

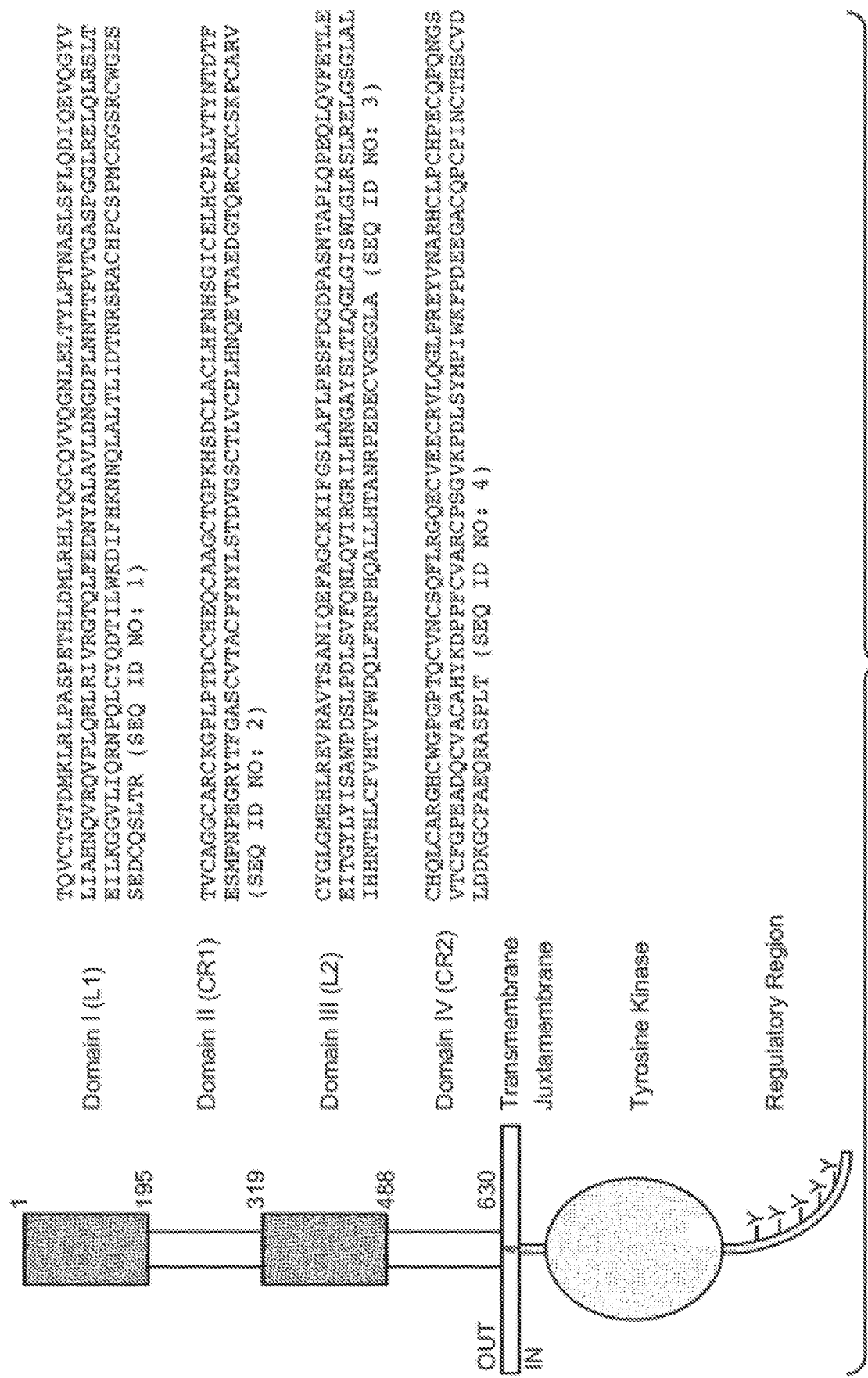


FIG. 1

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Variable Light

	10	20	30	40
2C4	DTVMTQSHKIMSTSVGDRVSITC	[KASQDVSIGVA]	WYQQRP	
	** ***** *	*		*
574	DIQMTQSPSSLSASVGDRVTITC	[KASQDVSIGVA]	WYQQKP	
		* ** ***		
hum κI	DIQMTQSPSSLSASVGDRVTITC	[RASQSIENYLA]	WYQQKP	

	50	60	0	80
2C4	GQSPKLLIY [SASYRYT]	GVPDRFTGSGSGTDFTFTISSVQA		
	** *	* *	*	**
574	GKAPKLLIY [SASYRYT]	GVPSRFTGSGSGTDFTLTISLQP		
	* *****			
hum κI	GKAPKLLIY [AASSLES]	GVPSRFTGSGSGTDFTLTISLQP		

	90	100	
2C4	EDLAVYYC [QYYIYPYT]	FGGGTKLEIK (SEQ ID NO:5)	
	* *	* *	
574	EDFATYYC [QYYIYPYT]	FGQGTKVEIK (SEQ ID NO:7)	
	*** *		
hum κI	EDFATYYC [QYNSLPWT]	FGQGTKVEIK (SEQ ID NO:9)	

FIG. 2A**Variable Heavy**

	10	20	30	40
2C4	EVQLQQSGPELVKPGTSTKISKAS	[GFTFTDYTMD]	WVKQS	
	** ** *	* *** *		**
574	EVQLVESGGGLVQPGGSLRLSAAAS	[GFTFTDYTMD]	WVRQA	
		** ** *		
hum III	EVQLVESGGGLVQPGGSLRLSAAAS	[GFTFSSYAMS]	WVRQA	

	50	a	60	70	80
2C4	HGKSLEWIG [DVNPNSGGSIYNQRFKG]	KASLTVDRSSRIVYM			
	* * **		*** *	***** *	
574	PGKGLEWVA [DVNPNSGGSIYNQRFKG]	RFTLSVDRSKNTLYL			
	***** ** *		* * *		
hum III	PGKGLEWVA [VISGDGGSTYYADSVKG]	RFTISRDNKNTLYL			

	abc	90	100ab	110
2C4	ELRSLTFEDTAVYYCAR [NLGPSFYFDY]	WGQGTTLTVSS (SEQ ID NO:6)		
	*** **		**	
574	QMNSLRAEDTAVYYCAR [NLGPSFYFDY]	WGQGTTLTVSS (SEQ ID NO:8)		

hum III	QMNSLRAEDTAVYYCAR [GRVGYSLYDY]	WGQGTTLTVSS (SEQ ID NO:10)		

FIG. 2B

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Amino Acid Sequence for Pertuzumab Light Chain

```

1      10      20      30      40      50      60
DIQMTQSPSSLSASVGDRVTITCKASQDVSIGVAWYQQKPGKAPKLLIYSASYRYTGVP
70      80      90      100     110     120
RFSGSGSGTDFTLTISSLPEDFATYYCQQYYIYPYTFGQGTKVEIKRTVAAPSVFIFPP
130     140     150     160     170     180
SDEQLKSGTASVVCLLNMFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSSTYSLSSTLT
190     200     210
LSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC (SEQ ID NO: 11)

```

FIG. 3A**Amino Acid Sequence for Pertuzumab Heavy Chain**

```

1      10      20      30      40      50      60
EVQLVESGGGLVQPGGSLRLSCAASGFTFTDYMWDVVRQAPGKGLEWVADVNPNSGGSIY
70      80      90      100     110     120
NQRFKGRFTLSVDRSKNTLYLQMNSLRAEDTAVYYCARNLGPSFYFDYWGGTLTVSSA
130     140     150     160     170     180
STKGPSVFPPLAPSSKSTSGGTAALGCLVKDYFPEPTVSWNSGALTSGVHTFPAVLQSSG
190     200     210     220     230     240
LYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGP
250     260     270     280     290     300
SVFLFPPKPKDITLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNS
310     320     330     340     350     360
TYRVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEM
370     380     390     400     410     420
TKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVLDSDGSFFLYSKLTVDKSRWQ
430     440     448
QGNVFSCSVMHEALHNHYTQKSLSLSPG (SEQ ID NO: 12)

```

FIG. 3B

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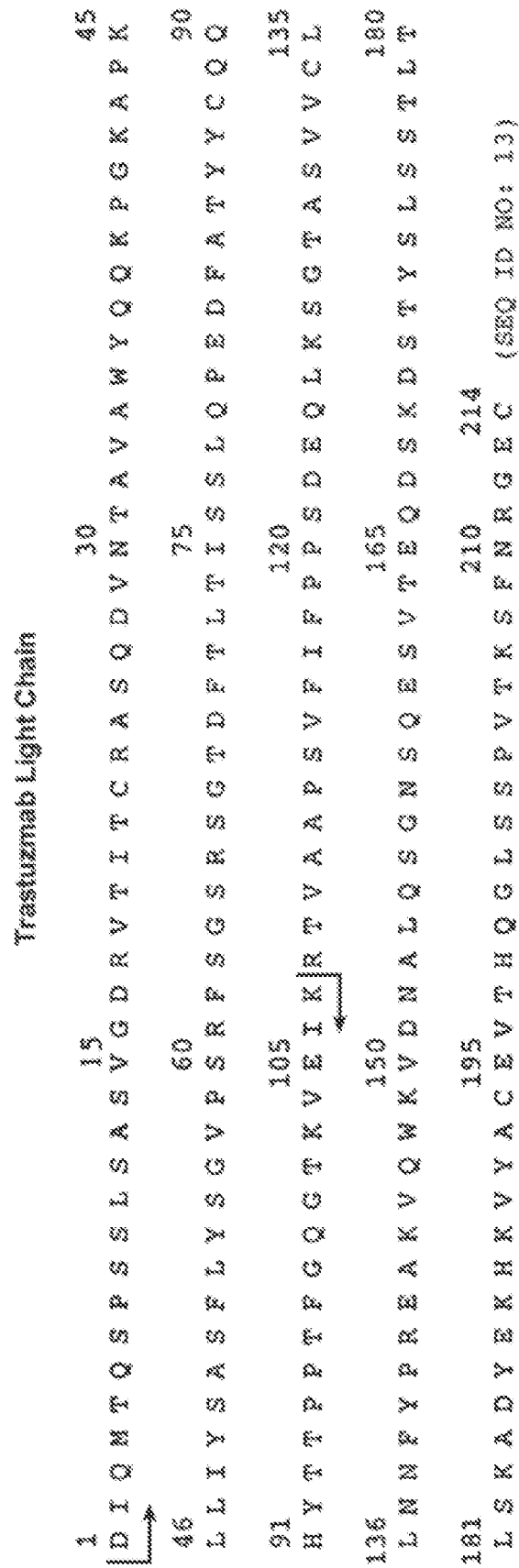


