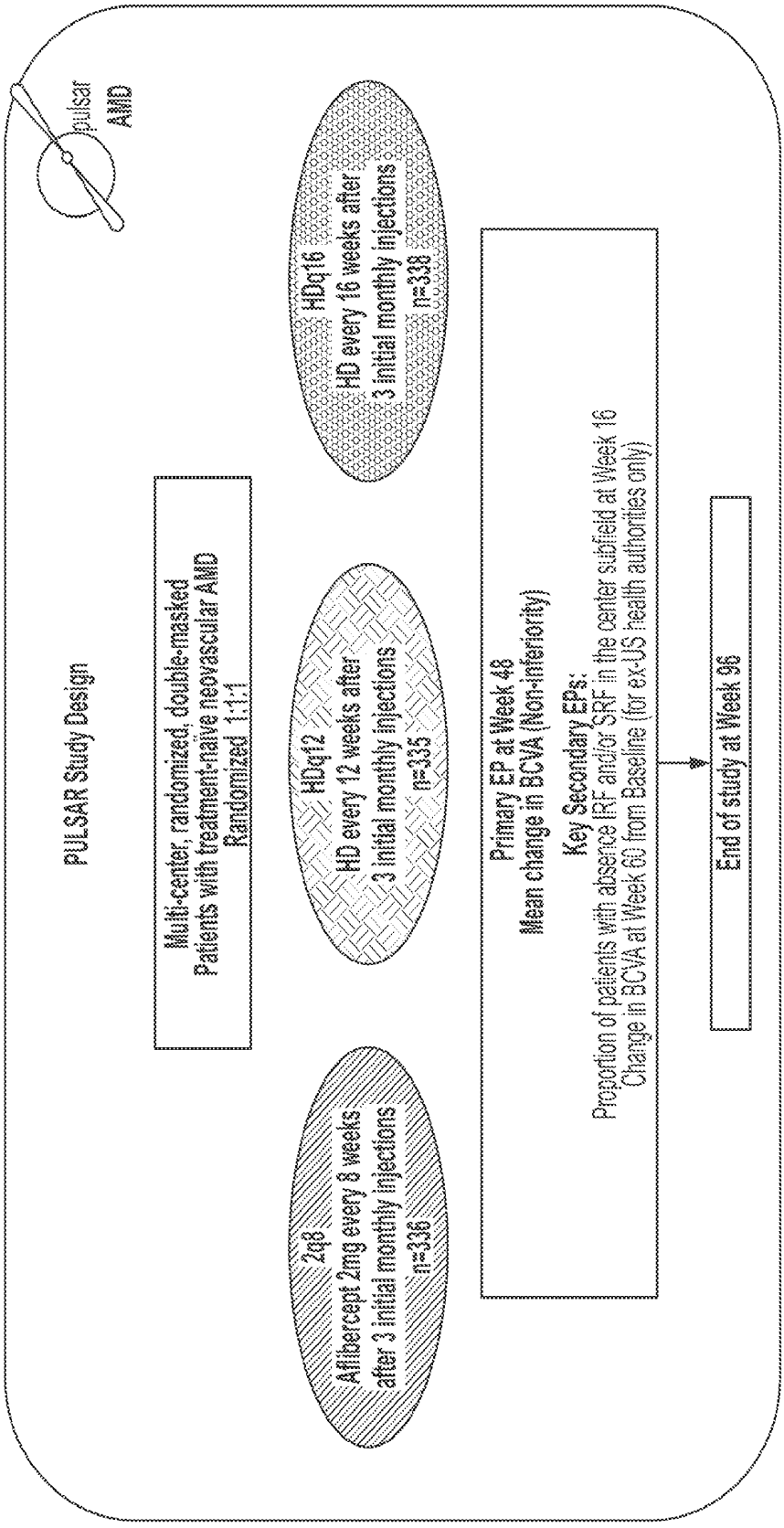

PULSAR Study Design
Pulsar AMD
Multi-center, randomized, double-masked
Patients with treatment-naive neovascular AMD
Randomized 1:1:1
2q8
Aflibercept 2mg every 8 weeks
after 3 initial monthly injections
n=336
HDq12
HD every 12 weeks after
3 initial monthly injections
n=335
HDq16
HD every 16 weeks after
3 initial monthly injections
n=338
Primary EP at Week 48
Mean change in BCVA (Non-inferiority)
Key Secondary EPs:
Proportion of patients with absence IRF and/or SRF in the center subfield at Week 16
Change in BCVA at Week 60 from Baseline (for ex-US health authorities only)
End of study at Week 96

FIG. 1

Key Eligibility Criteria
pulsar
AMD
Key Inclusion Criteria
Men or women ≥50 years of age with treatment-naive neovascular AMD (nAMD)
Active subfoveal CNV, with a total area > 50% of the total lesion area in the study eye
Presence of intraretinal and/or subretinal fluid in the central subfield on OCT
BCVA of 78 - 24 letters (Snellen equivalent 20/32 - 20/320) with decreased vision due to nAMD
Exclusion Criteria
Causes of CNV other than nAMD in the study eye
History or clinical evidence of diabetic retinopathy, diabetic macular edema, or any retinal vascular disease other than nAMD in either eye
Scar, fibrosis, atrophy or RPE tears/rips involving the central subfield in the study eye
IOP ≥25 mmHg in the study eye despite glaucoma treatment
Intraocular inflammation/infection in either eye within 12 weeks of the screening visit

FIG. 2

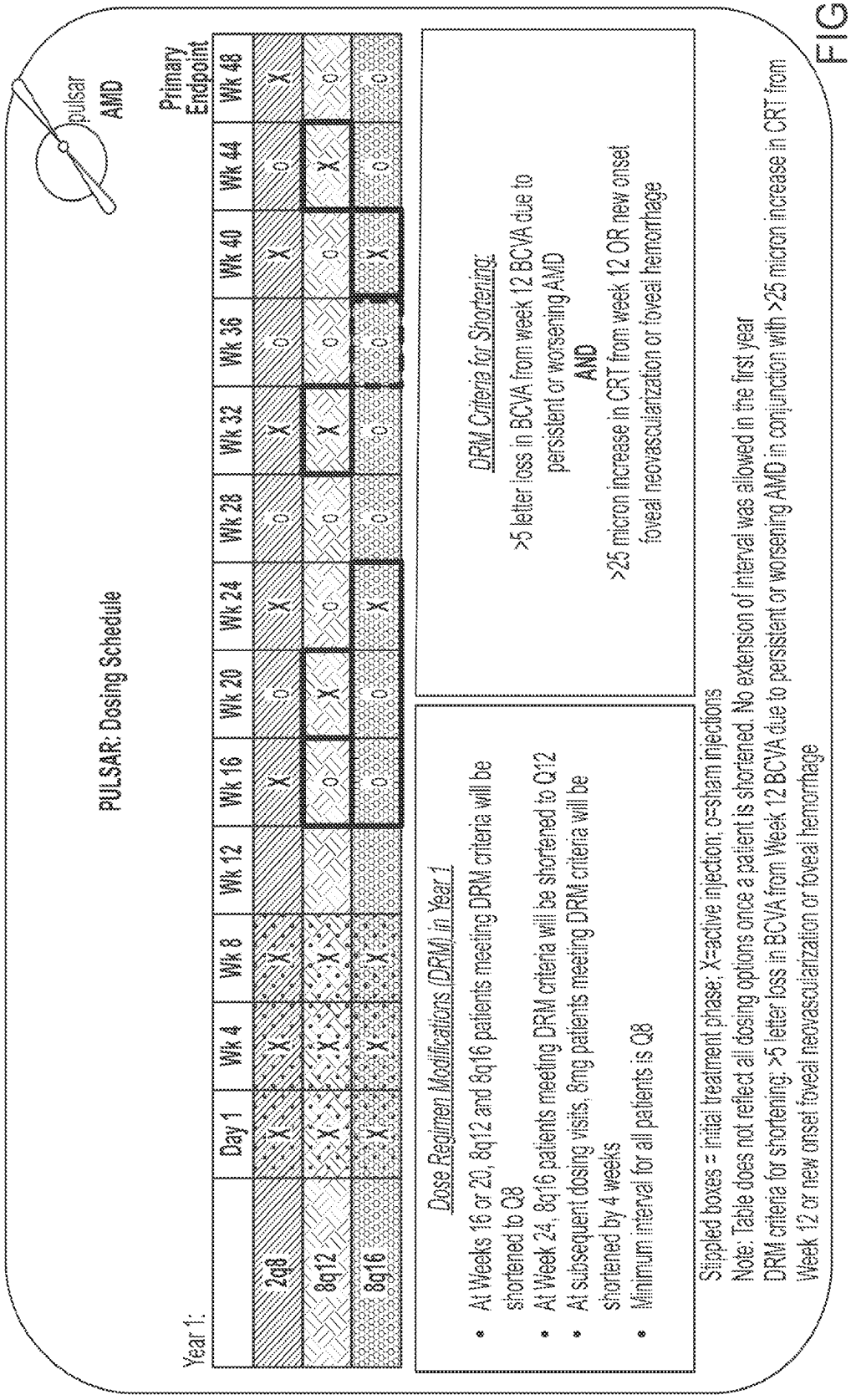

Year 1:
PULSAR: Dosing Schedule
Day 1
Wk 4
Wk 8
Wk 12
Wk 16
Wk 20
Wk 24
Wk 28
Wk 32
Wk 36
Wk 40
Wk 44
Wk 48
2q8
8q12
8q16
Primary Endpoint
pulsar AMD
Dose Regimen Modifications (DRM) in Year 1
At Weeks 16 or 20, 8q12 and 8q16 patients meeting DRM criteria will be shortened to Q8
At Week 24, 8q16 patients meeting DRM criteria will be shortened to Q12
At subsequent dosing visits, 8mg patients meeting DRM criteria will be shortened by 4 weeks
Minimum interval for all patients is Q8
DRM Criteria for Shortening:
>5 letter loss in BCVA from week 12 BCVA due to persistent or worsening AMD
AND
>25 micron increase in CRT from week 12 OR new onset foveal neovascularization or foveal hemorrhage
Stippled boxes = initial treatment phase; X=active injection; o=sham injections
Note: Table does not reflect all dosing options once a patient is shortened. No extension of interval was allowed in the first year
DRM criteria for shortening: >5 letter loss in BCVA from Week 12 BCVA due to persistent or worsening AMD in conjunction with >25 micron increase in CRT from Week 12 or new onset foveal neovascularization or foveal hemorrhage

FIG. 3

Criteria for Dose Regimen Modifications
Criteria for shortening*:
>5 letter loss in BCVA from week 12 BCVA due to persistent or worsening AMD
AND
>25 micron increase in CRT from week 12 value OR new onset foveal neovascularization or foveal hemorrhage
Apulsar AMD
HDq12 group:
If criteria are met at Week 16 or 20, patient will continue q8
HDq16 group:
If criteria are met at week 16 or 20, patient will continue q8
If criteria are met at week 24, patient will continue q12
For HD patients on a q12 or q16 interval, next dosing interval is reduced by 4 weeks if DRM criteria are met at dosing visits
For HD patients on a dosing interval of q8 weeks, no additional interval shortening can occur
*No extension of interval was allowed in the first year.

FIG. 4

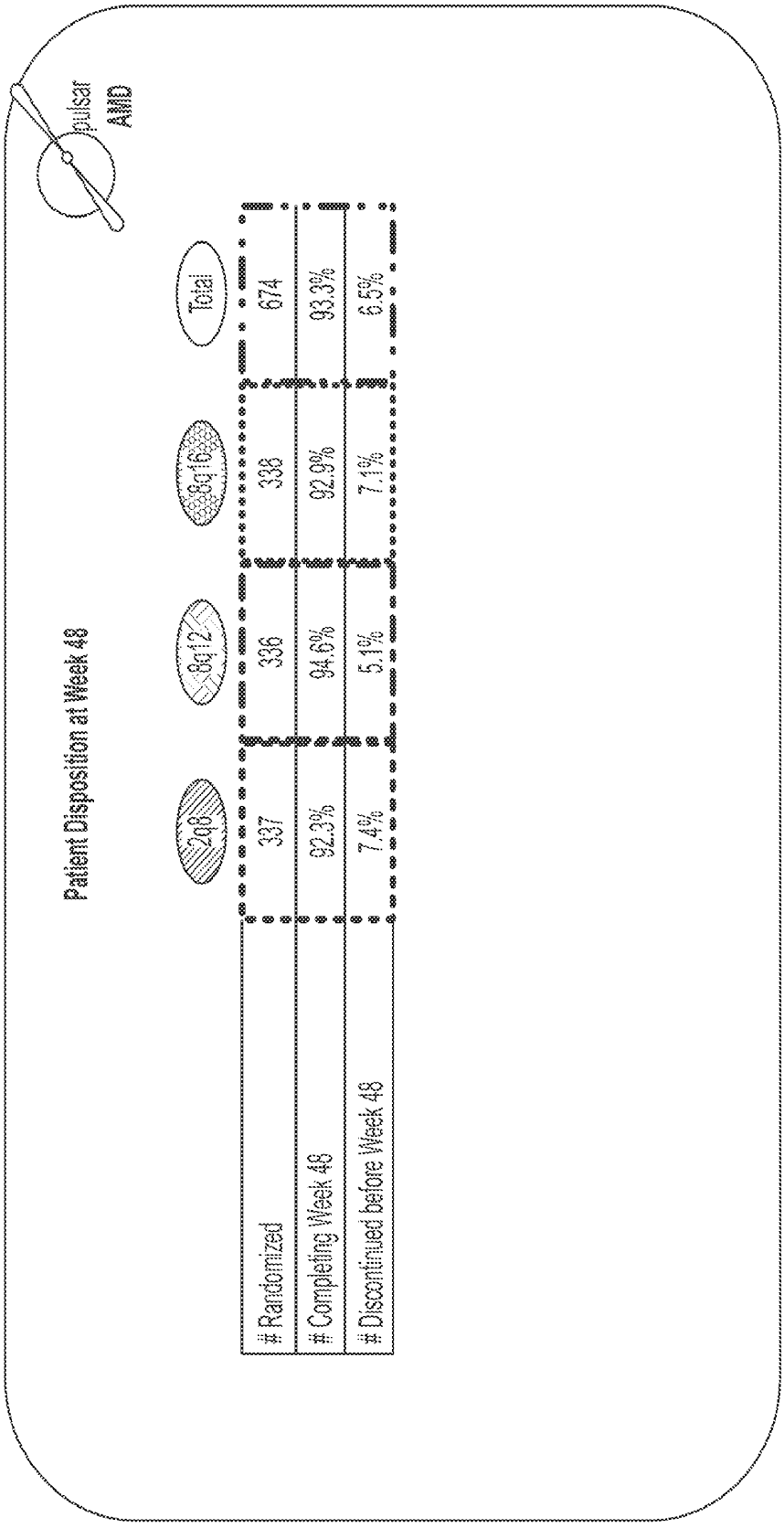

Patient Disposition at Week 48
Apulsar
AMD
2q8
8q12
8q16
Total
Randomized
337
336
338
674
Completing Week 48
92.3%
94.6%
92.9%
93.3%
Discontinued before Week 48
7.4%
5.1%
7.1%
6.5%

FIG. 5

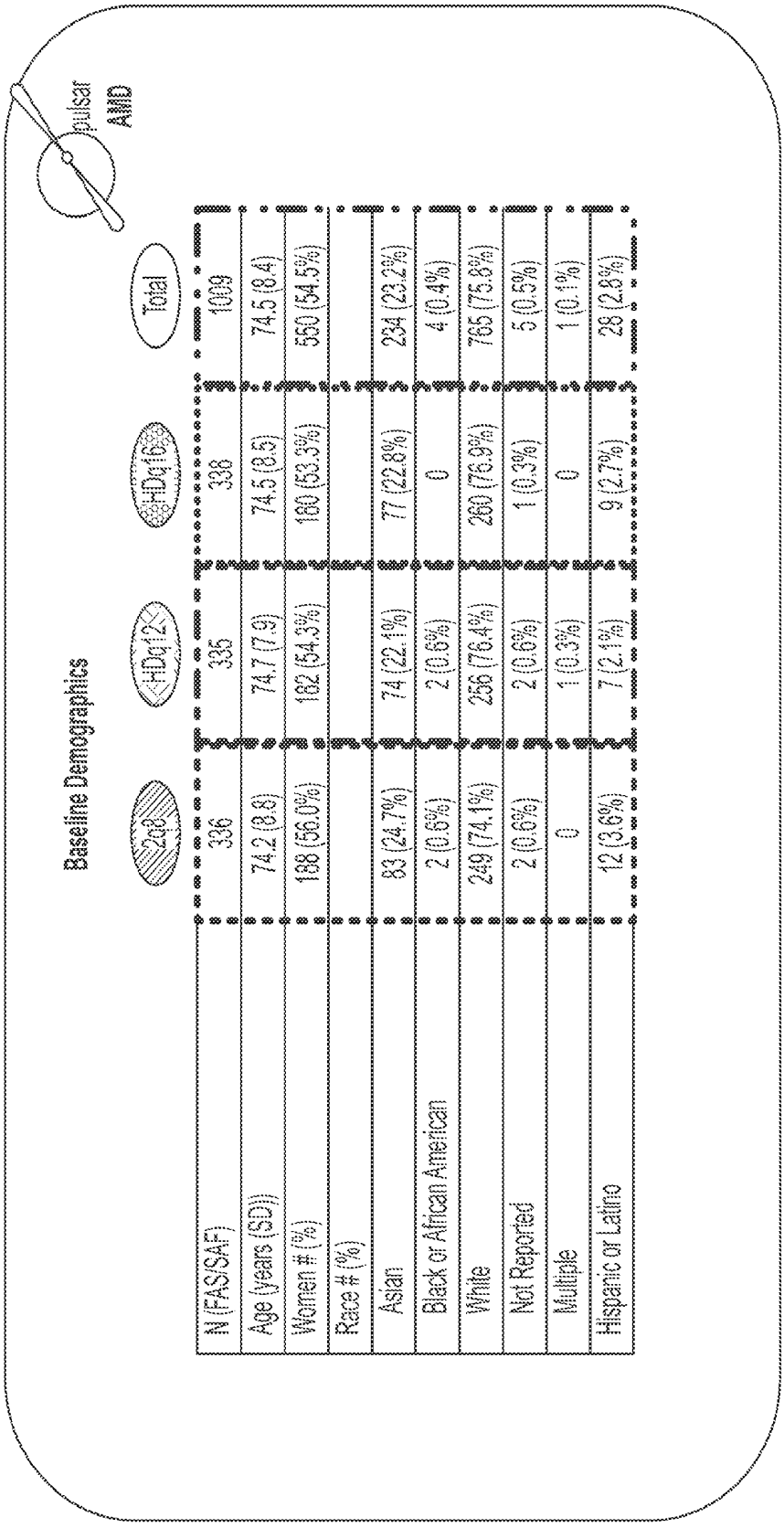

Pulsar
AMD
Baseline Demographics
2q8
HDq12
HDq16
Total
N (FAS/SAF) 336 335 336 1009
Age (years (SD)) 74.2 (8.8) 74.7 (7.9) 74.5 (8.5) 74.5 (8.4)
Women # (%) 188 (56.0%) 182 (54.3%) 180 (53.3%) 550 (54.5%)
Race # (%)
Asian 83 (24.7%) 74 (22.1%) 77 (22.8%) 234 (23.2%)
Black or African American 2 (0.6%) 2 (0.6%) 0 4 (0.4%)
White 249 (74.1%) 256 (76.4%) 260 (76.9%) 765 (75.8%)
Not Reported 2 (0.6%) 2 (0.6%) 1 (0.3%) 5 (0.5%)
Multiple 0 1 (0.3%) 0 1 (0.1%)
Hispanic or Latino 12 (3.6%) 7 (2.1%) 9 (2.7%) 28 (2.8%)

FIG. 6

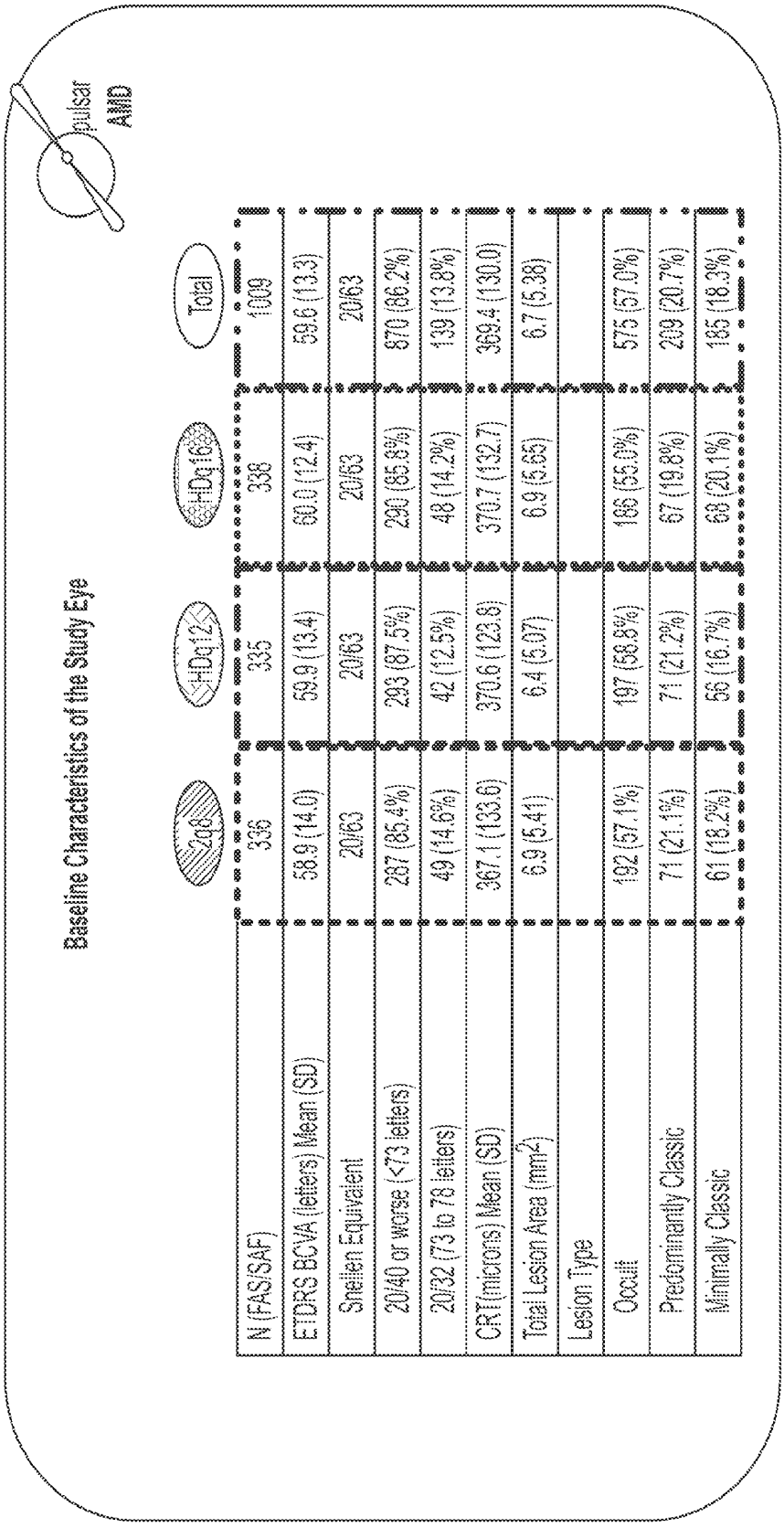

Pulsar
AMD
Baseline Characteristics of the Study Eye
2q8
1Dq12
1Dq16
Total
N (FAS/SAF) 336 335 338 1009
ETDRS BCVA (letters) Mean (SD) 58.9 (14.0) 59.9 (13.4) 60.0 (12.4) 59.6 (13.3)
Snellen Equivalent 20/63 20/63 20/63 20/63
20/40 or worse (<73 letters) 287 (85.4%) 293 (87.5%) 290 (85.8%) 870 (86.2%)
20/32 (73 to 78 letters) 49 (14.6%) 42 (12.5%) 48 (14.2%) 139 (13.8%)
CRT (microns) Mean (SD) 367.1 (133.6) 370.6 (123.8) 370.7 (132.7) 369.4 (130.0)
Total Lesion Area (mm2) 6.9 (5.41) 6.4 (5.07) 6.9 (5.65) 6.7 (5.38)
Lesion Type
Occult 192 (57.1%) 197 (58.8%) 186 (55.0%) 575 (57.0%)
Predominantly Classic 71 (21.1%) 71 (21.2%) 67 (19.8%) 209 (20.7%)
Minimally Classic 61 (18.2%) 56 (16.7%) 68 (20.1%) 185 (18.3%)

FIG. 7

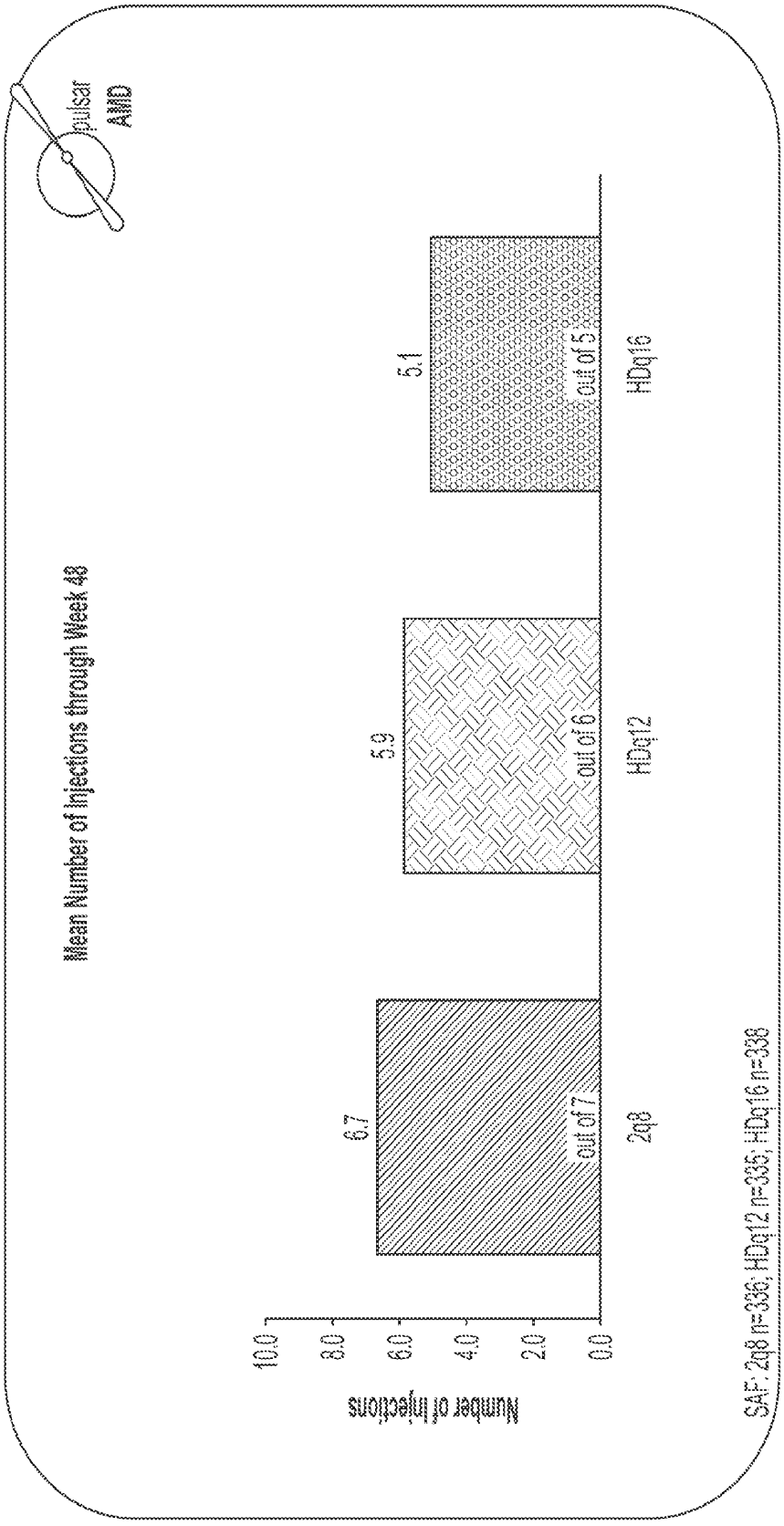

Apulsar
AMD
Mean Number of Injections through Week 48
Number of Injections
10.0
8.0
6.0
4.0
2.0
0.0
6.7
out of 7
2q8
5.9
out of 6
HDq12
5.1
out of 5
HDq16
SAF: 2q8 n=336; HDq12 n=335; HDq16 n=338

