search history.	08/24/2023	JML
	DAV: Inventor search.	08/24/2023	JML

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Issue Classification	Application/Control No.	Applicant(s)/Patent Under Reexamination
	17/384,070	Graham et al.
	Examiner	Art Unit
	JON M LOCKARD	1647

CPC										
Symbol									Type	Version
A61K	/	38	/	179					F	2013-01-01
A61P	/	27	/	02					I	2018-01-01
A61K	/	9	/	0048					I	2013-01-01
A61K	/	47	/	12					I	2013-01-01
A61K	/	47	/	183					I	2013-01-01
A61K	/	47	/	22					I	2013-01-01
A61K	/	47	/	26					I	2013-01-01

CPC Combination Sets										
Symbol									Type	Set	Ranking	Version
	/		/									

/JON M LOCKARD/ Examiner, Art Unit 1647	25 August 2023	Total Claims Allowed:	
(Assistant Examiner)	(Date)	38	
/CHRISTINE J SAOUD/ Primary Examiner, Art Unit 1645	26 August 2023	O.G. Print Claim(s)	O.G. Print Figure
(Primary Examiner)	(Date)	1	NONE

U.S. Patent and Trademark Office — Part of Paper No.: 20230824

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Issue Classification	Application/Control No.	Applicant(s)/Patent Under Reexamination
	17/384,070	Graham et al.
	Examiner	Art Unit
	JON M LOCKARD	1647

INTERNATIONAL CLASSIFICATION					
CLAIMED					
A61K	/	38	/	17	
A61K	/	38	/	18	
C07K	/	14	/	71	

NON-CLAIMED				
	/		/	

US ORIGINAL CLASSIFICATION	
CLASS	SUBCLASS

CROSS REFERENCES(S)						
CLASS	SUBCLASS (ONE SUBCLASS PER BLOCK)					

/JON M LOCKARD/ Examiner, Art Unit 1647	25 August 2023	Total Claims Allowed:	
(Assistant Examiner)	(Date)	38	
/CHRISTINE J SAOUD/ Primary Examiner, Art Unit 1645	26 August 2023	O.G. Print Claim(s)	O.G. Print Figure
(Primary Examiner)	(Date)	1	NONE

U.S. Patent and Trademark Office — Part of Paper No.: 20230824

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Issue Classification	Application/Control No.	Applicant(s)/Patent Under Reexamination
	17/384,070	Graham et al.
	Examiner	Art Unit
	JON M LOCKARD	1647

☐ Claims renumbered in the same order as presented by applicant ☐ CPA ☑ T.D. ☐ R.1.47

CLAIMS

Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original
1	30	10	59	12	68	28	77	37	86						
2	31	11	60	26	69	29	78	38	87						
3	32	13	61	15	70	30	79								
4	53	14	62	17	71	31	80								
5	54	16	63	19	72	32	81								
6	55	18	64	21	73	33	82								
7	56	20	65	23	74	34	83								
8	57	22	66	25	75	35	84								
9	58	24	67	27	76	36	85								

/JON M LOCKARD/ Examiner, Art Unit 1647 (Assistant Examiner)	25 August 2023 (Date)	**Total Claims Allowed:** 38	
/CHRISTINE J SAOUD/ Primary Examiner, Art Unit 1645 (Primary Examiner)	26 August 2023 (Date)	O.G. Print Claim(s) 1	O.G. Print Figure NONE

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Receipt date: 08/01/2023

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (not for submission under 37 CFR 1.99)		
	Application Number	17/384,070
	Filing Date	Jul-23-2021
	First Named Inventor	Kenneth S. Graham
	Art Unit	1647
	Confirmation Number	1061
	Examiner Name	Lockard, Jon McClelland
	Attorney Docket Number	125984-266215

U.S. PATENTS						
Examiner Initial*	Cite No	Patent Number	Kind Code[1]	Issue Date	Name of Patentee or Applicant of cited Document	Pages, Columns, Lines where Relevant Passages or Relevant Figures Appear
	550	7,070,959		07-04-2006	Papadopoulous	
	524	11,505,593		11-22-2022	Wang et al.	
	525	11,534,396		12-27-2022	Blizzard et al.	
	526	11,542,317		01-03-2023	Wang et al.	
	527	11,559,564		01-24-2023	Yancopoulos	
	528	11,596,667		03-07-2023	Rezaei	
	529	11,666,632		06-06-2023	Brockmeyer et al.	
	530	11,667,702		06-06-2023	Liu et al.	
	531	11,692,027		07-04-2023	Kraft et al.	

U.S. PATENT APPLICATION PUBLICATIONS						
Examiner Initial*	Cite No	Publication Number	Kind Code[1]	Publication Date	Name of Patentee or Applicant of cited Document	Pages, Columns, Lines where Relevant Passages or Relevant Figures Appear
	549	2005-0032699		02-10-2005	Holash et al.	
	551	2013-0295094		11-07-2013	Yancopoulos	
	532	2018-0298092		10-18-2018	Gekkiva et al.	
	534	2022-0356236		11-10-2022	Bigelow et al.	
	535	2023-0025418		01-26-2023	Wexler-Cohen et al.	
	536	2023-0063116		03-02-2023	Martin et al.	
	537	2023-0089914		03-23-2023	Kansara et al.	

FOREIGN PATENT DOCUMENTS								
Examiner Initial*	Cite No	Foreign Document Number[3]	Country Code[2]	Kind Code[4]	Publication Date	Name of Patentee or Applicant of cited Document	Pages, Columns, Lines where Relevant Passages or Relevant Figures Appear	T[5]
	491	102380096	CN	N	04-30-2014	Chengdu Kanghong Biotechnologies Co Ltd.		x
	494	2663325	EP	A1	11-20-2013	Yancopoulos		
	495	3222285	EP	A1	09-27-2017	Yancopoulos		
	496	4147709	EP	A1	03-15-2023	Doyle et al.		

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /J.L/

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Alvotech v. Regeneron
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INFORMATION DISCLOSURE STATEMENT BY APPLICANT (not for submission under 37 CFR 1.99)		
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	Art Unit	1647
	Confirmation Number	1061
	Examiner Name	Lockard, Jon McClelland
	Attorney Docket Number	125984-266215

FOREIGN PATENT DOCUMENTS								
Examiner Initial*	Cite No	Foreign Document Number[3]	Country Code[2]	Kind Code[4]	Publication Date	Name of Patentee or Applicant of cited Document	Pages, Columns, Lines where Relevant Passages or Relevant Figures Appear	T[5]
	497	4190310	EP	A1	06-07-2023	Kim et al.		
	538	2019/199476	WO	A1	10-17-2019	AMGEN INC.		
	539	2019/217927	WO	A1	11-14-2019	Regeneron Pharmaceuticals, Inc.		
	540	2022/025660	WO	A1	02-03-2022	CELLTRION INC.		x
	541	2022/229932	WO	A1	11-03-2022	Stefansson		
	542	2022/232790	WO	A1	11-03-2022	ADVERUM BIOTECHNOLOGIES, INC.		
	543	2022/245739	WO	A1	11-24-2022	Regeneron Pharmaceuticals, Inc.		
	544	2023/001288	WO	A1	01-26-2023	BIOTHERA SOLUTIONS, LTD.		x
	545	2023/023278	WO	A2	02-23-2023	UNIVERSITY OF UTAH RESEARCH FOUNDATION		
	546	2023/031478	WO	A1	03-09-2023	LEK PHARMACEUTICALS D.D.		
	547	2023/041569	WO	A1	03-23-2023	The Provost, Fellows, Foundation Scholars & the Other Members of Board, of the College of the Holy & Undiv. Trinity of Queen Elizabeth Near Dublin		
	548	2023/075506	WO	A1	05-04-2023	ALTEOGEN INC.		x

NON-PATENT LITERATURE DOCUMENTS			
Examiner Initial*	Cite No	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, pages(s), volume-issue number(s), publisher, city and/or country where published	T[5]
	466	Anonymous, Meeting Archive Titled "PA003 Eighteen-Month Results From an Extension Study of a Phase 2, Dose- and Interval-Ranging Study of VEGF Trap-Eye in Wet AMD," presented by David S Boyer, MD at Moscone Center (October 2009)	
	467	Anonymous, Meeting Archive Titled "PA080 One-Year Results of a Phase 2 Study of Intravitreal VEGF Trap-Eye in Patients with Neovascular Age-Related Macular Degeneration," presented by David S Boyer, MD at Georgia World Congress Center (November 2008)	

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /J.L/

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	Attorney Docket Number	125984-266215

NON-PATENT LITERATURE DOCUMENTS			
Examiner Initial*	Cite No	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, pages(s), volume-issue number(s), publisher, city and/or country where published	T 5
	468	Anonymous, Meeting Archive Titled "PO259 OCT and Fluorescein Angiography Outcomes Through 1 Year for a Phase 2 Study of Intravitreal VEGF Trap-Eye in Neovascular AMD," presented by Peter K Kaiser, MD at Moscone Center (October 2009)	
	469	Anonymous, Meeting Archive Titled "PO260 VEGF Trap-Eye Vision-Specific Quality of Life Through 52 Weeks in Patients with Neovascular AMD in CLEAR-IT 2: A Phase 2 Clinical Trial," presented by Allen C Ho, MD at Moscone Center (October 2009)	
	470	Anonymous, Meeting Archive Titled "PO571 OCT and Fluorescein Angiographic Outcomes Through 1 Year for the Phase 2 Study of Intravitreal VEGF Trap-Eye in Neovascular AMD," presented by Quan Dong Nguyen, MD at Georgia World Congress Center (November 2008)	
	471	Benz et al., "CLEAR-IT-2: Interim Results Of The Phase II, Randomized, Controlled Dose-and Interval-ranging Study Of Repeated Intravitreal VEGF Trap Administration In Patients With Neovascular Age-related Macular Degeneration (AMD)," ARVO Annual Meeting Abstract (May 2007)	
	511	BROWN, "High-Dose Aflibercept - Rationale & Clinical Studies" Houston, TX 9 Feb 2020	
	472	ClinicalTrials.gov Archive, History of Changes for Study: NCT00320775, "Safety and Tolerability Study of Intravitreal VEGF-Trap Administration in Patients With Neovascular AMD," Version 01 (April 28, 2006)	
	473	ClinicalTrials.gov Archive, History of Changes for Study: NCT00320775, "Safety and Tolerability Study of Intravitreal VEGF-Trap Administration in Patients With Neovascular AMD," Version 02 (October 3, 2006)	
	474	ClinicalTrials.gov Archive, History of Changes for Study: NCT00320775, "Safety and Tolerability Study of Intravitreal VEGF-Trap Administration in Patients With Neovascular AMD," Version 03 (July 25, 2007)	
	475	ClinicalTrials.gov Archive, History of Changes for Study: NCT00320775, "Safety and Tolerability Study of Intravitreal VEGF-Trap Administration in Patients With Neovascular AMD," Version 04 (January 23, 2009)	
	476	ClinicalTrials.gov Archive, History of Changes for Study: NCT00320775, "Safety and Tolerability Study of Intravitreal VEGF-Trap Administration in Patients With Neovascular AMD," Version 05 (April 29, 2009)	
	477	ClinicalTrials.gov Archive, History of Changes for Study: NCT00320775, "Safety and Tolerability Study of Intravitreal VEGF-Trap Administration in Patients With Neovascular AMD," Version 06 (January 26, 2010)	
	478	ClinicalTrials.gov Archive, History of Changes for Study: NCT00320775, "Safety and Tolerability Study of Intravitreal VEGF-Trap Administration in Patients With Neovascular AMD," Version 07 (January 25, 2011)	
	479	ClinicalTrials.gov Archive, History of Changes for Study: NCT00320775, "Safety and Tolerability Study of Intravitreal VEGF-Trap Administration in Patients With Neovascular AMD," Version 08 (June 8, 2011)	

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /J.L/

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (not for submission under 37 CFR 1.99)		
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	Art Unit	1647
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	Examiner Name	Lockard, Jon McClelland
	Attorney Docket Number	125984-266215

NON-PATENT LITERATURE DOCUMENTS			
Examiner Initial*	Cite No	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, pages(s), volume-issue number(s), publisher, city and/or country where published	T 5
	480	ClinicalTrials.gov Archive, History of Changes for Study: NCT00320775, "Safety and Tolerability Study of Intravitreal VEGF-Trap Administration in Patients With Neovascular AMD," Version 09 (March 16, 2015)	
	481	ClinicalTrials.gov Archive, History of Changes for Study: NCT00320788, "Safety and Efficacy of Repeated Intravitreal Administration of Vascular Endothelial Growth Factor (VEGF) Trap in Patients With Wet Age-Related Macular Degeneration (AMD)," Version 01 (April 28, 2006)	
	482	ClinicalTrials.gov Archive, History of Changes for Study: NCT00320788, "Safety and Efficacy of Repeated Intravitreal Administration of Vascular Endothelial Growth Factor (VEGF) Trap in Patients With Wet Age-Related Macular Degeneration (AMD)," Version 02 (August 1, 2006)	
	483	ClinicalTrials.gov Archive, History of Changes for Study: NCT00320788, "Safety and Efficacy of Repeated Intravitreal Administration of Vascular Endothelial Growth Factor (VEGF) Trap in Patients With Wet Age-Related Macular Degeneration (AMD)," Version 03 (October 3, 2006)	
	484	ClinicalTrials.gov Archive, History of Changes for Study: NCT00320788, "Safety and Efficacy of Repeated Intravitreal Administration of Vascular Endothelial Growth Factor (VEGF) Trap in Patients With Wet Age-Related Macular Degeneration (AMD)," Version 04 (July 24, 2007)	
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INFORMATION DISCLOSURE STATEMENT BY APPLICANT (not for submission under 37 CFR 1.99)		
	Application Number	17/384,070
	Filing Date	Jul-23-2021
	First Named Inventor	Kenneth S. Graham
	Art Unit	1647
	Confirmation Number	1061
	Examiner Name	Lockard, Jon McClelland
	Attorney Docket Number	125984-266215

NON-PATENT LITERATURE DOCUMENTS			
Examiner Initial*	Cite No	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, pages(s), volume-issue number(s), publisher, city and/or country where published	T 5
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Receipt date: 08/01/2023

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (not for submission under 37 CFR 1.99)		
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	Art Unit	1647
	Confirmation Number	1061
	Examiner Name	Lockard, Jon McClelland
	Attorney Docket Number	125984-266215

EXAMINER SIGNATURE			
Examiner Signature	/JON M LOCKARD/	Date Considered	08/24/2023

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through a citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

[1] See Kind Codes of USPTO Patent Documents at www.USPTO.GOV or MPEP 901.04. [2] Enter office that issued the document, by the two-letter code (WIPO Standard ST.3). [3] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [4] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [5] Applicant is to place a check mark here if English language translation is attached.

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Receipt date: 08/11/2023

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (not for submission under 37 CFR 1.99)		
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	Art Unit	1647
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	Examiner Name	Jon Mcclelland Lockard
	Attorney Docket Number	125984-266215

U.S. PATENTS						
Examiner Initial*	Cite No	Patent Number	Kind Code[1]	Issue Date	Name of Patentee or Applicant of cited Document	Pages, Columns, Lines where Relevant Passages or Relevant Figures Appear
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U.S. PATENT APPLICATION PUBLICATIONS						
Examiner Initial*	Cite No	Publication Number	Kind Code[1]	Publication Date	Name of Patentee or Applicant of cited Document	Pages, Columns, Lines where Relevant Passages or Relevant Figures Appear

FOREIGN PATENT DOCUMENTS								
Examiner Initial*	Cite No	Foreign Document Number[3]	Country Code[2]	Kind Code[4]	Publication Date	Name of Patentee or Applicant of cited Document	Pages, Columns, Lines where Relevant Passages or Relevant Figures Appear	T[5]
/J.L/	552	2014/005728	WO	A1	01-09-2014	Novartis AG		

NON-PATENT LITERATURE DOCUMENTS			
Examiner Initial*	Cite No	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, pages(s), volume-issue number(s), publisher, city and/or country where published	T[5]

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Receipt date: 08/11/2023

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (not for submission under 37 CFR 1.99)		
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	Art Unit	1647
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	Examiner Name	Jon Mcclelland Lockard
	Attorney Docket Number	125984-266215

EXAMINER SIGNATURE			
Examiner Signature	/JON M LOCKARD/	Date Considered	08/24/2023

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Alvotech v. Regeneron
PGR2025-00085
Page 322 of 531

PE2E SEARCH - Search History (Prior Art)

/J.L./

There are no Prior Art searches to show.

PE2E SEARCH - Search History (Interference)

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	British Equivalents	Time Stamp
N1	2547	L1	(USPAT)	OR	ON	ON	2023/08/24 11:38 PM
N2	2551	L2	(USPAT)	OR	ON	ON	2023/08/24 11:38 PM
N3	249	L3	(USPAT)	OR	ON	ON	2023/08/24 11:38 PM
N4	106	L4	(USPAT)	OR	ON	ON	2023/08/24 11:38 PM
N5	393	(N1 N2 N3 N4) SAME formulation	(USPAT)	OR	ON	ON	2023/08/24 11:39 PM
N6	12	N5 SAME "high concentration"	(USPAT)	OR	ON	ON	2023/08/24 11:39 PM
N7	24	N5 SAME (8mg OR "8 mg")	(USPAT)	OR	ON	ON	2023/08/24 11:40 PM
N8	1	N5 SAME (8mg OR "8 mg").clm.	(USPAT)	OR	ON	ON	2023/08/24 11:40 PM
N9	17	(graham-k$-s$ washawa-s$).in.	(USPAT)	OR	ON	ON	2023/08/24 11:41 PM
N10	5	N5 AND N9	(USPAT)	OR	ON	ON	2023/08/24 11:41 PM

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Alvotech v. Regeneron
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Receipt date: 12/03/2021

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (not for submission under 37 CFR 1.99)		
	Application Number	17/384,070
	Filing Date	Jul-23-2021
	First Named Inventor	Kenneth S. Graham
	Art Unit	~~Not Yet Assigned~~ 1647
	Confirmation Number	1061
	Examiner Name	~~Not Yet Assigned~~ Jon Lockard
	Attorney Docket Number	125984-266215 / 10430US02

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Regeneron Ex. 2001
Alvotech v. Regeneron
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APPLICATION NO.	ISSUE DATE	PATENT NO.	ATTORNEY DOCKET NO.	CONFIRMATION NO.
17/384,070	10/17/2023	11786576		1061

147803 7590 09/27/2023

Schwabe W&W, PC / Regeneron Pharmaceuticals, Inc.
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1211 SW Fifth Avenue, Suite 1900
Portland, OR 97204

ISSUE NOTIFICATION

The projected patent number and issue date are specified above. The patent will issue electronically. The electronically issued patent is the official patent grant pursuant to 35 U.S.C. § 153. The patent may be accessed on or after the issue date through Patent Center at https://patentcenter.uspto.gov/. The patent will be available in both the public and the private sides of Patent Center. Further assistance in electronically accessing the patent, or about Patent Center, is available by calling the Patent Electronic Business Center at 1-888-217-9197.

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Determination of Patent Term Adjustment under 35 U.S.C. 154 (b)
(application filed on or after May 29, 2000)

The Patent Term Adjustment is 130 day(s). Any patent to issue from the above-identified application will include an indication of the adjustment on the front page.

If a Continued Prosecution Application (CPA) was filed in the above-identified application, the filing date that determines Patent Term Adjustment is the filing date of the most recent CPA.

Applicant will be able to obtain more detailed information by accessing the Patent Center (https://patentcenter.uspto.gov).

Any questions regarding the Patent Term Extension or Adjustment determination should be directed to the Office of Patent Legal Administration at (571)-272-7702. Questions relating to issue and publication fee payments should be directed to the Application Assistance Unit (AAU) of the Office of Patents Stakeholder Experience (OPSE), Stakeholder Support Division (SSD) at (571)-272-4200.

IR103 (Rev. 10/09)

INVENTOR(s) (Please see PATENT CENTER site https://patentcenter.uspto.gov for additional inventors):

Kenneth S. Graham, Pleasant Valley, NY;
Saurabh WADHWA, Nanuet, NY;

APPLICANT(s) (Please see PATENT CENTER site https://patentcenter.uspto.gov for additional applicants):

Regeneron Pharmaceuticals, Inc., Tarrytown, NY;

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	Attorney Docket Number	125984-266215

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	Examiner Name	Lockard, Jon McClelland
	Attorney Docket Number	125984-266215

CERTIFICATION STATEMENT

Please see 37 CFR 1.97 and 1.98 to make the appropriate selection(s):

☐ That each item of information contained in the information disclosure statement was first cited in any communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(1).

OR

☐ That no item of information contained in the information disclosure statement was cited in a communication from a foreign patent office in a counterpart foreign application, and, to the knowledge of the person signing the certification after making reasonable inquiry, no item of information contained in the information disclosure statement was known to any individual designated in 37 CFR 1.56(c) more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(2).

☐ See attached certification statement.

☐ Fee set forth in 37 CFR 1.17 (p) has been submitted herewith.

☒ None

SIGNATURE

A signature of the applicant or representative is required in accordance with CFR 1.33, 10.18. Please see CFR 1.4(d) for the form of the signature.

Signature	/Lance A. Termes/	Date (YYYY-MM-DD)	2023-10-11
Name/Print	Lance A. Termes	Registration Number	43184

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Alvotech v. Regeneron
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PTO/SB/30 (11-17)
Approved for use through 05/31/2024. OMB 0651-0031
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Request for Continued Examination (RCE) Transmittal

Address to:
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Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Application Number	17/384,070
Filing Date	July 23, 2021
First Named Inventor	Kenneth S. Graham
Art Unit	1647
Examiner Name	Jon McClelland Lockard
Attorney Docket Number	125984-266215

This is a Request for Continued Examination (RCE) under 37 CFR 1.114 of the above-identified application.
Request for Continued Examination (RCE) practice under 37 CFR 1.114 does not apply to any utility or plant application filed prior to June 8, 1995, or to any design application. See Instruction Sheet for RCEs (not to be submitted to the USPTO) on page 2.

1. Submission required under 37 CFR 1.114 Note: If the RCE is proper, any previously filed unentered amendments and amendments enclosed with the RCE will be entered in the order in which they were filed unless applicant instructs otherwise. If applicant does not wish to have any previously filed unentered amendment(s) entered, applicant must request non-entry of such amendment(s).

   a. ☐ Previously submitted. If a final Office action is outstanding, any amendments filed after the final Office action may be considered as a submission even if this box is not checked.

      i. ☐ Consider the arguments in the Appeal Brief or Reply Brief previously filed on _____

      ii. ☐ Other _____

   b. ☑ Enclosed

      i. ☐ Amendment/Reply

      ii. ☐ Affidavit(s)/ Declaration(s)

      iii. ☑ Information Disclosure Statement (IDS)

      iv. ☐ Other _____

2. Miscellaneous

   a. ☐ Suspension of action on the above-identified application is requested under 37 CFR 1.103(c) for a period of _____ months. (Period of suspension shall not exceed 3 months; Fee under 37 CFR 1.17(i) required)

   b. ☐ Other _____

3. Fees The RCE fee under 37 CFR 1.17(e) is required by 37 CFR 1.114 when the RCE is filed.

   a. ☑ The Director is hereby authorized to charge the following fees, any underpayment of fees, or credit any overpayments, to Deposit Account No. 500393.

      i. ☑ RCE fee required under 37 CFR 1.17(e)

      ii. ☐ Extension of time fee (37 CFR 1.136 and 1.17)

      iii. ☐ Other _____

   b. ☐ Check in the amount of $ _____ enclosed

   c. ☐ Payment by credit card (Form PTO-2038 enclosed)

   d. ▩ Payment by EFS-Web

WARNING: Information on this form may become public. Credit card information should not be included on this form. Provide credit card information and authorization on PTO-2038.

SIGNATURE OF APPLICANT, ATTORNEY, OR AGENT REQUIRED

Signature	/Lance A. Termes/	Date	October 11, 2023
Name (Print/Type)	Lance A. Termes	Registration No.	43,184

CERTIFICATE OF MAILING OR TRANSMISSION

I hereby certify that this correspondence is being EFS-Web transmitted to the United States Patent and Trademark Office (USPTO), deposited with the United States Postal Service with sufficient postage as first class mail in an envelope addressed to: Mail Stop RCE, Commissioner for Patents, P. O. Box 1450, Alexandria, VA 22313-1450 or facsimile transmitted to the USPTO on the date shown below.

Signature	/Lance A. Termes/		
Name (Print/Type)	Lance A. Termes	Date	October 11, 2023

A Federal agency may not conduct or sponsor, and a person is not required to respond to, nor shall a person be subject to a penalty for failure to comply with an information collection subject to the requirements of the Paperwork Reduction Act of 1995, unless the information collection has a currently valid OMB Control Number. The OMB Control Number for this information collection is 0651-0031. Public burden for this form is estimated to average 12 minutes per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the information collection. Send comments regarding this burden estimate or any other aspect of this information collection, including suggestions for reducing this burden to the Chief Administrative Officer, United States Patent and Trademark Office, P.O. Box 1450, Alexandria, VA 22313-1450 or email InformationCollection@uspto.gov. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **If filing this completed form by mail, send to:**

Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.

If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (not for submission under 37 CFR 1.99)		
	Application Number	17/384,070
	Filing Date	Jul-23-2021
	First Named Inventor	Kenneth S. Graham
	Art Unit	1647
	Confirmation Number	1061
	Examiner Name	Lockard, Jon McClelland
	Attorney Docket Number	125984-266215

U.S. PATENTS						
Examiner Initial*	Cite No	Patent Number	Kind Code[1]	Issue Date	Name of Patentee or Applicant of cited Document	Pages, Columns, Lines where Relevant Passages or Relevant Figures Appear
	557	11,730,794		08-22-2023	Yancopoulos	
	558	11,732,024		08-22-2023	Furfine et al.	

U.S. PATENT APPLICATION PUBLICATIONS						
Examiner Initial*	Cite No	Publication Number	Kind Code[1]	Publication Date	Name of Patentee or Applicant of cited Document	Pages, Columns, Lines where Relevant Passages or Relevant Figures Appear

FOREIGN PATENT DOCUMENTS								
Examiner Initial*	Cite No	Foreign Document Number[3]	Country Code[2]	Kind Code[4]	Publication Date	Name of Patentee or Applicant of cited Document	Pages, Columns, Lines where Relevant Passages or Relevant Figures Appear	T[5]

NON-PATENT LITERATURE DOCUMENTS			
Examiner Initial*	Cite No	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, pages(s), volume-issue number(s), publisher, city and/or country where published	T[5]

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT (not for submission under 37 CFR 1.99)		
	Application Number	17/384,070
	Filing Date	Jul-23-2021
	First Named Inventor	Kenneth S. Graham
	Art Unit	1647
	Confirmation Number	1061
	Examiner Name	Lockard, Jon McClelland
	Attorney Docket Number	125984-266215

EXAMINER SIGNATURE			
Examiner Signature		Date Considered	

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through a citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

[1] See Kind Codes of USPTO Patent Documents at www.USPTO.GOV or MPEP 901.04. [2] Enter office that issued the document, by the two-letter code (WIPO Standard ST.3). [3] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [4] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [5] Applicant is to place a check mark here if English language translation is attached.

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (not for submission under 37 CFR 1.99)		
	Application Number	17/384,070
	Filing Date	Jul-23-2021
	First Named Inventor	Kenneth S. Graham
	Art Unit	1647
	Confirmation Number	1061
	Examiner Name	Lockard, Jon McClelland
	Attorney Docket Number	125984-266215

CERTIFICATION STATEMENT

Please see 37 CFR 1.97 and 1.98 to make the appropriate selection(s):

☐ That each item of information contained in the information disclosure statement was first cited in any communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(1).

OR

☐ That no item of information contained in the information disclosure statement was cited in a communication from a foreign patent office in a counterpart foreign application, and, to the knowledge of the person signing the certification after making reasonable inquiry, no item of information contained in the information disclosure statement was known to any individual designated in 37 CFR 1.56(c) more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(2).

☐ See attached certification statement.

☐ Fee set forth in 37 CFR 1.17 (p) has been submitted herewith.

☒ None

SIGNATURE

A signature of the applicant or representative is required in accordance with CFR 1.33, 10.18. Please see CFR 1.4(d) for the form of the signature.

Signature	/Lance A. Termes/	Date (YYYY-MM-DD)	2023-10-16
Name/Print	Lance A. Termes	Registration Number	43184

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UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

NOTICE OF ALLOWANCE AND FEE(S) DUE

147803 7590 11/08/2023

Schwabe W&W, PC / Regeneron Pharmaceuticals, Inc.
PacWest Center
1211 SW Fifth Avenue, Suite 1900
Portland, OR 97204

EXAMINER	
LOCKARD, JON MCCLELLAND	
ART UNIT	PAPER NUMBER
1647	

DATE MAILED: 11/08/2023

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
17/384,070	07/23/2021	Kenneth S. Graham		1061

TITLE OF INVENTION: Methods for Treating Angiogenic Eye Disorders with High Doses of VEGF Receptor Fusion Proteins

APPLN. TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	UNDISCOUNTED	$1200	$0.00	$1200.00	$0	02/08/2024

THE APPLICATION IDENTIFIED ABOVE HAS BEEN EXAMINED AND IS ALLOWED FOR ISSUANCE AS A PATENT. PROSECUTION ON THE MERITS IS CLOSED. THIS NOTICE OF ALLOWANCE IS NOT A GRANT OF PATENT RIGHTS. THIS APPLICATION IS SUBJECT TO WITHDRAWAL FROM ISSUE AT THE INITIATIVE OF THE OFFICE OR UPON PETITION BY THE APPLICANT. SEE 37 CFR 1.313 AND MPEP 1308.

THE ISSUE FEE AND PUBLICATION FEE (IF REQUIRED) MUST BE PAID WITHIN THREE MONTHS FROM THE MAILING DATE OF THIS NOTICE OR THIS APPLICATION SHALL BE REGARDED AS ABANDONED. THIS STATUTORY PERIOD CANNOT BE EXTENDED. SEE 35 U.S.C. 151. THE ISSUE FEE DUE INDICATED ABOVE DOES NOT REFLECT A CREDIT FOR ANY PREVIOUSLY PAID ISSUE FEE IN THIS APPLICATION. IF AN ISSUE FEE HAS PREVIOUSLY BEEN PAID IN THIS APPLICATION (AS SHOWN ABOVE), THE RETURN OF PART B OF THIS FORM WILL BE CONSIDERED A REQUEST TO REAPPLY THE PREVIOUSLY PAID ISSUE FEE TOWARD THE ISSUE FEE NOW DUE.

HOW TO REPLY TO THIS NOTICE:

I. Review the ENTITY STATUS shown above. If the ENTITY STATUS is shown as SMALL or MICRO, verify whether entitlement to that entity status still applies.

If the ENTITY STATUS is the same as shown above, pay the TOTAL FEE(S) DUE shown above.

If the ENTITY STATUS is changed from that shown above, on PART B - FEE(S) TRANSMITTAL, complete section number 5 titled "Change in Entity Status (from status indicated above)".

For purposes of this notice, small entity fees are 40% the amount of undiscounted fees, and micro entity fees are 20% the amount of undiscounted fees.

II. PART B - FEE(S) TRANSMITTAL, or its equivalent, must be completed and returned to the United States Patent and Trademark Office (USPTO) with your ISSUE FEE and PUBLICATION FEE (if required). If you are charging the fee(s) to your deposit account, section "4b" of Part B - Fee(s) Transmittal should be completed. If an equivalent of Part B is filed, a request to reapply a previously paid issue fee must be clearly made, and delays in processing may occur due to the difficulty in recognizing the paper as an equivalent of Part B.

III. All communications regarding this application must give the application number. Please direct all communications prior to issuance to Mail Stop ISSUE FEE unless advised to the contrary.

IMPORTANT REMINDER: Maintenance fees are due in utility patents issuing on applications filed on or after Dec. 12, 1980. It is patentee's responsibility to ensure timely payment of maintenance fees when due. More information is available at www.uspto.gov/PatentMaintenanceFees.

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PART B - FEE(S) TRANSMITTAL

Complete and send this form, together with applicable fee(s), by mail or fax, or via EFS-Web.

By mail, send to: Mail Stop ISSUE FEE
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450

By fax, send to: (571)-273-2885

INSTRUCTIONS: This form should be used for transmitting the ISSUE FEE and PUBLICATION FEE (if required). Blocks 1 through 5 should be completed where appropriate. All further correspondence will be mailed to the current correspondence address as indicated unless corrected below or directed otherwise in Block 1, by (a) specifying a new correspondence address; and/or (b) indicating a separate "FEE ADDRESS" for maintenance fee notifications. **Because electronic patent issuance may occur shortly after issue fee payment, any desired continuing application should preferably be filed prior to payment of this issue fee in order not to jeopardize copendency.**

CURRENT CORRESPONDENCE ADDRESS (Note: Use Block 1 for any change of address)

147803 7590 11/08/2023
Schwabe W&W, PC / Regeneron Pharmaceuticals, Inc.
PacWest Center
1211 SW Fifth Avenue, Suite 1900
Portland, OR 97204

Note: A certificate of mailing can only be used for domestic mailings of the Fee(s) Transmittal. This certificate cannot be used for any other accompanying papers. Each additional paper, such as an assignment or formal drawing, must have its own certificate of mailing or transmission.

Certificate of Mailing or Transmission

I hereby certify that this Fee(s) Transmittal is being deposited with the United States Postal Service with sufficient postage for first class mail in an envelope addressed to the Mail Stop ISSUE FEE address above, or being transmitted to the USPTO via EFS-Web or by facsimile to (571) 273-2885, on the date below.

(Typed or printed name)
(Signature)
(Date)

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
17/384,070	07/23/2021	Kenneth S. Graham		1061

TITLE OF INVENTION: Methods for Treating Angiogenic Eye Disorders with High Doses of VEGF Receptor Fusion Proteins

APPLN. TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	UNDISCOUNTED	$1200	$0.00	$1200.00	$0	02/08/2024

EXAMINER	ART UNIT	CLASS-SUBCLASS
LOCKARD, JON MCCLELLAND	1647	424-134100

1. Change of correspondence address or indication of "Fee Address" (37 CFR 1.363).

❑ Change of correspondence address (or Change of Correspondence Address form PTO/AIA/122 or PTO/SB/122) attached.

❑ "Fee Address" indication (or "Fee Address" Indication form PTO/AIA/47 or PTO/SB/47; Rev 03-02 or more recent) attached. **Use of a Customer Number is required.**

2. For printing on the patent front page, list
(1) The names of up to 3 registered patent attorneys or agents OR, alternatively,
(2) The name of a single firm (having as a member a registered attorney or agent) and the names of up to 2 registered patent attorneys or agents. If no name is listed, no name will be printed.

1 _____
2 _____
3 _____

3. ASSIGNEE NAME AND RESIDENCE DATA TO BE PRINTED ON THE PATENT (print or type)

PLEASE NOTE: Unless an assignee is identified below, no assignee data will appear on the patent. If an assignee is identified below, the document must have been previously recorded, or filed for recordation, as set forth in 37 CFR 3.11 and 37 CFR 3.81(a). Completion of this form is NOT a substitute for filing an assignment.

