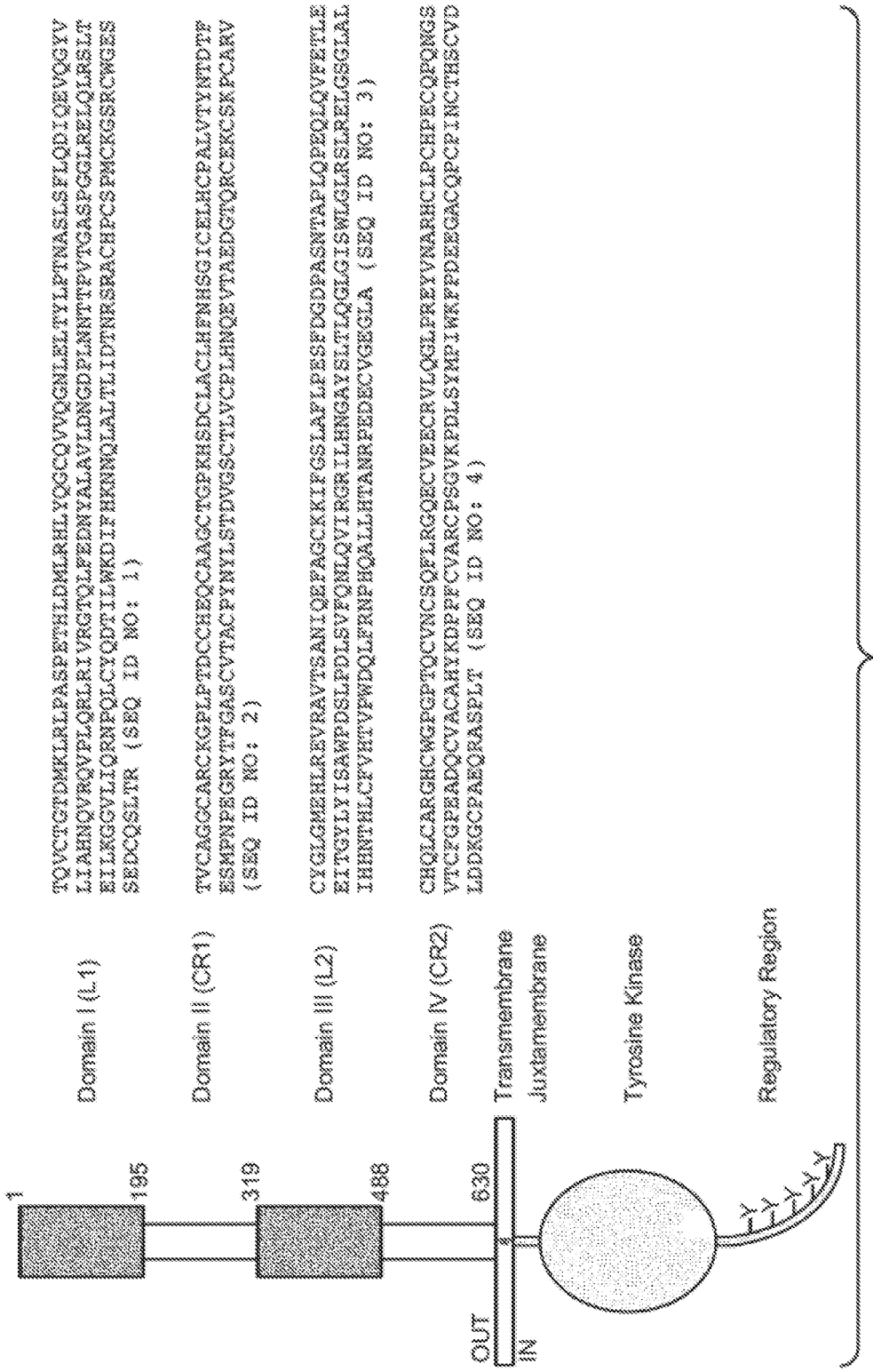

Domain I (L1)
Domain II (CR1)
Domain III (L2)
Domain IV (CR2)
Transmembrane
Juxtamembrane
Tyrosine Kinase
Regulatory Region
1
185
319
488
630
OUT
IN
TQVCTGTDMKLRLPASPETHLDMLRHLYQGCQVVQGNLELTYLPTNASLSFLQDIQEVQGYV
LIAHNQVRQVPLQRLRIVRGTQLFEDNYALAVLDNGDPLNNTTPVTGASPGGLRELQLRSLT
EILKGGVLIQRNPQLCYQDTILWKDIFHKNNQLALTLIDTNRSRACHPCSPMCKGSRCWGES
SEDCQSLTR (SEQ ID NO: 1)
TVCAGGCARCKGPLPTDCCHEQCAAGCTGPKHSDCLACLHFNHSGICELHCPALVTYNTDTF
ESMPNPEGRYTFGASCVTACPYNYLSTDVGSCTLVCPLHNQEVTAEDGTQRCEKCSKPCARV
(SEQ ID NO: 2)
CYGLGMEHLREVRAVTSANIQEFAGCKKIFGSLAFLPESFDGDPASNTAPLQPEQLQVFETLE
EITGYLYISAWPDSLPDLSVFQNLQVIRGRILHNGAYSLTLQGLGISWLGLRSLRELGSGLAL
IHHNTHLCFVHTVPWDQLFRNPHQALLHTANRPEDECVGEGLA (SEQ ID NO: 3)
CHQLCARGHCWGPGPTQCVNCSQFLRGQECVEECRVLQGLPREYVNARHCLPCHPECQPQNGS
VTCFGPEADQCVACAHYKDPPFCVARCPSGVKPDLSYMPIWKFPDEEGACQPCPINCTHSCVD
LDDKGCPAEQRASPLT (SEQ ID NO: 4)

FIG. 1

Variable Light

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

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

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

FIG. 2A

Variable Heavy

```
                10        20          30          40
2C4       EVQLQQSGPELVKPGTSVKISCKAS [GFTFTDYTMD] WVKQS
             **  **  *  * ***  *                   * *
574       EVQLVESGGGLVQPGGSLRLSCAAS [GFTFTDYTMD] WVRQA
                                      ** * *
hum III   EVQLVESGGGLVQPGGSLRLSCAAS [GFTFSSYAMS] WVRQA

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

            abc      90         100ab         110
2C4       ELRSLTFEDTAVYYCAR [NLGPSFYFDY] WGQGTTLTVSS (SEQ ID NO:6)
          ***  **                                **
574       QMNSLRAEDTAVYYCAR [NLGPSFYFDY] WGQGTLVTVSS (SEQ ID NO:8)
                             ********
hum III   QMNSLRAEDTAVYYCAR [GRVGYSLYDY] WGQGTLVTVSS (SEQ ID NO:10)
```

FIG. 2B

Amino Acid Sequence for Pertuzumab Light Chain

```
1         10         20         30         40         50         60
|         |          |          |          |          |          |
DIQMTQSPSSLSASVGDRVTITC**KASQDVSIGVA**WYQQKPGKAPKLLIYS**ASYRYT**GVPS

          70         80         90         100        110        120
          |          |          |          |          |          |
RFSGSGSGTDFTLTISSLQPEDFATYYC**QQYYIYPYT**FGQGTKVEIKRTVAAPSVFIFPP

          130        140        150        160        170        180
          |          |          |          |          |          |
SDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLT

          190        200        210
          |          |          |
LSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC (SEQ ID NO: 11)
```

FIG. 3A

Amino Acid Sequence for Pertuzumab Heavy Chain

```
1         10         20         30         40         50         60
|         |          |          |          |          |          |
EVQLVESGGGLVQPGGSLRLSCAAS**GFTFTDYTMD**WVRQAPGKGLEWVA**DVNPNSGGSIY**

          70         80         90         100        110        120
          |          |          |          |          |          |
**NQRFK**GRFTLSVDRSKNTLYLQMNSLRAEDTAVYYCARN**LGPSFYFDY**WGQGTLVTVSSA

          130        140        150        160        170        180
          |          |          |          |          |          |
STKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSG

          190        200        210        220        230        240
          |          |          |          |          |          |
LYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGP

          250        260        270        280        290        300
          |          |          |          |          |          *|
SVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNS

          310        320        330        340        350        360
          |          |          |          |          |          |
TYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEM

          370        380        390        400        410        420
          |          |          |          |          |          |
TKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQ

          430        440        448
          |          |          |
QGNVFSCSVMHEALHNHYTQKSLSLSPG  (SEQ ID NO: 12)
```

FIG. 3B

Trastuzmab Light Chain

```
1                                                                  45
D I Q M T Q S P S S L S A S V G D R V T I T C R A S Q D V N T A V A W Y Q Q K P G K A P K
                                                                   90
L L I Y S A S F L Y S G V P S R F S G S R S G T D F T L T I S S L Q P E D F A T Y Y C Q Q
                                                                  135
H Y T T P P T F G Q G T 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 V C L
                                                                  180
L M 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 Q D S K D S T Y S L S S T L T
                                                                  214
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  (SEQ ID NO: 13)
```

