

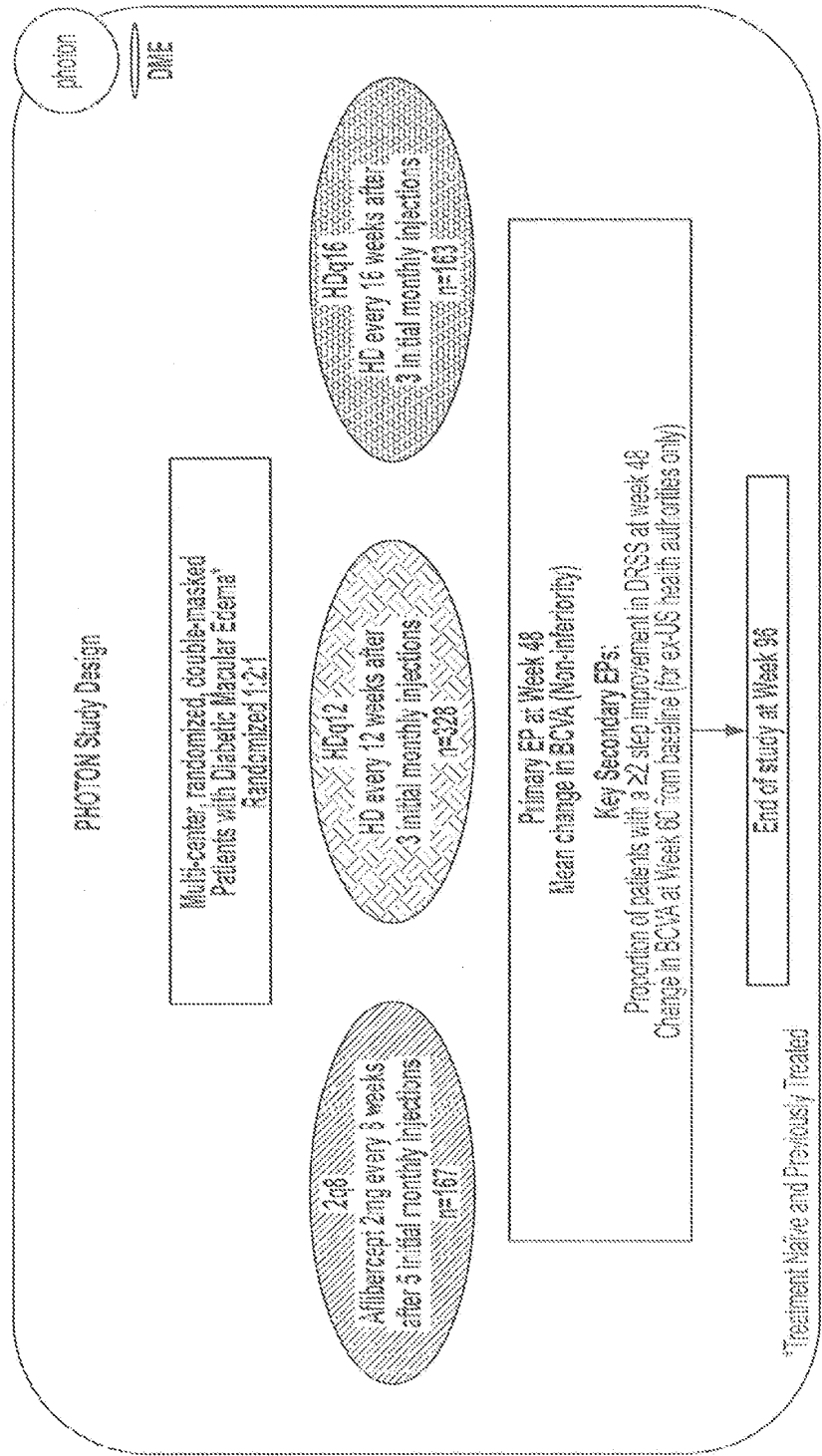


FIG. 1

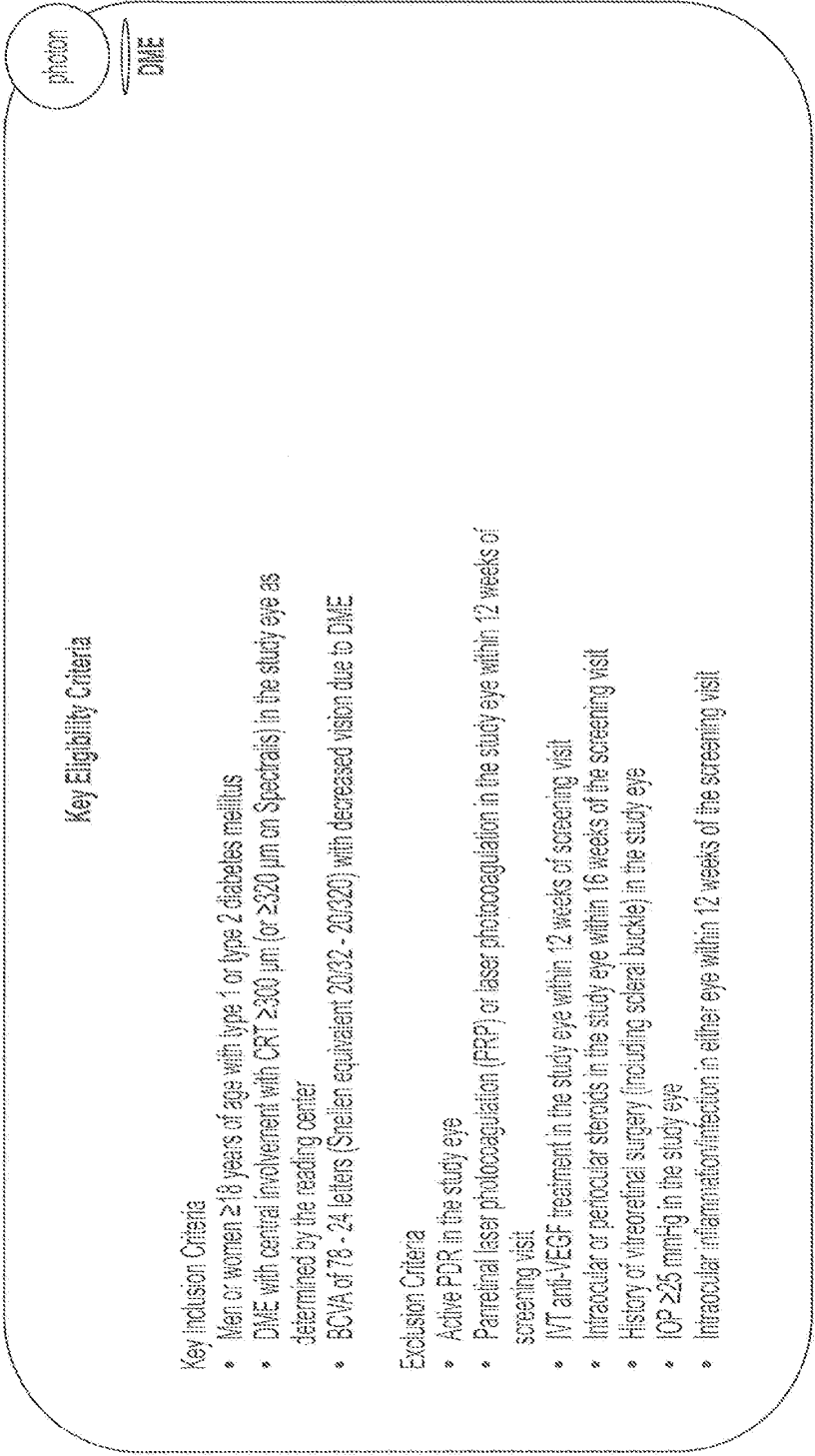


FIG. 2

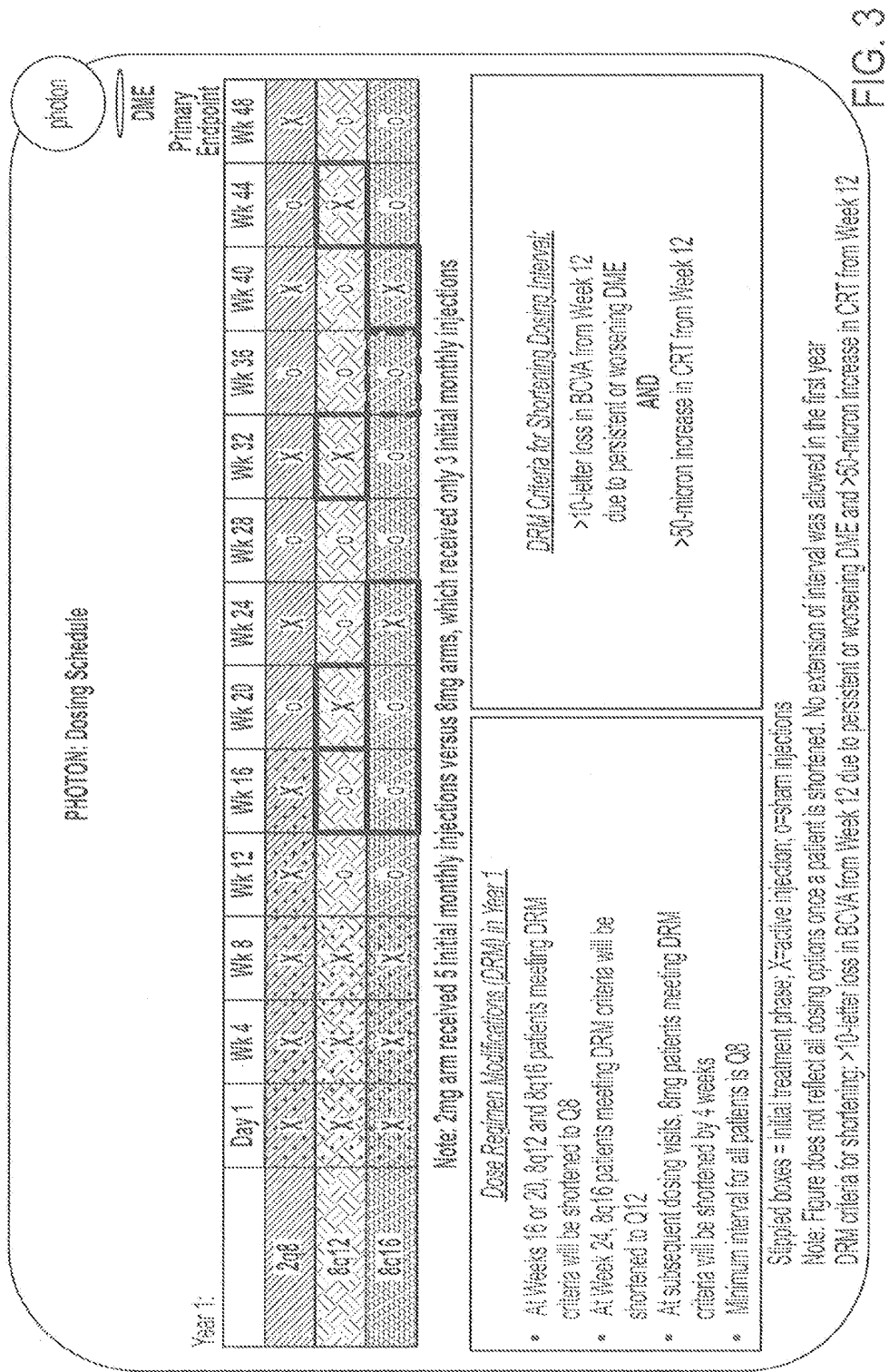


FIG. 3

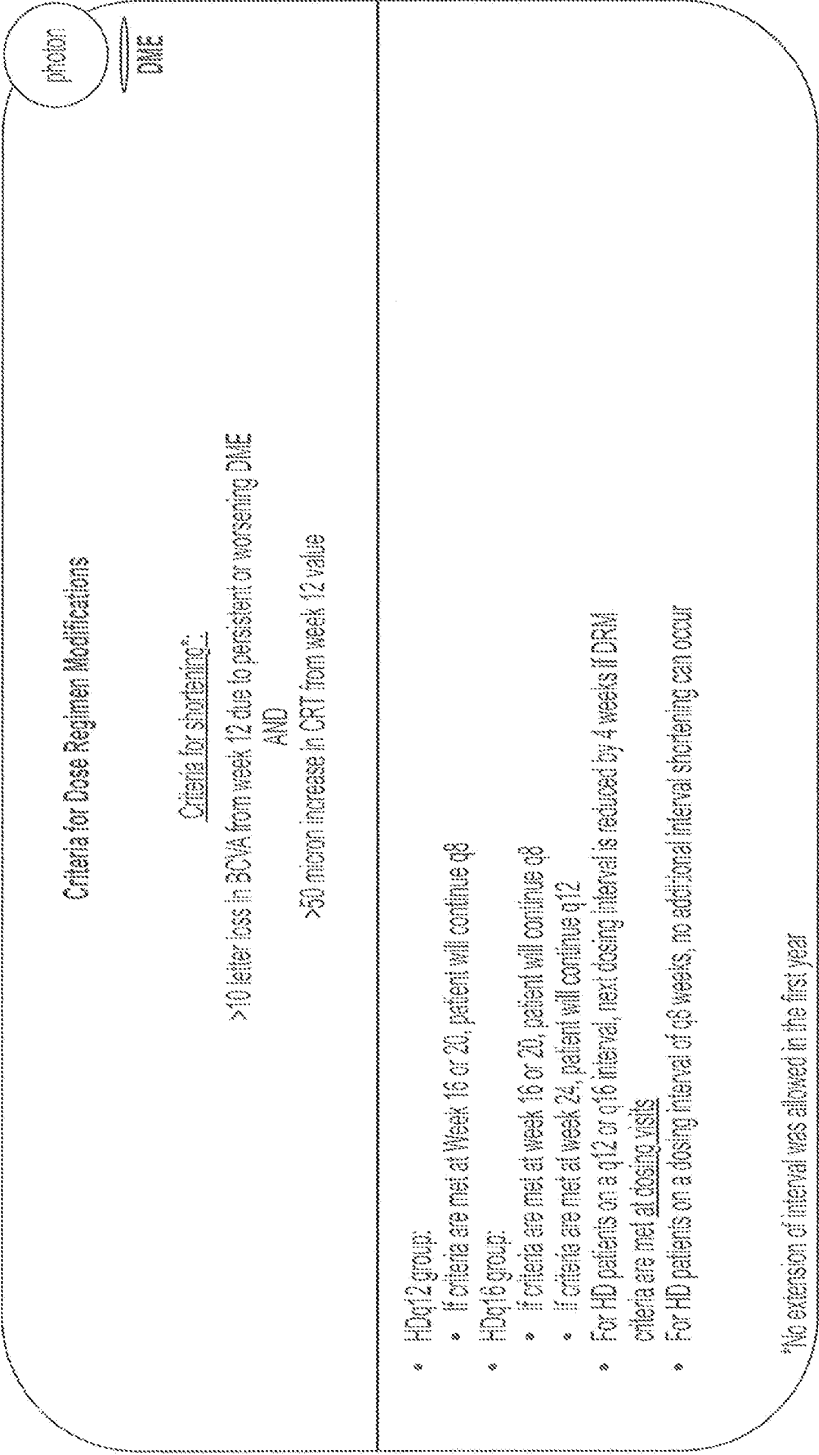


FIG. 4

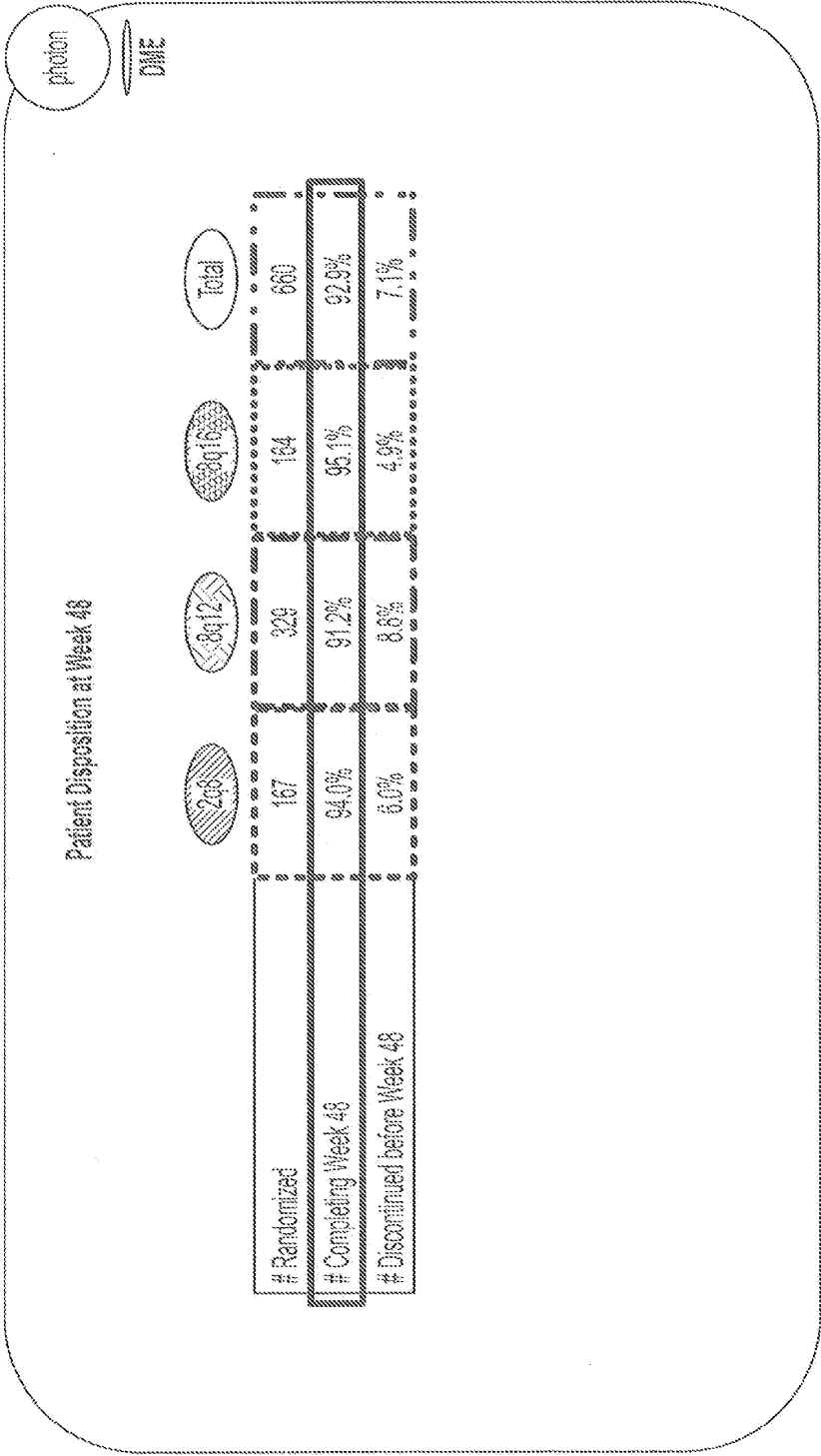


FIG. 5

proton

DME

Baseline Demographics

	2d	<HDq12>	HDq16	Total
N (FASISAF)	167	328	163	658
Age (years (SD))	63.0 (9.76)	62.1 (11.13)	61.9 (9.50)	62.3 (10.41)
Women # (%)	75 (44.9%)	118 (36.0%)	64 (39.3%)	257 (39.1%)
Race # (%)				
White	112 (67.1%)	231 (70.4%)	128 (78.5%)	471 (71.6%)
Black or African American	18 (10.8%)	35 (10.7%)	9 (5.5%)	62 (9.4%)
Asian	30 (18.0%)	48 (14.6%)	23 (14.1%)	101 (15.3%)
Other	4 (2.4%)	10 (3.0%)	1 (0.6%)	15 (2.4%)
Not Reported	3 (1.8%)	4 (1.2%)	2 (1.2%)	9 (1.4%)
Hispanic or Latino	31 (18.6%)	54 (16.5%)	34 (20.9%)	119 (18.1%)
Duration of Diabetes (years (SD))	15.9 (10.04)	15.1 (9.96)	15.7 (10.67)	15.5 (10.15)
Hemoglobin A1C (%)	8.14 (1.482)	7.94 (1.546)	7.84 (1.502)	7.97 (1.521)
BMI (kg/m ²)	29.91 (6.525)	30.44 (6.156)	31.02 (6.123)	30.45 (6.247)