(A) NAME OF ASSIGNEE (B) RESIDENCE: (CITY and STATE OR COUNTRY)

Please check the appropriate assignee category or categories (will not be printed on the patent) : ❑ Individual ❑ Corporation or other private group entity ❑ Government

4a. Fees submitted: ❑Issue Fee ❑Publication Fee (if required)

4b. Method of Payment: *(Please first reapply any previously paid fee shown above)*

❑ Electronic Payment via Patent Center or EFS-Web ❑ Enclosed check ❑ Non-electronic payment by credit card (Attach form PTO-2038)

❑ The Director is hereby authorized to charge the required fee(s), any deficiency, or credit any overpayment to Deposit Account No. _____

5. **Change in Entity Status** (from status indicated above)

❑ Applicant certifying micro entity status. See 37 CFR 1.29

NOTE: Absent a valid certification of Micro Entity Status (see forms PTO/SB/15A and 15B), issue fee payment in the micro entity amount will not be accepted at the risk of application abandonment.

❑ Applicant asserting small entity status. See 37 CFR 1.27

NOTE: If the application was previously under micro entity status, checking this box will be taken to be a notification of loss of entitlement to micro entity status.

❑ Applicant changing to regular undiscounted fee status.

NOTE: Checking this box will be taken to be a notification of loss of entitlement to small or micro entity status, as applicable.

NOTE: This form must be signed in accordance with 37 CFR 1.31 and 1.33. See 37 CFR 1.4 for signature requirements and certifications.

Authorized Signature _____ Date _____

Typed or printed name _____ Registration No. _____

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UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
17/384,070	07/23/2021	Kenneth S. Graham		1061

147803 7590 11/08/2023

Schwabe W&W, PC / Regeneron Pharmaceuticals, Inc.
PacWest Center
1211 SW Fifth Avenue, Suite 1900
Portland, OR 97204

EXAMINER	
LOCKARD, JON MCCLELLAND	
ART UNIT	**PAPER NUMBER**
1647	

DATE MAILED: 11/08/2023

Determination of Patent Term Adjustment under 35 U.S.C. 154 (b)
(Applications filed on or after May 29, 2000)

The Office has discontinued providing a Patent Term Adjustment (PTA) calculation with the Notice of Allowance.

Section 1(h)(2) of the AIA Technical Corrections Act amended 35 U.S.C. 154(b)(3)(B)(i) to eliminate the requirement that the Office provide a patent term adjustment determination with the notice of allowance. See Revisions to Patent Term Adjustment, 78 Fed. Reg. 19416, 19417 (Apr. 1, 2013). Therefore, the Office is no longer providing an initial patent term adjustment determination with the notice of allowance. The Office will continue to provide a patent term adjustment determination with the Issue Notification Letter that is mailed to applicant approximately three weeks prior to the issue date of the patent, and will include the patent term adjustment on the patent. Any request for reconsideration of the patent term adjustment determination (or reinstatement of patent term adjustment) should follow the process outlined in 37 CFR 1.705.

Any questions regarding the Patent Term Extension or Adjustment determination should be directed to the Office of Patent Legal Administration at (571)-272-7702. Questions relating to issue and publication fee payments should be directed to the Customer Service Center of the Office of Patent Publication at 1-(888)-786-0101 or (571)-272-4200.

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OMB Clearance and PRA Burden Statement for PTOL-85 Part B

The Paperwork Reduction Act (PRA) of 1995 requires Federal agencies to obtain Office of Management and Budget approval before requesting most types of information from the public. When OMB approves an agency request to collect information from the public, OMB (i) provides a valid OMB Control Number and expiration date for the agency to display on the instrument that will be used to collect the information and (ii) requires the agency to inform the public about the OMB Control Number's legal significance in accordance with 5 CFR 1320.5(b).

The information collected by PTOL-85 Part B is required by 37 CFR 1.311. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 30 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, Virginia 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, Virginia 22313-1450. Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

Privacy Act Statement

The Privacy Act of 1974 (P.L. 93-579) requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether disclosure of these records is required by the Freedom of Information Act.
2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.
3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.
4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).
5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.
6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).
7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.
8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspection or an issued patent.
9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

Notice of Allowability	Application No. 17/384,070	Applicant(s) Graham et al.	
	Examiner JON M LOCKARD	Art Unit 1647	AIA (FITF) Status Yes

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address--

All claims being allowable, PROSECUTION ON THE MERITS IS (OR REMAINS) CLOSED in this application. If not included herewith (or previously mailed), a Notice of Allowance (PTOL-85) or other appropriate communication will be mailed in due course. **THIS NOTICE OF ALLOWABILITY IS NOT A GRANT OF PATENT RIGHTS.** This application is subject to withdrawal from issue at the initiative of the Office or upon petition by the applicant. See 37 CFR 1.313 and MPEP 1308.

1. ☑ This communication is responsive to the Request for Continued Examination filed 11 October 2023.
   ☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on _____.

2. ☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.

3. ☑ The allowed claim(s) is/are See Continuation Sheet . As a result of the allowed claim(s), you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information, please see **http://www.uspto.gov/patents/init_events/pph/index.jsp** or send an inquiry to **PPHfeedback@uspto.gov.**

4. ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

   Certified copies:

   a) ☐ All b) ☐ Some* c) ☐ None of the:

   1. ☐ Certified copies of the priority documents have been received.
   2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
   3. ☐ Copies of the certified copies of the priority documents have been received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

   * Certified copies not received: _____ .

Applicant has THREE MONTHS FROM THE "MAILING DATE" of this communication to file a reply complying with the requirements noted below. Failure to timely comply will result in ABANDONMENT of this application.
THIS THREE-MONTH PERIOD IS NOT EXTENDABLE.

5. ☐ CORRECTED DRAWINGS (as "replacement sheets") must be submitted.
   ☐ including changes required by the attached Examiner's Amendment / Comment or in the Office action of Paper No./Mail Date _____ .

   Identifying indicia such as the application number (see 37 CFR 1.84(c)) should be written on the drawings in the front (not the back) of each sheet. Replacement sheet(s) should be labeled as such in the header according to 37 CFR 1.121(d).

6. ☐ DEPOSIT OF and/or INFORMATION about the deposit of BIOLOGICAL MATERIAL must be submitted. Note the attached Examiner's comment regarding REQUIREMENT FOR THE DEPOSIT OF BIOLOGICAL MATERIAL.

Attachment(s)

1. ☐ Notice of References Cited (PTO-892)
2. ☑ Information Disclosure Statements (PTO/SB/08), Paper No./Mail Date _____.
3. ☐ Examiner's Comment Regarding Requirement for Deposit of Biological Material _____.
4. ☐ Interview Summary (PTO-413), Paper No./Mail Date. _____.
5. ☐ Examiner's Amendment/Comment
6. ☑ Examiner's Statement of Reasons for Allowance
7. ☐ Other _____.

/J.L/ Examiner, Art Unit 1647	/CHRISTINE J SAOUD/ Primary Examiner, Art Unit 1645

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Continuation of 3. The allowed claim(s) is/are: 30-32 and 53-87 (renumbered as claims 1-11,13-14,16,18,20,22,24,12,26,15,17,19,21,23,25 and 27-38, respectively)

Notice of Pre-AIA or AIA Status

1. The present application, filed on or after March 16, 2013, is being examined under the first inventor to file provisions of the AIA.

Continued Examination Under 37 CFR 1.114

2. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after allowance or after an Office action under *Ex Parte Quayle*, 25 USPQ 74, 453 O.G. 213 (Comm'r Pat. 1935). Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, prosecution in this application has been reopened pursuant to 37 CFR 1.114. Applicant's submission filed on 11 October 2023 has been entered.

Information Disclosure Statement

3. The information disclosure statements (IDS) submitted on 11 October 2023 and 16 October 2023 have been considered by the examiner.

REASONS FOR ALLOWANCE

4. The following is an examiner's statement of reasons for allowance: The information disclosure statements (IDS) submitted on 11 October 2023 and 16 October 2023 have been considered by the Examiner. After careful consideration, the Examiner has determined that none of the information contained therein raises new issues of patentability.

5. Any comments considered necessary by applicant must be submitted no later than the payment of the issue fee and, to avoid processing delays, should preferably accompany the issue

fee. Such submissions should be clearly labeled "Comments on Statement of Reasons for Allowance."

Summary

6. Claims 30-32 and 53-87 are allowed.

Advisory Information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to **JON M LOCKARD** whose telephone number is **(571) 272-2717**. The examiner can normally be reached M-F 9-6 EST.

Examiner interviews are available via telephone, in-person, and video conferencing using a USPTO supplied web-based collaboration tool. To schedule an interview, applicant is encouraged to use the USPTO Automated Interview Request (AIR) at http://www.uspto.gov/interviewpractice. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, **Joanne Hama** can be reached on **(571) 272-2911**. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of published or unpublished applications may be obtained from Patent Center. Unpublished application information in Patent Center is available to registered users. To file and manage patent submissions in Patent Center, visit: https://patentcenter.uspto.gov. Visit https://www.uspto.gov/patents/apply/patent-center for more information about Patent Center and https://www.uspto.gov/patents/docx for information about filing in DOCX format. For additional questions, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Christine J Saoud/
Primary Examiner, Art Unit 1645

/J.L/
Examiner, Art Unit 1647
November 1, 2023

Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
	17/384,070	Graham et al.
	Examiner	Art Unit
	JON M LOCKARD	1647

CPC - Searched*		
Symbol	Date	Examiner

CPC Combination Sets - Searched*		
Symbol	Date	Examiner

US Classification - Searched*			
Class	Subclass	Date	Examiner
NONE		03/16/2023	JML

* See search history printout included with this form or the SEARCH NOTES box below to determine the scope of the search.

Search Notes		
Search Notes	Date	Examiner
PE2E Search (USPAT, US-PGPUB, EPO, DERWENT): See attached search history.	03/16/2023	JML
STN (MEDLINE, SCISEARCH, EMBASE, BIOSIS): See attached search history.	03/16/2023	JML
PALM: Inventor search.	03/16/2023	JML
PE2E Search (USPAT, US-PGPUB, EPO, DERWENT): See attached search history.	11/01/2023	JML

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Alvotech v. Regeneron
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Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
	17/384,070	Graham et al.
	Examiner	Art Unit
	JON M LOCKARD	1647

Interference Search			
US Class/CPC Symbol	**US Subclass/CPC Group**	**Date**	**Examiner**
	PE2E Search (USPAT): See attached search history.	08/24/2023	JML
	DAV: Inventor search.	08/24/2023	JML
	PE2E Search (USPAT): See attached search history.	11/01/2023	JML
	DAV: Inventor search.	11/01/2023	JML

Regeneron Ex. 2001
Alvotech v. Regeneron
PGR2025-00085
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Issue Classification	Application/Control No.	Applicant(s)/Patent Under Reexamination
	17/384,070	Graham et al.
	Examiner	Art Unit
	JON M LOCKARD	1647

CPC										
Symbol									Type	Version
A61K	/	38	/	179					F	2013-01-01
A61K	/	9	/	0048					I	2013-01-01
A61K	/	47	/	12					I	2013-01-01
A61P	/	27	/	02					I	2018-01-01
A61K	/	47	/	22					I	2013-01-01
A61K	/	47	/	26					I	2013-01-01
A61K	/	47	/	183					I	2013-01-01

CPC Combination Sets										
Symbol									Type	Set	Ranking	Version
	/		/									

/JON M LOCKARD/ Examiner, Art Unit 1647	01 November 2023	Total Claims Allowed:	
(Assistant Examiner)	(Date)	38	
/CHRISTINE J SAOUD/ Primary Examiner, Art Unit 1645	02 November 2023	O.G. Print Claim(s)	O.G. Print Figure
(Primary Examiner)	(Date)	1	NONE

U.S. Patent and Trademark Office — Part of Paper No.: 20231031

Regeneron Ex. 2001
Alvotech v. Regeneron
PGR2025-00085
Page 345 of 531

Issue Classification	Application/Control No.	Applicant(s)/Patent Under Reexamination
	17/384,070	Graham et al.
	Examiner	Art Unit
	JON M LOCKARD	1647

INTERNATIONAL CLASSIFICATION					
CLAIMED					
A61K	/	38	/	17	
A61K	/	38	/	18	
C07K	/	14	/	71	

NON-CLAIMED				
	/		/	

US ORIGINAL CLASSIFICATION	
CLASS	SUBCLASS

CROSS REFERENCES(S)						
CLASS	SUBCLASS (ONE SUBCLASS PER BLOCK)					

/JON M LOCKARD/ Examiner, Art Unit 1647	01 November 2023	Total Claims Allowed:	
(Assistant Examiner)	(Date)	38	
/CHRISTINE J SAOUD/ Primary Examiner, Art Unit 1645	02 November 2023	O.G. Print Claim(s)	O.G. Print Figure
(Primary Examiner)	(Date)	1	NONE

U.S. Patent and Trademark Office — Part of Paper No.: 20231031

Regeneron Ex. 2001
Alvotech v. Regeneron
PGR2025-00085
Page 346 of 531

Issue Classification	Application/Control No.	Applicant(s)/Patent Under Reexamination
	17/384,070	Graham et al.
	Examiner	Art Unit
	JON M LOCKARD	1647

☐ Claims renumbered in the same order as presented by applicant ☐ CPA ☑ T.D. ☐ R.1.47

CLAIMS

Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original
1	30	10	59	12	68	28	77	37	86						
2	31	11	60	26	69	29	78	38	87						
3	32	13	61	15	70	30	79								
4	53	14	62	17	71	31	80								
5	54	16	63	19	72	32	81								
6	55	18	64	21	73	33	82								
7	56	20	65	23	74	34	83								
8	57	22	66	25	75	35	84								
9	58	24	67	27	76	36	85								

/JON M LOCKARD/ Examiner, Art Unit 1647 (Assistant Examiner)	01 November 2023 (Date)	**Total Claims Allowed:** 38	
/CHRISTINE J SAOUD/ Primary Examiner, Art Unit 1645 (Primary Examiner)	02 November 2023 (Date)	O.G. Print Claim(s) 1	O.G. Print Figure NONE

Regeneron Ex. 2001
Alvotech v. Regeneron
PGR2025-00085
Page 347 of 531

PE2E SEARCH - Search History (Prior Art)

/J.L./

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	British Equivalents	Time Stamp
L15	7	"11730794".pn. "11732024".pn. "11103552".pn.	(US-PGPUB; USPAT; EPO; DERWENT)	OR	ON	ON	2023/11/01 03:27 PM
L16	1	wo-2019217927-$.did.	(US-PGPUB; USPAT; EPO; DERWENT)	OR	ON	ON	2023/11/01 03:27 PM
L17	2	wo-2019217927-$.did.	(US-PGPUB; USPAT; FIT (AU, AP, AT, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, OA, RU, SU, WO, MC, MD, MY, NL, NO, NZ, PH, PL, PT, RO, RS, SE, SG, SI, SK, TH, TN, TR, TW, UA, VN); EPO; DERWENT)	OR	ON	ON	2023/11/01 03:55 PM

PE2E SEARCH - Search History (Interference)

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	British Equivalents	Time Stamp
N11	3	"11730794".pn. "11732024".pn. "11103552".pn.	(US-PGPUB; USPAT)	OR	ON	ON	2023/11/01 04:04 PM

Regeneron Ex. 2001
Alvotech v. Regeneron
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Page 348 of 531

Receipt date: 10/11/2023

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (not for submission under 37 CFR 1.99)		
	Application Number	17/384,070
	Filing Date	Jul-23-2021
	First Named Inventor	Kenneth S. Graham
	Art Unit	1647
	Confirmation Number	1061
	Examiner Name	Lockard, Jon McClelland
	Attorney Docket Number	125984-266215

U.S. PATENTS						
Examiner Initial*	Cite No	Patent Number	Kind Code[1]	Issue Date	Name of Patentee or Applicant of cited Document	Pages, Columns, Lines where Relevant Passages or Relevant Figures Appear

U.S. PATENT APPLICATION PUBLICATIONS						
Examiner Initial*	Cite No	Publication Number	Kind Code[1]	Publication Date	Name of Patentee or Applicant of cited Document	Pages, Columns, Lines where Relevant Passages or Relevant Figures Appear

FOREIGN PATENT DOCUMENTS								
Examiner Initial*	Cite No	Foreign Document Number[3]	Country Code[2]	Kind Code[4]	Publication Date	Name of Patentee or Applicant of cited Document	Pages, Columns, Lines where Relevant Passages or Relevant Figures Appear	T[5]

NON-PATENT LITERATURE DOCUMENTS			
Examiner Initial*	Cite No	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, pages(s), volume-issue number(s), publisher, city and/or country where published	T[5]
/J.L/	555	BAKRI et al., "Pharmacokinetics of Intravitreal Ranibizumab (Lucentis)," American Academy of Ophthalmology, Volume 114, Number 12: 2179-2182, (2007). [doi:10.1016/j.ophtha.2007.09.012].	
/J.L/	556	CHOI et al., "Normative Data of Ocular Biometry, Optical Coherence Tomography, and Electrophysiology Conducted for Cynomolgus Macaque Monkeys," Translational Vision Science & Technology, Volume 10 (No. 13) Article 14: 1-11, (2021). [Retrieved from the Internet 10/04/2023: https://doi.org/10.1167/tvst.10.13.14].	

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Alvotech v. Regeneron
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INFORMATION DISCLOSURE STATEMENT BY APPLICANT (not for submission under 37 CFR 1.99)		
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	Art Unit	1647
	Confirmation Number	1061
	Examiner Name	Lockard, Jon McClelland
	Attorney Docket Number	125984-266215

EXAMINER SIGNATURE			
Examiner Signature	/JON M LOCKARD/	Date Considered	11/01/2023

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through a citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

[1] See Kind Codes of USPTO Patent Documents at www.USPTO.GOV or MPEP 901.04. [2] Enter office that issued the document, by the two-letter code (WIPO Standard ST.3). [3] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [4] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [5] Applicant is to place a check mark here if English language translation is attached.

Receipt date: 10/16/2023

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (not for submission under 37 CFR 1.99)		
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	Filing Date	Jul-23-2021
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	Confirmation Number	1061
	Examiner Name	Lockard, Jon McClelland
	Attorney Docket Number	125984-266215

U.S. PATENTS						
Examiner Initial*	Cite No	Patent Number	Kind Code[1]	Issue Date	Name of Patentee or Applicant of cited Document	Pages, Columns, Lines where Relevant Passages or Relevant Figures Appear
/J.L/	557	11,730,794		08-22-2023	Yancopoulos	
/J.L/	558	11,732,024		08-22-2023	Furfine et al.	

U.S. PATENT APPLICATION PUBLICATIONS						
Examiner Initial*	Cite No	Publication Number	Kind Code[1]	Publication Date	Name of Patentee or Applicant of cited Document	Pages, Columns, Lines where Relevant Passages or Relevant Figures Appear

FOREIGN PATENT DOCUMENTS								
Examiner Initial*	Cite No	Foreign Document Number[3]	Country Code[2]	Kind Code[4]	Publication Date	Name of Patentee or Applicant of cited Document	Pages, Columns, Lines where Relevant Passages or Relevant Figures Appear	T[5]

NON-PATENT LITERATURE DOCUMENTS			
Examiner Initial*	Cite No	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, pages(s), volume-issue number(s), publisher, city and/or country where published	T[5]

Receipt date: 10/16/2023

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (not for submission under 37 CFR 1.99)		
	Application Number	17/384,070
	Filing Date	Jul-23-2021
	First Named Inventor	Kenneth S. Graham
	Art Unit	1647
	Confirmation Number	1061
	Examiner Name	Lockard, Jon McClelland
	Attorney Docket Number	125984-266215

EXAMINER SIGNATURE			
Examiner Signature	/JON M LOCKARD/	Date Considered	11/01/2023

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through a citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

[1] See Kind Codes of USPTO Patent Documents at www.USPTO.GOV or MPEP 901.04. [2] Enter office that issued the document, by the two-letter code (WIPO Standard ST.3). [3] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [4] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [5] Applicant is to place a check mark here if English language translation is attached.

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Alvotech v. Regeneron
PGR2025-00085
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INFORMATION DISCLOSURE STATEMENT BY APPLICANT (not for submission under 37 CFR 1.99)		
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	Filing Date	Jul-23-2021
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U.S. PATENTS						
Examiner Initial*	Cite No	Patent Number	Kind Code[1]	Issue Date	Name of Patentee or Applicant of cited Document	Pages, Columns, Lines where Relevant Passages or Relevant Figures Appear

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Examiner Initial*	Cite No	Foreign Document Number[3]	Country Code[2]	Kind Code[4]	Publication Date	Name of Patentee or Applicant of cited Document	Pages, Columns, Lines where Relevant Passages or Relevant Figures Appear	T[5]

NON-PATENT LITERATURE DOCUMENTS			
Examiner Initial*	Cite No	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, pages(s), volume-issue number(s), publisher, city and/or country where published	T[5]
	560	AusPAR Eylea Aflibercept Bayer Australia Ltd., PM-2010-03802-3-5 Final; 30 July 2012, pages 1-24.	
	561	Eylea Assessment report; Committee for Medicinal Products for Human Use (CHMP), European Medicines Agency; EMA/646256/2012 corr; 20 September 2012, 1-83 pages.	
	562	History of Changes for Study: NCT00383370, "To Access the Safety and Tolerability of Repeated Intravitreal Administration of VEGF Trap in Subjects With Wet AMD," Clinical Trials.gov archive, 1-33 pages; 20 April 2011.	

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (not for submission under 37 CFR 1.99)		
	Application Number	17/384,070
	Filing Date	Jul-23-2021
	First Named Inventor	Kenneth S. Graham
	Art Unit	1647
	Confirmation Number	1061
	Examiner Name	Lockard, Jon McClelland
	Attorney Docket Number	125984-266215

EXAMINER SIGNATURE			
Examiner Signature		Date Considered	

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through a citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

[1] See Kind Codes of USPTO Patent Documents at www.USPTO.GOV or MPEP 901.04. [2] Enter office that issued the document, by the two-letter code (WIPO Standard ST.3). [3] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [4] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [5] Applicant is to place a check mark here if English language translation is attached.

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	Application Number	17/384,070
	Filing Date	Jul-23-2021
	First Named Inventor	Kenneth S. Graham
	Art Unit	1647
	Confirmation Number	1061
	Examiner Name	Lockard, Jon McClelland
	Attorney Docket Number	125984-266215

CERTIFICATION STATEMENT

Please see 37 CFR 1.97 and 1.98 to make the appropriate selection(s):

☐ That each item of information contained in the information disclosure statement was first cited in any communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(1).

OR

☐ That no item of information contained in the information disclosure statement was cited in a communication from a foreign patent office in a counterpart foreign application, and, to the knowledge of the person signing the certification after making reasonable inquiry, no item of information contained in the information disclosure statement was known to any individual designated in 37 CFR 1.56(c) more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(2).

☐ See attached certification statement.

☐ Fee set forth in 37 CFR 1.17 (p) has been submitted herewith.

☒ None

SIGNATURE

A signature of the applicant or representative is required in accordance with CFR 1.33, 10.18. Please see CFR 1.4(d) for the form of the signature.

Signature	/Lance A. Termes/	Date (YYYY-MM-DD)	2023-11-22
Name/Print	Lance A. Termes	Registration Number	43184

Regeneron Ex. 2001
Alvotech v. Regeneron
PGR2025-00085
Page 355 of 531

PTO/SB/30 (11-23)
Approved for use through 05/31/2024. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

Request for Continued Examination (RCE) Transmittal

Address to:
Mail Stop RCE
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Application Number	17/384,070
Filing Date	July 23, 2021
First Named Inventor	Kenneth S. Graham
Art Unit	1647
Examiner Name	Jon McClelland Lockard
Attorney Docket Number	125984-266215

This is a Request for Continued Examination (RCE) under 37 CFR 1.114 of the above-identified application.
Request for Continued Examination (RCE) practice under 37 CFR 1.114 does not apply to any utility or plant application filed prior to June 8, 1995, or to any design application. See Instruction Sheet for RCEs (not to be submitted to the USPTO) on page 2.

1. Submission required under 37 CFR 1.114 Note: If the RCE is proper, any previously filed unentered amendments and amendments enclosed with the RCE will be entered in the order in which they were filed unless applicant instructs otherwise. If applicant does not wish to have any previously filed unentered amendment(s) entered, applicant must request non-entry of such amendment(s).

   a. ☐ Previously submitted. If a final Office action is outstanding, any amendments filed after the final Office action may be considered as a submission even if this box is not checked.

      i. ☐ Consider the arguments in the Appeal Brief or Reply Brief previously filed on _____

      ii. ☐ Other _____

   b. ☑ Enclosed

      i. ☐ Amendment/Reply

      ii. ☐ Affidavit(s)/ Declaration(s)

      iii. ☑ Information Disclosure Statement (IDS)

      iv. ☐ Other _____

2. Miscellaneous

   a. ☐ Suspension of action on the above-identified application is requested under 37 CFR 1.103(c) for a period of _____ months. (Period of suspension shall not exceed 3 months; Fee under 37 CFR 1.17(i) required)

   b. ☐ Other _____

3. Fees The RCE fee under 37 CFR 1.17(e) is required by 37 CFR 1.114 when the RCE is filed.

   a. ☑ The Director is hereby authorized to charge the following fees, any underpayment of fees, or credit any overpayments, to Deposit Account No. 500393.

      i. ☑ RCE fee required under 37 CFR 1.17(e)

      ii. ☐ Extension of time fee (37 CFR 1.136 and 1.17)

      iii. ☐ Other _____

   b. ☐ Check in the amount of $ _____ enclosed

   c. ☐ Payment by credit card (Form PTO-2038 enclosed)

   d. ▩ Payment by USPTO patent electronic filing system.

WARNING: Information on this form may become public. Credit card information should not be included on this form. Provide credit card information and authorization on PTO-2038.

SIGNATURE OF APPLICANT, ATTORNEY, OR AGENT REQUIRED

Signature	/Lance A. Termes/	Date	November 22, 2023
Name (Print/Type)	Lance A. Termes	Registration No.	43,184

CERTIFICATE OF MAILING OR TRANSMISSION

I hereby certify that this correspondence is transmitted by the USPTO patent electronic filing system, or by facsimile to (571) 273-8300, to the USPTO, or deposited with the United States Postal Service with sufficient postage as first class mail in an envelope addressed to: Mail Stop RCE, Commissioner for Patents, P. O. Box 1450, Alexandria, VA 22313-1450, on the date shown below.

Signature	/Lance A. Termes/		
Name (Print/Type)	Lance A. Termes	Date	November 22, 2023

A Federal agency may not conduct or sponsor, and a person is not required to respond to, nor shall a person be subject to a penalty for failure to comply with an information collection subject to the requirements of the Paperwork Reduction Act of 1995, unless the information collection has a currently valid OMB Control Number. The OMB Control Number for this information collection is 0651-0031. Public burden for this form is estimated to average 12 minutes per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the information collection. Send comments regarding this burden estimate or any other aspect of this information collection, including suggestions for reducing this burden to the Chief Administrative Officer, United States Patent and Trademark Office, P.O. Box 1450, Alexandria, VA 22313-1450 or email InformationCollection@uspto.gov. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **If filing this completed form by mail, send to:**

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NOTICE OF ALLOWANCE AND FEE(S) DUE

147803 7590 12/06/2023

Schwabe W&W, PC / Regeneron Pharmaceuticals, Inc.
PacWest Center
1211 SW Fifth Avenue, Suite 1900
Portland, OR 97204

EXAMINER	
LOCKARD, JON MCCLELLAND	
ART UNIT	PAPER NUMBER
1647	

DATE MAILED: 12/06/2023

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
17/384,070	07/23/2021	Kenneth S. Graham		1061

TITLE OF INVENTION: Methods for Treating Angiogenic Eye Disorders with High Doses of VEGF Receptor Fusion Proteins

APPLN. TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	UNDISCOUNTED	$1200	$0.00	$1200.00	$0	03/06/2024

THE APPLICATION IDENTIFIED ABOVE HAS BEEN EXAMINED AND IS ALLOWED FOR ISSUANCE AS A PATENT. PROSECUTION ON THE MERITS IS CLOSED. THIS NOTICE OF ALLOWANCE IS NOT A GRANT OF PATENT RIGHTS. THIS APPLICATION IS SUBJECT TO WITHDRAWAL FROM ISSUE AT THE INITIATIVE OF THE OFFICE OR UPON PETITION BY THE APPLICANT. SEE 37 CFR 1.313 AND MPEP 1308.

THE ISSUE FEE AND PUBLICATION FEE (IF REQUIRED) MUST BE PAID WITHIN THREE MONTHS FROM THE MAILING DATE OF THIS NOTICE OR THIS APPLICATION SHALL BE REGARDED AS ABANDONED. THIS STATUTORY PERIOD CANNOT BE EXTENDED. SEE 35 U.S.C. 151. THE ISSUE FEE DUE INDICATED ABOVE DOES NOT REFLECT A CREDIT FOR ANY PREVIOUSLY PAID ISSUE FEE IN THIS APPLICATION. IF AN ISSUE FEE HAS PREVIOUSLY BEEN PAID IN THIS APPLICATION (AS SHOWN ABOVE), THE RETURN OF PART B OF THIS FORM WILL BE CONSIDERED A REQUEST TO REAPPLY THE PREVIOUSLY PAID ISSUE FEE TOWARD THE ISSUE FEE NOW DUE.

HOW TO REPLY TO THIS NOTICE:

I. Review the ENTITY STATUS shown above. If the ENTITY STATUS is shown as SMALL or MICRO, verify whether entitlement to that entity status still applies.

If the ENTITY STATUS is the same as shown above, pay the TOTAL FEE(S) DUE shown above.

If the ENTITY STATUS is changed from that shown above, on PART B - FEE(S) TRANSMITTAL, complete section number 5 titled "Change in Entity Status (from status indicated above)".

For purposes of this notice, small entity fees are 40% the amount of undiscounted fees, and micro entity fees are 20% the amount of undiscounted fees.

II. PART B - FEE(S) TRANSMITTAL, or its equivalent, must be completed and returned to the United States Patent and Trademark Office (USPTO) with your ISSUE FEE and PUBLICATION FEE (if required). If you are charging the fee(s) to your deposit account, section "4b" of Part B - Fee(s) Transmittal should be completed. If an equivalent of Part B is filed, a request to reapply a previously paid issue fee must be clearly made, and delays in processing may occur due to the difficulty in recognizing the paper as an equivalent of Part B.

III. All communications regarding this application must give the application number. Please direct all communications prior to issuance to Mail Stop ISSUE FEE unless advised to the contrary.

IMPORTANT REMINDER: Maintenance fees are due in utility patents issuing on applications filed on or after Dec. 12, 1980. It is patentee's responsibility to ensure timely payment of maintenance fees when due. More information is available at www.uspto.gov/PatentMaintenanceFees.

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PART B - FEE(S) TRANSMITTAL

Complete and send this form, together with applicable fee(s), by mail or fax, or via the USPTO patent electronic filing system.

By mail, send to: Mail Stop ISSUE FEE
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450

By fax, send to: (571)-273-2885

INSTRUCTIONS: This form should be used for transmitting the ISSUE FEE and PUBLICATION FEE (if required). Blocks 1 through 5 should be completed where appropriate. All further correspondence will be mailed to the current correspondence address as indicated unless corrected below or directed otherwise in Block 1, by (a) specifying a new correspondence address; and/or (b) indicating a separate "FEE ADDRESS" for maintenance fee notifications. **Because electronic patent issuance may occur shortly after issue fee payment, any desired continuing application should preferably be filed prior to payment of this issue fee in order not to jeopardize copendency.**

CURRENT CORRESPONDENCE ADDRESS (Note: Use Block 1 for any change of address)

147803 7590 12/06/2023
Schwabe W&W, PC / Regeneron Pharmaceuticals, Inc.
PacWest Center
1211 SW Fifth Avenue, Suite 1900
Portland, OR 97204

Note: A certificate of mailing can only be used for domestic mailings of the Fee(s) Transmittal. This certificate cannot be used for any other accompanying papers. Each additional paper, such as an assignment or formal drawing, must have its own certificate of mailing or transmission.

Certificate of Mailing or Transmission

I hereby certify that this Fee(s) Transmittal is being deposited with the United States Postal Service with sufficient postage for first class mail in an envelope addressed to the Mail Stop ISSUE FEE address above, or being transmitted to the USPTO via the USPTO patent electronic filing system or by facsimile to (571) 273-2885, on the date below.

(Typed or printed name)
(Signature)
(Date)

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
17/384,070	07/23/2021	Kenneth S. Graham		1061

TITLE OF INVENTION: Methods for Treating Angiogenic Eye Disorders with High Doses of VEGF Receptor Fusion Proteins

APPLN. TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	UNDISCOUNTED	$1200	$0.00	$1200.00	$0	03/06/2024

EXAMINER	ART UNIT	CLASS-SUBCLASS
LOCKARD, JON MCCLELLAND	1647	424-134100

1. Change of correspondence address or indication of "Fee Address" (37 CFR 1.363).

❑ Change of correspondence address (or Change of Correspondence Address form PTO/AIA/122 or PTO/SB/122) attached.

❑ "Fee Address" indication (or "Fee Address" Indication form PTO/AIA/47 or PTO/SB/47; Rev 03-02 or more recent) attached. **Use of a Customer Number is required.**

2. For printing on the patent front page, list
(1) The names of up to 3 registered patent attorneys or agents OR, alternatively,
(2) The name of a single firm (having as a member a registered attorney or agent) and the names of up to 2 registered patent attorneys or agents. If no name is listed, no name will be printed.

1 _____
2 _____
3 _____

3. ASSIGNEE NAME AND RESIDENCE DATA TO BE PRINTED ON THE PATENT (print or type)

PLEASE NOTE: Unless an assignee is identified below, no assignee data will appear on the patent. If an assignee is identified below, the document must have been previously recorded, or filed for recordation, as set forth in 37 CFR 3.11 and 37 CFR 3.81(a). Completion of this form is NOT a substitute for filing an assignment.

(A) NAME OF ASSIGNEE (B) RESIDENCE: (CITY and STATE OR COUNTRY)

Please check the appropriate assignee category or categories (will not be printed on the patent) : ❑ Individual ❑ Corporation or other private group entity ❑ Government

4a. Fees submitted: ❑Issue Fee ❑Publication Fee (if required)

4b. Method of Payment: *(Please first reapply any previously paid fee shown above)*

❑ Electronic Payment via the USPTO patent electronic filing system ❑ Enclosed check ❑ Non-electronic payment by credit card (Attach form PTO-2038)

❑ The Director is hereby authorized to charge the required fee(s), any deficiency, or credit any overpayment to Deposit Account No. _____

5. **Change in Entity Status** (from status indicated above)

❑ Applicant certifying micro entity status. See 37 CFR 1.29

NOTE: Absent a valid certification of Micro Entity Status (see forms PTO/SB/15A and 15B), issue fee payment in the micro entity amount will not be accepted at the risk of application abandonment.

❑ Applicant asserting small entity status. See 37 CFR 1.27

NOTE: If the application was previously under micro entity status, checking this box will be taken to be a notification of loss of entitlement to micro entity status.

❑ Applicant changing to regular undiscounted fee status.

NOTE: Checking this box will be taken to be a notification of loss of entitlement to small or micro entity status, as applicable.

NOTE: This form must be signed in accordance with 37 CFR 1.31 and 1.33. See 37 CFR 1.4 for signature requirements and certifications.