FIG. 8

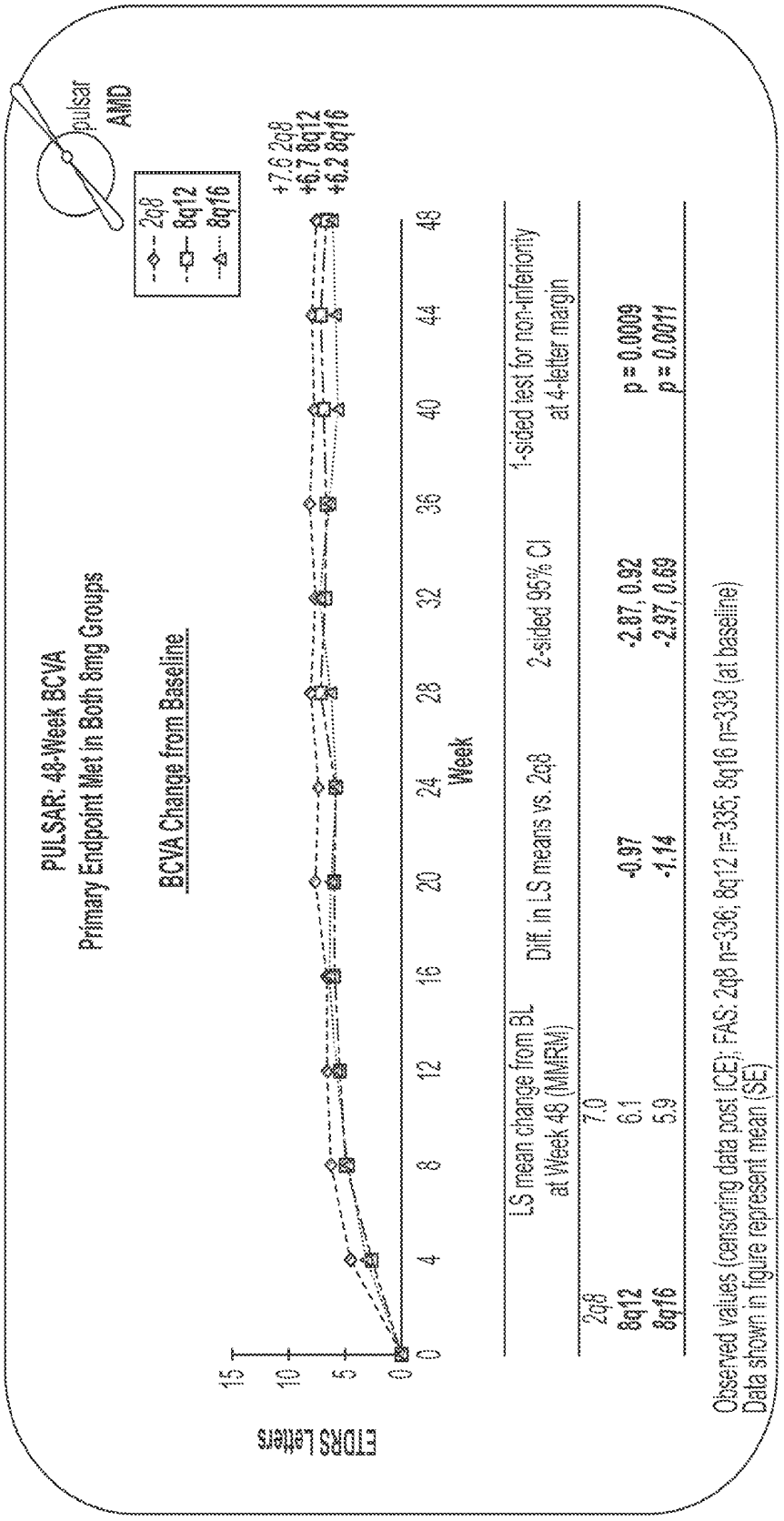

PULSAR: 48-Week BCVA
Primary Endpoint Met in Both 8mg Groups
BCVA Change from Baseline
pulsar
AMD
2q8
8q12
8q16
+7.6 2q8
+6.7 8q12
+6.2 8q16
ETDRS Letters
Week
LS mean change from BL at Week 48 (MMRM)
Diff. in LS means vs. 2q8
2-sided 95% CI
1-sided test for non-inferiority at 4-letter margin
2q8 7.0
8q12 6.1 -0.97 -2.87, 0.92 p = 0.0009
8q16 5.9 -1.14 -2.97, 0.69 p = 0.0011
Observed values (censoring data post ICE); FAS: 2q8 n=336; 8q12 n=336; 8q16 n=330 (at baseline)
Data shown in figure represent mean (SE)

FIG. 9

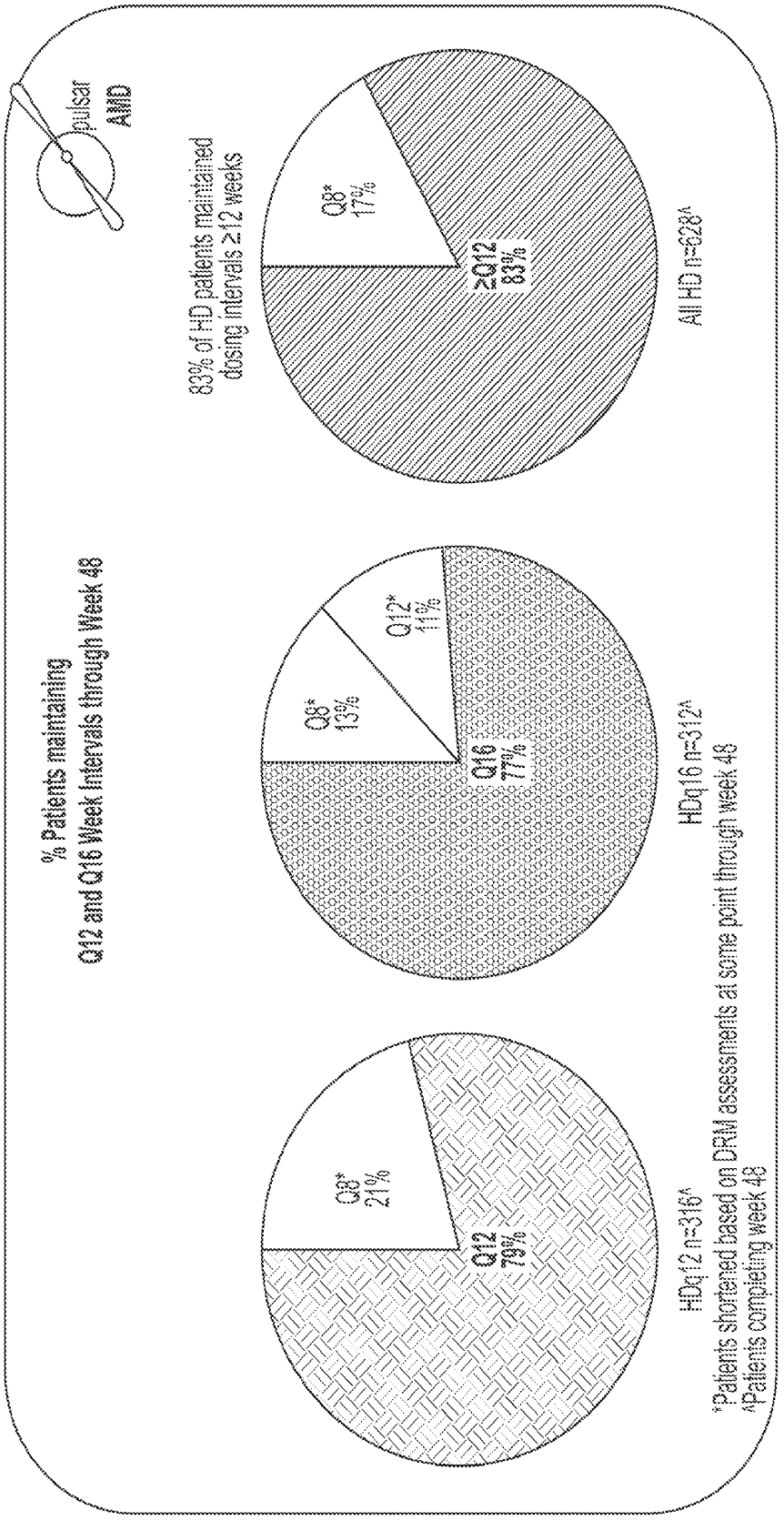

pulsar
AMD
% Patients maintaining
Q12 and Q16 Week Intervals through Week 48
83% of HD patients maintained dosing intervals ≥12 weeks
Q8*
17%
≥Q12
83%
All HD n=628^
Q8*
13%
Q12*
11%
Q16
77%
HDq16 n=312^
Q8*
21%
Q12
79%
HDq12 n=316^
*Patients shortened based on DRM assessments at some point through week 48
^Patients completing week 48

FIG. 10

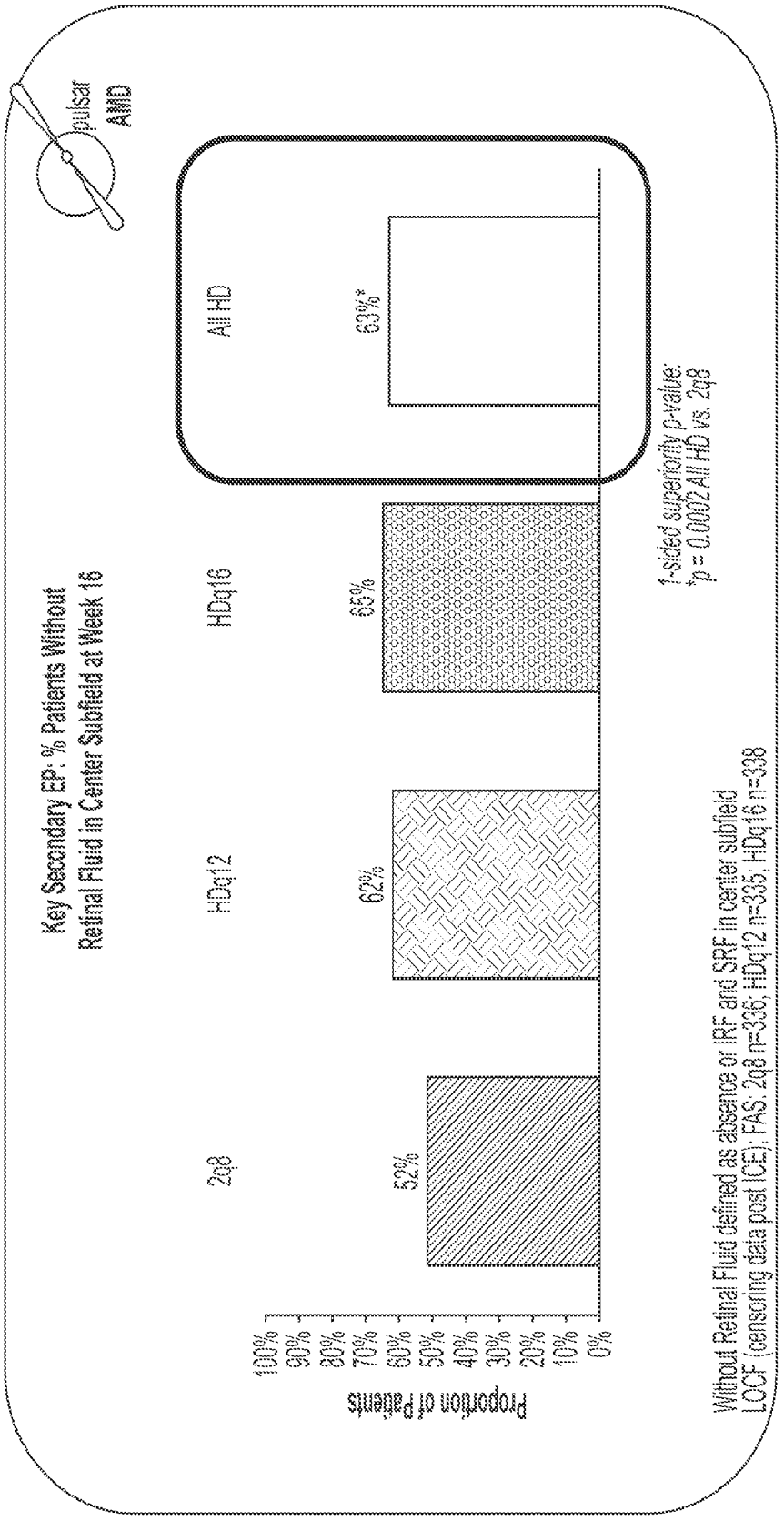

pulsar
AMD
Key Secondary EP: % Patients Without Retinal Fluid in Center Subfield at Week 16
Proportion of Patients
100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
2q8
HDq12
HDq16
All HD
52%
62%
65%
63%*
1-sided superiority p-value:
*p = 0.0002 All HD vs. 2q8
Without Retinal Fluid defined as absence of IRF and SRF in center subfield
LOCF (censoring data post (CE); FAS: 2q8 n=336; HDq12 n=335; HDq16 n=338

FIG. 11

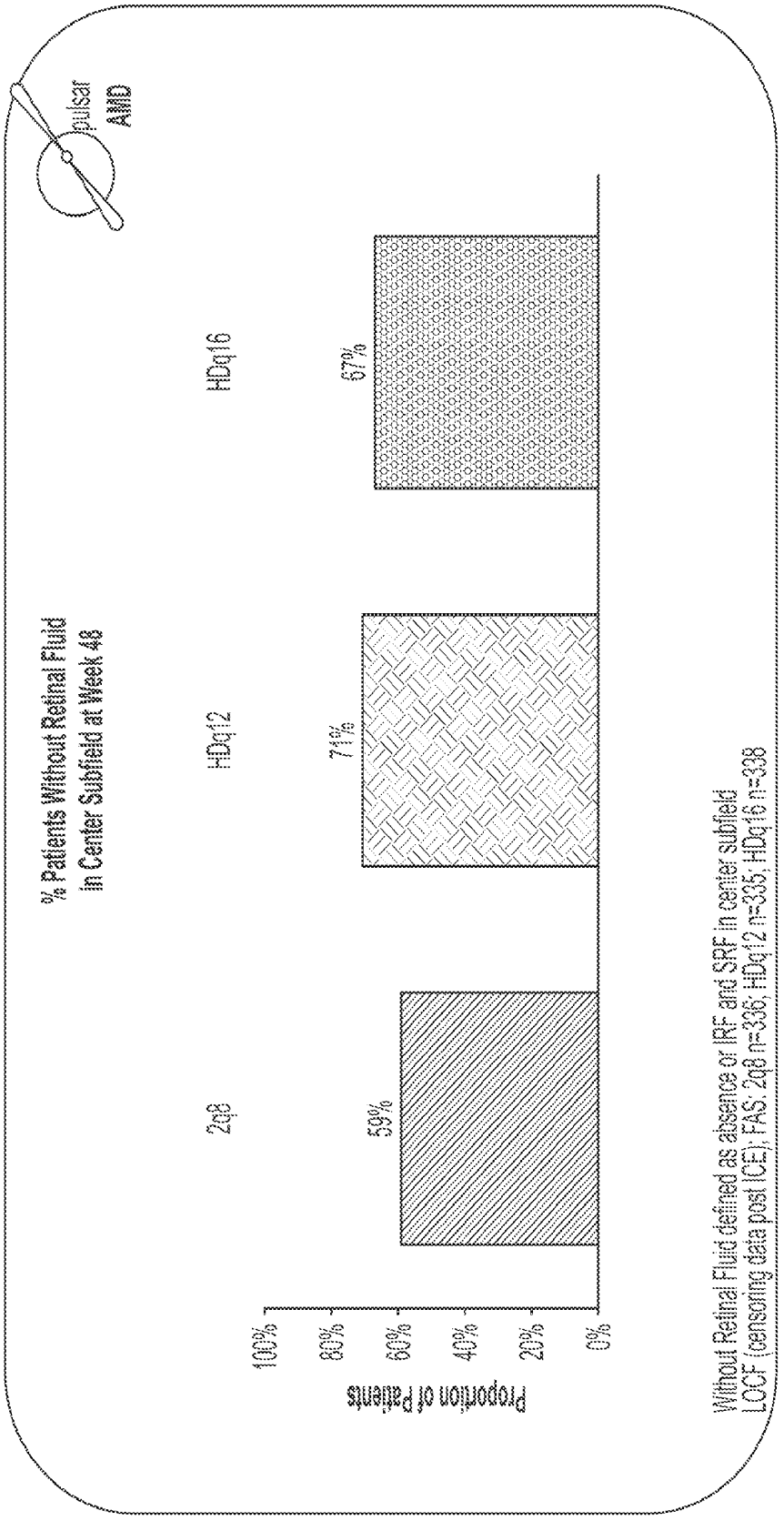

Apulsar
AMD
% Patients Without Retinal Fluid
in Center Subfield at Week 48
Proportion of Patients
100%
80%
60%
40%
20%
0%
59%
71%
67%
2q8
HDq12
HDq16
Without Retinal Fluid defined as absence of IRF and SRF in center subfield
LOCF (censoring data post ICE); FAS: 2q8 n=336; HDq12 n=335; HDq16 n=338

FIG. 12

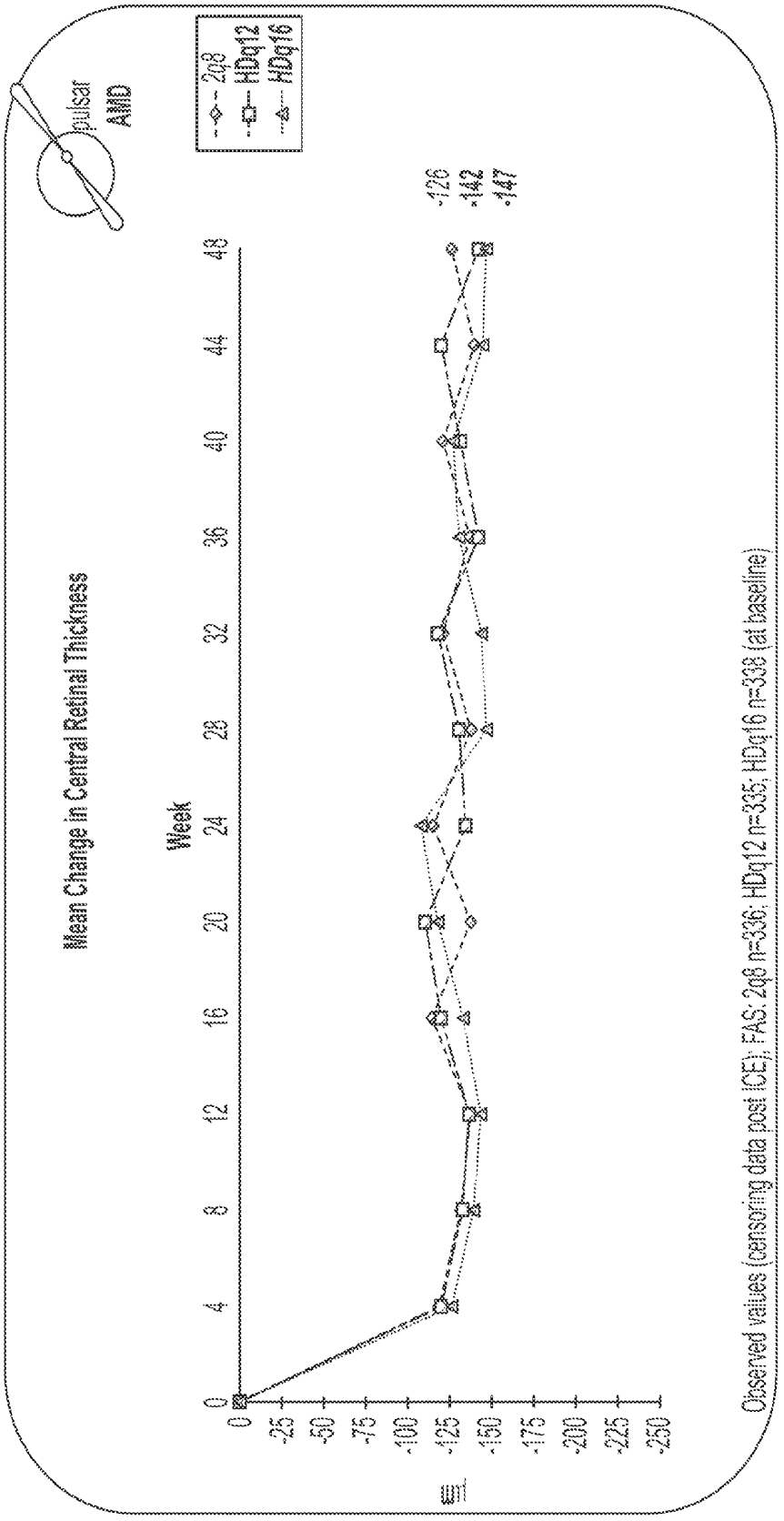

Mean Change in Central Retinal Thickness
Week
0
4
8
12
16
20
24
28
32
36
40
44
48
0
-25
-50
-75
-100
-125
-150
-175
-200
-225
-250
2q8
HDq12
HDq16
-126
-142
-147
Observed values (censoring data post ICE); FAS: 2q8 n=336; HDq12 n=335; HDq16 n=338 (at baseline)
pulsar
AMD

FIG. 13A

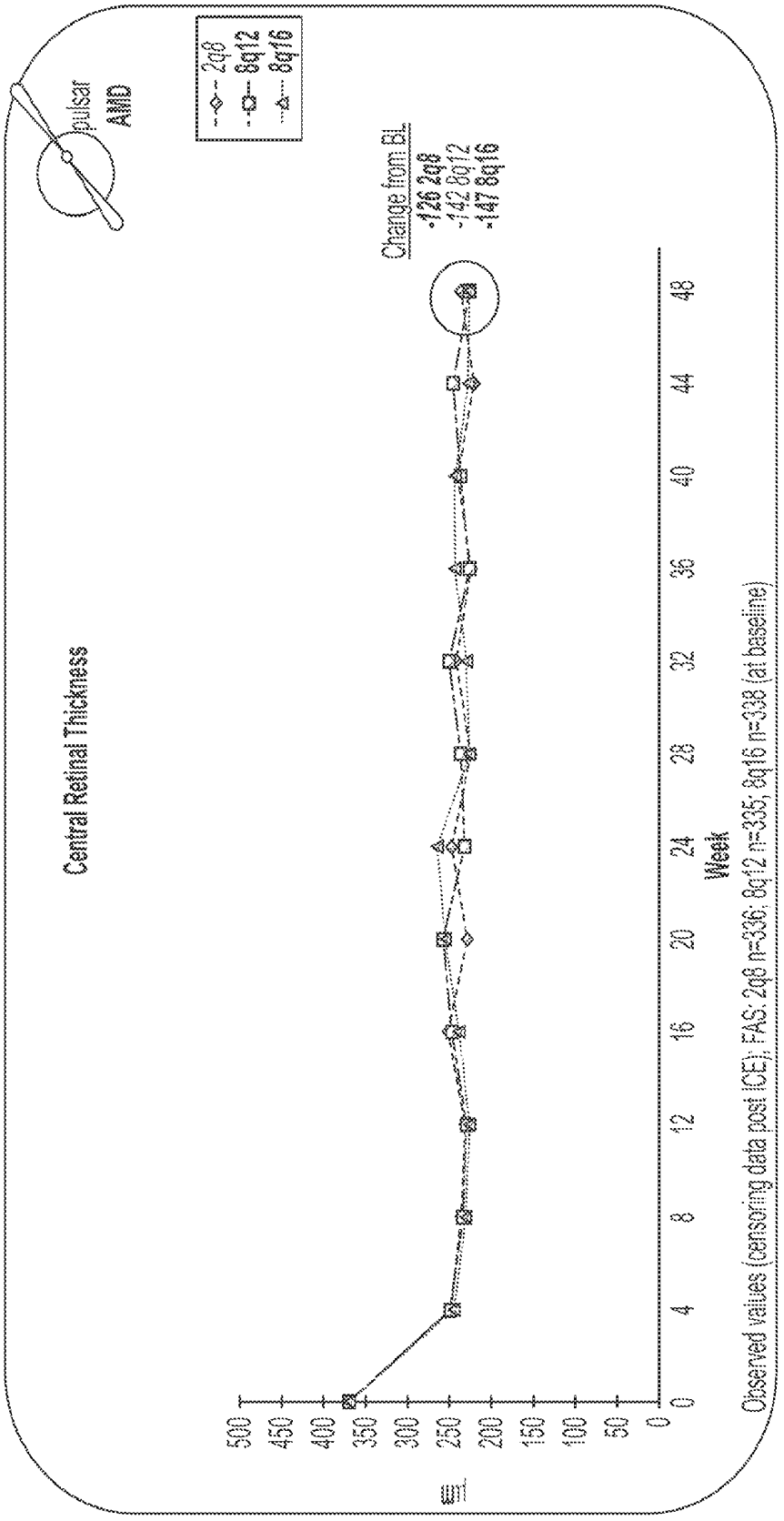
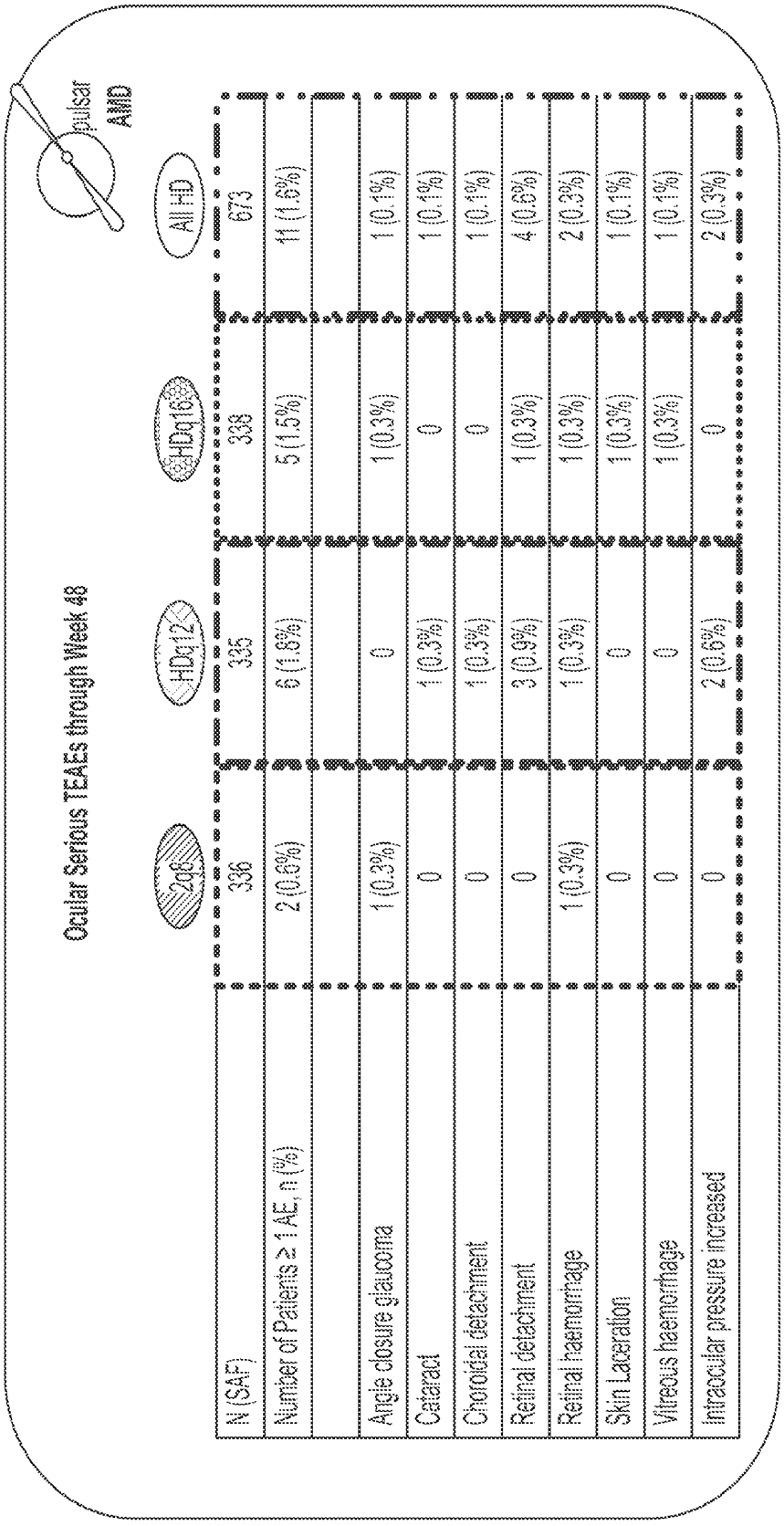

pulsar
AMD
2q8
8q12
8q16
Change from BL
-126 2q8
-142 8q12
-147 8q16
Central Retinal Thickness
Week
0
4
8
12
16
20
24
28
32
36
40
44
48
500
450
400
350
300
250
200
150
100
50
Observed values (censoring data post ICE); FAS: 2q8 n=336; 8q12 n=335; 8q16 n=338 (at baseline)