FIG. 4A

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Trastuzumab Heavy Chain

1 EVQLVESGGGLVQPFGSLRLSCAASGFTNISKDTYIHWVVRQAPGKGL 45
46 EWVARIRYPTNGYTRYADSVKGRFTISADTSKNTAYLQMNSLR AED 90
91 TAVYYCSRWGCGDGFYAMDYWGQGTLLVTVSSASTKGPSTVPPLAPSS 135
136 KSTSGGTAAAGCLVKDYFPPEPTVSWNSGALTSGVHTFPAVLQSS 180
181 GLYSSLSSVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDK 225
226 THTCPPCPAPELLGQPSVFLFPKPKD TLMISRTP E V T C V V D V S 270
271 HEDPEVKFNWYVDGVEVHNAAKTKPREEQYNSTYRVVSVLTVLHQD 315
316 WLNQKEYKCKVSNKALPAPIEK TISKAKGQPREPQVYTLPPSREE 360
361 MTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPPVLDSDG 405
406 SFFLYSKLTVDKSRWQQGNVFPSCSVMH EALHNH Y T Q K S L S L S P G 449

(SEQ ID NO: 14)

FIG. 4B

Pertuzumab Variant Light Chain

1 V H S D I Q M T Q S P S L S A S V G D R V T I T C K A S Q D V S I G V A W Y Q Q K P G K 45
46 A P K L L I Y S A S Y R Y T G V P S R F S G S G S G T D F T L T I S S L Q P P E D F A T Y Y 90
91 C Q Q Y Y I Y P Y T F G Q Q T K K V E I K R T V A A P S V F I F P P S D E Q L K S G T A S V 135
136 V C L L N N F Y P R E A K V Q W K V D N A L Q S G N S Q E S V T E E Q D S K D S T Y S L S S 180
181 T L T L S K A D Y E K H K V Y A C E V T H Q G L S S P V T K S F N R G E C 217 (SEQ ID NO: 15)

FIG. 5A

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Pertuzumab Variant Heavy Chain

```

1   EVQLVESGGGLVQPFGGSLRLSCAASGFTFTDYTMDWVRQAPGKGL      45
46  EWVADVNPNNSGGSIYNNQRFKGRFTLSVDKRSKNTLYLQMNSLR AED      90
91  TAVYYCARNLLGPSSFYFDYWGQGTLLVTVSSASTKGPSTVFPPLAPSSK      135
136 STSGGTAAALGCLVKDYFPPEPVTVSWNSSGALTSSGVHTFP AVLQSSG      180
181 LYSLSVVTVPSSSLGTQTYYICNVNHHKPSNTKV DKKVEPKSCDKT      225
226 HTCPPCPAPELLGGPSSVFLFPPKPKDTLMISRTPEVTCVVVDVSH      270
271 EDPEVKFNWYVDGVEVHNAAKTKKPREEQYNSTYRVVSVLTVLHQDW      315
316 LNKGEYKCKVSNKALPAPIEKTIISKAKGQPREPQVYTLPPSR EEM      360
361 TKNQVSLTCLVKGFYPSDIAVEWESNGQPENNNYKTTTPPV LDDSGS      405
406 FFLLYSKLTVDKSRWQQQGNVVFSSCSVMHHEALHNHHTYTKKSLSLSPGK      449

```

(SEQ ID NO: 16)

FIG. 5B

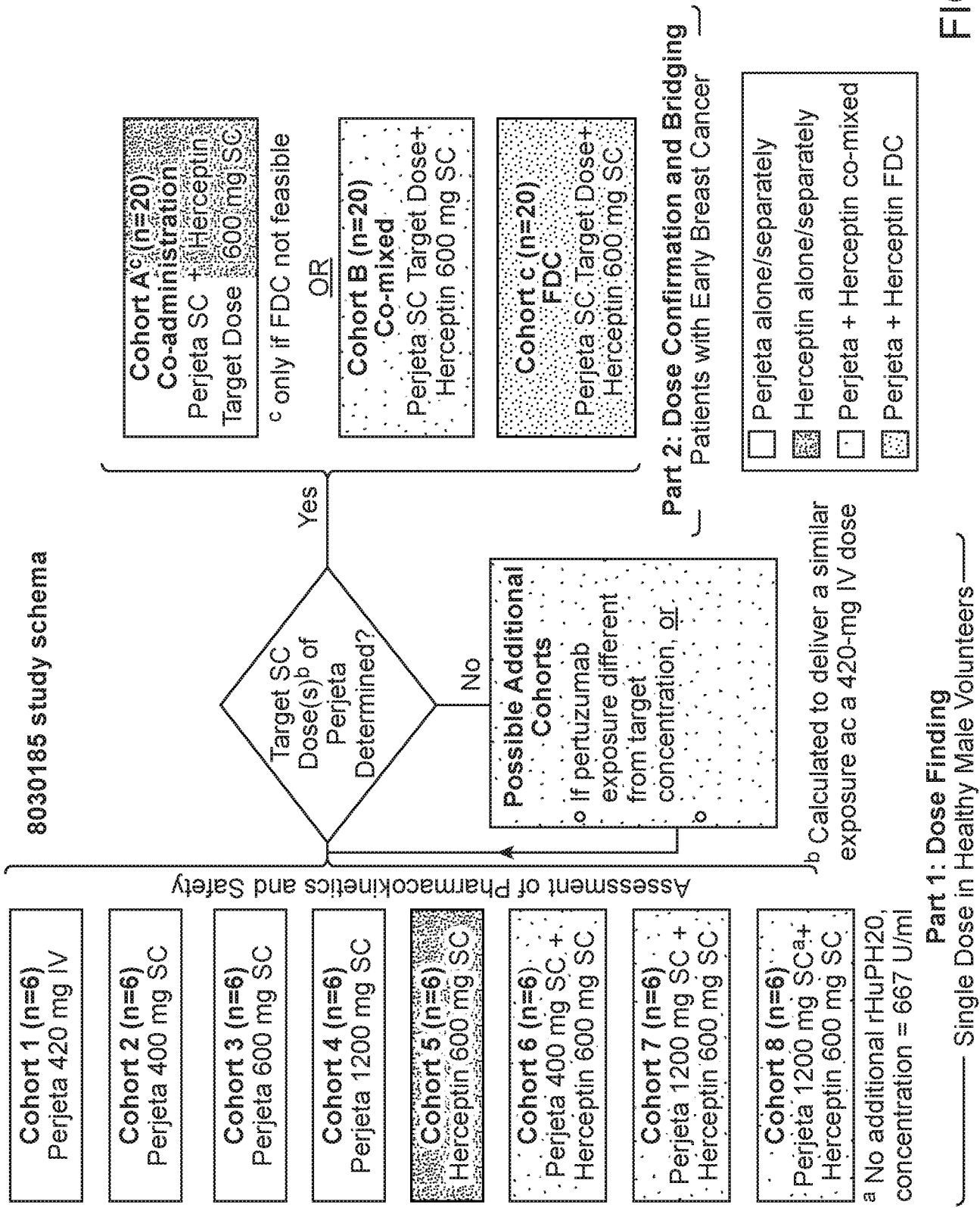


FIG. 6

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Decision Diagram

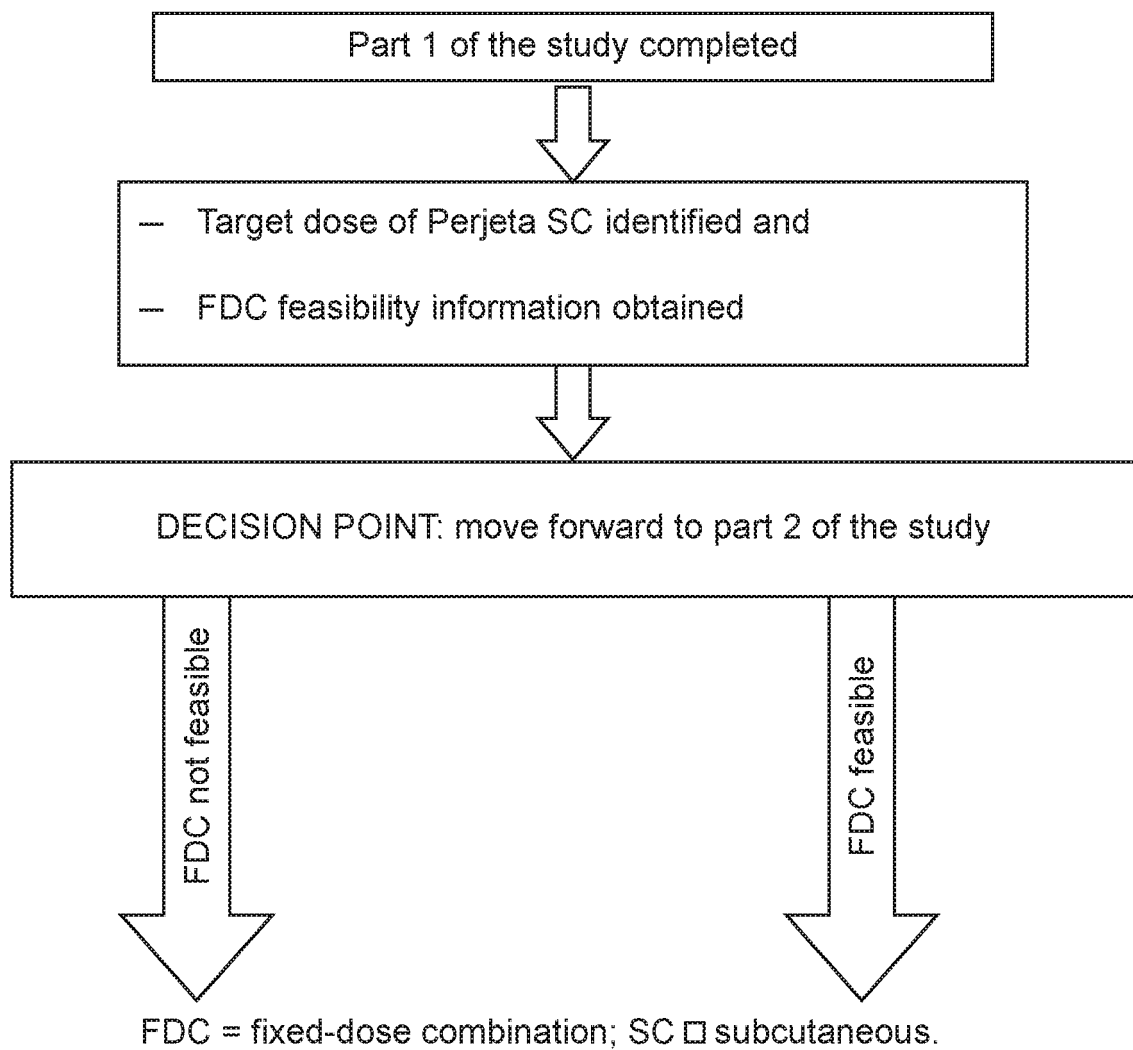


FIG. 7

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8030185 Study Overview

Cohort	Population	N	Agent	Dose (mg) Single Injection	Volume of Injection (mL)	Concentration of Halozyme (U/mL)#	Amount of Halozyme (Units)
Dose Finding							
1 (control)	HMV	6	Piv	420		NA	NA
2	HMV	6	Psc	400	3.3	2,000 U/mL	6,600 U
3	HMV	6	Psc	600	5	2,000 U/mL	10,000 U
4	HMV	6	Psc loading	1200	10	2,000 U/mL	20,000 U
5 (control)	HMV	6	Hsc	600	5	2,000 U/mL	10,000 U
6	HMV	6	Psc + Hsc (co-mix)	400 + 600	8.3	2,000 U/mL	16,600 U
7	HMV	6	Psc + Hsc (co-mix)	1200 + 600	15	2,000 U/mL	30,000 U
8 (Halozyme from Herceptin only)	HMV	6	Psc + Hsc (co-mix)	1200 + 600	15	667 U/mL	10,000 U
Dose Confirmation							
9*	EBC	20	Psc + Hsc (co-mix)	TBD + 600			
10^	EBC	20	Psc + Hsc (FDC)	TBD + 600			