Authorized Signature _____ Date _____

Typed or printed name _____ Registration No. _____

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UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
17/384,070	07/23/2021	Kenneth S. Graham		1061

147803 7590 12/06/2023

Schwabe W&W, PC / Regeneron Pharmaceuticals, Inc.
PacWest Center
1211 SW Fifth Avenue, Suite 1900
Portland, OR 97204

EXAMINER	
LOCKARD, JON MCCLELLAND	
ART UNIT	**PAPER NUMBER**
1647	

DATE MAILED: 12/06/2023

Determination of Patent Term Adjustment under 35 U.S.C. 154 (b)
(Applications filed on or after May 29, 2000)

The Office has discontinued providing a Patent Term Adjustment (PTA) calculation with the Notice of Allowance.

Section 1(h)(2) of the AIA Technical Corrections Act amended 35 U.S.C. 154(b)(3)(B)(i) to eliminate the requirement that the Office provide a patent term adjustment determination with the notice of allowance. See Revisions to Patent Term Adjustment, 78 Fed. Reg. 19416, 19417 (Apr. 1, 2013). Therefore, the Office is no longer providing an initial patent term adjustment determination with the notice of allowance. The Office will continue to provide a patent term adjustment determination with the Issue Notification Letter that is mailed to applicant approximately three weeks prior to the issue date of the patent, and will include the patent term adjustment on the patent. Any request for reconsideration of the patent term adjustment determination (or reinstatement of patent term adjustment) should follow the process outlined in 37 CFR 1.705.

Any questions regarding the Patent Term Extension or Adjustment determination should be directed to the Office of Patent Legal Administration at (571)-272-7702. Questions relating to issue and publication fee payments should be directed to the Customer Service Center of the Office of Patent Publication at 1-(888)-786-0101 or (571)-272-4200.

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OMB Clearance and PRA Burden Statement for PTOL-85 Part B

The Paperwork Reduction Act (PRA) of 1995 requires Federal agencies to obtain Office of Management and Budget approval before requesting most types of information from the public. When OMB approves an agency request to collect information from the public, OMB (i) provides a valid OMB Control Number and expiration date for the agency to display on the instrument that will be used to collect the information and (ii) requires the agency to inform the public about the OMB Control Number's legal significance in accordance with 5 CFR 1320.5(b).

The information collected by PTOL-85 Part B is required by 37 CFR 1.311. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 30 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, Virginia 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, Virginia 22313-1450. Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

Privacy Act Statement

The Privacy Act of 1974 (P.L. 93-579) requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. The United States Patent and Trademark Office (USPTO) collects the information in this record under authority of 35 U.S.C. 2. The USPTO's system of records is used to manage all applicant and owner information including name, citizenship, residence, post office address, and other information with respect to inventors and their legal representatives pertaining to the applicant's/owner's activities in connection with the invention for which a patent is sought or has been granted. The applicable Privacy Act System of Records Notice for the information collected in this form is COMMERCE/PAT-TM-7 Patent Application Files, available in the Federal Register at 78 FR 19243 (March 29, 2013).
https://www.govinfo.gov/content/pkg/FR-2013-03-29/pdf/2013-07341.pdf

Routine uses of the information in this record may include disclosure to:

1) law enforcement, in the event that the system of records indicates a violation or potential violation of law;
2) a federal, state, local, or international agency, in response to its request;
3) a contractor of the USPTO having need for the information in order to perform a contract;
4) the Department of Justice for determination of whether the Freedom of Information Act (FOIA) requires disclosure of the record;
5) a Member of Congress submitting a request involving an individual to whom the record pertains, when the individual has requested the Member's assistance with respect to the subject matter of the record;
6) a court, magistrate, or administrative tribunal, in the course of presenting evidence, including disclosures to opposing counsel in the course of settlement negotiations;
7) the Administrator, General Services Administration (GSA), or their designee, during an inspection of records conducted by GSA under authority of 44 U.S.C. 2904 and 2906, in accordance with the GSA regulations and any other relevant (i.e., GSA or Commerce) directive, where such disclosure shall not be used to make determinations about individuals;
8) another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c));
9) the Office of Personnel Management (OPM) for personnel research purposes; and
10) the Office of Management and Budget (OMB) for legislative coordination and clearance.

If you do not furnish the information requested on this form, the USPTO may not be able to process and/or examine your submission, which may result in termination of proceedings, abandonment of the application, and/or expiration of the patent.

Notice of Allowability	Application No. 17/384,070	Applicant(s) Graham et al.	
	Examiner JON M LOCKARD	Art Unit 1647	AIA (FITF) Status Yes

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address--

All claims being allowable, PROSECUTION ON THE MERITS IS (OR REMAINS) CLOSED in this application. If not included herewith (or previously mailed), a Notice of Allowance (PTOL-85) or other appropriate communication will be mailed in due course. **THIS NOTICE OF ALLOWABILITY IS NOT A GRANT OF PATENT RIGHTS.** This application is subject to withdrawal from issue at the initiative of the Office or upon petition by the applicant. See 37 CFR 1.313 and MPEP 1308.

1. ☑ This communication is responsive to the Request for Continued Examination filed 22 November 2023.
   ☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on _____.

2. ☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.

3. ☑ The allowed claim(s) is/are See Continuation Sheet . As a result of the allowed claim(s), you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information, please see **http://www.uspto.gov/patents/init_events/pph/index.jsp** or send an inquiry to **PPHfeedback@uspto.gov.**

4. ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

   Certified copies:

   a) ☐ All b) ☐ Some* c) ☐ None of the:

   1. ☐ Certified copies of the priority documents have been received.
   2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
   3. ☐ Copies of the certified copies of the priority documents have been received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

   * Certified copies not received: _____ .

Applicant has THREE MONTHS FROM THE "MAILING DATE" of this communication to file a reply complying with the requirements noted below. Failure to timely comply will result in ABANDONMENT of this application.
THIS THREE-MONTH PERIOD IS NOT EXTENDABLE.

5. ☐ CORRECTED DRAWINGS (as "replacement sheets") must be submitted.
   ☐ including changes required by the attached Examiner's Amendment / Comment or in the Office action of Paper No./Mail Date _____ .

   Identifying indicia such as the application number (see 37 CFR 1.84(c)) should be written on the drawings in the front (not the back) of each sheet. Replacement sheet(s) should be labeled as such in the header according to 37 CFR 1.121(d).

6. ☐ DEPOSIT OF and/or INFORMATION about the deposit of BIOLOGICAL MATERIAL must be submitted. Note the attached Examiner's comment regarding REQUIREMENT FOR THE DEPOSIT OF BIOLOGICAL MATERIAL.

Attachment(s)

1. ☐ Notice of References Cited (PTO-892)
2. ☑ Information Disclosure Statements (PTO/SB/08), Paper No./Mail Date _____.
3. ☐ Examiner's Comment Regarding Requirement for Deposit of Biological Material _____.
4. ☐ Interview Summary (PTO-413), Paper No./Mail Date. _____.
5. ☑ Examiner's Amendment/Comment
6. ☑ Examiner's Statement of Reasons for Allowance
7. ☐ Other _____.

/J.L/ Examiner, Art Unit 1647	/CHRISTINE J SAOUD/ Primary Examiner, Art Unit 1645

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Continuation of 3. The allowed claim(s) is/are: 30-32 and 53-87)renumbered as claims 1-11,13-14,16,18,20,22,24,12,26,15,17,19,21,23,25 and 27-38, respectively)

Notice of Pre-AIA or AIA Status

1. The present application, filed on or after March 16, 2013, is being examined under the first inventor to file provisions of the AIA.

Continued Examination Under 37 CFR 1.114

2. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after allowance or after an Office action under *Ex Parte Quayle*, 25 USPQ 74, 453 O.G. 213 (Comm'r Pat. 1935). Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, prosecution in this application has been reopened pursuant to 37 CFR 1.114. Applicant's submission filed on 22 November 2023 has been entered.

Information Disclosure Statement

3. The information disclosure statement (IDS) submitted on 22 November 2023 has been considered by the examiner.

REASONS FOR ALLOWANCE

4. The following is an examiner's statement of reasons for allowance: The information disclosure statement (IDS) submitted on 22 November 2023 has been considered by the Examiner. After careful consideration, the Examiner has determined that none of the information contained therein raises new issues of patentability.

5. Any comments considered necessary by applicant must be submitted no later than the payment of the issue fee and, to avoid processing delays, should preferably accompany the issue

fee. Such submissions should be clearly labeled "Comments on Statement of Reasons for Allowance."

Summary

6. Claims 30-32 and 53-87 are allowed.

Advisory Information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to **JON M LOCKARD** whose telephone number is **(571) 272-2717**. The examiner can normally be reached M-F 9-6 EST.

Examiner interviews are available via telephone, in-person, and video conferencing using a USPTO supplied web-based collaboration tool. To schedule an interview, applicant is encouraged to use the USPTO Automated Interview Request (AIR) at http://www.uspto.gov/interviewpractice. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, **Joanne Hama** can be reached on **(571) 272-2911**. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of published or unpublished applications may be obtained from Patent Center. Unpublished application information in Patent Center is available to registered users. To file and manage patent submissions in Patent Center, visit: https://patentcenter.uspto.gov. Visit https://www.uspto.gov/patents/apply/patent-center for more information about Patent Center and https://www.uspto.gov/patents/docx for information about filing in DOCX format. For additional questions, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Christine J Saoud/
Primary Examiner, Art Unit 1645

/J.L/
Examiner, Art Unit 1647
November 29, 2023

Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
	17/384,070	Graham et al.
	Examiner	Art Unit
	JON M LOCKARD	1647

CPC - Searched*		
Symbol	Date	Examiner

CPC Combination Sets - Searched*		
Symbol	Date	Examiner

US Classification - Searched*			
Class	Subclass	Date	Examiner
NONE		03/16/2023	JML

* See search history printout included with this form or the SEARCH NOTES box below to determine the scope of the search.

Search Notes		
Search Notes	Date	Examiner
PE2E Search (USPAT, US-PGPUB, EPO, DERWENT): See attached search history.	03/16/2023	JML
STN (MEDLINE, SCISEARCH, EMBASE, BIOSIS): See attached search history.	03/16/2023	JML
PALM: Inventor search.	03/16/2023	JML
PE2E Search (USPAT, US-PGPUB, EPO, DERWENT): See attached search history.	11/01/2023	JML

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Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
	17/384,070	Graham et al.
	Examiner	Art Unit
	JON M LOCKARD	1647

Interference Search			
US Class/CPC Symbol	**US Subclass/CPC Group**	**Date**	**Examiner**
	PE2E Search (USPAT): See attached search history.	08/24/2023	JML
	DAV: Inventor search.	08/24/2023	JML
	PE2E Search (USPAT): See attached search history.	11/01/2023	JML
	DAV: Inventor search.	11/01/2023	JML
	PE2E Search (USPAT): See attached search history.	11/29/2023	JML
	DAV: Inventor search.	11/29/2023	JML

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Issue Classification	Application/Control No.	Applicant(s)/Patent Under Reexamination
	17/384,070	Graham et al.
	Examiner	Art Unit
	JON M LOCKARD	1647

CPC										
Symbol									Type	Version
A61K	/	38	/	179					F	2013-01-01
A61K	/	9	/	0048					I	2013-01-01
A61K	/	47	/	12					I	2013-01-01
A61P	/	27	/	02					I	2018-01-01
A61K	/	47	/	22					I	2013-01-01
A61K	/	47	/	26					I	2013-01-01
A61K	/	47	/	183					I	2013-01-01

CPC Combination Sets										
Symbol									Type	Set	Ranking	Version
	/		/									

/JON M LOCKARD/ Examiner, Art Unit 1647	29 November 2023	Total Claims Allowed:	
(Assistant Examiner)	(Date)	38	
/CHRISTINE J SAOUD/ Primary Examiner, Art Unit 1645	30 November 2023	O.G. Print Claim(s)	O.G. Print Figure
(Primary Examiner)	(Date)	1	NONE

U.S. Patent and Trademark Office — Part of Paper No.: 20231129

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Issue Classification	Application/Control No.	Applicant(s)/Patent Under Reexamination
	17/384,070	Graham et al.
	Examiner	Art Unit
	JON M LOCKARD	1647

INTERNATIONAL CLASSIFICATION					
CLAIMED					
A61K	/	38	/	17	
A61K	/	38	/	18	
C07K	/	14	/	71	

NON-CLAIMED				
	/		/	

US ORIGINAL CLASSIFICATION	
CLASS	SUBCLASS

CROSS REFERENCES(S)						
CLASS	SUBCLASS (ONE SUBCLASS PER BLOCK)					

/JON M LOCKARD/ Examiner, Art Unit 1647	29 November 2023	Total Claims Allowed:	
(Assistant Examiner)	(Date)	38	
/CHRISTINE J SAOUD/ Primary Examiner, Art Unit 1645	30 November 2023	O.G. Print Claim(s)	O.G. Print Figure
(Primary Examiner)	(Date)	1	NONE

U.S. Patent and Trademark Office — Part of Paper No.: 20231129

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Issue Classification	Application/Control No.	Applicant(s)/Patent Under Reexamination
	17/384,070	Graham et al.
	Examiner	Art Unit
	JON M LOCKARD	1647

☐ Claims renumbered in the same order as presented by applicant ☐ CPA ☑ T.D. ☐ R.1.47

CLAIMS

Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original
1	30	10	59	12	68	28	77	37	86						
2	31	11	60	26	69	29	78	38	87						
3	32	13	61	15	70	30	79								
4	53	14	62	17	71	31	80								
5	54	16	63	19	72	32	81								
6	55	18	64	21	73	33	82								
7	56	20	65	23	74	34	83								
8	57	22	66	25	75	35	84								
9	58	24	67	27	76	36	85								

/JON M LOCKARD/ Examiner, Art Unit 1647 (Assistant Examiner)	29 November 2023 (Date)	Total Claims Allowed: 38	
/CHRISTINE J SAOUD/ Primary Examiner, Art Unit 1645 (Primary Examiner)	30 November 2023 (Date)	O.G. Print Claim(s) 1	O.G. Print Figure NONE

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Alvotech v. Regeneron
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Receipt date: 11/22/2023

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (not for submission under 37 CFR 1.99)		
	Application Number	17/384,070
	Filing Date	Jul-23-2021
	First Named Inventor	Kenneth S. Graham
	Art Unit	1647
	Confirmation Number	1061
	Examiner Name	Lockard, Jon McClelland
	Attorney Docket Number	125984-266215

U.S. PATENTS						
Examiner Initial*	Cite No	Patent Number	Kind Code[1]	Issue Date	Name of Patentee or Applicant of cited Document	Pages, Columns, Lines where Relevant Passages or Relevant Figures Appear

U.S. PATENT APPLICATION PUBLICATIONS						
Examiner Initial*	Cite No	Publication Number	Kind Code[1]	Publication Date	Name of Patentee or Applicant of cited Document	Pages, Columns, Lines where Relevant Passages or Relevant Figures Appear

FOREIGN PATENT DOCUMENTS								
Examiner Initial*	Cite No	Foreign Document Number[3]	Country Code[2]	Kind Code[4]	Publication Date	Name of Patentee or Applicant of cited Document	Pages, Columns, Lines where Relevant Passages or Relevant Figures Appear	T[5]

NON-PATENT LITERATURE DOCUMENTS			
Examiner Initial*	Cite No	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, pages(s), volume-issue number(s), publisher, city and/or country where published	T[5]
/J.L/	560	AusPAR Eylea Aflibercept Bayer Australia Ltd., PM-2010-03802-3-5 Final; 30 July 2012, pages 1-24.	
/J.L/	561	Eylea Assessment report; Committee for Medicinal Products for Human Use (CHMP), European Medicines Agency; EMA/646256/2012 corr; 20 September 2012, 1-83 pages.	
/J.L/	562	History of Changes for Study: NCT00383370, "To Access the Safety and Tolerability of Repeated Intravitreal Administration of VEGF Trap in Subjects With Wet AMD," Clinical Trials.gov archive, 1-33 pages; 20 April 2011.	

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (not for submission under 37 CFR 1.99)		
	Application Number	17/384,070
	Filing Date	Jul-23-2021
	First Named Inventor	Kenneth S. Graham
	Art Unit	1647
	Confirmation Number	1061
	Examiner Name	Lockard, Jon McClelland
	Attorney Docket Number	125984-266215

EXAMINER SIGNATURE			
Examiner Signature	/JON M LOCKARD/	Date Considered	11/29/2023

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through a citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

[1] See Kind Codes of USPTO Patent Documents at www.USPTO.GOV or MPEP 901.04. [2] Enter office that issued the document, by the two-letter code (WIPO Standard ST.3). [3] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [4] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [5] Applicant is to place a check mark here if English language translation is attached.

PE2E SEARCH - Search History (Prior Art)

/j.L./

There are no Prior Art searches to show.

PE2E SEARCH - Search History (Interference)

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	British Equivalents	Time Stamp
N12	2626	L1	(USPAT)	OR	ON	ON	2023/11/29 10:27 PM
N13	2676	L2	(USPAT)	OR	ON	ON	2023/11/29 10:27 PM
N14	259	L3	(USPAT)	OR	ON	ON	2023/11/29 10:27 PM
N15	110	L4	(USPAT)	OR	ON	ON	2023/11/29 10:27 PM
N16	408	(N1 N2 N3 N4) SAME formulation	(USPAT)	OR	ON	ON	2023/11/29 10:27 PM
N17	12	N5 SAME "high concentration"	(USPAT)	OR	ON	ON	2023/11/29 10:27 PM
N18	25	N5 SAME (8mg OR "8 mg")	(USPAT)	OR	ON	ON	2023/11/29 10:27 PM
N19	1	N5 SAME (8mg OR "8 mg").clm.	(USPAT)	OR	ON	ON	2023/11/29 10:27 PM
N20	17	(graham-k$-s$ washawa-s$).in.	(USPAT)	OR	ON	ON	2023/11/29 10:27 PM
N21	5	N5 AND N9	(USPAT)	OR	ON	ON	2023/11/29 10:27 PM
N22	3	"11730794".pn. "11732024".pn. "11103552".pn.	(US-PGPUB; USPAT)	OR	ON	ON	2023/11/29 10:27 PM

Regeneron Ex. 2001
Alvotech v. Regeneron
PGR2025-00085
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INFORMATION DISCLOSURE STATEMENT BY APPLICANT (not for submission under 37 CFR 1.99)		
	Application Number	17/384,070
	Filing Date	Jul-23-2021
	First Named Inventor	Kenneth S. Graham
	Art Unit	1647
	Confirmation Number	1061
	Examiner Name	Lockard, Jon McClelland
	Attorney Docket Number	125984-266215

U.S. PATENTS						
Examiner Initial*	Cite No	Patent Number	Kind Code[1]	Issue Date	Name of Patentee or Applicant of cited Document	Pages, Columns, Lines where Relevant Passages or Relevant Figures Appear

U.S. PATENT APPLICATION PUBLICATIONS						
Examiner Initial*	Cite No	Publication Number	Kind Code[1]	Publication Date	Name of Patentee or Applicant of cited Document	Pages, Columns, Lines where Relevant Passages or Relevant Figures Appear

FOREIGN PATENT DOCUMENTS								
Examiner Initial*	Cite No	Foreign Document Number[3]	Country Code[2]	Kind Code[4]	Publication Date	Name of Patentee or Applicant of cited Document	Pages, Columns, Lines where Relevant Passages or Relevant Figures Appear	T[5]

NON-PATENT LITERATURE DOCUMENTS			
Examiner Initial*	Cite No	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, pages(s), volume-issue number(s), publisher, city and/or country where published	T[5]
	564	"ZHANG et al., "A Phase 1 Study of KH902, a Vascular Endothelial Growth Factor Receptor Decoy, for Exudative Age-Related Macular Degeneration," American Academy of Ophthalmology, pages 672-678, (2011). [doi:10.1016/j.ophtha.2010.08.008; ISSN 0161-6420/11/$]."	

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT (not for submission under 37 CFR 1.99)		
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	Art Unit	1647
	Confirmation Number	1061
	Examiner Name	Lockard, Jon McClelland
	Attorney Docket Number	125984-266215

EXAMINER SIGNATURE			
Examiner Signature		Date Considered	

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through a citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

[1] See Kind Codes of USPTO Patent Documents at www.USPTO.GOV or MPEP 901.04. [2] Enter office that issued the document, by the two-letter code (WIPO Standard ST.3). [3] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [4] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [5] Applicant is to place a check mark here if English language translation is attached.

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Alvotech v. Regeneron
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INFORMATION DISCLOSURE STATEMENT BY APPLICANT (not for submission under 37 CFR 1.99)		
	Application Number	17/384,070
	Filing Date	Jul-23-2021
	First Named Inventor	Kenneth S. Graham
	Art Unit	1647
	Confirmation Number	1061
	Examiner Name	Lockard, Jon McClelland
	Attorney Docket Number	125984-266215

CERTIFICATION STATEMENT

Please see 37 CFR 1.97 and 1.98 to make the appropriate selection(s):

☐ That each item of information contained in the information disclosure statement was first cited in any communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(1).

OR

☐ That no item of information contained in the information disclosure statement was cited in a communication from a foreign patent office in a counterpart foreign application, and, to the knowledge of the person signing the certification after making reasonable inquiry, no item of information contained in the information disclosure statement was known to any individual designated in 37 CFR 1.56(c) more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(2).

☐ See attached certification statement.

☐ Fee set forth in 37 CFR 1.17 (p) has been submitted herewith.

☒ None

SIGNATURE

A signature of the applicant or representative is required in accordance with CFR 1.33, 10.18. Please see CFR 1.4(d) for the form of the signature.

Signature	/Lance A. Termes/	Date (YYYY-MM-DD)	2023-12-15
Name/Print	Lance A. Termes	Registration Number	43184

Regeneron Ex. 2001
Alvotech v. Regeneron
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PTO/SB/30 (11-23)
Approved for use through 05/31/2024. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

Request for Continued Examination (RCE) Transmittal

Address to:
Mail Stop RCE
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Application Number	17/384,070
Filing Date	July 23, 2021
First Named Inventor	Kenneth S. Graham
Art Unit	1647
Examiner Name	Jon McClelland Lockard
Attorney Docket Number	125984-266215

This is a Request for Continued Examination (RCE) under 37 CFR 1.114 of the above-identified application.
Request for Continued Examination (RCE) practice under 37 CFR 1.114 does not apply to any utility or plant application filed prior to June 8, 1995, or to any design application. See Instruction Sheet for RCEs (not to be submitted to the USPTO) on page 2

1. Submission required under 37 CFR 1.114 Note: If the RCE is proper, any previously filed unentered amendments and amendments enclosed with the RCE will be entered in the order in which they were filed unless applicant instructs otherwise. If applicant does not wish to have any previously filed unentered amendment(s) entered, applicant must request non-entry of such amendment(s).

   a. ☐ Previously submitted. If a final Office action is outstanding, any amendments filed after the final Office action may be considered as a submission even if this box is not checked.

      i. ☐ Consider the arguments in the Appeal Brief or Reply Brief previously filed on _____

      ii. ☐ Other _____

   b. ☑ Enclosed

      i. ☐ Amendment/Reply

      ii. ☐ Affidavit(s)/ Declaration(s)

      iii. ☑ Information Disclosure Statement (IDS)

      iv. ☐ Other _____

2. Miscellaneous

   a. ☐ Suspension of action on the above-identified application is requested under 37 CFR 1.103(c) for a period of _____ months. (Period of suspension shall not exceed 3 months; Fee under 37 CFR 1.17(i) required)

   b. ☐ Other _____

3. Fees The RCE fee under 37 CFR 1.17(e) is required by 37 CFR 1.114 when the RCE is filed.

   a. ☑ The Director is hereby authorized to charge the following fees, any underpayment of fees, or credit any overpayments, to Deposit Account No. 500393 .

      i. ☑ RCE fee required under 37 CFR 1.17(e)

      ii. ☐ Extension of time fee (37 CFR 1.136 and 1.17)

      iii. ☐ Other _____

   b. ☐ Check in the amount of $ _____ enclosed

   c. ☐ Payment by credit card (Form PTO-2038 enclosed)

   d. ▩ Payment by USPTO patent electronic filing system.

WARNING: Information on this form may become public. Credit card information should not be included on this form. Provide credit card information and authorization on PTO-2038.

SIGNATURE OF APPLICANT, ATTORNEY, OR AGENT REQUIRED

Signature	/Lance A. Termes/	Date	December 15, 2023
Name (Print/Type)	Lance A. Termes	Registration No.	43,184

CERTIFICATE OF MAILING OR TRANSMISSION

I hereby certify that this correspondence is transmitted by the USPTO patent electronic filing system, or by facsimile to (571) 273-8300, to the USPTO, or deposited with the United States Postal Service with sufficient postage as first class mail in an envelope addressed to: Mail Stop RCE, Commissioner for Patents, P. O. Box 1450, Alexandria, VA 22313-1450, on the date shown below.

Signature	/Lance A. Termes/		
Name (Print/Type)	Lance A. Termes	Date	December 15, 2023

A Federal agency may not conduct or sponsor, and a person is not required to respond to, nor shall a person be subject to a penalty for failure to comply with an information collection subject to the requirements of the Paperwork Reduction Act of 1995, unless the information collection has a currently valid OMB Control Number. The OMB Control Number for this information collection is 0651-0031. Public burden for this form is estimated to average 12 minutes per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the information collection. Send comments regarding this burden estimate or any other aspect of this information collection, including suggestions for reducing this burden to the Chief Administrative Officer, United States Patent and Trademark Office, P.O. Box 1450, Alexandria, VA 22313-1450 or email InformationCollection@uspto.gov. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **If filing this completed form by mail, send to:**

Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.

If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (not for submission under 37 CFR 1.99)		
	Application Number	17/384,070
	Filing Date	Jul-23-2021
	First Named Inventor	Kenneth S. Graham
	Art Unit	1647
	Confirmation Number	1061
	Examiner Name	Lockard, Jon McClelland
	Attorney Docket Number	125984-266215

U.S. PATENTS						
Examiner Initial*	Cite No	Patent Number	Kind Code[1]	Issue Date	Name of Patentee or Applicant of cited Document	Pages, Columns, Lines where Relevant Passages or Relevant Figures Appear
	565	11,806,398		11-07-2023	Dix et al.	

U.S. PATENT APPLICATION PUBLICATIONS						
Examiner Initial*	Cite No	Publication Number	Kind Code[1]	Publication Date	Name of Patentee or Applicant of cited Document	Pages, Columns, Lines where Relevant Passages or Relevant Figures Appear

FOREIGN PATENT DOCUMENTS								
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NON-PATENT LITERATURE DOCUMENTS			
Examiner Initial*	Cite No	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, pages(s), volume-issue number(s), publisher, city and/or country where published	T[5]

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT (not for submission under 37 CFR 1.99)		
	Application Number	17/384,070
	Filing Date	Jul-23-2021
	First Named Inventor	Kenneth S. Graham
	Art Unit	1647
	Confirmation Number	1061
	Examiner Name	Lockard, Jon McClelland
	Attorney Docket Number	125984-266215

EXAMINER SIGNATURE			
Examiner Signature		Date Considered	

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through a citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

[1] See Kind Codes of USPTO Patent Documents at www.USPTO.GOV or MPEP 901.04. [2] Enter office that issued the document, by the two-letter code (WIPO Standard ST.3). [3] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [4] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [5] Applicant is to place a check mark here if English language translation is attached.

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Alvotech v. Regeneron
PGR2025-00085
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INFORMATION DISCLOSURE STATEMENT BY APPLICANT (not for submission under 37 CFR 1.99)		
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	Art Unit	1647
	Confirmation Number	1061
	Examiner Name	Lockard, Jon McClelland
	Attorney Docket Number	125984-266215

CERTIFICATION STATEMENT

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☐ That each item of information contained in the information disclosure statement was first cited in any communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(1).

OR

☐ That no item of information contained in the information disclosure statement was cited in a communication from a foreign patent office in a counterpart foreign application, and, to the knowledge of the person signing the certification after making reasonable inquiry, no item of information contained in the information disclosure statement was known to any individual designated in 37 CFR 1.56(c) more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(2).

☐ See attached certification statement.

☐ Fee set forth in 37 CFR 1.17 (p) has been submitted herewith.

☒ None

SIGNATURE

A signature of the applicant or representative is required in accordance with CFR 1.33, 10.18. Please see CFR 1.4(d) for the form of the signature.

Signature	/Lance A. Termes/	Date (YYYY-MM-DD)	2024-01-16
Name/Print	Lance A. Termes	Registration Number	43184

Regeneron Ex. 2001
Alvotech v. Regeneron
PGR2025-00085
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UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

NOTICE OF ALLOWANCE AND FEE(S) DUE

147803 7590 01/31/2024

Schwabe W&W, PC / Regeneron Pharmaceuticals, Inc.
PacWest Center
1211 SW Fifth Avenue, Suite 1900
Portland, OR 97204

EXAMINER	
LOCKARD, JON MCCLELLAND	
ART UNIT	PAPER NUMBER
1647	

DATE MAILED: 01/31/2024

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
17/384,070	07/23/2021	Kenneth S. Graham		1061

TITLE OF INVENTION: Methods for Treating Angiogenic Eye Disorders with High Doses of VEGF Receptor Fusion Proteins

APPLN. TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	UNDISCOUNTED	$1200	$0.00	$1200.00	$0	04/30/2024

THE APPLICATION IDENTIFIED ABOVE HAS BEEN EXAMINED AND IS ALLOWED FOR ISSUANCE AS A PATENT. PROSECUTION ON THE MERITS IS CLOSED. THIS NOTICE OF ALLOWANCE IS NOT A GRANT OF PATENT RIGHTS. THIS APPLICATION IS SUBJECT TO WITHDRAWAL FROM ISSUE AT THE INITIATIVE OF THE OFFICE OR UPON PETITION BY THE APPLICANT. SEE 37 CFR 1.313 AND MPEP 1308.

THE ISSUE FEE AND PUBLICATION FEE (IF REQUIRED) MUST BE PAID WITHIN THREE MONTHS FROM THE MAILING DATE OF THIS NOTICE OR THIS APPLICATION SHALL BE REGARDED AS ABANDONED. THIS STATUTORY PERIOD CANNOT BE EXTENDED. SEE 35 U.S.C. 151. THE ISSUE FEE DUE INDICATED ABOVE DOES NOT REFLECT A CREDIT FOR ANY PREVIOUSLY PAID ISSUE FEE IN THIS APPLICATION. IF AN ISSUE FEE HAS PREVIOUSLY BEEN PAID IN THIS APPLICATION (AS SHOWN ABOVE), THE RETURN OF PART B OF THIS FORM WILL BE CONSIDERED A REQUEST TO REAPPLY THE PREVIOUSLY PAID ISSUE FEE TOWARD THE ISSUE FEE NOW DUE.

HOW TO REPLY TO THIS NOTICE:

I. Review the ENTITY STATUS shown above. If the ENTITY STATUS is shown as SMALL or MICRO, verify whether entitlement to that entity status still applies.

If the ENTITY STATUS is the same as shown above, pay the TOTAL FEE(S) DUE shown above.

If the ENTITY STATUS is changed from that shown above, on PART B - FEE(S) TRANSMITTAL, complete section number 5 titled "Change in Entity Status (from status indicated above)".

For purposes of this notice, small entity fees are 40% the amount of undiscounted fees, and micro entity fees are 20% the amount of undiscounted fees.

II. PART B - FEE(S) TRANSMITTAL, or its equivalent, must be completed and returned to the United States Patent and Trademark Office (USPTO) with your ISSUE FEE and PUBLICATION FEE (if required). If you are charging the fee(s) to your deposit account, section "4b" of Part B - Fee(s) Transmittal should be completed. If an equivalent of Part B is filed, a request to reapply a previously paid issue fee must be clearly made, and delays in processing may occur due to the difficulty in recognizing the paper as an equivalent of Part B.

III. All communications regarding this application must give the application number. Please direct all communications prior to issuance to Mail Stop ISSUE FEE unless advised to the contrary.

IMPORTANT REMINDER: Maintenance fees are due in utility patents issuing on applications filed on or after Dec. 12, 1980. It is patentee's responsibility to ensure timely payment of maintenance fees when due. More information is available at www.uspto.gov/PatentMaintenanceFees.

PTOL-85 (Rev. 11/23)

Regeneron Ex. 2001
Alvotech v. Regeneron
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PART B - FEE(S) TRANSMITTAL

Complete and send this form, together with applicable fee(s), by mail or fax, or via the USPTO patent electronic filing system.

By mail, send to: Mail Stop ISSUE FEE
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450

By fax, send to: (571)-273-2885

INSTRUCTIONS: This form should be used for transmitting the ISSUE FEE and PUBLICATION FEE (if required). Blocks 1 through 5 should be completed where appropriate. All further correspondence will be mailed to the current correspondence address as indicated unless corrected below or directed otherwise in Block 1, by (a) specifying a new correspondence address; and/or (b) indicating a separate "FEE ADDRESS" for maintenance fee notifications. **Because electronic patent issuance may occur shortly after issue fee payment, any desired continuing application should preferably be filed prior to payment of this issue fee in order not to jeopardize copendency.**

CURRENT CORRESPONDENCE ADDRESS (Note: Use Block 1 for any change of address)

147803 7590 01/31/2024
Schwabe W&W, PC / Regeneron Pharmaceuticals, Inc.
PacWest Center
1211 SW Fifth Avenue, Suite 1900
Portland, OR 97204

Note: A certificate of mailing can only be used for domestic mailings of the Fee(s) Transmittal. This certificate cannot be used for any other accompanying papers. Each additional paper, such as an assignment or formal drawing, must have its own certificate of mailing or transmission.

Certificate of Mailing or Transmission

I hereby certify that this Fee(s) Transmittal is being deposited with the United States Postal Service with sufficient postage for first class mail in an envelope addressed to the Mail Stop ISSUE FEE address above, or being transmitted to the USPTO via the USPTO patent electronic filing system or by facsimile to (571) 273-2885, on the date below.

(Typed or printed name)
(Signature)
(Date)

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
17/384,070	07/23/2021	Kenneth S. Graham		1061

TITLE OF INVENTION: Methods for Treating Angiogenic Eye Disorders with High Doses of VEGF Receptor Fusion Proteins

APPLN. TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	UNDISCOUNTED	$1200	$0.00	$1200.00	$0	04/30/2024

EXAMINER	ART UNIT	CLASS-SUBCLASS
LOCKARD, JON MCCLELLAND	1647	424-134100

1. Change of correspondence address or indication of "Fee Address" (37 CFR 1.363).

❑ Change of correspondence address (or Change of Correspondence Address form PTO/AIA/122 or PTO/SB/122) attached.

❑ "Fee Address" indication (or "Fee Address" Indication form PTO/AIA/47 or PTO/SB/47; Rev 03-02 or more recent) attached. **Use of a Customer Number is required.**

2. For printing on the patent front page, list
(1) The names of up to 3 registered patent attorneys or agents OR, alternatively,
(2) The name of a single firm (having as a member a registered attorney or agent) and the names of up to 2 registered patent attorneys or agents. If no name is listed, no name will be printed.

1 _____
2 _____
3 _____

3. ASSIGNEE NAME AND RESIDENCE DATA TO BE PRINTED ON THE PATENT (print or type)

PLEASE NOTE: Unless an assignee is identified below, no assignee data will appear on the patent. If an assignee is identified below, the document must have been previously recorded, or filed for recordation, as set forth in 37 CFR 3.11 and 37 CFR 3.81(a). Completion of this form is NOT a substitute for filing an assignment.