FIG. 13B



N (SAF)	336	335	338	673
Number of Patients ≥ 1 AE, n (%)	2 (0.6%)	6 (1.8%)	5 (1.5%)	11 (1.6%)
Angle closure glaucoma	1 (0.3%)	0	1 (0.3%)	1 (0.1%)
Cataract	0	1 (0.3%)	0	1 (0.1%)
Choroidal detachment	0	1 (0.3%)	0	1 (0.1%)
Retinal detachment	0	3 (0.9%)	1 (0.3%)	4 (0.6%)
Retinal haemorrhage	1 (0.3%)	1 (0.3%)	1 (0.3%)	2 (0.3%)
Skin Laceration	0	0	1 (0.3%)	1 (0.1%)
Vitreous haemorrhage	0	0	1 (0.3%)	1 (0.1%)
Intraocular pressure increased	0	2 (0.6%)	0	2 (0.3%)

FIG. 14A

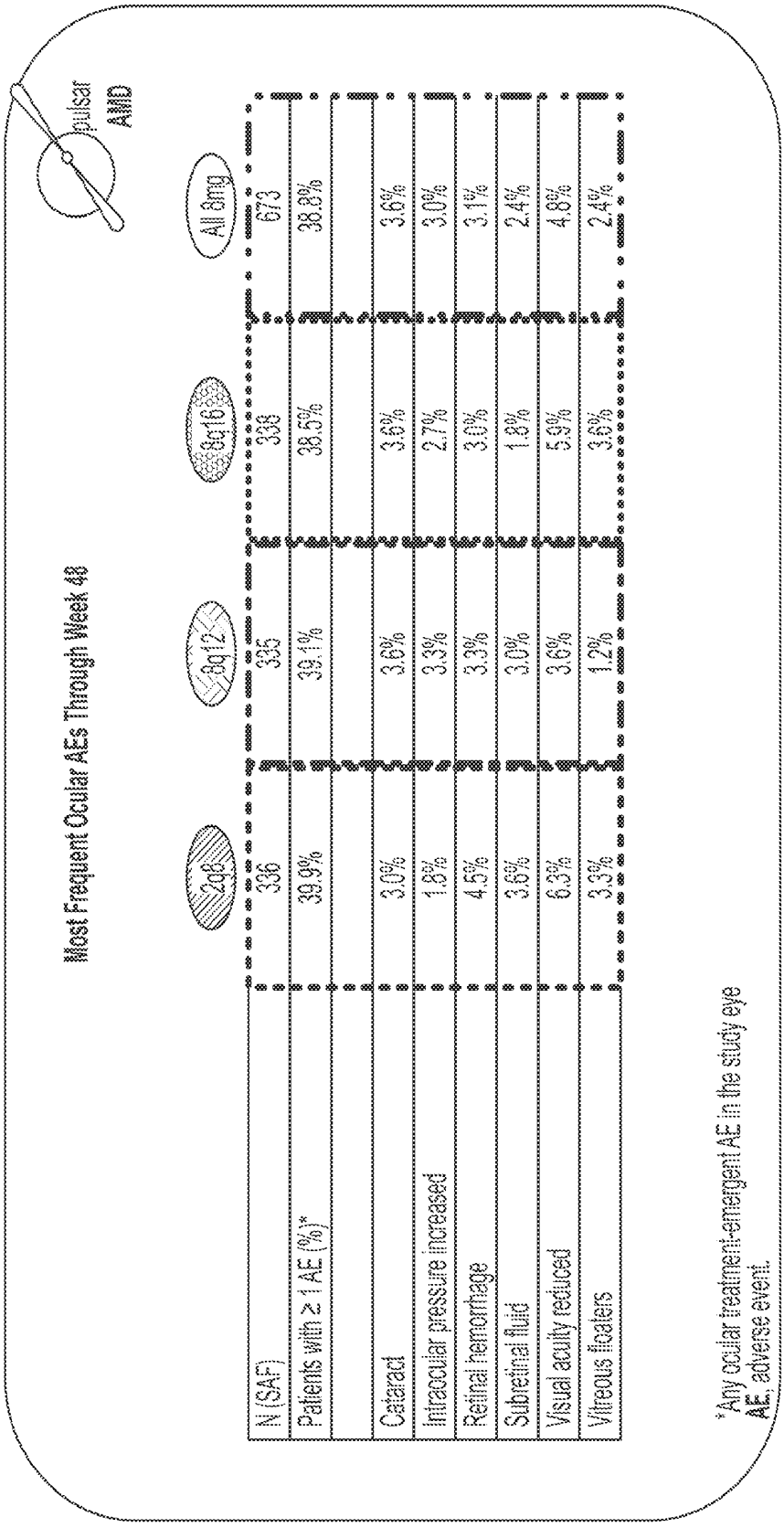

pulsar
AMD
Most Frequent Ocular AEs Through Week 48
2q8
8q12
8q16
All 8mg
N (SAF) 336 335 336 673
Patients with ≥ 1 AE (%)* 39.9% 39.1% 38.5% 38.8%
Cataract 3.0% 3.6% 3.6% 3.6%
Intraocular pressure increased 1.8% 3.3% 2.7% 3.0%
Retinal hemorrhage 4.5% 3.3% 3.0% 3.1%
Subretinal fluid 3.6% 3.0% 1.8% 2.4%
Visual acuity reduced 6.3% 3.6% 5.9% 4.8%
Vitreous floaters 3.3% 1.2% 3.6% 2.4%
*Any ocular treatment-emergent AE in the study eye
AE, adverse event.

FIG. 14B

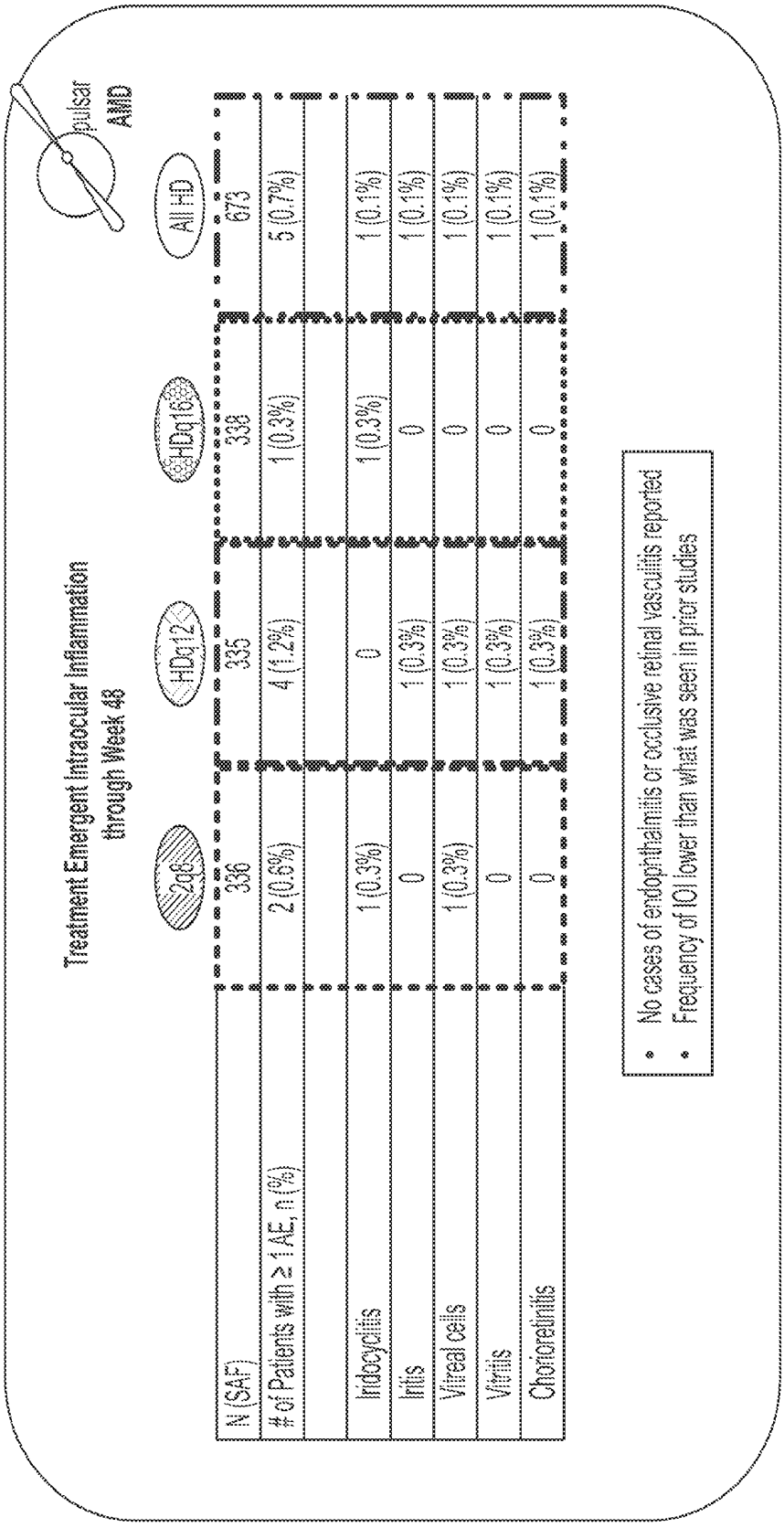

Treatment Emergent Intraocular Inflammation through Week 48
2q8
HDq12
HDq16
All HD
N (SAF) 336 335 338 673
# of Patients with ≥ 1 AE, n (%) 2 (0.6%) 4 (1.2%) 1 (0.3%) 5 (0.7%)
Iridocyclitis 1 (0.3%) 0 1 (0.3%) 1 (0.1%)
Iritis 0 1 (0.3%) 0 1 (0.1%)
Vitreal cells 1 (0.3%) 1 (0.3%) 0 1 (0.1%)
Vitritis 0 1 (0.3%) 0 1 (0.1%)
Chorioretinitis 0 1 (0.3%) 0 1 (0.1%)
No cases of endophthalmitis or occlusive retinal vasculitis reported
Frequency of IOI lower than what was seen in prior studies
pulsar
AMD

FIG. 15

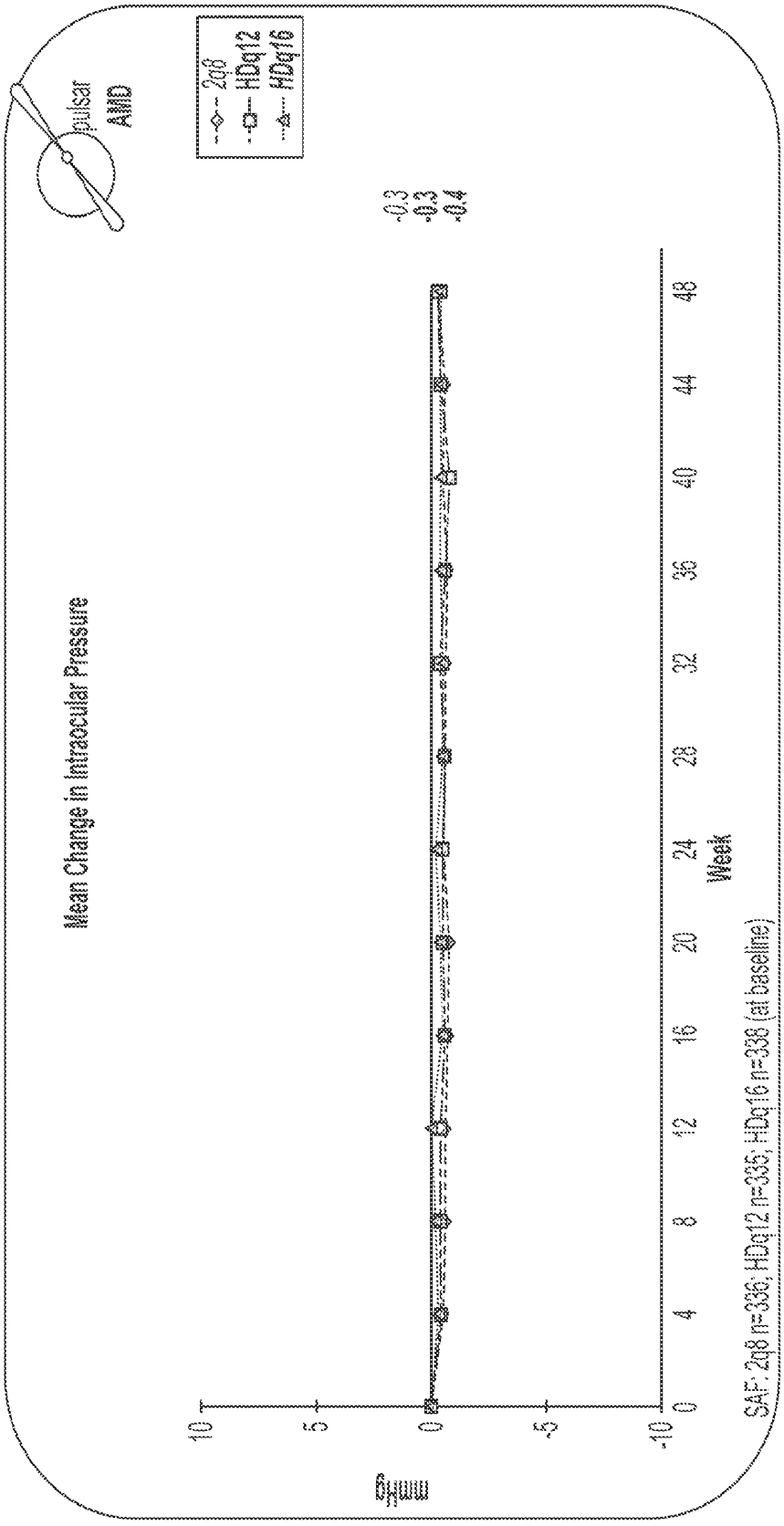

Mean Change in Intraocular Pressure
Pulsar
AMD
2q8
HDq12
HDq16
-0.3
-0.3
-0.4
mmHg
10
5
0
-5
-10
0
4
8
12
16
20
24
28
32
36
40
44
48
Week
SAF: 2q8 n=336; HDq12 n=335; HDq16 n=338 (at baseline)

FIG. 16

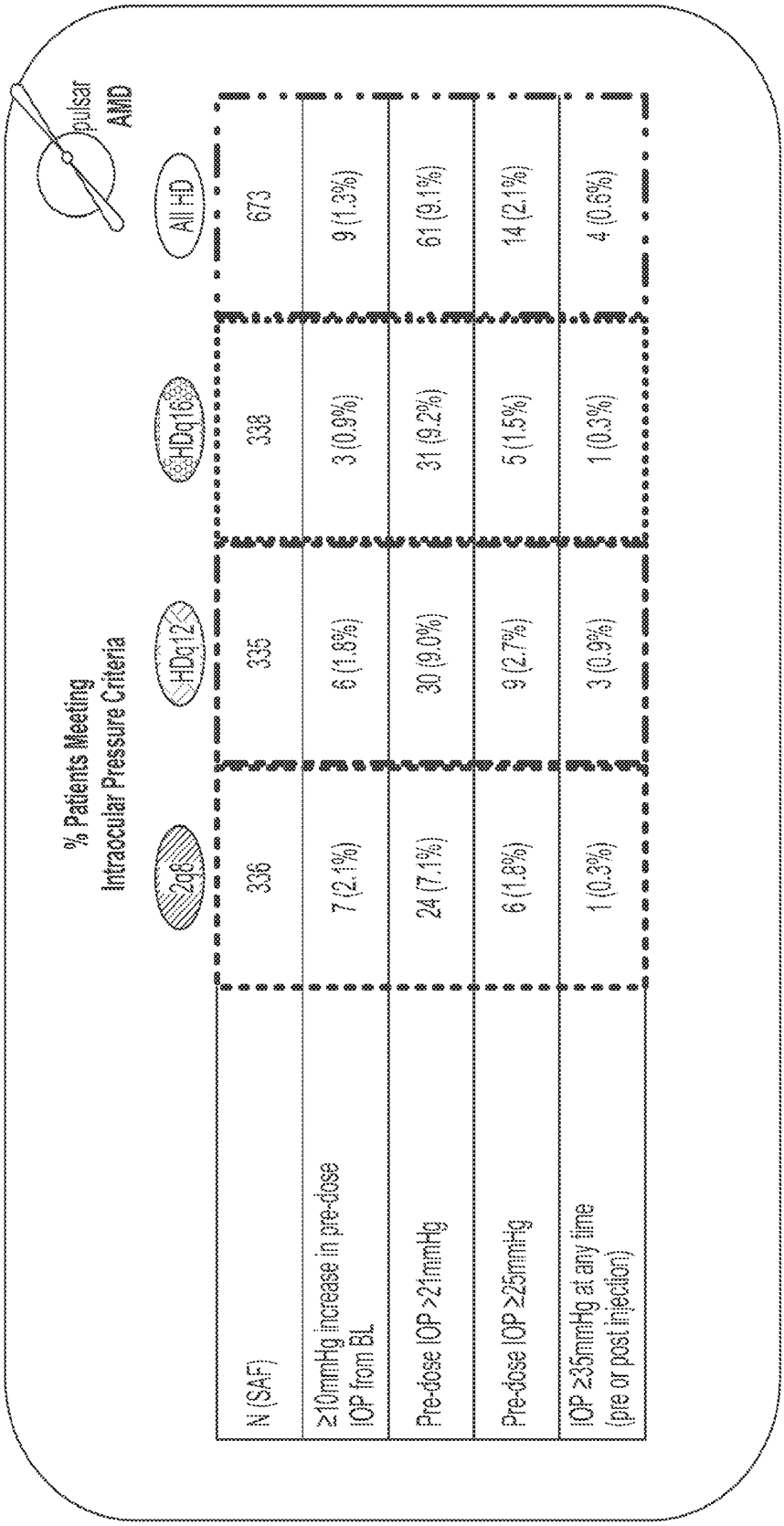
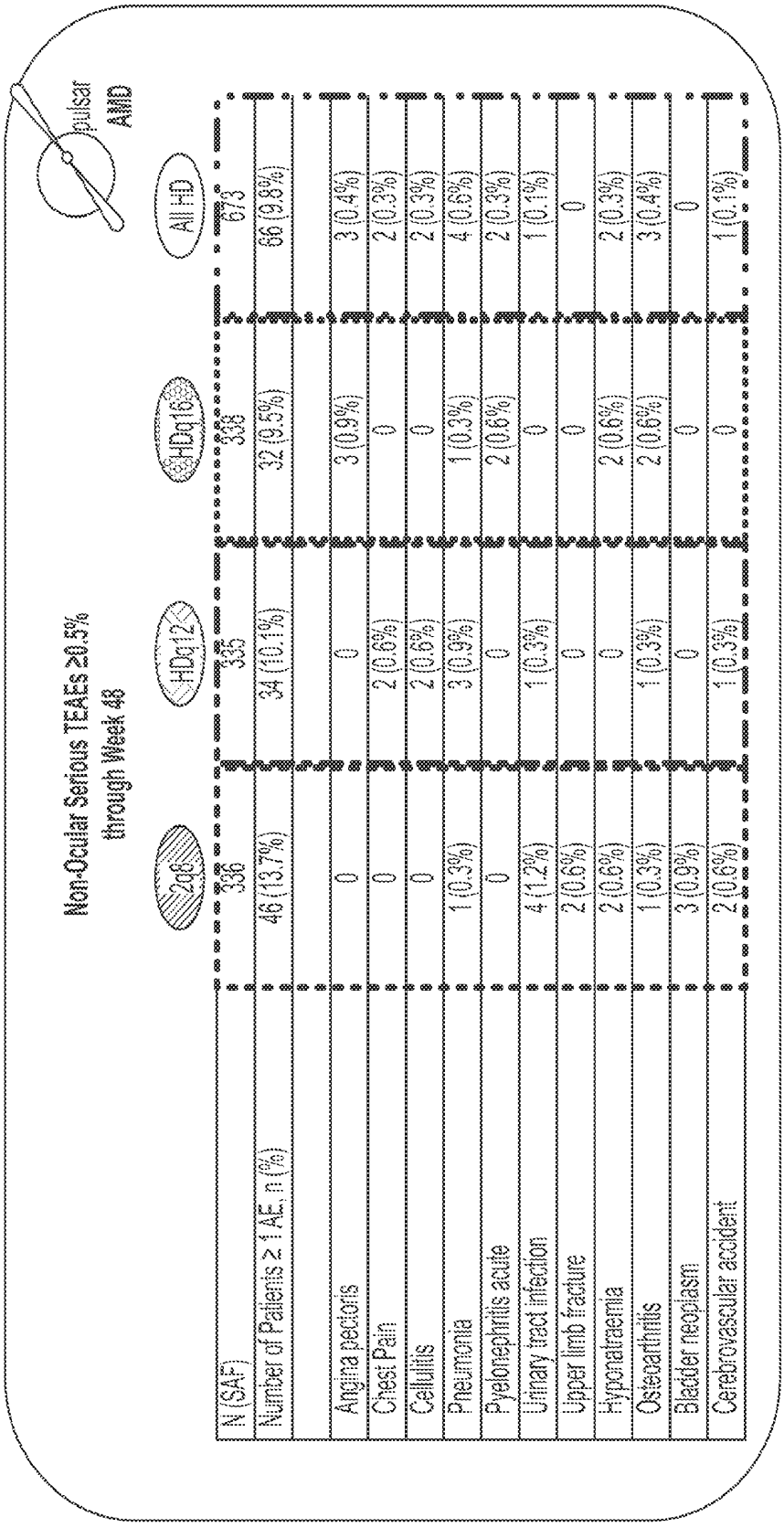

Apulsar
AMD
% Patients Meeting
Intraocular Pressure Criteria
2q8
HDq12
HDq16
All HD
N (SAF) 336 335 338 673
≥10mmHg increase in pre-dose IOP from BL 7 (2.1%) 6 (1.8%) 3 (0.9%) 9 (1.3%)
Pre-dose IOP >21mmHg 24 (7.1%) 30 (9.0%) 31 (9.2%) 61 (9.1%)
Pre-dose IOP ≥25mmHg 6 (1.8%) 9 (2.7%) 5 (1.5%) 14 (2.1%)
IOP ≥35mmHg at any time (pre or post injection) 1 (0.3%) 3 (0.9%) 1 (0.3%) 4 (0.6%)

FIG. 17



N (SAF)	336	335	338	673
Number of Patients ≥ 1 AE, n (%)	46 (13.7%)	34 (10.1%)	32 (9.5%)	66 (9.8%)
Angina pectoris	0	0	3 (0.9%)	3 (0.4%)
Chest Pain	0	2 (0.6%)	0	2 (0.3%)
Cellulitis	0	2 (0.6%)	0	2 (0.3%)
Pneumonia	1 (0.3%)	3 (0.9%)	1 (0.3%)	4 (0.6%)
Pyelonephritis acute	0	0	2 (0.6%)	2 (0.3%)
Urinary tract infection	4 (1.2%)	1 (0.3%)	0	1 (0.1%)
Upper limb fracture	2 (0.6%)	0	0	0
Hyponatraemia	2 (0.6%)	0	2 (0.6%)	2 (0.3%)
Osteoarthritis	1 (0.3%)	1 (0.3%)	2 (0.6%)	3 (0.4%)
Bladder neoplasm	3 (0.9%)	0	0	0
Cerebrovascular accident	2 (0.6%)	1 (0.3%)	0	1 (0.1%)