Part 1

Part 2

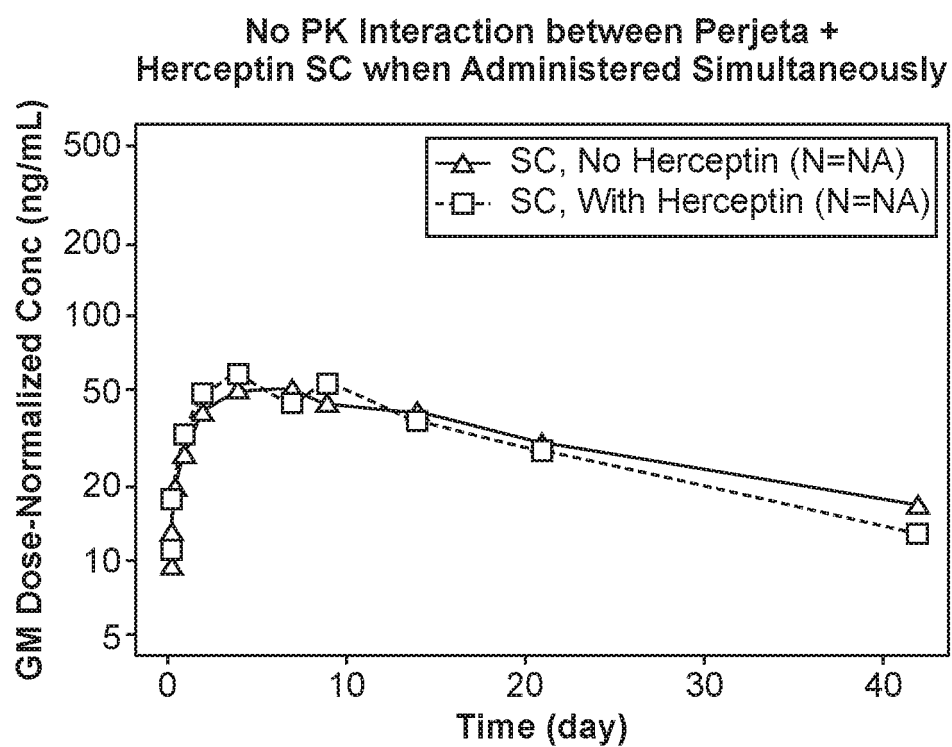
#MabThera and Herceptin SC use 2,000 U/mL

*Enrollment planned January 2017

^Enrollment planned October 2017

FIG. 8

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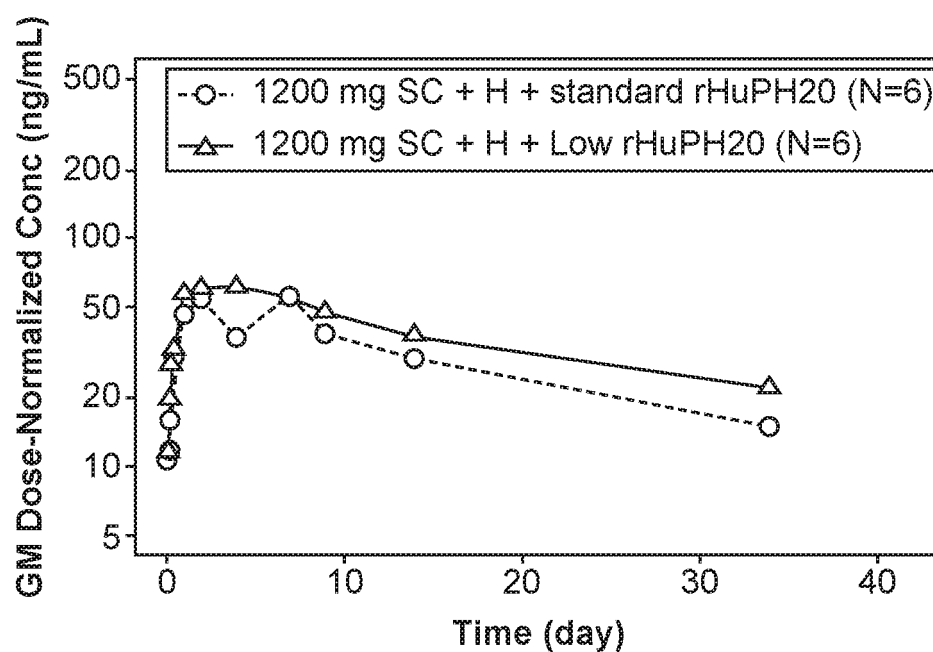
No PK interactions between Perjeta SC and Herceptin SC.
No differences in Herceptin PK as monotherapy, with Perjeta
SC or with different rHuPH20 concentrations.

FIG. 9

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No Impact of Lower rHuPH20 Concentration/
Amount on Perjeta PK

Pertuzumab Concentrations with standard (2,000 U/mL) and low
(667 U/mL) rHuPH20



No significant differences in Perjeta PK or Herceptin PK (not shown) when administered with standard (2,000 U/mL) or low (667 U/mL) rHuPH20.

FIG. 10

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Parameter Estimations – Historical IV and
BO30185 SC Data vs. BO30185 IV and BO30185 SC Data