(A) NAME OF ASSIGNEE (B) RESIDENCE: (CITY and STATE OR COUNTRY)

Please check the appropriate assignee category or categories (will not be printed on the patent) : ❑ Individual ❑ Corporation or other private group entity ❑ Government

4a. Fees submitted: ❑Issue Fee ❑Publication Fee (if required)

4b. Method of Payment: *(Please first reapply any previously paid fee shown above)*

❑ Electronic Payment via the USPTO patent electronic filing system ❑ Enclosed check ❑ Non-electronic payment by credit card (Attach form PTO-2038)

❑ The Director is hereby authorized to charge the required fee(s), any deficiency, or credit any overpayment to Deposit Account No. _____

5. **Change in Entity Status** (from status indicated above)

❑ Applicant certifying micro entity status. See 37 CFR 1.29

NOTE: Absent a valid certification of Micro Entity Status (see forms PTO/SB/15A and 15B), issue fee payment in the micro entity amount will not be accepted at the risk of application abandonment.

❑ Applicant asserting small entity status. See 37 CFR 1.27

NOTE: If the application was previously under micro entity status, checking this box will be taken to be a notification of loss of entitlement to micro entity status.

❑ Applicant changing to regular undiscounted fee status.

NOTE: Checking this box will be taken to be a notification of loss of entitlement to small or micro entity status, as applicable.

NOTE: This form must be signed in accordance with 37 CFR 1.31 and 1.33. See 37 CFR 1.4 for signature requirements and certifications.

Authorized Signature _____ Date _____

Typed or printed name _____ Registration No. _____

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UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
17/384,070	07/23/2021	Kenneth S. Graham		1061

147803 7590 01/31/2024

Schwabe W&W, PC / Regeneron Pharmaceuticals, Inc.
PacWest Center
1211 SW Fifth Avenue, Suite 1900
Portland, OR 97204

EXAMINER	
LOCKARD, JON MCCLELLAND	
ART UNIT	**PAPER NUMBER**
1647	

DATE MAILED: 01/31/2024

Determination of Patent Term Adjustment under 35 U.S.C. 154 (b)
(Applications filed on or after May 29, 2000)

The Office has discontinued providing a Patent Term Adjustment (PTA) calculation with the Notice of Allowance.

Section 1(h)(2) of the AIA Technical Corrections Act amended 35 U.S.C. 154(b)(3)(B)(i) to eliminate the requirement that the Office provide a patent term adjustment determination with the notice of allowance. See Revisions to Patent Term Adjustment, 78 Fed. Reg. 19416, 19417 (Apr. 1, 2013). Therefore, the Office is no longer providing an initial patent term adjustment determination with the notice of allowance. The Office will continue to provide a patent term adjustment determination with the Issue Notification Letter that is mailed to applicant approximately three weeks prior to the issue date of the patent, and will include the patent term adjustment on the patent. Any request for reconsideration of the patent term adjustment determination (or reinstatement of patent term adjustment) should follow the process outlined in 37 CFR 1.705.

Any questions regarding the Patent Term Extension or Adjustment determination should be directed to the Office of Patent Legal Administration at (571)-272-7702. Questions relating to issue and publication fee payments should be directed to the Customer Service Center of the Office of Patent Publication at 1-(888)-786-0101 or (571)-272-4200.

PTOL-85 (Rev. 11/23)

Regeneron Ex. 2001
Alvotech v. Regeneron
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Page 383 of 531

OMB Clearance and PRA Burden Statement for PTOL-85 Part B

The Paperwork Reduction Act (PRA) of 1995 requires Federal agencies to obtain Office of Management and Budget approval before requesting most types of information from the public. When OMB approves an agency request to collect information from the public, OMB (i) provides a valid OMB Control Number and expiration date for the agency to display on the instrument that will be used to collect the information and (ii) requires the agency to inform the public about the OMB Control Number's legal significance in accordance with 5 CFR 1320.5(b).

The information collected by PTOL-85 Part B is required by 37 CFR 1.311. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 30 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, Virginia 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, Virginia 22313-1450. Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

Privacy Act Statement

The Privacy Act of 1974 (P.L. 93-579) requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. The United States Patent and Trademark Office (USPTO) collects the information in this record under authority of 35 U.S.C. 2. The USPTO's system of records is used to manage all applicant and owner information including name, citizenship, residence, post office address, and other information with respect to inventors and their legal representatives pertaining to the applicant's/owner's activities in connection with the invention for which a patent is sought or has been granted. The applicable Privacy Act System of Records Notice for the information collected in this form is COMMERCE/PAT-TM-7 Patent Application Files, available in the Federal Register at 78 FR 19243 (March 29, 2013).
https://www.govinfo.gov/content/pkg/FR-2013-03-29/pdf/2013-07341.pdf

Routine uses of the information in this record may include disclosure to:

1) law enforcement, in the event that the system of records indicates a violation or potential violation of law;
2) a federal, state, local, or international agency, in response to its request;
3) a contractor of the USPTO having need for the information in order to perform a contract;
4) the Department of Justice for determination of whether the Freedom of Information Act (FOIA) requires disclosure of the record;
5) a Member of Congress submitting a request involving an individual to whom the record pertains, when the individual has requested the Member's assistance with respect to the subject matter of the record;
6) a court, magistrate, or administrative tribunal, in the course of presenting evidence, including disclosures to opposing counsel in the course of settlement negotiations;
7) the Administrator, General Services Administration (GSA), or their designee, during an inspection of records conducted by GSA under authority of 44 U.S.C. 2904 and 2906, in accordance with the GSA regulations and any other relevant (i.e., GSA or Commerce) directive, where such disclosure shall not be used to make determinations about individuals;
8) another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c));
9) the Office of Personnel Management (OPM) for personnel research purposes; and
10) the Office of Management and Budget (OMB) for legislative coordination and clearance.

If you do not furnish the information requested on this form, the USPTO may not be able to process and/or examine your submission, which may result in termination of proceedings, abandonment of the application, and/or expiration of the patent.

Notice of Allowability	Application No. 17/384,070	Applicant(s) Graham et al.	
	Examiner JON M LOCKARD	Art Unit 1647	AIA (FITF) Status Yes

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address--

All claims being allowable, PROSECUTION ON THE MERITS IS (OR REMAINS) CLOSED in this application. If not included herewith (or previously mailed), a Notice of Allowance (PTOL-85) or other appropriate communication will be mailed in due course. **THIS NOTICE OF ALLOWABILITY IS NOT A GRANT OF PATENT RIGHTS.** This application is subject to withdrawal from issue at the initiative of the Office or upon petition by the applicant. See 37 CFR 1.313 and MPEP 1308.

1. ☑ This communication is responsive to the Request for Continued Examination filed 15 December 2023.
   ☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on _____.

2. ☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.

3. ☑ The allowed claim(s) is/are See Continuation Sheet . As a result of the allowed claim(s), you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information, please see **http://www.uspto.gov/patents/init_events/pph/index.jsp** or send an inquiry to **PPHfeedback@uspto.gov.**

4. ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

   Certified copies:

   a) ☐ All b) ☐ Some* c) ☐ None of the:

   1. ☐ Certified copies of the priority documents have been received.
   2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
   3. ☐ Copies of the certified copies of the priority documents have been received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

   * Certified copies not received: _____ .

Applicant has THREE MONTHS FROM THE "MAILING DATE" of this communication to file a reply complying with the requirements noted below. Failure to timely comply will result in ABANDONMENT of this application.
THIS THREE-MONTH PERIOD IS NOT EXTENDABLE.

5. ☐ CORRECTED DRAWINGS (as "replacement sheets") must be submitted.
   ☐ including changes required by the attached Examiner's Amendment / Comment or in the Office action of Paper No./Mail Date _____ .

   Identifying indicia such as the application number (see 37 CFR 1.84(c)) should be written on the drawings in the front (not the back) of each sheet. Replacement sheet(s) should be labeled as such in the header according to 37 CFR 1.121(d).

6. ☐ DEPOSIT OF and/or INFORMATION about the deposit of BIOLOGICAL MATERIAL must be submitted. Note the attached Examiner's comment regarding REQUIREMENT FOR THE DEPOSIT OF BIOLOGICAL MATERIAL.

Attachment(s)

1. ☐ Notice of References Cited (PTO-892)
2. ☑ Information Disclosure Statements (PTO/SB/08), Paper No./Mail Date _____.
3. ☐ Examiner's Comment Regarding Requirement for Deposit of Biological Material _____.
4. ☐ Interview Summary (PTO-413), Paper No./Mail Date. _____.
5. ☑ Examiner's Amendment/Comment
6. ☑ Examiner's Statement of Reasons for Allowance
7. ☐ Other _____.

/J.L/ Examiner, Art Unit 1647	/CHRISTINE J SAOUD/ Primary Examiner, Art Unit 1645

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Continuation of 3. The allowed claim(s) is/are: 30-32 and 53-87)renumbered as claims 1-11,13-14,16,18,20,22,24,12,26,15,17,19,21,23,25 and 27-38, respectively)

Notice of Pre-AIA or AIA Status

1. The present application, filed on or after March 16, 2013, is being examined under the first inventor to file provisions of the AIA.

Continued Examination Under 37 CFR 1.114

2. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after allowance or after an Office action under *Ex Parte Quayle*, 25 USPQ 74, 453 O.G. 213 (Comm'r Pat. 1935). Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, prosecution in this application has been reopened pursuant to 37 CFR 1.114. Applicant's submission filed on 15 December 2023 has been entered.

Information Disclosure Statement

3. The information disclosure statements (IDS) submitted on 15 December 2023 and 16 January 2024 have been considered by the examiner. Additionally, the IDS filed 03 December 2021, previously considered by the Examiner, is being provided to show that NPL references 140, 162, 167, 180, 193, 201 and 218 have been lined through. The references have been considered, but will not appear on the cover of the issued patent as they do not provide a date.

REASONS FOR ALLOWANCE

4. The following is an examiner's statement of reasons for allowance: The information disclosure statement (IDS) submitted on 15 December 2023 and 16 January 2024 have been

considered by the Examiner. After careful consideration, the Examiner has determined that none of the information contained therein raises new issues of patentability.

5. Any comments considered necessary by applicant must be submitted no later than the payment of the issue fee and, to avoid processing delays, should preferably accompany the issue fee. Such submissions should be clearly labeled "Comments on Statement of Reasons for Allowance."

Summary

6. Claims 30-32 and 53-87 are allowed.

Advisory Information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to **JON M LOCKARD** whose telephone number is **(571) 272-2717**. The examiner can normally be reached M-F 9-6 EST.

Examiner interviews are available via telephone, in-person, and video conferencing using a USPTO supplied web-based collaboration tool. To schedule an interview, applicant is encouraged to use the USPTO Automated Interview Request (AIR) at http://www.uspto.gov/interviewpractice. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, **Joanne Hama** can be reached on **(571) 272-2911**. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of published or unpublished applications may be obtained from Patent Center. Unpublished application information in Patent Center is available to registered users. To file and manage patent submissions in Patent Center, visit: https://patentcenter.uspto.gov. Visit https://www.uspto.gov/patents/apply/patent-center for more information about Patent Center and https://www.uspto.gov/patents/docx for information about filing in DOCX format. For additional questions, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/J.L/
Examiner, Art Unit 1647
January 24, 2024

/Christine J Saoud/
Primary Examiner, Art Unit 1645

Issue Classification	Application/Control No.	Applicant(s)/Patent Under Reexamination
	17/384,070	Graham et al.
	Examiner	Art Unit
	JON M LOCKARD	1647

CPC										
Symbol									Type	Version
A61K	/	38	/	179					F	2013-01-01
A61K	/	9	/	0048					I	2013-01-01
A61K	/	47	/	12					I	2013-01-01
A61P	/	27	/	02					I	2018-01-01
A61K	/	47	/	22					I	2013-01-01
A61K	/	47	/	26					I	2013-01-01
A61K	/	47	/	183					I	2013-01-01

CPC Combination Sets										
Symbol									Type	Set	Ranking	Version
	/		/									

/JON M LOCKARD/ Examiner, Art Unit 1647	11 January 2024	Total Claims Allowed:	
(Assistant Examiner)	(Date)	38	
/CHRISTINE J SAOUD/ Primary Examiner, Art Unit 1645	12 January 2024	O.G. Print Claim(s)	O.G. Print Figure
(Primary Examiner)	(Date)	1	NONE

U.S. Patent and Trademark Office — Part of Paper No.: 20240111

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Issue Classification	Application/Control No.	Applicant(s)/Patent Under Reexamination
	17/384,070	Graham et al.
	Examiner	Art Unit
	JON M LOCKARD	1647

INTERNATIONAL CLASSIFICATION					
CLAIMED					
A61K	/	38	/	17	
A61K	/	38	/	18	
C07K	/	14	/	71	

NON-CLAIMED				
	/		/	

US ORIGINAL CLASSIFICATION	
CLASS	SUBCLASS

CROSS REFERENCES(S)						
CLASS	SUBCLASS (ONE SUBCLASS PER BLOCK)					

/JON M LOCKARD/ Examiner, Art Unit 1647	11 January 2024	Total Claims Allowed:	
(Assistant Examiner)	(Date)	38	
/CHRISTINE J SAOUD/ Primary Examiner, Art Unit 1645	12 January 2024	O.G. Print Claim(s)	O.G. Print Figure
(Primary Examiner)	(Date)	1	NONE

U.S. Patent and Trademark Office — Part of Paper No.: 20240111

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Issue Classification	Application/Control No.	Applicant(s)/Patent Under Reexamination
	17/384,070	Graham et al.
	Examiner	Art Unit
	JON M LOCKARD	1647

☐ Claims renumbered in the same order as presented by applicant ☐ CPA ☑ T.D. ☐ R.1.47

CLAIMS

Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original
1	30	10	59	12	68	28	77	37	86						
2	31	11	60	26	69	29	78	38	87						
3	32	13	61	15	70	30	79								
4	53	14	62	17	71	31	80								
5	54	16	63	19	72	32	81								
6	55	18	64	21	73	33	82								
7	56	20	65	23	74	34	83								
8	57	22	66	25	75	35	84								
9	58	24	67	27	76	36	85								

/JON M LOCKARD/ Examiner, Art Unit 1647 (Assistant Examiner)	11 January 2024 (Date)	**Total Claims Allowed:** 38	
/CHRISTINE J SAOUD/ Primary Examiner, Art Unit 1645 (Primary Examiner)	12 January 2024 (Date)	O.G. Print Claim(s) 1	O.G. Print Figure NONE

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Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
	17/384,070	Graham et al.
	Examiner	Art Unit
	JON M LOCKARD	1647

CPC - Searched*		
Symbol	Date	Examiner

CPC Combination Sets - Searched*		
Symbol	Date	Examiner

US Classification - Searched*			
Class	Subclass	Date	Examiner
NONE		03/16/2023	JML

* See search history printout included with this form or the SEARCH NOTES box below to determine the scope of the search.

Search Notes		
Search Notes	Date	Examiner
PE2E Search (USPAT, US-PGPUB, EPO, DERWENT): See attached search history.	03/16/2023	JML
STN (MEDLINE, SCISEARCH, EMBASE, BIOSIS): See attached search history.	03/16/2023	JML
PALM: Inventor search.	03/16/2023	JML
PE2E Search (USPAT, US-PGPUB, EPO, DERWENT): See attached search history.	11/01/2023	JML

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Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
	17/384,070	Graham et al.
	Examiner	Art Unit
	JON M LOCKARD	1647

Interference Search			
US Class/CPC Symbol	**US Subclass/CPC Group**	**Date**	**Examiner**
	PE2E Search (USPAT): See attached search history.	08/24/2023	JML
	DAV: Inventor search.	08/24/2023	JML
	PE2E Search (USPAT): See attached search history.	11/01/2023	JML
	DAV: Inventor search.	11/01/2023	JML
	PE2E Search (USPAT): See attached search history.	11/29/2023	JML
	DAV: Inventor search.	11/29/2023	JML
	PE2E Search (USPAT): See attached search history.	01/11/2024	JML
	DAV: Inventor search.	01/11/2024	JML

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PE2E SEARCH - Search History (Prior Art)

/J.L./

There are no Prior Art searches to show.

PE2E SEARCH - Search History (Interference)

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	British Equivalents	Time Stamp
N23	2661	vegf ADJ trap	(USPAT)	OR	ON	ON	2024/01/11 11:22 PM
N24	2745	aflibercept	(USPAT)	OR	ON	ON	2024/01/11 11:22 PM
N25	266	eylea	(USPAT)	OR	ON	ON	2024/01/11 11:23 PM
N26	113	vegf ADJ trap-eye	(USPAT)	OR	ON	ON	2024/01/11 11:23 PM
N27	417	(N23 N24 N25 N26) SAME formulation	(USPAT)	OR	ON	ON	2024/01/11 11:23 PM
N28	12	N27 SAME "high concentration"	(USPAT)	OR	ON	ON	2024/01/11 11:24 PM
N29	1	N27 AND (8mg OR "8 mg").clm.	(USPAT)	OR	ON	ON	2024/01/11 11:24 PM
N30	17	(graham-k$-s$ washawa-s$).in.	(USPAT)	OR	ON	ON	2024/01/11 11:25 PM
N31	1	N28 AND N30	(USPAT)	OR	ON	ON	2024/01/11 11:25 PM

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Receipt date: 12/03/2021

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (not for submission under 37 CFR 1.99)		
	Application Number	17/384,070
	Filing Date	Jul-23-2021
	First Named Inventor	Kenneth S. Graham
	Art Unit	~~Not Yet Assigned~~ 1647
	Confirmation Number	1061
	Examiner Name	~~Not Yet Assigned~~ Jon Lockard
	Attorney Docket Number	125984-266215 / 10430US02

U.S. PATENTS						
Examiner Initial*	Cite No	Patent Number	Kind Code[1]	Issue Date	Name of Patentee or Applicant of cited Document	Pages, Columns, Lines where Relevant Passages or Relevant Figures Appear
	231	5,580,856		12-03-1996	Prestrelski et al.	
	232	6,136,346		10-24-2000	Eljamal et al.	
	101	6,171,586		01-09-2001	Lam et al.	
	102	6,267,958		07-31-2001	Andya et al.	
	233	6,358,530		03-19-2002	Eljamal et al.	
	234	6,582,729		06-24-2003	Eljamal et al.	
	235	6,586,574		07-01-2003	Hansen	
	236	6,652,875		11-25-2003	Bannister	
	103	6,685,940		02-03-2004	Andya et al.	
	034	6,833,349		12-21-2004	Xia et al.	
	237	6,875,432		04-05-2005	Liu et al.	
	035	7,070,959		07-04-2006	Papadopoulos et al.	
	036	7,087,411		08-08-2006	Daly et al.	
	104	7,060,268		06-13-2006	Andya et al.	
	037	7,279,159		10-09-2007	Daly et al.	
	051	7,303,746		12-04-2007	Wiegand et al.	
	056	7,303,747		12-04-2007	Wiegand et al.	
	054	7,306,799		12-11-2007	Wiegand et al.	
	053	7,374,757		05-20-2008	Papadopoulos et al.	
	052	7,374,758		05-20-2008	Papadopoulos et al.	
	055	7,396,664		07-08-2008	Daly et al.	
	045	7,399,612		07-15-2008	Daly et al.	
	046	7,521,049		04-21-2009	Wiegand et al.	
	048	7,524,499		04-28-2009	Papadopoulos et al.	
	064	7,608,261		10-27-2009	Furfine et al.	
	050	7,635,474		12-22-2009	Daly et al.	
	005	7,648,702		01-19-2010	Gombotz et al.	
	105	7,682,609		03-23-2010	Andya et al.	
	047	7,704,500		04-27-2010	Papadopoulos et al.	
	239	7,956,160		06-07-2010	Krishnan et al.	
	065	7,807,164		10-05-2010	Furfine et al.	
	238	7,851,443		12-14-2010	Bissery et al.	
	040	7,964,377		06-21-2011	Papadopoulos et al.	

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /J.L/

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT (not for submission under 37 CFR 1.99)		
	Application Number	17/384,070
	Filing Date	Jul-23-2021
	First Named Inventor	Kenneth S. Graham
	Art Unit	Not Yet Assigned
	Confirmation Number	1061
	Examiner Name	Not Yet Assigned
	Attorney Docket Number	125984-266215 / 10430US02

U.S. PATENTS						
Examiner Initial*	Cite No	Patent Number	Kind Code[1]	Issue Date	Name of Patentee or Applicant of cited Document	Pages, Columns, Lines where Relevant Passages or Relevant Figures Appear
	041	7,972,598		07-05-2011	Daly et al.	
	049	8,029,791		10-04-2011	Papadopoulos et al.	
	042	8,084,234		12-27-2011	Papadopoulos et al.	
	066	8,092,803		01-10-2012	Furfine et al.	
	072	8,110,546		02-07-2012	Dix et al.	
	106	8,216,575		07-10-2012	Yu	
	107	8,372,396		02-12-2013	Andya et al.	
	043	8,343,737		01-01-2013	Papadopoulos et al.	
	073	8,404,638		03-26-2013	Dix et al.	
	067	8,481,046		07-09-2013	Furfine et al.	
	108	8,568,720		10-29-2013	Morichika et al.	
	027	8,623,395		01-07-2014	de Juan, Jr. et al.	
	044	8,647,842		02-11-2014	Papadopoulos et al.	
	074	8,710,004		04-29-2014	Dix et al.	
	068	8,802,107		08-12-2014	Furfine et al.	
	075	8,921,316		12-30-2014	Dix et al.	
	109	8,961,964		02-24-2015	Liu et al.	
	038	9,139,644		09-22-2015	Papadopoulos et al.	
	060	9,254,338		02-09-2016	Yancopoulos	
	110	9,283,273		03-15-2016	Andya et al.	
	069	9,340,594		05-17-2016	Furfine et al.	
	080	9,402,898		08-02-2016	Walsh et al.	
	076	9,416,167		08-16-2016	Dix et al.	
	018	9,474,803		10-25-2016	Park et al.	
	077	9,511,140		12-06-2016	Dix et al.	
	071	9,580,489		02-28-2017	Furfine et al.	
	078	9,636,400		05-02-2017	Dix et al.	
	061	9,669,069		06-06-2017	Yancopoulos	
	039	9,708,386		07-18-2017	Papadopoulos et al.	
	240	9,884,019		02-06-2018	Tchessalov et al.	
	070	9,914,763		03-13-2018	Furfine et al.	
	016	9,982,032		05-29-2018	Park et al.	
	062	10,130,681		11-20-2018	Yancopoulos	

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /J.L/

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (not for submission under 37 CFR 1.99)		
	Application Number	17/384,070
	Filing Date	Jul-23-2021
	First Named Inventor	Kenneth S. Graham
	Art Unit	Not Yet Assigned
	Confirmation Number	1061
	Examiner Name	Not Yet Assigned
	Attorney Docket Number	125984-266215 / 10430US02

U.S. PATENTS						
Examiner Initial*	Cite No	Patent Number	Kind Code[1]	Issue Date	Name of Patentee or Applicant of cited Document	Pages, Columns, Lines where Relevant Passages or Relevant Figures Appear
	241	10,166,293		01-01-2019	Liu et al.	
	111	10,400,025		09-03-2019	Furfine et al.	
	112	10,406,226		09-10-2019	Dix et al.	
	242	10,413,513		09-17-2019	Fabio et al.	
	113	10,464,992		11-05-2019	Furfine et al.	
	243	10,501,523		12-10-2019	Chiron-Blondel et al.	
	244	10,576,128		03-03-2020	Sigl	
	309	10,610,600		04-07-2020	Soane et al.	
	114	10,689,438		06-23-2020	Zhang et al.	
	310	10,799,642		10-13-2020	Wong et al.	
	221	10,828,345		11-10-2020	Yancopoulos	
	222	10,857,205		12-08-2020	Yancopoulos	
	115	10,857,231		12-08-2020	Dix et al.	
	313	10,869,924		12-22-2020	Andrews et al.	
	223	10,888,601		01-12-2021	Yancopoulos	
	315	10,898,572		01-26-2021	Kameoka et al.	
	316	10,925,927		02-23-2021	Brockmeyer et al.	
	317	10,973,879		04-13-2021	Vitti et al.	
	375	11,033,606		06-15-2021	Castan	
	376	11,053,278		07-06-2021	Blum et al.	
	377	11,066,458		07-20-2021	Furfine et al.	
	378	11,077,059		08-03-2021	Coffman et al	
	379	11,077,188		08-03-2021	Kauvar et al.	
	380	11,084,865		08-10-2021	Furfine et al.	
	381	11,103,552		08-31-2021	Graham et al.	
	382	11,110,226		09-07-2021	Bryant et al.	
	383	11,123,411		09-21-2021	Borodic	
	384	11,135,266		10-05-2021	Kerwin et al.	

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /J.L/

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (not for submission under 37 CFR 1.99)		
	Application Number	17/384,070
	Filing Date	Jul-23-2021
	First Named Inventor	Kenneth S. Graham
	Art Unit	Not Yet Assigned
	Confirmation Number	1061
	Examiner Name	Not Yet Assigned
	Attorney Docket Number	125984-266215 / 10430US02

U.S. PATENT APPLICATION PUBLICATIONS						
Examiner Initial*	Cite No	Publication Number	Kind Code[1]	Publication Date	Name of Patentee or Applicant of cited Document	Pages, Columns, Lines where Relevant Passages or Relevant Figures Appear
	116	2003-0113316		06-19-2003	Kaisheva et al.	
	117	2003-0138417		07-24-2003	Kaisheva et al.	
	245	2003-0180287		09-25-2003	Gombotz et al.	
	246	2003-0206939		11-06-2003	Bannister	
	118	2004-0197324		10-07-2004	Liu et al.	
	225	2004-0266686		12-30-2004	Xia et al.	
	247	2005-0013867		01-20-2005	Lehrman et al.	
	248	2005-0112061		05-26-2005	Holash et al.	
	249	2005-0123509		06-09-2005	Lehrman et al.	
	250	2005-0196340		09-08-2005	Holash et al.	
	119	2006-0217311		09-28-2006	Dix et al.	
	251	2007-0053900		03-08-2007	Liu et al.	
	006	2007-0172479		07-26-2007	Warne et al.	
	120	2007-0190058		08-16-2007	Shams	
	252	2007-0237758		10-11-2007	Barry et al.	
	253	2008-0064856		03-13-2008	Warne et al.	
	254	2008-0071063		03-20-2008	Allan et al.	
	255	2009-0280129		11-12-2009	LIU et al.	
	256	2010-0158899		06-24-2010	Andya et al.	
	007	2010-0254985		10-07-2010	ALLAN et al.	
	226	2011-0028698		02-03-2011	Papadopoulos et al.	
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	First Named Inventor	Kenneth S. Graham
	Art Unit	Not Yet Assigned
	Confirmation Number	1061
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EXAMINER SIGNATURE			
Examiner Signature	/JON M LOCKARD/	Date Considered	03/15/2023

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☒ None

SIGNATURE

A signature of the applicant or representative is required in accordance with CFR 1.33, 10.18. Please see CFR 1.4(d) for the form of the signature.

Signature	/Lance A. Termes/	Date (YYYY-MM-DD)	2021-12-03
Name/Print	Lance A. Termes	Registration Number	43184

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Receipt date: 01/16/2024

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U.S. PATENTS						
Examiner Initial*	Cite No	Patent Number	Kind Code[1]	Issue Date	Name of Patentee or Applicant of cited Document	Pages, Columns, Lines where Relevant Passages or Relevant Figures Appear
/J.L/	565	11,806,398		11-07-2023	Dix et al.	

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT (not for submission under 37 CFR 1.99)		
	Application Number	17/384,070
	Filing Date	Jul-23-2021
	First Named Inventor	Kenneth S. Graham
	Art Unit	1647
	Confirmation Number	1061
	Examiner Name	Lockard, Jon McClelland
	Attorney Docket Number	125984-266215

U.S. PATENTS						
Examiner Initial*	Cite No	Patent Number	Kind Code[1]	Issue Date	Name of Patentee or Applicant of cited Document	Pages, Columns, Lines where Relevant Passages or Relevant Figures Appear

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	273	2022-0162296		05-26-2022	Lin et al.	

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Examiner Initial*	Cite No	Foreign Document Number[3]	Country Code[2]	Kind Code[4]	Publication Date	Name of Patentee or Applicant of cited Document	Pages, Columns, Lines where Relevant Passages or Relevant Figures Appear	T[5]
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	569	17/075252	WO	A1	05-04-2017	GENENTECH, INC.		
	571	19/108770	WO	A1	06-06-2019	Regeneron Pharmaceuticals, Inc.		

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Examiner Initial*	Cite No	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, pages(s), volume-issue number(s), publisher, city and/or country where published	T[5]
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EXAMINER SIGNATURE			
Examiner Signature		Date Considered	

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through a citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

[1] See Kind Codes of USPTO Patent Documents at www.USPTO.GOV or MPEP 901.04. [2] Enter office that issued the document, by the two-letter code (WIPO Standard ST.3). [3] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [4] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [5] Applicant is to place a check mark here if English language translation is attached.

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	Examiner Name	Lockard, Jon McClelland
	Attorney Docket Number	125984-266215

CERTIFICATION STATEMENT

Please see 37 CFR 1.97 and 1.98 to make the appropriate selection(s):

☐ That each item of information contained in the information disclosure statement was first cited in any communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(1).

OR

☐ That no item of information contained in the information disclosure statement was cited in a communication from a foreign patent office in a counterpart foreign application, and, to the knowledge of the person signing the certification after making reasonable inquiry, no item of information contained in the information disclosure statement was known to any individual designated in 37 CFR 1.56(c) more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(2).

☐ See attached certification statement.

☐ Fee set forth in 37 CFR 1.17 (p) has been submitted herewith.

☒ None

SIGNATURE

A signature of the applicant or representative is required in accordance with CFR 1.33, 10.18. Please see CFR 1.4(d) for the form of the signature.

Signature	/Lance A. Termes/	Date (YYYY-MM-DD)	2024-04-29
Name/Print	Lance A. Termes	Registration Number	43184

Regeneron Ex. 2001
Alvotech v. Regeneron
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PTO/SB/30 (11-23)
Approved for use through 05/31/2024. OMB 0651-0031
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Request for Continued Examination (RCE) Transmittal

Address to:
Mail Stop RCE
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Application Number	17/384,070
Filing Date	July 23, 2021
First Named Inventor	Kenneth S. Graham
Art Unit	1647
Examiner Name	Jon McClelland Lockard
Attorney Docket Number	125984-266215

This is a Request for Continued Examination (RCE) under 37 CFR 1.114 of the above-identified application.
Request for Continued Examination (RCE) practice under 37 CFR 1.114 does not apply to any utility or plant application filed prior to June 8, 1995, or to any design application. See Instruction Sheet for RCEs (not to be submitted to the USPTO) on page 2

1. Submission required under 37 CFR 1.114 Note: If the RCE is proper, any previously filed unentered amendments and amendments enclosed with the RCE will be entered in the order in which they were filed unless applicant instructs otherwise. If applicant does not wish to have any previously filed unentered amendment(s) entered, applicant must request non-entry of such amendment(s).

   a. ☐ Previously submitted. If a final Office action is outstanding, any amendments filed after the final Office action may be considered as a submission even if this box is not checked.

      i. ☐ Consider the arguments in the Appeal Brief or Reply Brief previously filed on _____

      ii. ☐ Other _____

   b. ☑ Enclosed

      i. ☐ Amendment/Reply

      ii. ☐ Affidavit(s)/ Declaration(s)

      iii. ☑ Information Disclosure Statement (IDS)

      iv. ☐ Other _____

2. Miscellaneous

   a. ☐ Suspension of action on the above-identified application is requested under 37 CFR 1.103(c) for a period of _____ months. (Period of suspension shall not exceed 3 months; Fee under 37 CFR 1.17(i) required)

   b. ☐ Other _____

3. Fees The RCE fee under 37 CFR 1.17(e) is required by 37 CFR 1.114 when the RCE is filed.

   a. ☑ The Director is hereby authorized to charge the following fees, any underpayment of fees, or credit any overpayments, to Deposit Account No. 500393 .

      i. ☑ RCE fee required under 37 CFR 1.17(e)

      ii. ☐ Extension of time fee (37 CFR 1.136 and 1.17)

      iii. ☐ Other _____

   b. ☐ Check in the amount of $ _____ enclosed

   c. ☐ Payment by credit card (Form PTO-2038 enclosed)

   d. ▩ Payment by USPTO patent electronic filing system.

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SIGNATURE OF APPLICANT, ATTORNEY, OR AGENT REQUIRED

Signature	/Lance A. Termes/	Date	April 29, 2024
Name (Print/Type)	Lance A. Termes	Registration No.	43,184

CERTIFICATE OF MAILING OR TRANSMISSION

I hereby certify that this correspondence is transmitted by the USPTO patent electronic filing system, or by facsimile to (571) 273-8300, to the USPTO, or deposited with the United States Postal Service with sufficient postage as first class mail in an envelope addressed to: Mail Stop RCE, Commissioner for Patents, P. O. Box 1450, Alexandria, VA 22313-1450, on the date shown below.

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	616	11,975,045		05-07-2024	Yancopoulos	

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	617	clinicaltrialsgov posting NCT00090623, A Study of rhuFab V2 (Ranibizumab) in Subjects With Subfoveal Choroidal Neovascularization Secondary to Age-Related Macular Degeneration (AMD), PIER, 06212013	
	618	clinicaltrialsgov posting NCT01217944, Efficacy and Safety of Ranibizumab in Patients With Visual Impairment Due to Choroidal Neovascularization Secondary to Pathologic Myopia, RADIANCE, 02102014	
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	621	clinicaltrialsgov posting NCT00056836, A Study to Evaluate rhuFab V2 in Subjects With Minimally Classic or Occult Subfoveal Neovascular Macular Degeneration, MARINA, 05162014	
	622	clinicaltrialsgov posting NCT00061594, A Study to Compare rhuFab V2 With Verteporfin Photodynamic in Treating Subfoveal Neovascular Macular Degeneration, ANCHOR, 03192014	
	623	clinicaltrialsgov posting NCT00473382, A Study of Ranibizumab Injection in Subjects With Clinically Significant Macular Edema (ME) With Center Involvement Secondary to Diabetes Mellitus (RIDE), 04172017	
	624	clinicaltrialsgov posting NCT00473330, A Study of Ranibizumab Injection in Subjects With Clinically Significant Macular Edema (ME) With Center Involvement Secondary to Diabetes Mellitus (RISE), 04172017	
	625	clinicaltrialsgov posting NCT02434328, Efficacy and Safety of RTH258 Versus Aflibercept - Study 2, HARRIER, 03282018	
	626	clinicaltrialsgov posting NCT02307682, Efficacy and Safety of RTH258 Versus Aflibercept - Study 1, HAWK, 05082018	
	627	clinicaltrialsgov posting NCT00891735, A Study of Ranibizumab Administered Monthly or on an As-needed Basis in Patients With Subfoveal Neovascular Age-related Macular Degeneration (HARBOR), 01182013	
	628	clinicaltrialsgov posting NCT00036946, VEGF Trap in Treating Patients With Relapsed or Refractory Solid Tumors or Non-Hodgkin's Lymphoma, REGENERON-VGFT-ST-0103, 060320156	
	629	clinicaltrialsgov posting NCT00527423, Randomized, Single-Masked, Long-Term, Safety and Tolerability Study of VEGF Trap-Eye in AMD, 06122013	
	630	clinicaltrialsgov posting NCT00383370, Safety and Tolerability of Intravitreal VEGF Trap Formulations in Subjects With Neovacular AMD, VGFT-OD-0603, 04212011	
	631	clinicaltrialsgov posting NCT00320775, Safety and Tolerability Study of Intravitreal VEGF-Trap Administration in Patients With Neovascular AMD, CLEAR-IT1, 03182015	
	632	clinicaltrialsgov posting NCT00789477, DME And VEGF Trap-Eye [Intravitreal Aflibercept Injection (IAI;EYLEA®;BAY86-5321)] INvestigation of Clinical Impact, Da Vinci, 09092014	
	633	clinicaltrialsgov posting NCT00320788, Safety and Efficacy of Repeated Intravitreal Administration of Vascular Endothelial Growth Factor (VEGF) Trap in Patients With Wet Age-Related Macular Degeneration (AMD), CLEAR-IT2, 03012012	

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (not for submission under 37 CFR 1.99)		
	Application Number	17/384,070
	Filing Date	Jul-23-2021
	First Named Inventor	Kenneth S. Graham
	Art Unit	1647
	Confirmation Number	1061
	Examiner Name	Lockard, Jon McClelland
	Attorney Docket Number	125984-266215

EXAMINER SIGNATURE			
Examiner Signature		Date Considered	

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through a citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

[1] See Kind Codes of USPTO Patent Documents at www.USPTO.GOV or MPEP 901.04. [2] Enter office that issued the document, by the two-letter code (WIPO Standard ST.3). [3] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [4] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [5] Applicant is to place a check mark here if English language translation is attached.