FIG. 4A

Trastuzmab Heavy Chain

```
                15                  30                  45
1   EVQLVESGGGLVQPGGSLRLSCAASGFNIKDTYIHWVRQAPGKGL
46  EWVARIYPTNGYTRYADSVKGRFTISADTSKNTAYLQMNSLRAED
91  TAVYYCSRWGGDGFYAMDYWGQGTLVTVSSASTKGPSVFPLAPSS
136 KSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSS
181 GLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDK
226 THTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVS
271 HEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQD
316 WLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREE
361 MTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDG
406 SFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPG
(SEQ ID NO: 14)
```

FIG. 4B

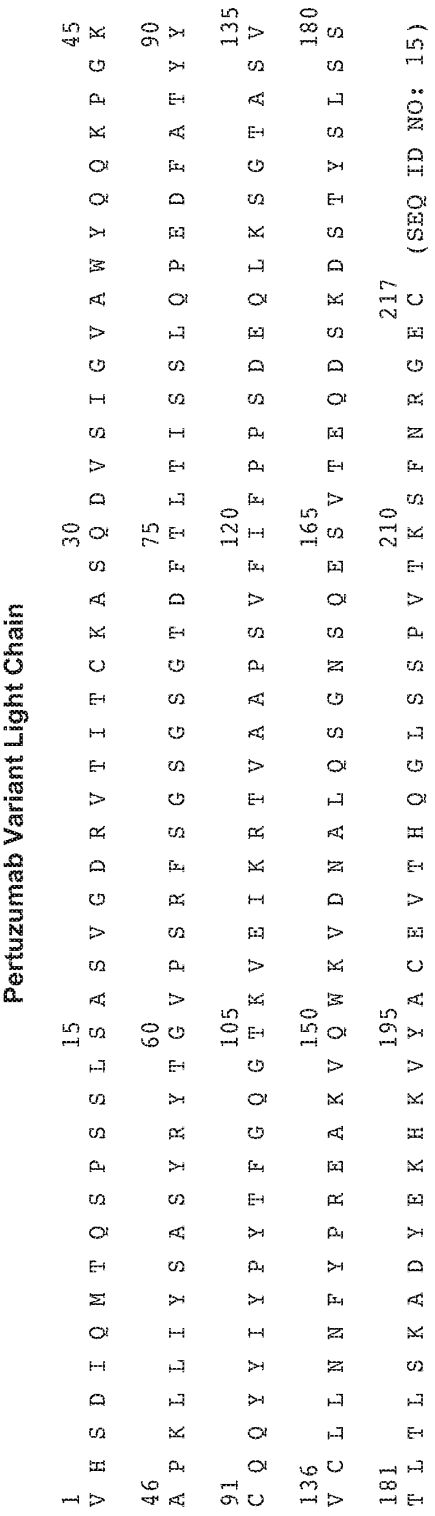

Pertuzumab Variant Light Chain
1
V H S D I Q M T Q S P S S L S A S V G D R V T I T C K A S Q D V S I G V A W Y Q Q K P G K
15
30
45
46
A P K L L I Y S A S Y R Y T G V P S R F S G S G S G T D F T L T I S S L Q P E D F A T Y Y
60
75
90
91
C Q Q Y Y I Y P Y T F G Q G T K V E I K R T V A A P S V F I F P P S D E Q L K S G T A S V
105
120
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 Q D S K D S T Y S L S S
150
165
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 (SEQ ID NO: 15)
195
210
217

FIG. 5A

Pertuzumab Variant Heavy Chain

```
1                                                                  15
E V Q L V E S G G G L V Q P G G S L R L S C A A S G F T F T D Y T M D W V R Q A P G K G L
                                                                   30                  45
46                                                                 60
E W V A D V N P N S G G S I Y N Q R F K G R F T L S V D R S K N T L Y L Q M N S L R A E D
                                                                   75                  90
91                                                                 105
T A V Y Y C A R N L G P S F Y F D Y W G Q G T L V T V S S A S T K G P S V F P L A P S S K
                                                                   120                 135
136                                                                150
S T S G G T A A L G C L V K D Y F P E P V T V S W N S G A L T S G V H T F P A V L Q S S G
                                                                   165                 180
181                                                                195
L Y S L S S V V T V P S S S L G T Q T Y I C N V N H K P S N T K V D K K V E P K S C D K T
                                                                   210                 225
226                                                                240
H T C P P C P A P E L L G G P S V F L F P P K P K D T L M I S R T P E V T C V V V D V S H
                                                                   255                 270
271                                                                285
E D P E V K F N W Y V D G V E V H N A K T K P R E E Q Y N S T Y R V V S V L T V L H Q D W
                                                                   300                 315
316                                                                330
L N G K E Y K C K V S N K A L P A P I E K T I S K A K G Q P R E P Q V Y T L P P S R E E M
                                                                   345                 360
361                                                                375
T K N Q V S L T C L V K G F Y P S D I A V E W E S N G Q P E N N Y K T T P P V L D S D G S
                                                                   390                 405
406                                                                420
F F L Y S K L T V D K S R W Q Q G N V F S C S V M H E A L H N H Y T Q K S L S L S P G K
                                                                   435                 449
(SEQ ID NO: 16)
```

FIG. 5B

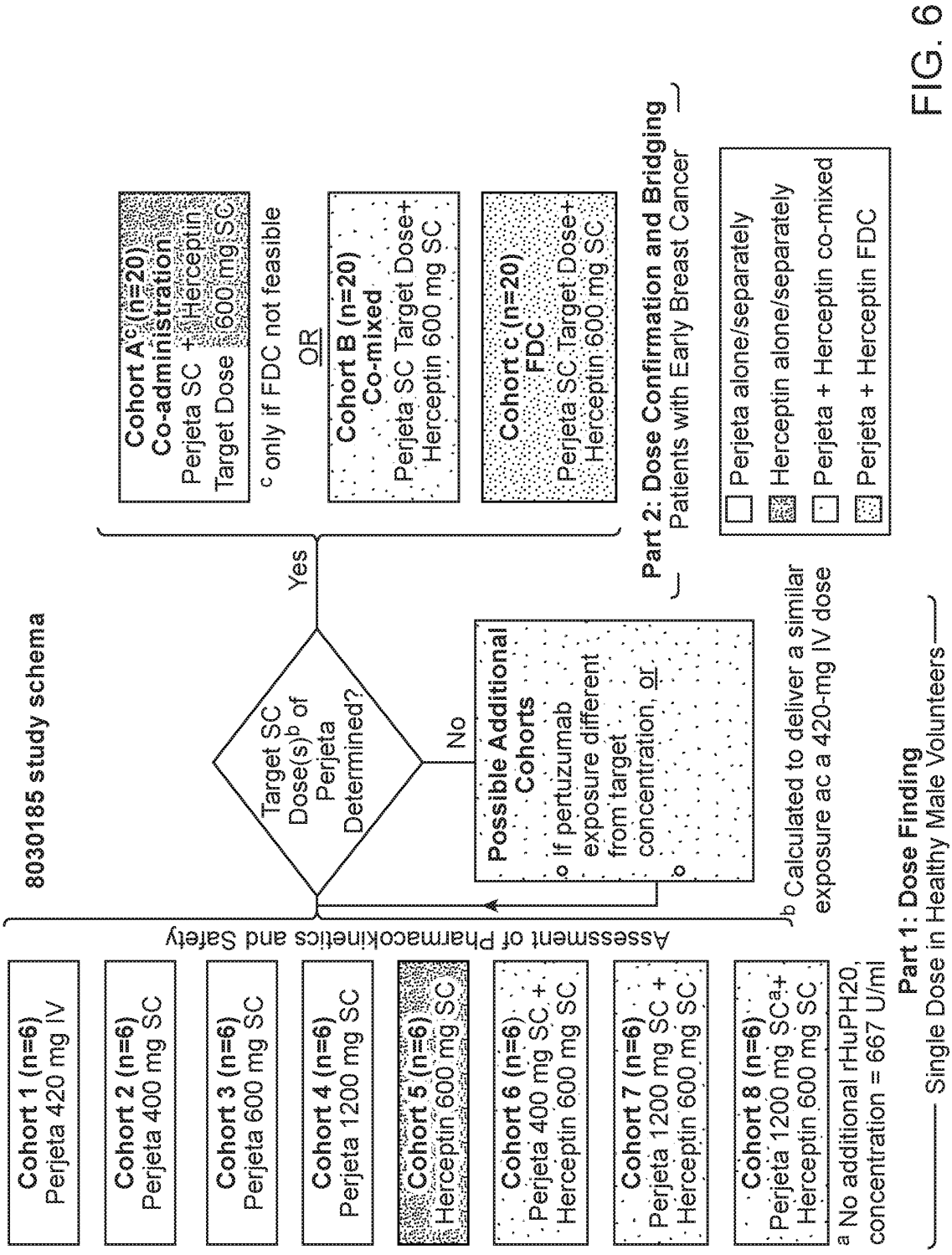

8030185 study schema
Part 1: Dose Finding
Single Dose in Healthy Male Volunteers
Cohort 1 (n=6) Perjeta 420 mg IV
Cohort 2 (n=6) Perjeta 400 mg SC
Cohort 3 (n=6) Perjeta 600 mg SC
Cohort 4 (n=6) Perjeta 1200 mg SC
Cohort 5 (n=6) Herceptin 600 mg SC
Cohort 6 (n=6) Perjeta 400 mg SC + Herceptin 600 mg SC
Cohort 7 (n=6) Perjeta 1200 mg SC + Herceptin 600 mg SC
Cohort 8 (n=6) Perjeta 1200 mg SC[a]+ Herceptin 600 mg SC
[a] No additional rHuPH20, concentration = 667 U/ml
Assessment of Pharmacokinetics and Safety
Target SC Dose(s)[b] of Perjeta Determined?
Yes
No
Possible Additional Cohorts
o If pertuzumab exposure different from target concentration, or
o
[b] Calculated to deliver a similar exposure ac a 420-mg IV dose
Part 2: Dose Confirmation and Bridging
Patients with Early Breast Cancer
Cohort A[c] (n=20) Co-administration
Perjeta SC + Herceptin Target Dose 600 mg SC
[c] only if FDC not feasible
OR
Cohort B (n=20) Co-mixed
Perjeta SC Target Dose+ Herceptin 600 mg SC
Cohort c (n=20) FDC
Perjeta SC Target Dose+ Herceptin 600 mg SC
Perjeta alone/separately
Herceptin alone/separately
Perjeta + Herceptin co-mixed
Perjeta + Herceptin FDC