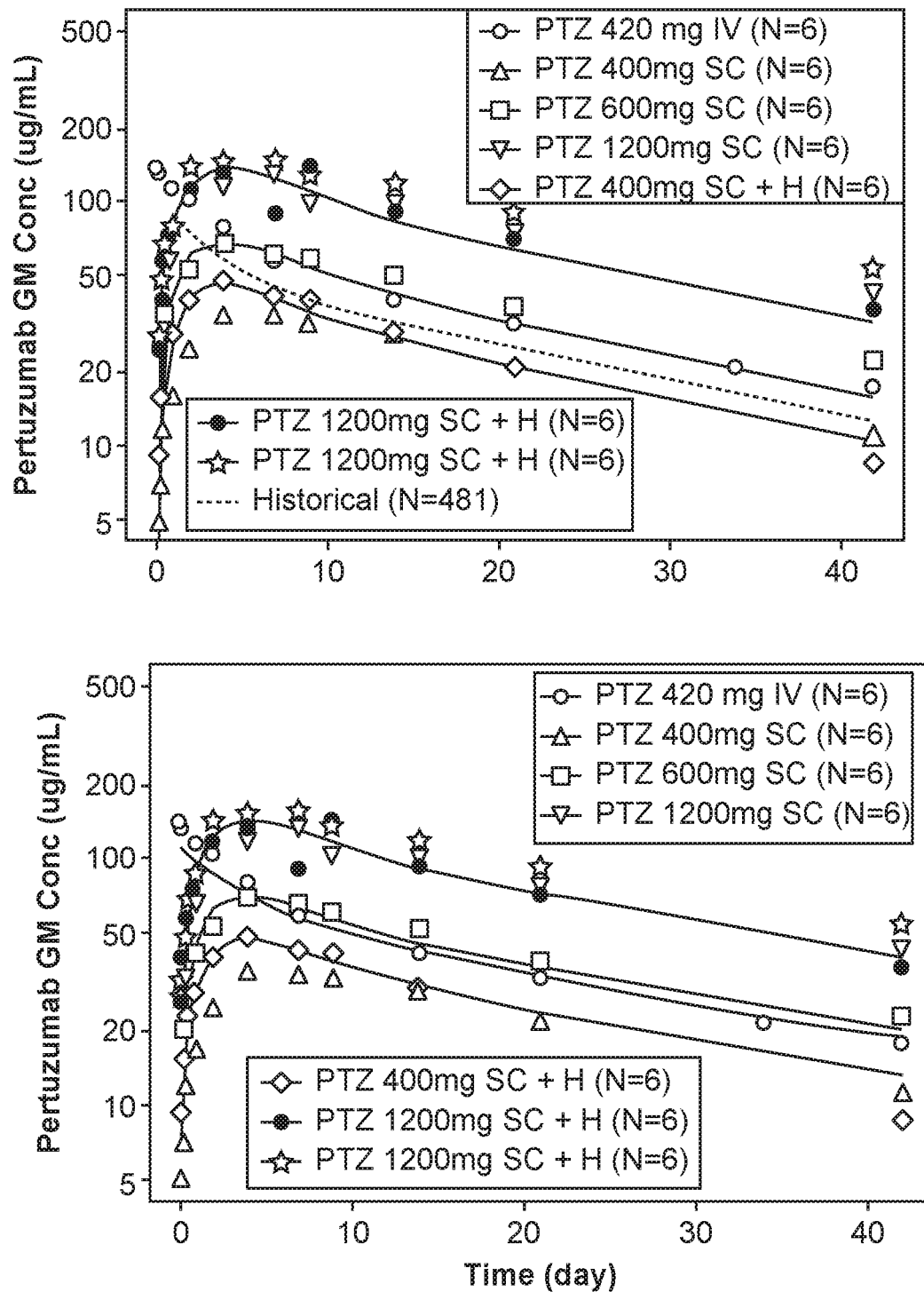


FIG. 11

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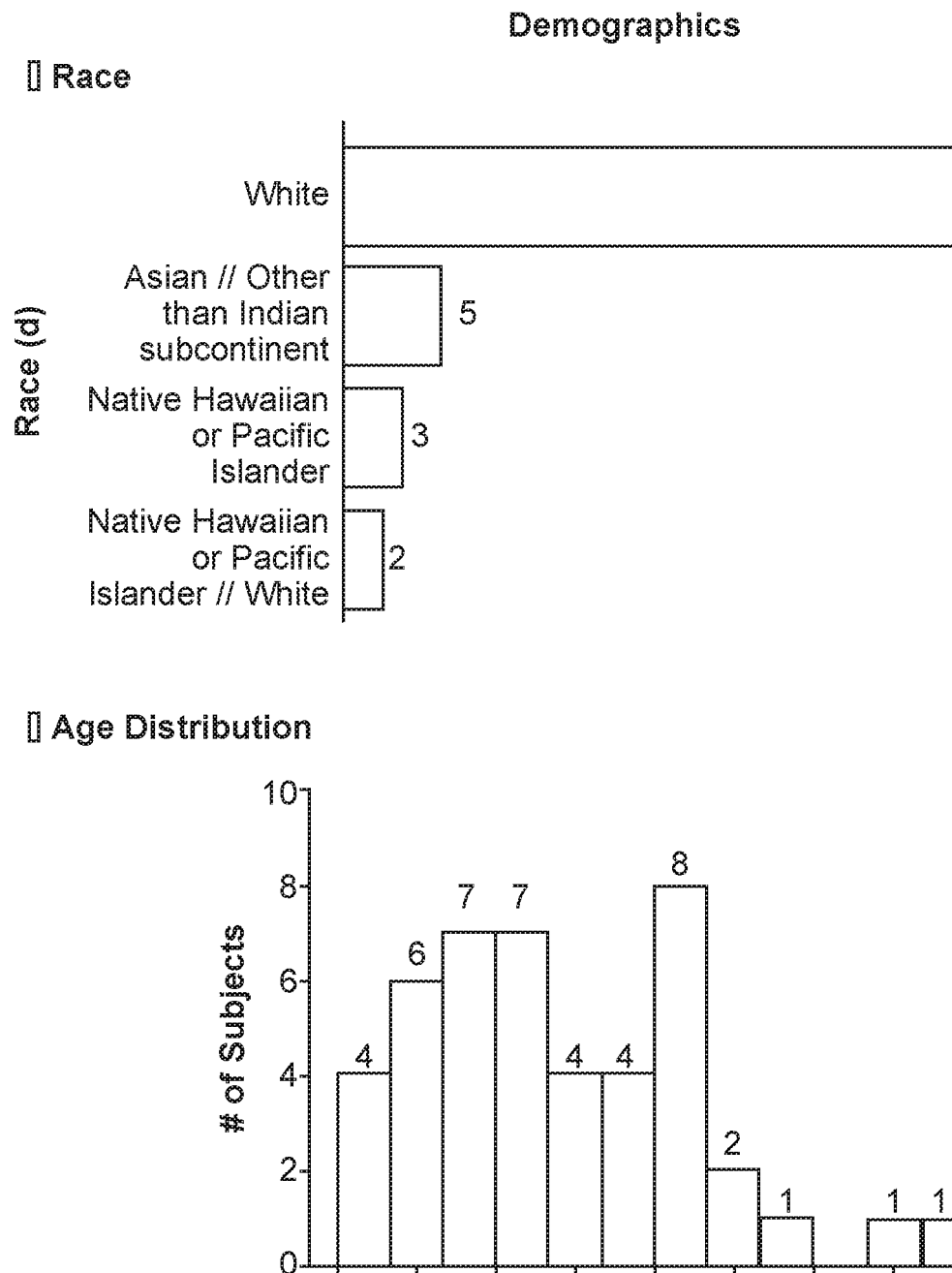


FIG. 12

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Overview of Adverse Events in Part 1

Extreme Grade	Cohort 1 (P IV 420mg) N = 6	Cohort 5 (H 600mg) N = 6	Cohort 2 (P 400mg) N = 6	Cohort 3 (P 600mg) N = 6	Cohort 4 (P 1200 mg) N = 6	Cohort 6 (P 400mg+ H 600mg) N = 6	Cohort 7 (P 1200mg+ H 600mg) N = 6	Cohort 8 (P 1200mg* + H 600mg) N = 6
Total AEs n = 145 (%)	15 (10)	10 (7)	10 (7)	22 (15)	24 (17)	33 (23)	18 (13)	13 (9)
Grade 1	9 (6)	9 (6)	6 (4)	19 (13)	17 (12)	21 (15)	9 (6)	8 (6)
Grade 2	2 (1)	1 (1)	4 (3)	1 (1)	2 (1)	6 (4)	4 (3)	2 (1)
Grade >=3	1 (1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)

- One Grade 3 AE of diarrhoea , onset Day 32: unrelated, concurrent illness.
 - Possible viral infection as concurrent URTI
- No SAE, AESI, AE leading to discontinuation, AE leading to death
- Some AEs ongoing so no final Extreme Grade

*No additional rHuPH20

FIG. 13

Overview of Adverse Events in Part 1
No. of subjects

No. of subjects with AE	Cohort 1 (P IV 420mg) N = 6	Cohort 5 (H 600mg) N = 6	Cohort 2 (P400mg) N = 6	Cohort 3 (P 600mg) N = 6	Cohort 4 (P 1200 mg) N = 6	Cohort 6 (P 400 mg+ H 600mg) N = 6	Cohort 7 (P 1200 mg+ H 600mg) N = 6	Cohort 8 (P 1200 mg*+ H 600mg) N = 6
Any AE, n (%)	5 (83)	5 (83)	5 (83)	6 (100)	5 (83)	6 (100)	6 (100)	6 (100)
Grade 1	4 (67)	5 (83)	4 (67)	6 (100)	5 (83)	6 (100)	6 (100)	5 (83)
Grade 2	2 (33)	1 (17)	3 (50)	1 (17)	2 (33)	5 (83)	2 (33)	2 (33)
Grade >= 3	1 (17)	0	0	0	0	0	0	0

*No additional rHuPH20

FIG. 14

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Most Common Adverse Events (all grades) – incidence $\geq 5\%$ overall in study No. of subjects

Adverse event preferred term	Cohort 1 (P IV 420mg) N = 6	Cohort 5 (H 600mg) N = 6	Cohort 2 (P 400mg) N = 6	Cohort 3 (P 600mg) N = 6	Cohort 4 (P 1200mg) N = 6	Cohort 6 (P 400 mg+ H 600mg) N = 6	Cohort 7 (P 1200 mg+ H 600mg) N = 6	Cohort 8 (P 1200 mg+ H 600mg) N = 6
UPPER RESPIRATORY TRACT INFECTION	2 (33)	0	0	2 (33)	2 (33)	3 (50)	2 (33)	2 (33)
DIARRHOEA	3 (50)	0	1 (17)	2 (33)	1 (17)	1 (17)	1 (17)	0
HEADACHE	1 (17)	1 (17)	0	1 (17)	2 (33)	0	4 (67)	0
DRUG ERUPTION	1 (17)	0	0	0	1 (17)	2 (33)	3 (50)	2 (33)
ANGULAR CHEILITIS	2 (33)	0	0	1 (17)	0	3 (50)	0	1 (17)
PAIN IN EXTREMITY	0	2 (33)	0	1 (17)	2 (33)	1 (17)	0	0
EPISTAXIS	1 (17)	0	0	0	1 (17)	3 (50)	0	0
RASH	0	1 (17)	1 (17)	2 (33)	1 (17)	0	0	0
ABDOMINAL PAIN	0	0	2 (33)	0	0	1 (17)	1 (17)	0
DRY SKIN	0	0	0	1 (17)	1 (17)	2 (33)	0	0
INJECTION RELATED REACTION	0	1 (17)	0	0	0	2 (33)	0	1 (17)
NASAL CONGESTION	0	1 (17)	1 (17)	1 (17)	0	0	0	1 (17)
OROPHARYNGEAL PAIN	1 (17)	0	0	0	2 (33)	0	0	1 (17)
ECZEMA	0	1 (17)	0	0	1 (17)	1 (17)	0	0
FOLLICULITIS	0	0	0	1 (17)	1 (17)	0	0	0

FIG. 15

EGFR Related Toxicity

AEGT basket term/ No. of subjects (%)	Cohort 1 (P IV 420mg) N = 6	Cohort 5 (H 600mg) N = 6	Cohort 2 (P 400mg) N = 6	Cohort 3 (P 600mg) N = 6	Cohort 4 (P 1200mg) N = 6	Cohort 6 (P 400 mg+ H 600mg) N = 6	Cohort 7 (P 1200 mg+ H 600mg) N = 6	Cohort 8 (P 1200 mg*+ H 600mg) N = 6
Diarrhoea	3 (50)	0	1 (17)	2 (33)	2 (33)	2 (33)	1 (17)	0
Mucositis	2 (33)	0	2 (33)	1 (17)	0	4 (67)	0	1 (17)
EGFR Rash	1 (17)	2 (33)	1 (17)	3 (50)	3 (50)	3 (50)	4 (67)	2 (33)

Diarrhoea [PT: Diarrhoea (9), Frequent Bowel Movements (2)]
Onset range: Day 2- 36 with most in first 10 days after drug

Mucositis [PT: Angular Cheilitis (7), Mouth Ulceration (2), Aphthous Ulcer (2) and Gastroenteritis (1)]
Onset range: Day 8- 38, majority occurring between 13 - 29

EGFR Associated Rash [PT: Drug Eruption (9), Rash (5), Eczema (3), Folliculitis (2), Acne (1) and Dermatitis Acneform (1)]

Onset range: Day 4 - 54, no pattern

*No additional rHuPH20

FIG. 16

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Injection Related Reactions and Injection Site Reactions

No. of subjects (%)	Cohort 1 (P IV 420mg) N=6	Cohort 5 (H 600mg) N=6	Cohort 2 (P 400mg) N=6	Cohort 3 (P 600mg) N=6	Cohort 4 (P 1200mg) N=6	Cohort 6 (P 400mg+ H 600mg) N=6	Cohort 7 (P 1200mg+ H 600mg) N=6	Cohort 8 (P 1200mg*+ H 600mg) N=6
Infusion Related Reaction (Systemic)	0							
Injection Related Reaction (Systemic)	1 (17)	0	0	0	0	2 (33)	0	1 (17)
Injection Site Reaction (Local)	0	0	0	0	0	0	1 (17)	0

Injection Site Reaction (Local): any morphological or physiological change at or near the injection site

- 1 Injection Site Reaction in Cohort 7
- 1200mg P SC + 600mg H SC with rHuPH20
- Symptoms were discomfort, pain, tightness and numbness at injection site

Injection Related Reactions (Systemic)

- Symptoms included fever, chills, nausea, stiffness, lightheadedness, skin sensitivity, photophobia, temperature fluctuation, headache

*No additional rHuPH20

FIG. 17

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LVEF – ECHO Assessments

No. of subjects (%)	Cohort 1 (P IV) N=6	Cohort 5 (H SC) N=6	Cohort 2, 3, 4 (P SC) N=18	Cohort 6, 7, 8 (P+H SC) N=18
LVEF measurement (%) - Baseline	6 (100)	6 (100)	18 (100)	18 (100)
Absolute value <50% and decrease from baseline $\geq$ 10%	0	0	0	0
Absolute value <50% <u>OR</u> decrease from baseline $\geq$ 10% points	0	0	1*	0