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (not for submission under 37 CFR 1.99)		
	Application Number	17/384,070
	Filing Date	Jul-23-2021
	First Named Inventor	Kenneth S. Graham
	Art Unit	1647
	Confirmation Number	1061
	Examiner Name	Lockard, Jon McClelland
	Attorney Docket Number	125984-266215

CERTIFICATION STATEMENT

Please see 37 CFR 1.97 and 1.98 to make the appropriate selection(s):

☐ That each item of information contained in the information disclosure statement was first cited in any communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(1).

OR

☐ That no item of information contained in the information disclosure statement was cited in a communication from a foreign patent office in a counterpart foreign application, and, to the knowledge of the person signing the certification after making reasonable inquiry, no item of information contained in the information disclosure statement was known to any individual designated in 37 CFR 1.56(c) more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(2).

☐ See attached certification statement.

☐ Fee set forth in 37 CFR 1.17 (p) has been submitted herewith.

☒ None

SIGNATURE

A signature of the applicant or representative is required in accordance with CFR 1.33, 10.18. Please see CFR 1.4(d) for the form of the signature.

Signature	/Lance A. Termes/	Date (YYYY-MM-DD)	2024-05-10
Name/Print	Lance A. Termes	Registration Number	43184

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UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

NOTICE OF ALLOWANCE AND FEE(S) DUE

147803 7590 05/28/2024

Schwabe W&W, PC / Regeneron Pharmaceuticals, Inc.
PacWest Center
1211 SW Fifth Avenue, Suite 1900
Portland, OR 97204

EXAMINER	
LOCKARD, JON MCCLELLAND	
ART UNIT	PAPER NUMBER
1647	

DATE MAILED: 05/28/2024

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
17/384,070	07/23/2021	Kenneth S. Graham		1061

TITLE OF INVENTION: Methods for Treating Angiogenic Eye Disorders with High Doses of VEGF Receptor Fusion Proteins

APPLN. TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	UNDISCOUNTED	$1200	$0.00	$1200.00	$0	08/28/2024

THE APPLICATION IDENTIFIED ABOVE HAS BEEN EXAMINED AND IS ALLOWED FOR ISSUANCE AS A PATENT. PROSECUTION ON THE MERITS IS CLOSED. THIS NOTICE OF ALLOWANCE IS NOT A GRANT OF PATENT RIGHTS. THIS APPLICATION IS SUBJECT TO WITHDRAWAL FROM ISSUE AT THE INITIATIVE OF THE OFFICE OR UPON PETITION BY THE APPLICANT. SEE 37 CFR 1.313 AND MPEP 1308.

THE ISSUE FEE AND PUBLICATION FEE (IF REQUIRED) MUST BE PAID WITHIN THREE MONTHS FROM THE MAILING DATE OF THIS NOTICE OR THIS APPLICATION SHALL BE REGARDED AS ABANDONED. THIS STATUTORY PERIOD CANNOT BE EXTENDED. SEE 35 U.S.C. 151. THE ISSUE FEE DUE INDICATED ABOVE DOES NOT REFLECT A CREDIT FOR ANY PREVIOUSLY PAID ISSUE FEE IN THIS APPLICATION. IF AN ISSUE FEE HAS PREVIOUSLY BEEN PAID IN THIS APPLICATION (AS SHOWN ABOVE), THE RETURN OF PART B OF THIS FORM WILL BE CONSIDERED A REQUEST TO REAPPLY THE PREVIOUSLY PAID ISSUE FEE TOWARD THE ISSUE FEE NOW DUE.

HOW TO REPLY TO THIS NOTICE:

I. Review the ENTITY STATUS shown above. If the ENTITY STATUS is shown as SMALL or MICRO, verify whether entitlement to that entity status still applies.

If the ENTITY STATUS is the same as shown above, pay the TOTAL FEE(S) DUE shown above.

If the ENTITY STATUS is changed from that shown above, on PART B - FEE(S) TRANSMITTAL, complete section number 5 titled "Change in Entity Status (from status indicated above)".

For purposes of this notice, small entity fees are 40% the amount of undiscounted fees, and micro entity fees are 20% the amount of undiscounted fees.

II. PART B - FEE(S) TRANSMITTAL, or its equivalent, must be completed and returned to the United States Patent and Trademark Office (USPTO) with your ISSUE FEE and PUBLICATION FEE (if required). If you are charging the fee(s) to your deposit account, section "4b" of Part B - Fee(s) Transmittal should be completed. If an equivalent of Part B is filed, a request to reapply a previously paid issue fee must be clearly made, and delays in processing may occur due to the difficulty in recognizing the paper as an equivalent of Part B.

III. All communications regarding this application must give the application number. Please direct all communications prior to issuance to Mail Stop ISSUE FEE unless advised to the contrary.

IMPORTANT REMINDER: Maintenance fees are due in utility patents issuing on applications filed on or after Dec. 12, 1980. It is patentee's responsibility to ensure timely payment of maintenance fees when due. More information is available at www.uspto.gov/PatentMaintenanceFees.

PTOL-85 (Rev. 11/23)

Regeneron Ex. 2001
Alvotech v. Regeneron
PGR2025-00085
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PART B - FEE(S) TRANSMITTAL

Complete and send this form, together with applicable fee(s), by mail or fax, or via the USPTO patent electronic filing system.

By mail, send to: Mail Stop ISSUE FEE
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450

By fax, send to: (571)-273-2885

INSTRUCTIONS: This form should be used for transmitting the ISSUE FEE and PUBLICATION FEE (if required). Blocks 1 through 5 should be completed where appropriate. All further correspondence will be mailed to the current correspondence address as indicated unless corrected below or directed otherwise in Block 1, by (a) specifying a new correspondence address; and/or (b) indicating a separate "FEE ADDRESS" for maintenance fee notifications. **Because electronic patent issuance may occur shortly after issue fee payment, any desired continuing application should preferably be filed prior to payment of this issue fee in order not to jeopardize copendency.**

CURRENT CORRESPONDENCE ADDRESS (Note: Use Block 1 for any change of address)

147803 7590 05/28/2024
Schwabe W&W, PC / Regeneron Pharmaceuticals, Inc.
PacWest Center
1211 SW Fifth Avenue, Suite 1900
Portland, OR 97204

Note: A certificate of mailing can only be used for domestic mailings of the Fee(s) Transmittal. This certificate cannot be used for any other accompanying papers. Each additional paper, such as an assignment or formal drawing, must have its own certificate of mailing or transmission.

Certificate of Mailing or Transmission

I hereby certify that this Fee(s) Transmittal is being deposited with the United States Postal Service with sufficient postage for first class mail in an envelope addressed to the Mail Stop ISSUE FEE address above, or being transmitted to the USPTO via the USPTO patent electronic filing system or by facsimile to (571) 273-2885, on the date below.

(Typed or printed name)
(Signature)
(Date)

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
17/384,070	07/23/2021	Kenneth S. Graham		1061

TITLE OF INVENTION: Methods for Treating Angiogenic Eye Disorders with High Doses of VEGF Receptor Fusion Proteins

APPLN. TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	UNDISCOUNTED	$1200	$0.00	$1200.00	$0	08/28/2024

EXAMINER	ART UNIT	CLASS-SUBCLASS
LOCKARD, JON MCCLELLAND	1647	424-134100

1. Change of correspondence address or indication of "Fee Address" (37 CFR 1.363).

❑ Change of correspondence address (or Change of Correspondence Address form PTO/AIA/122 or PTO/SB/122) attached.

❑ "Fee Address" indication (or "Fee Address" Indication form PTO/AIA/47 or PTO/SB/47; Rev 03-02 or more recent) attached. **Use of a Customer Number is required.**

2. For printing on the patent front page, list
(1) The names of up to 3 registered patent attorneys or agents OR, alternatively,
(2) The name of a single firm (having as a member a registered attorney or agent) and the names of up to 2 registered patent attorneys or agents. If no name is listed, no name will be printed.

1 _____
2 _____
3 _____

3. ASSIGNEE NAME AND RESIDENCE DATA TO BE PRINTED ON THE PATENT (print or type)

PLEASE NOTE: Unless an assignee is identified below, no assignee data will appear on the patent. If an assignee is identified below, the document must have been previously recorded, or filed for recordation, as set forth in 37 CFR 3.11 and 37 CFR 3.81(a). Completion of this form is NOT a substitute for filing an assignment.

(A) NAME OF ASSIGNEE (B) RESIDENCE: (CITY and STATE OR COUNTRY)

Please check the appropriate assignee category or categories (will not be printed on the patent) : ❑ Individual ❑ Corporation or other private group entity ❑ Government

4a. Fees submitted: ❑Issue Fee ❑Publication Fee (if required)

4b. Method of Payment: *(Please first reapply any previously paid fee shown above)*

❑ Electronic Payment via the USPTO patent electronic filing system ❑ Enclosed check ❑ Non-electronic payment by credit card (Attach form PTO-2038)

❑ The Director is hereby authorized to charge the required fee(s), any deficiency, or credit any overpayment to Deposit Account No. _____

5. **Change in Entity Status** (from status indicated above)

❑ Applicant certifying micro entity status. See 37 CFR 1.29

NOTE: Absent a valid certification of Micro Entity Status (see forms PTO/SB/15A and 15B), issue fee payment in the micro entity amount will not be accepted at the risk of application abandonment.

❑ Applicant asserting small entity status. See 37 CFR 1.27

NOTE: If the application was previously under micro entity status, checking this box will be taken to be a notification of loss of entitlement to micro entity status.

❑ Applicant changing to regular undiscounted fee status.

NOTE: Checking this box will be taken to be a notification of loss of entitlement to small or micro entity status, as applicable.

NOTE: This form must be signed in accordance with 37 CFR 1.31 and 1.33. See 37 CFR 1.4 for signature requirements and certifications.

Authorized Signature _____ Date _____

Typed or printed name _____ Registration No. _____

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UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
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Alexandria, Virginia 22313-1450
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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
17/384,070	07/23/2021	Kenneth S. Graham		1061

147803 7590 05/28/2024

Schwabe W&W, PC / Regeneron Pharmaceuticals, Inc.
PacWest Center
1211 SW Fifth Avenue, Suite 1900
Portland, OR 97204

EXAMINER	
LOCKARD, JON MCCLELLAND	
ART UNIT	**PAPER NUMBER**
1647	

DATE MAILED: 05/28/2024

Determination of Patent Term Adjustment under 35 U.S.C. 154 (b)
(Applications filed on or after May 29, 2000)

The Office has discontinued providing a Patent Term Adjustment (PTA) calculation with the Notice of Allowance.

Section 1(h)(2) of the AIA Technical Corrections Act amended 35 U.S.C. 154(b)(3)(B)(i) to eliminate the requirement that the Office provide a patent term adjustment determination with the notice of allowance. See Revisions to Patent Term Adjustment, 78 Fed. Reg. 19416, 19417 (Apr. 1, 2013). Therefore, the Office is no longer providing an initial patent term adjustment determination with the notice of allowance. The Office will continue to provide a patent term adjustment determination with the Issue Notification Letter that is mailed to applicant approximately three weeks prior to the issue date of the patent, and will include the patent term adjustment on the patent. Any request for reconsideration of the patent term adjustment determination (or reinstatement of patent term adjustment) should follow the process outlined in 37 CFR 1.705.

Any questions regarding the Patent Term Extension or Adjustment determination should be directed to the Office of Patent Legal Administration at (571)-272-7702. Questions relating to issue and publication fee payments should be directed to the Customer Service Center of the Office of Patent Publication at 1-(888)-786-0101 or (571)-272-4200.

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OMB Clearance and PRA Burden Statement for PTOL-85 Part B

The Paperwork Reduction Act (PRA) of 1995 requires Federal agencies to obtain Office of Management and Budget approval before requesting most types of information from the public. When OMB approves an agency request to collect information from the public, OMB (i) provides a valid OMB Control Number and expiration date for the agency to display on the instrument that will be used to collect the information and (ii) requires the agency to inform the public about the OMB Control Number's legal significance in accordance with 5 CFR 1320.5(b).

The information collected by PTOL-85 Part B is required by 37 CFR 1.311. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 30 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, Virginia 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, Virginia 22313-1450. Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

Privacy Act Statement

The Privacy Act of 1974 (P.L. 93-579) requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. The United States Patent and Trademark Office (USPTO) collects the information in this record under authority of 35 U.S.C. 2. The USPTO's system of records is used to manage all applicant and owner information including name, citizenship, residence, post office address, and other information with respect to inventors and their legal representatives pertaining to the applicant's/owner's activities in connection with the invention for which a patent is sought or has been granted. The applicable Privacy Act System of Records Notice for the information collected in this form is COMMERCE/PAT-TM-7 Patent Application Files, available in the Federal Register at 78 FR 19243 (March 29, 2013).
https://www.govinfo.gov/content/pkg/FR-2013-03-29/pdf/2013-07341.pdf

Routine uses of the information in this record may include disclosure to:

1) law enforcement, in the event that the system of records indicates a violation or potential violation of law;
2) a federal, state, local, or international agency, in response to its request;
3) a contractor of the USPTO having need for the information in order to perform a contract;
4) the Department of Justice for determination of whether the Freedom of Information Act (FOIA) requires disclosure of the record;
5) a Member of Congress submitting a request involving an individual to whom the record pertains, when the individual has requested the Member's assistance with respect to the subject matter of the record;
6) a court, magistrate, or administrative tribunal, in the course of presenting evidence, including disclosures to opposing counsel in the course of settlement negotiations;
7) the Administrator, General Services Administration (GSA), or their designee, during an inspection of records conducted by GSA under authority of 44 U.S.C. 2904 and 2906, in accordance with the GSA regulations and any other relevant (i.e., GSA or Commerce) directive, where such disclosure shall not be used to make determinations about individuals;
8) another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c));
9) the Office of Personnel Management (OPM) for personnel research purposes; and
10) the Office of Management and Budget (OMB) for legislative coordination and clearance.

If you do not furnish the information requested on this form, the USPTO may not be able to process and/or examine your submission, which may result in termination of proceedings, abandonment of the application, and/or expiration of the patent.

Notice of Allowability	Application No. 17/384,070	Applicant(s) Graham et al.	
	Examiner JON M LOCKARD	Art Unit 1647	AIA (FITF) Status Yes

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address--

All claims being allowable, PROSECUTION ON THE MERITS IS (OR REMAINS) CLOSED in this application. If not included herewith (or previously mailed), a Notice of Allowance (PTOL-85) or other appropriate communication will be mailed in due course. **THIS NOTICE OF ALLOWABILITY IS NOT A GRANT OF PATENT RIGHTS.** This application is subject to withdrawal from issue at the initiative of the Office or upon petition by the applicant. See 37 CFR 1.313 and MPEP 1308.

1. ☑ This communication is responsive to the Request for Continued Examination filed 29 April 2024.
   ☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on _____.

2. ☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.

3. ☑ The allowed claim(s) is/are See Continuation Sheet . As a result of the allowed claim(s), you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information, please see **http://www.uspto.gov/patents/init_events/pph/index.jsp** or send an inquiry to **PPHfeedback@uspto.gov.**

4. ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

   Certified copies:

   a) ☐ All b) ☐ Some* c) ☐ None of the:

   1. ☐ Certified copies of the priority documents have been received.
   2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
   3. ☐ Copies of the certified copies of the priority documents have been received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

   * Certified copies not received: _____ .

Applicant has THREE MONTHS FROM THE "MAILING DATE" of this communication to file a reply complying with the requirements noted below. Failure to timely comply will result in ABANDONMENT of this application.
THIS THREE-MONTH PERIOD IS NOT EXTENDABLE.

5. ☐ CORRECTED DRAWINGS (as "replacement sheets") must be submitted.
   ☐ including changes required by the attached Examiner's Amendment / Comment or in the Office action of Paper No./Mail Date _____ .

   Identifying indicia such as the application number (see 37 CFR 1.84(c)) should be written on the drawings in the front (not the back) of each sheet. Replacement sheet(s) should be labeled as such in the header according to 37 CFR 1.121(d).

6. ☐ DEPOSIT OF and/or INFORMATION about the deposit of BIOLOGICAL MATERIAL must be submitted. Note the attached Examiner's comment regarding REQUIREMENT FOR THE DEPOSIT OF BIOLOGICAL MATERIAL.

Attachment(s)

1. ☐ Notice of References Cited (PTO-892)
2. ☑ Information Disclosure Statements (PTO/SB/08), Paper No./Mail Date _____.
3. ☐ Examiner's Comment Regarding Requirement for Deposit of Biological Material _____.
4. ☐ Interview Summary (PTO-413), Paper No./Mail Date. _____.
5. ☑ Examiner's Amendment/Comment
6. ☑ Examiner's Statement of Reasons for Allowance
7. ☐ Other _____.

/J.L/ Examiner, Art Unit 1647	/CHRISTINE J SAOUD/ Primary Examiner, Art Unit 1645

Regeneron Ex. 2001
Alvotech v. Regeneron
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Continuation of 3. The allowed claim(s) is/are: 30-32 and 53-87)renumbered as claims 1-11,13-14,16,18,20,22,24,12,26,15,17,19,21,23,25 and 27-38, respectively)

Notice of Pre-AIA or AIA Status

1. The present application, filed on or after March 16, 2013, is being examined under the first inventor to file provisions of the AIA.

Continued Examination Under 37 CFR 1.114

2. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after allowance or after an Office action under *Ex Parte Quayle*, 25 USPQ 74, 453 O.G. 213 (Comm'r Pat. 1935). Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, prosecution in this application has been reopened pursuant to 37 CFR 1.114. Applicant's submission filed on 29 April 2024 has been entered.

Information Disclosure Statement

3. The information disclosure statements (IDS) submitted on 29 April 2024, 08 May 2024 and 10 May 2024 have been considered by the examiner. NPL references 585, 586, 601, 602 and 611 (filed 29 April 2024) have been lined through. The references have been considered, but will not appear on the cover of the issued patent as they do not provide a date.

REASONS FOR ALLOWANCE

4. The following is an examiner's statement of reasons for allowance: The information disclosure statements (IDS) submitted on 29 April 2024, 08 May 2024 and 10 May 2024 have been considered by the Examiner. After careful consideration, the Examiner has determined that none of the information contained therein raises new issues of patentability.

5. Any comments considered necessary by applicant must be submitted no later than the payment of the issue fee and, to avoid processing delays, should preferably accompany the issue fee. Such submissions should be clearly labeled "Comments on Statement of Reasons for Allowance."

Summary

6. Claims 30-32 and 53-87 are allowed.

Advisory Information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to **JON M LOCKARD** whose telephone number is **(571) 272-2717**. The examiner can normally be reached M-F 9-6 EST.

Examiner interviews are available via telephone, in-person, and video conferencing using a USPTO supplied web-based collaboration tool. To schedule an interview, applicant is encouraged to use the USPTO Automated Interview Request (AIR) at http://www.uspto.gov/interviewpractice. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, **Joanne Hama** can be reached on **(571) 272-2911**. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of published or unpublished applications may be obtained from Patent Center. Unpublished application information in Patent Center is available to registered users. To file and manage patent submissions in Patent Center, visit: https://patentcenter.uspto.gov. Visit https://www.uspto.gov/patents/apply/patent-center for more information about Patent Center and https://www.uspto.gov/patents/docx for information about filing in DOCX format. For additional questions, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/J.L/
Examiner, Art Unit 1647
May 10, 2024

/Christine J Saoud/
Primary Examiner, Art Unit 1645

Issue Classification	Application/Control No.	Applicant(s)/Patent Under Reexamination
	17/384,070	Graham et al.
	Examiner	Art Unit
	JON M LOCKARD	1647

CPC										
Symbol									Type	Version
A61K	/	38	/	179					F	2013-01-01
A61K	/	9	/	0048					I	2013-01-01
A61K	/	47	/	12					I	2013-01-01
A61P	/	27	/	02					I	2018-01-01
A61K	/	47	/	22					I	2013-01-01
A61K	/	47	/	26					I	2013-01-01
A61K	/	47	/	183					I	2013-01-01

CPC Combination Sets										
Symbol									Type	Set	Ranking	Version
	/		/									

/JON M LOCKARD/ Examiner, Art Unit 1647	10 May 2024	Total Claims Allowed:	
(Assistant Examiner)	(Date)	38	
/CHRISTINE J SAOUD/ Primary Examiner, Art Unit 1645	15 May 2024	O.G. Print Claim(s)	O.G. Print Figure
(Primary Examiner)	(Date)	1	NONE

U.S. Patent and Trademark Office — Part of Paper No.: 20240510

Regeneron Ex. 2001
Alvotech v. Regeneron
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Issue Classification	Application/Control No.	Applicant(s)/Patent Under Reexamination
	17/384,070	Graham et al.
	Examiner	Art Unit
	JON M LOCKARD	1647

INTERNATIONAL CLASSIFICATION					
CLAIMED					
A61K	/	38	/	17	
A61K	/	38	/	18	
C07K	/	14	/	71	

NON-CLAIMED				
	/		/	

US ORIGINAL CLASSIFICATION	
CLASS	SUBCLASS

CROSS REFERENCES(S)						
CLASS	SUBCLASS (ONE SUBCLASS PER BLOCK)					

/JON M LOCKARD/ Examiner, Art Unit 1647	10 May 2024	Total Claims Allowed:	
(Assistant Examiner)	(Date)	38	
/CHRISTINE J SAOUD/ Primary Examiner, Art Unit 1645	15 May 2024	O.G. Print Claim(s)	O.G. Print Figure
(Primary Examiner)	(Date)	1	NONE

U.S. Patent and Trademark Office — Part of Paper No.: 20240510

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Alvotech v. Regeneron
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Issue Classification	Application/Control No.	Applicant(s)/Patent Under Reexamination
	17/384,070	Graham et al.
	Examiner	Art Unit
	JON M LOCKARD	1647

☐ Claims renumbered in the same order as presented by applicant ☐ CPA ☑ T.D. ☐ R.1.47

CLAIMS

Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original
1	30	10	59	12	68	28	77	37	86						
2	31	11	60	26	69	29	78	38	87						
3	32	13	61	15	70	30	79								
4	53	14	62	17	71	31	80								
5	54	16	63	19	72	32	81								
6	55	18	64	21	73	33	82								
7	56	20	65	23	74	34	83								
8	57	22	66	25	75	35	84								
9	58	24	67	27	76	36	85								

/JON M LOCKARD/ Examiner, Art Unit 1647 (Assistant Examiner)	10 May 2024 (Date)	**Total Claims Allowed:** 38	
/CHRISTINE J SAOUD/ Primary Examiner, Art Unit 1645 (Primary Examiner)	15 May 2024 (Date)	O.G. Print Claim(s) 1	O.G. Print Figure NONE

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CPC - Searched*		
Symbol	Date	Examiner

CPC Combination Sets - Searched*		
Symbol	Date	Examiner

US Classification - Searched*			
Class	Subclass	Date	Examiner
NONE		03/16/2023	JML

* See search history printout included with this form or the SEARCH NOTES box below to determine the scope of the search.

Search Notes		
Search Notes	Date	Examiner
PE2E Search (USPAT, US-PGPUB, EPO, DERWENT): See attached search history.	03/16/2023	JML
STN (MEDLINE, SCISEARCH, EMBASE, BIOSIS): See attached search history.	03/16/2023	JML
PALM: Inventor search.	03/16/2023	JML
PE2E Search (USPAT, US-PGPUB, EPO, DERWENT): See attached search history.	11/01/2023	JML

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Interference Search			
US Class/CPC Symbol	**US Subclass/CPC Group**	**Date**	**Examiner**
	PE2E Search (USPAT): See attached search history.	08/24/2023	JML
	DAV: Inventor search.	08/24/2023	JML
	PE2E Search (USPAT): See attached search history.	11/01/2023	JML
	DAV: Inventor search.	11/01/2023	JML
	PE2E Search (USPAT): See attached search history.	11/29/2023	JML
	DAV: Inventor search.	11/29/2023	JML
	PE2E Search (USPAT): See attached search history.	01/11/2024	JML
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	PE2E Search (USPAT): See attached search history.	05/10/2024	JML
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Receipt date: 05/08/2024

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	First Named Inventor	Kenneth S. Graham
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	Confirmation Number	1061
	Examiner Name	Lockard, Jon McClelland
	Attorney Docket Number	125984-266215

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/J.L/	615	10,392,430		08-27-2019	Papadopoulos et al.	
/J.L/	616	11,975,045		05-07-2024	Yancopoulos	

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	569	17/075252	WO	A1	05-04-2017	GENENTECH, INC.		
	571	19/108770	WO	A1	06-06-2019	Regeneron Pharmaceuticals, Inc.		

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Examiner Signature	/JON M LOCKARD/	Date Considered	05/16/2024

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[1] See Kind Codes of USPTO Patent Documents at www.USPTO.GOV or MPEP 901.04. [2] Enter office that issued the document, by the two-letter code (WIPO Standard ST.3). [3] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [4] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [5] Applicant is to place a check mark here if English language translation is attached.

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /J.L/

PE2E SEARCH - Search History (Prior Art)

/J.L./

There are no Prior Art searches to show.

PE2E SEARCH - Search History (Interference)

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	British Equivalents	Time Stamp
N32	2771	vegf ADJ trap	(USPAT)	OR	ON	ON	2024/05/10 02:08 PM
N33	2897	aflibercept	(USPAT)	OR	ON	ON	2024/05/10 02:08 PM
N34	363	eylea	(USPAT)	OR	ON	ON	2024/05/10 02:08 PM
N35	118	vegf ADJ trap-eye	(USPAT)	OR	ON	ON	2024/05/10 02:08 PM
N36	443	(N32 N33 N34 N35) SAME formulation	(USPAT)	OR	ON	ON	2024/05/10 02:08 PM
N37	12	N36 SAME "high concentration"	(USPAT)	OR	ON	ON	2024/05/10 02:09 PM
N38	1	N36 AND (8mg OR "8 mg").clm.	(USPAT)	OR	ON	ON	2024/05/10 02:10 PM
N39	17	(graham-k$-s$ washawa-s$).in.	(USPAT)	OR	ON	ON	2024/05/10 02:10 PM
N40	1	N37 AND N39	(USPAT)	OR	ON	ON	2024/05/10 02:11 PM

Regeneron Ex. 2001
Alvotech v. Regeneron
PGR2025-00085
Page 456 of 531

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (not for submission under 37 CFR 1.99)		
	Application Number	17/384,070
	Filing Date	Jul-23-2021
	First Named Inventor	Kenneth S. Graham
	Art Unit	1647
	Confirmation Number	1061
	Examiner Name	Lockard, Jon McClelland
	Attorney Docket Number	125984-266215

U.S. PATENTS						
Examiner Initial*	Cite No	Patent Number	Kind Code[1]	Issue Date	Name of Patentee or Applicant of cited Document	Pages, Columns, Lines where Relevant Passages or Relevant Figures Appear

U.S. PATENT APPLICATION PUBLICATIONS						
Examiner Initial*	Cite No	Publication Number	Kind Code[1]	Publication Date	Name of Patentee or Applicant of cited Document	Pages, Columns, Lines where Relevant Passages or Relevant Figures Appear

FOREIGN PATENT DOCUMENTS								
Examiner Initial*	Cite No	Foreign Document Number[3]	Country Code[2]	Kind Code[4]	Publication Date	Name of Patentee or Applicant of cited Document	Pages, Columns, Lines where Relevant Passages or Relevant Figures Appear	T[5]

NON-PATENT LITERATURE DOCUMENTS			
Examiner Initial*	Cite No	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, pages(s), volume-issue number(s), publisher, city and/or country where published	T[5]
	585	clinicaltrialsgov posting-NCT02305238-11282014 to 12202018, December 20, 2018.	
	586	clinicaltrialsgov posting-NCT02581891-10202015 to 05122020, May 12, 2020.	
	601	clinicaltrialsgov posting NCT00036946, June 1, 2016.	
	602	clinicaltrialsgov posting NCT00527423, June 10, 2013.	
	611	clinicaltrialsgov posting NCT01331681, March 20, 2016.	
	636	GAUDREAULT et al., "PHARMACOKINETICS AND RETINAL DISTRIBUTION OF RANIBIZUMAB, A HUMANIZED ANTIBODY FRAGMENT DIRECTED AGAINST VEGF-A, FOLLOWING INTRAVITREAL ADMINISTRATION IN RABBITS," RETINA, THE JOURNAL OF RETINAL AND VITREOUS DISEASES, Volume 27 (No 9): 1260-1266, (2007).	
	637	GAUDREAULT et al., "Preclinical Pharmacokinetics of Ranibizumab (rhuFabV2) after a Single Intravitreal Administration," Publication, Volume 46 (No 2): 726-733, (2005). [downloaded from lovs.arvojournals.org on 10/03/2023].	

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NON-PATENT LITERATURE DOCUMENTS			
Examiner Initial*	Cite No	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, pages(s), volume-issue number(s), publisher, city and/or country where published	T [5]
	638	Assessment report; International non-proprietary name: faricimab; Procedure No. EMEA/H/C/005642/0000. Committee for Medicinal Products for Human Use (CHMP) 319 pages (21 July 2022). [EMA/687844/2022]	
	634	U.S. Application No. 18/367,444, Non-Final Office Action mailed 05-21-2024.	

EXAMINER SIGNATURE			
Examiner Signature		Date Considered	

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[1] See Kind Codes of USPTO Patent Documents at www.USPTO.GOV or MPEP 901.04. [2] Enter office that issued the document, by the two-letter code (WIPO Standard ST.3). [3] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [4] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [5] Applicant is to place a check mark here if English language translation is attached.

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	Art Unit	1647
	Confirmation Number	1061
	Examiner Name	Lockard, Jon McClelland
	Attorney Docket Number	125984-266215

CERTIFICATION STATEMENT

Please see 37 CFR 1.97 and 1.98 to make the appropriate selection(s):

☐ That each item of information contained in the information disclosure statement was first cited in any communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(1).

OR

☐ That no item of information contained in the information disclosure statement was cited in a communication from a foreign patent office in a counterpart foreign application, and, to the knowledge of the person signing the certification after making reasonable inquiry, no item of information contained in the information disclosure statement was known to any individual designated in 37 CFR 1.56(c) more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(2).

☐ See attached certification statement.

☐ Fee set forth in 37 CFR 1.17 (p) has been submitted herewith.

☒ None

SIGNATURE

A signature of the applicant or representative is required in accordance with CFR 1.33, 10.18. Please see CFR 1.4(d) for the form of the signature.

Signature	/Lance A. Termes/	Date (YYYY-MM-DD)	2024-06-07
Name/Print	Lance A. Termes	Registration Number	43184

Regeneron Ex. 2001
Alvotech v. Regeneron
PGR2025-00085
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PTO/SB/30 (11-23)
Approved for use through 05/31/2024. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

Request for Continued Examination (RCE) Transmittal

Address to:
Mail Stop RCE
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Application Number	17/384,070
Filing Date	July 23, 2021
First Named Inventor	Kenneth S. Graham
Art Unit	1647
Examiner Name	Jon McClelland Lockard
Attorney Docket Number	125984-266215

This is a Request for Continued Examination (RCE) under 37 CFR 1.114 of the above-identified application.
Request for Continued Examination (RCE) practice under 37 CFR 1.114 does not apply to any utility or plant application filed prior to June 8, 1995, or to any design application. See Instruction Sheet for RCEs (not to be submitted to the USPTO) on page 2.

1. Submission required under 37 CFR 1.114 Note: If the RCE is proper, any previously filed unentered amendments and amendments enclosed with the RCE will be entered in the order in which they were filed unless applicant instructs otherwise. If applicant does not wish to have any previously filed unentered amendment(s) entered, applicant must request non-entry of such amendment(s).

   a. ☐ Previously submitted. If a final Office action is outstanding, any amendments filed after the final Office action may be considered as a submission even if this box is not checked.

      i. ☐ Consider the arguments in the Appeal Brief or Reply Brief previously filed on _____

      ii. ☐ Other _____

   b. ☑ Enclosed

      i. ☐ Amendment/Reply

      ii. ☐ Affidavit(s)/ Declaration(s)

      iii. ☑ Information Disclosure Statement (IDS)

      iv. ☐ Other _____

2. Miscellaneous

   a. ☐ Suspension of action on the above-identified application is requested under 37 CFR 1.103(c) for a period of _____ months. (Period of suspension shall not exceed 3 months; Fee under 37 CFR 1.17(i) required)

   b. ☐ Other _____

3. Fees The RCE fee under 37 CFR 1.17(e) is required by 37 CFR 1.114 when the RCE is filed.

   a. ☑ The Director is hereby authorized to charge the following fees, any underpayment of fees, or credit any overpayments, to Deposit Account No. 500393.

      i. ☑ RCE fee required under 37 CFR 1.17(e)

      ii. ☐ Extension of time fee (37 CFR 1.136 and 1.17)

      iii. ☐ Other _____

   b. ☐ Check in the amount of $ _____ enclosed

   c. ☐ Payment by credit card (Form PTO-2038 enclosed)

   d. ▩ Payment by USPTO patent electronic filing system.

WARNING: Information on this form may become public. Credit card information should not be included on this form. Provide credit card information and authorization on PTO-2038.

SIGNATURE OF APPLICANT, ATTORNEY, OR AGENT REQUIRED

Signature	/Lance A. Termes/	Date	June 7, 2024
Name (Print/Type)	Lance A. Termes	Registration No.	43,184

CERTIFICATE OF MAILING OR TRANSMISSION

I hereby certify that this correspondence is transmitted by the USPTO patent electronic filing system, or by facsimile to (571) 273-8300, to the USPTO, or deposited with the United States Postal Service with sufficient postage as first class mail in an envelope addressed to: Mail Stop RCE, Commissioner for Patents, P. O. Box 1450, Alexandria, VA 22313-1450, on the date shown below.

Signature	/Lance A. Termes/		
Name (Print/Type)	Lance A. Termes	Date	June 7, 2024

A Federal agency may not conduct or sponsor, and a person is not required to respond to, nor shall a person be subject to a penalty for failure to comply with an information collection subject to the requirements of the Paperwork Reduction Act of 1995, unless the information collection has a currently valid OMB Control Number. The OMB Control Number for this information collection is 0651-0031. Public burden for this form is estimated to average 12 minutes per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the information collection. Send comments regarding this burden estimate or any other aspect of this information collection, including suggestions for reducing this burden to the Chief Administrative Officer, United States Patent and Trademark Office, P.O. Box 1450, Alexandria, VA 22313-1450 or email InformationCollection@uspto.gov. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **If filing this completed form by mail, send to:**

Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.