FIG. 18

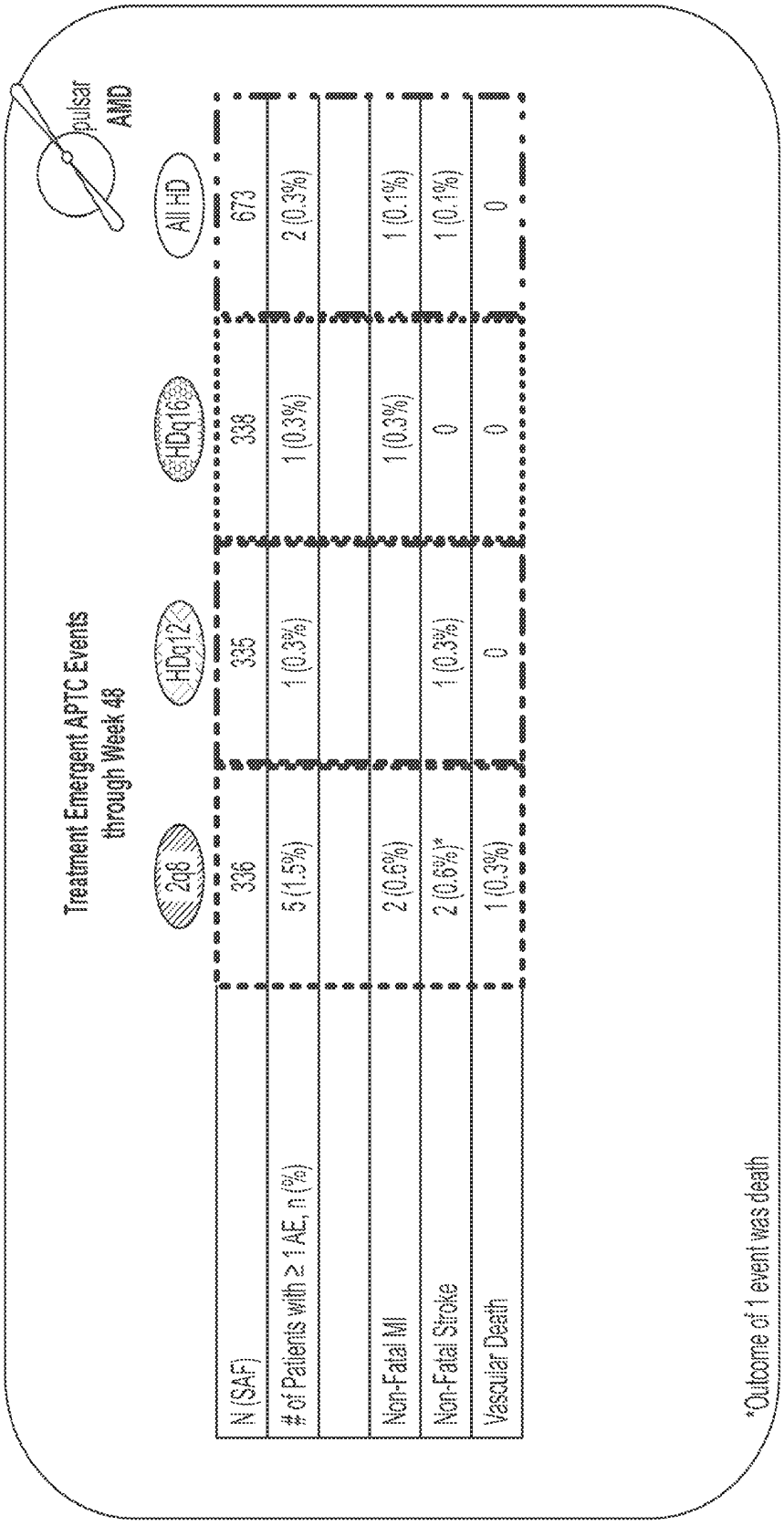

Treatment Emergent APTC Events
through Week 48
2q6
HDq12
eHDq16
All HD
Apulsar
AMD
N (SAF) 336 335 338 673
# of Patients with ≥ 1 AE, n (%) 5 (1.5%) 1 (0.3%) 1 (0.3%) 2 (0.3%)
Non-Fatal MI 2 (0.6%) 1 (0.3%) 1 (0.1%)
Non-Fatal Stroke 2 (0.6%)* 1 (0.3%) 0 1 (0.1%)
Vascular Death 1 (0.3%) 0 0 0
*Outcome of 1 event was death

FIG. 19A

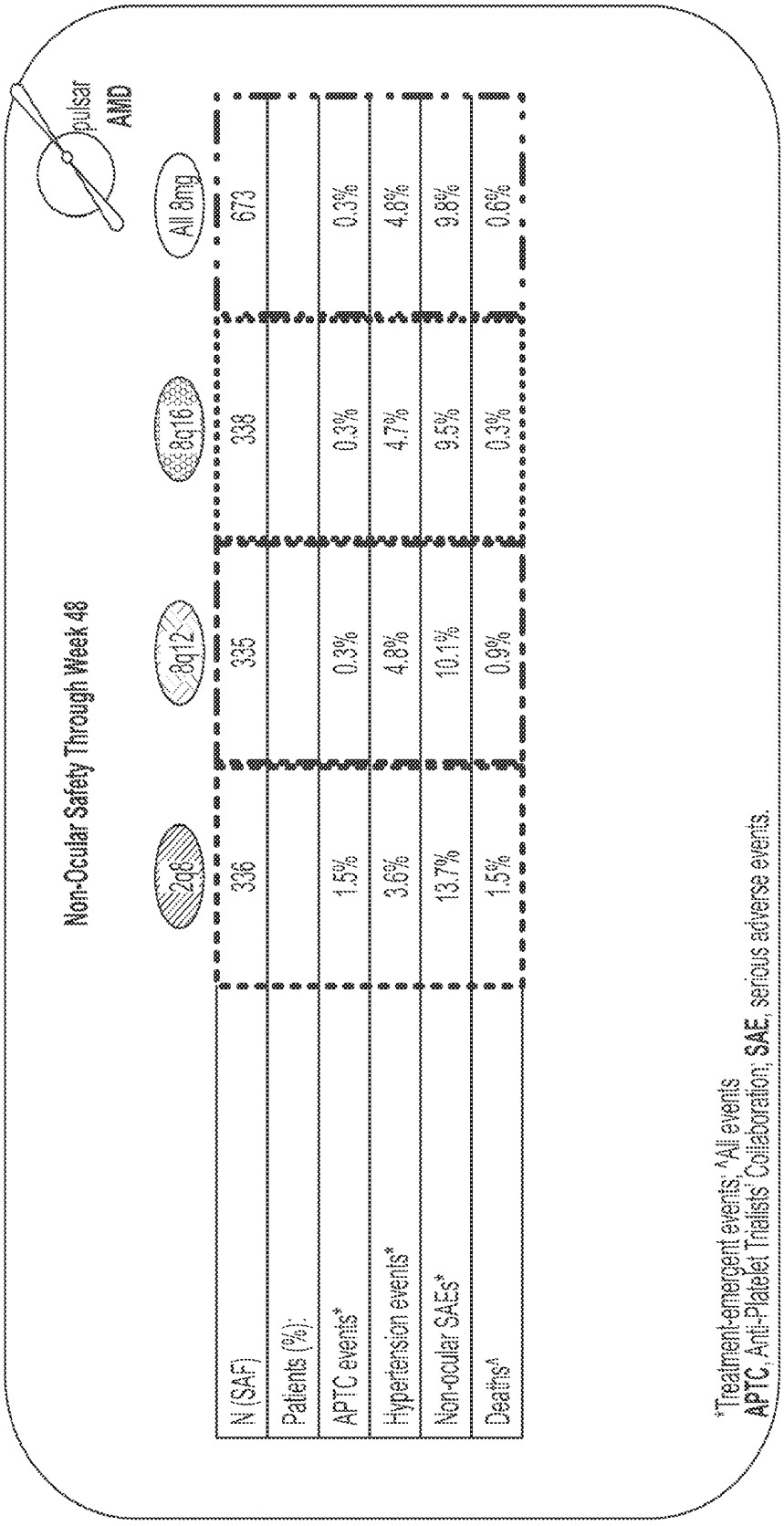

Non-Ocular Safety Through Week 48
2q8
3q12
8q16
All 8mg
N (SAF) 336 335 338 673
Patients (%):
APTC events* 1.5% 0.3% 0.3% 0.3%
Hypertension events* 3.6% 4.8% 4.7% 4.8%
Non-ocular SAEs* 13.7% 10.1% 9.5% 9.8%
Deaths^ 1.5% 0.9% 0.3% 0.6%
*Treatment-emergent events; ^All events
APTC, Anti-Platelet Trialists' Collaboration; SAE, serious adverse events.

FIG. 19B

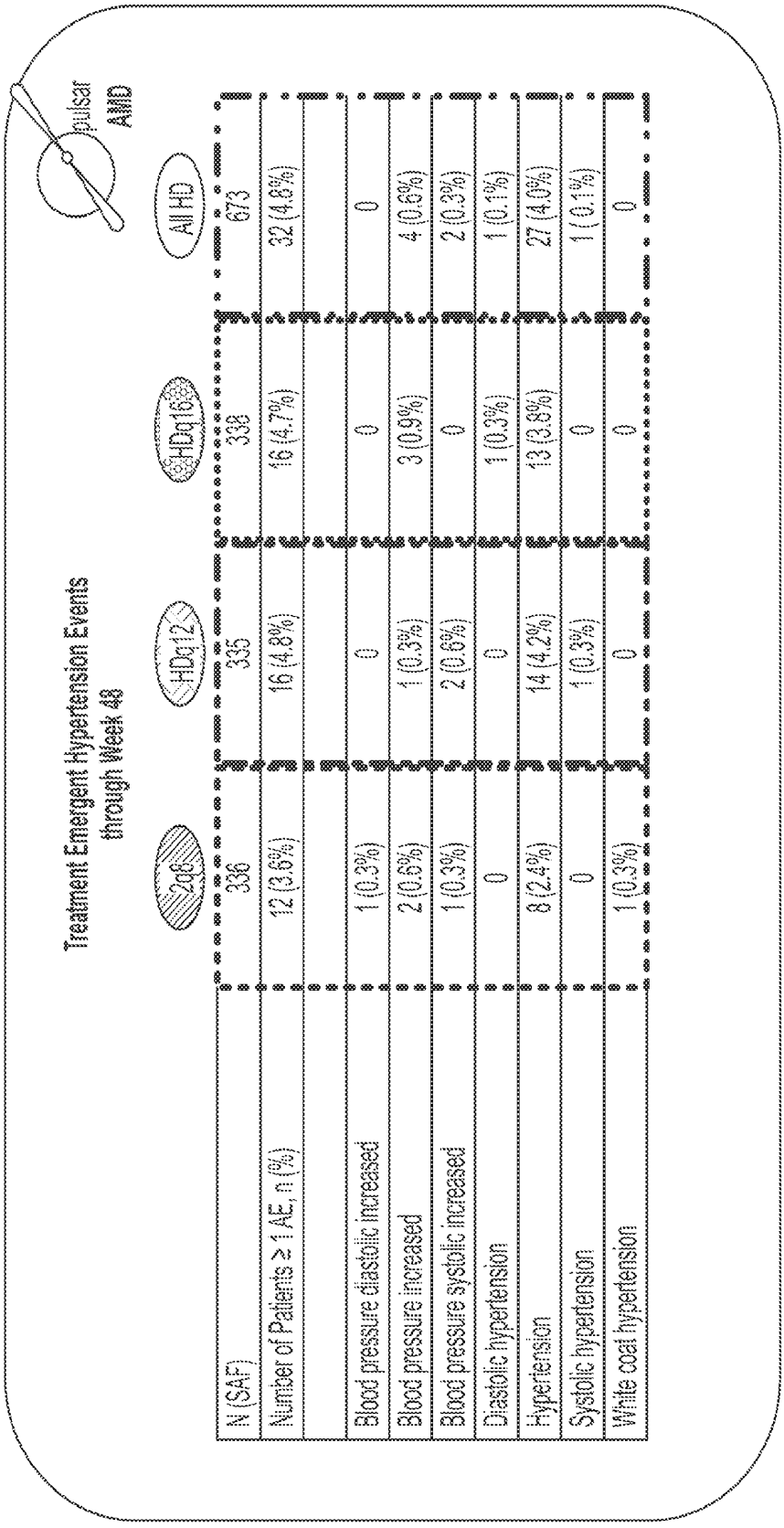

pulsar
AMD
Treatment Emergent Hypertension Events
through Week 48
2q8
HDq12
HDq16
All HD
N (SAF) 336 335 338 673
Number of Patients ≥ 1 AE, n (%) 12 (3.6%) 16 (4.8%) 16 (4.7%) 32 (4.8%)
Blood pressure diastolic increased 1 (0.3%) 0 0 0
Blood pressure increased 2 (0.6%) 1 (0.3%) 3 (0.9%) 4 (0.6%)
Blood pressure systolic increased 1 (0.3%) 2 (0.6%) 0 2 (0.3%)
Diastolic hypertension 0 0 1 (0.3%) 1 (0.1%)
Hypertension 8 (2.4%) 14 (4.2%) 13 (3.8%) 27 (4.0%)
Systolic hypertension 0 1 (0.3%) 0 1 (0.1%)
White coat hypertension 1 (0.3%) 0 0 0

FIG. 20

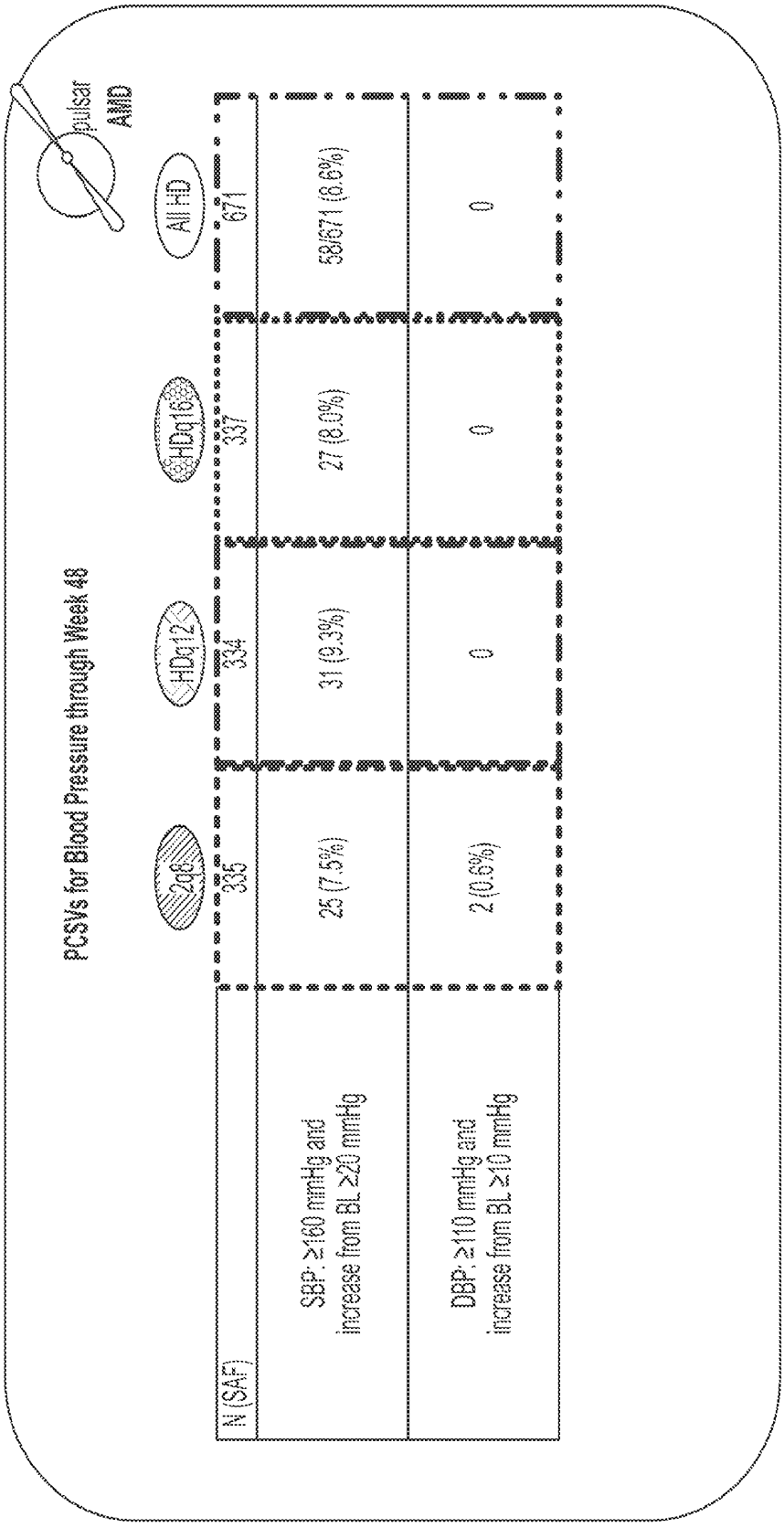

Apulsar
AMD
PCSVs for Blood Pressure through Week 48
2q8
HDq12
HDq16
All HD
N (SAF)
335
334
337
671
SBP: ≥160 mmHg and increase from BL ≥20 mmHg
25 (7.5%)
31 (9.3%)
27 (8.0%)
58/671 (8.6%)
DBP: ≥110 mmHg and increase from BL ≥10 mmHg
2 (0.6%)
0
0
0

FIG. 21

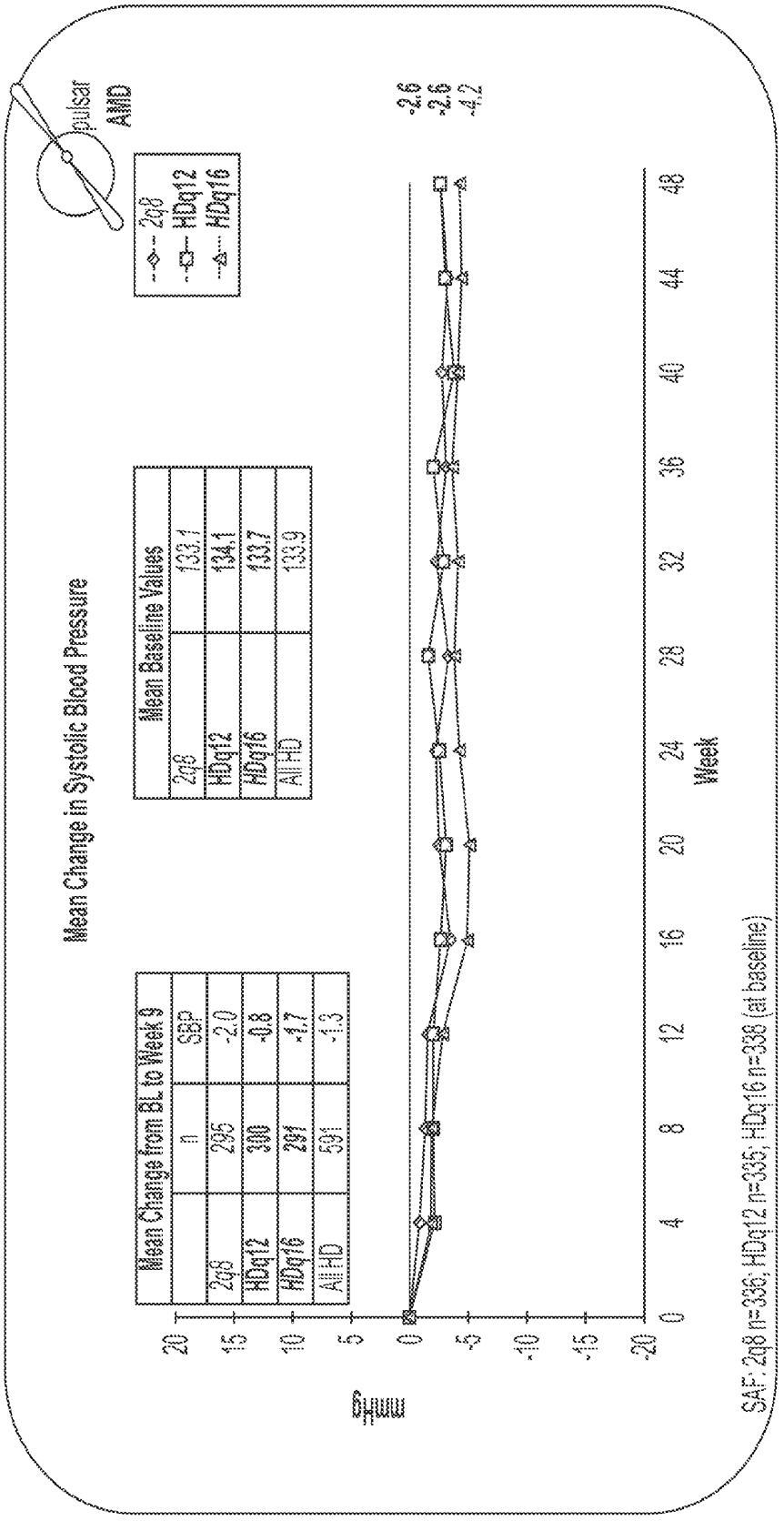

Pulsar
AMD
Mean Change in Systolic Blood Pressure
2q8
HDq12
HDq16
Mean Baseline Values
2q8 133.7
HDq12 134.1
HDq16 133.7
All HD 133.9
Mean Change from BL to Week 9
n SBP
2q8 295 -2.0
HDq12 300 -0.8
HDq16 291 -1.7
All HD 591 -1.3
-2.6
-2.6
-4.2
mmHg
Week
SAF: 2q8 n=336; HDq12 n=335; HDq16 n=336 (at baseline)

FIG. 22

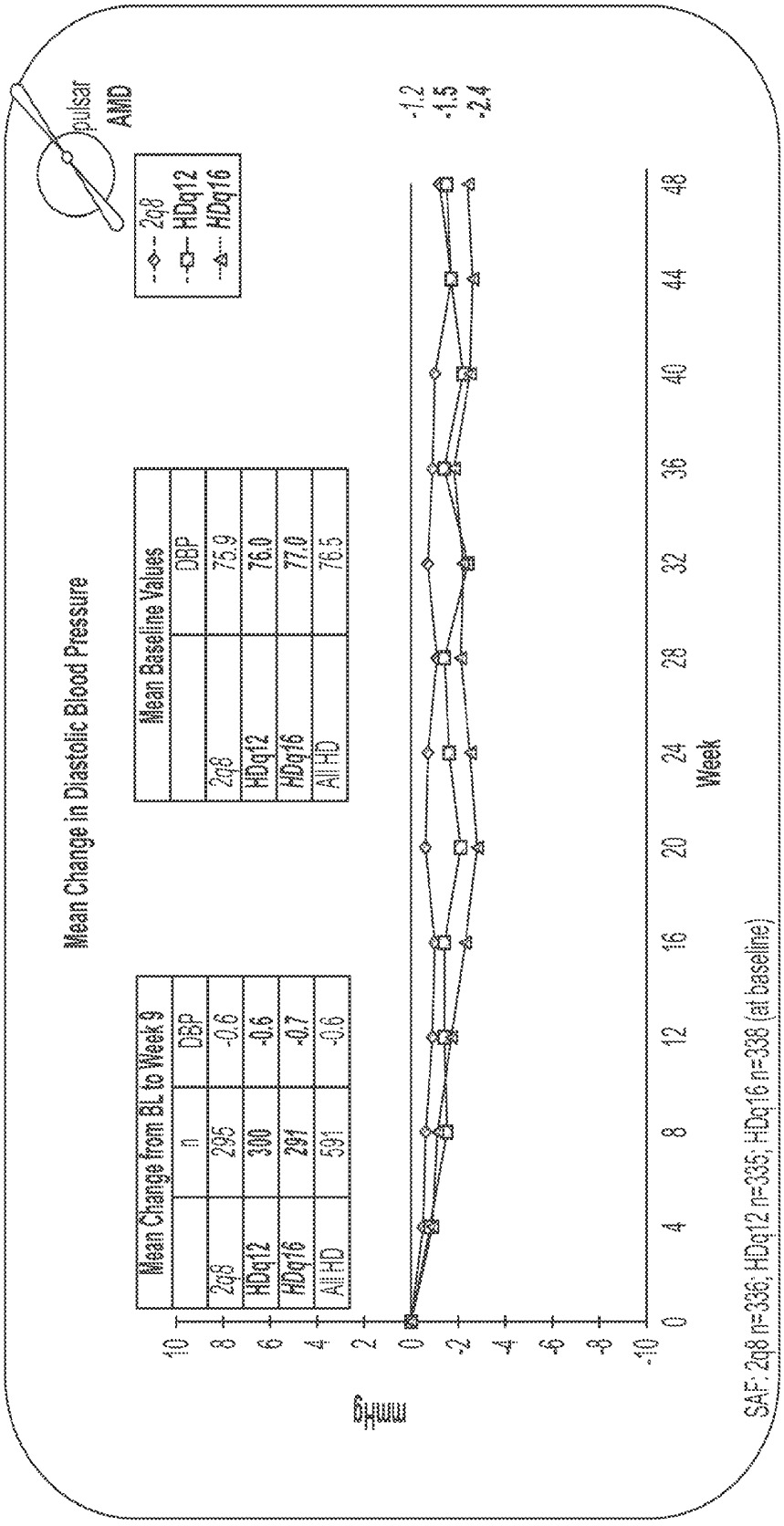
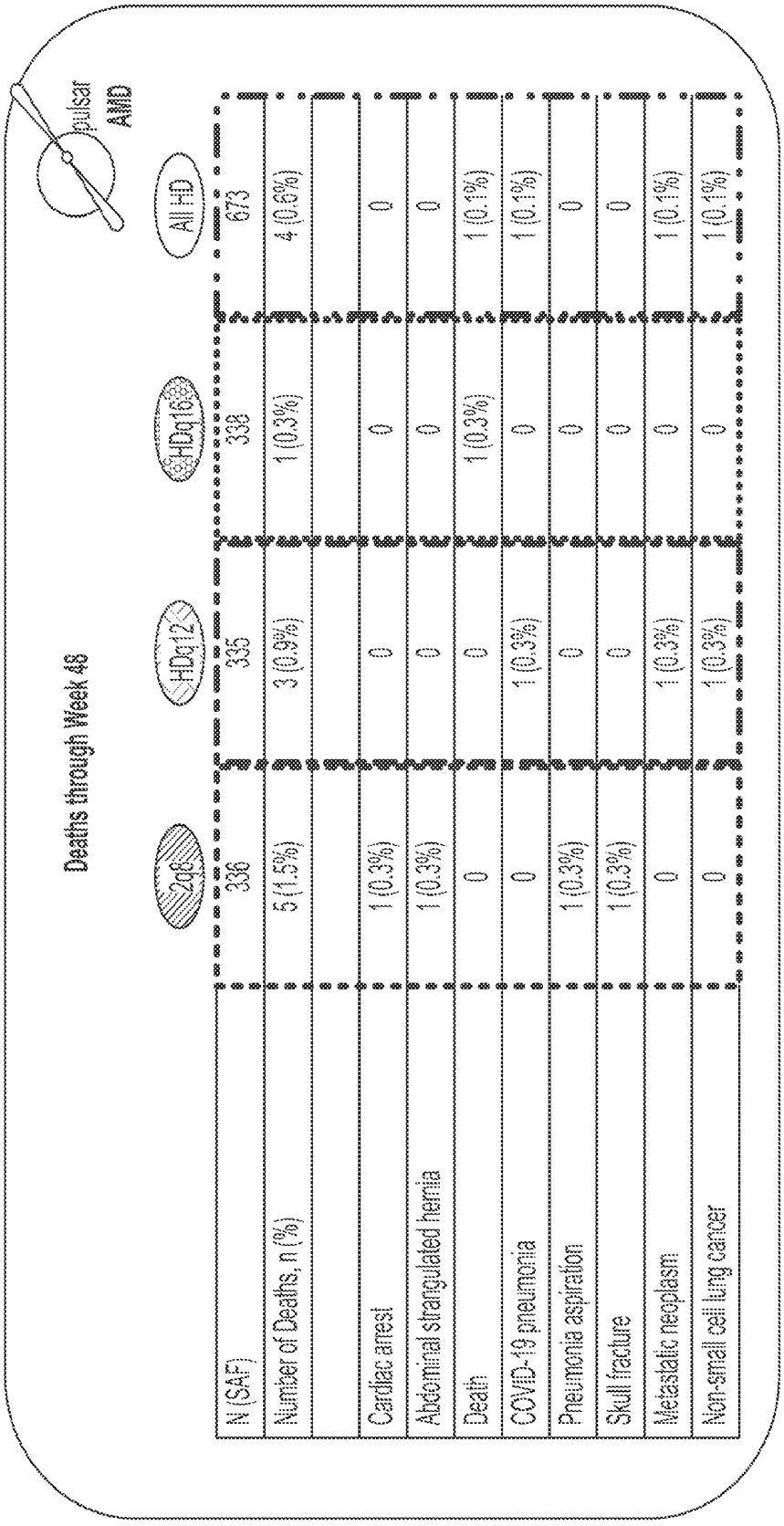