FIG. 6

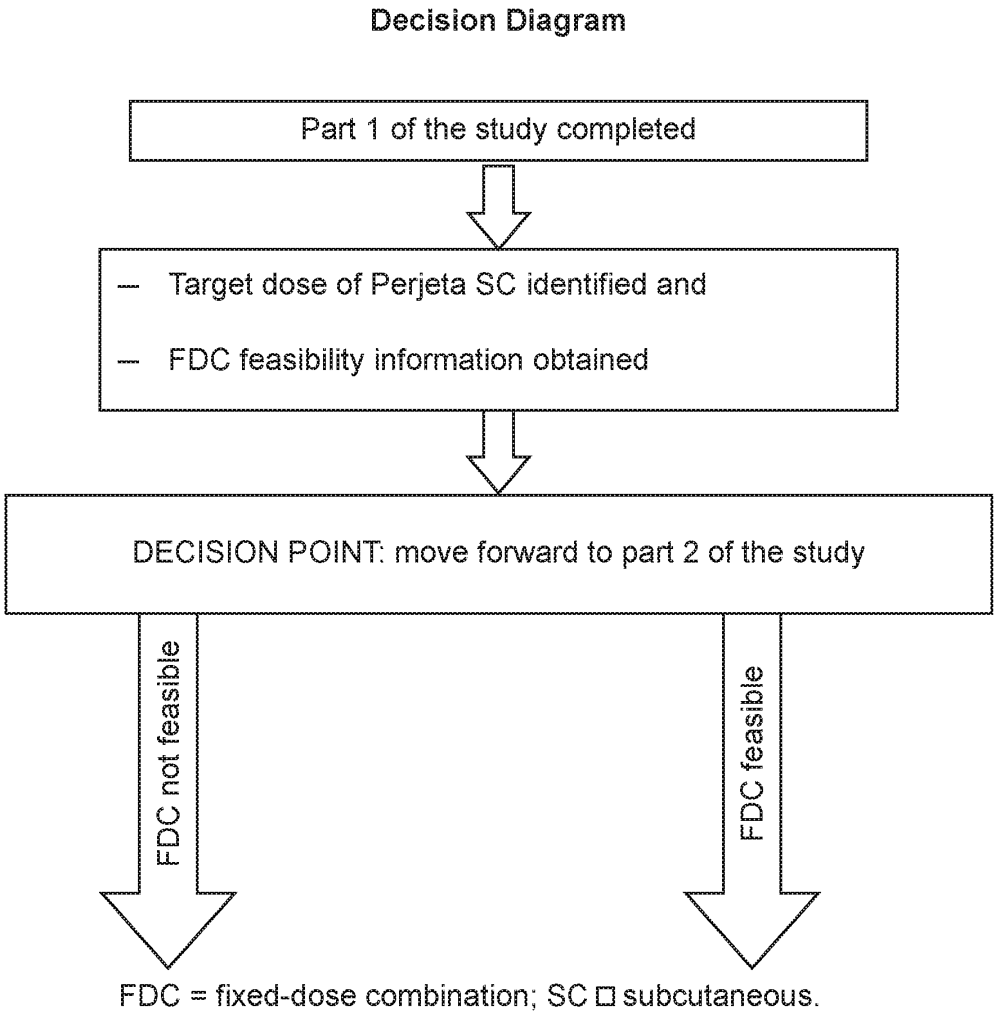

Decision Diagram
Part 1 of the study completed
– Target dose of Perjeta SC identified and
– FDC feasibility information obtained
DECISION POINT: move forward to part 2 of the study
FDC not feasible
FDC feasible
FDC = fixed-dose combination; SC □ subcutaneous.

FIG. 7

8030185 Study Overview

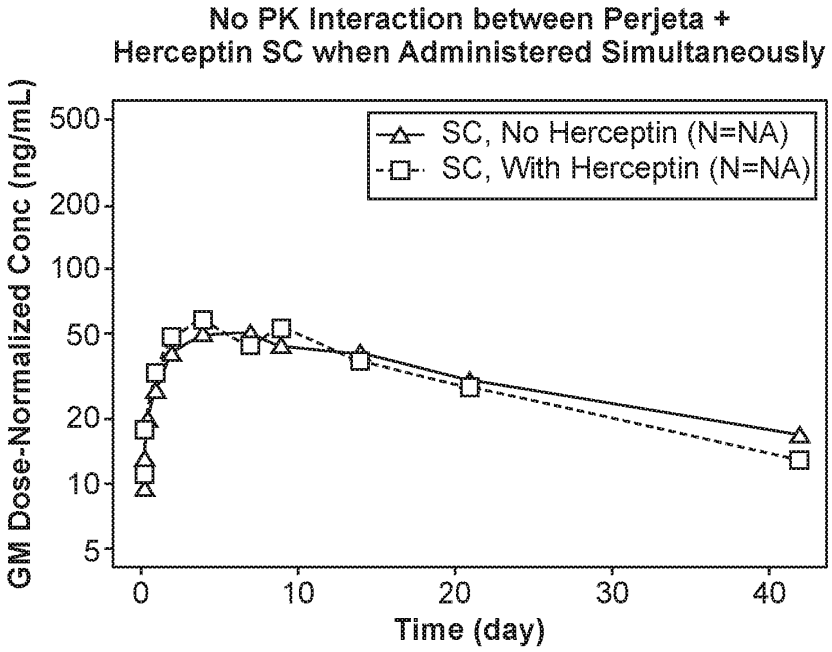
	Cohort	Population	N	Agent	Dose (mg) Single Injection	Volume of Injection (mL)	Concentration of Halozyme (U/mL)#	Amount of Halozyme (Units)
	Dose Finding							
Part 1	1 (control)	HMV	6	Piv	420		NA	NA
	2	HMV	6	Psc	400	3.3	2,000 U/mL	6,600 U
	3	HMV	6	Psc	600	5	2,000 U/mL	10,000 U
	4	HMV	6	Psc loading	1200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

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

*Enrollment planned January 2017

^Enrollment planned October 2017

FIG. 8

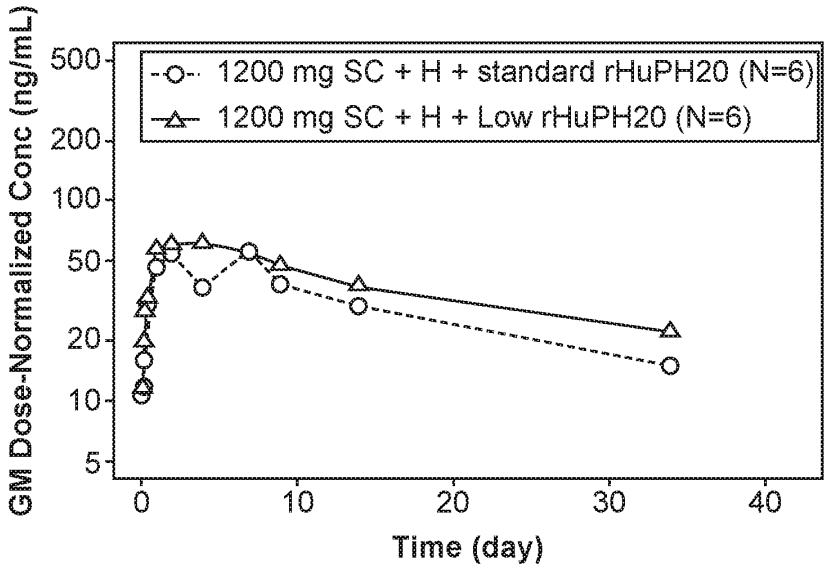


No PK interactions between Perjeta SC and Herceptin SC. No differences in Herceptin PK as monotherapy, with Perjeta SC or with different rHuPH20 concentrations.