If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (not for submission under 37 CFR 1.99)		
	Application Number	17/384,070
	Filing Date	Jul-23-2021
	First Named Inventor	Kenneth S. Graham
	Art Unit	1647
	Confirmation Number	1061
	Examiner Name	Lockard, Jon McClelland
	Attorney Docket Number	125984-266215

U.S. PATENTS						
Examiner Initial*	Cite No	Patent Number	Kind Code[1]	Issue Date	Name of Patentee or Applicant of cited Document	Pages, Columns, Lines where Relevant Passages or Relevant Figures Appear
	639	11,986,511		05-21-2024	Yancopoulos et al.	

U.S. PATENT APPLICATION PUBLICATIONS						
Examiner Initial*	Cite No	Publication Number	Kind Code[1]	Publication Date	Name of Patentee or Applicant of cited Document	Pages, Columns, Lines where Relevant Passages or Relevant Figures Appear

FOREIGN PATENT DOCUMENTS								
Examiner Initial*	Cite No	Foreign Document Number[3]	Country Code[2]	Kind Code[4]	Publication Date	Name of Patentee or Applicant of cited Document	Pages, Columns, Lines where Relevant Passages or Relevant Figures Appear	T[5]

NON-PATENT LITERATURE DOCUMENTS			
Examiner Initial*	Cite No	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, pages(s), volume-issue number(s), publisher, city and/or country where published	T[5]

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	Attorney Docket Number	125984-266215

EXAMINER SIGNATURE			
Examiner Signature		Date Considered	

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	Attorney Docket Number	125984-266215

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☐ See attached certification statement.

☐ Fee set forth in 37 CFR 1.17 (p) has been submitted herewith.

☒ None

SIGNATURE

A signature of the applicant or representative is required in accordance with CFR 1.33, 10.18. Please see CFR 1.4(d) for the form of the signature.

Signature	/Lance A. Termes/	Date (YYYY-MM-DD)	2024-06-18
Name/Print	Lance A. Termes	Registration Number	43184

Regeneron Ex. 2001
Alvotech v. Regeneron
PGR2025-00085
Page 463 of 531

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

NOTICE OF ALLOWANCE AND FEE(S) DUE

147803 7590 07/01/2024

Schwabe W&W, PC / Regeneron Pharmaceuticals, Inc.
PacWest Center
1211 SW Fifth Avenue, Suite 1900
Portland, OR 97204

EXAMINER	
LOCKARD, JON MCCLELLAND	
ART UNIT	PAPER NUMBER
1647	

DATE MAILED: 07/01/2024

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
17/384,070	07/23/2021	Kenneth S. Graham		1061

TITLE OF INVENTION: Methods for Treating Angiogenic Eye Disorders with High Doses of VEGF Receptor Fusion Proteins

APPLN. TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	UNDISCOUNTED	$1200	$0.00	$1200.00	$0	10/01/2024

THE APPLICATION IDENTIFIED ABOVE HAS BEEN EXAMINED AND IS ALLOWED FOR ISSUANCE AS A PATENT. PROSECUTION ON THE MERITS IS CLOSED. THIS NOTICE OF ALLOWANCE IS NOT A GRANT OF PATENT RIGHTS. THIS APPLICATION IS SUBJECT TO WITHDRAWAL FROM ISSUE AT THE INITIATIVE OF THE OFFICE OR UPON PETITION BY THE APPLICANT. SEE 37 CFR 1.313 AND MPEP 1308.

THE ISSUE FEE AND PUBLICATION FEE (IF REQUIRED) MUST BE PAID WITHIN THREE MONTHS FROM THE MAILING DATE OF THIS NOTICE OR THIS APPLICATION SHALL BE REGARDED AS ABANDONED. THIS STATUTORY PERIOD CANNOT BE EXTENDED. SEE 35 U.S.C. 151. THE ISSUE FEE DUE INDICATED ABOVE DOES NOT REFLECT A CREDIT FOR ANY PREVIOUSLY PAID ISSUE FEE IN THIS APPLICATION. IF AN ISSUE FEE HAS PREVIOUSLY BEEN PAID IN THIS APPLICATION (AS SHOWN ABOVE), THE RETURN OF PART B OF THIS FORM WILL BE CONSIDERED A REQUEST TO REAPPLY THE PREVIOUSLY PAID ISSUE FEE TOWARD THE ISSUE FEE NOW DUE.

HOW TO REPLY TO THIS NOTICE:

I. Review the ENTITY STATUS shown above. If the ENTITY STATUS is shown as SMALL or MICRO, verify whether entitlement to that entity status still applies.

If the ENTITY STATUS is the same as shown above, pay the TOTAL FEE(S) DUE shown above.

If the ENTITY STATUS is changed from that shown above, on PART B - FEE(S) TRANSMITTAL, complete section number 5 titled "Change in Entity Status (from status indicated above)".

For purposes of this notice, small entity fees are 40% the amount of undiscounted fees, and micro entity fees are 20% the amount of undiscounted fees.

II. PART B - FEE(S) TRANSMITTAL, or its equivalent, must be completed and returned to the United States Patent and Trademark Office (USPTO) with your ISSUE FEE and PUBLICATION FEE (if required). If you are charging the fee(s) to your deposit account, section "4b" of Part B - Fee(s) Transmittal should be completed. If an equivalent of Part B is filed, a request to reapply a previously paid issue fee must be clearly made, and delays in processing may occur due to the difficulty in recognizing the paper as an equivalent of Part B.

III. All communications regarding this application must give the application number. Please direct all communications prior to issuance to Mail Stop ISSUE FEE unless advised to the contrary.

IMPORTANT REMINDER: Maintenance fees are due in utility patents issuing on applications filed on or after Dec. 12, 1980. It is patentee's responsibility to ensure timely payment of maintenance fees when due. More information is available at www.uspto.gov/PatentMaintenanceFees.

PTOL-85 (Rev. 11/23)

PART B - FEE(S) TRANSMITTAL

Complete and send this form, together with applicable fee(s), by mail or fax, or via the USPTO patent electronic filing system.

By mail, send to: Mail Stop ISSUE FEE
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450

By fax, send to: (571)-273-2885

INSTRUCTIONS: This form should be used for transmitting the ISSUE FEE and PUBLICATION FEE (if required). Blocks 1 through 5 should be completed where appropriate. All further correspondence will be mailed to the current correspondence address as indicated unless corrected below or directed otherwise in Block 1, by (a) specifying a new correspondence address; and/or (b) indicating a separate "FEE ADDRESS" for maintenance fee notifications. **Because electronic patent issuance may occur shortly after issue fee payment, any desired continuing application should preferably be filed prior to payment of this issue fee in order not to jeopardize copendency.**

CURRENT CORRESPONDENCE ADDRESS (Note: Use Block 1 for any change of address)

147803 7590 07/01/2024
Schwabe W&W, PC / Regeneron Pharmaceuticals, Inc.
PacWest Center
1211 SW Fifth Avenue, Suite 1900
Portland, OR 97204

Note: A certificate of mailing can only be used for domestic mailings of the Fee(s) Transmittal. This certificate cannot be used for any other accompanying papers. Each additional paper, such as an assignment or formal drawing, must have its own certificate of mailing or transmission.

Certificate of Mailing or Transmission

I hereby certify that this Fee(s) Transmittal is being deposited with the United States Postal Service with sufficient postage for first class mail in an envelope addressed to the Mail Stop ISSUE FEE address above, or being transmitted to the USPTO via the USPTO patent electronic filing system or by facsimile to (571) 273-2885, on the date below.

(Typed or printed name)
(Signature)
(Date)

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
17/384,070	07/23/2021	Kenneth S. Graham		1061

TITLE OF INVENTION: Methods for Treating Angiogenic Eye Disorders with High Doses of VEGF Receptor Fusion Proteins

APPLN. TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	UNDISCOUNTED	$1200	$0.00	$1200.00	$0	10/01/2024

EXAMINER	ART UNIT	CLASS-SUBCLASS
LOCKARD, JON MCCLELLAND	1647	424-134100

1. Change of correspondence address or indication of "Fee Address" (37 CFR 1.363).

❑ Change of correspondence address (or Change of Correspondence Address form PTO/AIA/122 or PTO/SB/122) attached.

❑ "Fee Address" indication (or "Fee Address" Indication form PTO/AIA/47 or PTO/SB/47; Rev 03-02 or more recent) attached. **Use of a Customer Number is required.**

2. For printing on the patent front page, list
(1) The names of up to 3 registered patent attorneys or agents OR, alternatively,
(2) The name of a single firm (having as a member a registered attorney or agent) and the names of up to 2 registered patent attorneys or agents. If no name is listed, no name will be printed.

1 _____
2 _____
3 _____

3. ASSIGNEE NAME AND RESIDENCE DATA TO BE PRINTED ON THE PATENT (print or type)

PLEASE NOTE: Unless an assignee is identified below, no assignee data will appear on the patent. If an assignee is identified below, the document must have been previously recorded, or filed for recordation, as set forth in 37 CFR 3.11 and 37 CFR 3.81(a). Completion of this form is NOT a substitute for filing an assignment.

(A) NAME OF ASSIGNEE (B) RESIDENCE: (CITY and STATE OR COUNTRY)

Please check the appropriate assignee category or categories (will not be printed on the patent) : ❑ Individual ❑ Corporation or other private group entity ❑ Government

4a. Fees submitted: ❑ Issue Fee ❑ Publication Fee (if required)

4b. Method of Payment: *(Please first reapply any previously paid fee shown above)*

❑ Electronic Payment via the USPTO patent electronic filing system ❑ Enclosed check ❑ Non-electronic payment by credit card (Attach form PTO-2038)

❑ The Director is hereby authorized to charge the required fee(s), any deficiency, or credit any overpayment to Deposit Account No. _____

5. **Change in Entity Status** (from status indicated above)

❑ Applicant certifying micro entity status. See 37 CFR 1.29

NOTE: Absent a valid certification of Micro Entity Status (see forms PTO/SB/15A and 15B), issue fee payment in the micro entity amount will not be accepted at the risk of application abandonment.

❑ Applicant asserting small entity status. See 37 CFR 1.27

NOTE: If the application was previously under micro entity status, checking this box will be taken to be a notification of loss of entitlement to micro entity status.

❑ Applicant changing to regular undiscounted fee status.

NOTE: Checking this box will be taken to be a notification of loss of entitlement to small or micro entity status, as applicable.

NOTE: This form must be signed in accordance with 37 CFR 1.31 and 1.33. See 37 CFR 1.4 for signature requirements and certifications.

Authorized Signature _____ Date _____

Typed or printed name _____ Registration No. _____

Regeneron Ex. 2001
Alvotech v. Regeneron
PGR2025-00085
Page 465 of 531

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
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www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
17/384,070	07/23/2021	Kenneth S. Graham		1061

147803 7590 07/01/2024

Schwabe W&W, PC / Regeneron Pharmaceuticals, Inc.
PacWest Center
1211 SW Fifth Avenue, Suite 1900
Portland, OR 97204

EXAMINER	
LOCKARD, JON MCCLELLAND	
ART UNIT	**PAPER NUMBER**
1647	

DATE MAILED: 07/01/2024

Determination of Patent Term Adjustment under 35 U.S.C. 154 (b)
(Applications filed on or after May 29, 2000)

The Office has discontinued providing a Patent Term Adjustment (PTA) calculation with the Notice of Allowance.

Section 1(h)(2) of the AIA Technical Corrections Act amended 35 U.S.C. 154(b)(3)(B)(i) to eliminate the requirement that the Office provide a patent term adjustment determination with the notice of allowance. See Revisions to Patent Term Adjustment, 78 Fed. Reg. 19416, 19417 (Apr. 1, 2013). Therefore, the Office is no longer providing an initial patent term adjustment determination with the notice of allowance. The Office will continue to provide a patent term adjustment determination with the Issue Notification Letter that is mailed to applicant approximately three weeks prior to the issue date of the patent, and will include the patent term adjustment on the patent. Any request for reconsideration of the patent term adjustment determination (or reinstatement of patent term adjustment) should follow the process outlined in 37 CFR 1.705.

Any questions regarding the Patent Term Extension or Adjustment determination should be directed to the Office of Patent Legal Administration at (571)-272-7702. Questions relating to issue and publication fee payments should be directed to the Customer Service Center of the Office of Patent Publication at 1-(888)-786-0101 or (571)-272-4200.

PTOL-85 (Rev. 11/23)

Regeneron Ex. 2001
Alvotech v. Regeneron
PGR2025-00085
Page 466 of 531

OMB Clearance and PRA Burden Statement for PTOL-85 Part B

The Paperwork Reduction Act (PRA) of 1995 requires Federal agencies to obtain Office of Management and Budget approval before requesting most types of information from the public. When OMB approves an agency request to collect information from the public, OMB (i) provides a valid OMB Control Number and expiration date for the agency to display on the instrument that will be used to collect the information and (ii) requires the agency to inform the public about the OMB Control Number's legal significance in accordance with 5 CFR 1320.5(b).

The information collected by PTOL-85 Part B is required by 37 CFR 1.311. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 30 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, Virginia 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, Virginia 22313-1450. Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

Privacy Act Statement

The Privacy Act of 1974 (P.L. 93-579) requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. The United States Patent and Trademark Office (USPTO) collects the information in this record under authority of 35 U.S.C. 2. The USPTO's system of records is used to manage all applicant and owner information including name, citizenship, residence, post office address, and other information with respect to inventors and their legal representatives pertaining to the applicant's/owner's activities in connection with the invention for which a patent is sought or has been granted. The applicable Privacy Act System of Records Notice for the information collected in this form is COMMERCE/PAT-TM-7 Patent Application Files, available in the Federal Register at 78 FR 19243 (March 29, 2013).
https://www.govinfo.gov/content/pkg/FR-2013-03-29/pdf/2013-07341.pdf

Routine uses of the information in this record may include disclosure to:

1) law enforcement, in the event that the system of records indicates a violation or potential violation of law;
2) a federal, state, local, or international agency, in response to its request;
3) a contractor of the USPTO having need for the information in order to perform a contract;
4) the Department of Justice for determination of whether the Freedom of Information Act (FOIA) requires disclosure of the record;
5) a Member of Congress submitting a request involving an individual to whom the record pertains, when the individual has requested the Member's assistance with respect to the subject matter of the record;
6) a court, magistrate, or administrative tribunal, in the course of presenting evidence, including disclosures to opposing counsel in the course of settlement negotiations;
7) the Administrator, General Services Administration (GSA), or their designee, during an inspection of records conducted by GSA under authority of 44 U.S.C. 2904 and 2906, in accordance with the GSA regulations and any other relevant (i.e., GSA or Commerce) directive, where such disclosure shall not be used to make determinations about individuals;
8) another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c));
9) the Office of Personnel Management (OPM) for personnel research purposes; and
10) the Office of Management and Budget (OMB) for legislative coordination and clearance.

If you do not furnish the information requested on this form, the USPTO may not be able to process and/or examine your submission, which may result in termination of proceedings, abandonment of the application, and/or expiration of the patent.

Notice of Allowability	Application No. 17/384,070	Applicant(s) Graham et al.	
	Examiner JON M LOCKARD	Art Unit 1647	AIA (FITF) Status Yes

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address--

All claims being allowable, PROSECUTION ON THE MERITS IS (OR REMAINS) CLOSED in this application. If not included herewith (or previously mailed), a Notice of Allowance (PTOL-85) or other appropriate communication will be mailed in due course. **THIS NOTICE OF ALLOWABILITY IS NOT A GRANT OF PATENT RIGHTS.** This application is subject to withdrawal from issue at the initiative of the Office or upon petition by the applicant. See 37 CFR 1.313 and MPEP 1308.

1. ☑ This communication is responsive to the Request for Continued Examination filed 07 June 2024.
   ☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on _____.

2. ☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.

3. ☑ The allowed claim(s) is/are See Continuation Sheet . As a result of the allowed claim(s), you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information, please see **http://www.uspto.gov/patents/init_events/pph/index.jsp** or send an inquiry to **PPHfeedback@uspto.gov.**

4. ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

   Certified copies:

   a) ☐ All b) ☐ Some* c) ☐ None of the:

   1. ☐ Certified copies of the priority documents have been received.
   2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
   3. ☐ Copies of the certified copies of the priority documents have been received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

   * Certified copies not received: _____ .

Applicant has THREE MONTHS FROM THE "MAILING DATE" of this communication to file a reply complying with the requirements noted below. Failure to timely comply will result in ABANDONMENT of this application.
THIS THREE-MONTH PERIOD IS NOT EXTENDABLE.

5. ☐ CORRECTED DRAWINGS (as "replacement sheets") must be submitted.
   ☐ including changes required by the attached Examiner's Amendment / Comment or in the Office action of Paper No./Mail Date _____ .

   Identifying indicia such as the application number (see 37 CFR 1.84(c)) should be written on the drawings in the front (not the back) of each sheet. Replacement sheet(s) should be labeled as such in the header according to 37 CFR 1.121(d).

6. ☐ DEPOSIT OF and/or INFORMATION about the deposit of BIOLOGICAL MATERIAL must be submitted. Note the attached Examiner's comment regarding REQUIREMENT FOR THE DEPOSIT OF BIOLOGICAL MATERIAL.

Attachment(s)

1. ☐ Notice of References Cited (PTO-892)
2. ☑ Information Disclosure Statements (PTO/SB/08), Paper No./Mail Date _____.
3. ☐ Examiner's Comment Regarding Requirement for Deposit of Biological Material _____.
4. ☐ Interview Summary (PTO-413), Paper No./Mail Date. _____.
5. ☑ Examiner's Amendment/Comment
6. ☑ Examiner's Statement of Reasons for Allowance
7. ☐ Other _____.

/J.L/ Examiner, Art Unit 1647	/CHRISTINE J SAOUD/ Primary Examiner, Art Unit 1645

Regeneron Ex. 2001
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Continuation of 3. The allowed claim(s) is/are: 30-32 and 53-87 (renumbered as claims 1-11,13-14,16,18,20,22,24,12,26,15,17,19,21,23,25 and 27-38, respectively)

Notice of Pre-AIA or AIA Status

1. The present application, filed on or after March 16, 2013, is being examined under the first inventor to file provisions of the AIA.

Continued Examination Under 37 CFR 1.114

2. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after allowance or after an Office action under *Ex Parte Quayle*, 25 USPQ 74, 453 O.G. 213 (Comm'r Pat. 1935). Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, prosecution in this application has been reopened pursuant to 37 CFR 1.114. Applicant's submission filed on 07 June 2024 has been entered.

Information Disclosure Statement

3. The information disclosure statement (IDS) submitted on 07 June 2024 has been considered by the examiner.

REASONS FOR ALLOWANCE

4. The following is an examiner's statement of reasons for allowance: The information disclosure statement (IDS) submitted on 07 June 2024 has been considered by the Examiner. After careful consideration, the Examiner has determined that none of the information contained therein raises new issues of patentability.

5. Any comments considered necessary by applicant must be submitted no later than the payment of the issue fee and, to avoid processing delays, should preferably accompany the issue

fee. Such submissions should be clearly labeled "Comments on Statement of Reasons for Allowance."

Summary

6. Claims 30-32 and 53-87 are allowed.

Advisory Information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to **JON M LOCKARD** whose telephone number is **(571) 272-2717**. The examiner can normally be reached M-F 9-6 EST.

Examiner interviews are available via telephone, in-person, and video conferencing using a USPTO supplied web-based collaboration tool. To schedule an interview, applicant is encouraged to use the USPTO Automated Interview Request (AIR) at http://www.uspto.gov/interviewpractice. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, **Joanne Hama** can be reached on **(571) 272-2911**. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of published or unpublished applications may be obtained from Patent Center. Unpublished application information in Patent Center is available to registered users. To file and manage patent submissions in Patent Center, visit: https://patentcenter.uspto.gov. Visit https://www.uspto.gov/patents/apply/patent-center for more information about Patent Center and https://www.uspto.gov/patents/docx for information about filing in DOCX format. For additional questions, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/J.L/
Examiner, Art Unit 1647
June 11, 2024

/Christine J Saoud/
Primary Examiner, Art Unit 1645

Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
	17/384,070	Graham et al.
	Examiner	Art Unit
	JON M LOCKARD	1647

CPC - Searched*		
Symbol	Date	Examiner

CPC Combination Sets - Searched*		
Symbol	Date	Examiner

US Classification - Searched*			
Class	Subclass	Date	Examiner
NONE		03/16/2023	JML

* See search history printout included with this form or the SEARCH NOTES box below to determine the scope of the search.

Search Notes		
Search Notes	Date	Examiner
PE2E Search (USPAT, US-PGPUB, EPO, DERWENT): See attached search history.	03/16/2023	JML
STN (MEDLINE, SCISEARCH, EMBASE, BIOSIS): See attached search history.	03/16/2023	JML
PALM: Inventor search.	03/16/2023	JML
PE2E Search (USPAT, US-PGPUB, EPO, DERWENT): See attached search history.	11/01/2023	JML

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Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
	17/384,070	Graham et al.
	Examiner	Art Unit
	JON M LOCKARD	1647

Interference Search			
US Class/CPC Symbol	**US Subclass/CPC Group**	**Date**	**Examiner**
	PE2E Search (USPAT): See attached search history.	08/24/2023	JML
	DAV: Inventor search.	08/24/2023	JML
	PE2E Search (USPAT): See attached search history.	11/01/2023	JML
	DAV: Inventor search.	11/01/2023	JML
	PE2E Search (USPAT): See attached search history.	11/29/2023	JML
	DAV: Inventor search.	11/29/2023	JML
	PE2E Search (USPAT): See attached search history.	01/11/2024	JML
	DAV: Inventor search.	01/11/2024	JML
	PE2E Search (USPAT): See attached search history.	05/10/2024	JML
	DAV: Inventor search.	05/10/2024	JML
	PE2E Search (USPAT): See attached search history.	06/11/2024	JML
	DAV: Inventor search.	06/11/2024	JML

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Issue Classification	Application/Control No.	Applicant(s)/Patent Under Reexamination
	17/384,070	Graham et al.
	Examiner	Art Unit
	JON M LOCKARD	1647

CPC								
Symbol							Type	Version
A61K	/	38	/	179			F	2013-01-01
A61K	/	9	/	0048			I	2013-01-01
A61K	/	47	/	12			I	2013-01-01
A61P	/	27	/	02			I	2018-01-01
A61K	/	47	/	22			I	2013-01-01
A61K	/	47	/	26			I	2013-01-01
A61K	/	47	/	183			I	2013-01-01

CPC Combination Sets								
Symbol					Type	Set	Ranking	Version
	/		/					

/JON M LOCKARD/ Examiner, Art Unit 1647 (Assistant Examiner)	11 June 2024 (Date)	Total Claims Allowed: 38	
/CHRISTINE J SAOUD/ Primary Examiner, Art Unit 1645 (Primary Examiner)	14 June 2024 (Date)	O.G. Print Claim(s) 1	O.G. Print Figure NONE

U.S. Patent and Trademark Office — Part of Paper No.: 20240611

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Issue Classification	Application/Control No.	Applicant(s)/Patent Under Reexamination
	17/384,070	Graham et al.
	Examiner	Art Unit
	JON M LOCKARD	1647

INTERNATIONAL CLASSIFICATION					
CLAIMED					
A61K	/	38	/	17	
A61K	/	38	/	18	
C07K	/	14	/	71	

NON-CLAIMED				
	/		/	

US ORIGINAL CLASSIFICATION	
CLASS	SUBCLASS

CROSS REFERENCES(S)						
CLASS	SUBCLASS (ONE SUBCLASS PER BLOCK)					

/JON M LOCKARD/ Examiner, Art Unit 1647	11 June 2024	Total Claims Allowed:	
(Assistant Examiner)	(Date)	38	
/CHRISTINE J SAOUD/ Primary Examiner, Art Unit 1645	14 June 2024	O.G. Print Claim(s)	O.G. Print Figure
(Primary Examiner)	(Date)	1	NONE

U.S. Patent and Trademark Office — Part of Paper No.: 20240611

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Issue Classification	Application/Control No.	Applicant(s)/Patent Under Reexamination
	17/384,070	Graham et al.
	Examiner	Art Unit
	JON M LOCKARD	1647

☐ Claims renumbered in the same order as presented by applicant ☐ CPA ☑ T.D. ☐ R.1.47

CLAIMS

Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original
1	30	10	59	12	68	28	77	37	86						
2	31	11	60	26	69	29	78	38	87						
3	32	13	61	15	70	30	79								
4	53	14	62	17	71	31	80								
5	54	16	63	19	72	32	81								
6	55	18	64	21	73	33	82								
7	56	20	65	23	74	34	83								
8	57	22	66	25	75	35	84								
9	58	24	67	27	76	36	85								

/JON M LOCKARD/ Examiner, Art Unit 1647 (Assistant Examiner)	11 June 2024 (Date)	**Total Claims Allowed:** 38	
/CHRISTINE J SAOUD/ Primary Examiner, Art Unit 1645 (Primary Examiner)	14 June 2024 (Date)	O.G. Print Claim(s) 1	O.G. Print Figure NONE

U.S. Patent and Trademark Office — Part of Paper No.: 20240611

Regeneron Ex. 2001
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PGR2025-00085
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PE2E SEARCH - Search History (Prior Art)

/j.L./

There are no Prior Art searches to show.

PE2E SEARCH - Search History (Interference)

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	British Equivalents	Time Stamp
N41	2795	vegf ADJ trap	(USPAT)	OR	ON	ON	2024/06/11 08:22 PM
N42	2941	aflibercept	(USPAT)	OR	ON	ON	2024/06/11 08:22 PM
N43	393	eylea	(USPAT)	OR	ON	ON	2024/06/11 08:22 PM
N44	121	vegf ADJ trap-eye	(USPAT)	OR	ON	ON	2024/06/11 08:22 PM
N45	449	(N41 N42 N43 N44) SAME formulation	(USPAT)	OR	ON	ON	2024/06/11 08:22 PM
N46	12	N45 SAME "high concentration"	(USPAT)	OR	ON	ON	2024/06/11 08:23 PM
N47	1	N45 AND (8mg OR "8 mg").clm.	(USPAT)	OR	ON	ON	2024/06/11 08:23 PM
N48	17	(graham-k$-s$ washawa-s$).in.	(USPAT)	OR	ON	ON	2024/06/11 08:24 PM
N49	1	N46 AND N48	(USPAT)	OR	ON	ON	2024/06/11 08:24 PM

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Receipt date: 06/07/2024

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (not for submission under 37 CFR 1.99)		
	Application Number	17/384,070
	Filing Date	Jul-23-2021
	First Named Inventor	Kenneth S. Graham
	Art Unit	1647
	Confirmation Number	1061
	Examiner Name	Lockard, Jon McClelland
	Attorney Docket Number	125984-266215

U.S. PATENTS						
Examiner Initial*	Cite No	Patent Number	Kind Code[1]	Issue Date	Name of Patentee or Applicant of cited Document	Pages, Columns, Lines where Relevant Passages or Relevant Figures Appear

U.S. PATENT APPLICATION PUBLICATIONS						
Examiner Initial*	Cite No	Publication Number	Kind Code[1]	Publication Date	Name of Patentee or Applicant of cited Document	Pages, Columns, Lines where Relevant Passages or Relevant Figures Appear

FOREIGN PATENT DOCUMENTS								
Examiner Initial*	Cite No	Foreign Document Number[3]	Country Code[2]	Kind Code[4]	Publication Date	Name of Patentee or Applicant of cited Document	Pages, Columns, Lines where Relevant Passages or Relevant Figures Appear	T[5]

NON-PATENT LITERATURE DOCUMENTS			
Examiner Initial*	Cite No	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, pages(s), volume-issue number(s), publisher, city and/or country where published	T[5]
	585	clinicaltrialsgov posting-NCT02305238-11282014 to 12202018, December 20, 2018.	
	586	clinicaltrialsgov posting-NCT02581891-10202015 to 05122020, May 12, 2020.	
	601	clinicaltrialsgov posting NCT00036946, June 1, 2016.	
	602	clinicaltrialsgov posting NCT00527423, June 10, 2013.	
	611	clinicaltrialsgov posting NCT01331681, March 20, 2016.	
	636	GAUDREAULT et al., "PHARMACOKINETICS AND RETINAL DISTRIBUTION OF RANIBIZUMAB, A HUMANIZED ANTIBODY FRAGMENT DIRECTED AGAINST VEGF-A, FOLLOWING INTRAVITREAL ADMINISTRATION IN RABBITS," RETINA, THE JOURNAL OF RETINAL AND VITREOUS DISEASES, Volume 27 (No 9): 1260-1266, (2007).	
	637	GAUDREAULT et al., "Preclinical Pharmacokinetics of Ranibizumab (rhuFabV2) after a Single Intravitreal Administration," Publication, Volume 46 (No 2): 726-733, (2005). [downloaded from lovs.arvojournals.org on 10/03/2023].	

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /J.L/

Receipt date: 06/07/2024

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (not for submission under 37 CFR 1.99)		
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	Attorney Docket Number	125984-266215

NON-PATENT LITERATURE DOCUMENTS			
Examiner Initial*	Cite No	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, pages(s), volume-issue number(s), publisher, city and/or country where published	T [5]
	638	Assessment report; International non-proprietary name: faricimab; Procedure No. EMEA/H/C/005642/0000. Committee for Medicinal Products for Human Use (CHMP) 319 pages (21 July 2022). [EMA/687844/2022]	
	634	U.S. Application No. 18/367,444, Non-Final Office Action mailed 05-21-2024.	

EXAMINER SIGNATURE			
Examiner Signature	/JON M LOCKARD/	Date Considered	06/11/2024

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through a citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

[1] See Kind Codes of USPTO Patent Documents at www.USPTO.GOV or MPEP 901.04. [2] Enter office that issued the document, by the two-letter code (WIPO Standard ST.3). [3] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [4] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [5] Applicant is to place a check mark here if English language translation is attached.

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /J.L/

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (not for submission under 37 CFR 1.99)		
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	Examiner Name	Lockard, Jon McClelland
	Attorney Docket Number	125984-266215

U.S. PATENTS						
Examiner Initial*	Cite No	Patent Number	Kind Code[1]	Issue Date	Name of Patentee or Applicant of cited Document	Pages, Columns, Lines where Relevant Passages or Relevant Figures Appear
	646	11,958,894		04-16-2024	Wang et al.	
	647	12,005,097		06-11-2024	Kerwin et al.	

U.S. PATENT APPLICATION PUBLICATIONS						
Examiner Initial*	Cite No	Publication Number	Kind Code[1]	Publication Date	Name of Patentee or Applicant of cited Document	Pages, Columns, Lines where Relevant Passages or Relevant Figures Appear
	644	2024-0029897		01-25-2024	Perlee et al.	
	645	2024-0189402		06-13-2024	Borodic	

FOREIGN PATENT DOCUMENTS								
Examiner Initial*	Cite No	Foreign Document Number[3]	Country Code[2]	Kind Code[4]	Publication Date	Name of Patentee or Applicant of cited Document	Pages, Columns, Lines where Relevant Passages or Relevant Figures Appear	T[5]

NON-PATENT LITERATURE DOCUMENTS			
Examiner Initial*	Cite No	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, pages(s), volume-issue number(s), publisher, city and/or country where published	T[5]
	641	Anonymous: "Product information EYLA aflibercept (rch)", 15 April 2015 (2015-04-15), XP093174268, [Retrieved from the Internet: URL:https://www.tga.gov.au/sites/default/f iles/auspar-aflibercept-150721-pi.pdf]	
	642	Australian Public Assessment Report for Aflibercept, Australian Government, Department of Health & Aging, Therapeutic Goods Administration, Proprietary Product Name: Eylea sponsored by Bayer Australia Ltd (publication date 07-21-2015).	
	643	Clinical Trials for "Phase 1 Study of VEGF Trap in Patients With Diabetic Macular Edema," sponsored by Regeneron Pharmaceuticals, NCT00320814 (publication date 06-10-2011).	

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (not for submission under 37 CFR 1.99)		
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	Filing Date	Jul-23-2021
	First Named Inventor	Kenneth S. Graham
	Art Unit	1647
	Confirmation Number	1061
	Examiner Name	Lockard, Jon McClelland
	Attorney Docket Number	125984-266215

EXAMINER SIGNATURE			
Examiner Signature		Date Considered	

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through a citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

[1] See Kind Codes of USPTO Patent Documents at www.USPTO.GOV or MPEP 901.04. [2] Enter office that issued the document, by the two-letter code (WIPO Standard ST.3). [3] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [4] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [5] Applicant is to place a check mark here if English language translation is attached.

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT (not for submission under 37 CFR 1.99)		
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	First Named Inventor	Kenneth S. Graham
	Art Unit	1647
	Confirmation Number	1061
	Examiner Name	Lockard, Jon McClelland
	Attorney Docket Number	125984-266215

CERTIFICATION STATEMENT

Please see 37 CFR 1.97 and 1.98 to make the appropriate selection(s):

☐ That each item of information contained in the information disclosure statement was first cited in any communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(1).

OR

☐ That no item of information contained in the information disclosure statement was cited in a communication from a foreign patent office in a counterpart foreign application, and, to the knowledge of the person signing the certification after making reasonable inquiry, no item of information contained in the information disclosure statement was known to any individual designated in 37 CFR 1.56(c) more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(2).

☐ See attached certification statement.

☐ Fee set forth in 37 CFR 1.17 (p) has been submitted herewith.

☒ None

SIGNATURE

A signature of the applicant or representative is required in accordance with CFR 1.33, 10.18. Please see CFR 1.4(d) for the form of the signature.

Signature	/Lance A. Termes/	Date (YYYY-MM-DD)	2024-07-15
Name/Print	Lance A. Termes	Registration Number	43184

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Alvotech v. Regeneron
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PTO/SB/30 (11-23)
Approved for use through 05/31/2024. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

Request for Continued Examination (RCE) Transmittal

Address to:
Mail Stop RCE
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Application Number	17/384,070
Filing Date	July 23, 2021
First Named Inventor	Kenneth S. Graham
Art Unit	1647
Examiner Name	Jon McClelland Lockard
Attorney Docket Number	125984-266215

This is a Request for Continued Examination (RCE) under 37 CFR 1.114 of the above-identified application.
Request for Continued Examination (RCE) practice under 37 CFR 1.114 does not apply to any utility or plant application filed prior to June 8, 1995, or to any design application. See Instruction Sheet for RCEs (not to be submitted to the USPTO) on page 2

1. Submission required under 37 CFR 1.114 Note: If the RCE is proper, any previously filed unentered amendments and amendments enclosed with the RCE will be entered in the order in which they were filed unless applicant instructs otherwise. If applicant does not wish to have any previously filed unentered amendment(s) entered, applicant must request non-entry of such amendment(s).

   a. ☐ Previously submitted. If a final Office action is outstanding, any amendments filed after the final Office action may be considered as a submission even if this box is not checked.

      i. ☐ Consider the arguments in the Appeal Brief or Reply Brief previously filed on _____

      ii. ☐ Other _____

   b. ☑ Enclosed

      i. ☐ Amendment/Reply

      ii. ☐ Affidavit(s)/ Declaration(s)

      iii. ☑ Information Disclosure Statement (IDS)

      iv. ☐ Other _____

2. Miscellaneous

   a. ☐ Suspension of action on the above-identified application is requested under 37 CFR 1.103(c) for a period of _____ months. (Period of suspension shall not exceed 3 months; Fee under 37 CFR 1.17(i) required)

   b. ☐ Other _____

3. Fees The RCE fee under 37 CFR 1.17(e) is required by 37 CFR 1.114 when the RCE is filed.

   a. ☑ The Director is hereby authorized to charge the following fees, any underpayment of fees, or credit any overpayments, to Deposit Account No. 500393 .

      i. ☑ RCE fee required under 37 CFR 1.17(e)

      ii. ☐ Extension of time fee (37 CFR 1.136 and 1.17)

      iii. ☐ Other _____

   b. ☐ Check in the amount of $ _____ enclosed

   c. ☐ Payment by credit card (Form PTO-2038 enclosed)

   d. ▩ Payment by USPTO patent electronic filing system.