Mean Change in Diastolic Blood Pressure
Pulsar
AMD
2q8
HDq12
HDq16
Mean Baseline Values
DBP
2q8 75.9
HDq12 76.0
HDq16 77.0
All HD 76.5
Mean Change from BL to Week 9
n DBP
2q8 295 -0.6
HDq12 300 -0.6
HDq16 291 -0.7
All HD 591 -0.6
-1.2
-1.5
-2.4
mmHg
Week
SAF: 2q8 n=336; HDq12 n=335; HDq16 n=336 (at baseline)

FIG. 23



N (SAF)	336	335	338	673
Number of Deaths, n (%)	5 (1.5%)	3 (0.9%)	1 (0.3%)	4 (0.6%)
Cardiac arrest	1 (0.3%)	0	0	0
Abdominal strangulated hernia	1 (0.3%)	0	0	0
Death	0	0	1 (0.3%)	1 (0.1%)
COVID-19 pneumonia	0	1 (0.3%)	0	1 (0.1%)
Pneumonia aspiration	1 (0.3%)	0	0	0
Skull fracture	1 (0.3%)	0	0	0
Metastatic neoplasm	0	1 (0.3%)	0	1 (0.1%)
Non-small cell lung cancer	0	1 (0.3%)	0	1 (0.1%)

FIG. 24

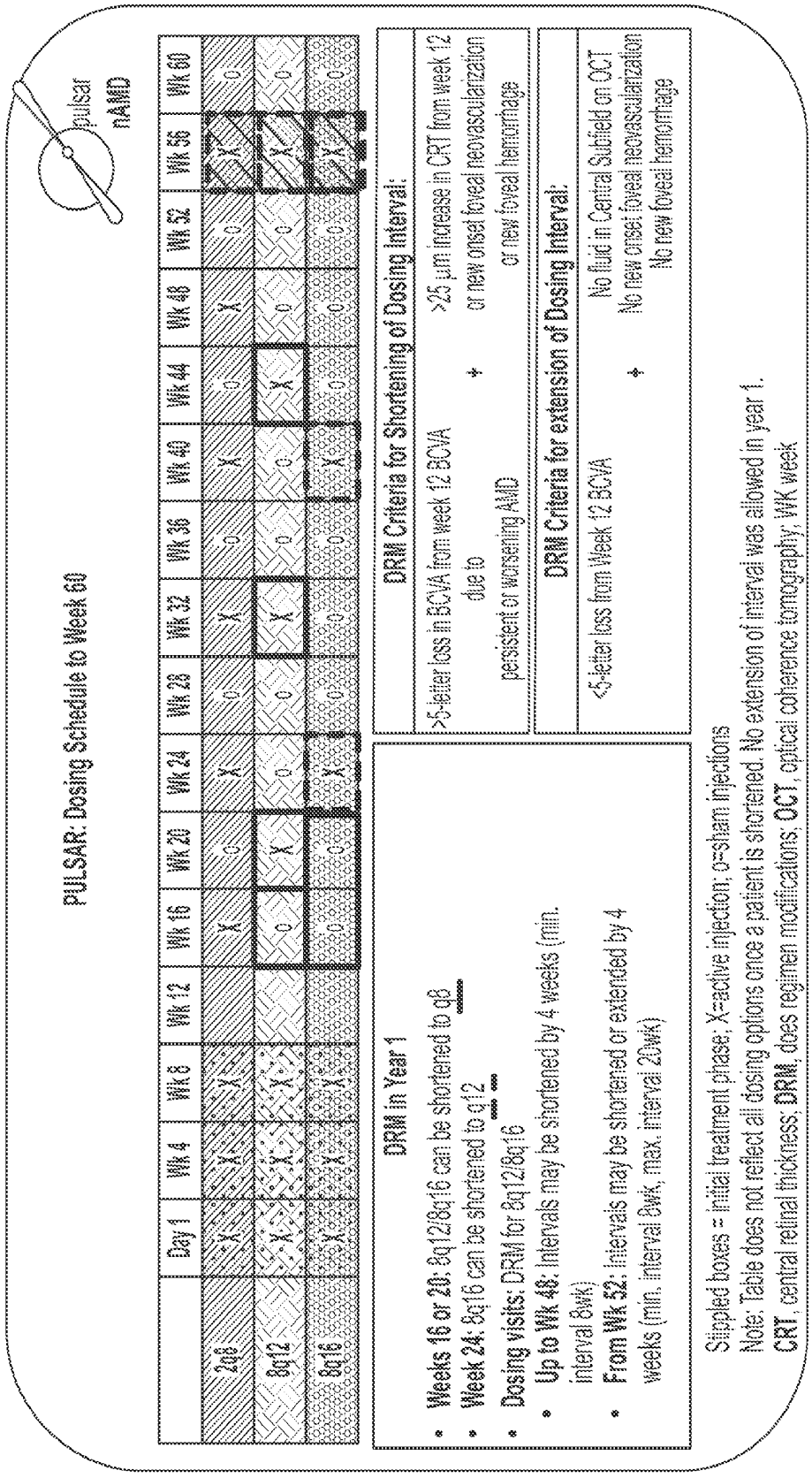

PULSAR: Dosing Schedule to Week 60
pulsar
nAMD
Day 1
Wk 4
Wk 8
Wk 12
Wk 16
Wk 20
Wk 24
Wk 28
Wk 32
Wk 36
Wk 40
Wk 44
Wk 48
Wk 52
Wk 56
Wk 60
2q8
8q12
8q16
DRM in Year 1
Weeks 16 or 20: 8q12/8q16 can be shortened to q8
Week 24: 8q16 can be shortened to q12
Dosing visits: DRM for 8q12/8q16
Up to Wk 48: Intervals may be shortened by 4 weeks (min. interval 8wk)
From Wk 52: Intervals may be shortened or extended by 4 weeks (min. interval 8wk, max. interval 20wk)
DRM Criteria for Shortening of Dosing Interval:
>5-letter loss in BCVA from week 12 BCVA due to persistent or worsening AMD
+
>25 µm increase in CRT from week 12 or new onset foveal neovascularization or new foveal hemorrhage
DRM Criteria for extension of Dosing Interval:
<5-letter loss from Week 12 BCVA
+
No fluid in Central Subfield on OCT
No new onset foveal neovascularization
No new foveal hemorrhage
Stippled boxes = initial treatment phase; X=active injection; o=sham injections
Note: Table does not reflect all dosing options once a patient is shortened. No extension of interval was allowed in year 1.
CRT, central retinal thickness; DRM, does regimen modifications; OCT, optical coherence tomography; WK week

FIG. 25

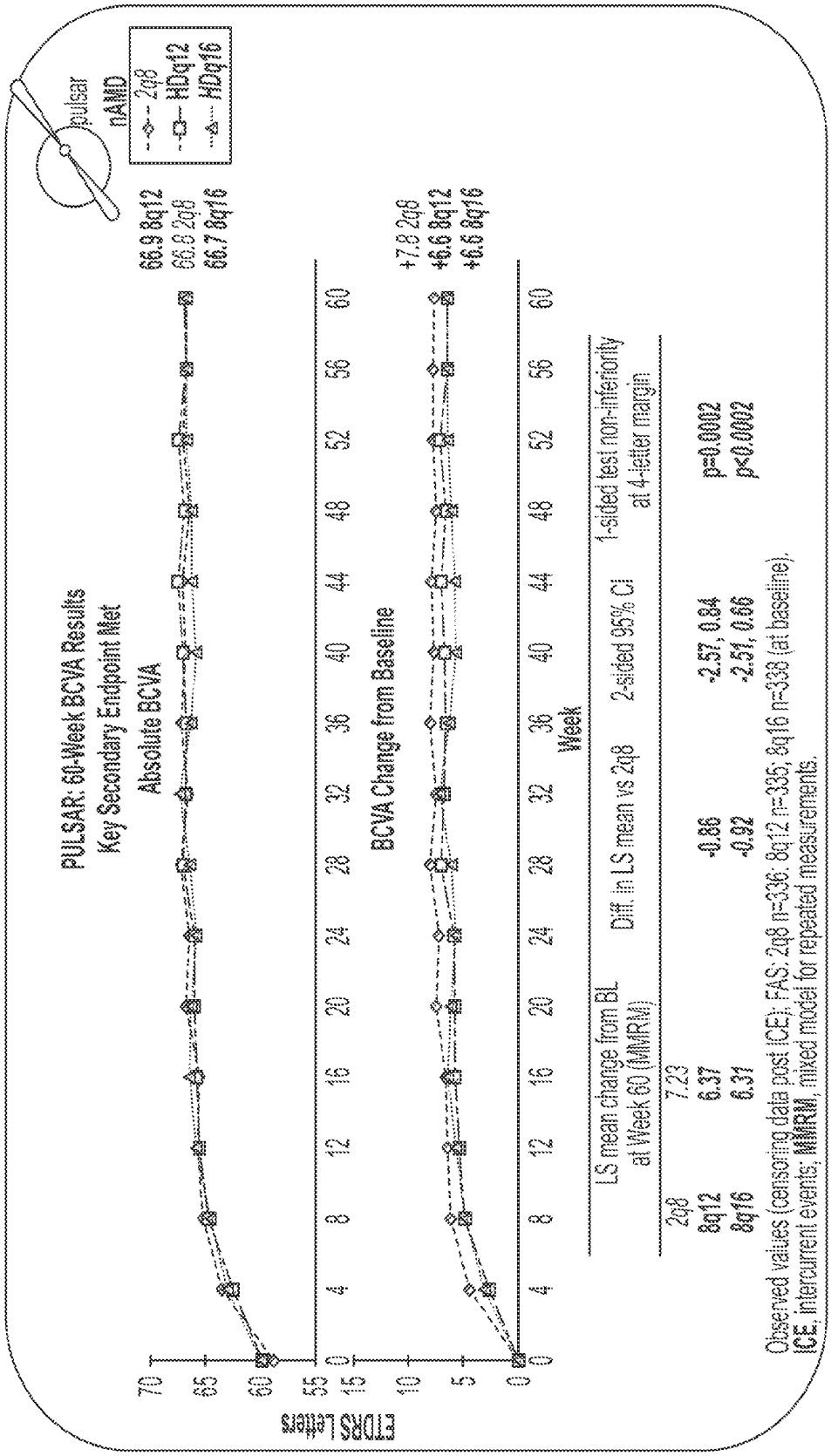

PULSAR: 60-Week BCVA Results
Key Secondary Endpoint Met
Absolute BCVA
BCVA Change from Baseline
ETDRS Letters
Week
pulsar
nAMD
2q8
HDq12
HDq16
66.9 8q12
66.8 2q8
66.7 8q16
+7.8 2q8
+6.6 8q12
+6.6 8q16
LS mean change from BL at Week 60 (MMRM)
Diff. in LS mean vs 2q8
2-sided 95% CI
1-sided test non-inferiority at 4-letter margin
2q8 7.23
8q12 6.37 -0.86 -2.57, 0.84 p=0.0002
8q16 6.31 -0.92 -2.51, 0.66 p<0.0002
Observed values (censoring data post ICE). FAS: 2q8 n=336; 8q12 n=335; 8q16 n=338 (at baseline).
ICE, intercurrent events; MMRM, mixed model for repeated measurements.

FIG. 26

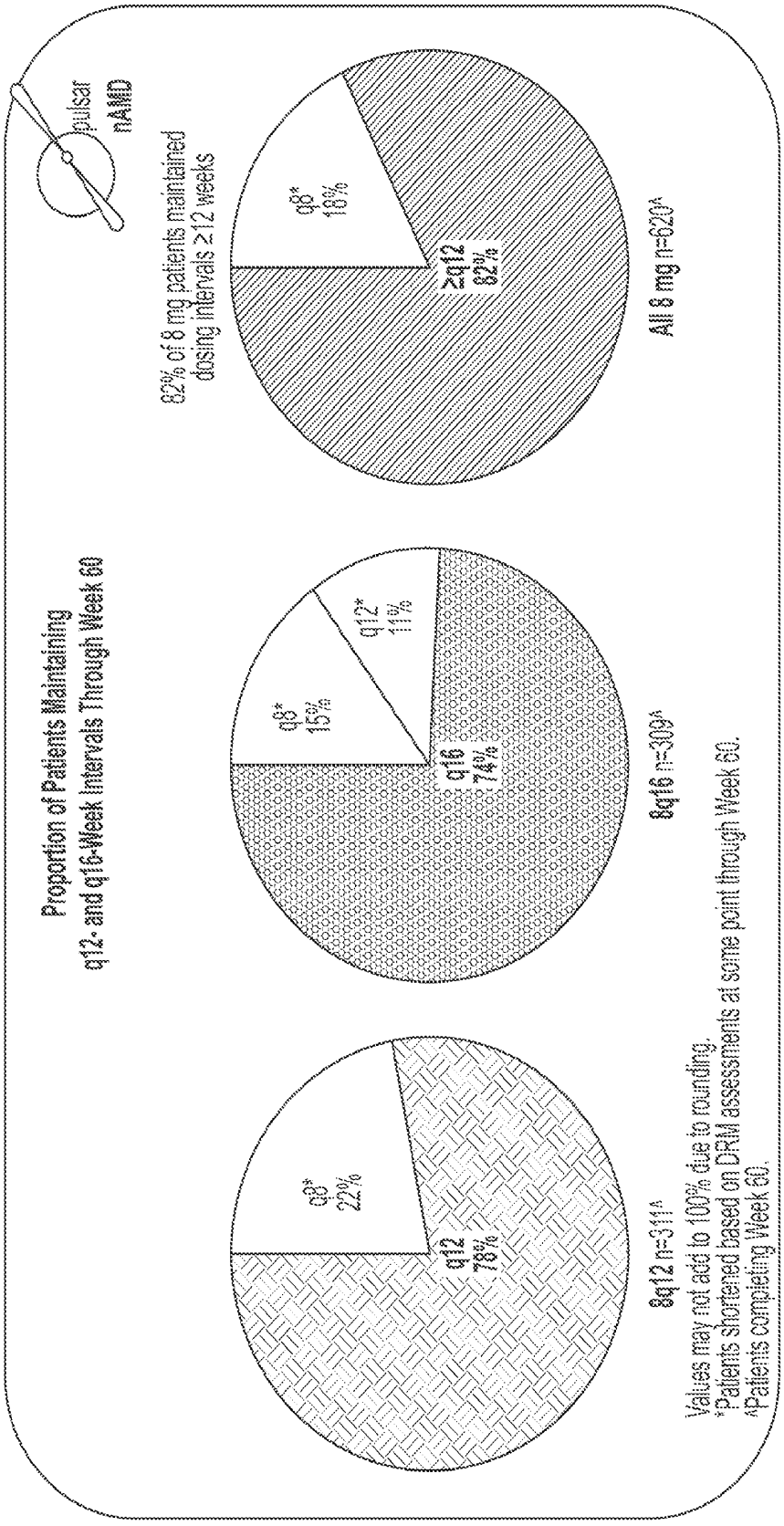

pulsar
nAMD
Proportion of Patients Maintaining
q12- and q16-Week Intervals Through Week 60
82% of 8 mg patients maintained
dosing intervals ≥12 weeks
q8*
16%
≥q12
82%
All 8 mg n=620^
q8*
15%
q12*
11%
q16
74%
8q16 n=309^
q8*
22%
q12
78%
8q12 n=311^
Values may not add to 100% due to rounding.
*Patients shortened based on DRM assessments at some point through Week 60.
^Patients completing Week 60.

FIG. 27

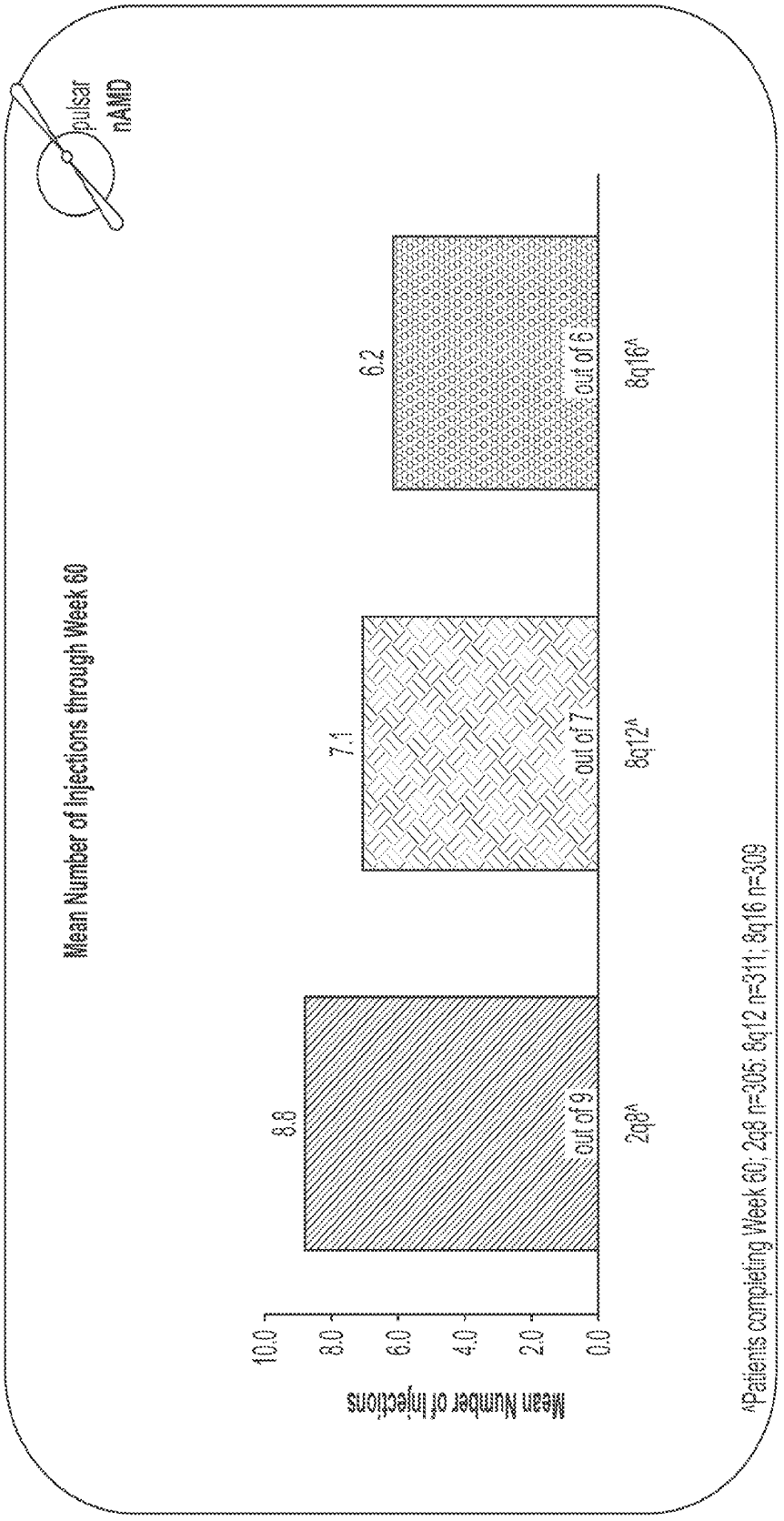

Mean Number of Injections through Week 60
Mean Number of Injections
10.0
8.0
6.0
4.0
2.0
0.0
8.8
out of 9
2q8^
7.1
out of 7
8q12^
6.2
out of 6
8q16^
^Patients completing Week 60: 2q8 n=305; 8q12 n=311; 8q16 n=309

FIG. 28

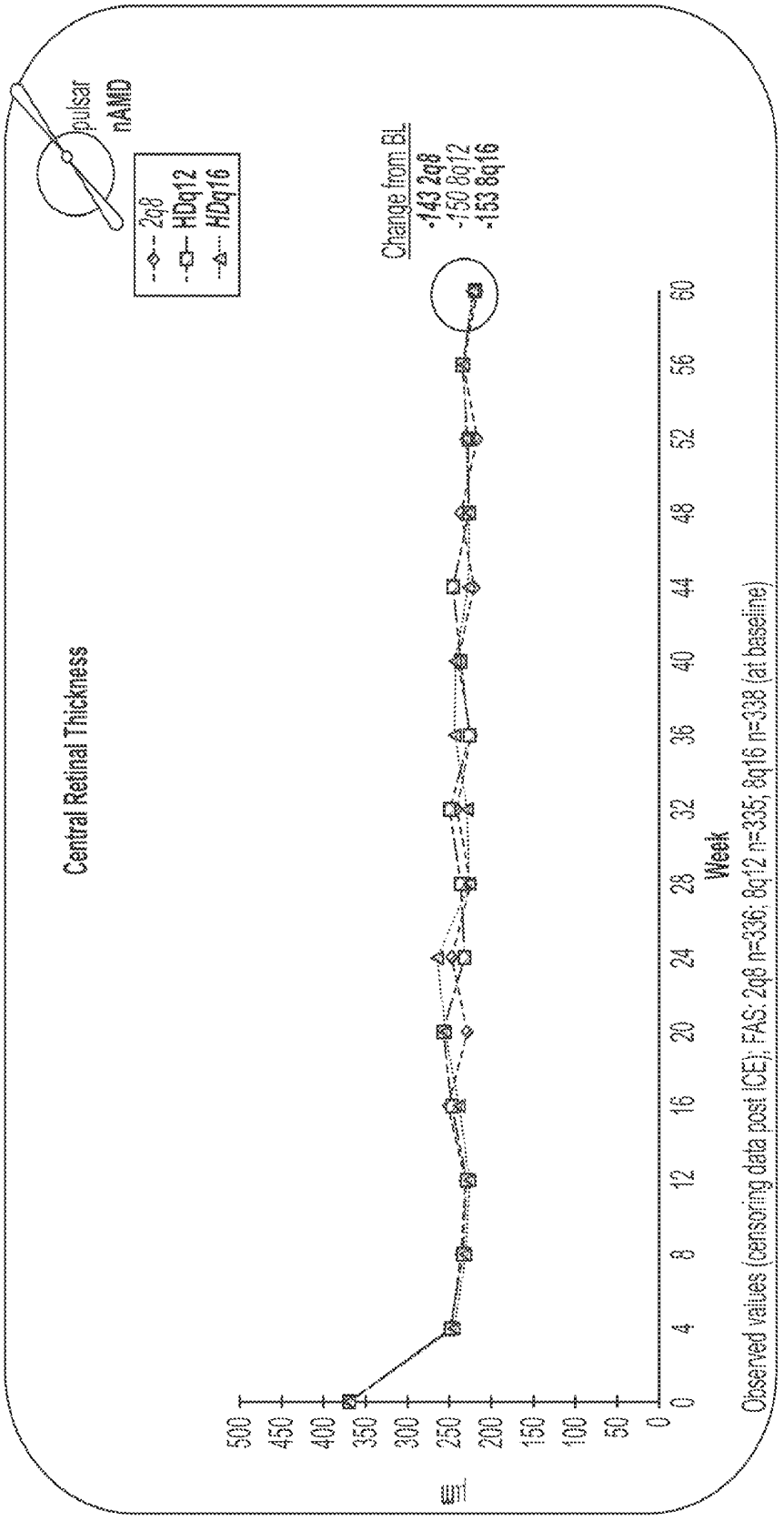

Apulsar
nAMD
2q8
HDq12
HDq16
Change from BL
-143 2q8
-150 8q12
-153 8q16
Central Retinal Thickness
Week
Observed values (censoring data post ICE); FAS: 2q8 n=336; 8q12 n=335; 8q16 n=338 (at baseline)

FIG. 29A

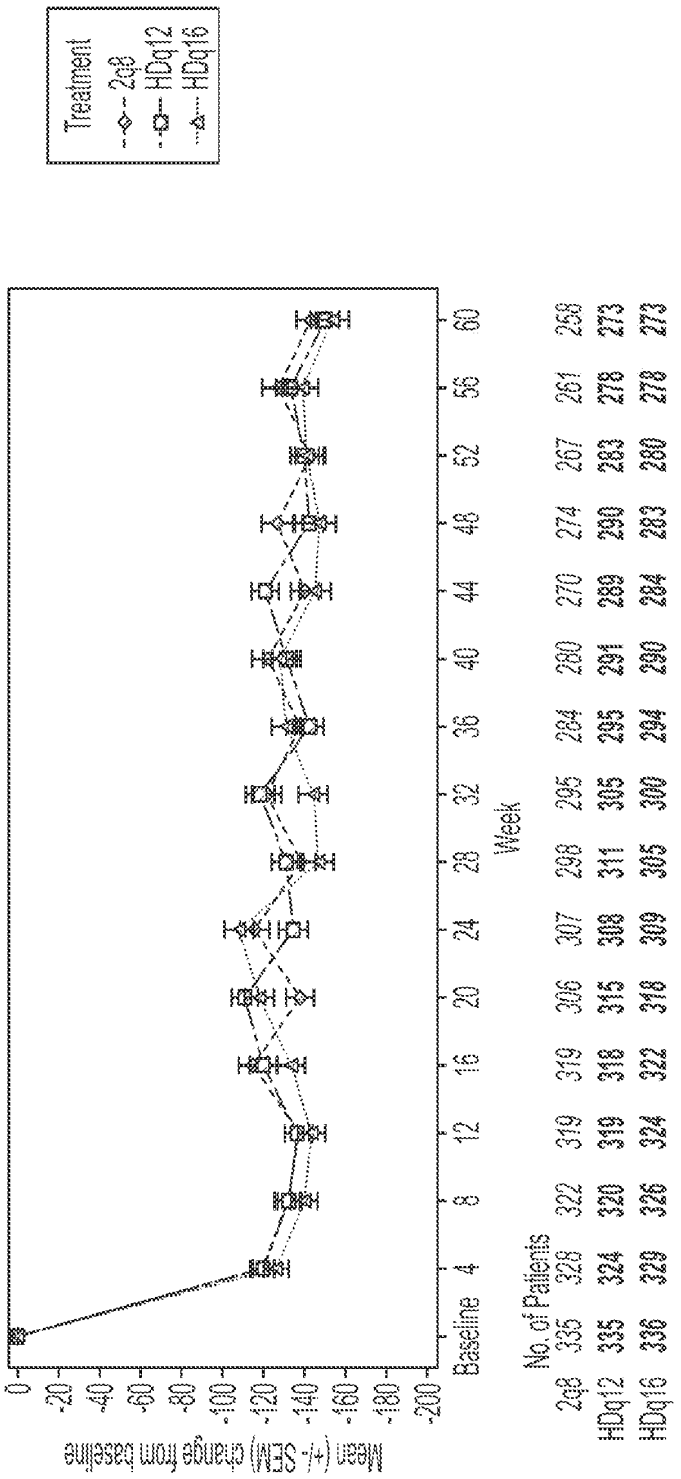

Treatment
2q8
HDq12
HDq16
Mean (+/- SEM) change from baseline
0
-20
-40
-60
-80
-100
-120
-140
-160
-180
-200
Baseline 4 8 12 16 20 24 28 32 36 40 44 48 52 56 60
Week
No. of Patients
2q8 335 328 322 319 319 318 306 307 298 295 284 280 270 274 267 261 258
HDq12 335 324 320 319 318 315 308 311 305 300 295 291 289 290 283 278 273
HDq16 336 329 326 324 322 318 309 305 300 294 290 290 284 283 280 278 273