FIG. 9

No Impact of Lower rHuPH20 Concentration/ Amount on Perjeta PK

Pertuzumab Concentrations with standard (2,000 U/m L) and low (667 U/m L) 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

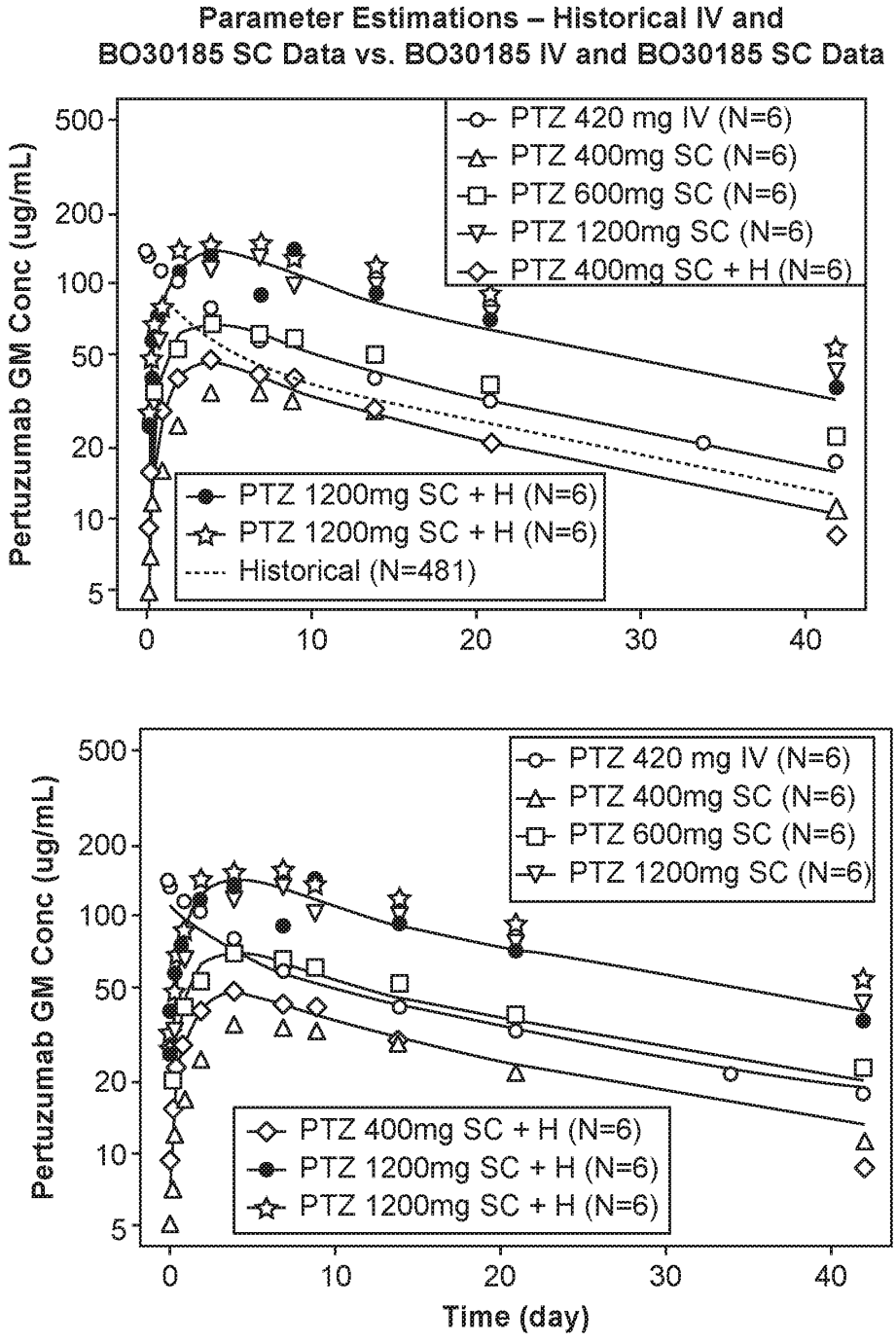

Parameter Estimations – Historical IV and
BO30185 SC Data vs. BO30185 IV and BO30185 SC Data
Pertuzumab GM Conc (ug/mL)
500
200
100
50
20
10
5
0
10
20
30
40
PTZ 420 mg IV (N=6)
PTZ 400mg SC (N=6)
PTZ 600mg SC (N=6)
PTZ 1200mg SC (N=6)
PTZ 400mg SC + H (N=6)
PTZ 1200mg SC + H (N=6)
PTZ 1200mg SC + H (N=6)
Historical (N=481)
Pertuzumab GM Conc (ug/mL)
500
200
100
50
20
10
5
0
10
20
30
40
Time (day)
PTZ 420 mg IV (N=6)
PTZ 400mg SC (N=6)
PTZ 600mg SC (N=6)
PTZ 1200mg SC (N=6)
PTZ 400mg SC + H (N=6)
PTZ 1200mg SC + H (N=6)
PTZ 1200mg SC + H (N=6)

FIG. 11

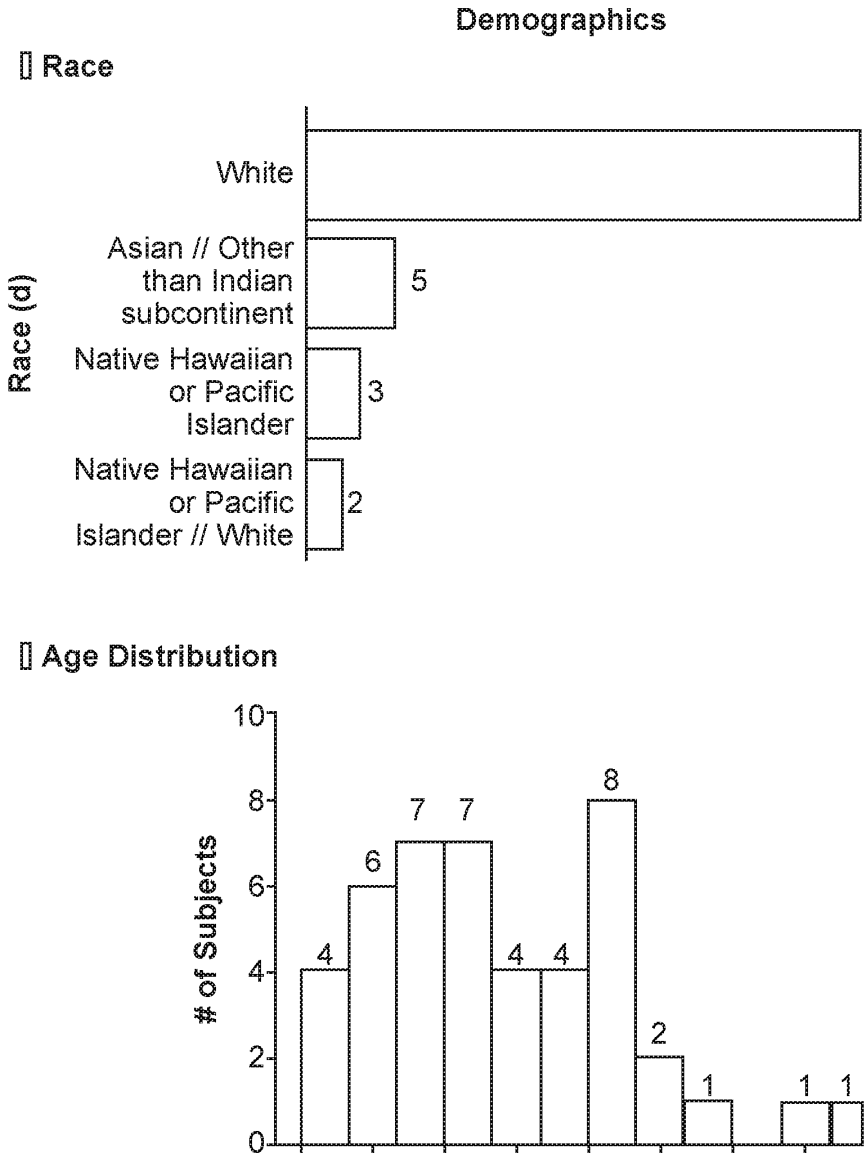

Demographics
Race
White
Asian // Other than Indian subcontinent
5
Native Hawaiian or Pacific Islander
3
Native Hawaiian or Pacific Islander // White
2
Race (d)
Age Distribution
# of Subjects
10
8
6
4
2
0
4
6
7
7
4
4
8
2
1
1
1

FIG. 12

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 (P400mg+ 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

Most Common Adverse Events (all grades) – incidence ≥ 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 (5O)	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 (5O)	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 (5O)	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

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	2 (33)	0	1 (17)
Injection Site Reaction (Local)		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

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 ≥10%	0	0	0	0
Absolute value <50% OR decrease from baseline ≥10%points	0	0	1*	0

* Cohort 3 (600mg P SC):
  - One HMV had a drop of >10% from 67% at Baseline to 56% at Day 22
  - Follow up EF at Day 85 = 60 %
  - Cardiologist confirmed no evidence of cardiotoxicity
  - Drop due to variability of imaging method