WARNING: Information on this form may become public. Credit card information should not be included on this form. Provide credit card information and authorization on PTO-2038.

SIGNATURE OF APPLICANT, ATTORNEY, OR AGENT REQUIRED

Signature	/Lance A. Termes/	Date	July 15, 2024
Name (Print/Type)	Lance A. Termes	Registration No.	43,184

CERTIFICATE OF MAILING OR TRANSMISSION

I hereby certify that this correspondence is transmitted by the USPTO patent electronic filing system, or by facsimile to (571) 273-8300, to the USPTO, or deposited with the United States Postal Service with sufficient postage as first class mail in an envelope addressed to: Mail Stop RCE, Commissioner for Patents, P. O. Box 1450, Alexandria, VA 22313-1450, on the date shown below.

Signature	/Lance A. Termes/		
Name (Print/Type)	Lance A. Termes	Date	July 15, 2024

A Federal agency may not conduct or sponsor, and a person is not required to respond to, nor shall a person be subject to a penalty for failure to comply with an information collection subject to the requirements of the Paperwork Reduction Act of 1995, unless the information collection has a currently valid OMB Control Number. The OMB Control Number for this information collection is 0651-0031. Public burden for this form is estimated to average 12 minutes per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the information collection. Send comments regarding this burden estimate or any other aspect of this information collection, including suggestions for reducing this burden to the Chief Administrative Officer, United States Patent and Trademark Office, P.O. Box 1450, Alexandria, VA 22313-1450 or email InformationCollection@uspto.gov. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **If filing this completed form by mail, send to:**

Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.

If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (not for submission under 37 CFR 1.99)		
	Application Number	17/384,070
	Filing Date	Jul-23-2021
	First Named Inventor	Kenneth S. Graham
	Art Unit	1647
	Confirmation Number	1061
	Examiner Name	Lockard, Jon McClelland
	Attorney Docket Number	125984-266215

U.S. PATENTS						
Examiner Initial*	Cite No	Patent Number	Kind Code[1]	Issue Date	Name of Patentee or Applicant of cited Document	Pages, Columns, Lines where Relevant Passages or Relevant Figures Appear

U.S. PATENT APPLICATION PUBLICATIONS						
Examiner Initial*	Cite No	Publication Number	Kind Code[1]	Publication Date	Name of Patentee or Applicant of cited Document	Pages, Columns, Lines where Relevant Passages or Relevant Figures Appear

FOREIGN PATENT DOCUMENTS								
Examiner Initial*	Cite No	Foreign Document Number[3]	Country Code[2]	Kind Code[4]	Publication Date	Name of Patentee or Applicant of cited Document	Pages, Columns, Lines where Relevant Passages or Relevant Figures Appear	T[5]

NON-PATENT LITERATURE DOCUMENTS			
Examiner Initial*	Cite No	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, pages(s), volume-issue number(s), publisher, city and/or country where published	T[5]
	648	AVASTIN label (revised December 2017)	
	649	HERCEPTIN label (September 1998)	
	650	LUCENTIS label (revised October 2014)	
	651	REMICADE label (revised November 2013)	
	652	SIMULECT label (May 1998)	
	653	XOLAIR label (2003)	

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (not for submission under 37 CFR 1.99)		
	Application Number	17/384,070
	Filing Date	Jul-23-2021
	First Named Inventor	Kenneth S. Graham
	Art Unit	1647
	Confirmation Number	1061
	Examiner Name	Lockard, Jon McClelland
	Attorney Docket Number	125984-266215

EXAMINER SIGNATURE			
Examiner Signature		Date Considered	

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through a citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

[1] See Kind Codes of USPTO Patent Documents at www.USPTO.GOV or MPEP 901.04. [2] Enter office that issued the document, by the two-letter code (WIPO Standard ST.3). [3] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [4] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [5] Applicant is to place a check mark here if English language translation is attached.

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (not for submission under 37 CFR 1.99)		
	Application Number	17/384,070
	Filing Date	Jul-23-2021
	First Named Inventor	Kenneth S. Graham
	Art Unit	1647
	Confirmation Number	1061
	Examiner Name	Lockard, Jon McClelland
	Attorney Docket Number	125984-266215

CERTIFICATION STATEMENT

Please see 37 CFR 1.97 and 1.98 to make the appropriate selection(s):

☐ That each item of information contained in the information disclosure statement was first cited in any communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(1).

OR

☐ That no item of information contained in the information disclosure statement was cited in a communication from a foreign patent office in a counterpart foreign application, and, to the knowledge of the person signing the certification after making reasonable inquiry, no item of information contained in the information disclosure statement was known to any individual designated in 37 CFR 1.56(c) more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(2).

☐ See attached certification statement.

☐ Fee set forth in 37 CFR 1.17 (p) has been submitted herewith.

☒ None

SIGNATURE

A signature of the applicant or representative is required in accordance with CFR 1.33, 10.18. Please see CFR 1.4(d) for the form of the signature.

Signature	/Lance A. Termes/	Date (YYYY-MM-DD)	2024-07-23
Name/Print	Lance A. Termes	Registration Number	43184

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UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

NOTICE OF ALLOWANCE AND FEE(S) DUE

147803 7590 08/14/2024

Schwabe W&W, PC / Regeneron Pharmaceuticals, Inc.
PacWest Center
1211 SW Fifth Avenue, Suite 1900
Portland, OR 97204

EXAMINER	
LOCKARD, JON MCCLELLAND	
ART UNIT	PAPER NUMBER
1647	

DATE MAILED: 08/14/2024

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
17/384,070	07/23/2021	Kenneth S. Graham		1061

TITLE OF INVENTION: Methods for Treating Angiogenic Eye Disorders with High Doses of VEGF Receptor Fusion Proteins

APPLN. TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	UNDISCOUNTED	$1200	$0.00	$1200.00	$0	11/14/2024

THE APPLICATION IDENTIFIED ABOVE HAS BEEN EXAMINED AND IS ALLOWED FOR ISSUANCE AS A PATENT. PROSECUTION ON THE MERITS IS CLOSED. THIS NOTICE OF ALLOWANCE IS NOT A GRANT OF PATENT RIGHTS. THIS APPLICATION IS SUBJECT TO WITHDRAWAL FROM ISSUE AT THE INITIATIVE OF THE OFFICE OR UPON PETITION BY THE APPLICANT. SEE 37 CFR 1.313 AND MPEP 1308.

THE ISSUE FEE AND PUBLICATION FEE (IF REQUIRED) MUST BE PAID WITHIN THREE MONTHS FROM THE MAILING DATE OF THIS NOTICE OR THIS APPLICATION SHALL BE REGARDED AS ABANDONED. THIS STATUTORY PERIOD CANNOT BE EXTENDED. SEE 35 U.S.C. 151. THE ISSUE FEE DUE INDICATED ABOVE DOES NOT REFLECT A CREDIT FOR ANY PREVIOUSLY PAID ISSUE FEE IN THIS APPLICATION. IF AN ISSUE FEE HAS PREVIOUSLY BEEN PAID IN THIS APPLICATION (AS SHOWN ABOVE), THE RETURN OF PART B OF THIS FORM WILL BE CONSIDERED A REQUEST TO REAPPLY THE PREVIOUSLY PAID ISSUE FEE TOWARD THE ISSUE FEE NOW DUE.

HOW TO REPLY TO THIS NOTICE:

I. Review the ENTITY STATUS shown above. If the ENTITY STATUS is shown as SMALL or MICRO, verify whether entitlement to that entity status still applies.

If the ENTITY STATUS is the same as shown above, pay the TOTAL FEE(S) DUE shown above.

If the ENTITY STATUS is changed from that shown above, on PART B - FEE(S) TRANSMITTAL, complete section number 5 titled "Change in Entity Status (from status indicated above)".

For purposes of this notice, small entity fees are 40% the amount of undiscounted fees, and micro entity fees are 20% the amount of undiscounted fees.

II. PART B - FEE(S) TRANSMITTAL, or its equivalent, must be completed and returned to the United States Patent and Trademark Office (USPTO) with your ISSUE FEE and PUBLICATION FEE (if required). If you are charging the fee(s) to your deposit account, section "4b" of Part B - Fee(s) Transmittal should be completed. If an equivalent of Part B is filed, a request to reapply a previously paid issue fee must be clearly made, and delays in processing may occur due to the difficulty in recognizing the paper as an equivalent of Part B.

III. All communications regarding this application must give the application number. Please direct all communications prior to issuance to Mail Stop ISSUE FEE unless advised to the contrary.

IMPORTANT REMINDER: Maintenance fees are due in utility patents issuing on applications filed on or after Dec. 12, 1980. It is patentee's responsibility to ensure timely payment of maintenance fees when due. More information is available at www.uspto.gov/PatentMaintenanceFees.

PTOL-85 (Rev. 11/23)

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PART B - FEE(S) TRANSMITTAL

Complete and send this form, together with applicable fee(s), by mail or fax, or via the USPTO patent electronic filing system.

By mail, send to: Mail Stop ISSUE FEE
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450

By fax, send to: (571)-273-2885

INSTRUCTIONS: This form should be used for transmitting the ISSUE FEE and PUBLICATION FEE (if required). Blocks 1 through 5 should be completed where appropriate. All further correspondence will be mailed to the current correspondence address as indicated unless corrected below or directed otherwise in Block 1, by (a) specifying a new correspondence address; and/or (b) indicating a separate "FEE ADDRESS" for maintenance fee notifications. **Because electronic patent issuance may occur shortly after issue fee payment, any desired continuing application should preferably be filed prior to payment of this issue fee in order not to jeopardize copendency.**

CURRENT CORRESPONDENCE ADDRESS (Note: Use Block 1 for any change of address)

147803 7590 08/14/2024
Schwabe W&W, PC / Regeneron Pharmaceuticals, Inc.
PacWest Center
1211 SW Fifth Avenue, Suite 1900
Portland, OR 97204

Note: A certificate of mailing can only be used for domestic mailings of the Fee(s) Transmittal. This certificate cannot be used for any other accompanying papers. Each additional paper, such as an assignment or formal drawing, must have its own certificate of mailing or transmission.

Certificate of Mailing or Transmission

I hereby certify that this Fee(s) Transmittal is being deposited with the United States Postal Service with sufficient postage for first class mail in an envelope addressed to the Mail Stop ISSUE FEE address above, or being transmitted to the USPTO via the USPTO patent electronic filing system or by facsimile to (571) 273-2885, on the date below.

(Typed or printed name)
(Signature)
(Date)

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
17/384,070	07/23/2021	Kenneth S. Graham		1061

TITLE OF INVENTION: Methods for Treating Angiogenic Eye Disorders with High Doses of VEGF Receptor Fusion Proteins

APPLN. TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	UNDISCOUNTED	$1200	$0.00	$1200.00	$0	11/14/2024

EXAMINER	ART UNIT	CLASS-SUBCLASS
LOCKARD, JON MCCLELLAND	1647	424-134100

1. Change of correspondence address or indication of "Fee Address" (37 CFR 1.363).

❑ Change of correspondence address (or Change of Correspondence Address form PTO/AIA/122 or PTO/SB/122) attached.

❑ "Fee Address" indication (or "Fee Address" Indication form PTO/AIA/47 or PTO/SB/47; Rev 03-02 or more recent) attached. **Use of a Customer Number is required.**

2. For printing on the patent front page, list
(1) The names of up to 3 registered patent attorneys or agents OR, alternatively,
(2) The name of a single firm (having as a member a registered attorney or agent) and the names of up to 2 registered patent attorneys or agents. If no name is listed, no name will be printed.

1 _____
2 _____
3 _____

3. ASSIGNEE NAME AND RESIDENCE DATA TO BE PRINTED ON THE PATENT (print or type)

PLEASE NOTE: Unless an assignee is identified below, no assignee data will appear on the patent. If an assignee is identified below, the document must have been previously recorded, or filed for recordation, as set forth in 37 CFR 3.11 and 37 CFR 3.81(a). Completion of this form is NOT a substitute for filing an assignment.

(A) NAME OF ASSIGNEE (B) RESIDENCE: (CITY and STATE OR COUNTRY)

Please check the appropriate assignee category or categories (will not be printed on the patent) : ❑ Individual ❑ Corporation or other private group entity ❑ Government

4a. Fees submitted: ❑ Issue Fee ❑ Publication Fee (if required)

4b. Method of Payment: *(Please first reapply any previously paid fee shown above)*

❑ Electronic Payment via the USPTO patent electronic filing system ❑ Enclosed check ❑ Non-electronic payment by credit card (Attach form PTO-2038)

❑ The Director is hereby authorized to charge the required fee(s), any deficiency, or credit any overpayment to Deposit Account No. _____

5. **Change in Entity Status** (from status indicated above)

❑ Applicant certifying micro entity status. See 37 CFR 1.29

NOTE: Absent a valid certification of Micro Entity Status (see forms PTO/SB/15A and 15B), issue fee payment in the micro entity amount will not be accepted at the risk of application abandonment.

❑ Applicant asserting small entity status. See 37 CFR 1.27

NOTE: If the application was previously under micro entity status, checking this box will be taken to be a notification of loss of entitlement to micro entity status.

❑ Applicant changing to regular undiscounted fee status.

NOTE: Checking this box will be taken to be a notification of loss of entitlement to small or micro entity status, as applicable.

NOTE: This form must be signed in accordance with 37 CFR 1.31 and 1.33. See 37 CFR 1.4 for signature requirements and certifications.

Authorized Signature _____ Date _____

Typed or printed name _____ Registration No. _____

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UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
17/384,070	07/23/2021	Kenneth S. Graham		1061

147803 7590 08/14/2024

Schwabe W&W, PC / Regeneron Pharmaceuticals, Inc.
PacWest Center
1211 SW Fifth Avenue, Suite 1900
Portland, OR 97204

EXAMINER	
LOCKARD, JON MCCLELLAND	
ART UNIT	**PAPER NUMBER**
1647	

DATE MAILED: 08/14/2024

Determination of Patent Term Adjustment under 35 U.S.C. 154 (b)
(Applications filed on or after May 29, 2000)

The Office has discontinued providing a Patent Term Adjustment (PTA) calculation with the Notice of Allowance.

Section 1(h)(2) of the AIA Technical Corrections Act amended 35 U.S.C. 154(b)(3)(B)(i) to eliminate the requirement that the Office provide a patent term adjustment determination with the notice of allowance. See Revisions to Patent Term Adjustment, 78 Fed. Reg. 19416, 19417 (Apr. 1, 2013). Therefore, the Office is no longer providing an initial patent term adjustment determination with the notice of allowance. The Office will continue to provide a patent term adjustment determination with the Issue Notification Letter that is mailed to applicant approximately three weeks prior to the issue date of the patent, and will include the patent term adjustment on the patent. Any request for reconsideration of the patent term adjustment determination (or reinstatement of patent term adjustment) should follow the process outlined in 37 CFR 1.705.

Any questions regarding the Patent Term Extension or Adjustment determination should be directed to the Office of Patent Legal Administration at (571)-272-7702. Questions relating to issue and publication fee payments should be directed to the Customer Service Center of the Office of Patent Publication at 1-(888)-786-0101 or (571)-272-4200.

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OMB Clearance and PRA Burden Statement for PTOL-85 Part B

The Paperwork Reduction Act (PRA) of 1995 requires Federal agencies to obtain Office of Management and Budget approval before requesting most types of information from the public. When OMB approves an agency request to collect information from the public, OMB (i) provides a valid OMB Control Number and expiration date for the agency to display on the instrument that will be used to collect the information and (ii) requires the agency to inform the public about the OMB Control Number's legal significance in accordance with 5 CFR 1320.5(b).

The information collected by PTOL-85 Part B is required by 37 CFR 1.311. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 30 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, Virginia 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, Virginia 22313-1450. Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

Privacy Act Statement

The Privacy Act of 1974 (P.L. 93-579) requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. The United States Patent and Trademark Office (USPTO) collects the information in this record under authority of 35 U.S.C. 2. The USPTO's system of records is used to manage all applicant and owner information including name, citizenship, residence, post office address, and other information with respect to inventors and their legal representatives pertaining to the applicant's/owner's activities in connection with the invention for which a patent is sought or has been granted. The applicable Privacy Act System of Records Notice for the information collected in this form is COMMERCE/PAT-TM-7 Patent Application Files, available in the Federal Register at 78 FR 19243 (March 29, 2013).
https://www.govinfo.gov/content/pkg/FR-2013-03-29/pdf/2013-07341.pdf

Routine uses of the information in this record may include disclosure to:

1) law enforcement, in the event that the system of records indicates a violation or potential violation of law;
2) a federal, state, local, or international agency, in response to its request;
3) a contractor of the USPTO having need for the information in order to perform a contract;
4) the Department of Justice for determination of whether the Freedom of Information Act (FOIA) requires disclosure of the record;
5) a Member of Congress submitting a request involving an individual to whom the record pertains, when the individual has requested the Member's assistance with respect to the subject matter of the record;
6) a court, magistrate, or administrative tribunal, in the course of presenting evidence, including disclosures to opposing counsel in the course of settlement negotiations;
7) the Administrator, General Services Administration (GSA), or their designee, during an inspection of records conducted by GSA under authority of 44 U.S.C. 2904 and 2906, in accordance with the GSA regulations and any other relevant (i.e., GSA or Commerce) directive, where such disclosure shall not be used to make determinations about individuals;
8) another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c));
9) the Office of Personnel Management (OPM) for personnel research purposes; and
10) the Office of Management and Budget (OMB) for legislative coordination and clearance.

If you do not furnish the information requested on this form, the USPTO may not be able to process and/or examine your submission, which may result in termination of proceedings, abandonment of the application, and/or expiration of the patent.

Notice of Allowability	Application No. 17/384,070	Applicant(s) Graham et al.	
	Examiner JON M LOCKARD	Art Unit 1647	AIA (FITF) Status Yes

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address--

All claims being allowable, PROSECUTION ON THE MERITS IS (OR REMAINS) CLOSED in this application. If not included herewith (or previously mailed), a Notice of Allowance (PTOL-85) or other appropriate communication will be mailed in due course. **THIS NOTICE OF ALLOWABILITY IS NOT A GRANT OF PATENT RIGHTS.** This application is subject to withdrawal from issue at the initiative of the Office or upon petition by the applicant. See 37 CFR 1.313 and MPEP 1308.

1. ☑ This communication is responsive to the Request for Continued Examination filed 15 July 2024.
   ☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on _____.

2. ☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.

3. ☑ The allowed claim(s) is/are See Continuation Sheet . As a result of the allowed claim(s), you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information, please see **http://www.uspto.gov/patents/init_events/pph/index.jsp** or send an inquiry to **PPHfeedback@uspto.gov.**

4. ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

   Certified copies:

   a) ☐ All b) ☐ Some* c) ☐ None of the:

   1. ☐ Certified copies of the priority documents have been received.
   2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
   3. ☐ Copies of the certified copies of the priority documents have been received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

   * Certified copies not received: _____ .

Applicant has THREE MONTHS FROM THE "MAILING DATE" of this communication to file a reply complying with the requirements noted below. Failure to timely comply will result in ABANDONMENT of this application.
THIS THREE-MONTH PERIOD IS NOT EXTENDABLE.

5. ☐ CORRECTED DRAWINGS (as "replacement sheets") must be submitted.
   ☐ including changes required by the attached Examiner's Amendment / Comment or in the Office action of Paper No./Mail Date _____ .

   Identifying indicia such as the application number (see 37 CFR 1.84(c)) should be written on the drawings in the front (not the back) of each sheet. Replacement sheet(s) should be labeled as such in the header according to 37 CFR 1.121(d).

6. ☐ DEPOSIT OF and/or INFORMATION about the deposit of BIOLOGICAL MATERIAL must be submitted. Note the attached Examiner's comment regarding REQUIREMENT FOR THE DEPOSIT OF BIOLOGICAL MATERIAL.

Attachment(s)

1. ☐ Notice of References Cited (PTO-892)
2. ☑ Information Disclosure Statements (PTO/SB/08), Paper No./Mail Date _____.
3. ☐ Examiner's Comment Regarding Requirement for Deposit of Biological Material _____.
4. ☐ Interview Summary (PTO-413), Paper No./Mail Date. _____.
5. ☑ Examiner's Amendment/Comment
6. ☑ Examiner's Statement of Reasons for Allowance
7. ☐ Other _____.

/J.L/ Examiner, Art Unit 1647	/CHRISTINE J SAOUD/ Primary Examiner, Art Unit 1645

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Continuation of 3. The allowed claim(s) is/are: 30-32 and 53-87 (renumbered as claims 1-11,13-14,16,18,20,22,24,12,26,15,17,19,21,23,25 and 27-38, respectively)

Notice of Pre-AIA or AIA Status

1. The present application, filed on or after March 16, 2013, is being examined under the first inventor to file provisions of the AIA.

Continued Examination Under 37 CFR 1.114

2. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after allowance or after an Office action under *Ex Parte Quayle*, 25 USPQ 74, 453 O.G. 213 (Comm'r Pat. 1935). Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, prosecution in this application has been reopened pursuant to 37 CFR 1.114. Applicant's submission filed on 15 July 2024 has been entered.

Information Disclosure Statement

3. The information disclosure statements (IDS) submitted on 18 June 2024, 15 July 2024 and 23 July 2024 have been considered by the examiner.

REASONS FOR ALLOWANCE

4. The following is an examiner's statement of reasons for allowance: The information disclosure statements (IDS) submitted on 18 June 2024, 15 July 2024 and 23 July 2024 have been considered by the Examiner. After careful consideration, the Examiner has determined that none of the information contained therein raises new issues of patentability.

5. Any comments considered necessary by applicant must be submitted no later than the payment of the issue fee and, to avoid processing delays, should preferably accompany the issue

fee. Such submissions should be clearly labeled "Comments on Statement of Reasons for Allowance."

Summary

6. Claims 30-32 and 53-87 are allowed.

Advisory Information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to **JON M LOCKARD** whose telephone number is **(571) 272-2717**. The examiner can normally be reached M-F 9-6 EST.

Examiner interviews are available via telephone, in-person, and video conferencing using a USPTO supplied web-based collaboration tool. To schedule an interview, applicant is encouraged to use the USPTO Automated Interview Request (AIR) at http://www.uspto.gov/interviewpractice. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, **Joanne Hama** can be reached on **(571) 272-2911**. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of published or unpublished applications may be obtained from Patent Center. Unpublished application information in Patent Center is available to registered users. To file and manage patent submissions in Patent Center, visit: https://patentcenter.uspto.gov. Visit https://www.uspto.gov/patents/apply/patent-center for more information about Patent Center and https://www.uspto.gov/patents/docx for information about filing in DOCX format. For additional questions, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/J.L/
Examiner, Art Unit 1647
July 25, 2024

/Christine J Saoud/
Primary Examiner, Art Unit 1645

Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
	17/384,070	Graham et al.
	Examiner	Art Unit
	JON M LOCKARD	1647

CPC - Searched*		
Symbol	Date	Examiner

CPC Combination Sets - Searched*		
Symbol	Date	Examiner

US Classification - Searched*			
Class	Subclass	Date	Examiner
NONE		03/16/2023	JML

* See search history printout included with this form or the SEARCH NOTES box below to determine the scope of the search.

Search Notes		
Search Notes	Date	Examiner
PE2E Search (USPAT, US-PGPUB, EPO, DERWENT): See attached search history.	03/16/2023	JML
STN (MEDLINE, SCISEARCH, EMBASE, BIOSIS): See attached search history.	03/16/2023	JML
PALM: Inventor search.	03/16/2023	JML
PE2E Search (USPAT, US-PGPUB, EPO, DERWENT): See attached search history.	11/01/2023	JML

Regeneron Ex. 2001
Alvotech v. Regeneron
PGR2025-00085
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Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
	17/384,070	Graham et al.
	Examiner	Art Unit
	JON M LOCKARD	1647

Interference Search			
US Class/CPC Symbol	**US Subclass/CPC Group**	**Date**	**Examiner**
	PE2E Search (USPAT): See attached search history.	08/24/2023	JML
	DAV: Inventor search.	08/24/2023	JML
	PE2E Search (USPAT): See attached search history.	11/01/2023	JML
	DAV: Inventor search.	11/01/2023	JML
	PE2E Search (USPAT): See attached search history.	11/29/2023	JML
	DAV: Inventor search.	11/29/2023	JML
	PE2E Search (USPAT): See attached search history.	01/11/2024	JML
	DAV: Inventor search.	01/11/2024	JML
	PE2E Search (USPAT): See attached search history.	05/10/2024	JML
	DAV: Inventor search.	05/10/2024	JML
	PE2E Search (USPAT): See attached search history.	06/11/2024	JML
	DAV: Inventor search.	06/11/2024	JML
	PE2E Search (USPAT): See attached search history.	07/25/2024	JML
	DAV: Inventor search.	07/25/2024	JML

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Alvotech v. Regeneron
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Issue Classification	Application/Control No.	Applicant(s)/Patent Under Reexamination
	17/384,070	Graham et al.
	Examiner	**Art Unit**
	JON M LOCKARD	1647

CPC										
Symbol									**Type**	**Version**
A61K	/	38	/	179					F	2013-01-01
A61K	/	9	/	0048					I	2013-01-01
A61K	/	47	/	12					I	2013-01-01
A61P	/	27	/	02					I	2018-01-01
A61K	/	47	/	22					I	2013-01-01
A61K	/	47	/	26					I	2013-01-01
A61K	/	47	/	183					I	2013-01-01

CPC Combination Sets										
Symbol									**Type**	**Set**	**Ranking**	**Version**
	/		/									

/JON M LOCKARD/ Examiner, Art Unit 1647	25 July 2024	**Total Claims Allowed:**	
(Assistant Examiner)	(Date)	38	
/CHRISTINE J SAOUD/ Primary Examiner, Art Unit 1645	26 July 2024	O.G. Print Claim(s)	O.G. Print Figure
(Primary Examiner)	(Date)	1	NONE

U.S. Patent and Trademark Office — Part of Paper No.: 20240725

Regeneron Ex. 2001
Alvotech v. Regeneron
PGR2025-00085
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Issue Classification	Application/Control No.	Applicant(s)/Patent Under Reexamination
	17/384,070	Graham et al.
	Examiner	Art Unit
	JON M LOCKARD	1647

INTERNATIONAL CLASSIFICATION					
CLAIMED					
A61K	/	38	/	17	
A61K	/	38	/	18	
C07K	/	14	/	71	

NON-CLAIMED				
	/		/	

US ORIGINAL CLASSIFICATION	
CLASS	SUBCLASS

CROSS REFERENCES(S)						
CLASS	SUBCLASS (ONE SUBCLASS PER BLOCK)					

/JON M LOCKARD/ Examiner, Art Unit 1647	25 July 2024	Total Claims Allowed:	
(Assistant Examiner)	(Date)	38	
/CHRISTINE J SAOUD/ Primary Examiner, Art Unit 1645	26 July 2024	O.G. Print Claim(s)	O.G. Print Figure
(Primary Examiner)	(Date)	1	NONE

U.S. Patent and Trademark Office — Part of Paper No.: 20240725

Regeneron Ex. 2001
Alvotech v. Regeneron
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Issue Classification	Application/Control No.	Applicant(s)/Patent Under Reexamination
	17/384,070	Graham et al.
	Examiner	Art Unit
	JON M LOCKARD	1647

☐ Claims renumbered in the same order as presented by applicant ☐ CPA ☑ T.D. ☐ R.1.47

CLAIMS

Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original
1	30	10	59	12	68	28	77	37	86						
2	31	11	60	26	69	29	78	38	87						
3	32	13	61	15	70	30	79								
4	53	14	62	17	71	31	80								
5	54	16	63	19	72	32	81								
6	55	18	64	21	73	33	82								
7	56	20	65	23	74	34	83								
8	57	22	66	25	75	35	84								
9	58	24	67	27	76	36	85								

/JON M LOCKARD/ Examiner, Art Unit 1647 (Assistant Examiner)	25 July 2024 (Date)	**Total Claims Allowed:** 38	
/CHRISTINE J SAOUD/ Primary Examiner, Art Unit 1645 (Primary Examiner)	26 July 2024 (Date)	O.G. Print Claim(s) 1	O.G. Print Figure NONE

U.S. Patent and Trademark Office Part of Paper No.: 20240725

Regeneron Ex. 2001
Alvotech v. Regeneron
PGR2025-00085
Page 501 of 531

Receipt date: 07/15/2024

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (not for submission under 37 CFR 1.99)		
	Application Number	17/384,070
	Filing Date	Jul-23-2021
	First Named Inventor	Kenneth S. Graham
	Art Unit	1647
	Confirmation Number	1061
	Examiner Name	Lockard, Jon McClelland
	Attorney Docket Number	125984-266215

U.S. PATENTS						
Examiner Initial*	Cite No	Patent Number	Kind Code[1]	Issue Date	Name of Patentee or Applicant of cited Document	Pages, Columns, Lines where Relevant Passages or Relevant Figures Appear
	646	11,958,894		04-16-2024	Wang et al.	
	647	12,005,097		06-11-2024	Kerwin et al.	

U.S. PATENT APPLICATION PUBLICATIONS						
Examiner Initial*	Cite No	Publication Number	Kind Code[1]	Publication Date	Name of Patentee or Applicant of cited Document	Pages, Columns, Lines where Relevant Passages or Relevant Figures Appear
	644	2024-0029897		01-25-2024	Perlee et al.	
	645	2024-0189402		06-13-2024	Borodic	

FOREIGN PATENT DOCUMENTS								
Examiner Initial*	Cite No	Foreign Document Number[3]	Country Code[2]	Kind Code[4]	Publication Date	Name of Patentee or Applicant of cited Document	Pages, Columns, Lines where Relevant Passages or Relevant Figures Appear	T[5]

NON-PATENT LITERATURE DOCUMENTS			
Examiner Initial*	Cite No	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, pages(s), volume-issue number(s), publisher, city and/or country where published	T[5]
	641	Anonymous: "Product information EYLA aflibercept (rch)", 15 April 2015 (2015-04-15), XP093174268, [Retrieved from the Internet: URL:https://www.tga.gov.au/sites/default/f iles/auspar-aflibercept-150721-pi.pdf]	
	642	Australian Public Assessment Report for Aflibercept, Australian Government, Department of Health & Aging, Therapeutic Goods Administration, Proprietary Product Name: Eylea sponsored by Bayer Australia Ltd (publication date 07-21-2015).	
	643	Clinical Trials for "Phase 1 Study of VEGF Trap in Patients With Diabetic Macular Edema," sponsored by Regeneron Pharmaceuticals, NCT00320814 (publication date 06-10-2011).	

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /J.L/

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	Art Unit	1647
	Confirmation Number	1061
	Examiner Name	Lockard, Jon McClelland
	Attorney Docket Number	125984-266215

EXAMINER SIGNATURE			
Examiner Signature	/JON M LOCKARD/	Date Considered	07/25/2024

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through a citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

[1] See Kind Codes of USPTO Patent Documents at www.USPTO.GOV or MPEP 901.04. [2] Enter office that issued the document, by the two-letter code (WIPO Standard ST.3). [3] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [4] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [5] Applicant is to place a check mark here if English language translation is attached.

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Examiner Initial*	Cite No	Patent Number	Kind Code[1]	Issue Date	Name of Patentee or Applicant of cited Document	Pages, Columns, Lines where Relevant Passages or Relevant Figures Appear

U.S. PATENT APPLICATION PUBLICATIONS						
Examiner Initial*	Cite No	Publication Number	Kind Code[1]	Publication Date	Name of Patentee or Applicant of cited Document	Pages, Columns, Lines where Relevant Passages or Relevant Figures Appear

FOREIGN PATENT DOCUMENTS								
Examiner Initial*	Cite No	Foreign Document Number[3]	Country Code[2]	Kind Code[4]	Publication Date	Name of Patentee or Applicant of cited Document	Pages, Columns, Lines where Relevant Passages or Relevant Figures Appear	T[5]

NON-PATENT LITERATURE DOCUMENTS			
Examiner Initial*	Cite No	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, pages(s), volume-issue number(s), publisher, city and/or country where published	T[5]
	648	AVASTIN label (revised December 2017)	
	649	HERCEPTIN label (September 1998)	
	650	LUCENTIS label (revised October 2014)	
	651	REMICADE label (revised November 2013)	
	652	SIMULECT label (May 1998)	
	653	XOLAIR label (2003)	

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /J.L/

Receipt date: 07/23/2024

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	Art Unit	1647
	Confirmation Number	1061
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	Attorney Docket Number	125984-266215

EXAMINER SIGNATURE			
Examiner Signature	/JON M LOCKARD/	Date Considered	07/25/2024

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ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /J.L/

Receipt date: 06/18/2024

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (not for submission under 37 CFR 1.99)		
	Application Number	17/384,070
	Filing Date	Jul-23-2021
	First Named Inventor	Kenneth S. Graham
	Art Unit	1647
	Confirmation Number	1061
	Examiner Name	Lockard, Jon McClelland
	Attorney Docket Number	125984-266215

U.S. PATENTS						
Examiner Initial*	Cite No	Patent Number	Kind Code[1]	Issue Date	Name of Patentee or Applicant of cited Document	Pages, Columns, Lines where Relevant Passages or Relevant Figures Appear
	639	11,986,511		05-21-2024	Yancopoulos et al.	

U.S. PATENT APPLICATION PUBLICATIONS						
Examiner Initial*	Cite No	Publication Number	Kind Code[1]	Publication Date	Name of Patentee or Applicant of cited Document	Pages, Columns, Lines where Relevant Passages or Relevant Figures Appear

FOREIGN PATENT DOCUMENTS								
Examiner Initial*	Cite No	Foreign Document Number[3]	Country Code[2]	Kind Code[4]	Publication Date	Name of Patentee or Applicant of cited Document	Pages, Columns, Lines where Relevant Passages or Relevant Figures Appear	T[5]

NON-PATENT LITERATURE DOCUMENTS			
Examiner Initial*	Cite No	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, pages(s), volume-issue number(s), publisher, city and/or country where published	T[5]

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /J.L/

Regeneron Ex. 2001
Alvotech v. Regeneron
PGR2025-00085
Page 506 of 531

Receipt date: 06/18/2024

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (not for submission under 37 CFR 1.99)		
	Application Number	17/384,070
	Filing Date	Jul-23-2021
	First Named Inventor	Kenneth S. Graham
	Art Unit	1647
	Confirmation Number	1061
	Examiner Name	Lockard, Jon McClelland
	Attorney Docket Number	125984-266215

EXAMINER SIGNATURE			
Examiner Signature	/JON M LOCKARD/	Date Considered	07/25/2024

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ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /J.L/

PE2E SEARCH - Search History (Prior Art)

/J.L./

There are no Prior Art searches to show.