FIG. 6

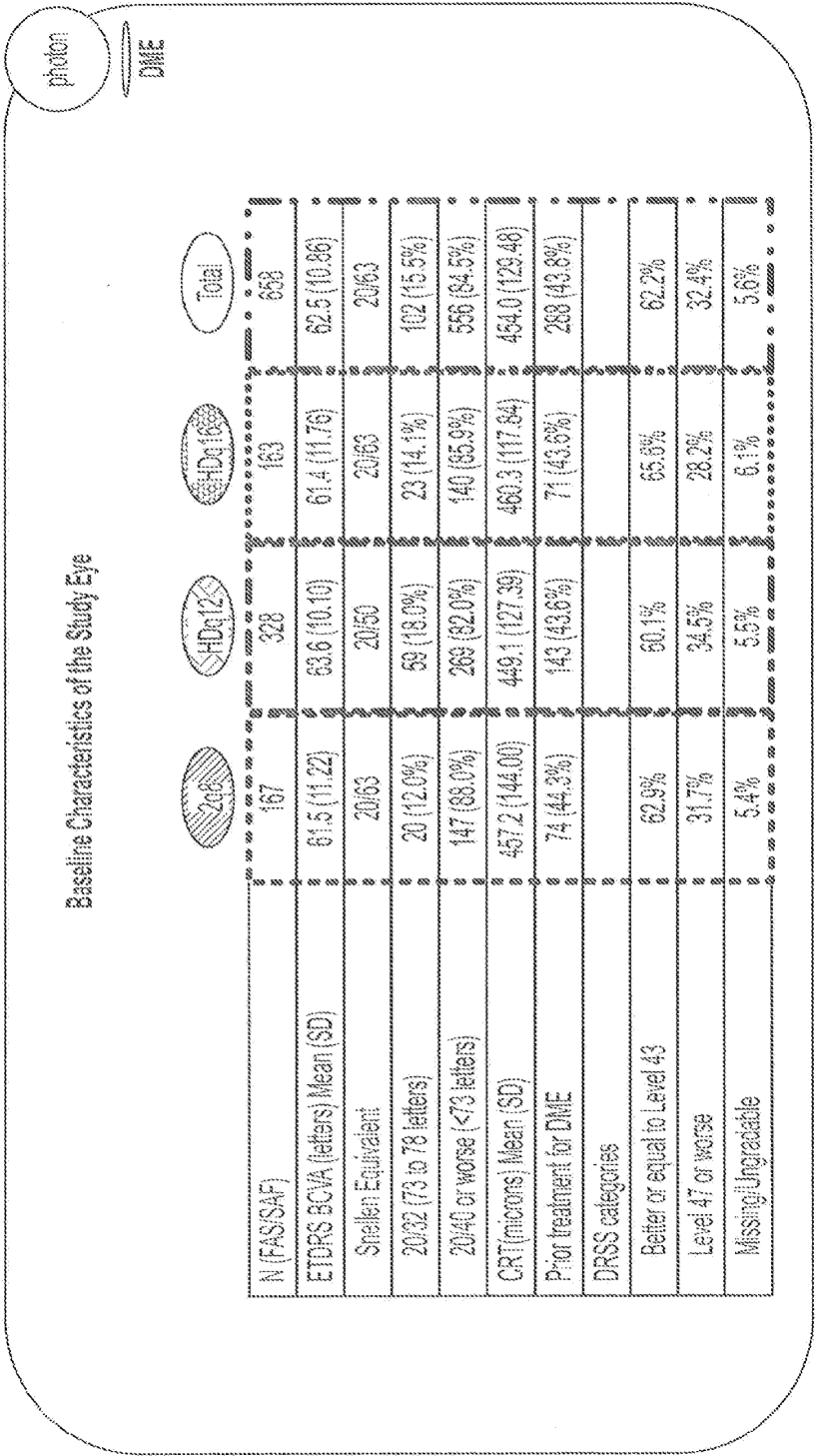


FIG. 7

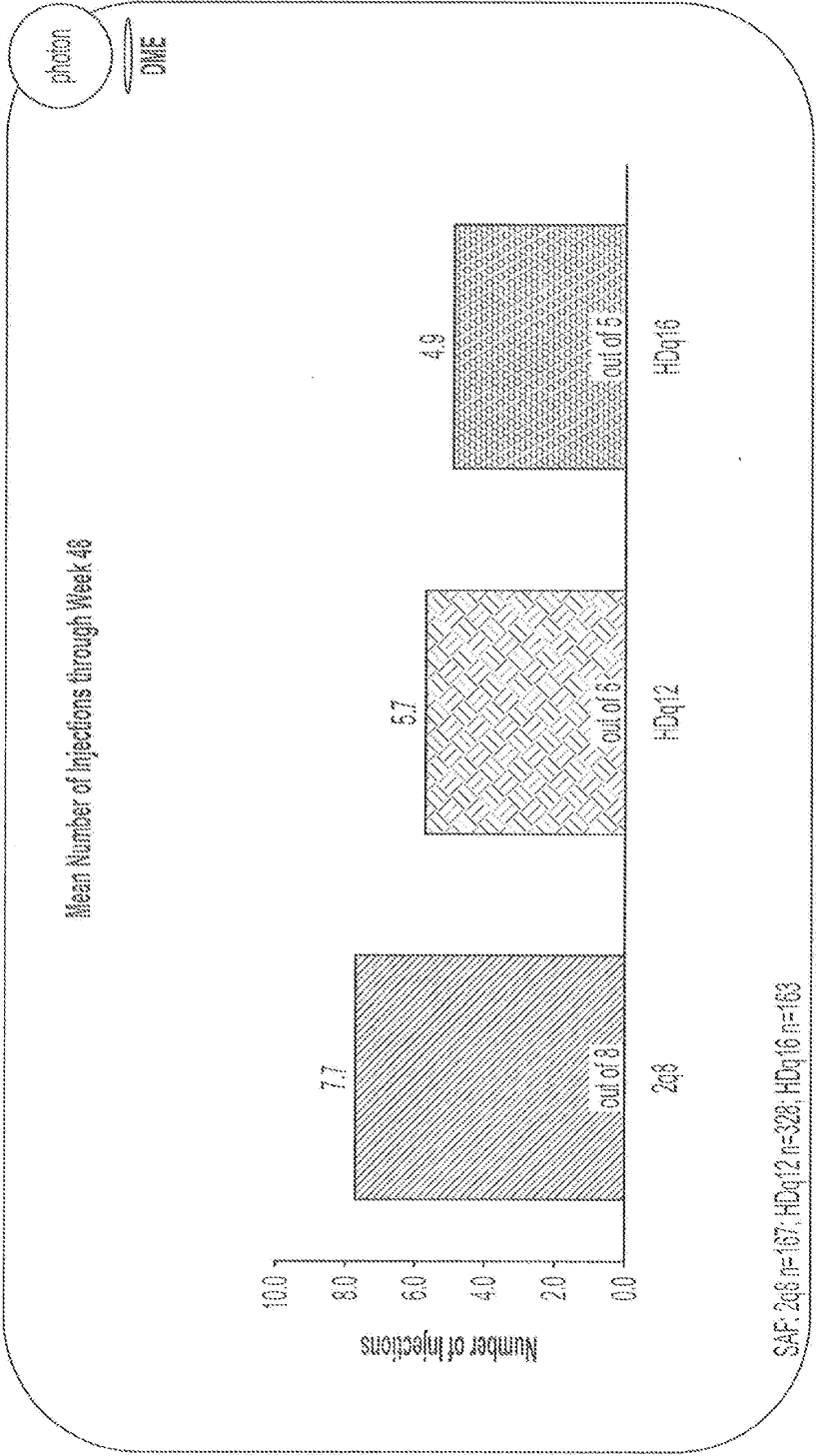


FIG. 8

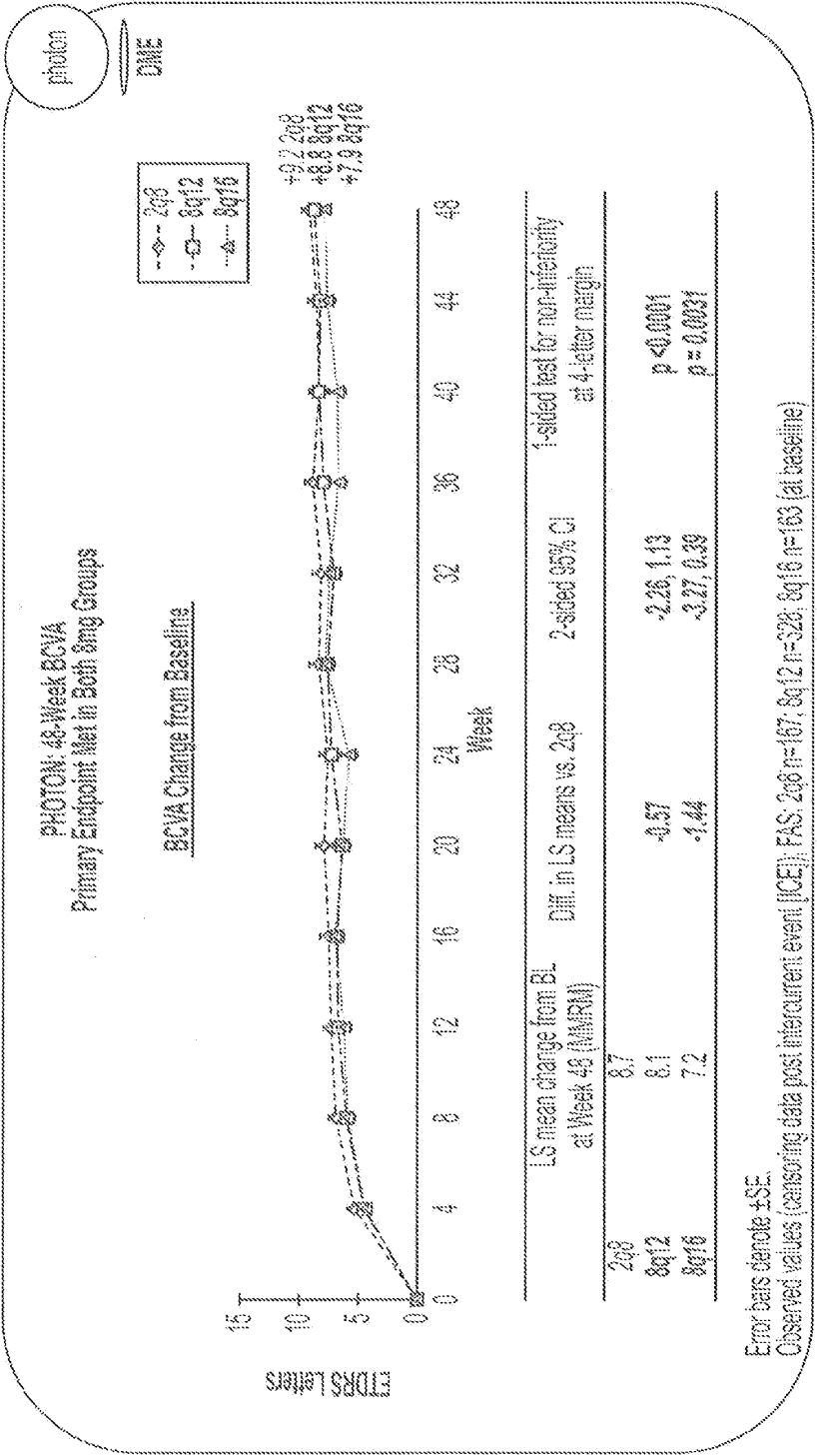


FIG. 9

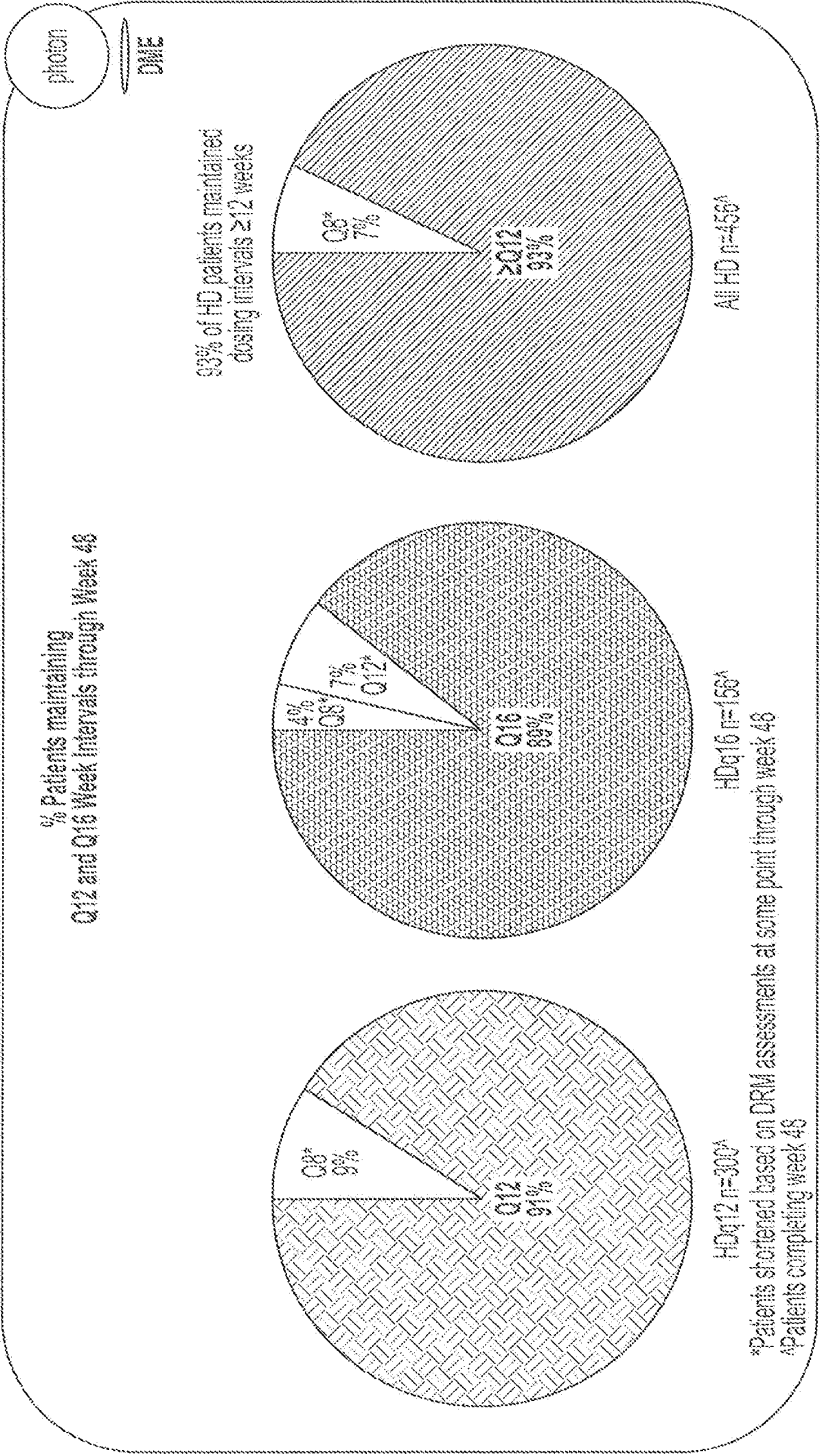


FIG. 10

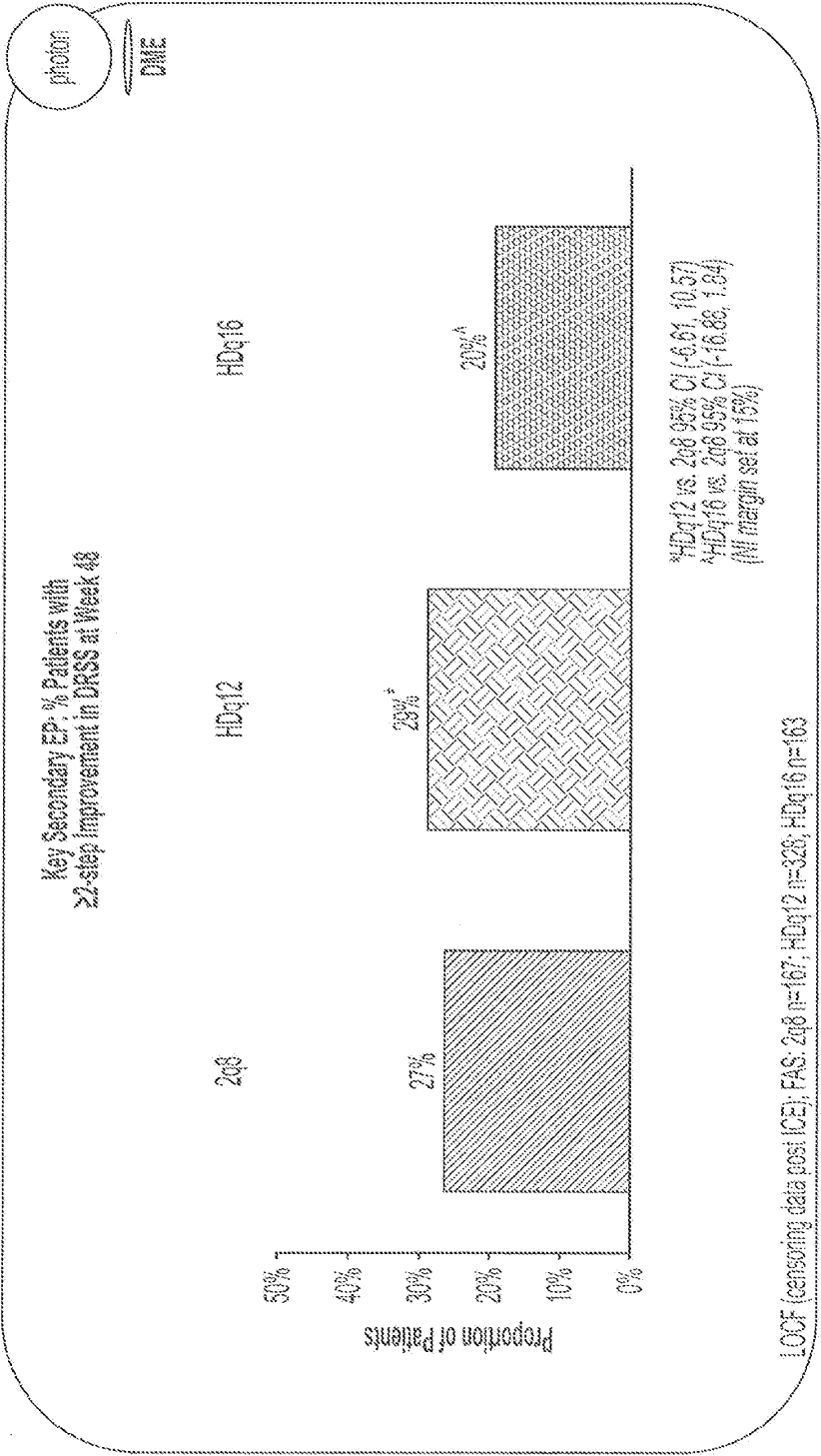


FIG. 11

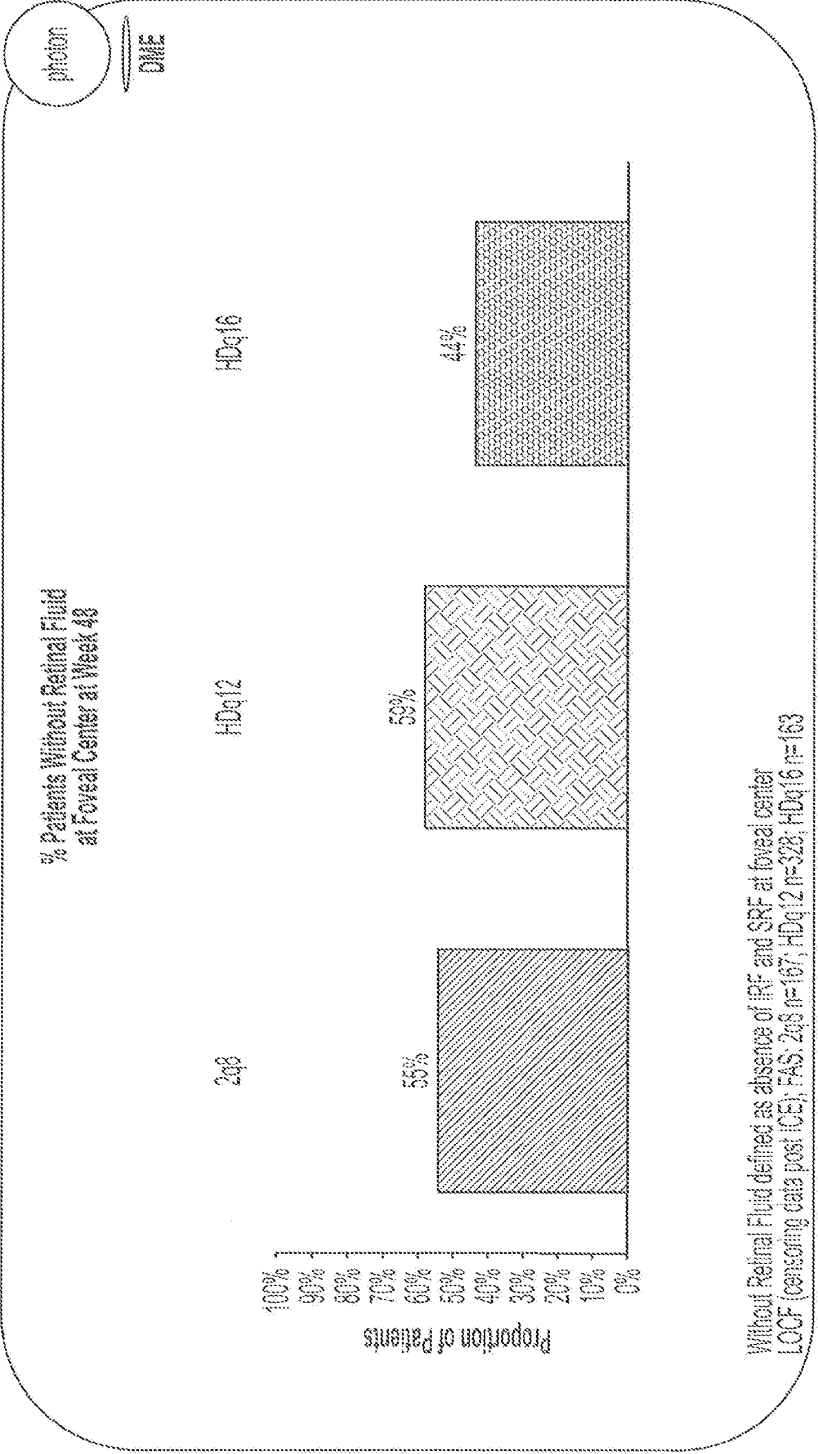


FIG. 12

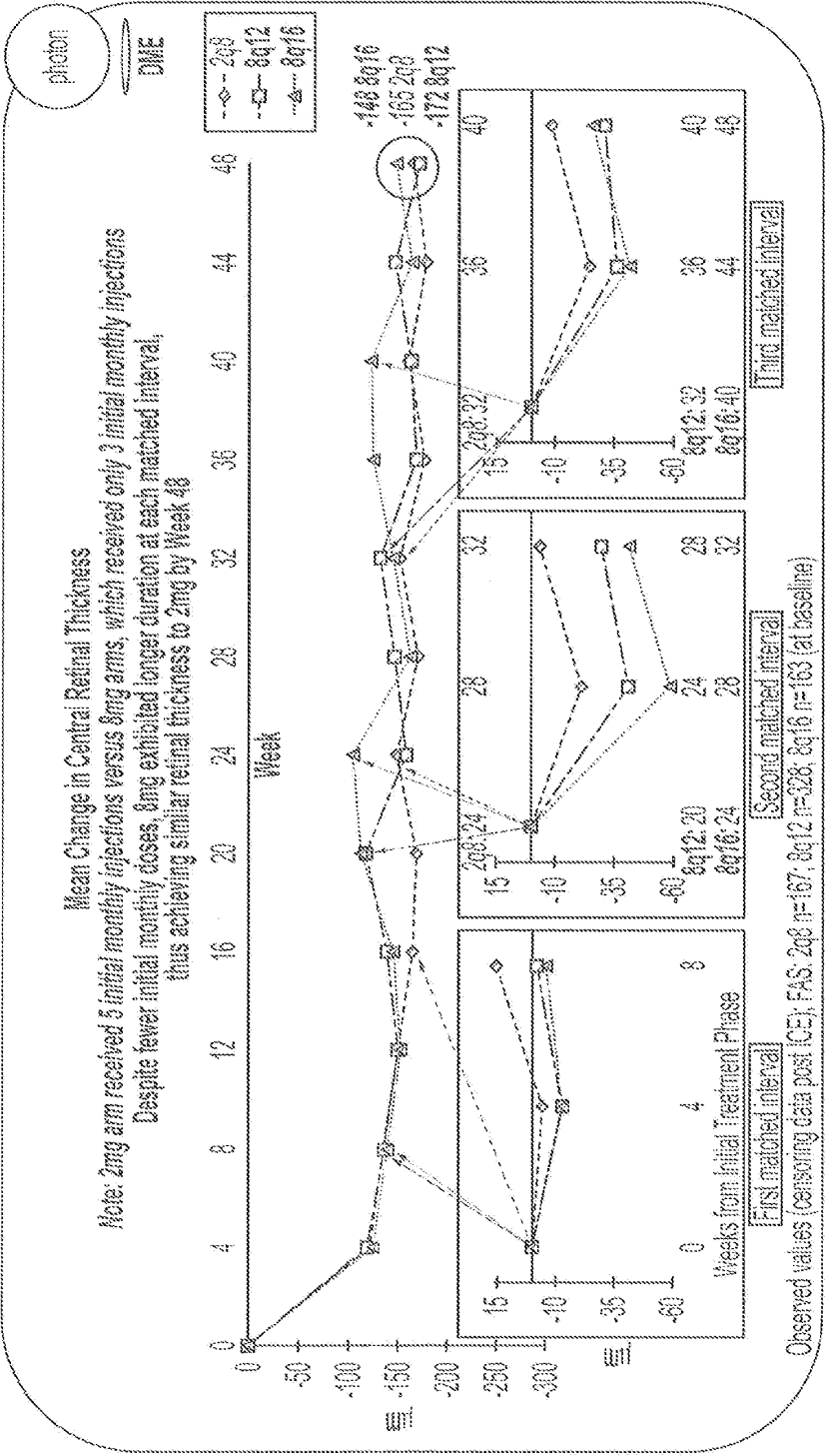


FIG. 13

photon

Ocular Serious TEAEs through Week 48

DME

	208	HDq12	HDq18	All HD
N (SAF)	167	328	163	491
Number of Patients ≥ 1 AE, n (%)	1 (0.6%)	2 (0.6%)	1 (0.6%)	3 (0.6%)
Cataract subcapsular	0	1 (0.3%)	0	1 (0.2%)
Retinal detachment	0	0	1 (0.6%)	1 (0.2%)
Ulcerative keratitis	1 (0.6%)	0	0	0
Vitreous haemorrhage	0	0	1 (0.6%)	1 (0.2%)
Intraocular pressure increased	0	1 (0.3%)	0	1 (0.2%)