FIG. 29B

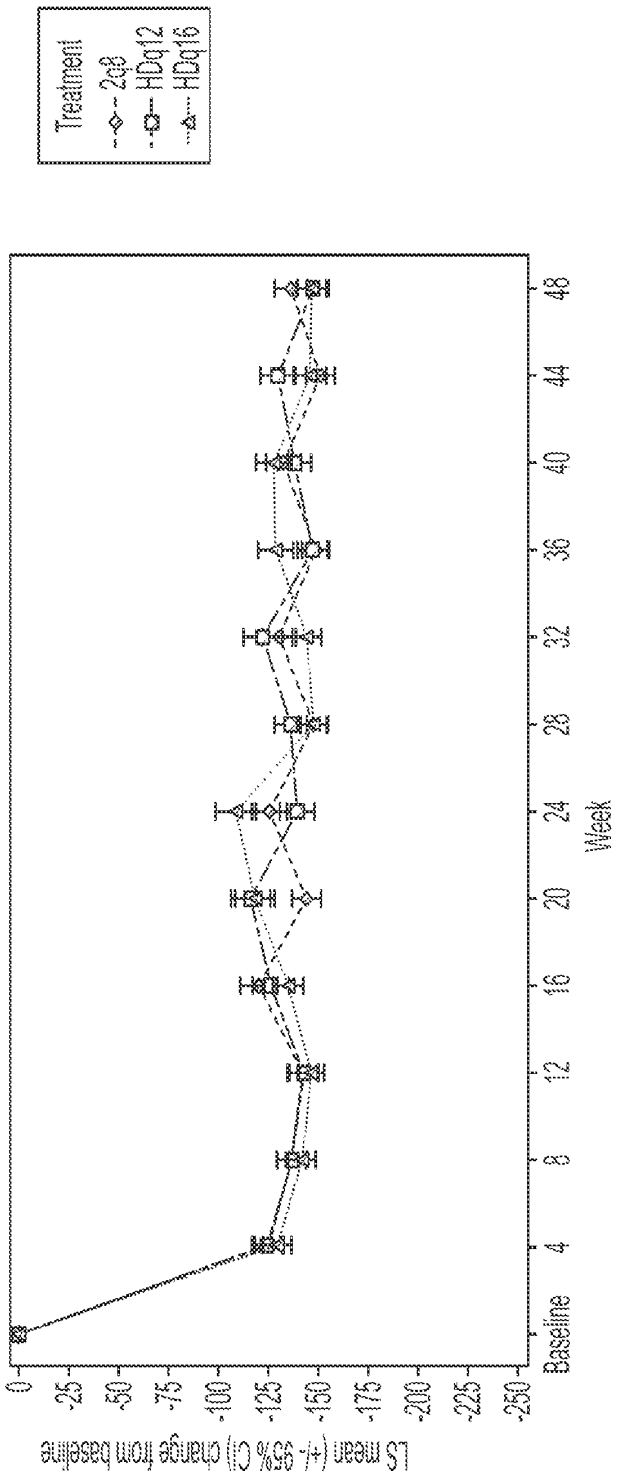
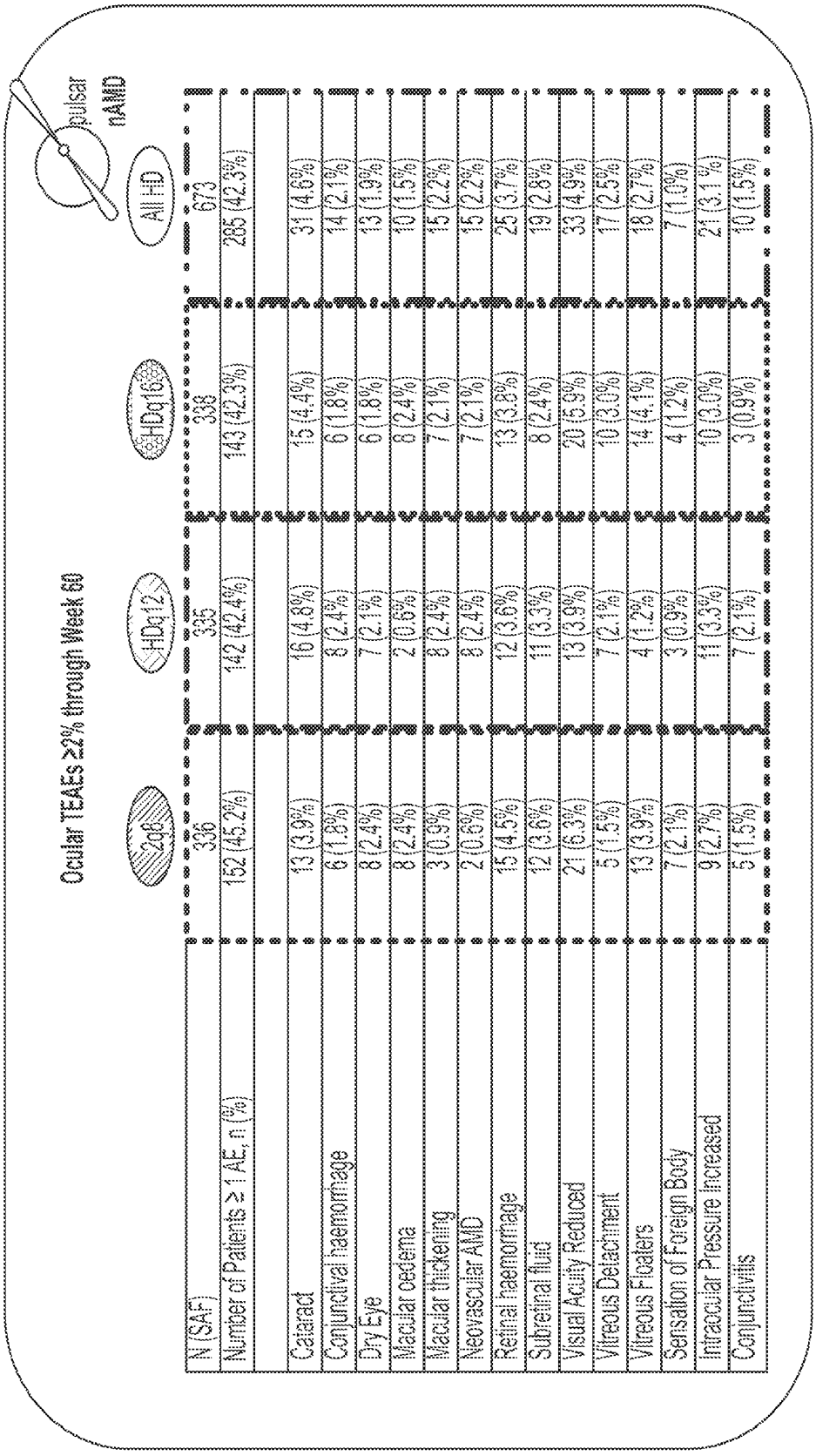
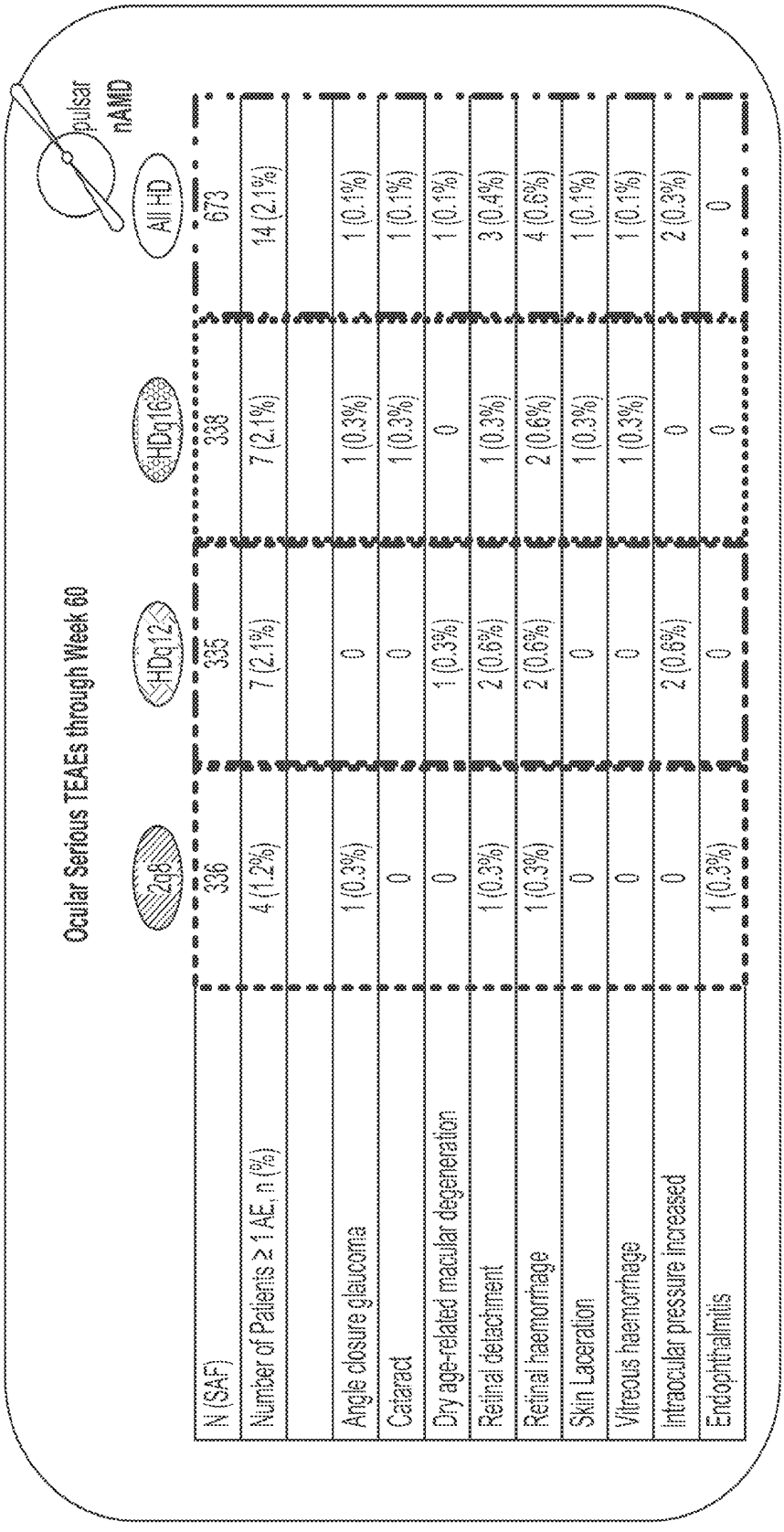

Treatment
2q8
HDq12
HDq16
LS mean (+/- 95% CI) change from baseline
0
-25
-50
-75
-100
-125
-150
-175
-200
-225
-250
Baseline
4
8
12
16
20
24
28
32
36
40
44
48
Week

FIG. 29C



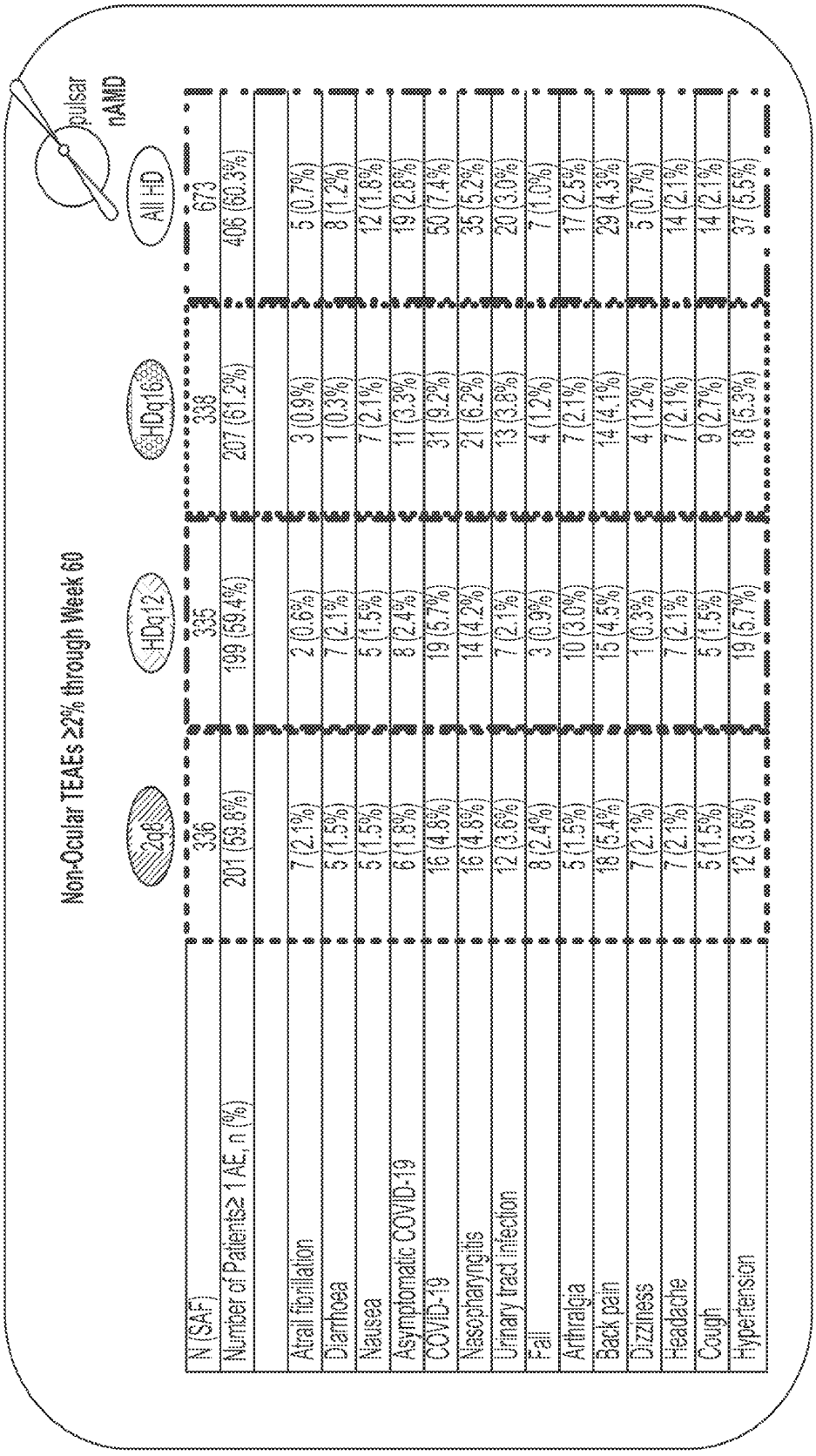
N (SAF)	336	335	338	673
Number of Patients ≥ 1 AE, n (%)	152 (45.2%)	142 (42.4%)	143 (42.3%)	285 (42.3%)
Cataract	13 (3.9%)	16 (4.8%)	15 (4.4%)	31 (4.6%)
Conjunctival haemorrhage	6 (1.8%)	8 (2.4%)	6 (1.8%)	14 (2.1%)
Dry Eye	8 (2.4%)	7 (2.1%)	6 (1.8%)	13 (1.9%)
Macular oedema	8 (2.4%)	2 (0.6%)	8 (2.4%)	10 (1.5%)
Macular thickening	3 (0.9%)	8 (2.4%)	7 (2.1%)	15 (2.2%)
Neovascular AMD	2 (0.6%)	8 (2.4%)	7 (2.1%)	15 (2.2%)
Retinal haemorrhage	15 (4.5%)	12 (3.6%)	13 (3.8%)	25 (3.7%)
Subretinal fluid	12 (3.6%)	11 (3.3%)	8 (2.4%)	19 (2.8%)
Visual Acuity Reduced	21 (6.3%)	13 (3.9%)	20 (5.9%)	33 (4.9%)
Vitreous Detachment	5 (1.5%)	7 (2.1%)	10 (3.0%)	17 (2.5%)
Vitreous Floaters	13 (3.9%)	4 (1.2%)	14 (4.1%)	18 (2.7%)
Sensation of Foreign Body	7 (2.1%)	3 (0.9%)	4 (1.2%)	7 (1.0%)
Intraocular Pressure Increased	9 (2.7%)	11 (3.3%)	10 (3.0%)	21 (3.1%)
Conjunctivitis	5 (1.5%)	7 (2.1%)	3 (0.9%)	10 (1.5%)

FIG. 30A



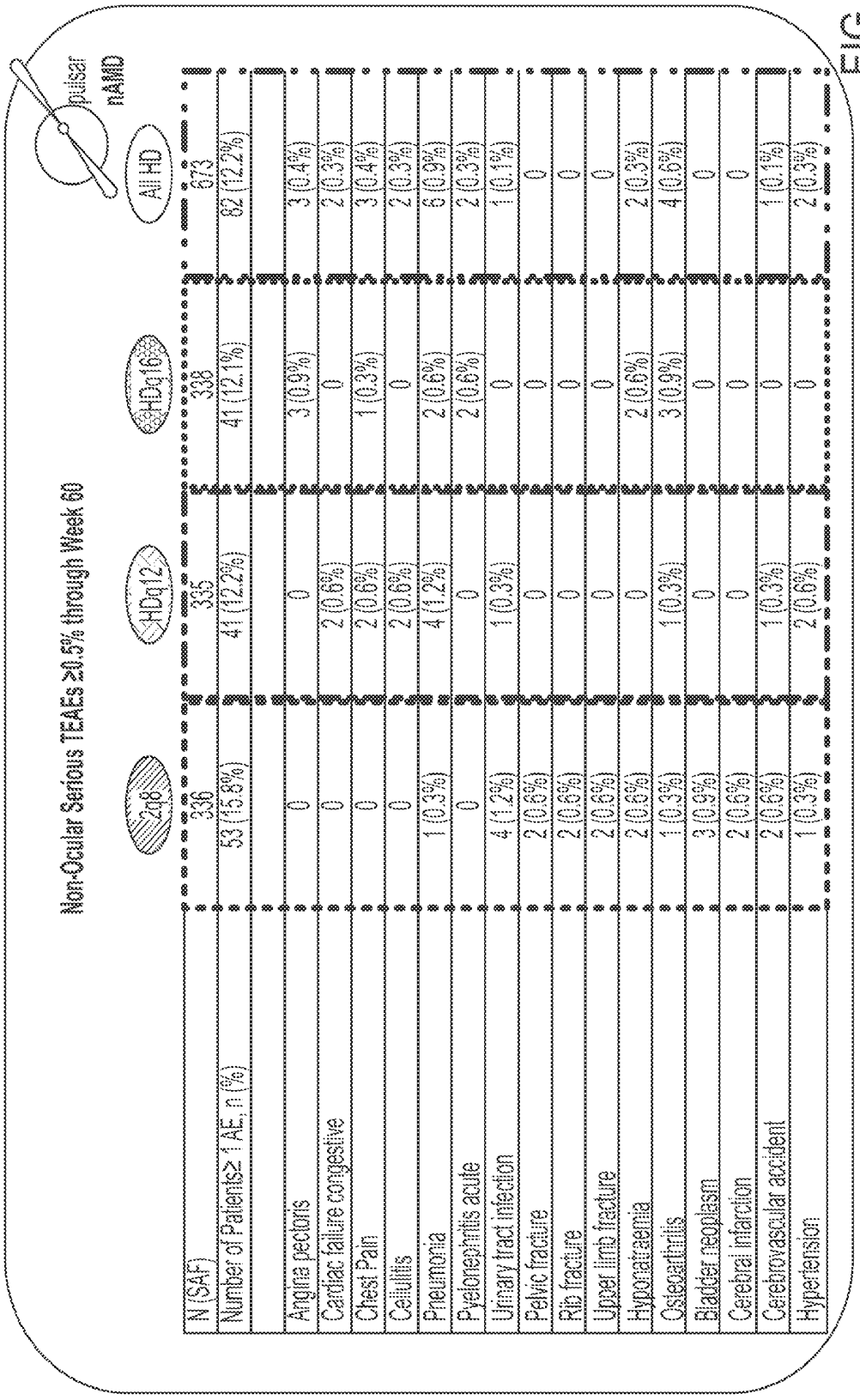
N (SAF)	336	335	338	673
Number of Patients ≥ 1 AE, n (%)	4 (1.2%)	7 (2.1%)	7 (2.1%)	14 (2.1%)
Angle closure glaucoma	1 (0.3%)	0	1 (0.3%)	1 (0.1%)
Cataract	0	0	1 (0.3%)	1 (0.1%)
Dry age-related macular degeneration	0	1 (0.3%)	0	1 (0.1%)
Retinal detachment	1 (0.3%)	2 (0.6%)	1 (0.3%)	3 (0.4%)
Retinal haemorrhage	1 (0.3%)	2 (0.6%)	2 (0.6%)	4 (0.6%)
Skin Laceration	0	0	1 (0.3%)	1 (0.1%)
Vitreous haemorrhage	0	0	1 (0.3%)	1 (0.1%)
Intraocular pressure increased	0	2 (0.6%)	0	2 (0.3%)
Endophthalmitis	1 (0.3%)	0	0	0

FIG. 30B



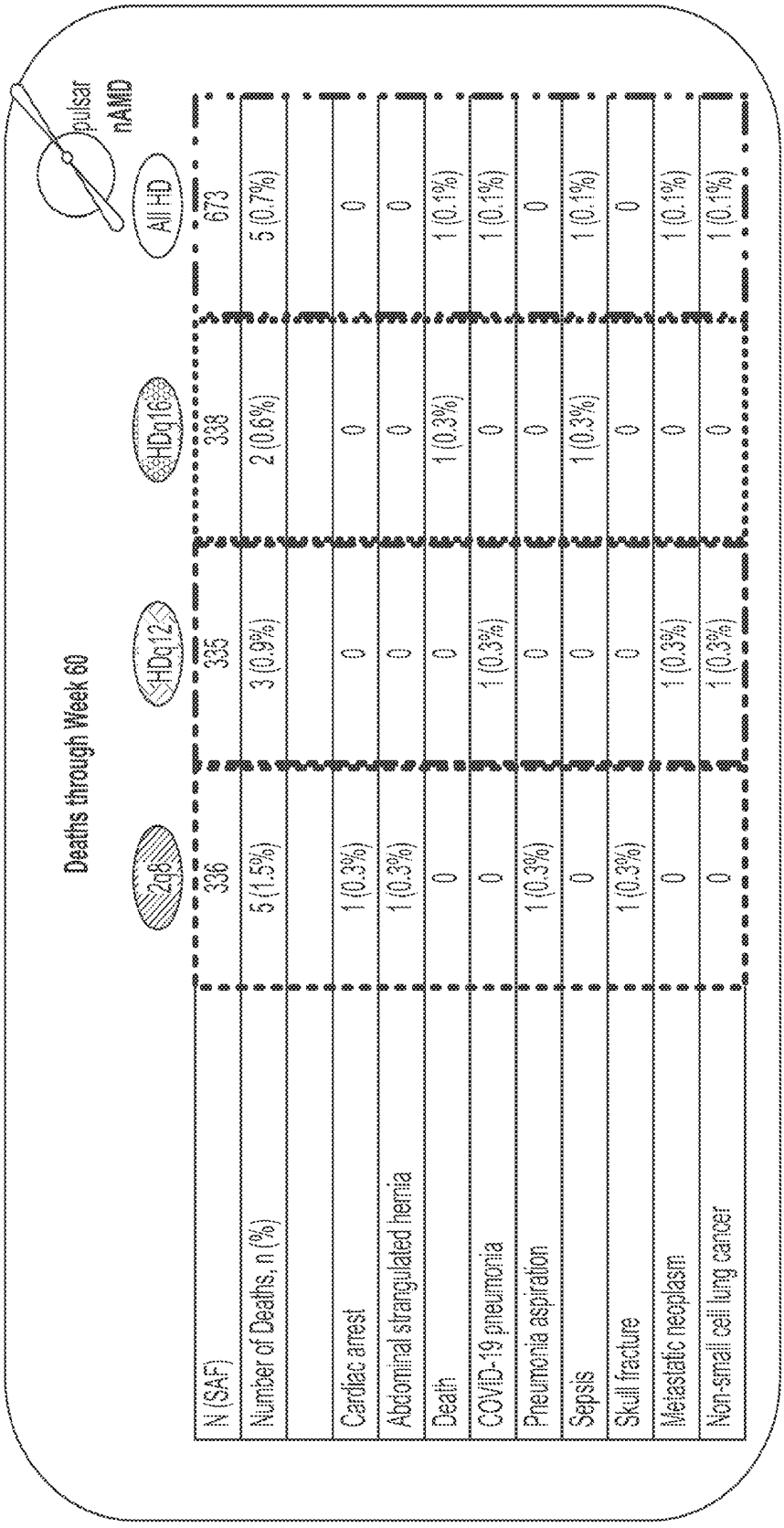
N (SAF)	336	335	338	673
Number of Patients≥ 1 AE, n (%)	201 (59.8%)	199 (59.4%)	207 (61.2%)	406 (60.3%)
Atrial fibrillation	7 (2.1%)	2 (0.6%)	3 (0.9%)	5 (0.7%)
Diarrhoea	5 (1.5%)	7 (2.1%)	1 (0.3%)	8 (1.2%)
Nausea	5 (1.5%)	5 (1.5%)	7 (2.1%)	12 (1.8%)
Asymptomatic COVID-19	6 (1.8%)	8 (2.4%)	11 (3.3%)	19 (2.8%)
COVID-19	16 (4.8%)	19 (5.7%)	31 (9.2%)	50 (7.4%)
Nasopharyngitis	16 (4.8%)	14 (4.2%)	21 (6.2%)	35 (5.2%)
Urinary tract infection	12 (3.6%)	7 (2.1%)	13 (3.8%)	20 (3.0%)
Fall	8 (2.4%)	3 (0.9%)	4 (1.2%)	7 (1.0%)
Arthralgia	5 (1.5%)	10 (3.0%)	7 (2.1%)	17 (2.5%)
Back pain	18 (5.4%)	15 (4.5%)	14 (4.1%)	29 (4.3%)
Dizziness	7 (2.1%)	1 (0.3%)	4 (1.2%)	5 (0.7%)
Headache	7 (2.1%)	7 (2.1%)	7 (2.1%)	14 (2.1%)
Cough	5 (1.5%)	5 (1.5%)	9 (2.7%)	14 (2.1%)
Hypertension	12 (3.6%)	19 (5.7%)	18 (5.3%)	37 (5.5%)