* Cohort 3 (600mg P SC):

- o One HMV had a drop of > 10% from 67% at Baseline to 56% at Day 22
- o Follow up EF at Day 85 = 60 %
- o Cardiologist confirmed no evidence of cardiotoxicity
- o Drop due to variability of imaging method

FIG. 18

Drug Substance to support FDCs

Trastuzumab (Herceptin SC DS)

- Trastuzumab: 120 mg/ml
- pH 5.5
- 20 mM His-HCl
- 210 mM trehalose
- 0.04% PS20
- 10 mM methionine

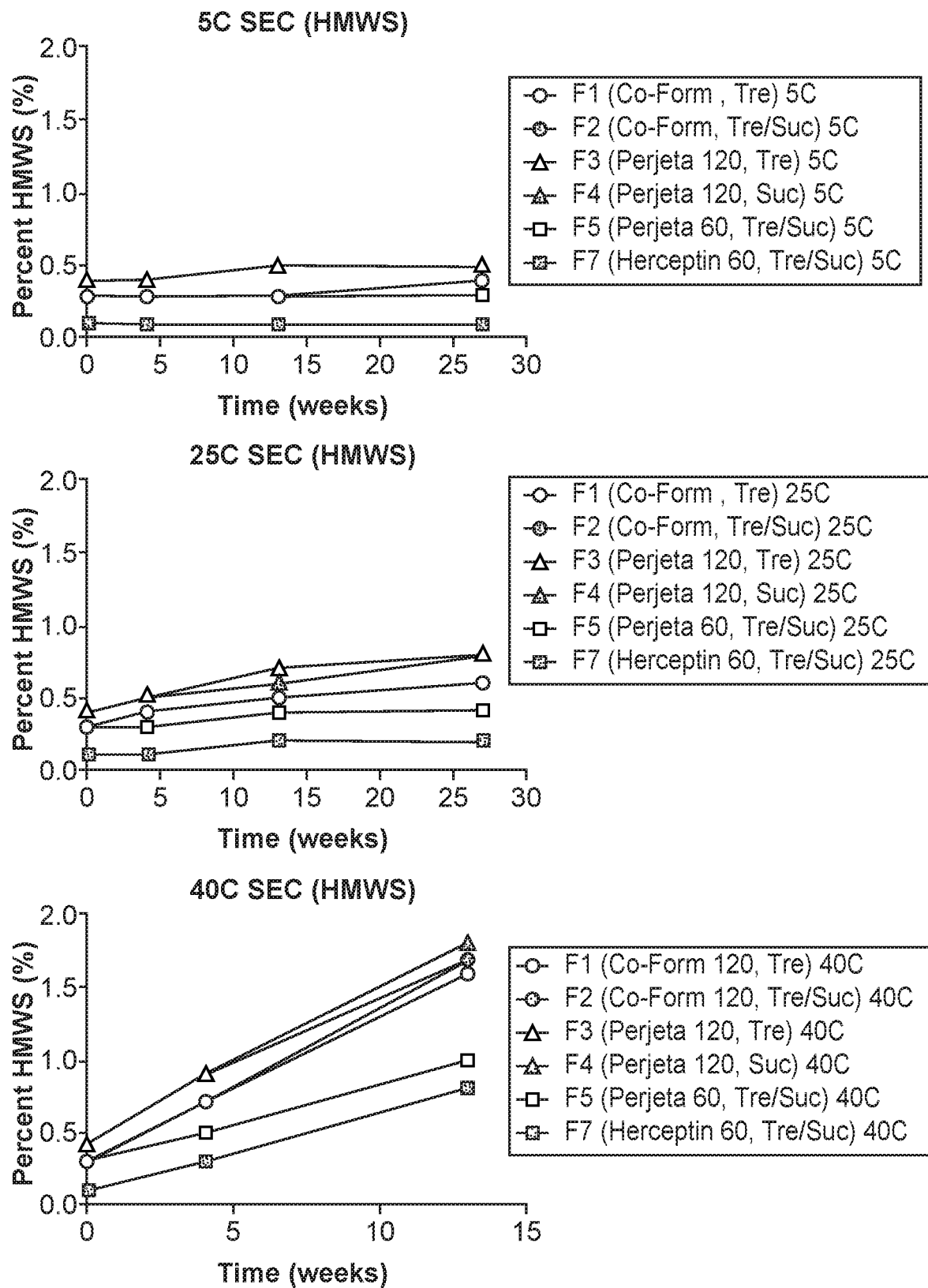
Pertuzumab SC DS

- Pertuzumab: 120 mg/ml
- pH 5.5
- 20 mM His-HCl
- 200 mM sucrose
- 0.04% PS20
- 10 mM methionine

rHuPH20

10 mg/mL rhuPH20 in His-HCl buffer pH 6.5, 130 mM NaCl, 0.05% (w/v) Polysorbate 80
Diluted ~ 435X in DP (negligible)

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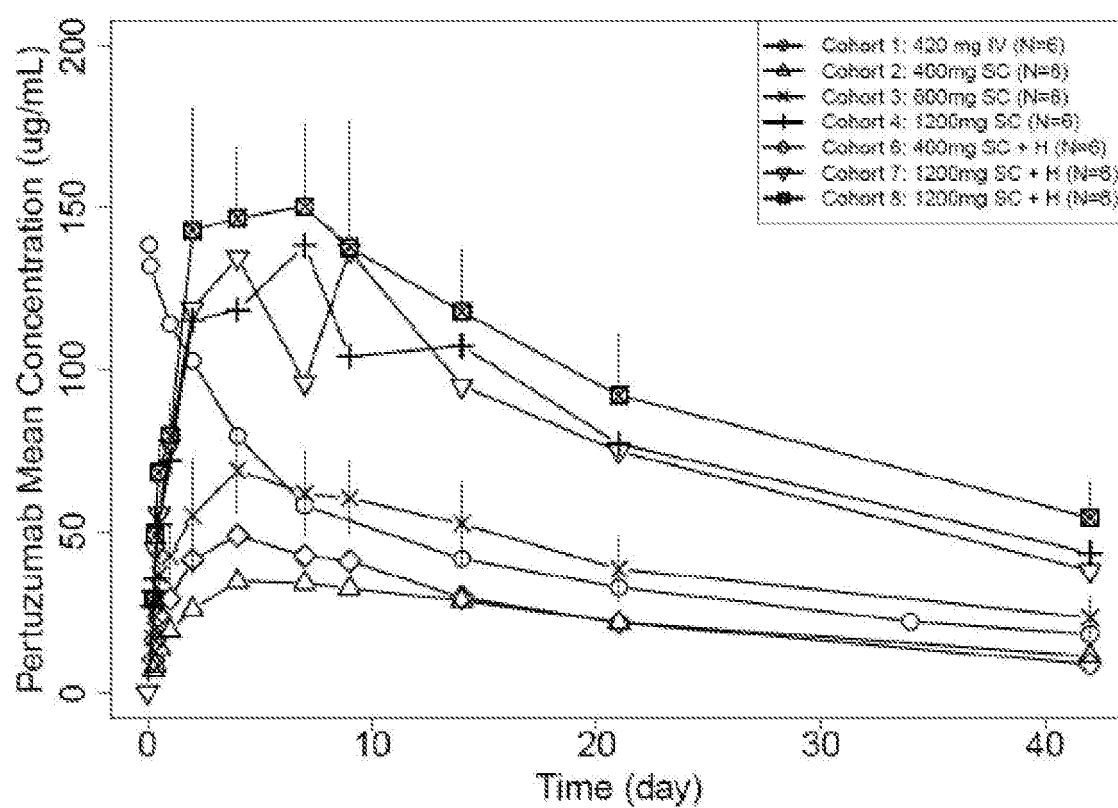
Note: Higher HMWS for higher total mAb concentration

FIG. 20

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FIG. 21

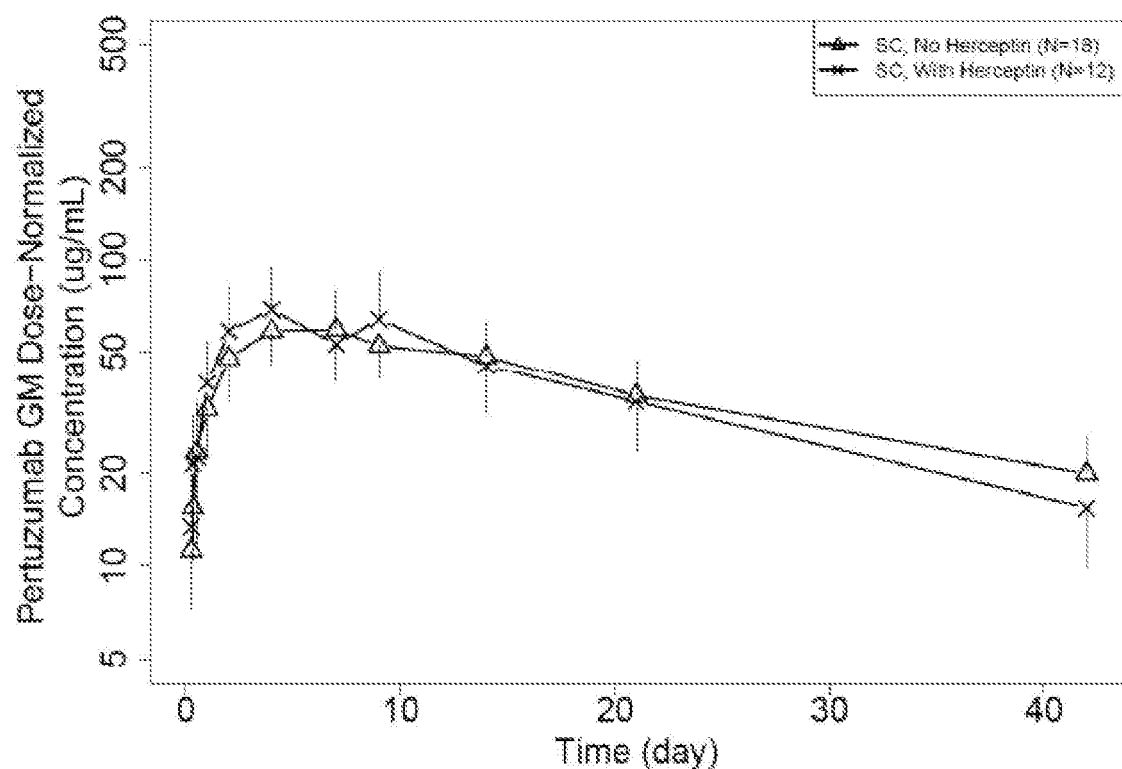
Mean Serum Pertuzumab Concentration-Time Profile by Cohort (HMV)



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FIG. 22

**Geometric Mean Dose-Normalized Serum Pertuzumab
Concentration-Time Profile, With and Without Concomitant
Herceptin**



GM = geometric mean; SC = subcutaneous.