FIG. 14A

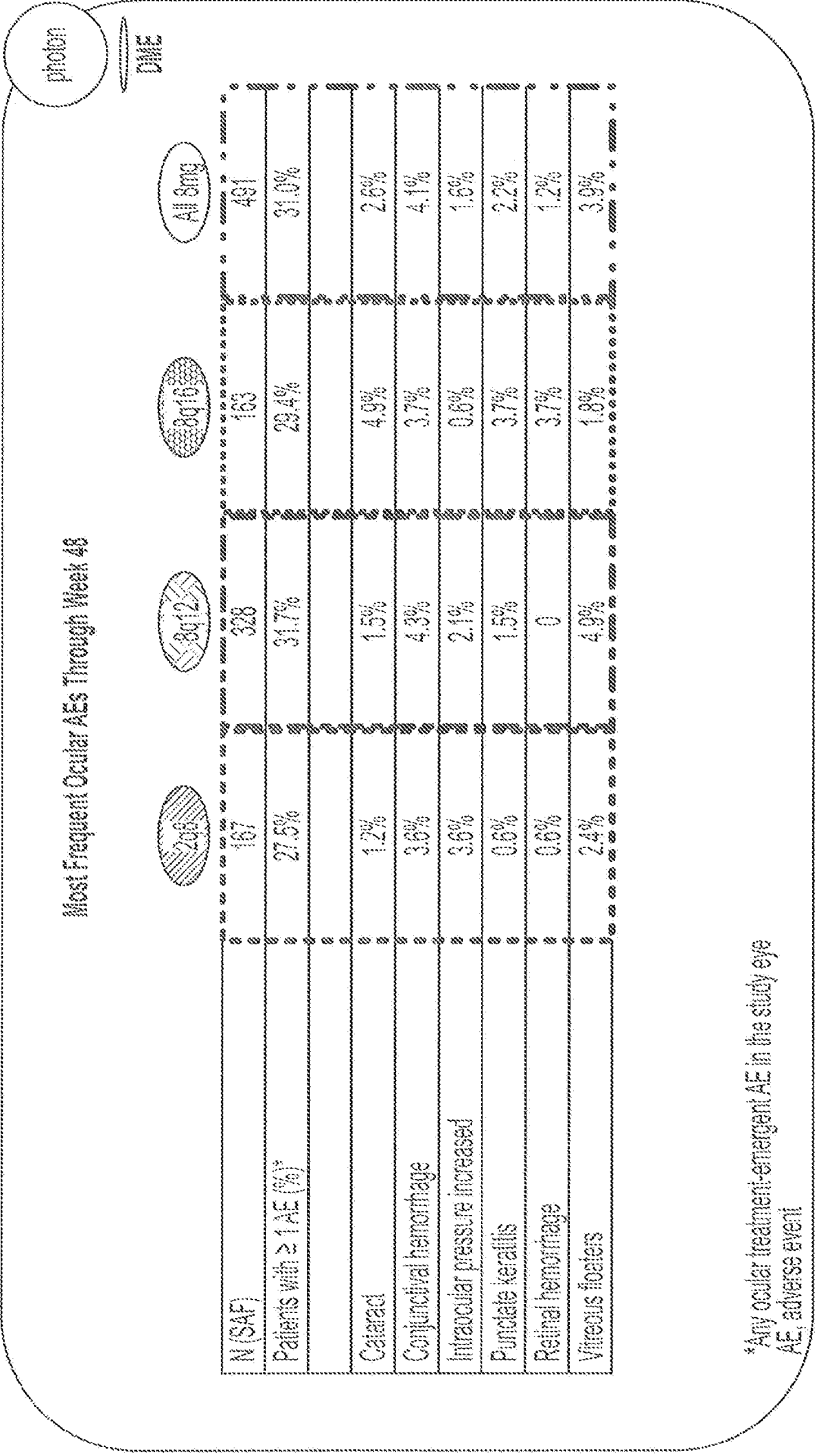


FIG. 14B

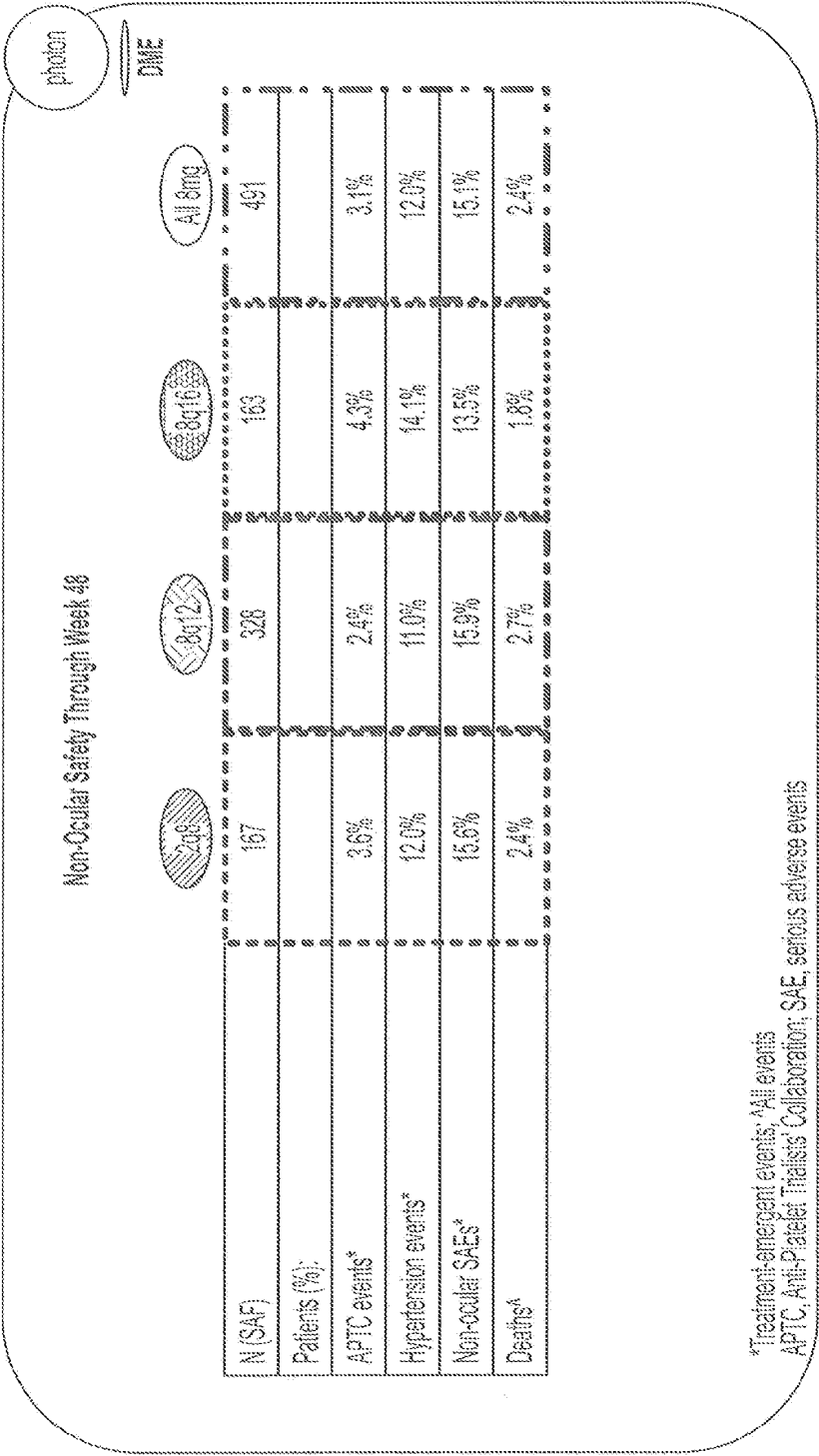


FIG. 14C

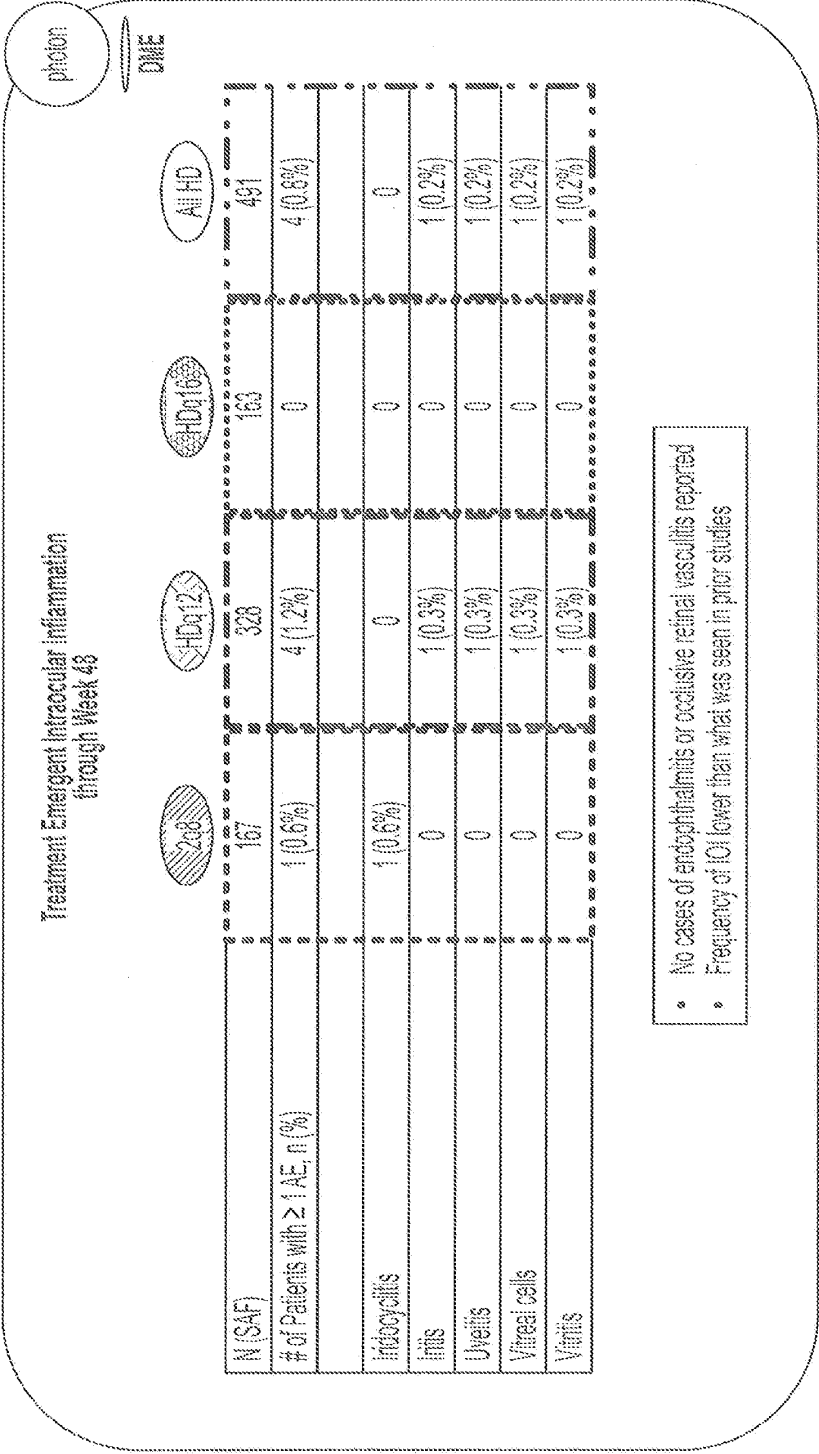


FIG. 15

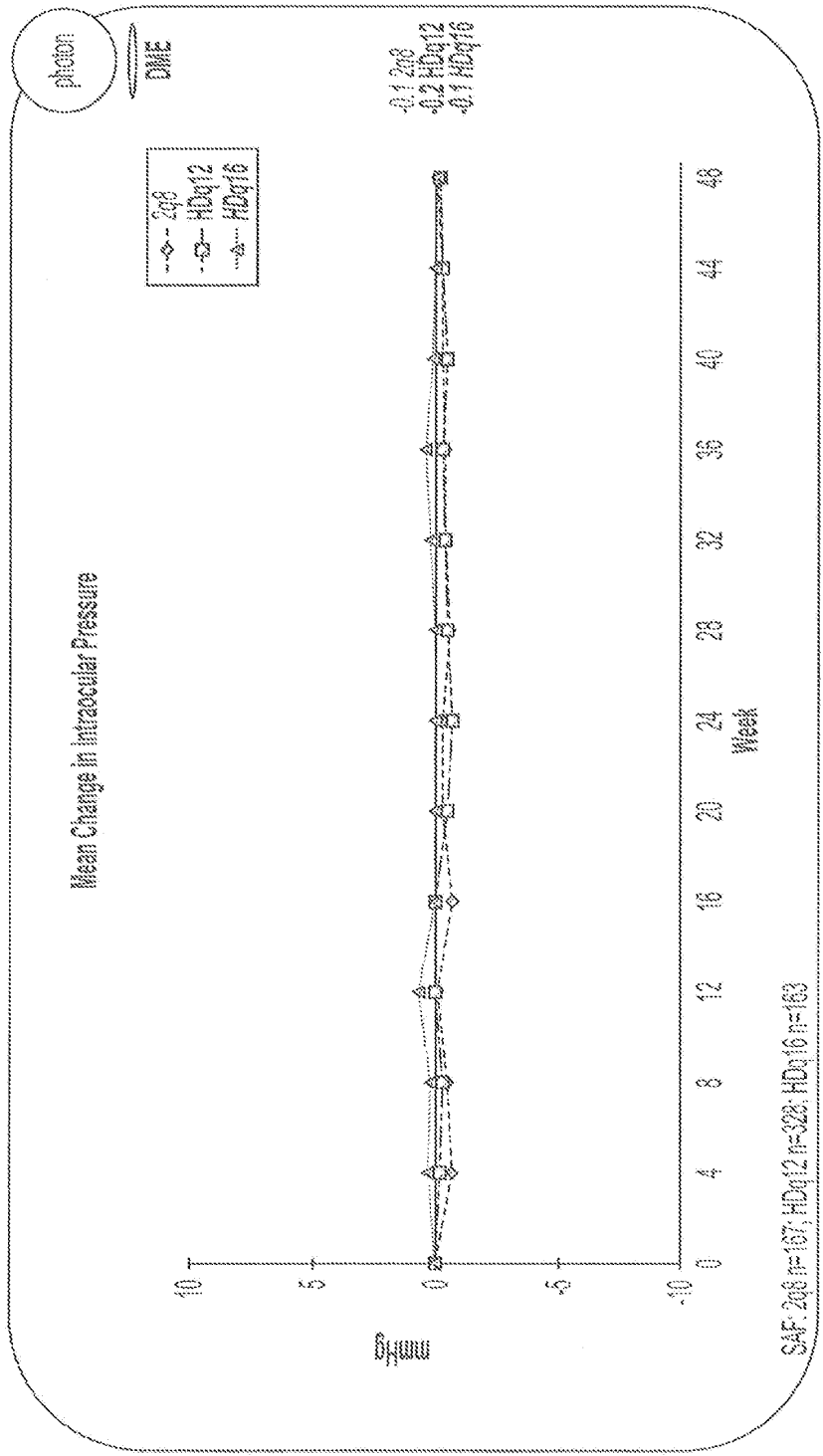
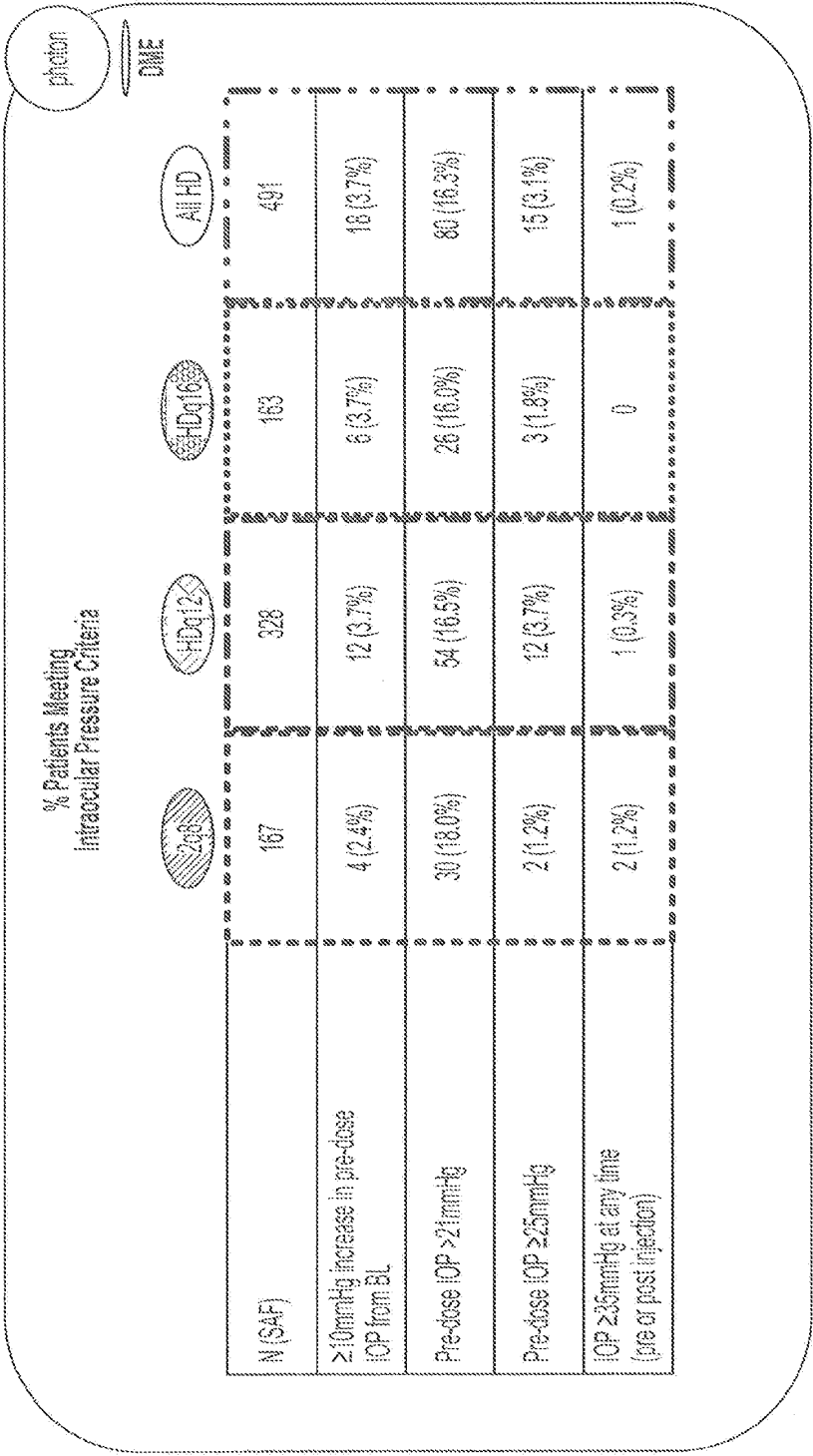


FIG. 16



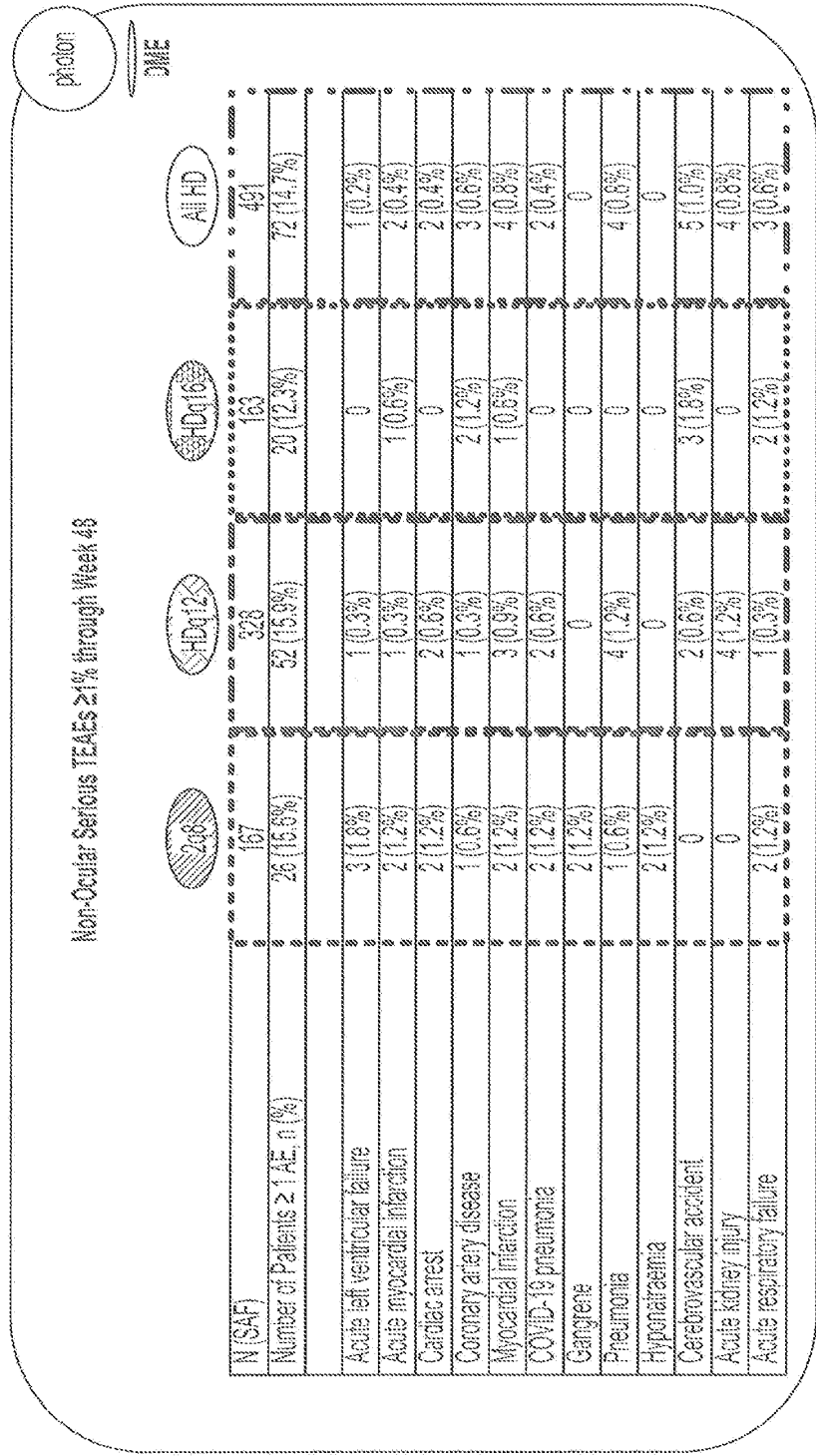
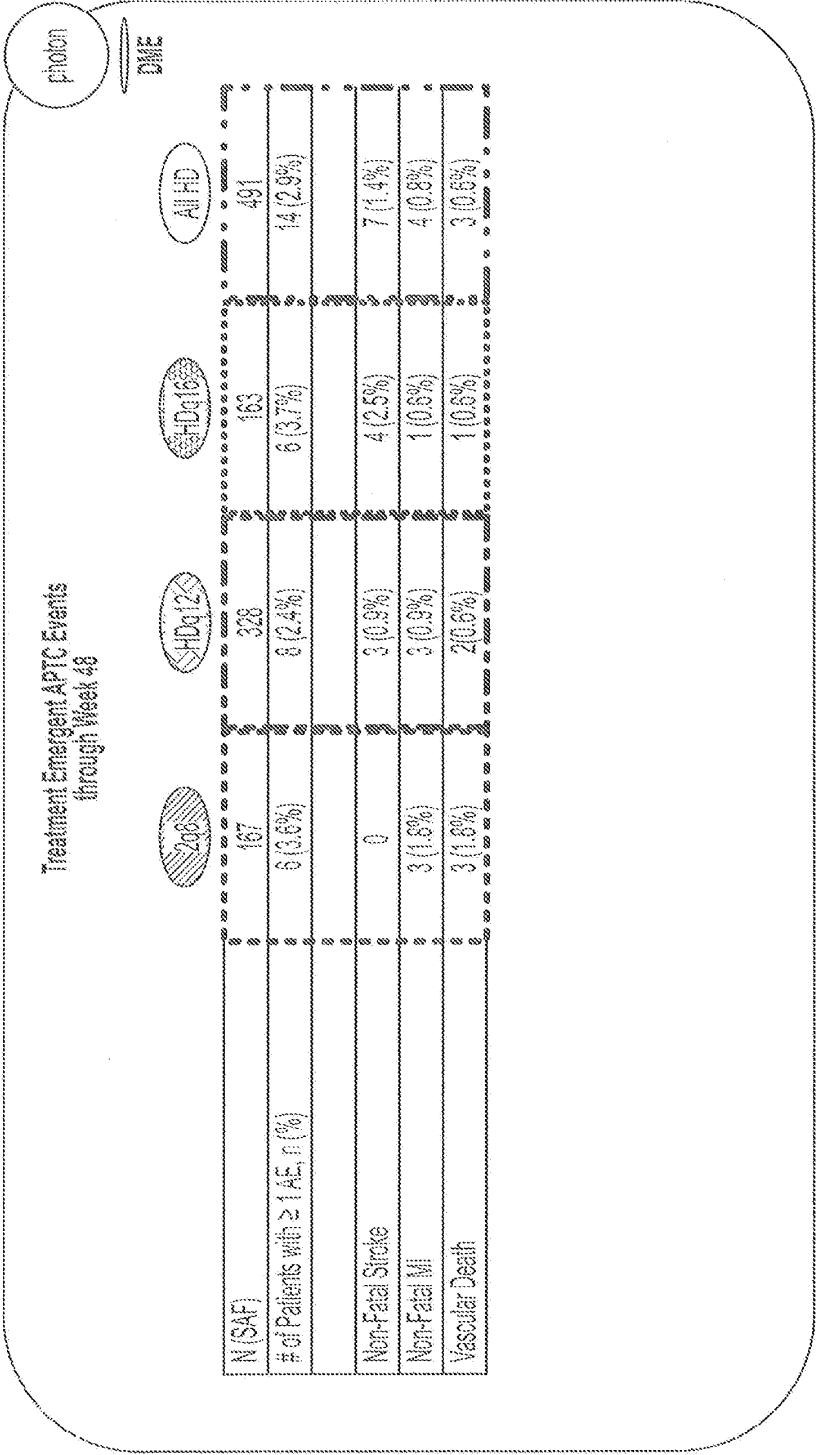


FIG. 18



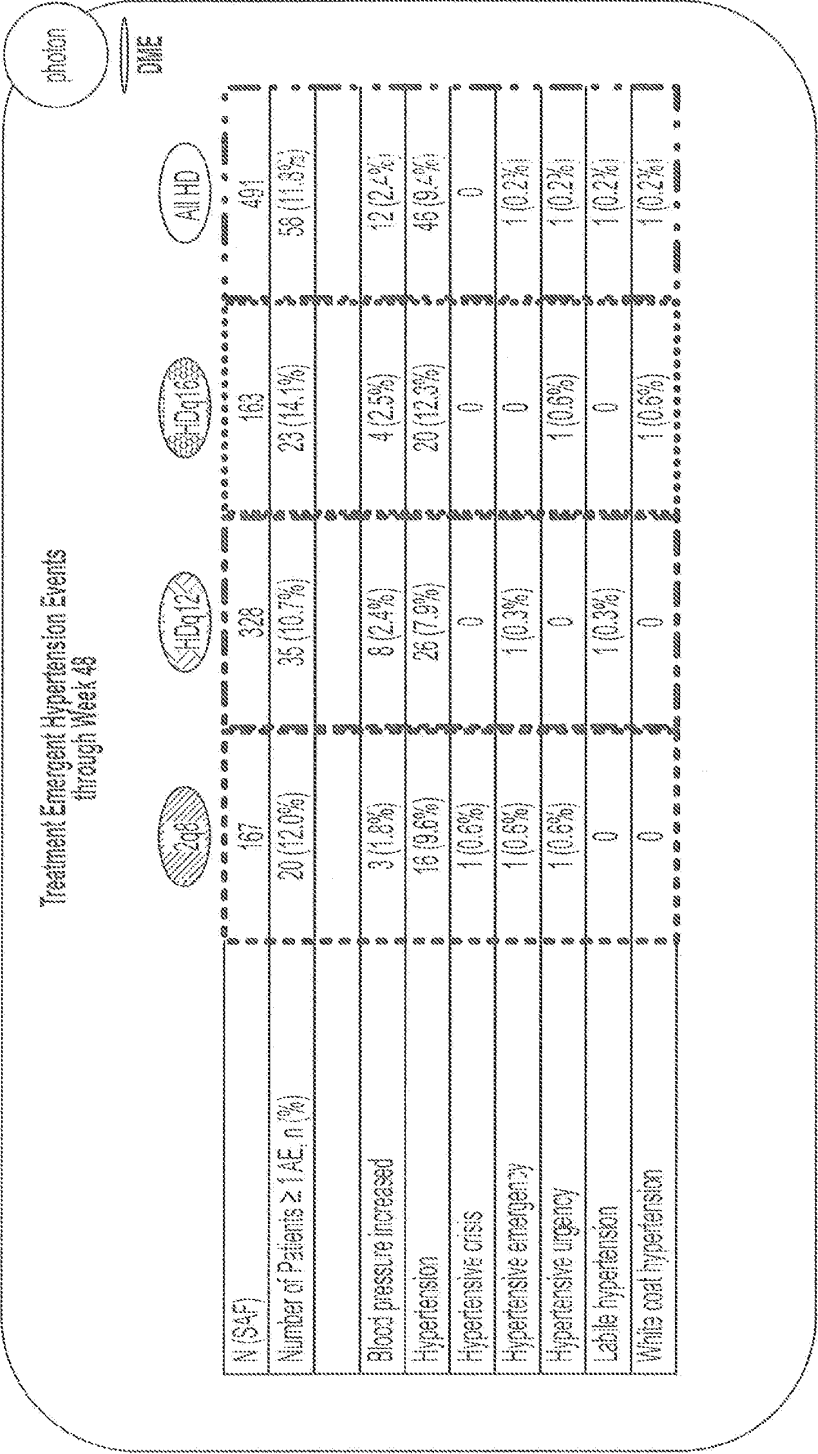
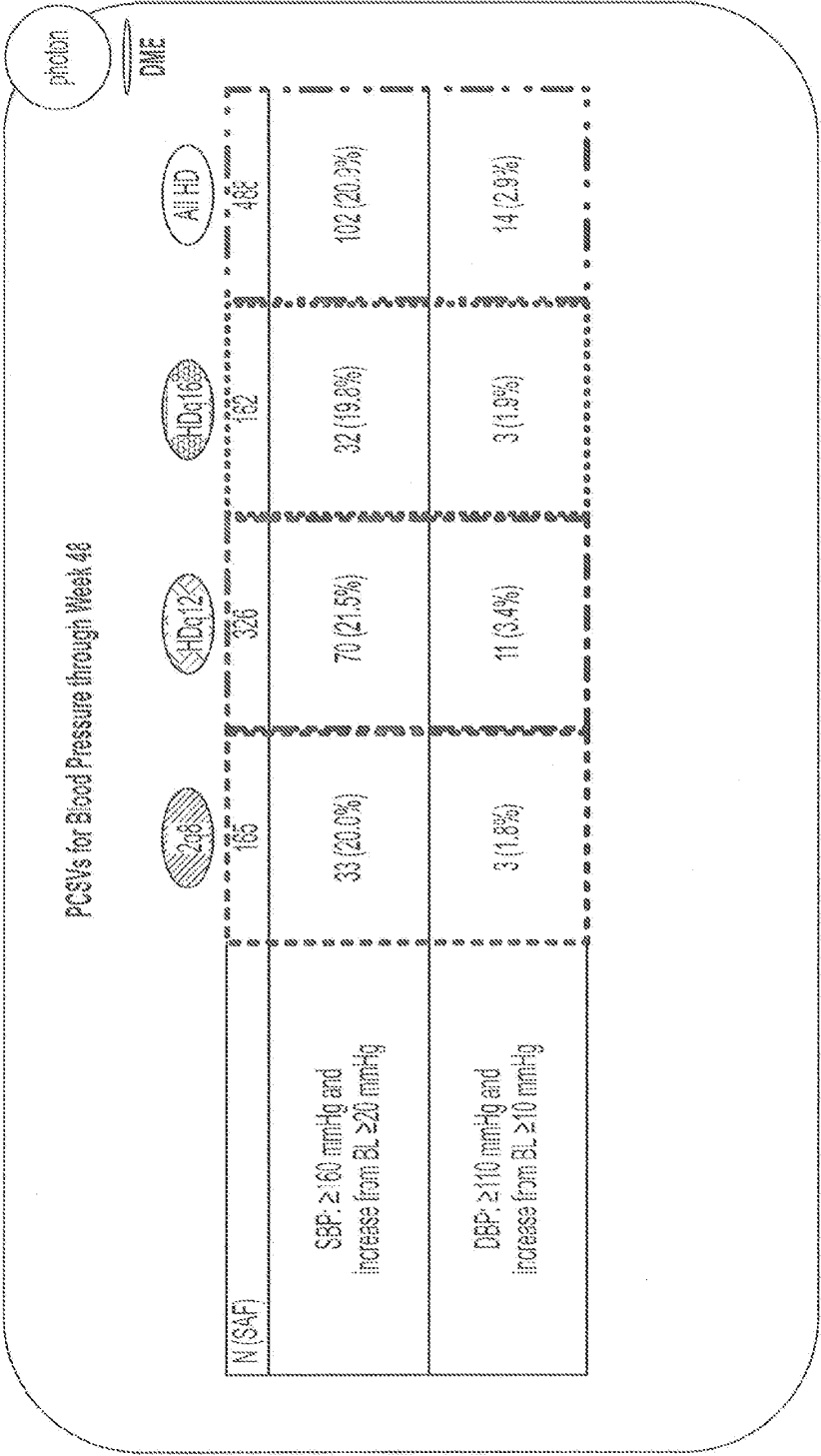