FIG. 18

FIG. 19

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

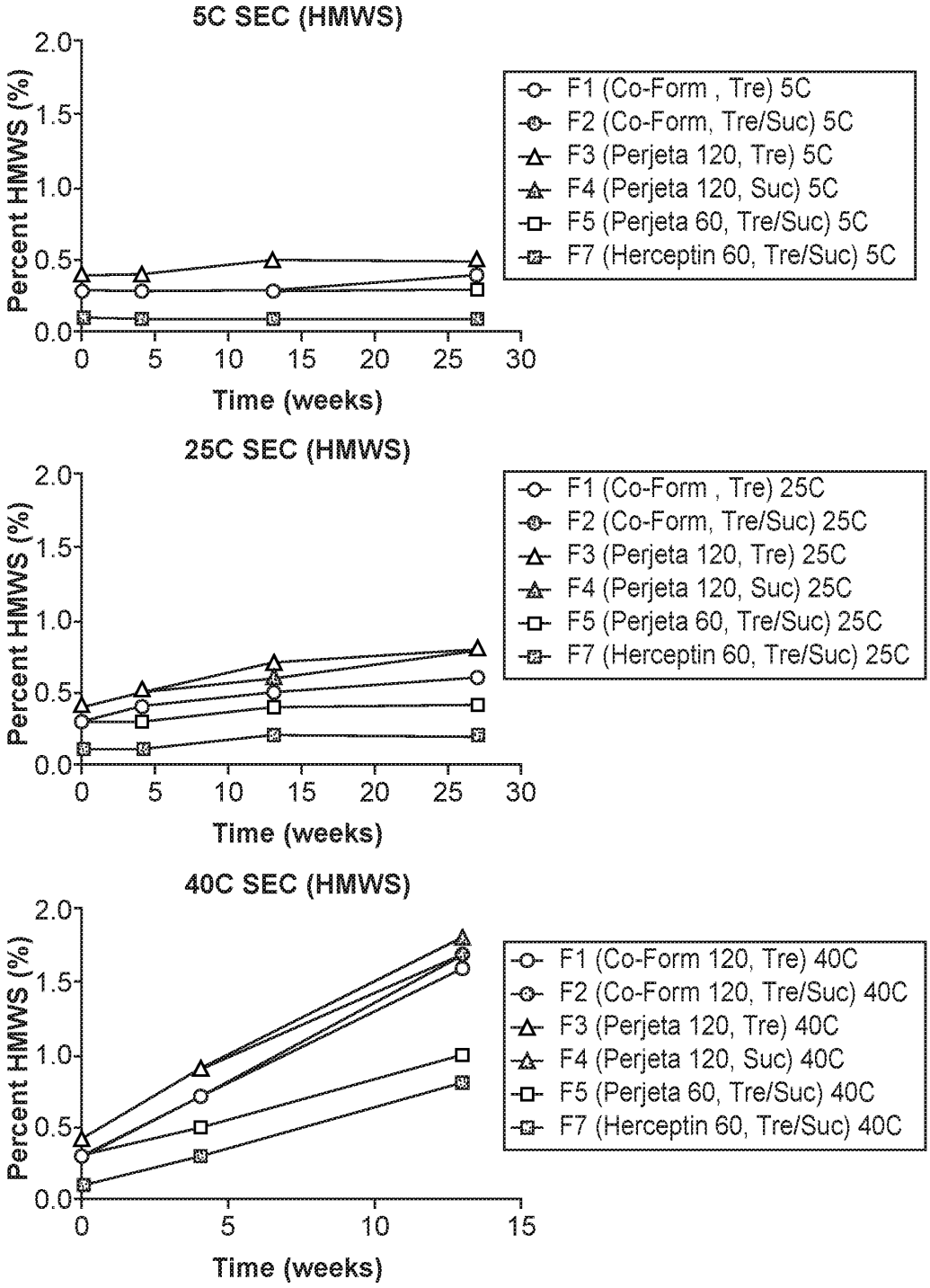
Pertuzumab SC DS

- 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)



Note: Higher HMWS for higher total mAb concentration

FIG. 20

FIG. 21

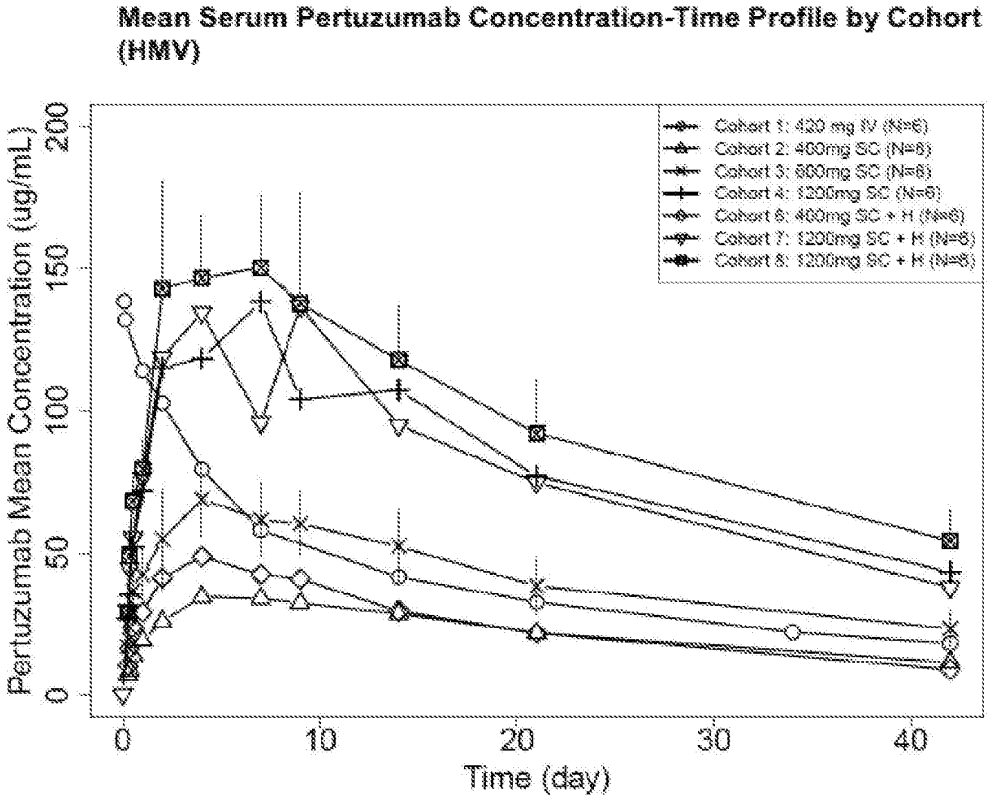
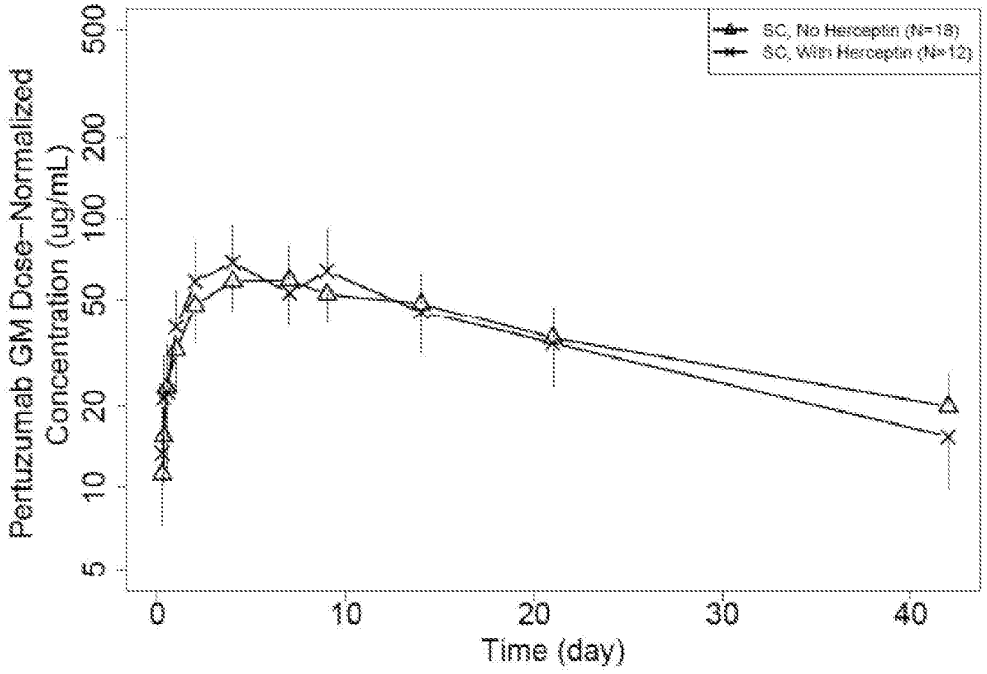

Mean Serum Pertuzumab Concentration-Time Profile by Cohort (HMV)
Pertuzumab Mean Concentration (ug/mL)
0
50
100
150
200
0
10
20
30
40
Time (day)
Cohort 1: 420 mg IV (N=6)
Cohort 2: 400mg SC (N=6)
Cohort 3: 600mg SC (N=6)
Cohort 4: 1200mg SC (N=6)
Cohort 6: 400mg SC + H (N=6)
Cohort 7: 1200mg SC + H (N=6)
Cohort 8: 1200mg SC + H (N=6)