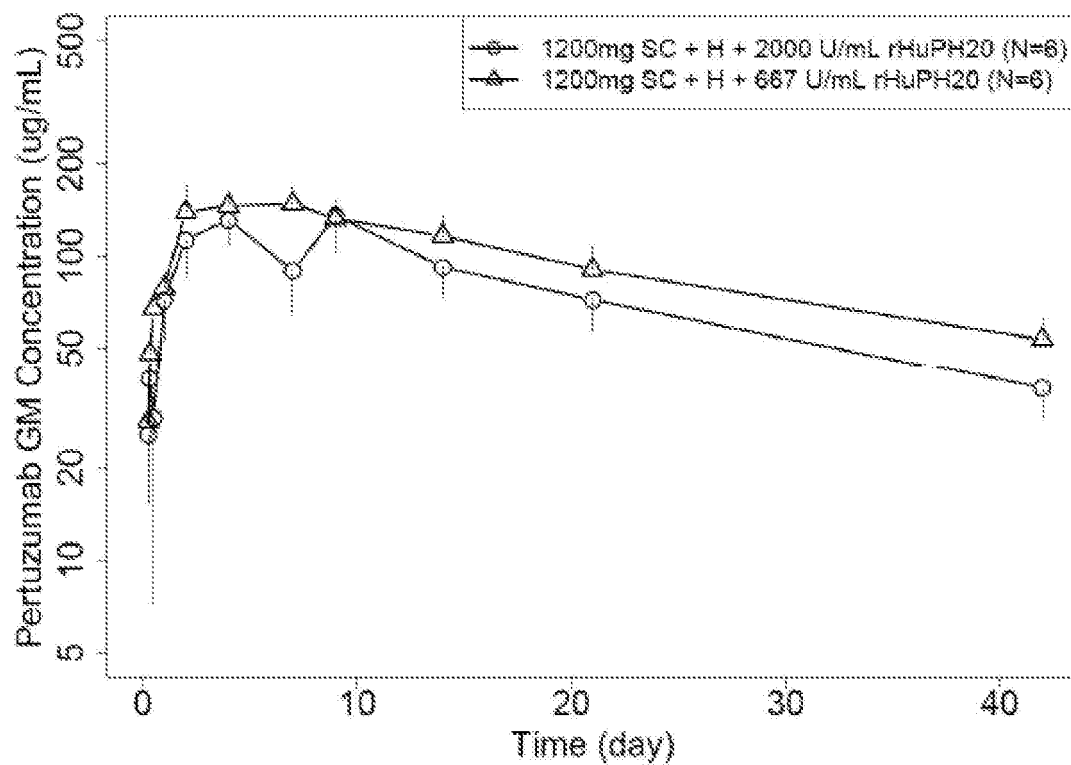
All pertuzumab concentration values normalized to a dose of 600 mg.

Vertical bars, when shown, represent 2.5 or 97.5 percentile confidence intervals on geometric mean.

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FIG. 23

**Geometric Mean Serum Pertuzumab Concentration-Time Profile,
With 667 U/mL or 2,000 U/mL rHuPH20 (HMV)**



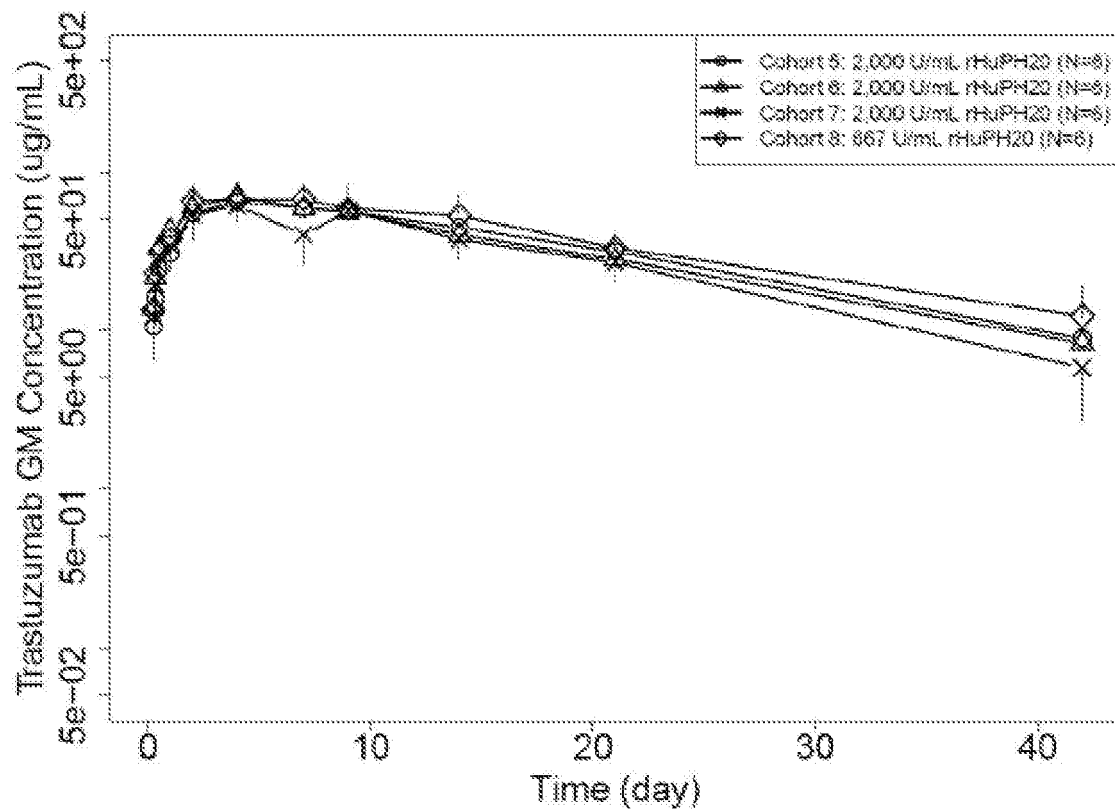
GM = geometric mean; H = Herceptin; SC = subcutaneous.

Vertical bars, when shown, represent 2.5 or 97.5 percentile confidence intervals on geometric mean.

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FIG. 24

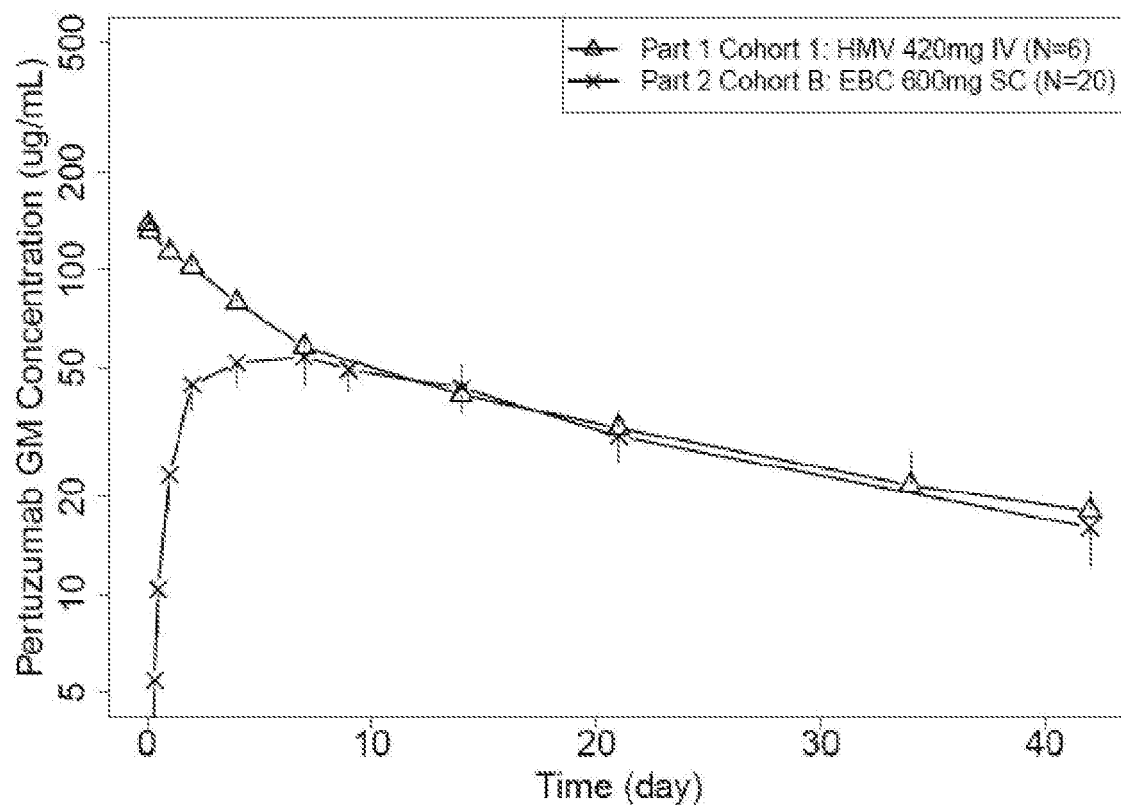
**Geometric Mean Serum Trastuzumab Concentration-Time Profile,
With 667 U/mL or 2,000 U/mL rHuPH20 (HNV)**



GM = geometric mean.

Vertical bars, when shown, represent 2.5 or 97.5 percentile confidence intervals on geometric mean.