FIG. 30C



N (SAF)	336	335	338	673
Number of Patients≥ 1 AE, n (%)	53 (15.8%)	41 (12.2%)	41 (12.1%)	82 (12.2%)
Angina pectoris	0	0	3 (0.9%)	3 (0.4%)
Cardiac failure congestive	0	2 (0.6%)	0	2 (0.3%)
Chest Pain	0	2 (0.6%)	1 (0.3%)	3 (0.4%)
Cellulitis	0	2 (0.6%)	0	2 (0.3%)
Pneumonia	1 (0.3%)	4 (1.2%)	2 (0.6%)	6 (0.9%)
Pyelonephritis acute	0	0	2 (0.6%)	2 (0.3%)
Urinary tract infection	4 (1.2%)	1 (0.3%)	0	1 (0.1%)
Pelvic fracture	2 (0.6%)	0	0	0
Rib fracture	2 (0.6%)	0	0	0
Upper limb fracture	2 (0.6%)	0	0	0
Hyponatraemia	2 (0.6%)	0	2 (0.6%)	2 (0.3%)
Osteoarthritis	1 (0.3%)	1 (0.3%)	3 (0.9%)	4 (0.6%)
Bladder neoplasm	3 (0.9%)	0	0	0
Cerebral infarction	2 (0.6%)	0	0	0
Cerebrovascular accident	2 (0.6%)	1 (0.3%)	0	1 (0.1%)
Hypertension	1 (0.3%)	2 (0.6%)	0	2 (0.3%)

FIG. 30D



N (SAF)	336	335	338	673
Number of Deaths, n (%)	5 (1.5%)	3 (0.9%)	2 (0.6%)	5 (0.7%)
Cardiac arrest	1 (0.3%)	0	0	0
Abdominal strangulated hernia	1 (0.3%)	0	0	0
Death	0	0	1 (0.3%)	1 (0.1%)
COVID-19 pneumonia	0	1 (0.3%)	0	1 (0.1%)
Pneumonia aspiration	1 (0.3%)	0	0	0
Sepsis	0	0	1 (0.3%)	1 (0.1%)
Skull fracture	1 (0.3%)	0	0	0
Metastatic neoplasm	0	1 (0.3%)	0	1 (0.1%)
Non-small cell lung cancer	0	1 (0.3%)	0	1 (0.1%)

FIG. 30E

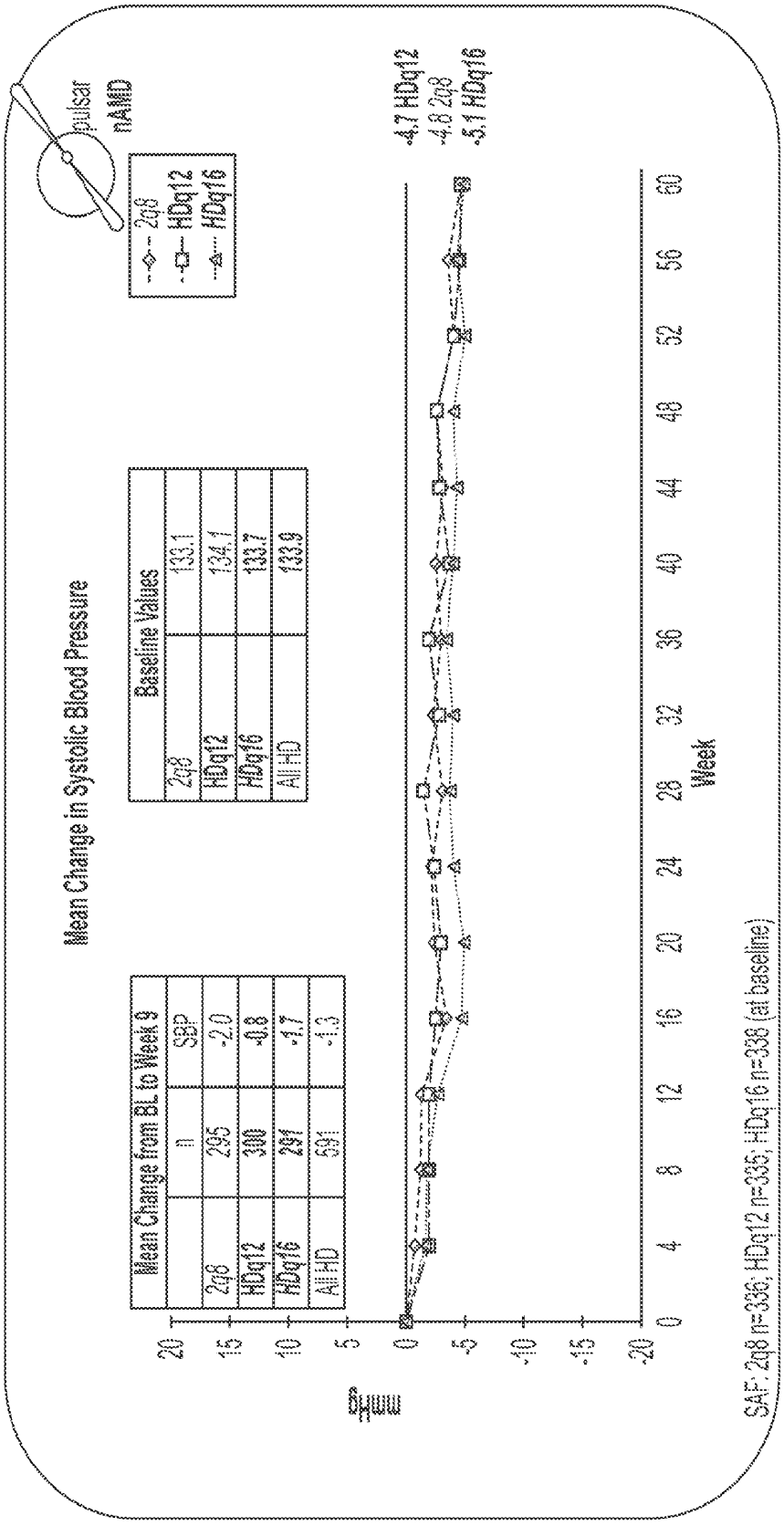

Mean Change in Systolic Blood Pressure
Spulsar
nAMD
2q8
HDq12
HDq16
-4.7 HDq12
-4.6 2q8
-5.1 HDq16
Baseline Values
2q8 133.1
HDq12 134.1
HDq16 133.7
All HD 133.9
Mean Change from BL to Week 9
n SBP
2q8 295 -2.0
HDq12 300 -0.8
HDq16 297 -1.7
All HD 691 -1.3
mmHg
Week
SAF: 2q8 n=336; HDq12 n=335; HDq16 n=336 (at baseline)

FIG. 30F

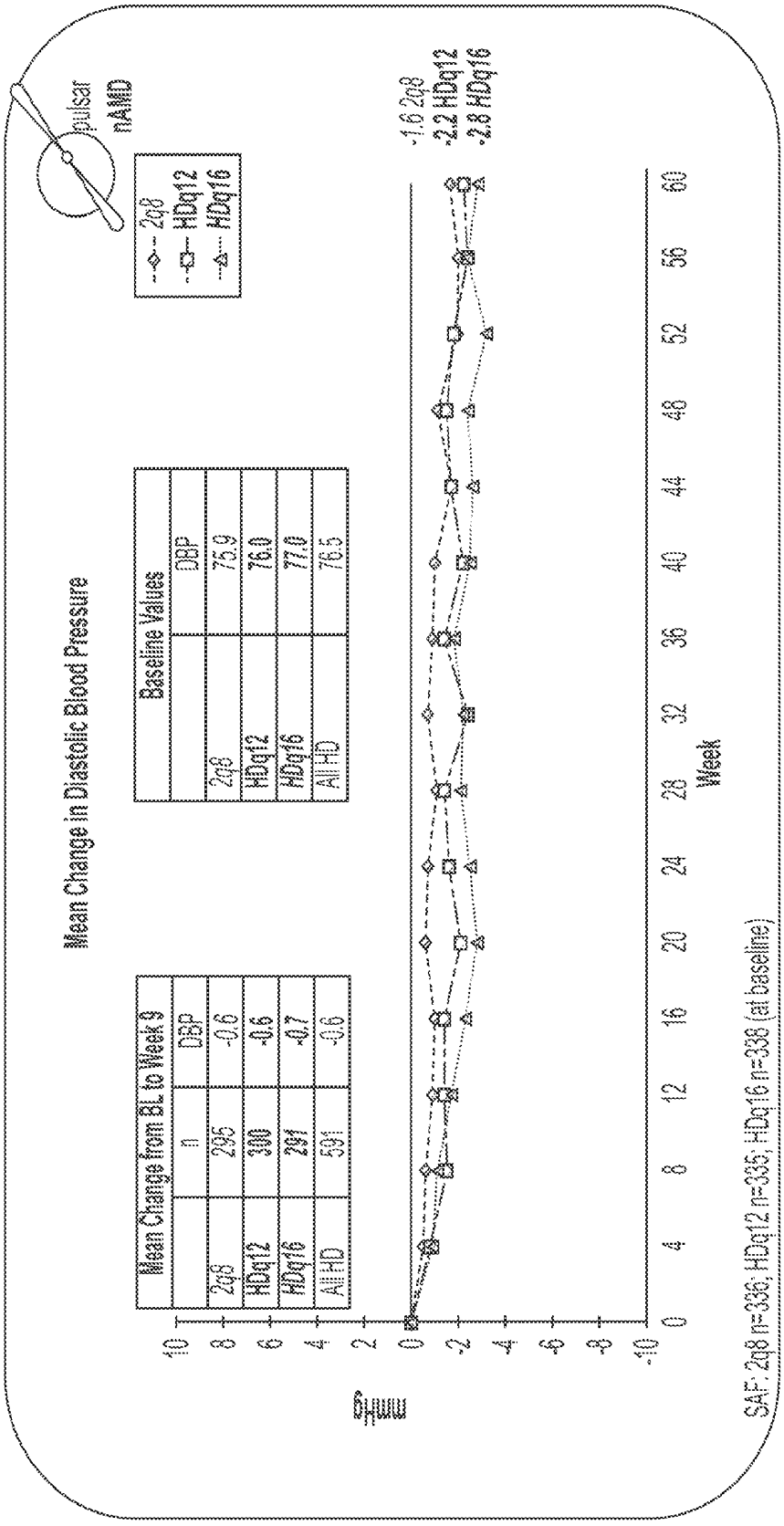

Mean Change in Diastolic Blood Pressure
Apulsar
nAMD
2q8
HDq12
HDq16
-1.6 2q8
-2.2 HDq12
-2.8 HDq16
Baseline Values
DBP
2q8 75.9
HDq12 76.0
HDq16 77.0
All HD 76.5
Mean Change from BL to Week 9
n DBP
2q8 295 -0.6
HDq12 300 -0.6
HDq16 291 -0.7
All HD 591 -0.6
mmHg
10 8 6 4 2 0 -2 -4 -6 -8 -10
0 4 8 12 16 20 24 28 32 36 40 44 48 52 56 60
Week
SAF: 2q8 n=330; HDq12 n=335; HDq16 n=338 (at baseline)

FIG. 30G

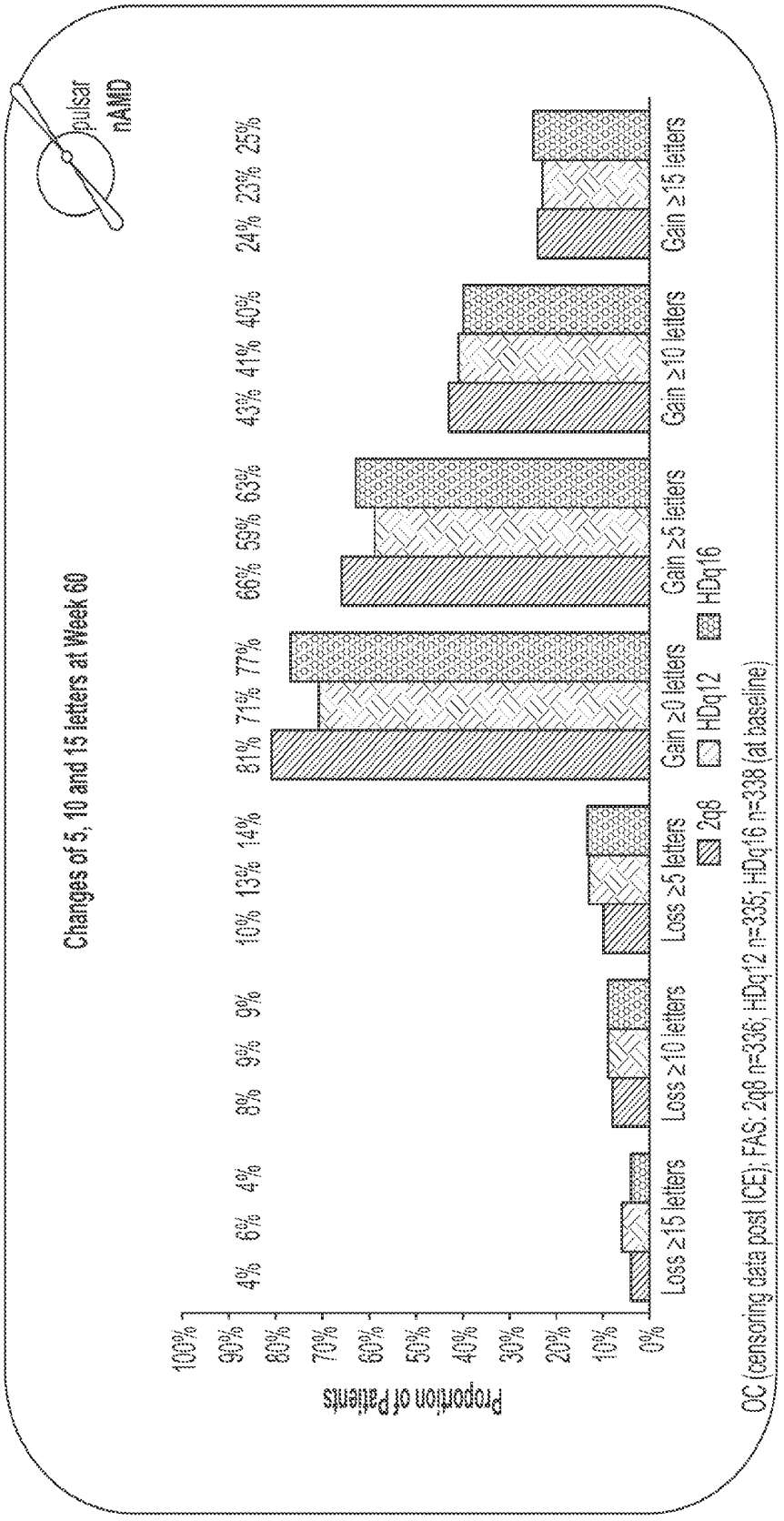

Apulsar
nAMD
Changes of 5, 10 and 15 letters at Week 60
Proportion of Patients
100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
4%
6%
4%
8%
9%
9%
10%
13%
14%
81%
71%
77%
66%
59%
63%
43%
41%
40%
24%
23%
25%
Loss ≥15 letters
Loss ≥10 letters
Loss ≥5 letters
Gain ≥0 letters
Gain ≥5 letters
Gain ≥10 letters
Gain ≥15 letters
2q8
HDq12
HDq16
OC (censoring data post ICE); FAS: 2q8 n=336; HDq12 n=335; HDq16 n=338 (at baseline)

FIG. 31

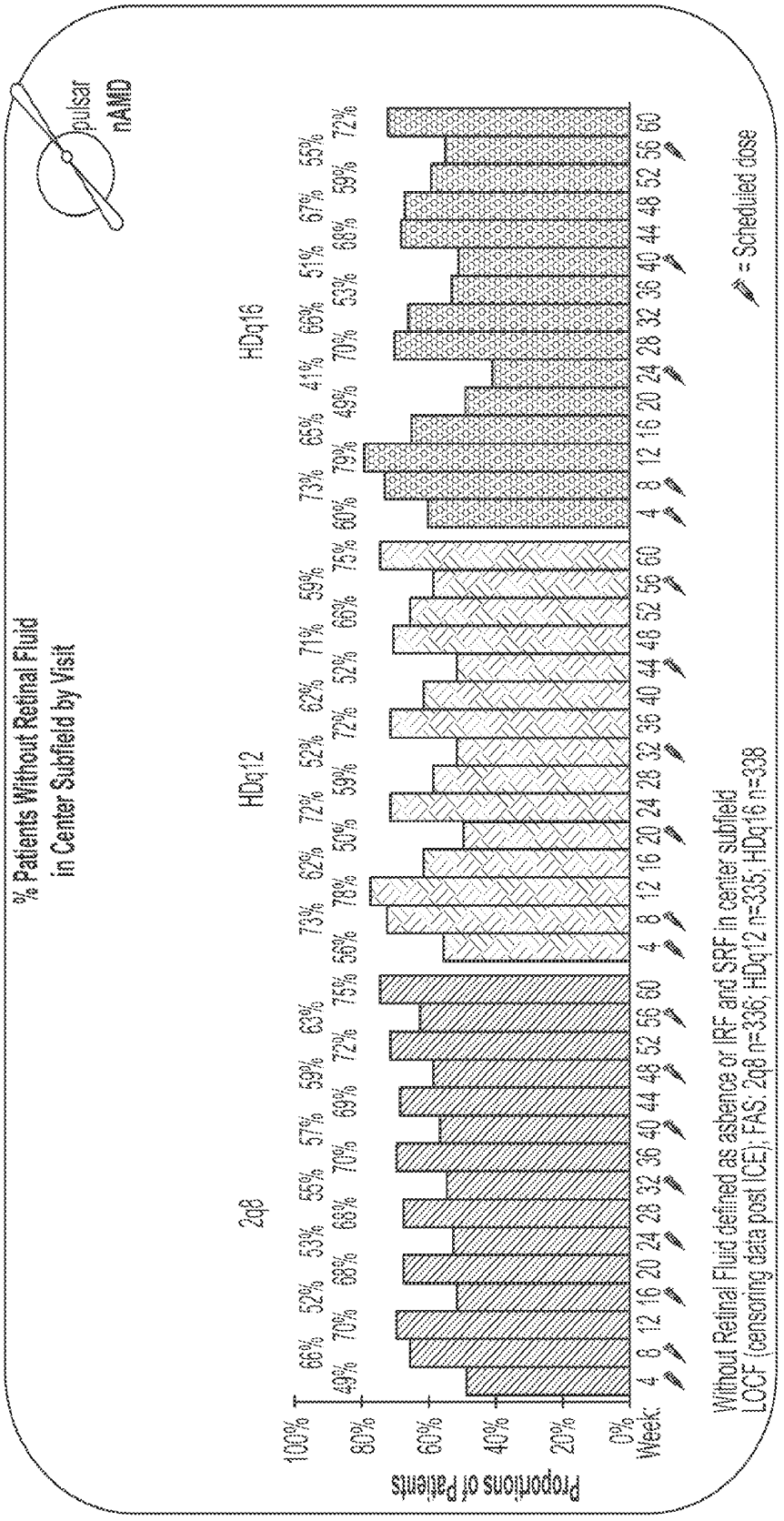

% Patients Without Retinal Fluid
in Center Subfield by Visit
pulsar
nAMD
2q8
HDq12
HDq16
Proportions of Patients
100%
80%
60%
40%
20%
0%
Week
Without Retinal Fluid defined as absence of IRF and SRF in center subfield
LOCF (censoring data post (CE); FAS: 2q8 n=336; HDq12 n=335; HDq16 n=338
= Scheduled dose

FIG. 32

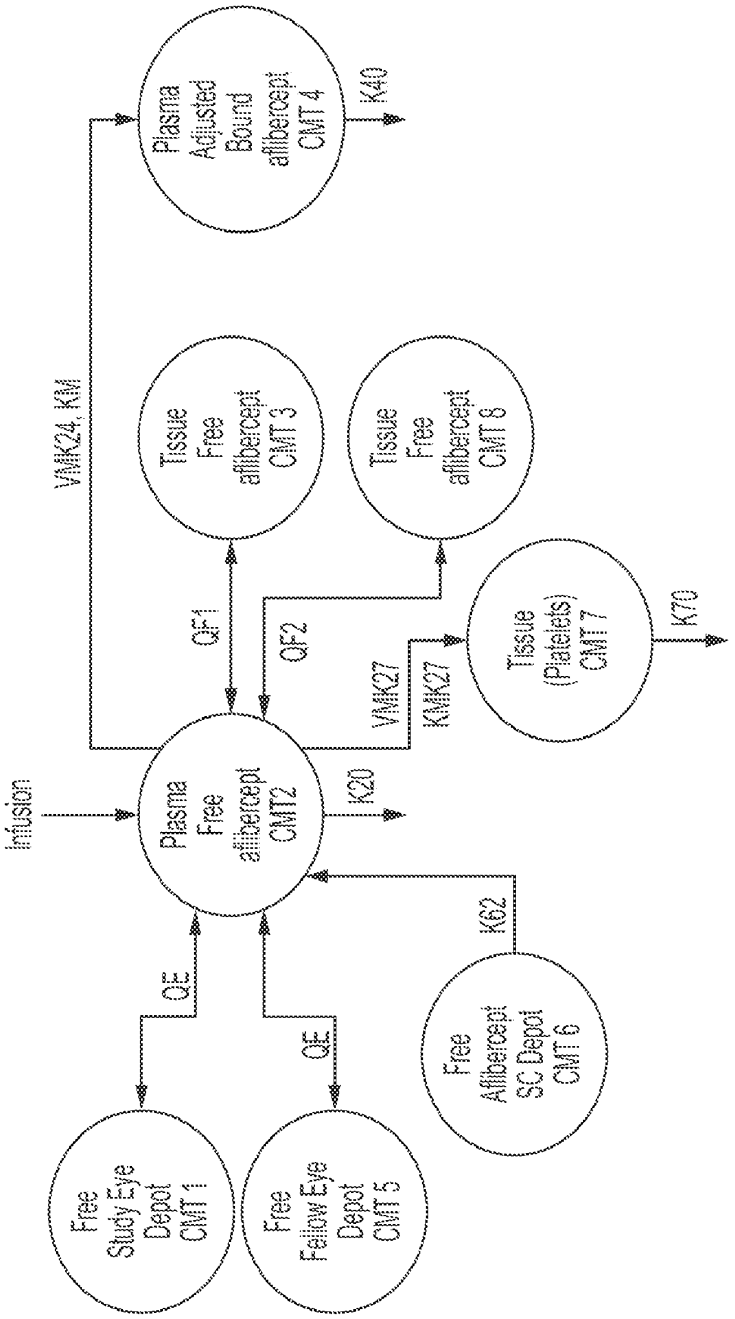

Plasma Adjusted Bound aflibercept CMT 4
K40
VMK24, KM
Tissue Free aflibercept CMT 3
Tissue Free aflibercept CMT 8
QF1
QF2
VMK27
KMK27
Tissue (Platelets) CMT 7
K70
Infusion
Plasma Free aflibercept CMT2
K20
K62
QE
QE
Free Aflibercept SC Depot CMT 6
Free Study Eye Depot CMT 1
Free Fellow Eye Depot CMT 5

FIG. 33

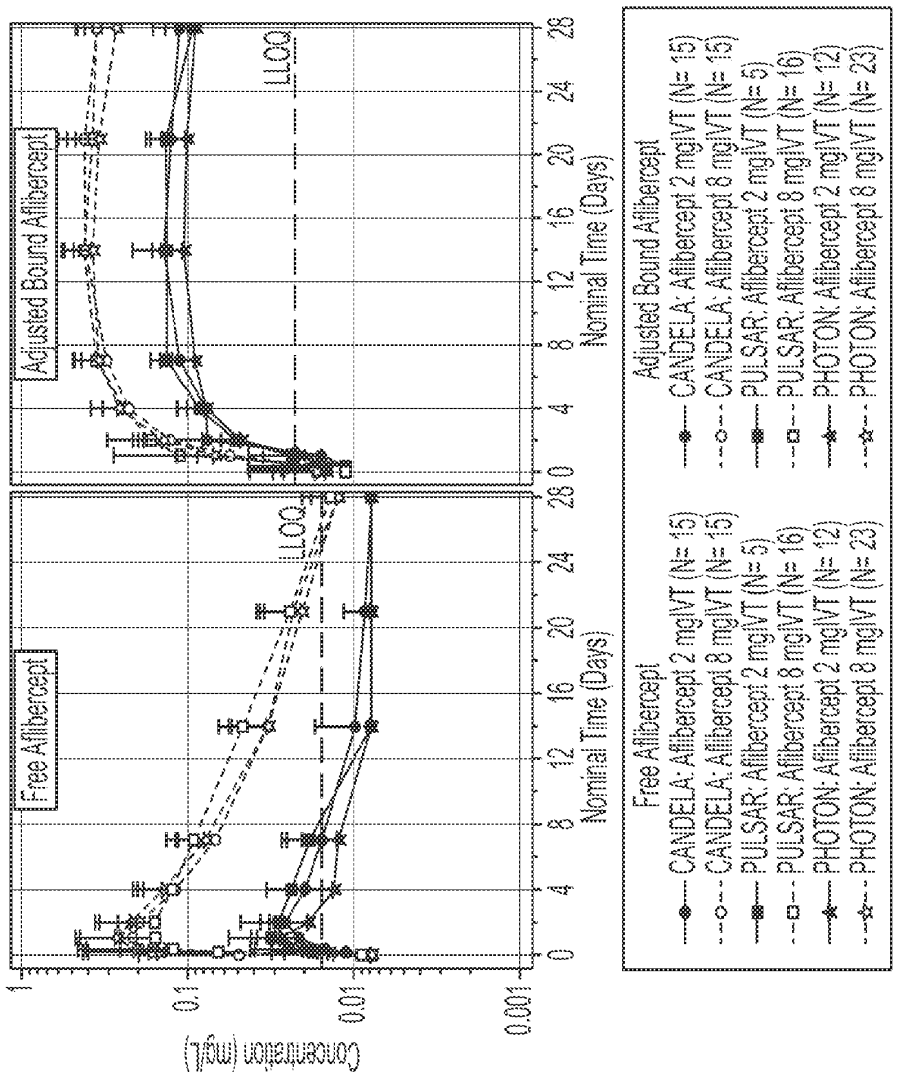

Free Aflibercept
Adjusted Bound Aflibercept
LLOQ
Concentration (mg/L)
1
0.1
0.01
0.001
0
4
8
12
16
20
24
28
Nominal Time (Days)
Free Aflibercept
CANDELA: Aflibercept 2 mg/VT (N= 15)
CANDELA: Aflibercept 8 mg/VT (N= 15)
PULSAR: Aflibercept 2 mg/VT (N= 5)
PULSAR: Aflibercept 8 mg/VT (N= 16)
PHOTON: Aflibercept 2 mg/VT (N= 12)
PHOTON: Aflibercept 8 mg/VT (N= 23)
Adjusted Bound Aflibercept
CANDELA: Aflibercept 2 mg/VT (N= 15)
CANDELA: Aflibercept 8 mg/VT (N= 15)
PULSAR: Aflibercept 2 mg/VT (N= 5)
PULSAR: Aflibercept 8 mg/VT (N= 16)
PHOTON: Aflibercept 2 mg/VT (N= 12)
PHOTON: Aflibercept 8 mg/VT (N= 23)