FIG. 22

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



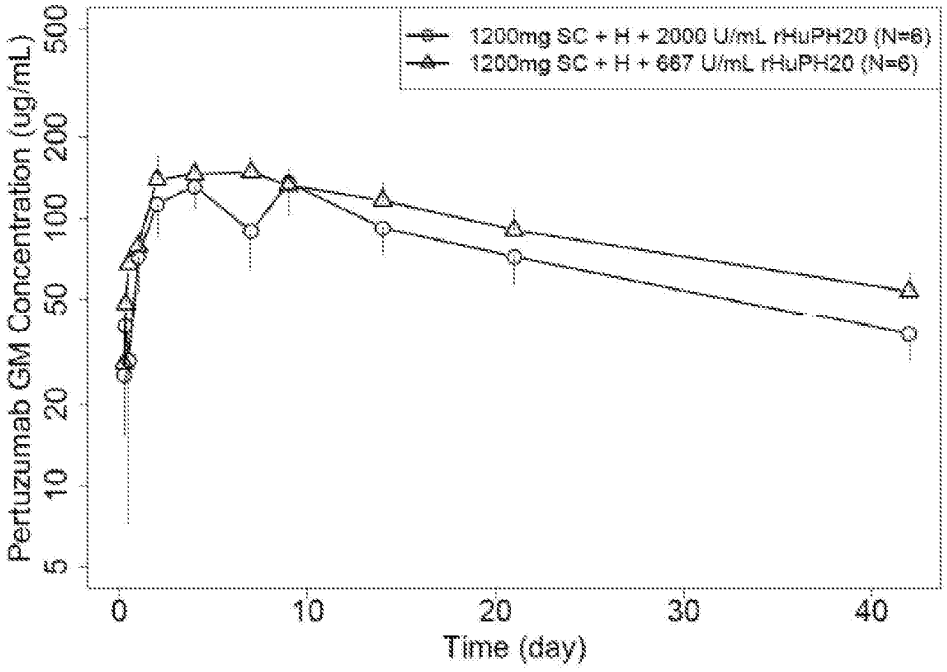
GM = geometric mean; SC = subcutaneous.

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.

FIG. 23

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

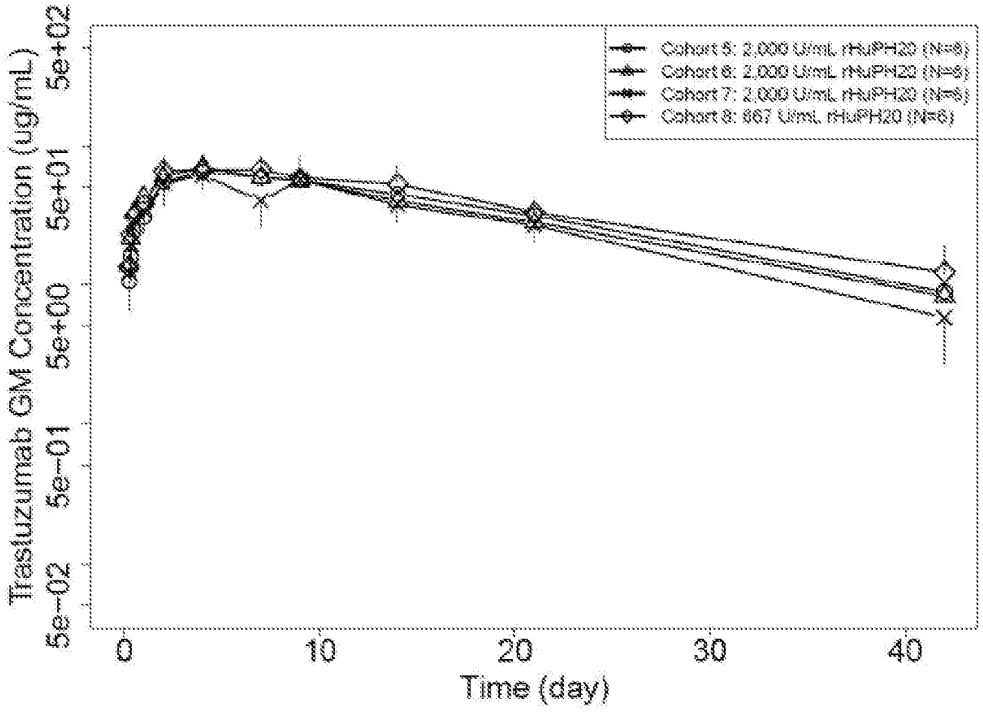


GM = geometric mean; H = Herceptin; SC = subcutaneous.

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

FIG. 24

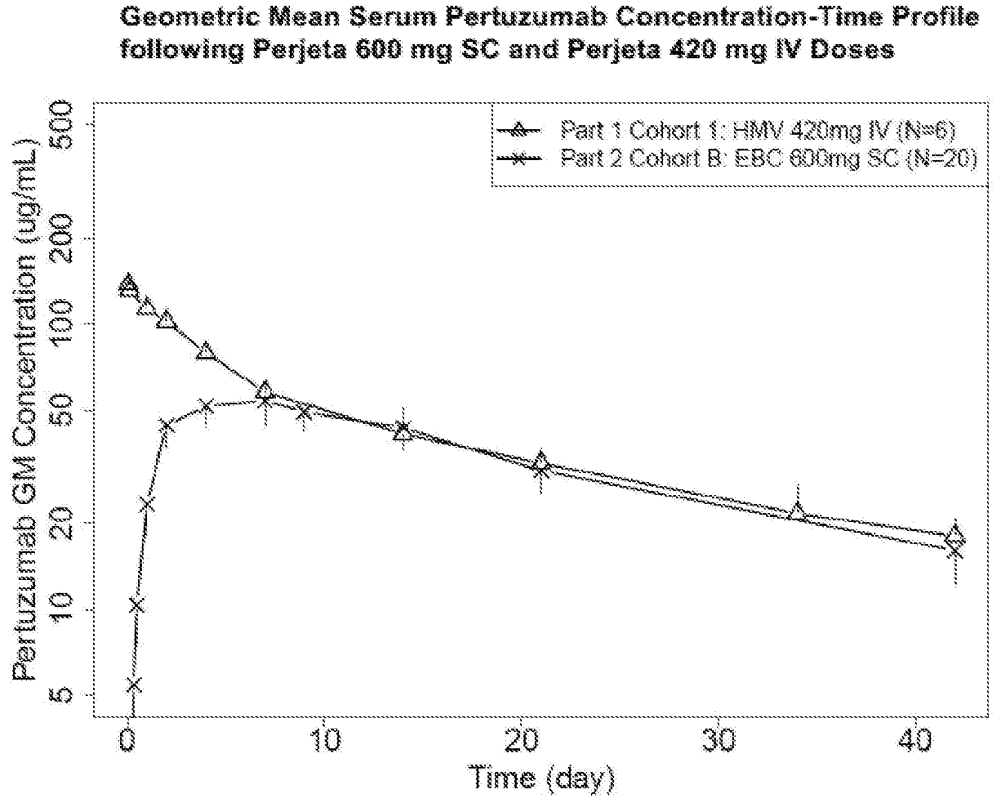
Geometric Mean Serum Trastuzumab Concentration-Time Profile, With 667 U/mL or 2,000 U/mL rHuPH20 (HMV)



GM = geometric mean.

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

FIG. 25

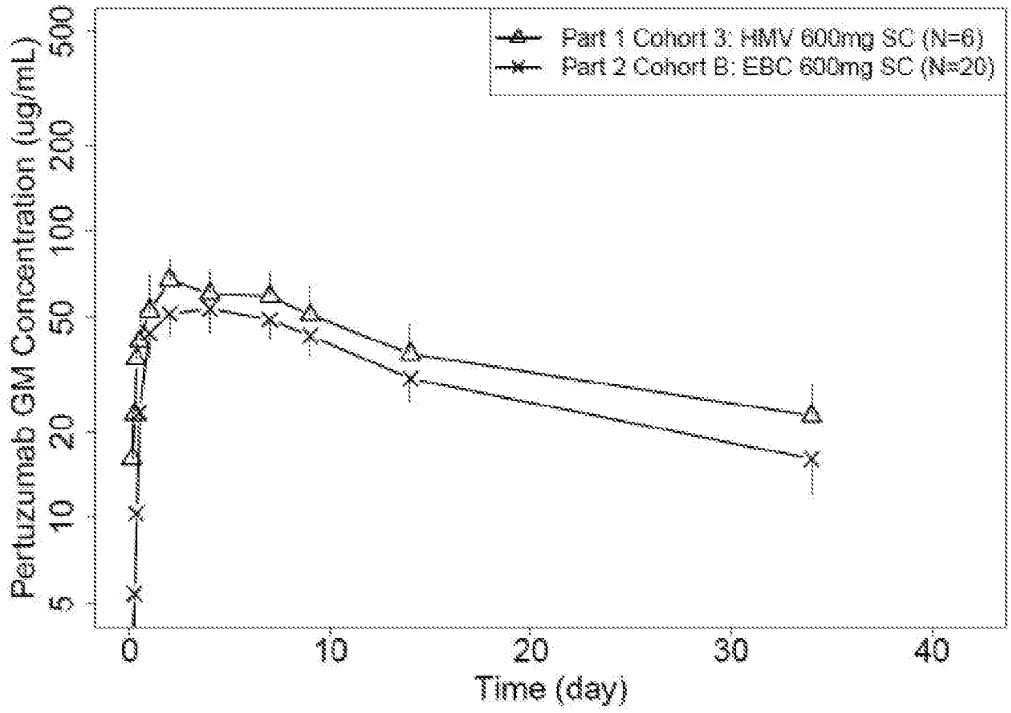


EBC = early breast cancer; GM = geometric mean; HMV = healthy male volunteer; IV = intravenous SC = subcutaneous.