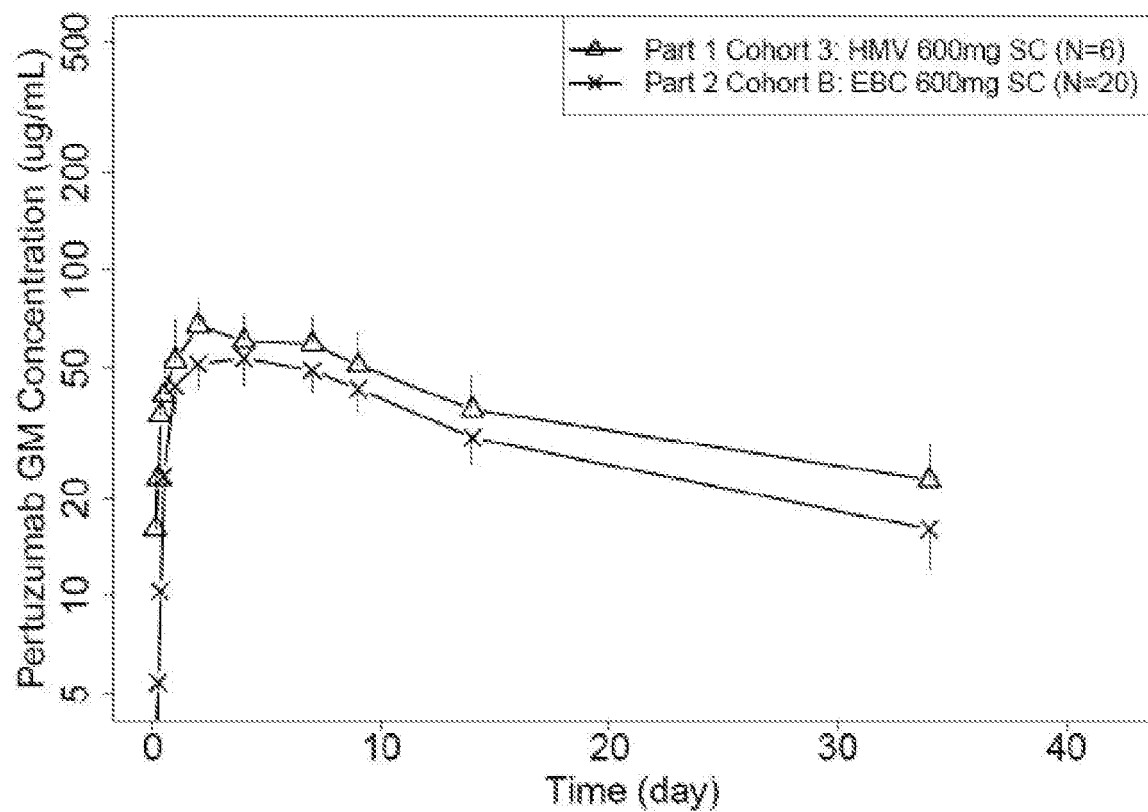
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FIG. 25**Geometric Mean Serum Pertuzumab Concentration-Time Profile following Perjeta 600 mg SC and Perjeta 420 mg IV Doses**

EBC = early breast cancer; GM = geometric mean; HMV = healthy male volunteer; IV = intravenous SC = subcutaneous.

Vertical bars, when shown, represent 2.5 or 97.5 percentile confidence intervals on geometric mean.

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FIG. 26**Geometric Mean Serum Pertuzumab Concentration-Time Profile
in HMV or EBC Patients**

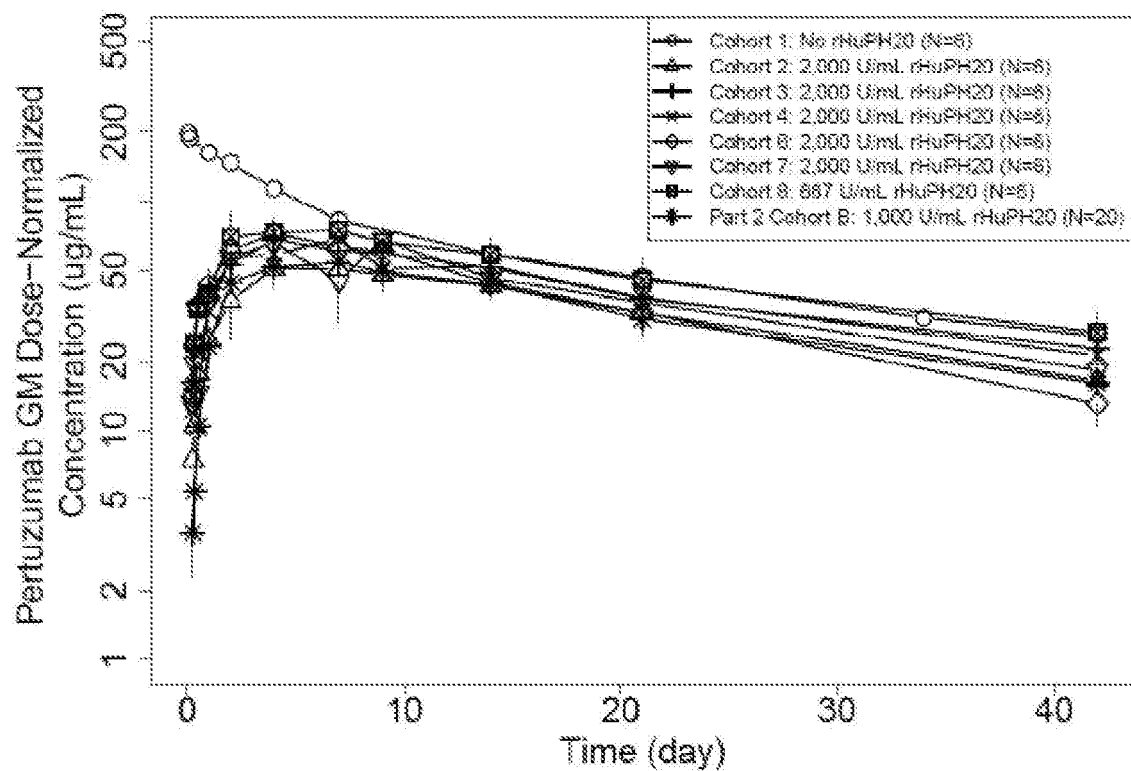
EBC = early breast cancer; GM = geometric mean; HMV = healthy male volunteer;
SC = subcutaneous.

Vertical bars, when shown, represent 2.5 or 97.5 percentile confidence intervals on geometric mean.

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FIG. 27

**Geometric Mean Dose-Normalized Serum Pertuzumab
Concentration-Time Profile, With 667 U/mL, 1,000 U/mL or
2,000 U/mL rHuPH20**



GM = geometric mean.

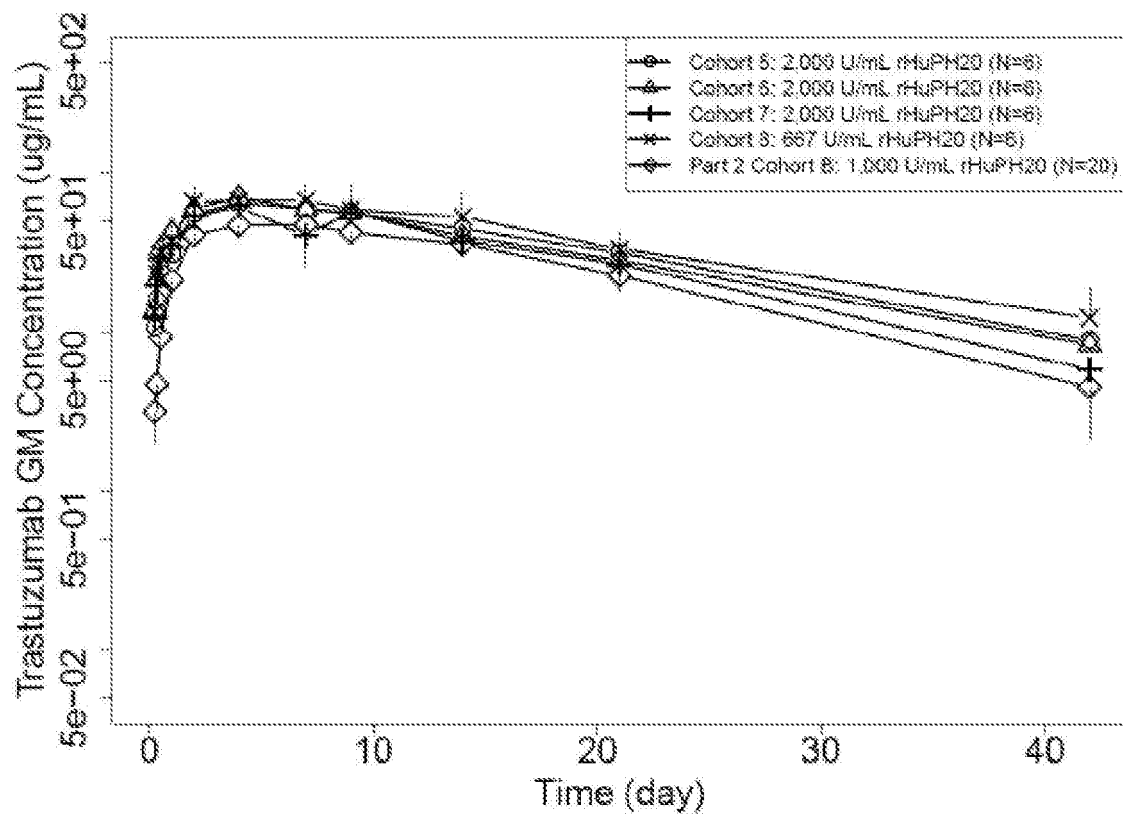
All pertuzumab concentration values normalized to a dose of 600 mg.

Vertical bars, when shown, represent 2.5 or 97.5 percentile confidence intervals on geometric mean.

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FIG. 28

**Geometric Mean Serum Trastuzumab Concentration-Time Profile,
With 667 U/mL, 1,000 U/mL, or 2,000 U/mL rHuPH20**



GM = geometric mean.

Vertical bars, when shown, represent 2.5 or 97.5 percentile confidence intervals on geometric mean.

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52 weeks SEC overlay of S&S test samples
stored at -20°C: trehalose (F3) vs sucrose (F4)