FIG. 20



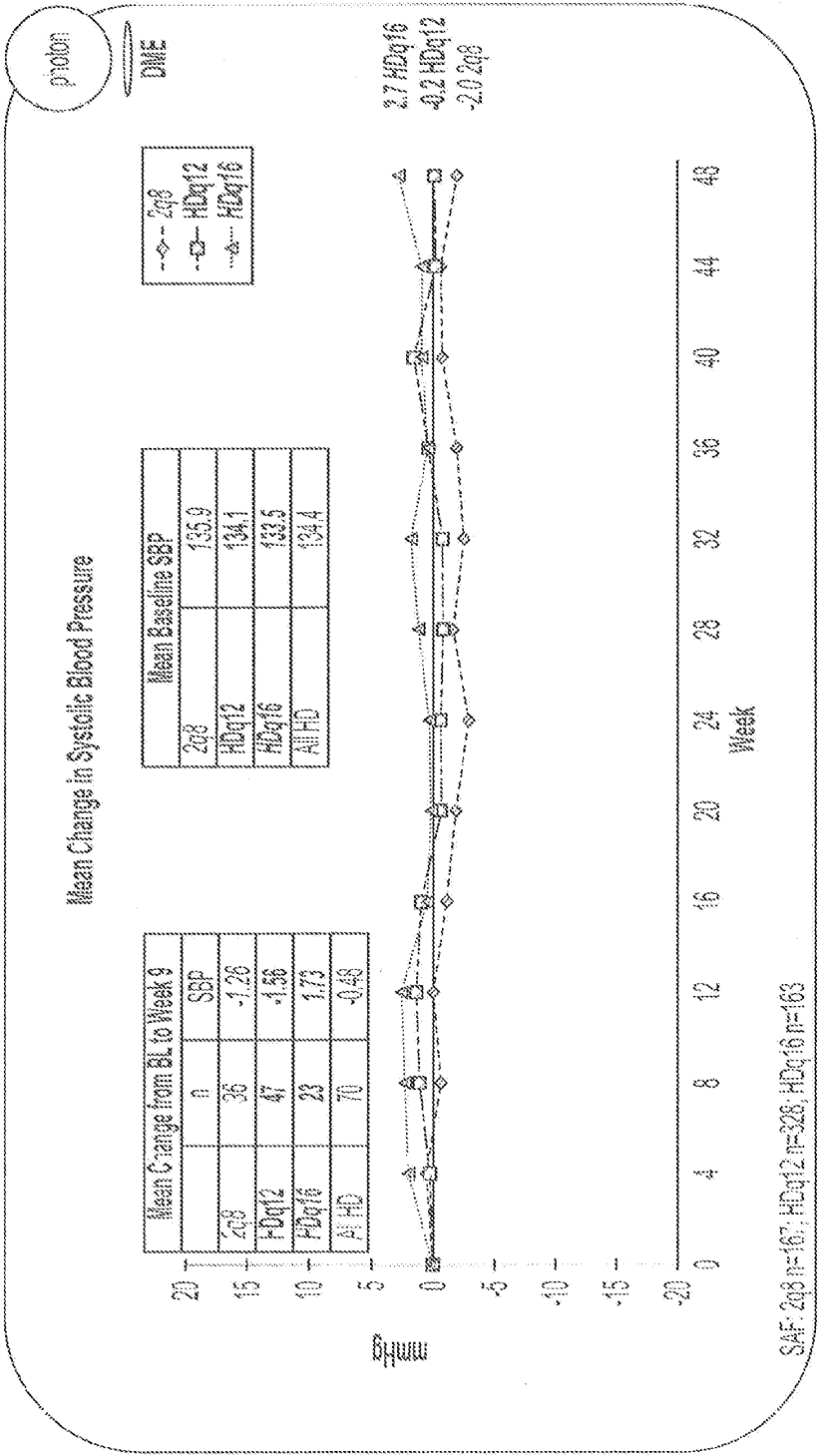


FIG. 22

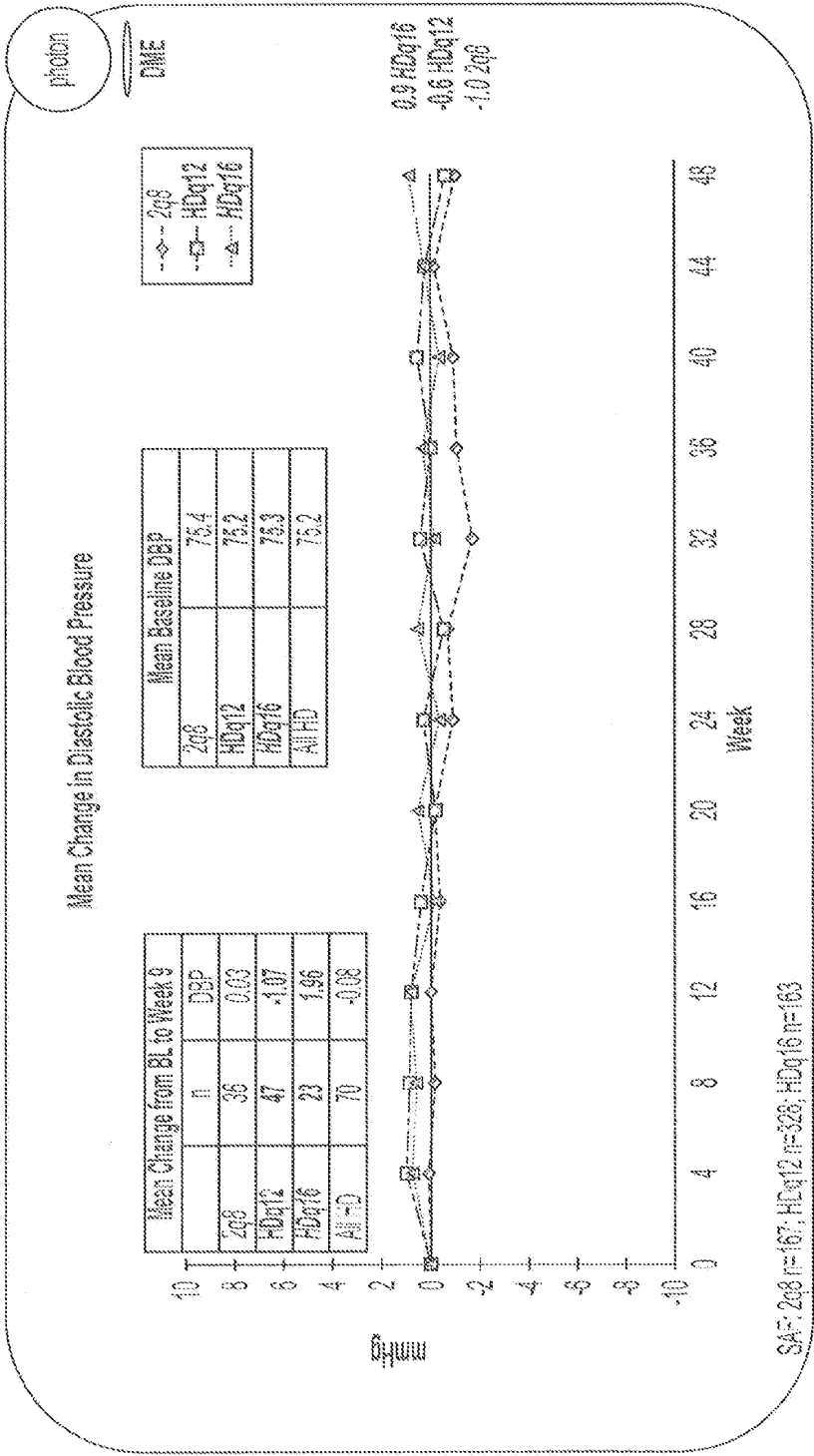


FIG. 23

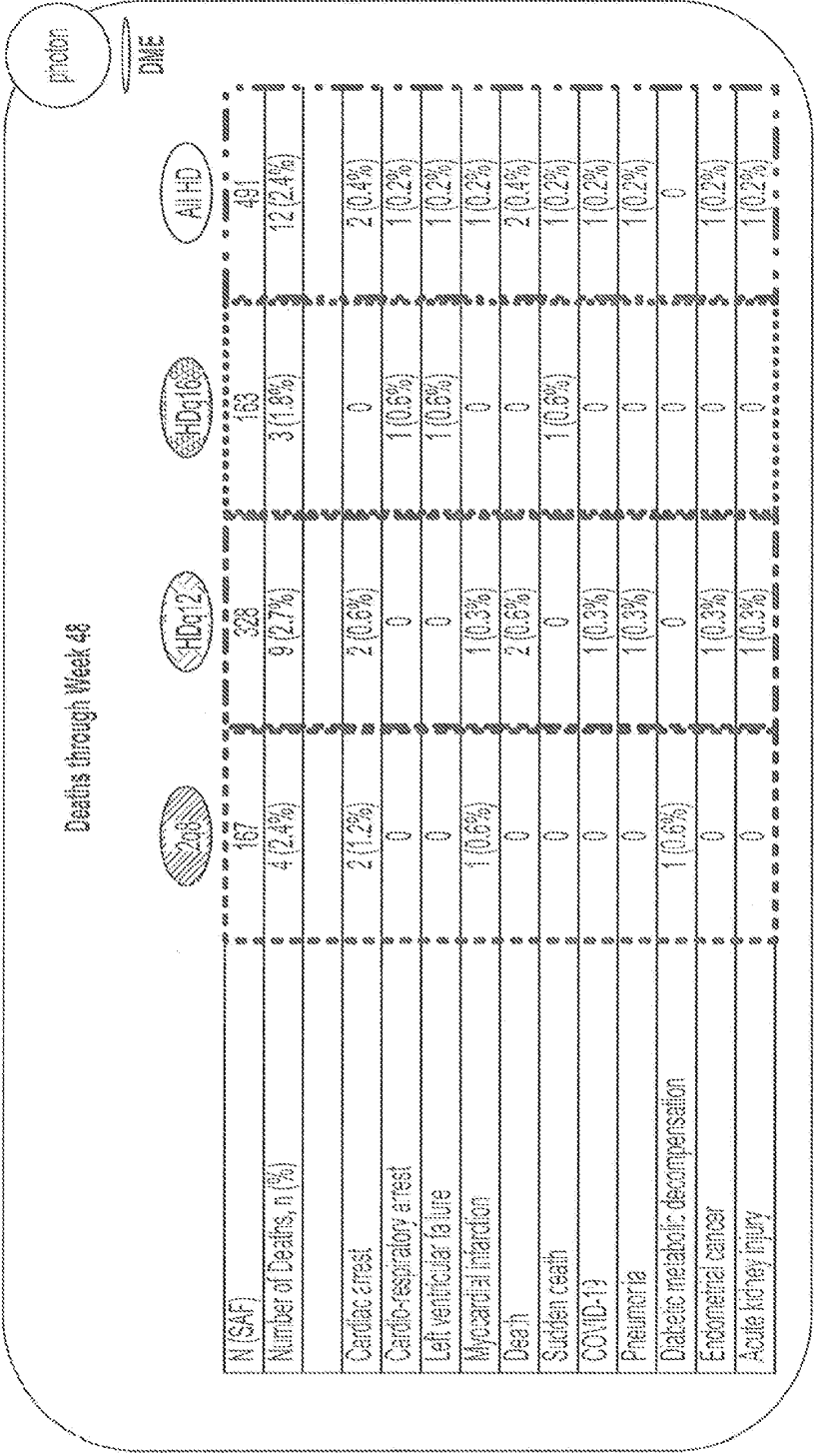


FIG. 24

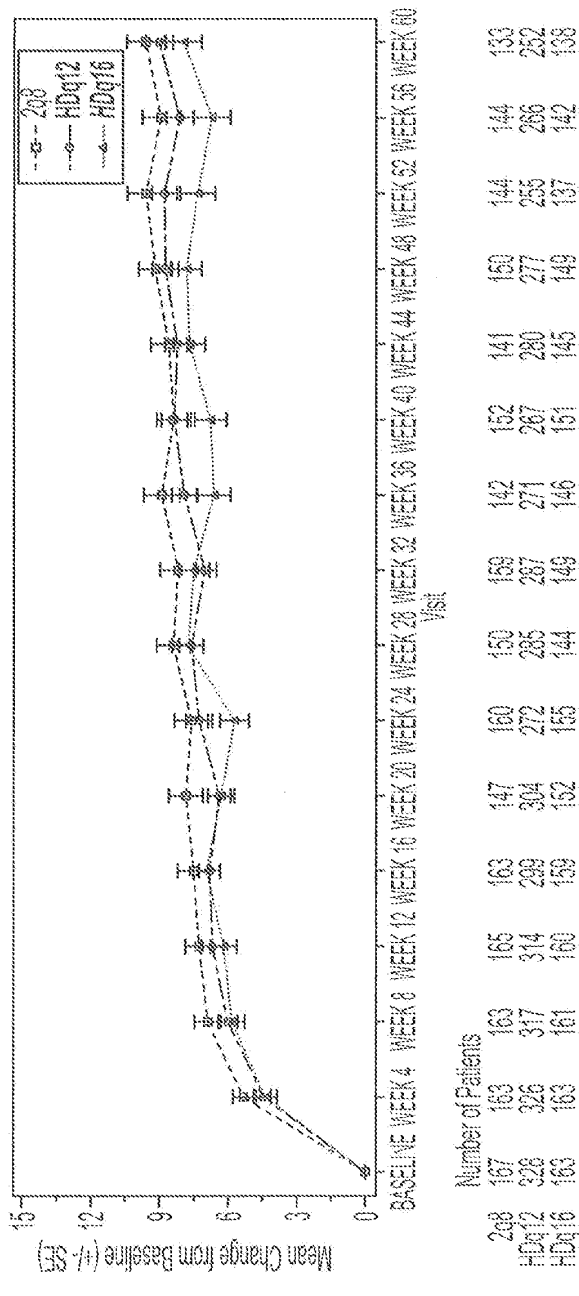
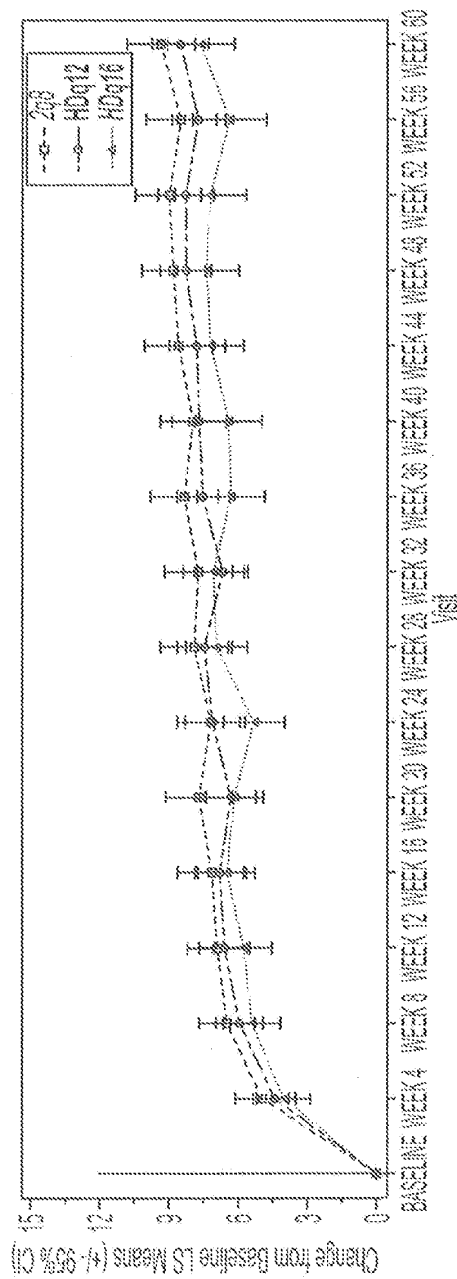


FIG. 25A



Abbreviations: 2q8: Afibercept 2 mg administered every 8 weeks after 5 initial injections at 4-week intervals; HDq12: High dose aflibercept 8 mg administered every 12 weeks after 3 initial injections at 4-week intervals; HDq16: High dose aflibercept 8 mg administered every 16 weeks after 3 initial injections at 4-week intervals.

BCVA=best-corrected visual acuity; ETDRS=Early Treatment of Diabetic Retinopathy Study; HD=high dose; OC=observed cases; CI=confidence interval.

Least square mean (LSM) was generated from a mixed model for repeated measurements (MMRM) with baseline BCVA measurement as a covariate, treatment group and the stratification variables (geographic region [Japan vs. Rest of World], baseline CRT (from reading center) [$<40\mu\text{m}$ vs. $\geq 40\mu\text{m}$], prior treatment for DME (per EDC) [yes vs. no]) as fixed factors, and terms for the interaction between baseline and visit and the interaction between treatment and visit. A Kenward-Roger approximation was used for the denominator degrees of freedom. An unstructured covariance structure was used to model the within-subject error.