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

FIG. 26

Geometric Mean Serum Pertuzumab Concentration-Time Profile in HMV or EBC Patients

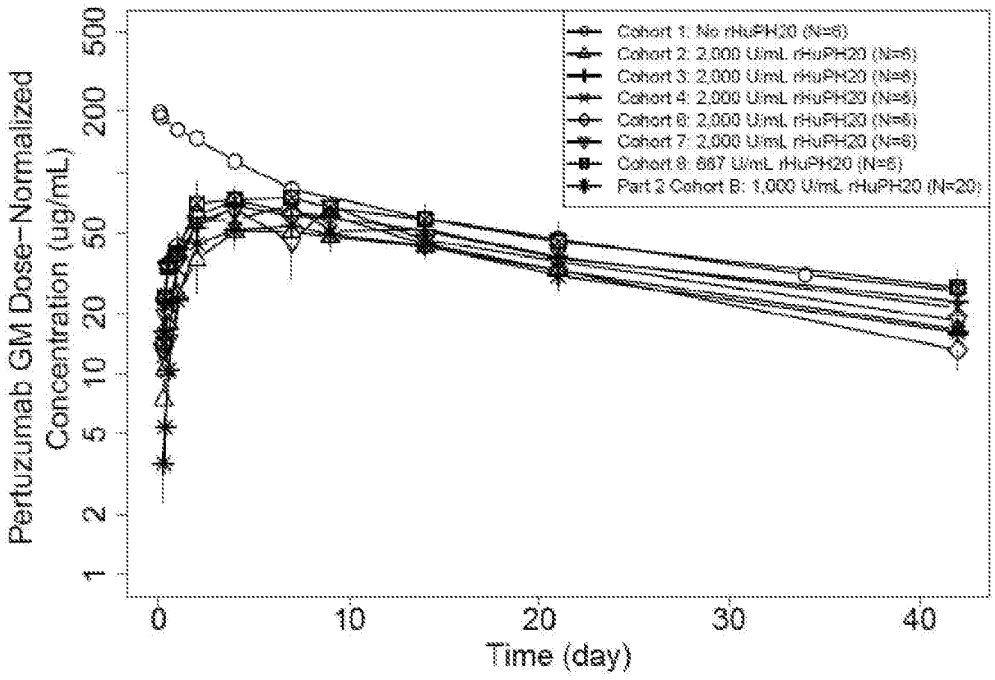


EBC = early breast cancer; GM = geometric mean; HMV = healthy male volunteer; SC = subcutaneous.

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

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



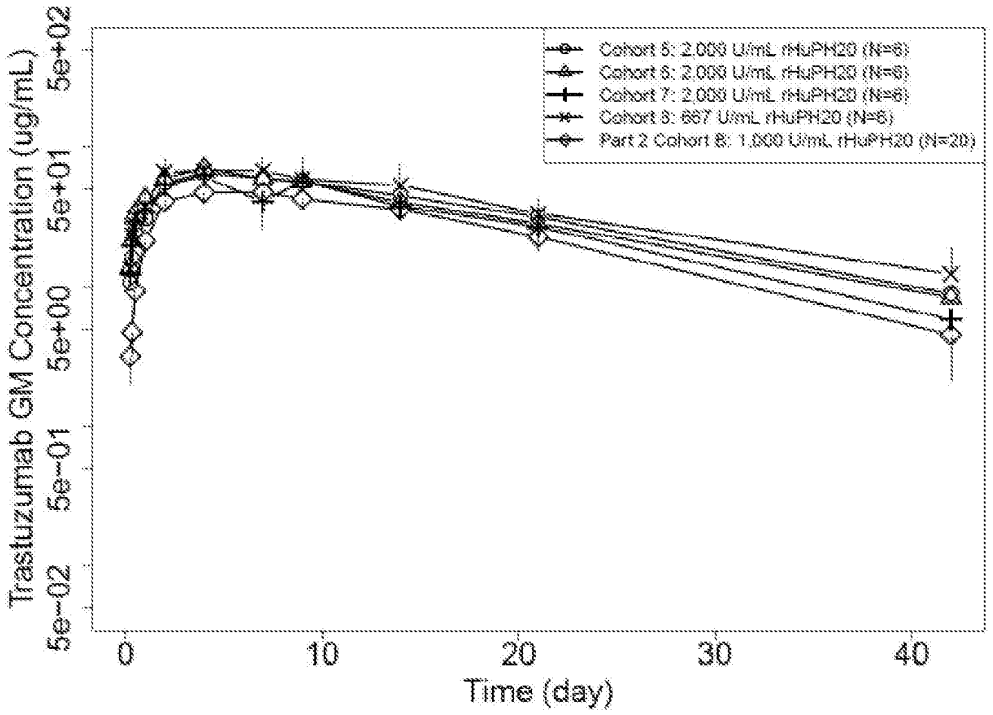
GM = geometric mean.

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.

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.

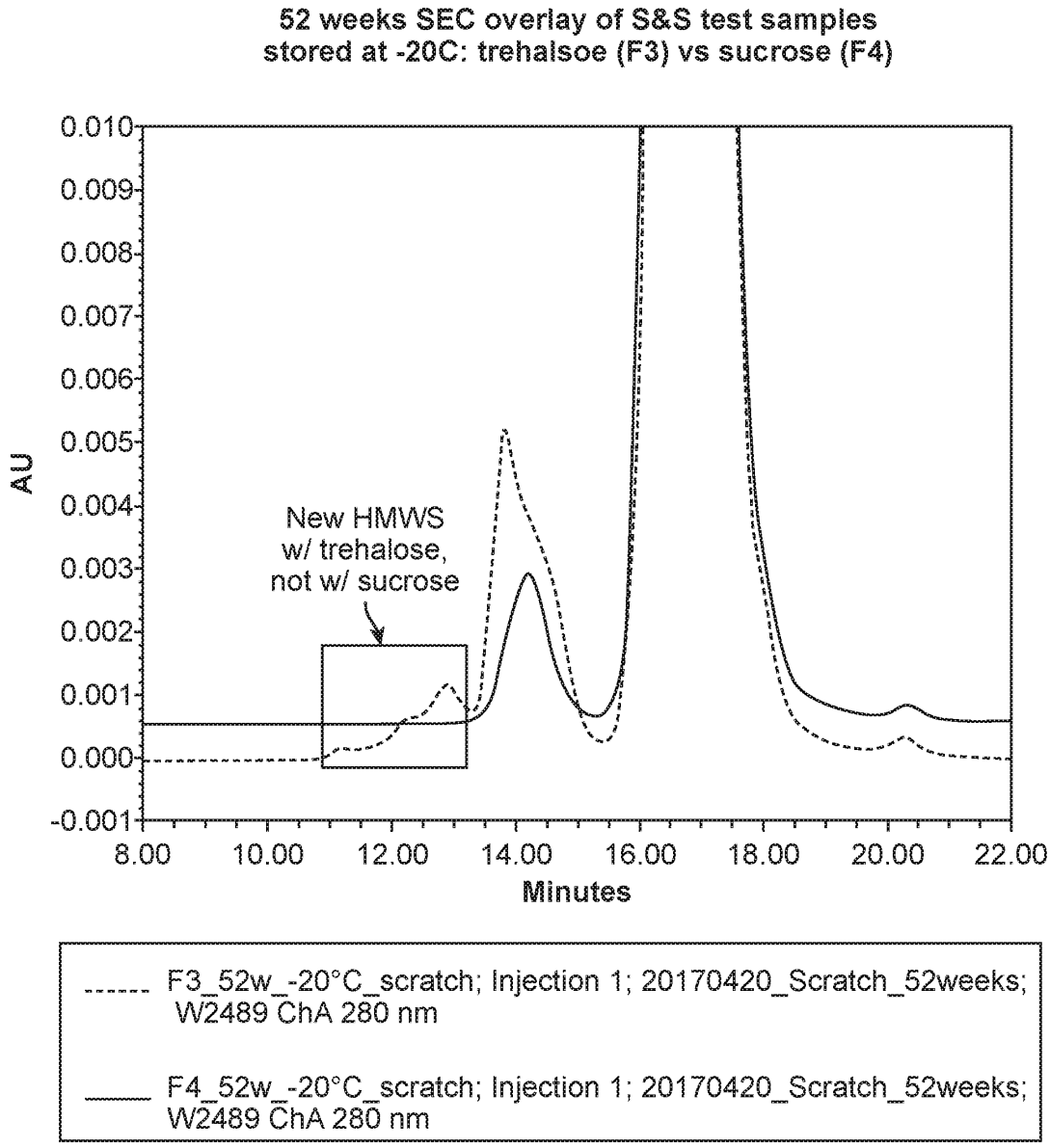

52 weeks SEC overlay of S&S test samples
stored at -20C: trehalsoe (F3) vs sucrose (F4)
AU
0.010
0.009
0.008
0.007
0.006
0.005
0.004
0.003
0.002
0.001
0.000
-0.001
New HMWS
w/ trehalose,
not w/ sucrose
8.00
10.00
12.00
14.00
16.00
18.00
20.00
22.00
Minutes
F3_52w_-20°C_scratch; Injection 1; 20170420_Scratch_52weeks; W2489 ChA 280 nm
F4_52w_-20°C_scratch; Injection 1; 20170420_Scratch_52weeks; W2489 ChA 280 nm