FIG. 34

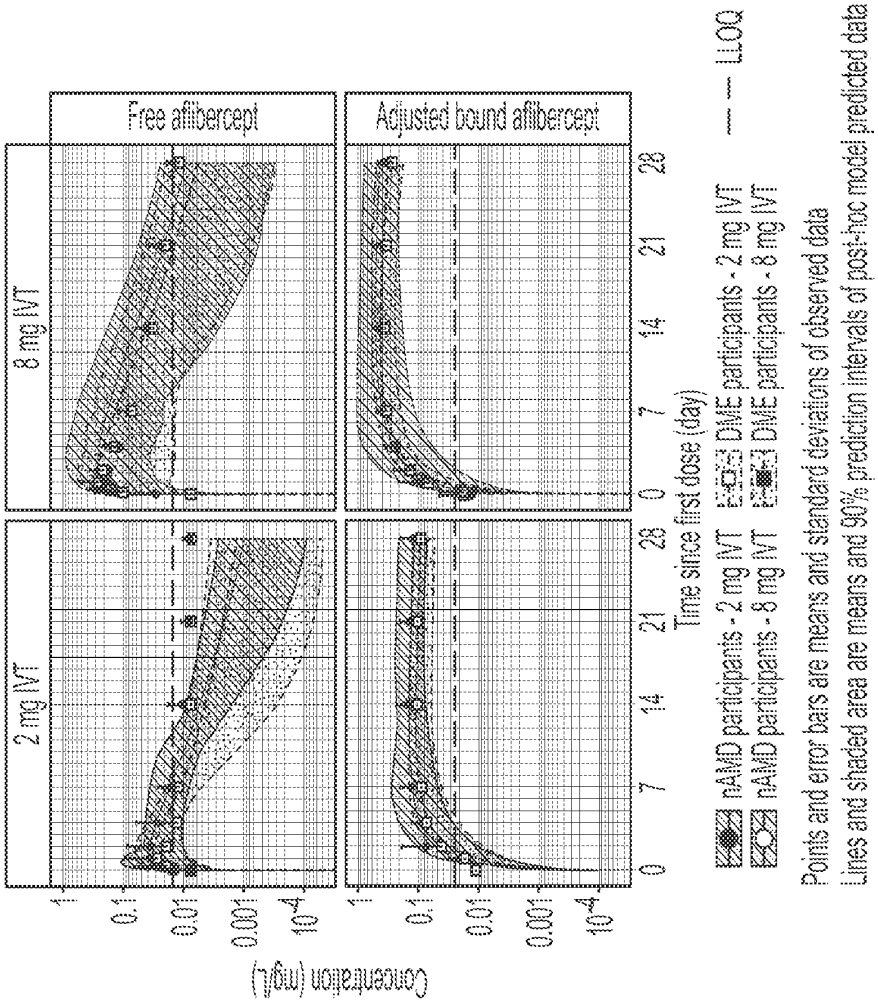

Free aflibercept
Adjusted bound aflibercept
2 mg IVT
8 mg IVT
Concentration (mg/L)
1
0.1
0.01
0.001
10-4
0
7
14
21
28
Time since first dose (day)
nAMD participants - 2 mg IVT
nAMD participants - 8 mg IVT
DME participants - 2 mg IVT
DME participants - 8 mg IVT
LLOQ
Points and error bars are means and standard deviations of observed data
Lines and shaded area are means and 90% prediction intervals of post-hoc model predicted data

FIG. 35

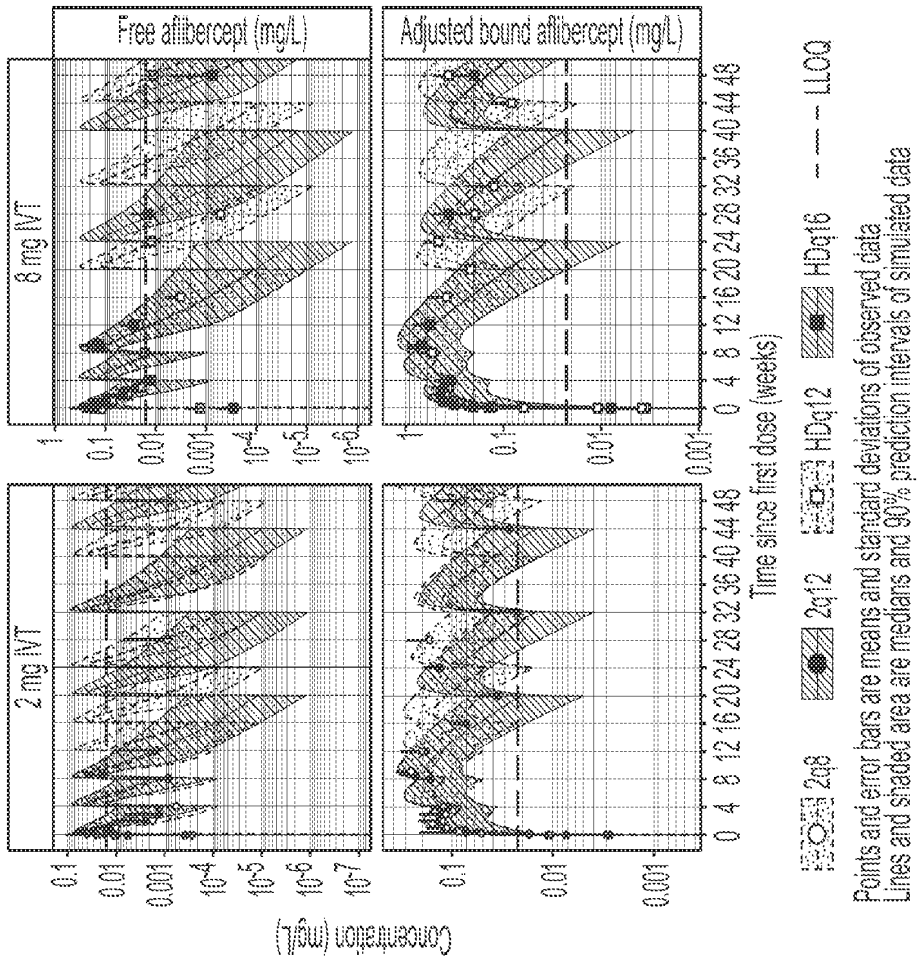

Free aflibercept (mg/L)
Adjusted bound aflibercept (mg/L)
2 mg IVT
8 mg IVT
Concentration (mg/L)
Time since first dose (weeks)
2q8
2q12
HDq12
HDq16
LLOQ
Points and error bars are means and standard deviations of observed data
Lines and shaded area are medians and 90% prediction intervals of simulated data

FIG. 36

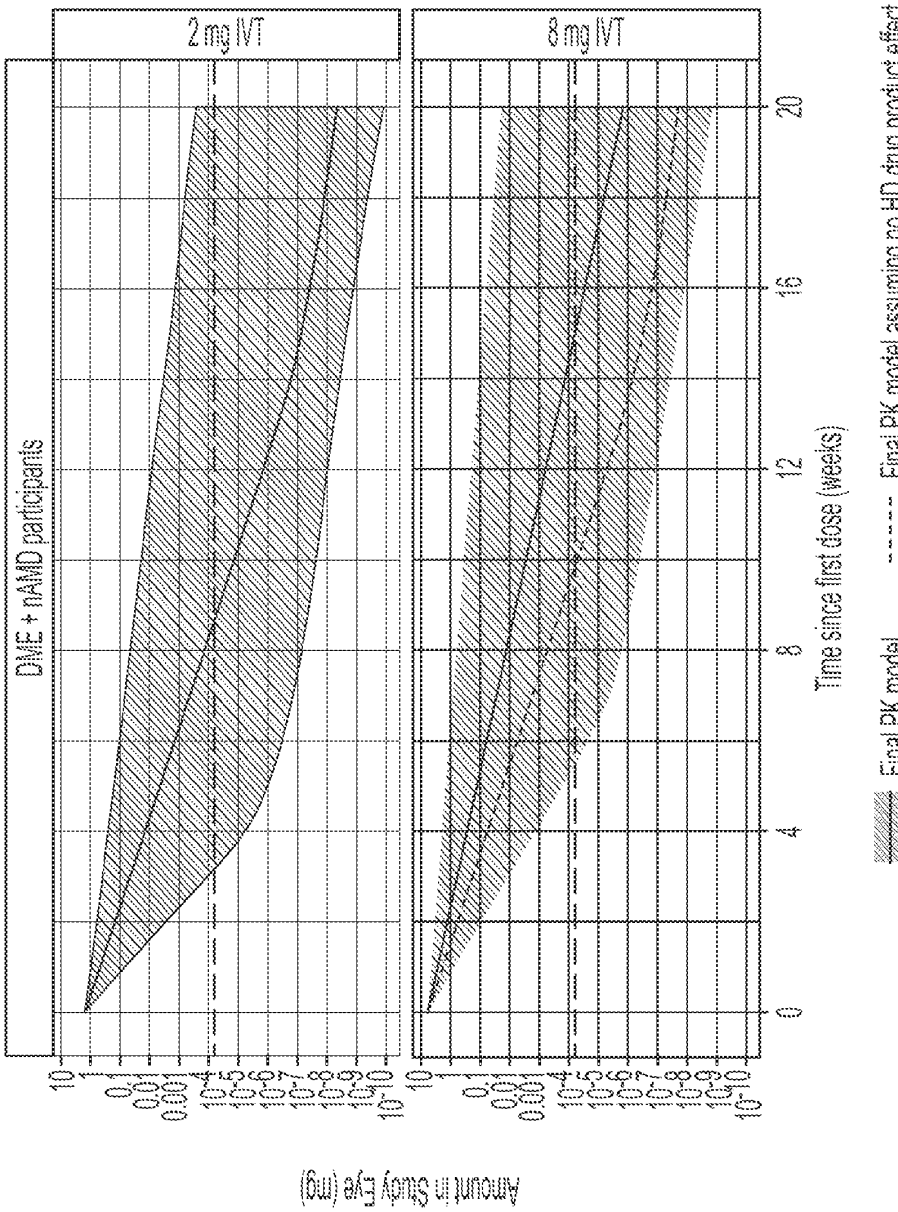

DME + nAMD participants
2 mg IVT
8 mg IVT
Amount in Study Eye (mg)
Time since first dose (weeks)
Median + 90% PI
Final PK model
Adjusted LLOQ
Final PK model assuming no HD drug product effect on QE
Adjusted LLOQ = LLOQ of free aflibercept in plasma (0.0156 mg/L) x the assumed volume of the study eye (4 mL)

FIG. 37

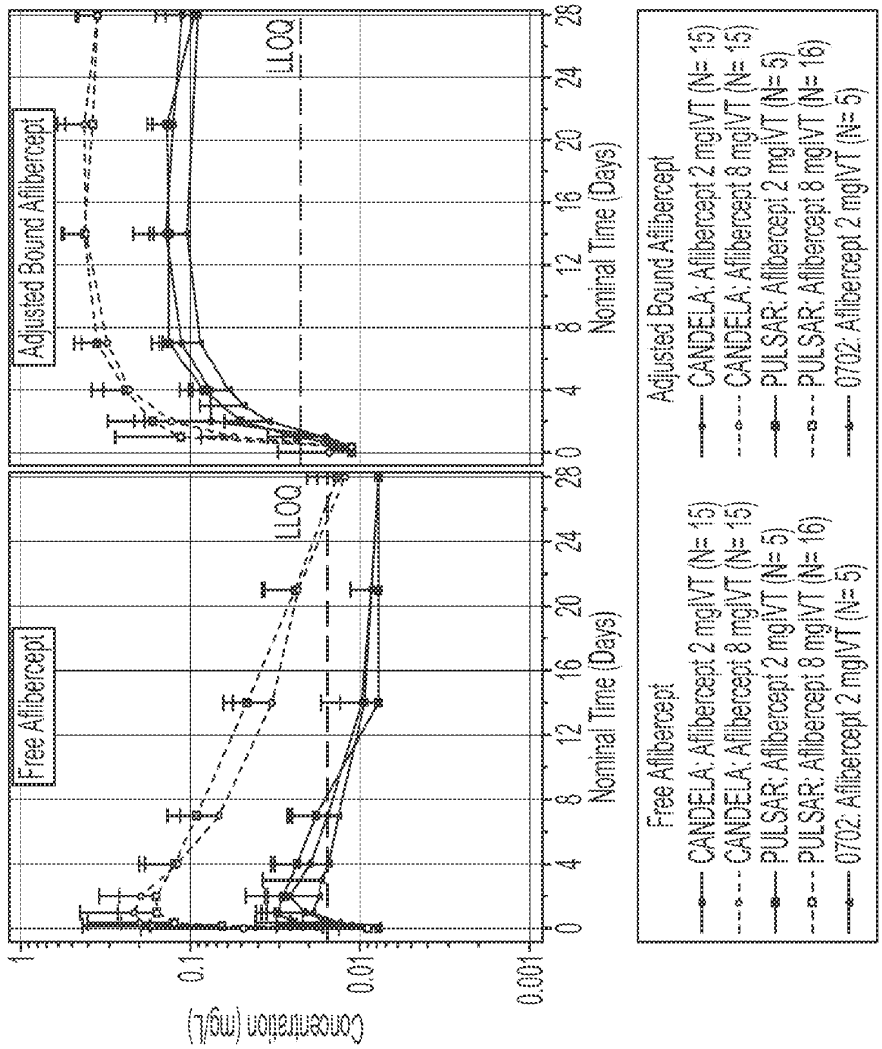

Free Aflibercept
Adjusted Bound Aflibercept
LLOQ
Concentration (mg/L)
1
0.1
0.01
0.001
0
4
8
12
16
20
24
28
Nominal Time (Days)
Free Aflibercept
CANDELA: Aflibercept 2 mg/VT (N= 15)
CANDELA: Aflibercept 8 mg/VT (N= 15)
PULSAR: Aflibercept 2 mg/VT (N= 5)
PULSAR: Aflibercept 8 mg/VT (N= 16)
0702: Aflibercept 2 mg/VT (N= 5)
Adjusted Bound Aflibercept
CANDELA: Aflibercept 2 mg/VT (N= 15)
CANDELA: Aflibercept 8 mg/VT (N= 15)
PULSAR: Aflibercept 2 mg/VT (N= 5)
PULSAR: Aflibercept 8 mg/VT (N= 16)
0702: Aflibercept 2 mg/VT (N= 5)

FIG. 38

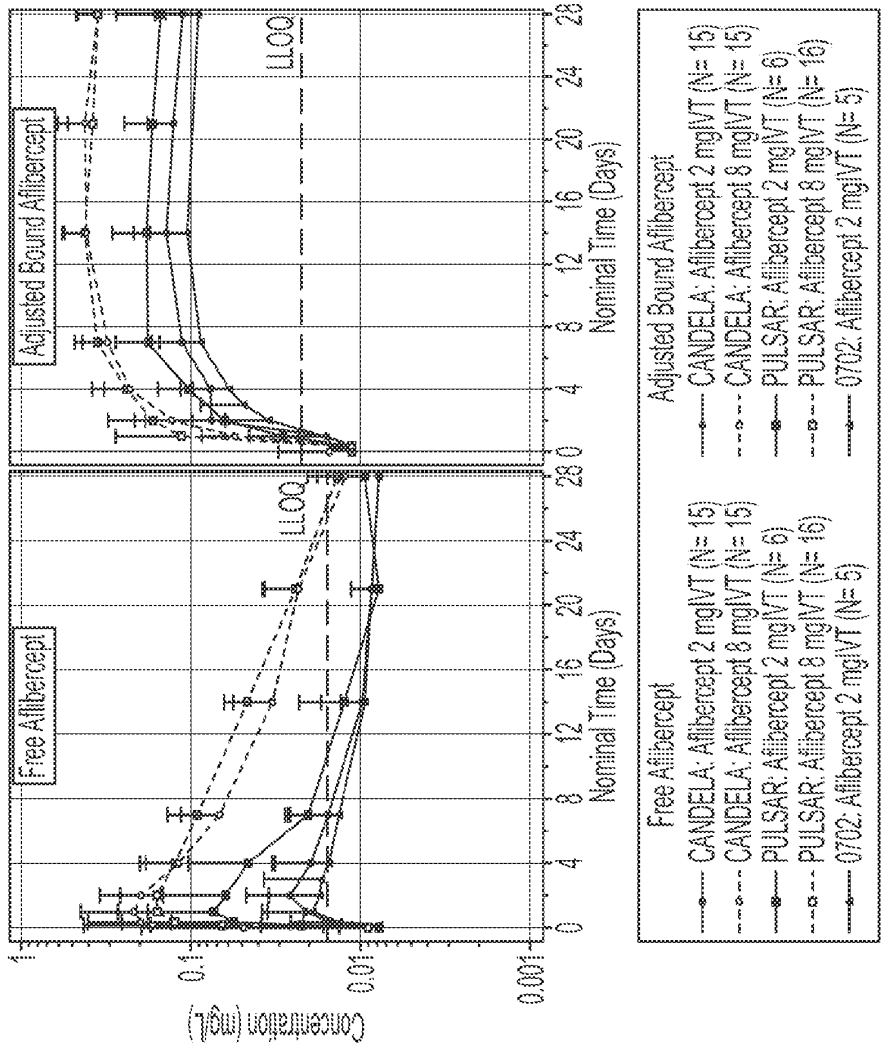

Free Aflibercept
Adjusted Bound Aflibercept
LLOQ
LLOQ
Concentration (mg/L)
1
0.1
0.01
0.001
0
4
8
12
16
20
24
28
Nominal Time (Days)
Free Aflibercept
CANDELA: Aflibercept 2 mg/VT (N= 15)
CANDELA: Aflibercept 8 mg/VT (N= 15)
PULSAR: Aflibercept 2 mg/VT (N= 6)
PULSAR: Aflibercept 8 mg/VT (N= 16)
0702: Aflibercept 2 mg/VT (N= 5)
Adjusted Bound Aflibercept
CANDELA: Aflibercept 2 mg/VT (N= 15)
CANDELA: Aflibercept 8 mg/VT (N= 15)
PULSAR: Aflibercept 2 mg/VT (N= 6)
PULSAR: Aflibercept 8 mg/VT (N= 16)
0702: Aflibercept 2 mg/VT (N= 5)

FIG. 39

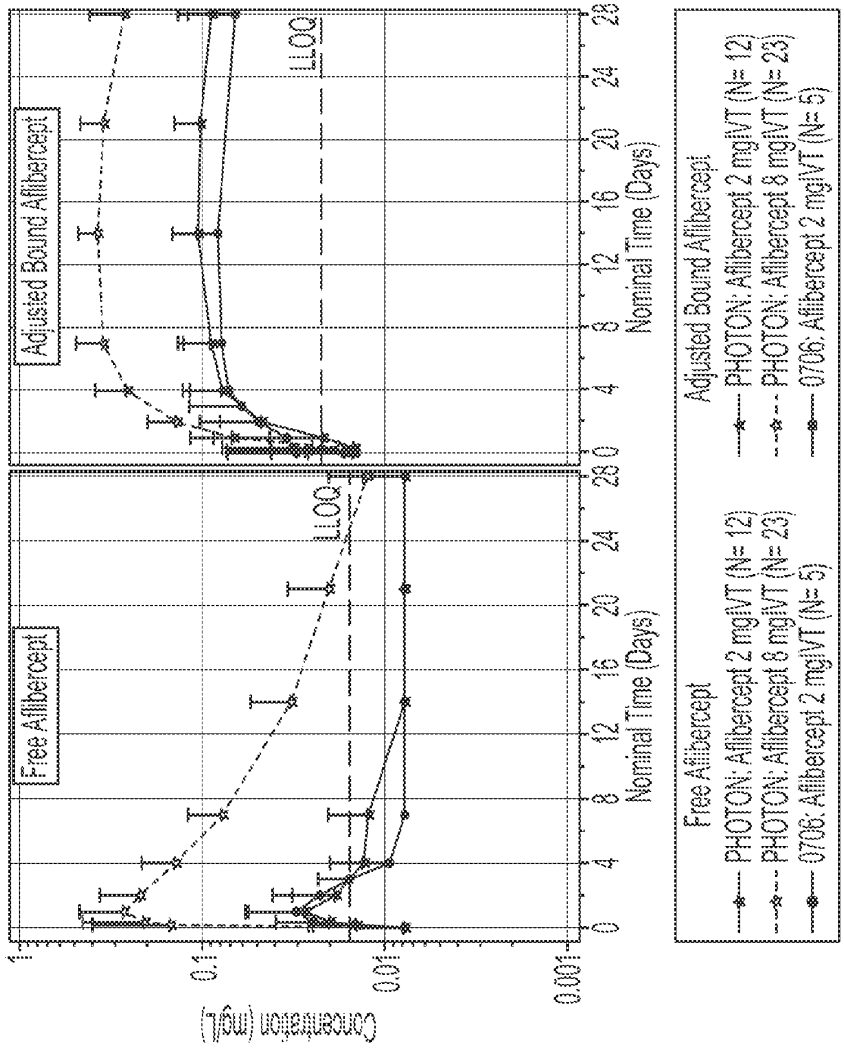

Free Aflibercept
Adjusted Bound Aflibercept
LLOQ
LLOQ
Concentration (mg/L)
1
0.1
0.01
0.001
0
4
8
12
16
20
24
28
Nominal Time (Days)
Free Aflibercept
PHOTON: Aflibercept 2 mg/VT (N= 12)
PHOTON: Aflibercept 8 mg/VT (N= 23)
0706: Aflibercept 2 mg/VT (N= 5)
Adjusted Bound Aflibercept
PHOTON: Aflibercept 2 mg/VT (N= 12)
PHOTON: Aflibercept 8 mg/VT (N= 23)
0706: Aflibercept 2 mg/VT (N= 5)

FIG. 40

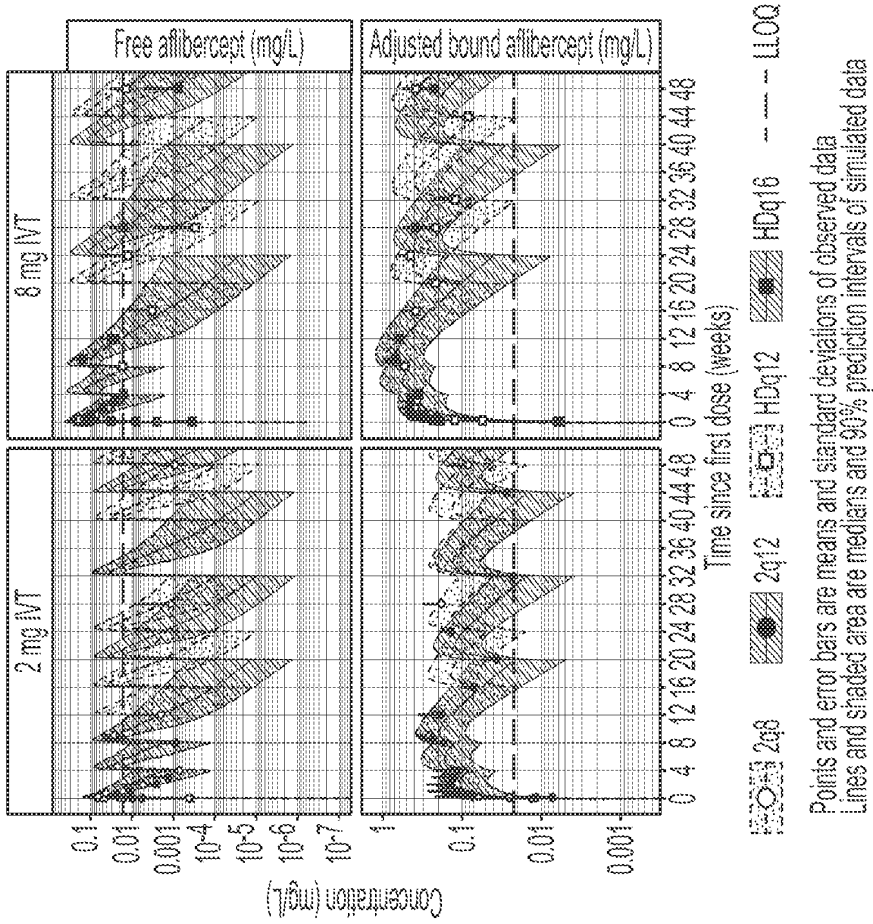

Free aflibercept (mg/L)
Adjusted bound aflibercept (mg/L)
2 mg IVT
8 mg IVT
Concentration (mg/L)
Time since first dose (weeks)
2q8
2q12
HDq12
HDq16
LLOQ
Points and error bars are means and standard deviations of observed data
Lines and shaded area are medians and 90% prediction intervals of simulated data

FIG. 41

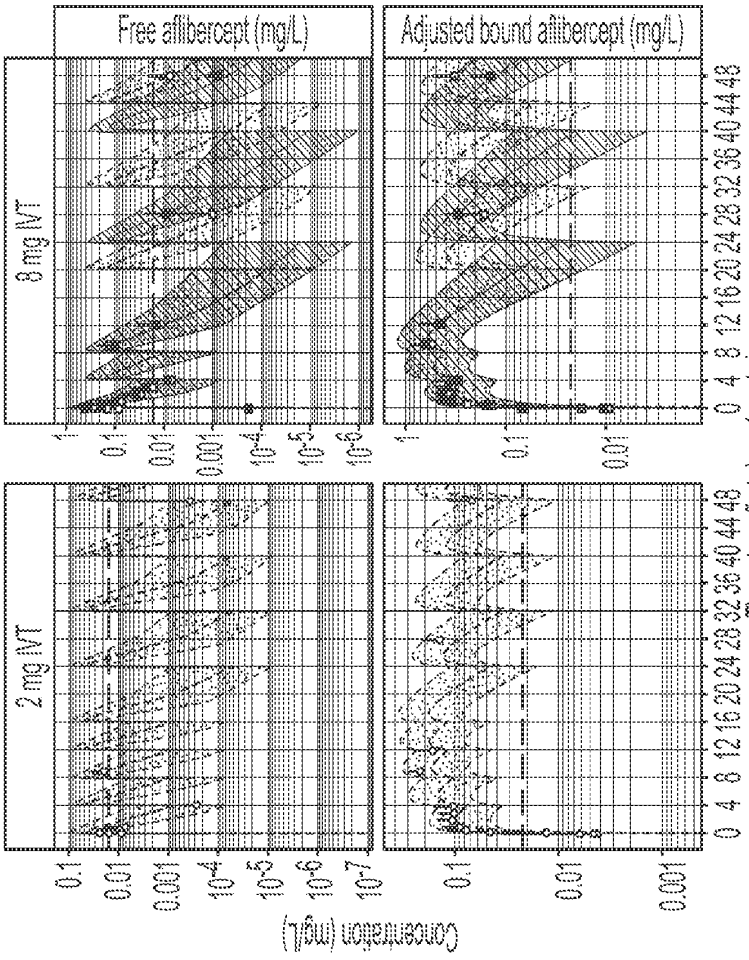

Free aflibercept (mg/L)
Adjusted bound aflibercept (mg/L)
8 mg IVT
2 mg IVT
Concentration (mg/L)
Time since first dose (weeks)
HDq12
HDq16
LLOQ
Points and error bars are means and standard deviations of observed data
Lines and shaded area are medians and 90% prediction intervals of simulated data

FIG. 42