FIG. 25B

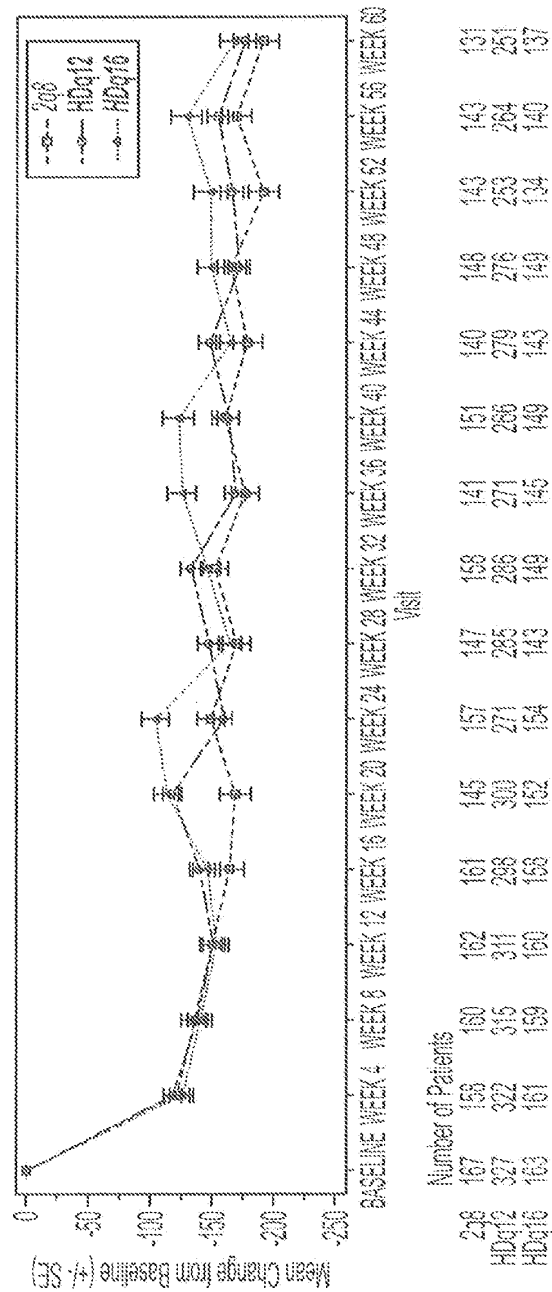
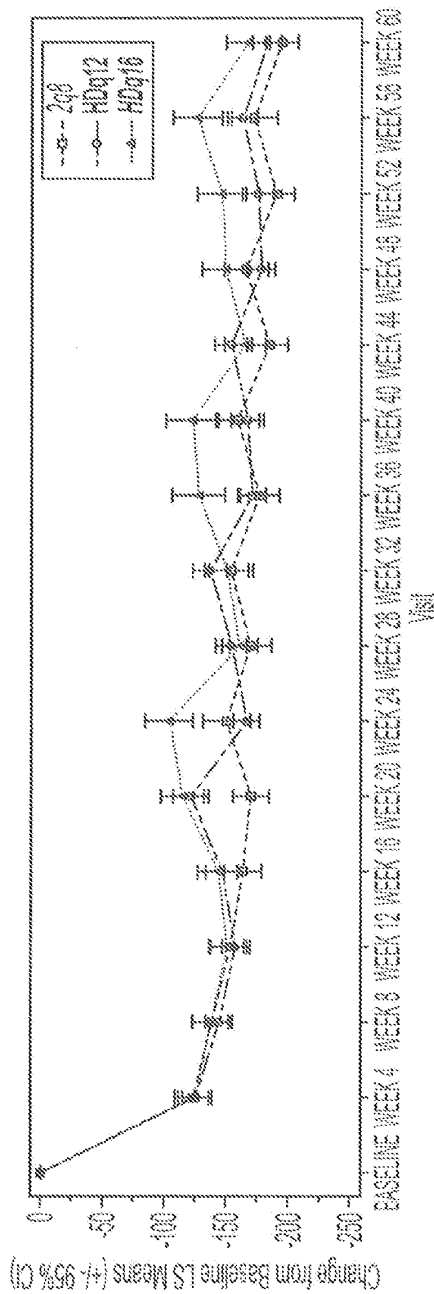


FIG. 26A



Abbreviations: 2q6: Aflibercept 2 mg administered every 8 weeks after 5 initial injections at 4-week intervals; HDq12: High dose aflibercept 8 mg administered every 12 weeks after 3 initial injections at 4-week intervals; HDq16: High dose aflibercept 8 mg administered every 16 weeks after 3 initial injections at 4-week intervals.

BCVA=best-corrected visual activity; CI=confidence interval; CRT=central retinal thickness; HD=high dose; LS=least square; OC=observed cases.

Least square mean (LSM) was generated from a mixed model for repeated measurements (MMRM) with baseline CRT measurement as a covariate, treatment group and the stratification variables (geographic region (Japan vs. Rest of World), baseline CRT (from reading center) [$<400\mu\text{m}$ vs. $\geq 400\mu\text{m}$], prior treatment for DME (per EDC) (yes vs. no)) as fixed factors, and terms for the interaction between baseline and visit and the interaction between treatment and visit. A Kenward-Roger approximation was used for the denominator degrees of freedom. An unstructured covariance structure was used to model the within-subject error.