FIG. 29

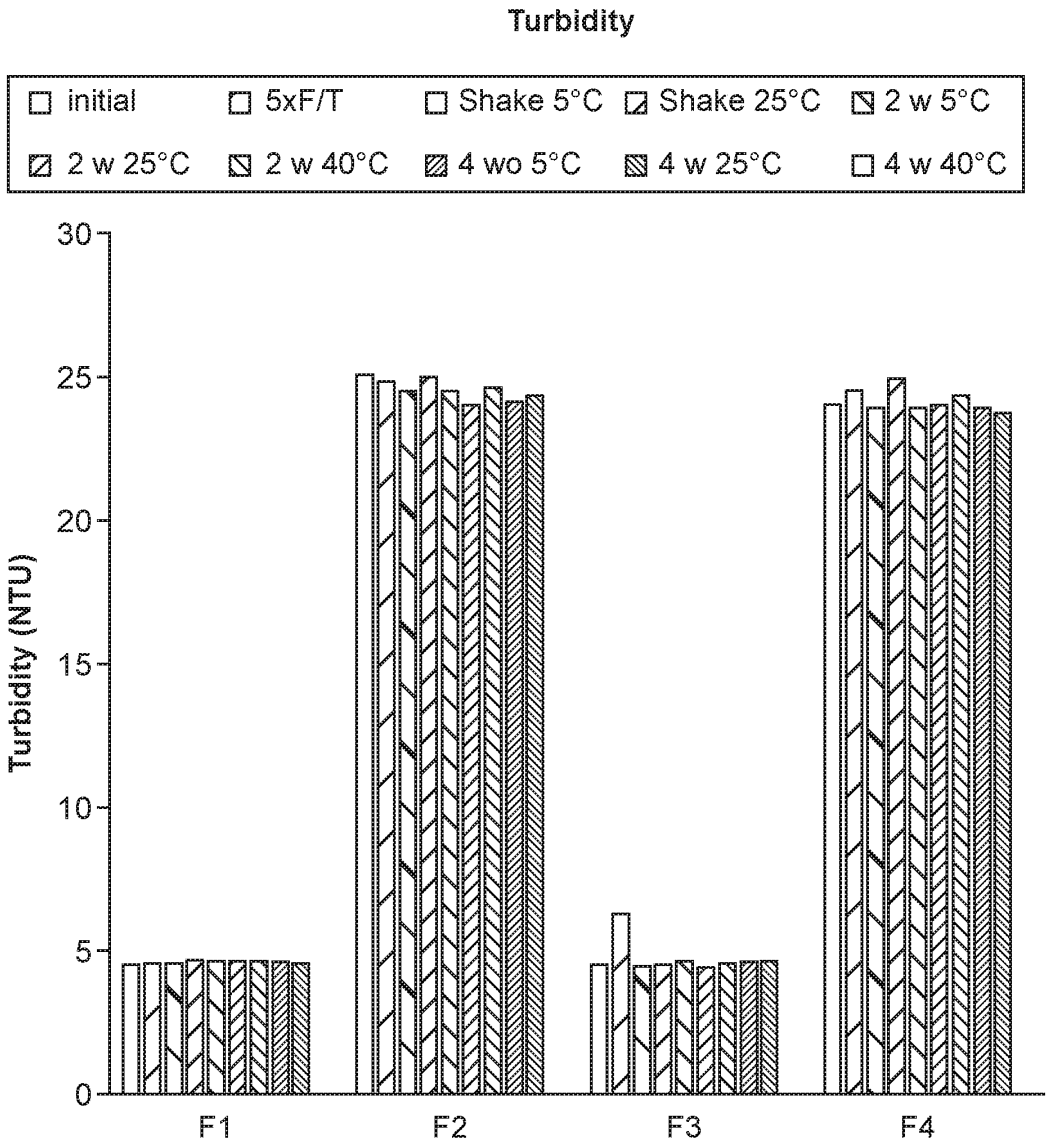

Turbidity
initial
5xF/T
Shake 5°C
Shake 25°C
2 w 5°C
2 w 25°C
2 w 40°C
4 wo 5°C
4 w 25°C
4 w 40°C
Turbidity (NTU)
30
25
20
15
10
5
0
F1
F2
F3
F4

FIG. 30

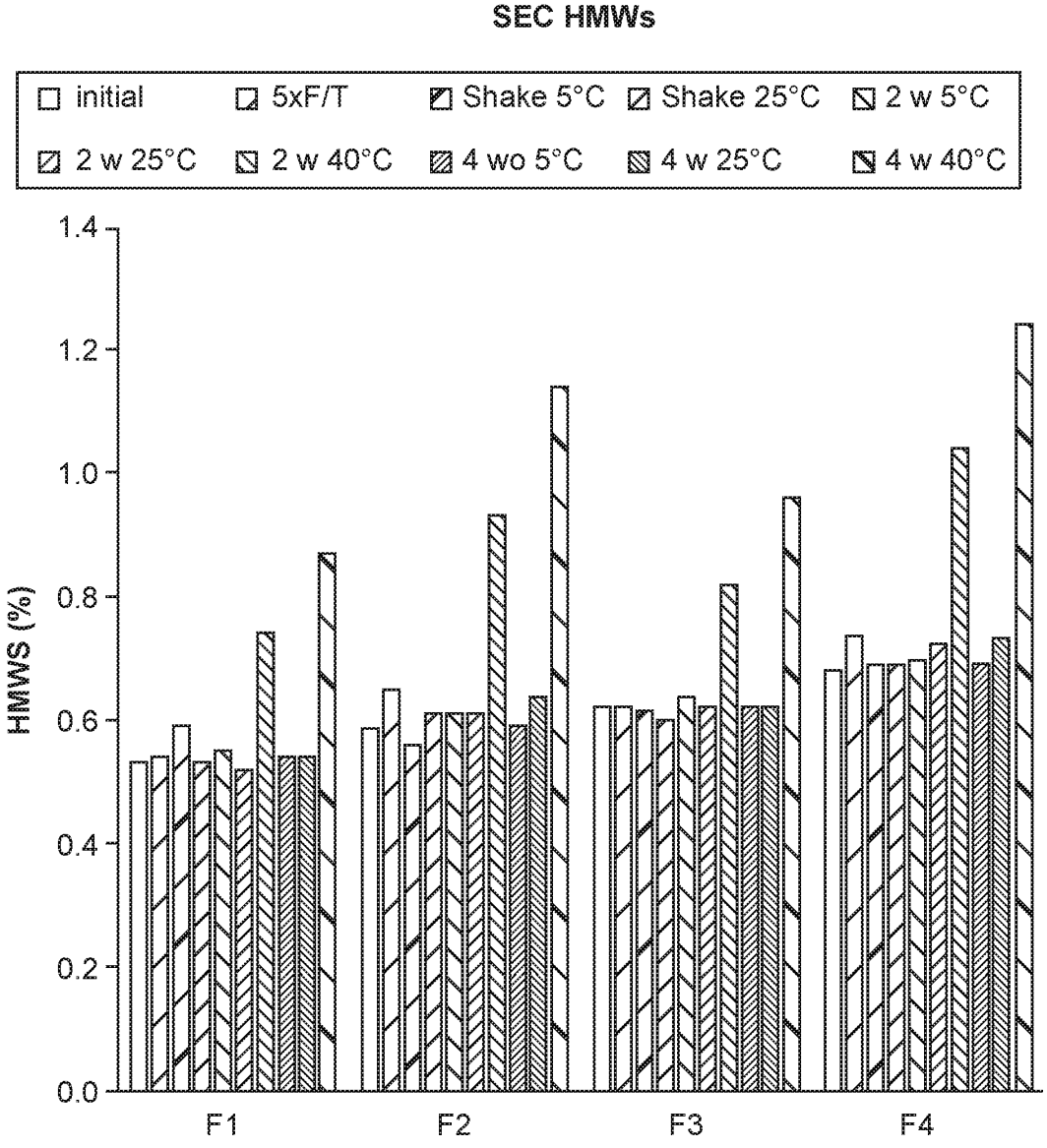

SEC HMWs
initial
5xF/T
Shake 5°C
Shake 25°C
2 w 5°C
2 w 25°C
2 w 40°C
4 wo 5°C
4 w 25°C
4 w 40°C
HMWS (%)
1.4
1.2
1.0
0.8
0.6
0.4
0.2
0.0
F1
F2
F3
F4

FIG. 31