PE2E SEARCH - Search History (Interference)

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	British Equivalents	Time Stamp
N50	2831	vegf ADJ trap	(USPAT)	OR	ON	ON	2024/07/25 09:43 PM
N51	2990	aflibercept	(USPAT)	OR	ON	ON	2024/07/25 09:43 PM
N52	462	eylea	(USPAT)	OR	ON	ON	2024/07/25 09:43 PM
N53	125	vegf ADJ trap-eye	(USPAT)	OR	ON	ON	2024/07/25 09:43 PM
N54	456	(N41 N42 N43 N44) SAME formulation	(USPAT)	OR	ON	ON	2024/07/25 09:43 PM
N55	12	N45 SAME "high concentration"	(USPAT)	OR	ON	ON	2024/07/25 09:43 PM
N56	1	N45 AND (8mg OR "8 mg").clm.	(USPAT)	OR	ON	ON	2024/07/25 09:43 PM
N57	18	(graham-k$-s$ washawa-s$).in.	(USPAT)	OR	ON	ON	2024/07/25 09:43 PM
N58	1	N46 AND N48	(USPAT)	OR	ON	ON	2024/07/25 09:43 PM

Regeneron Ex. 2001
Alvotech v. Regeneron
PGR2025-00085
Page 508 of 531

PTO/SB/30 (11-23)
Approved for use through 05/31/2024. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

Request for Continued Examination (RCE) Transmittal

Address to:
Mail Stop RCE
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Application Number	17/384,070
Filing Date	July 23, 2021
First Named Inventor	Kenneth S. Graham
Art Unit	1647
Examiner Name	Jon McClelland Lockard
Attorney Docket Number	125984-266215

This is a Request for Continued Examination (RCE) under 37 CFR 1.114 of the above-identified application.
Request for Continued Examination (RCE) practice under 37 CFR 1.114 does not apply to any utility or plant application filed prior to June 8, 1995, or to any design application. See Instruction Sheet for RCEs (not to be submitted to the USPTO) on page 2.

1. Submission required under 37 CFR 1.114 Note: If the RCE is proper, any previously filed unentered amendments and amendments enclosed with the RCE will be entered in the order in which they were filed unless applicant instructs otherwise. If applicant does not wish to have any previously filed unentered amendment(s) entered, applicant must request non-entry of such amendment(s).

   a. ☐ Previously submitted. If a final Office action is outstanding, any amendments filed after the final Office action may be considered as a submission even if this box is not checked.

      i. ☐ Consider the arguments in the Appeal Brief or Reply Brief previously filed on _____

      ii. ☐ Other _____

   b. ☑ Enclosed

      i. ☐ Amendment/Reply

      ii. ☐ Affidavit(s)/ Declaration(s)

      iii. ☑ Information Disclosure Statement (IDS)

      iv. ☐ Other _____

2. Miscellaneous

   a. ☐ Suspension of action on the above-identified application is requested under 37 CFR 1.103(c) for a period of _____ months. (Period of suspension shall not exceed 3 months; Fee under 37 CFR 1.17(i) required)

   b. ☐ Other _____

3. Fees The RCE fee under 37 CFR 1.17(e) is required by 37 CFR 1.114 when the RCE is filed.

   a. ☑ The Director is hereby authorized to charge the following fees, any underpayment of fees, or credit any overpayments, to Deposit Account No. 500393.

      i. ☑ RCE fee required under 37 CFR 1.17(e)

      ii. ☐ Extension of time fee (37 CFR 1.136 and 1.17)

      iii. ☐ Other _____

   b. ☐ Check in the amount of $ _____ enclosed

   c. ☐ Payment by credit card (Form PTO-2038 enclosed)

   d. ▩ Payment by USPTO patent electronic filing system.

WARNING: Information on this form may become public. Credit card information should not be included on this form. Provide credit card information and authorization on PTO-2038.

SIGNATURE OF APPLICANT, ATTORNEY, OR AGENT REQUIRED

Signature	/Lance A. Termes/	Date	August 27, 2024
Name (Print/Type)	Lance A. Termes	Registration No.	43,184

CERTIFICATE OF MAILING OR TRANSMISSION

I hereby certify that this correspondence is transmitted by the USPTO patent electronic filing system, or by facsimile to (571) 273-8300, to the USPTO, or deposited with the United States Postal Service with sufficient postage as first class mail in an envelope addressed to: Mail Stop RCE, Commissioner for Patents, P. O. Box 1450, Alexandria, VA 22313-1450, on the date shown below.

Signature	/Lance A. Termes/		
Name (Print/Type)	Lance A. Termes	Date	August 27, 2024

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Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.

If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (not for submission under 37 CFR 1.99)		
	Application Number	17/384,070
	Filing Date	Jul-23-2021
	First Named Inventor	Kenneth S. Graham
	Art Unit	1647
	Confirmation Number	1061
	Examiner Name	Lockard, Jon McClelland
	Attorney Docket Number	125984-266215

U.S. PATENTS						
Examiner Initial*	Cite No	Patent Number	Kind Code[1]	Issue Date	Name of Patentee or Applicant of cited Document	Pages, Columns, Lines where Relevant Passages or Relevant Figures Appear

U.S. PATENT APPLICATION PUBLICATIONS						
Examiner Initial*	Cite No	Publication Number	Kind Code[1]	Publication Date	Name of Patentee or Applicant of cited Document	Pages, Columns, Lines where Relevant Passages or Relevant Figures Appear

FOREIGN PATENT DOCUMENTS								
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NON-PATENT LITERATURE DOCUMENTS			
Examiner Initial*	Cite No	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, pages(s), volume-issue number(s), publisher, city and/or country where published	T[5]
	655	BORWANKAR et al., "Viscosity Reduction of a Concentrated Monoclonal Antibody with Arginine·HCl and Arginine·Glutamate," I&EC Research, American Chemical Sociaet, Volume (No 55): 11225−11234, (2016). [DOI: 10.1021/acs.iecr.6b02042].	

Regeneron Ex. 2001
Alvotech v. Regeneron
PGR2025-00085
Page 510 of 531

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EXAMINER SIGNATURE			
Examiner Signature		Date Considered	

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	Confirmation Number	1061
	Examiner Name	Lockard, Jon McClelland
	Attorney Docket Number	125984-266215

CERTIFICATION STATEMENT

Please see 37 CFR 1.97 and 1.98 to make the appropriate selection(s):

☐ That each item of information contained in the information disclosure statement was first cited in any communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(1).

OR

☐ That no item of information contained in the information disclosure statement was cited in a communication from a foreign patent office in a counterpart foreign application, and, to the knowledge of the person signing the certification after making reasonable inquiry, no item of information contained in the information disclosure statement was known to any individual designated in 37 CFR 1.56(c) more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(2).

☐ See attached certification statement.

☐ Fee set forth in 37 CFR 1.17 (p) has been submitted herewith.

☒ None

SIGNATURE

A signature of the applicant or representative is required in accordance with CFR 1.33, 10.18. Please see CFR 1.4(d) for the form of the signature.

Signature	/Lance A. Termes/	Date (YYYY-MM-DD)	2024-08-27
Name/Print	Lance A. Termes	Registration Number	43184

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UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

NOTICE OF ALLOWANCE AND FEE(S) DUE

147803 7590 09/11/2024

Schwabe W&W, PC / Regeneron Pharmaceuticals, Inc.
PacWest Center
1211 SW Fifth Avenue, Suite 1900
Portland, OR 97204

EXAMINER	
LOCKARD, JON MCCLELLAND	
ART UNIT	PAPER NUMBER
1647	

DATE MAILED: 09/11/2024

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
17/384,070	07/23/2021	Kenneth S. Graham		1061

TITLE OF INVENTION: Methods for Treating Angiogenic Eye Disorders with High Doses of VEGF Receptor Fusion Proteins

APPLN. TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	UNDISCOUNTED	$1200	$0.00	$1200.00	$0	12/11/2024

THE APPLICATION IDENTIFIED ABOVE HAS BEEN EXAMINED AND IS ALLOWED FOR ISSUANCE AS A PATENT. PROSECUTION ON THE MERITS IS CLOSED. THIS NOTICE OF ALLOWANCE IS NOT A GRANT OF PATENT RIGHTS. THIS APPLICATION IS SUBJECT TO WITHDRAWAL FROM ISSUE AT THE INITIATIVE OF THE OFFICE OR UPON PETITION BY THE APPLICANT. SEE 37 CFR 1.313 AND MPEP 1308.

THE ISSUE FEE AND PUBLICATION FEE (IF REQUIRED) MUST BE PAID WITHIN THREE MONTHS FROM THE MAILING DATE OF THIS NOTICE OR THIS APPLICATION SHALL BE REGARDED AS ABANDONED. THIS STATUTORY PERIOD CANNOT BE EXTENDED. SEE 35 U.S.C. 151. THE ISSUE FEE DUE INDICATED ABOVE DOES NOT REFLECT A CREDIT FOR ANY PREVIOUSLY PAID ISSUE FEE IN THIS APPLICATION. IF AN ISSUE FEE HAS PREVIOUSLY BEEN PAID IN THIS APPLICATION (AS SHOWN ABOVE), THE RETURN OF PART B OF THIS FORM WILL BE CONSIDERED A REQUEST TO REAPPLY THE PREVIOUSLY PAID ISSUE FEE TOWARD THE ISSUE FEE NOW DUE.

HOW TO REPLY TO THIS NOTICE:

I. Review the ENTITY STATUS shown above. If the ENTITY STATUS is shown as SMALL or MICRO, verify whether entitlement to that entity status still applies.

If the ENTITY STATUS is the same as shown above, pay the TOTAL FEE(S) DUE shown above.

If the ENTITY STATUS is changed from that shown above, on PART B - FEE(S) TRANSMITTAL, complete section number 5 titled "Change in Entity Status (from status indicated above)".

For purposes of this notice, small entity fees are 40% the amount of undiscounted fees, and micro entity fees are 20% the amount of undiscounted fees.

II. PART B - FEE(S) TRANSMITTAL, or its equivalent, must be completed and returned to the United States Patent and Trademark Office (USPTO) with your ISSUE FEE and PUBLICATION FEE (if required). If you are charging the fee(s) to your deposit account, section "4b" of Part B - Fee(s) Transmittal should be completed. If an equivalent of Part B is filed, a request to reapply a previously paid issue fee must be clearly made, and delays in processing may occur due to the difficulty in recognizing the paper as an equivalent of Part B.

III. All communications regarding this application must give the application number. Please direct all communications prior to issuance to Mail Stop ISSUE FEE unless advised to the contrary.

IMPORTANT REMINDER: Maintenance fees are due in utility patents issuing on applications filed on or after Dec. 12, 1980. It is patentee's responsibility to ensure timely payment of maintenance fees when due. More information is available at www.uspto.gov/PatentMaintenanceFees.

PTOL-85 (Rev. 11/23)

Regeneron Ex. 2001
Alvotech v. Regeneron
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PART B - FEE(S) TRANSMITTAL

Complete and send this form, together with applicable fee(s), by mail or fax, or via the USPTO patent electronic filing system.

By mail, send to: Mail Stop ISSUE FEE
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450

By fax, send to: (571)-273-2885

INSTRUCTIONS: This form should be used for transmitting the ISSUE FEE and PUBLICATION FEE (if required). Blocks 1 through 5 should be completed where appropriate. All further correspondence will be mailed to the current correspondence address as indicated unless corrected below or directed otherwise in Block 1, by (a) specifying a new correspondence address; and/or (b) indicating a separate "FEE ADDRESS" for maintenance fee notifications. **Because electronic patent issuance may occur shortly after issue fee payment, any desired continuing application should preferably be filed prior to payment of this issue fee in order not to jeopardize copendency.**

CURRENT CORRESPONDENCE ADDRESS (Note: Use Block 1 for any change of address)

147803 7590 09/11/2024

Schwabe W&W, PC / Regeneron Pharmaceuticals, Inc.
PacWest Center
1211 SW Fifth Avenue, Suite 1900
Portland, OR 97204

Note: A certificate of mailing can only be used for domestic mailings of the Fee(s) Transmittal. This certificate cannot be used for any other accompanying papers. Each additional paper, such as an assignment or formal drawing, must have its own certificate of mailing or transmission.

Certificate of Mailing or Transmission

I hereby certify that this Fee(s) Transmittal is being deposited with the United States Postal Service with sufficient postage for first class mail in an envelope addressed to the Mail Stop ISSUE FEE address above, or being transmitted to the USPTO via the USPTO patent electronic filing system or by facsimile to (571) 273-2885, on the date below.

(Typed or printed name)
(Signature)
(Date)

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
17/384,070	07/23/2021	Kenneth S. Graham		1061

TITLE OF INVENTION: Methods for Treating Angiogenic Eye Disorders with High Doses of VEGF Receptor Fusion Proteins

APPLN. TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	UNDISCOUNTED	$1200	$0.00	$1200.00	$0	12/11/2024

EXAMINER	ART UNIT	CLASS-SUBCLASS
LOCKARD, JON MCCLELLAND	1647	424-134100

1. Change of correspondence address or indication of "Fee Address" (37 CFR 1.363).

❑ Change of correspondence address (or Change of Correspondence Address form PTO/AIA/122 or PTO/SB/122) attached.

❑ "Fee Address" indication (or "Fee Address" Indication form PTO/AIA/47 or PTO/SB/47; Rev 03-02 or more recent) attached. **Use of a Customer Number is required.**

2. For printing on the patent front page, list
(1) The names of up to 3 registered patent attorneys or agents OR, alternatively,
(2) The name of a single firm (having as a member a registered attorney or agent) and the names of up to 2 registered patent attorneys or agents. If no name is listed, no name will be printed.

1 _____
2 _____
3 _____

3. ASSIGNEE NAME AND RESIDENCE DATA TO BE PRINTED ON THE PATENT (print or type)

PLEASE NOTE: Unless an assignee is identified below, no assignee data will appear on the patent. If an assignee is identified below, the document must have been previously recorded, or filed for recordation, as set forth in 37 CFR 3.11 and 37 CFR 3.81(a). Completion of this form is NOT a substitute for filing an assignment.

(A) NAME OF ASSIGNEE (B) RESIDENCE: (CITY and STATE OR COUNTRY)

Please check the appropriate assignee category or categories (will not be printed on the patent) : ❑ Individual ❑ Corporation or other private group entity ❑ Government

4a. Fees submitted: ❑ Issue Fee ❑ Publication Fee (if required)

4b. Method of Payment: *(Please first reapply any previously paid fee shown above)*

❑ Electronic Payment via the USPTO patent electronic filing system ❑ Enclosed check ❑ Non-electronic payment by credit card (Attach form PTO-2038)

❑ The Director is hereby authorized to charge the required fee(s), any deficiency, or credit any overpayment to Deposit Account No. _____

5. **Change in Entity Status** (from status indicated above)

❑ Applicant certifying micro entity status. See 37 CFR 1.29

NOTE: Absent a valid certification of Micro Entity Status (see forms PTO/SB/15A and 15B), issue fee payment in the micro entity amount will not be accepted at the risk of application abandonment.

❑ Applicant asserting small entity status. See 37 CFR 1.27

NOTE: If the application was previously under micro entity status, checking this box will be taken to be a notification of loss of entitlement to micro entity status.

❑ Applicant changing to regular undiscounted fee status.

NOTE: Checking this box will be taken to be a notification of loss of entitlement to small or micro entity status, as applicable.

NOTE: This form must be signed in accordance with 37 CFR 1.31 and 1.33. See 37 CFR 1.4 for signature requirements and certifications.

Authorized Signature _____ Date _____

Typed or printed name _____ Registration No. _____

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UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
17/384,070	07/23/2021	Kenneth S. Graham		1061

147803 7590 09/11/2024

Schwabe W&W, PC / Regeneron Pharmaceuticals, Inc.
PacWest Center
1211 SW Fifth Avenue, Suite 1900
Portland, OR 97204

EXAMINER	
LOCKARD, JON MCCLELLAND	
ART UNIT	**PAPER NUMBER**
1647	

DATE MAILED: 09/11/2024

Determination of Patent Term Adjustment under 35 U.S.C. 154 (b)
(Applications filed on or after May 29, 2000)

The Office has discontinued providing a Patent Term Adjustment (PTA) calculation with the Notice of Allowance.

Section 1(h)(2) of the AIA Technical Corrections Act amended 35 U.S.C. 154(b)(3)(B)(i) to eliminate the requirement that the Office provide a patent term adjustment determination with the notice of allowance. See Revisions to Patent Term Adjustment, 78 Fed. Reg. 19416, 19417 (Apr. 1, 2013). Therefore, the Office is no longer providing an initial patent term adjustment determination with the notice of allowance. The Office will continue to provide a patent term adjustment determination with the Issue Notification Letter that is mailed to applicant approximately three weeks prior to the issue date of the patent, and will include the patent term adjustment on the patent. Any request for reconsideration of the patent term adjustment determination (or reinstatement of patent term adjustment) should follow the process outlined in 37 CFR 1.705.

Any questions regarding the Patent Term Extension or Adjustment determination should be directed to the Office of Patent Legal Administration at (571)-272-7702. Questions relating to issue and publication fee payments should be directed to the Customer Service Center of the Office of Patent Publication at 1-(888)-786-0101 or (571)-272-4200.

PTOL-85 (Rev. 11/23)

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OMB Clearance and PRA Burden Statement for PTOL-85 Part B

The Paperwork Reduction Act (PRA) of 1995 requires Federal agencies to obtain Office of Management and Budget approval before requesting most types of information from the public. When OMB approves an agency request to collect information from the public, OMB (i) provides a valid OMB Control Number and expiration date for the agency to display on the instrument that will be used to collect the information and (ii) requires the agency to inform the public about the OMB Control Number's legal significance in accordance with 5 CFR 1320.5(b).

The information collected by PTOL-85 Part B is required by 37 CFR 1.311. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 30 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, Virginia 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, Virginia 22313-1450. Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

Privacy Act Statement

The Privacy Act of 1974 (P.L. 93-579) requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. The United States Patent and Trademark Office (USPTO) collects the information in this record under authority of 35 U.S.C. 2. The USPTO's system of records is used to manage all applicant and owner information including name, citizenship, residence, post office address, and other information with respect to inventors and their legal representatives pertaining to the applicant's/owner's activities in connection with the invention for which a patent is sought or has been granted. The applicable Privacy Act System of Records Notice for the information collected in this form is COMMERCE/PAT-TM-7 Patent Application Files, available in the Federal Register at 78 FR 19243 (March 29, 2013).
https://www.govinfo.gov/content/pkg/FR-2013-03-29/pdf/2013-07341.pdf

Routine uses of the information in this record may include disclosure to:

1) law enforcement, in the event that the system of records indicates a violation or potential violation of law;
2) a federal, state, local, or international agency, in response to its request;
3) a contractor of the USPTO having need for the information in order to perform a contract;
4) the Department of Justice for determination of whether the Freedom of Information Act (FOIA) requires disclosure of the record;
5) a Member of Congress submitting a request involving an individual to whom the record pertains, when the individual has requested the Member's assistance with respect to the subject matter of the record;
6) a court, magistrate, or administrative tribunal, in the course of presenting evidence, including disclosures to opposing counsel in the course of settlement negotiations;
7) the Administrator, General Services Administration (GSA), or their designee, during an inspection of records conducted by GSA under authority of 44 U.S.C. 2904 and 2906, in accordance with the GSA regulations and any other relevant (i.e., GSA or Commerce) directive, where such disclosure shall not be used to make determinations about individuals;
8) another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c));
9) the Office of Personnel Management (OPM) for personnel research purposes; and
10) the Office of Management and Budget (OMB) for legislative coordination and clearance.

If you do not furnish the information requested on this form, the USPTO may not be able to process and/or examine your submission, which may result in termination of proceedings, abandonment of the application, and/or expiration of the patent.

Notice of Allowability	Application No. 17/384,070	Applicant(s) Graham et al.	
	Examiner JON M LOCKARD	Art Unit 1647	AIA (FITF) Status Yes

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address--

All claims being allowable, PROSECUTION ON THE MERITS IS (OR REMAINS) CLOSED in this application. If not included herewith (or previously mailed), a Notice of Allowance (PTOL-85) or other appropriate communication will be mailed in due course. **THIS NOTICE OF ALLOWABILITY IS NOT A GRANT OF PATENT RIGHTS.** This application is subject to withdrawal from issue at the initiative of the Office or upon petition by the applicant. See 37 CFR 1.313 and MPEP 1308.

1. ☑ This communication is responsive to the Request for Continued Examination filed 27 August 2024.
   ☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on _____.

2. ☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.

3. ☑ The allowed claim(s) is/are See Continuation Sheet . As a result of the allowed claim(s), you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information, please see **http://www.uspto.gov/patents/init_events/pph/index.jsp** or send an inquiry to **PPHfeedback@uspto.gov.**

4. ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

   Certified copies:

   a) ☐ All b) ☐ Some* c) ☐ None of the:

   1. ☐ Certified copies of the priority documents have been received.
   2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
   3. ☐ Copies of the certified copies of the priority documents have been received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

   * Certified copies not received: _____ .

Applicant has THREE MONTHS FROM THE "MAILING DATE" of this communication to file a reply complying with the requirements noted below. Failure to timely comply will result in ABANDONMENT of this application.
THIS THREE-MONTH PERIOD IS NOT EXTENDABLE.

5. ☐ CORRECTED DRAWINGS (as "replacement sheets") must be submitted.
   ☐ including changes required by the attached Examiner's Amendment / Comment or in the Office action of Paper No./Mail Date _____ .

   Identifying indicia such as the application number (see 37 CFR 1.84(c)) should be written on the drawings in the front (not the back) of each sheet. Replacement sheet(s) should be labeled as such in the header according to 37 CFR 1.121(d).

6. ☐ DEPOSIT OF and/or INFORMATION about the deposit of BIOLOGICAL MATERIAL must be submitted. Note the attached Examiner's comment regarding REQUIREMENT FOR THE DEPOSIT OF BIOLOGICAL MATERIAL.

Attachment(s)

1. ☐ Notice of References Cited (PTO-892)
2. ☑ Information Disclosure Statements (PTO/SB/08), Paper No./Mail Date _____.
3. ☐ Examiner's Comment Regarding Requirement for Deposit of Biological Material _____.
4. ☐ Interview Summary (PTO-413), Paper No./Mail Date. _____.
5. ☑ Examiner's Amendment/Comment
6. ☑ Examiner's Statement of Reasons for Allowance
7. ☐ Other _____.

/J.L/ Examiner, Art Unit 1647	/CHRISTINE J SAOUD/ Primary Examiner, Art Unit 1645

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Alvotech v. Regeneron
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Continuation of 3. The allowed claim(s) is/are: 30-32 and 53-87 (renumbered as claims 1-11,13-14,16,18,20,22,24,12,26,15,17,19,21,23,25 and 27-38, respectively)

Notice of Pre-AIA or AIA Status

1. The present application, filed on or after March 16, 2013, is being examined under the first inventor to file provisions of the AIA.

Continued Examination Under 37 CFR 1.114

2. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after allowance or after an Office action under *Ex Parte Quayle*, 25 USPQ 74, 453 O.G. 213 (Comm'r Pat. 1935). Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, prosecution in this application has been reopened pursuant to 37 CFR 1.114. Applicant's submission filed on 27 August 2024 has been entered.

Information Disclosure Statement

3. The information disclosure statement (IDS) submitted on 27 August 2024 has been considered by the examiner.

REASONS FOR ALLOWANCE

4. The following is an examiner's statement of reasons for allowance: The information disclosure statement (IDS) submitted on 27 August 2024 has been considered by the Examiner. After careful consideration, the Examiner has determined that none of the information contained therein raises new issues of patentability.

5. Any comments considered necessary by applicant must be submitted no later than the payment of the issue fee and, to avoid processing delays, should preferably accompany the issue

fee. Such submissions should be clearly labeled "Comments on Statement of Reasons for Allowance."

Summary

6. Claims 30-32 and 53-87 are allowed.

Advisory Information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to **JON M LOCKARD** whose telephone number is **(571) 272-2717**. The examiner can normally be reached M-F 9-6 EST.

Examiner interviews are available via telephone, in-person, and video conferencing using a USPTO supplied web-based collaboration tool. To schedule an interview, applicant is encouraged to use the USPTO Automated Interview Request (AIR) at http://www.uspto.gov/interviewpractice. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, **Joanne Hama** can be reached on **(571) 272-2911**. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of published or unpublished applications may be obtained from Patent Center. Unpublished application information in Patent Center is available to registered users. To file and manage patent submissions in Patent Center, visit: https://patentcenter.uspto.gov. Visit https://www.uspto.gov/patents/apply/patent-center for more information about Patent Center and https://www.uspto.gov/patents/docx for information about filing in DOCX format. For additional questions, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/J.L/
Examiner, Art Unit 1647
September 6, 2024

/Christine J Saoud/
Primary Examiner, Art Unit 1645

Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
	17/384,070	Graham et al.
	Examiner	Art Unit
	JON M LOCKARD	1647

CPC - Searched*		
Symbol	Date	Examiner

CPC Combination Sets - Searched*		
Symbol	Date	Examiner

US Classification - Searched*			
Class	Subclass	Date	Examiner
NONE		03/16/2023	JML

* See search history printout included with this form or the SEARCH NOTES box below to determine the scope of the search.

Search Notes		
Search Notes	Date	Examiner
PE2E Search (USPAT, US-PGPUB, EPO, DERWENT): See attached search history.	03/16/2023	JML
STN (MEDLINE, SCISEARCH, EMBASE, BIOSIS): See attached search history.	03/16/2023	JML
PALM: Inventor search.	03/16/2023	JML
PE2E Search (USPAT, US-PGPUB, EPO, DERWENT): See attached search history.	11/01/2023	JML

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Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
	17/384,070	Graham et al.
	Examiner	Art Unit
	JON M LOCKARD	1647

Interference Search			
US Class/CPC Symbol	**US Subclass/CPC Group**	**Date**	**Examiner**
	PE2E Search (USPAT): See attached search history.	08/24/2023	JML
	DAV: Inventor search.	08/24/2023	JML
	PE2E Search (USPAT): See attached search history.	11/01/2023	JML
	DAV: Inventor search.	11/01/2023	JML
	PE2E Search (USPAT): See attached search history.	11/29/2023	JML
	DAV: Inventor search.	11/29/2023	JML
	PE2E Search (USPAT): See attached search history.	01/11/2024	JML
	DAV: Inventor search.	01/11/2024	JML
	PE2E Search (USPAT): See attached search history.	05/10/2024	JML
	DAV: Inventor search.	05/10/2024	JML
	PE2E Search (USPAT): See attached search history.	06/11/2024	JML
	DAV: Inventor search.	06/11/2024	JML
	PE2E Search (USPAT): See attached search history.	07/25/2024	JML
	DAV: Inventor search.	07/25/2024	JML
	PE2E Search (USPAT): See attached search history.	09/06/2024	JML
	DAV: Inventor search.	09/06/2024	JML

Regeneron Ex. 2001
Alvotech v. Regeneron
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Issue Classification	Application/Control No.	Applicant(s)/Patent Under Reexamination
	17/384,070	Graham et al.
	Examiner	Art Unit
	JON M LOCKARD	1647

CPC												
Symbol										Type	Version	
A61K	/	38	/	179						F	2013-01-01	
A61K	/	9	/	0048						I	2013-01-01	
A61K	/	47	/	12						I	2013-01-01	
A61P	/	27	/	02						I	2018-01-01	
A61K	/	47	/	22						I	2013-01-01	
A61K	/	47	/	26						I	2013-01-01	
A61K	/	47	/	183						I	2013-01-01	

CPC Combination Sets												
Symbol										Type	Set	Ranking	Version
	/		/										

Use images from artifact folder? ◉ Yes ○ No

/JON M LOCKARD/ Examiner, Art Unit 1647 (Assistant Examiner)	06 September 2024 (Date)	**Total Claims Allowed:** 38
/CHRISTINE J SAOUD/ Primary Examiner, Art Unit 1645 (Primary Examiner)	07 September 2024 (Date)	O.G. Print Claim(s): 1 O.G. Print Figure: NONE

Regeneron Ex. 2001
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Issue Classification	Application/Control No.	Applicant(s)/Patent Under Reexamination
	17/384,070	Graham et al.
	Examiner	Art Unit
	JON M LOCKARD	1647

INTERNATIONAL CLASSIFICATION					
CLAIMED					
A61K	/	38	/	17	
A61K	/	38	/	18	
C07K	/	14	/	71	

NON-CLAIMED				
	/		/	

US ORIGINAL CLASSIFICATION	
CLASS	SUBCLASS

CROSS REFERENCES(S)						
CLASS	SUBCLASS (ONE SUBCLASS PER BLOCK)					

Use images from artifact folder? ◉ Yes ○ No

/JON M LOCKARD/ Examiner, Art Unit 1647 (Assistant Examiner)	06 September 2024 (Date)	Total Claims Allowed: 38	
/CHRISTINE J SAOUD/ Primary Examiner, Art Unit 1645 (Primary Examiner)	07 September 2024 (Date)	O.G. Print Claim(s) 1	O.G. Print Figure NONE

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Issue Classification	Application/Control No.	Applicant(s)/Patent Under Reexamination
	17/384,070	Graham et al.
	Examiner	Art Unit
	JON M LOCKARD	1647

☐ Claims renumbered in the same order as presented by applicant ☐ CPA ☑ T.D. ☐ R.1.47

CLAIMS

Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original
1	30	10	59	12	68	28	77	37	86						
2	31	11	60	26	69	29	78	38	87						
3	32	13	61	15	70	30	79								
4	53	14	62	17	71	31	80								
5	54	16	63	19	72	32	81								
6	55	18	64	21	73	33	82								
7	56	20	65	23	74	34	83								
8	57	22	66	25	75	35	84								
9	58	24	67	27	76	36	85								

Use images from artifact folder? ◉ Yes ○ No

/JON M LOCKARD/ Examiner, Art Unit 1647 (Assistant Examiner)	06 September 2024 (Date)	**Total Claims Allowed:** 38
/CHRISTINE J SAOUD/ Primary Examiner, Art Unit 1645 (Primary Examiner)	07 September 2024 (Date)	O.G. Print Claim(s): 1 O.G. Print Figure: NONE

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Alvotech v. Regeneron
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Receipt date: 08/27/2024

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (not for submission under 37 CFR 1.99)		
	Application Number	17/384,070
	Filing Date	Jul-23-2021
	First Named Inventor	Kenneth S. Graham
	Art Unit	1647
	Confirmation Number	1061
	Examiner Name	Lockard, Jon McClelland
	Attorney Docket Number	125984-266215

U.S. PATENTS						
Examiner Initial*	Cite No	Patent Number	Kind Code[1]	Issue Date	Name of Patentee or Applicant of cited Document	Pages, Columns, Lines where Relevant Passages or Relevant Figures Appear

U.S. PATENT APPLICATION PUBLICATIONS						
Examiner Initial*	Cite No	Publication Number	Kind Code[1]	Publication Date	Name of Patentee or Applicant of cited Document	Pages, Columns, Lines where Relevant Passages or Relevant Figures Appear

FOREIGN PATENT DOCUMENTS								
Examiner Initial*	Cite No	Foreign Document Number[3]	Country Code[2]	Kind Code[4]	Publication Date	Name of Patentee or Applicant of cited Document	Pages, Columns, Lines where Relevant Passages or Relevant Figures Appear	T[5]

NON-PATENT LITERATURE DOCUMENTS			
Examiner Initial*	Cite No	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, pages(s), volume-issue number(s), publisher, city and/or country where published	T[5]
/J.L/	655	BORWANKAR et al., "Viscosity Reduction of a Concentrated Monoclonal Antibody with Arginine·HCl and Arginine·Glutamate," I&EC Research, American Chemical Sociaet, Volume (No 55): 11225−11234, (2016). [DOI: 10.1021/acs.iecr.6b02042].	

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EXAMINER SIGNATURE			
Examiner Signature	/JON M LOCKARD/	Date Considered	09/06/2024

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through a citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

[1] See Kind Codes of USPTO Patent Documents at www.USPTO.GOV or MPEP 901.04. [2] Enter office that issued the document, by the two-letter code (WIPO Standard ST.3). [3] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [4] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [5] Applicant is to place a check mark here if English language translation is attached.

PE2E SEARCH - Search History (Prior Art)

/J.L./

There are no Prior Art searches to show.

PE2E SEARCH - Search History (Interference)

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	British Equivalents	Time Stamp
N59	2888	vegf ADJ trap	(USPAT)	OR	ON	ON	2024/09/06 06:31 PM
N60	3056	aflibercept	(USPAT)	OR	ON	ON	2024/09/06 06:31 PM
N61	503	eylea	(USPAT)	OR	ON	ON	2024/09/06 06:31 PM
N62	129	vegf ADJ trap-eye	(USPAT)	OR	ON	ON	2024/09/06 06:31 PM
N63	469	(N41 N42 N43 N44) SAME formulation	(USPAT)	OR	ON	ON	2024/09/06 06:31 PM
N64	12	N45 SAME "high concentration"	(USPAT)	OR	ON	ON	2024/09/06 06:31 PM
N65	1	N45 AND (8mg OR "8 mg").clm.	(USPAT)	OR	ON	ON	2024/09/06 06:31 PM
N66	19	(graham-k$-s$ washawa-s$).in.	(USPAT)	OR	ON	ON	2024/09/06 06:31 PM
N67	1	N46 AND N48	(USPAT)	OR	ON	ON	2024/09/06 06:31 PM

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APPLICATION NO.	ISSUE DATE	PATENT NO.	ATTORNEY DOCKET NO.	CONFIRMATION NO.
17/384,070	12/17/2024	12168036		1061

147803 7590 11/27/2024

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PacWest Center
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Portland, OR 97204

ISSUE NOTIFICATION

The projected patent number and issue date are specified above. The patent will issue electronically. The electronically issued patent is the official patent grant pursuant to 35 U.S.C. § 153. The patent may be accessed on or after the issue date through Patent Center at https://patentcenter.uspto.gov/. The patent will be available in both the public and the private sides of Patent Center. Further assistance in electronically accessing the patent, or about Patent Center, is available by calling the Patent Electronic Business Center at 1-888-217-9197.

The USPTO is implementing electronic patent issuance with a transition period, during which period the USPTO will mail a ceremonial paper copy of the electronic patent grant to the correspondence address of record. Additional copies of the patent (i.e., certified and presentation copies) may be ordered for a fee from the USPTO's Certified Copy Center at https://certifiedcopycenter.uspto.gov/index.html. The Certified Copy Center may be reached at (800)972-6382.

Determination of Patent Term Adjustment under 35 U.S.C. 154 (b)
(application filed on or after May 29, 2000)

The Patent Term Adjustment is 0 day(s). Any patent to issue from the above-identified application will include an indication of the adjustment on the front page.

If a Continued Prosecution Application (CPA) was filed in the above-identified application, the filing date that determines Patent Term Adjustment is the filing date of the most recent CPA.

Applicant will be able to obtain more detailed information by accessing the Patent Center (https://patentcenter.uspto.gov).

Any questions regarding the Patent Term Extension or Adjustment determination should be directed to the Office of Patent Legal Administration at (571)-272-7702. Questions relating to issue and publication fee payments should be directed to the Application Assistance Unit (AAU) of the Office of Patents Stakeholder Experience (OPSE), Stakeholder Support Division (SSD) at (571)-272-4200.

INVENTOR(s) (Please see PATENT CENTER site https://patentcenter.uspto.gov for additional inventors):

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APPLICANT(s) (Please see PATENT CENTER site https://patentcenter.uspto.gov for additional applicants):

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