FIG. 26B

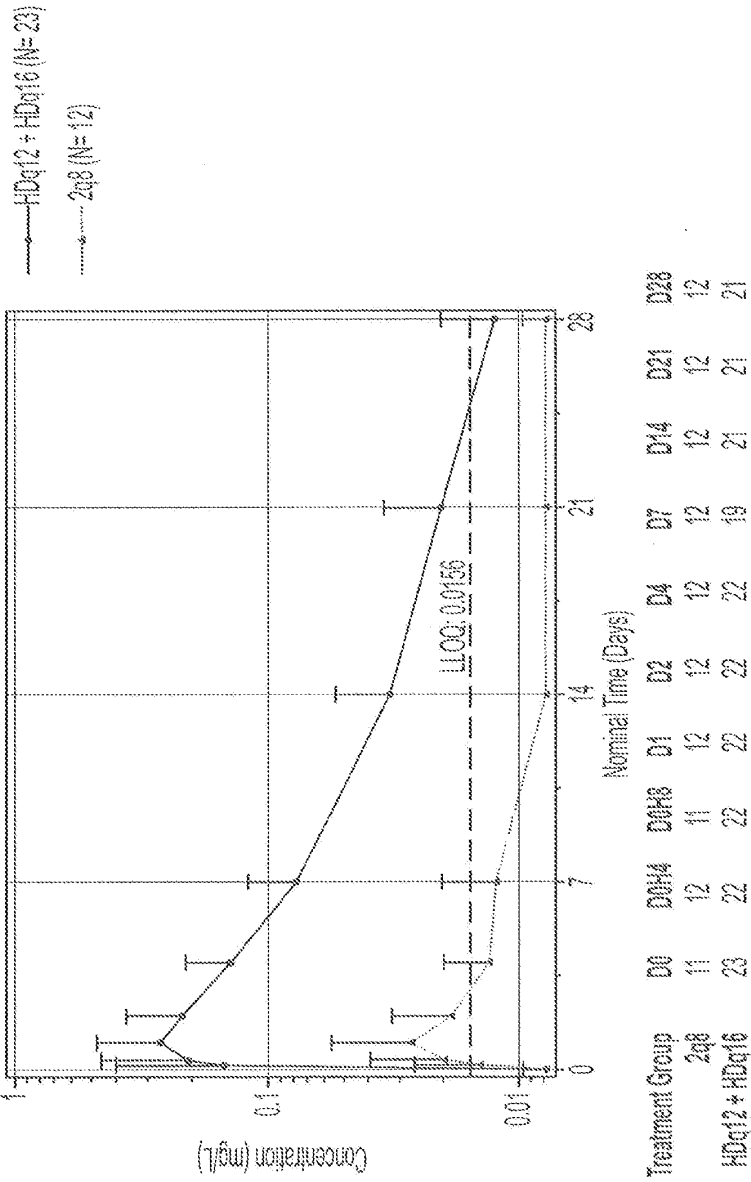


FIG. 27

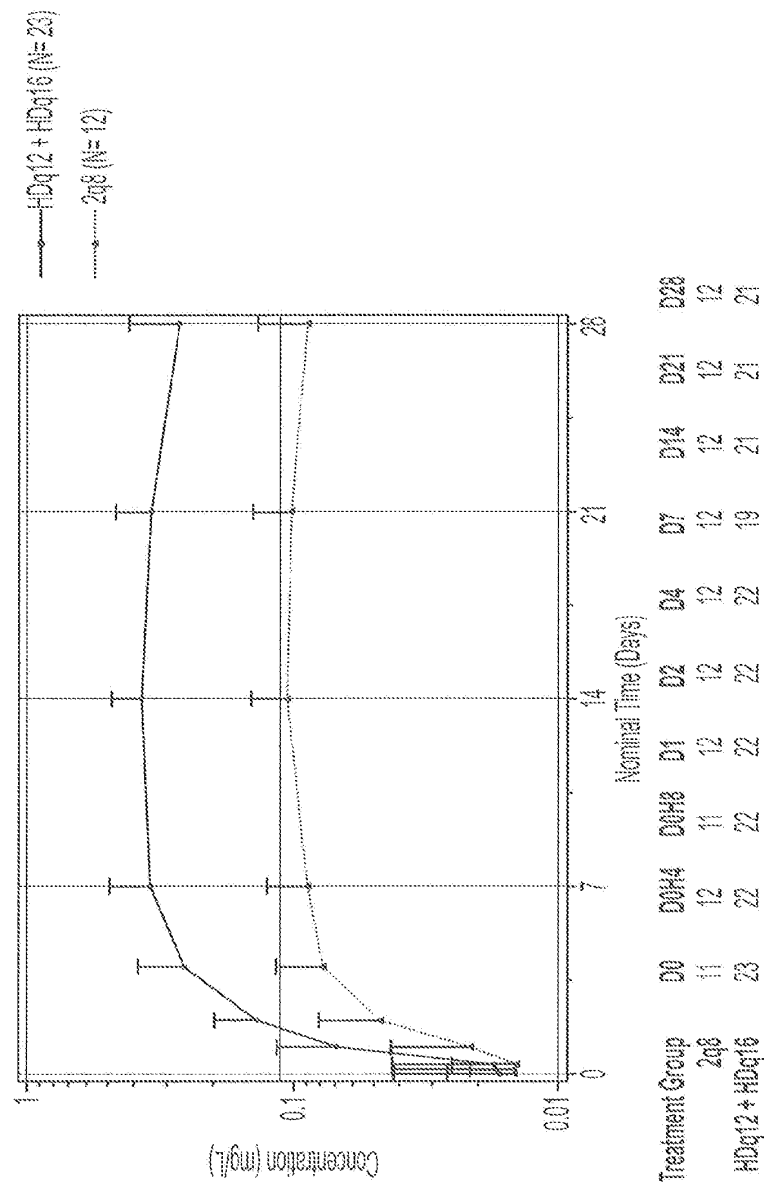


FIG. 28

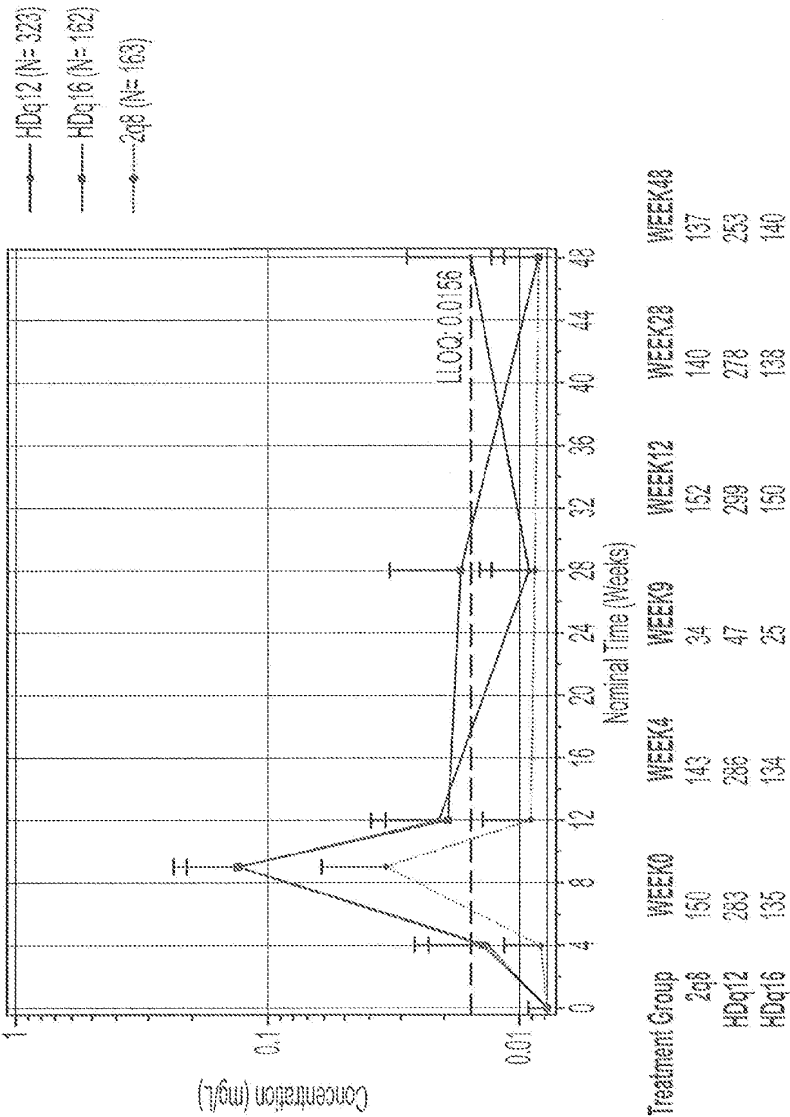


FIG. 29

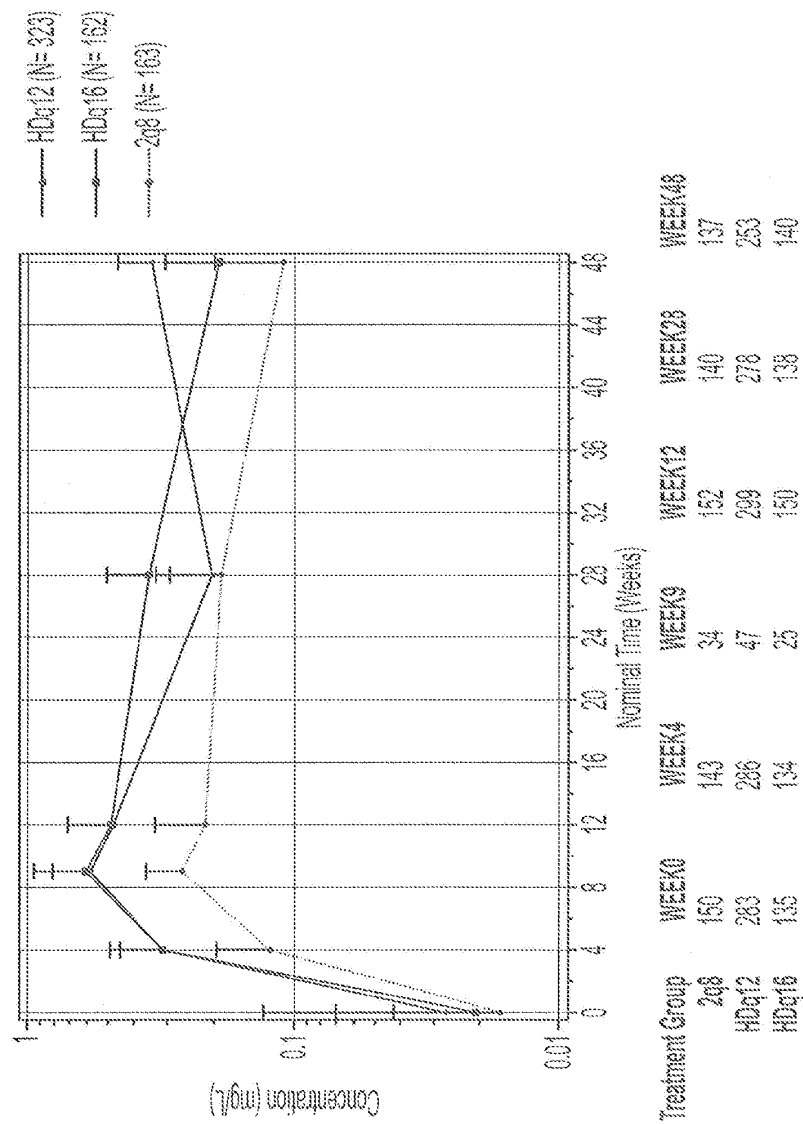


FIG. 30

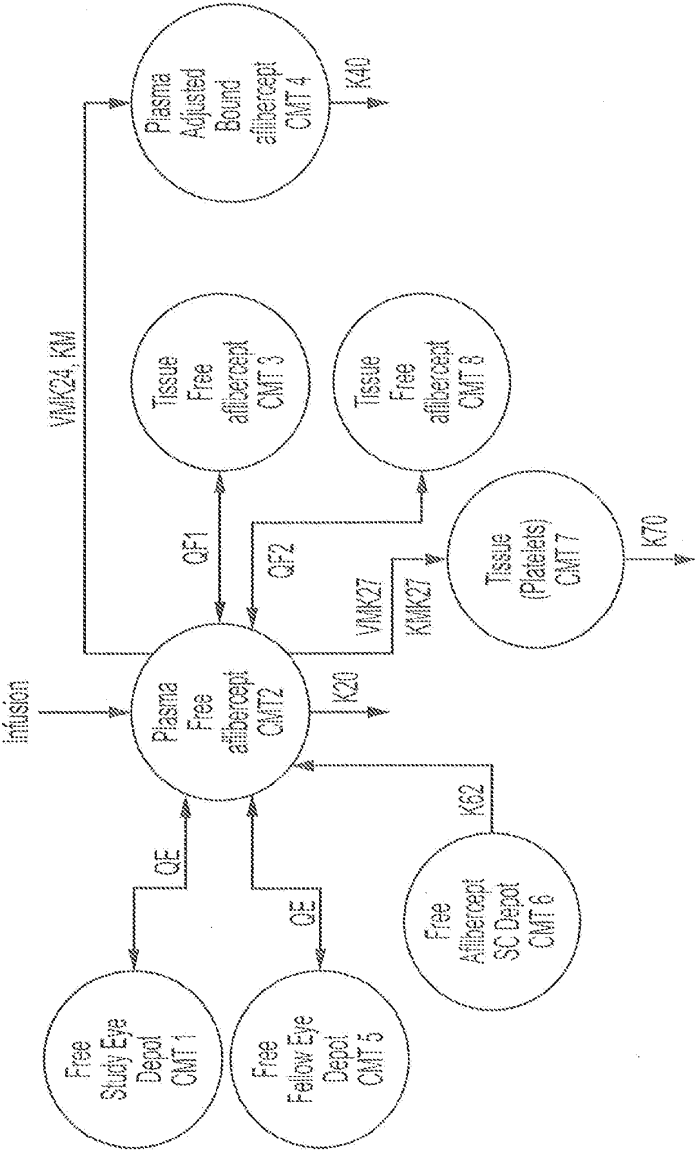


FIG. 31

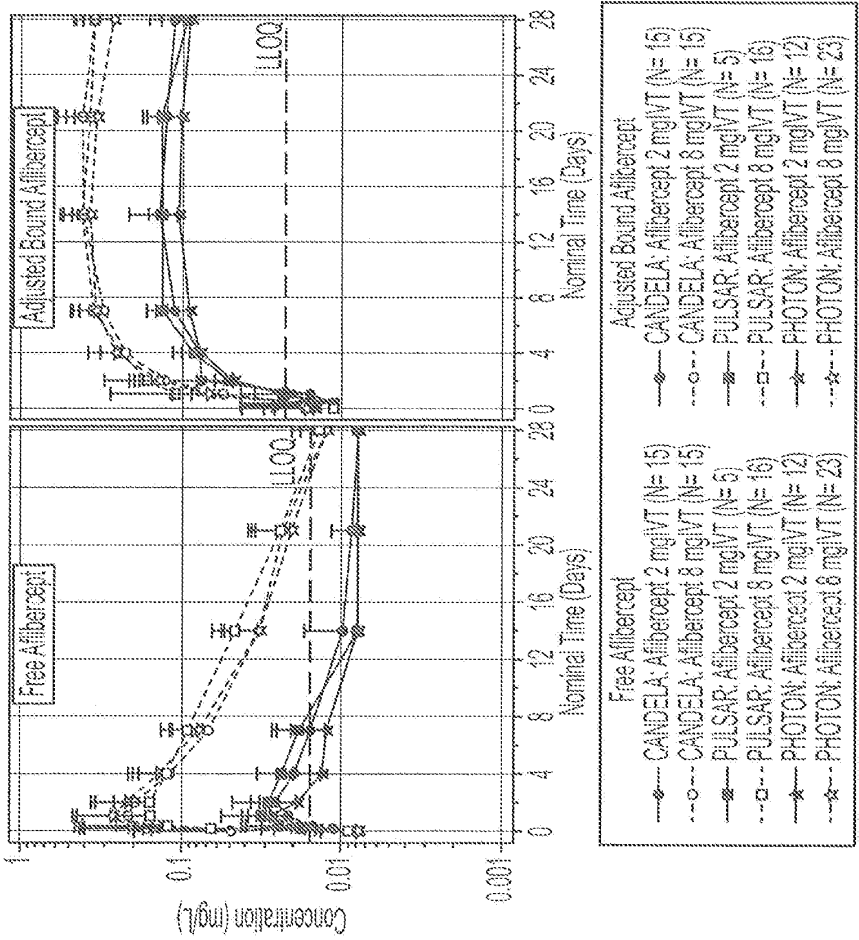


FIG. 32

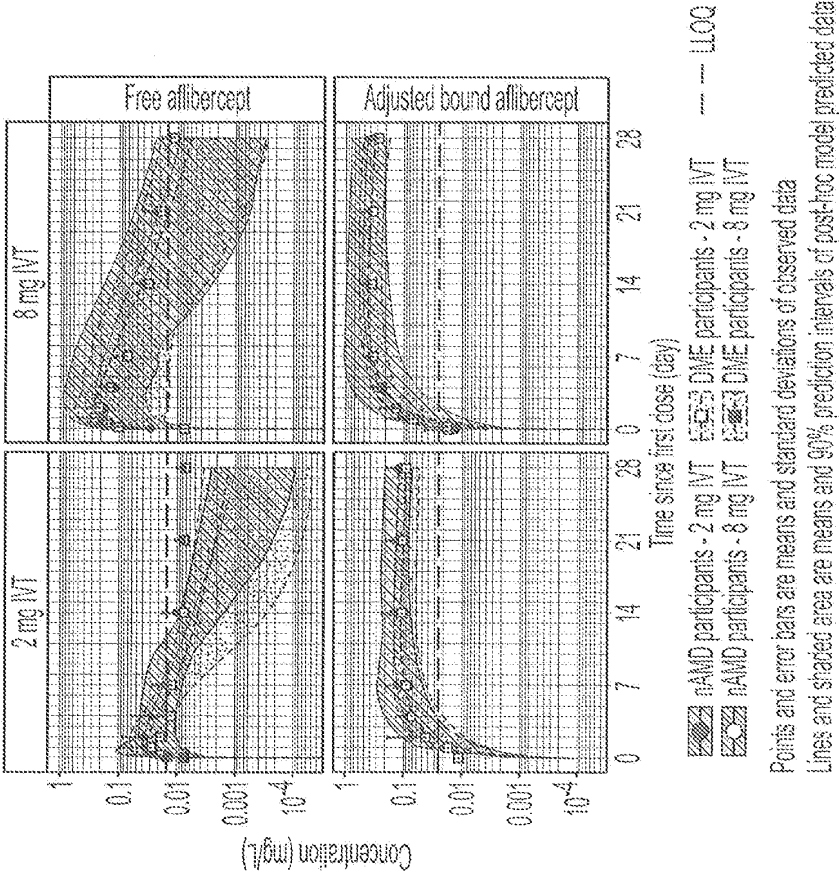


FIG. 33

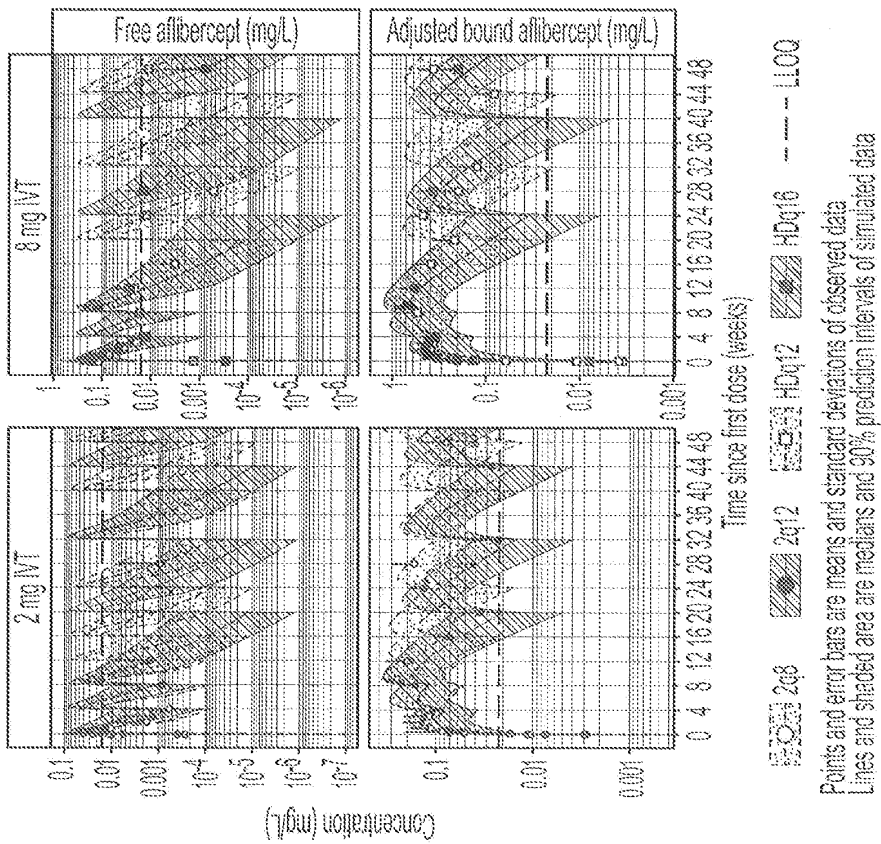