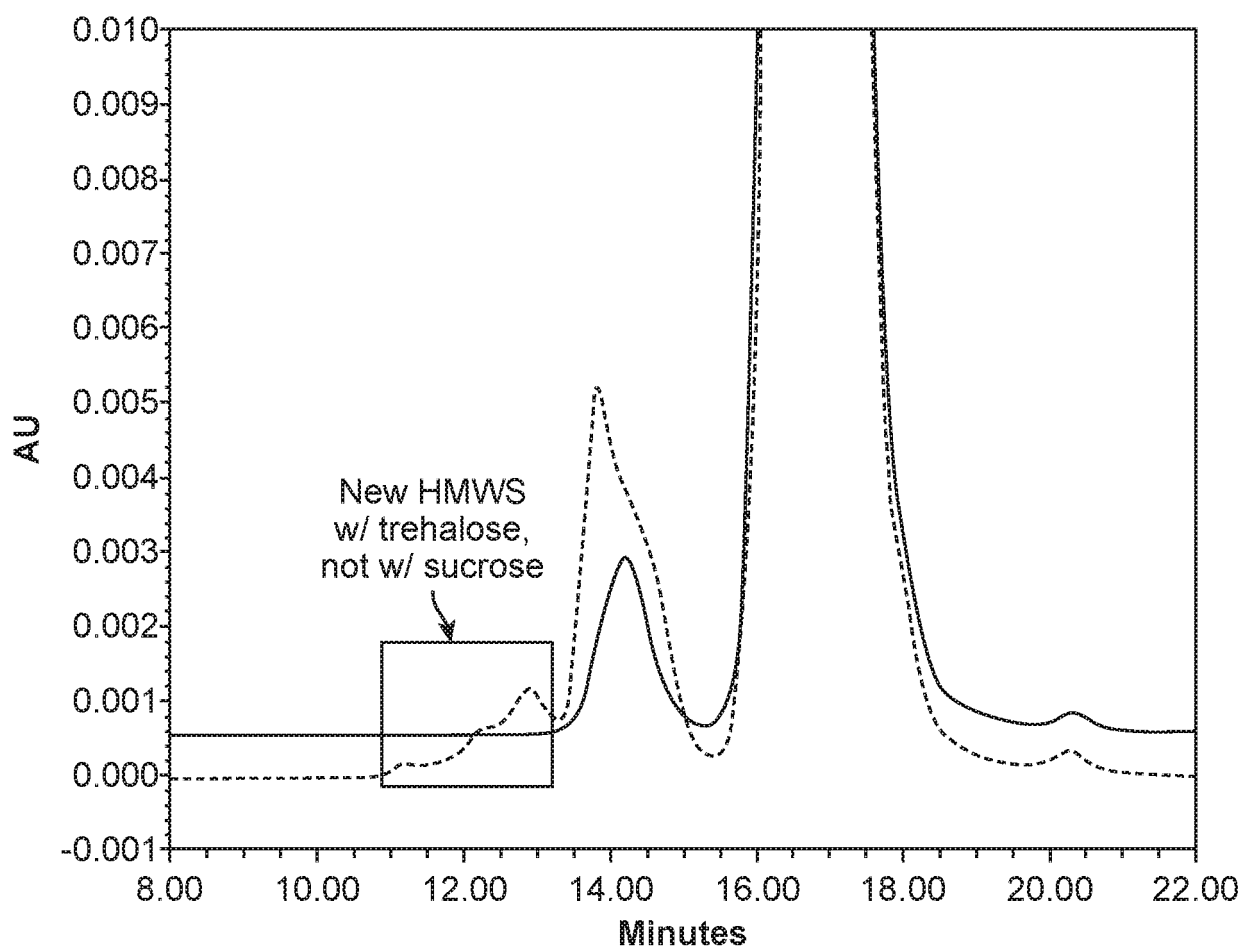
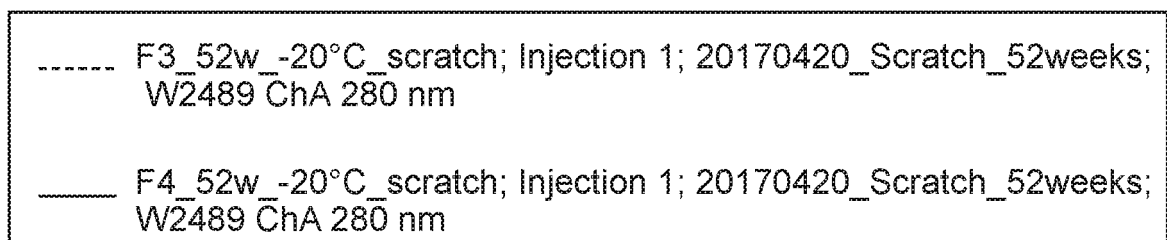


FIG. 29

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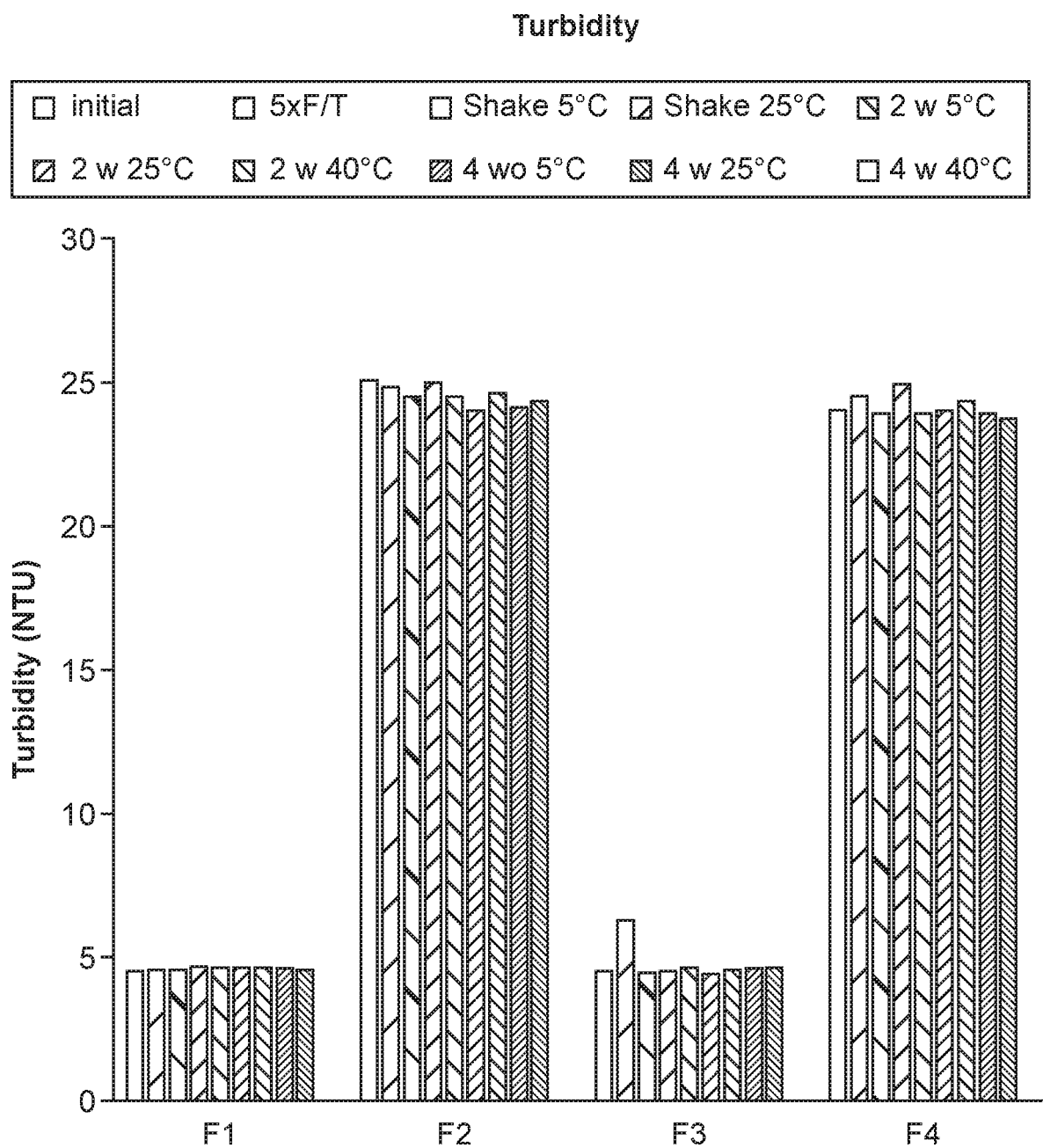


FIG. 30

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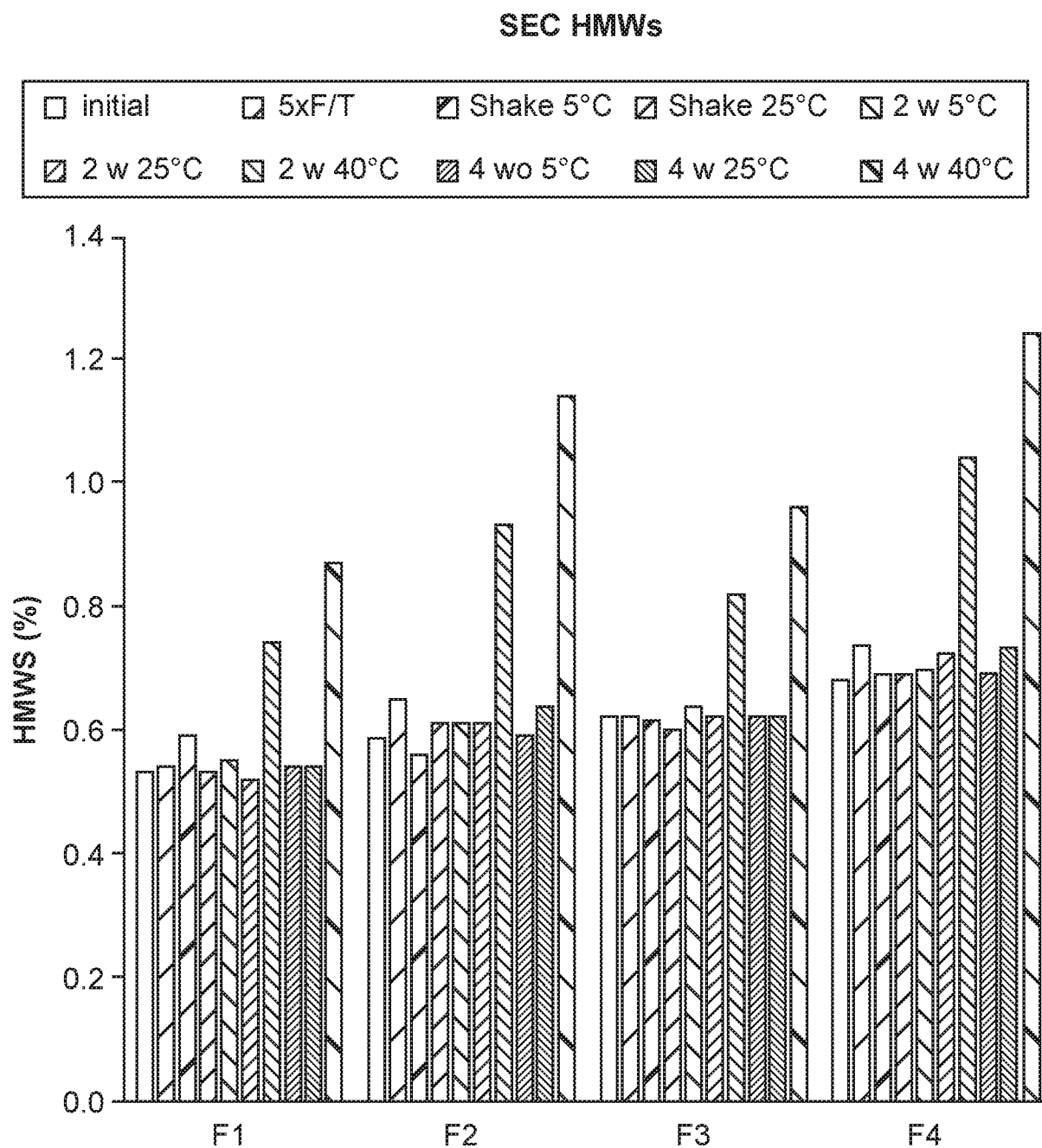


FIG. 31