FIG. 34

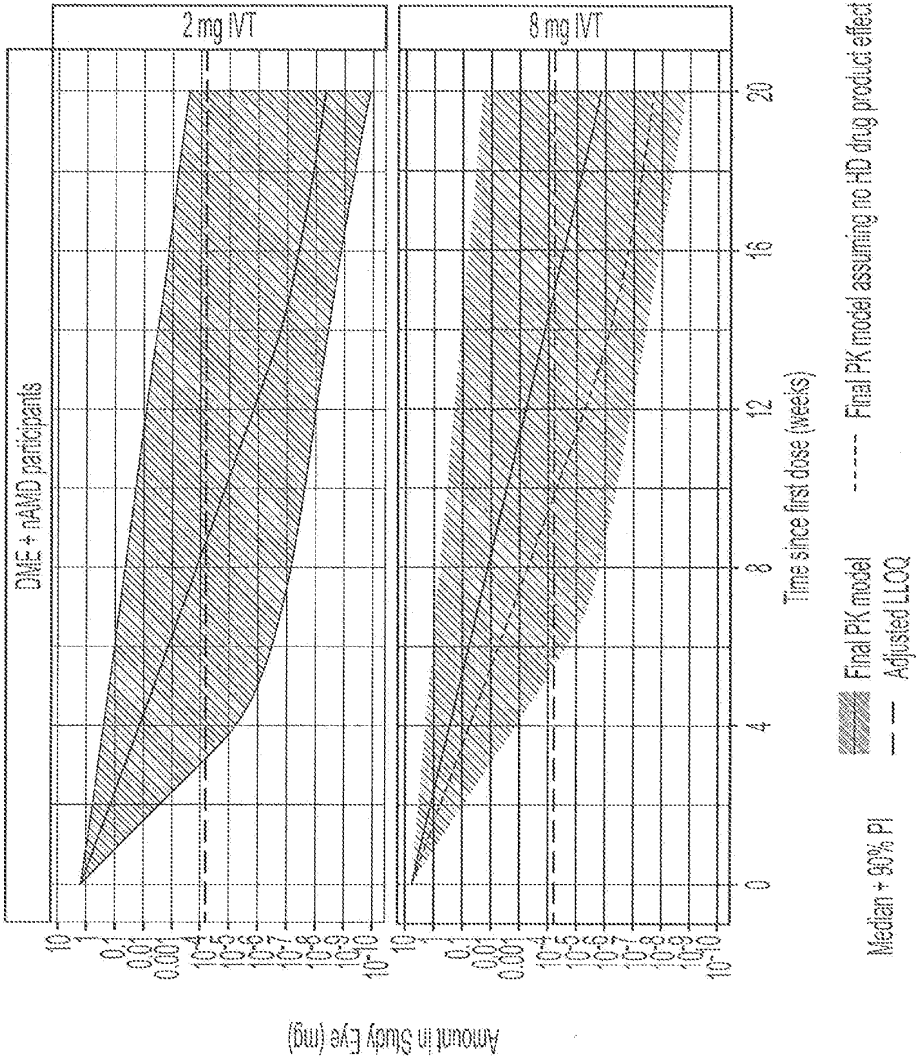


FIG. 35

Adjusted LLOQ = LLOQ of free aflibercept in plasma (0.0166 mg/L) x the assumed volume of the study eye (4 mL)

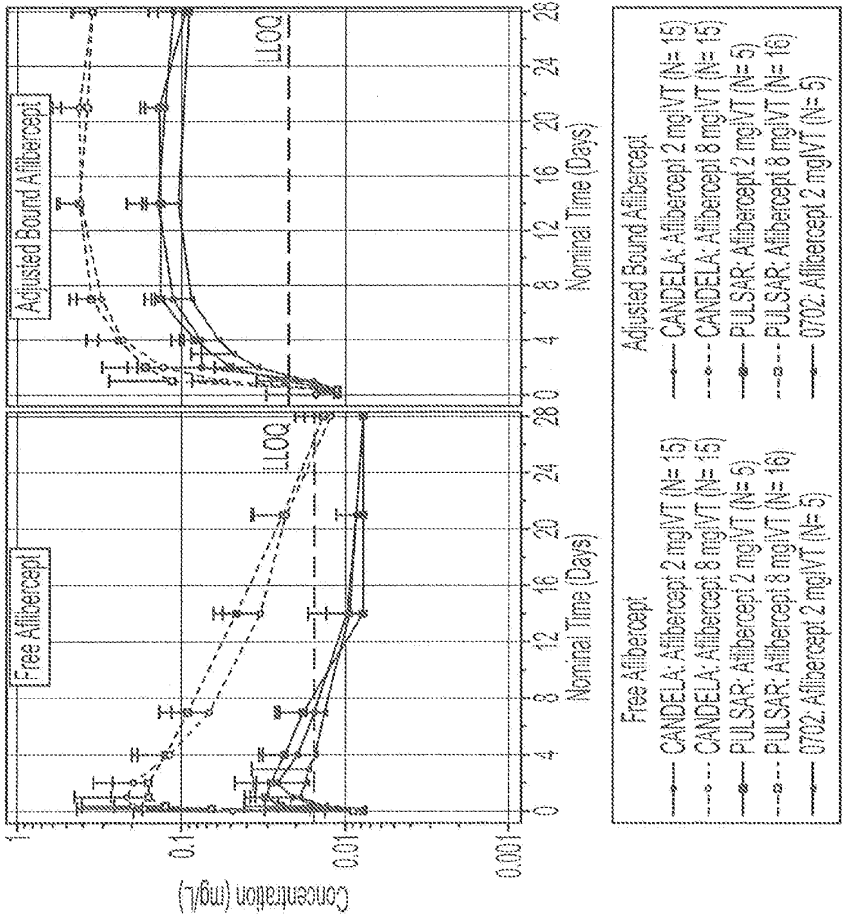


FIG. 36

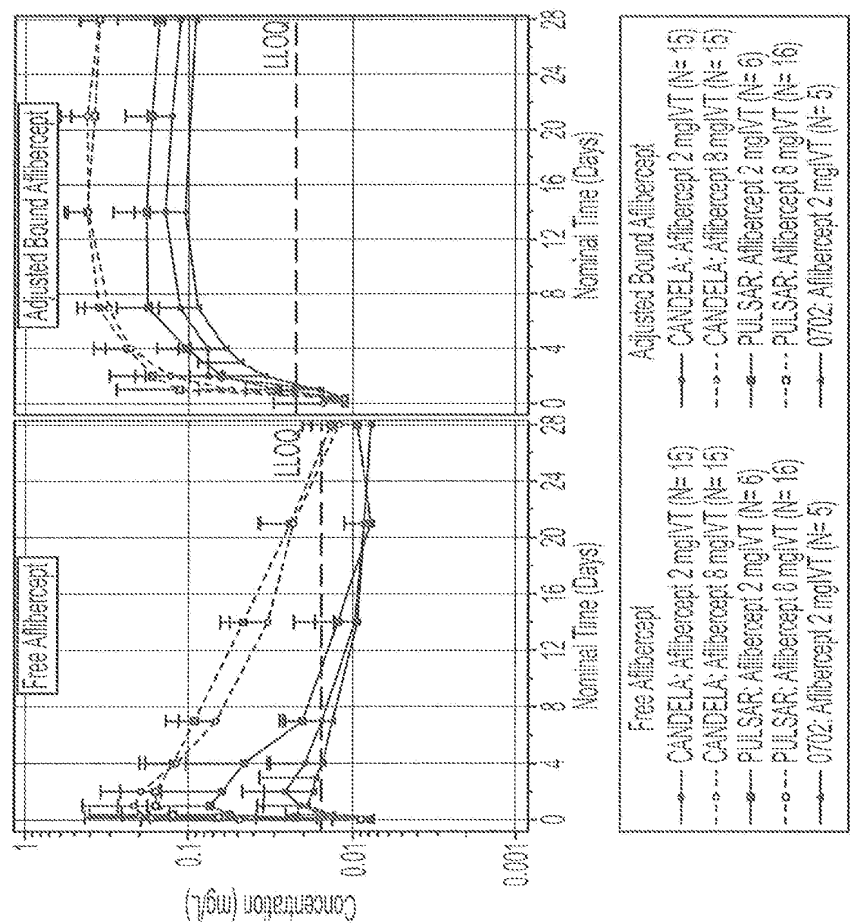


FIG. 37

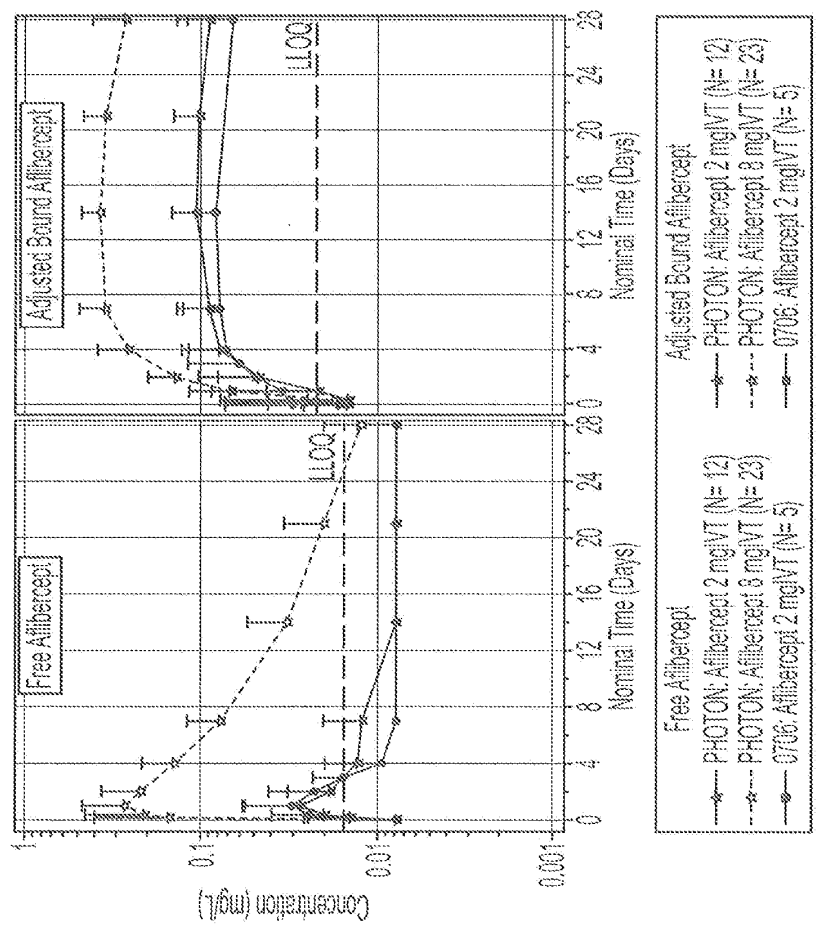
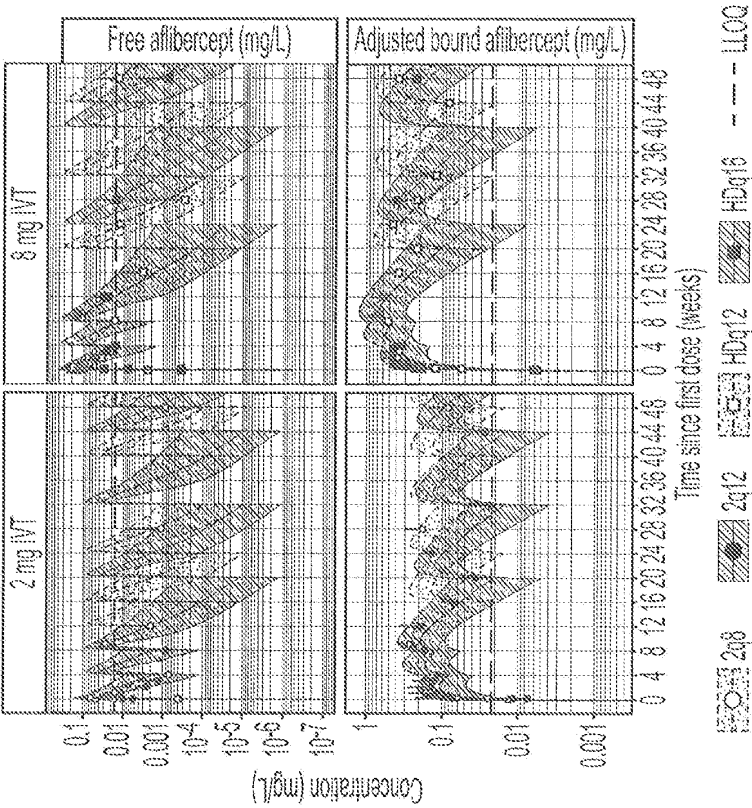
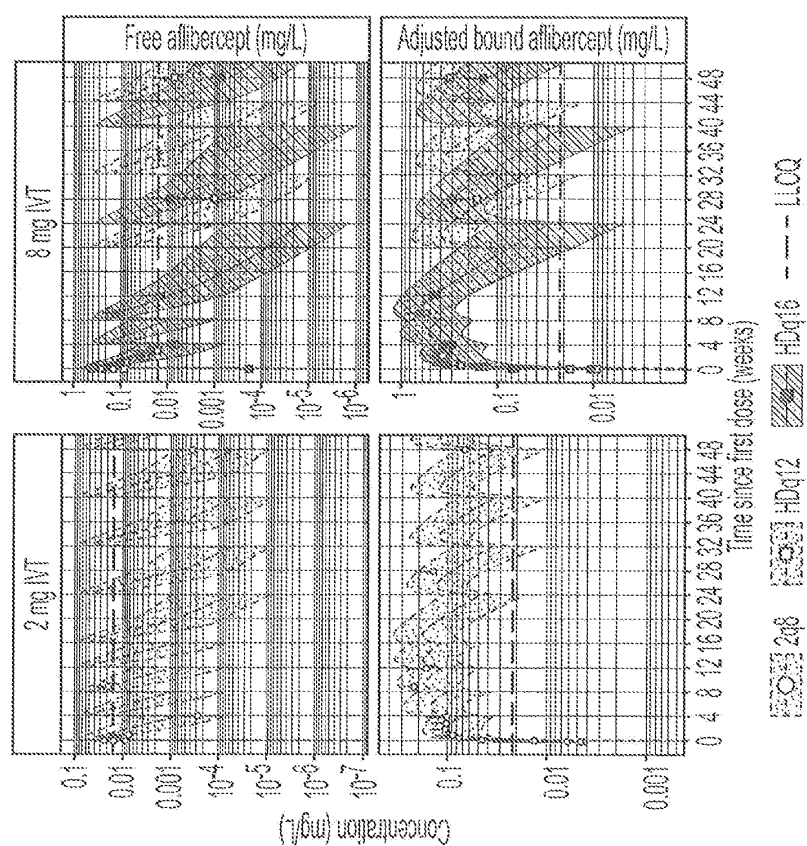


FIG. 38



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. 39



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. 40

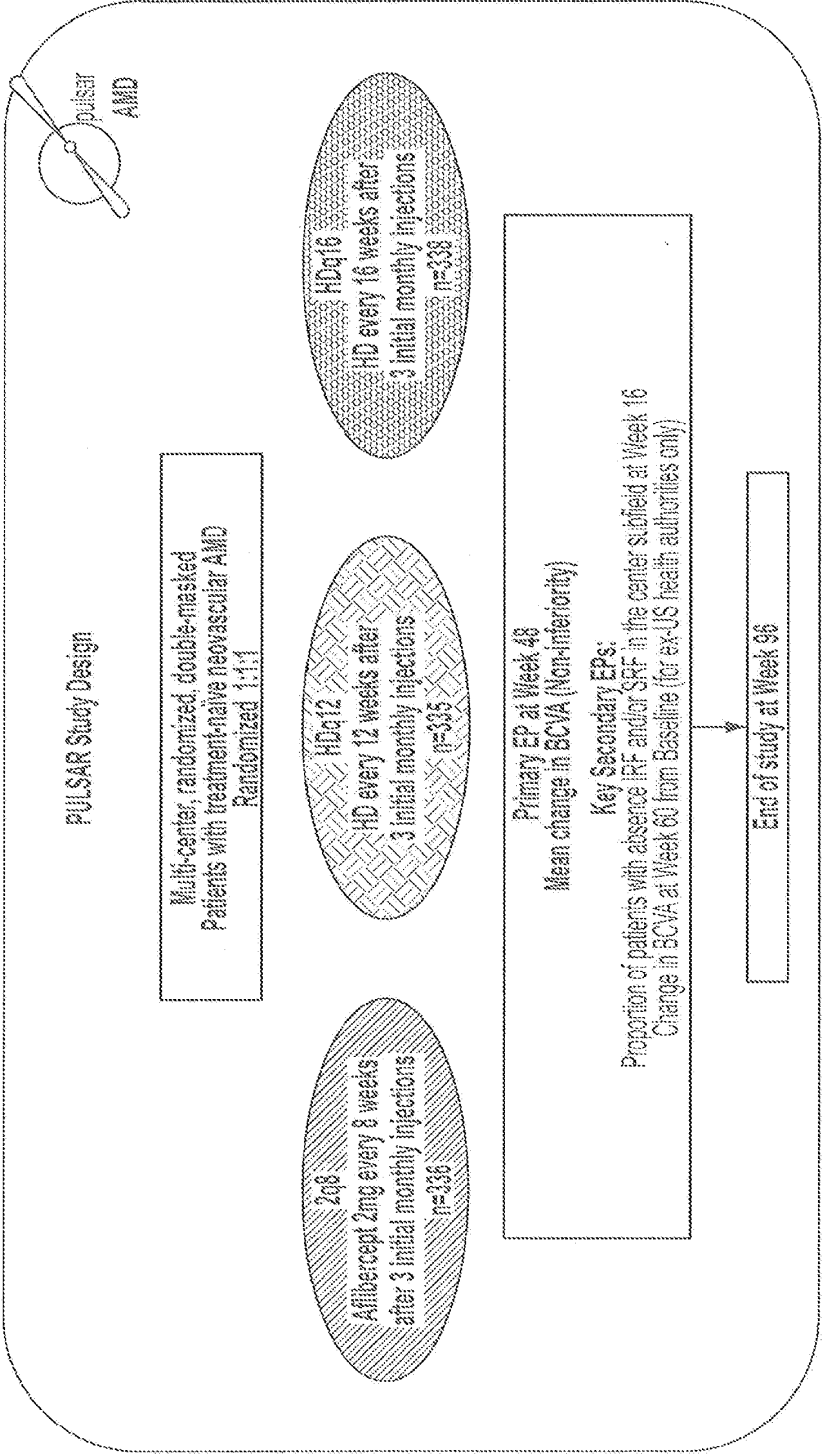
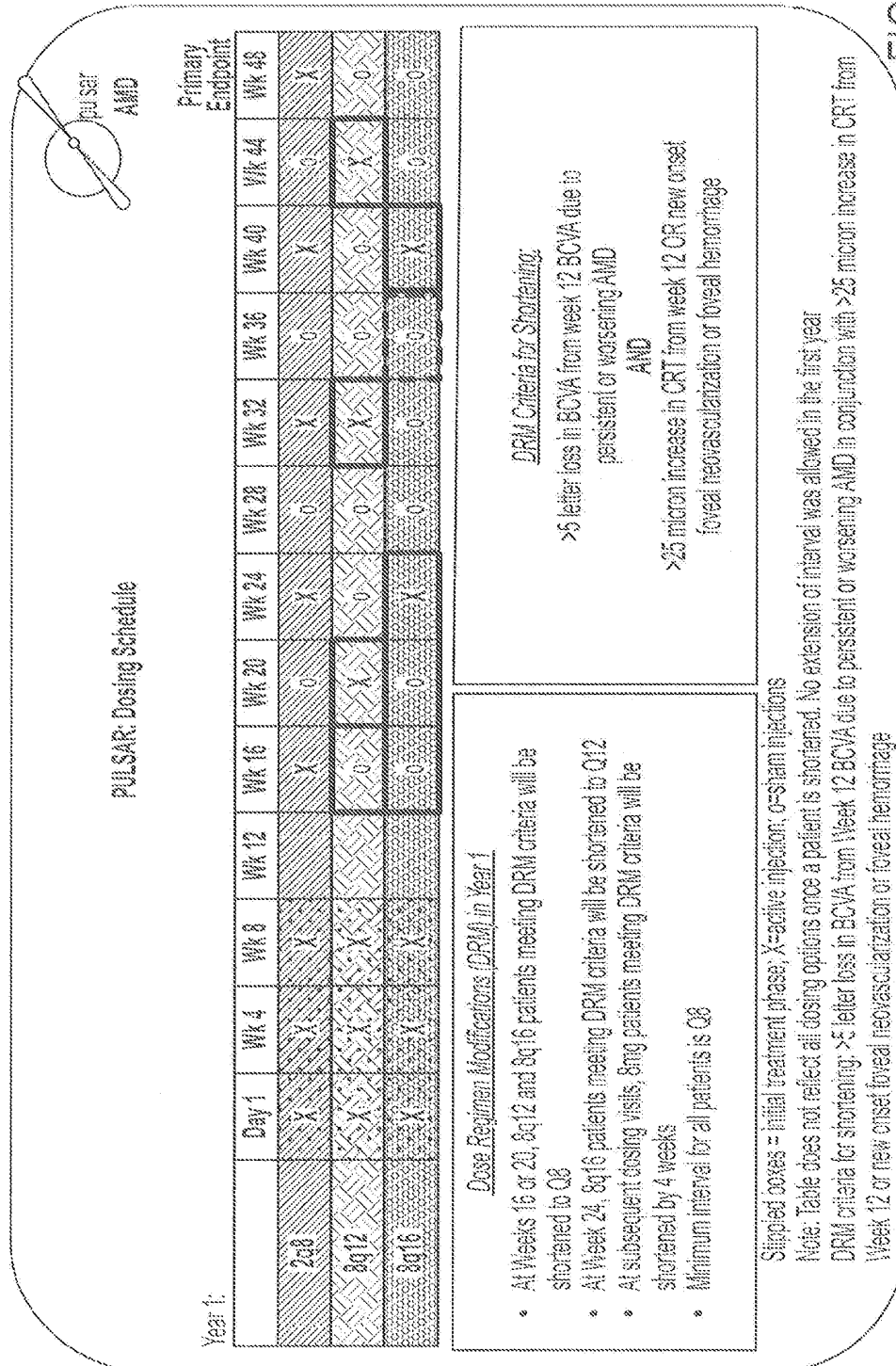


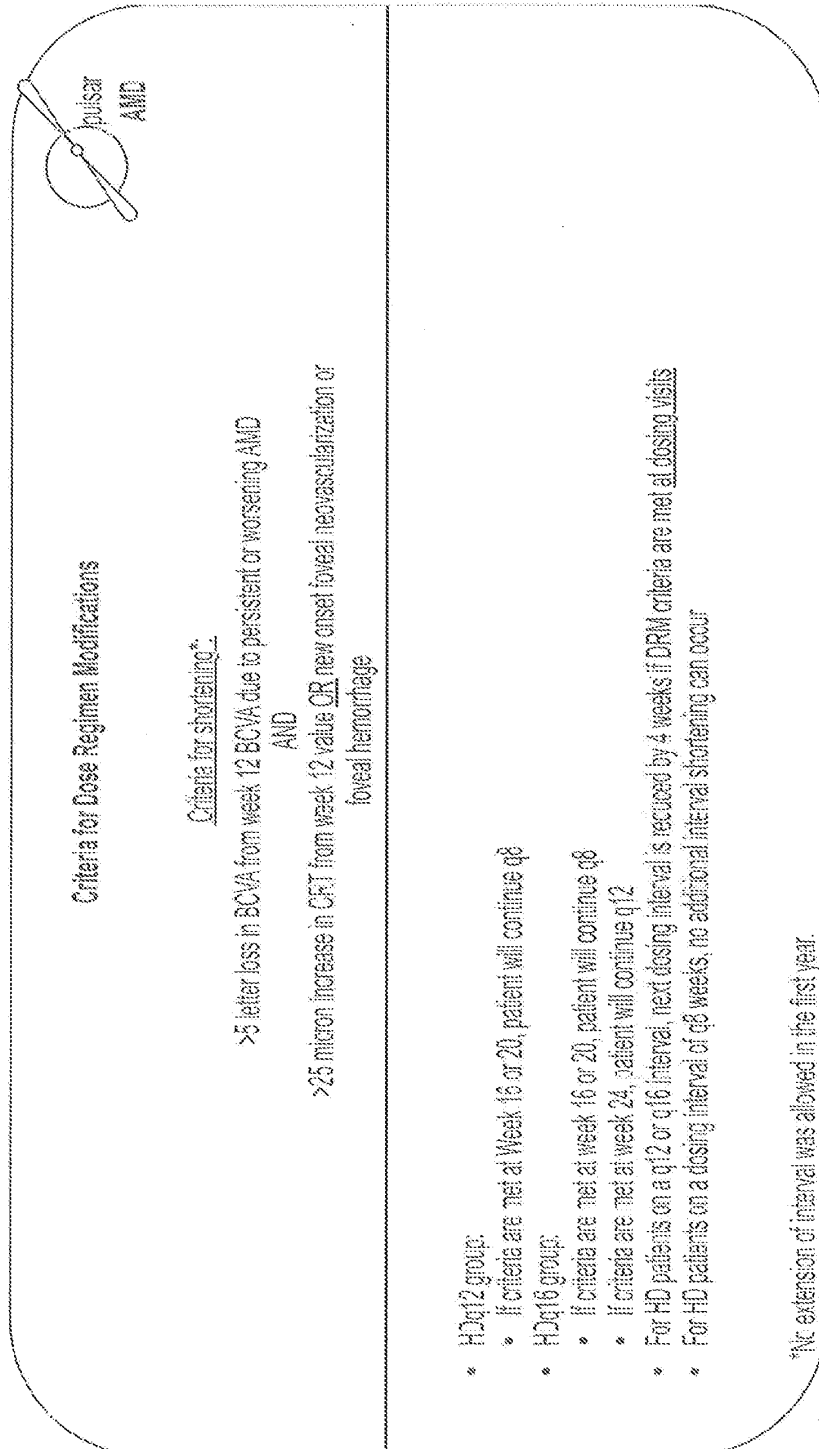
FIG. 41



FIG. 42



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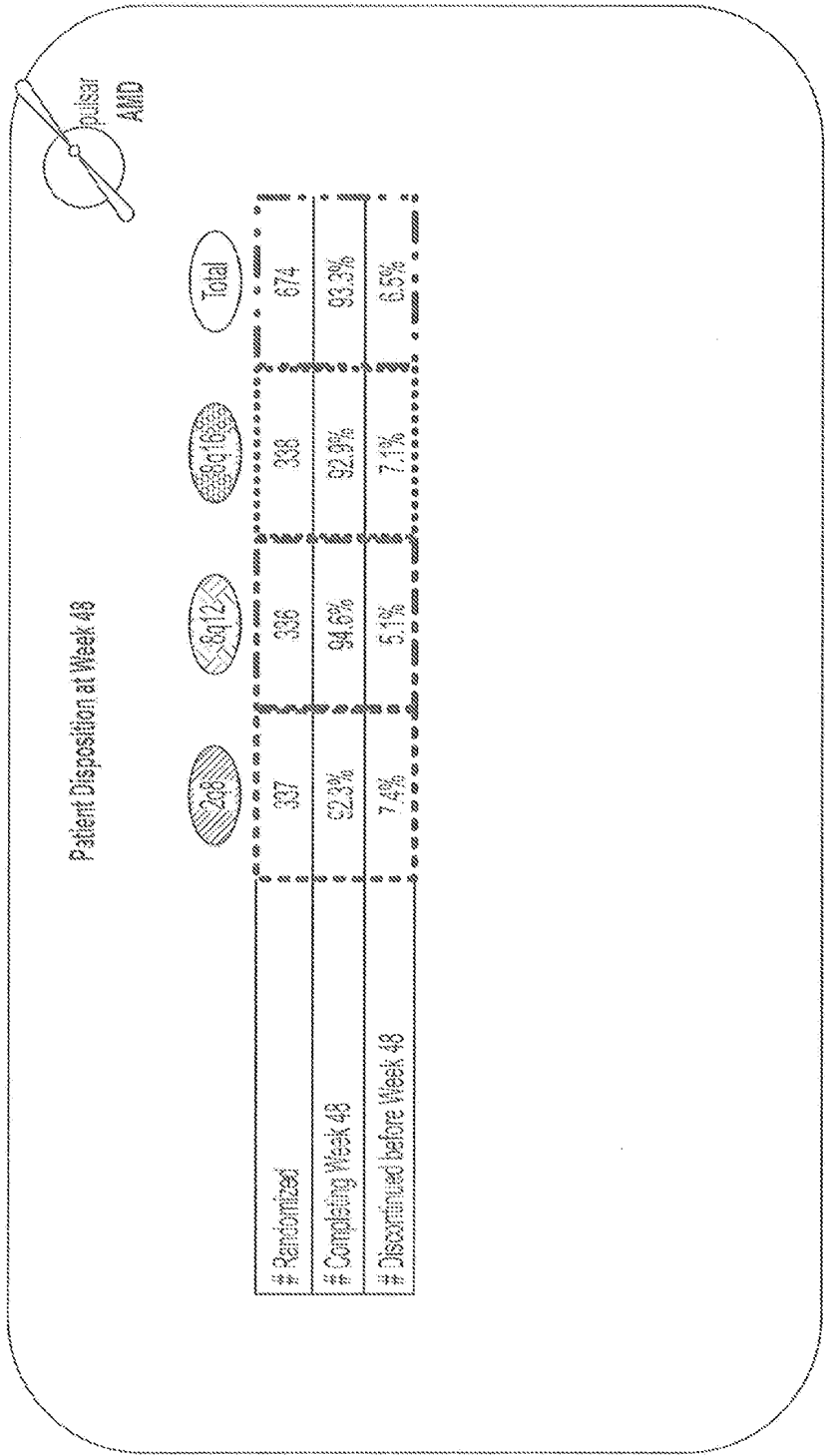
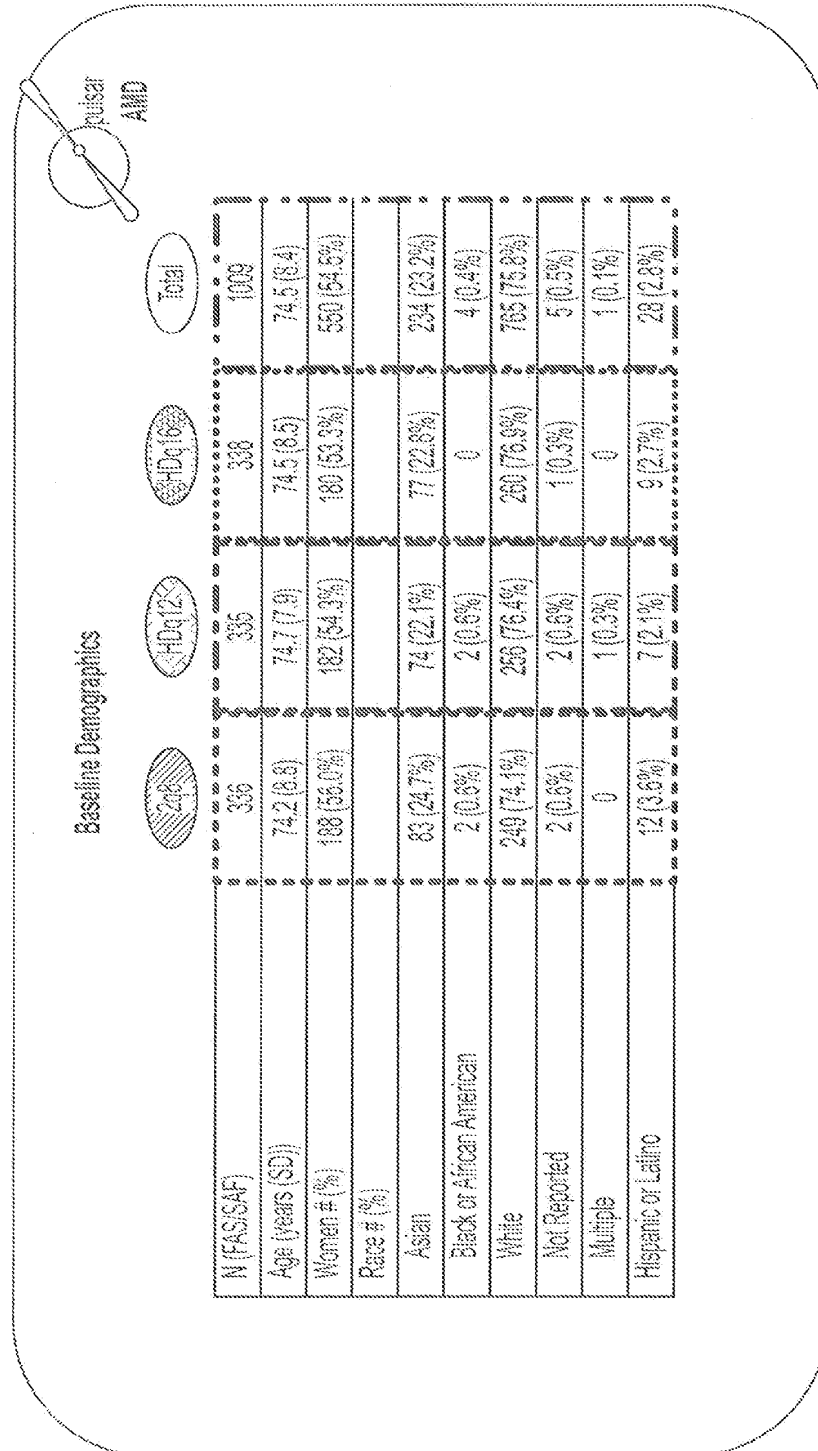


FIG. 45



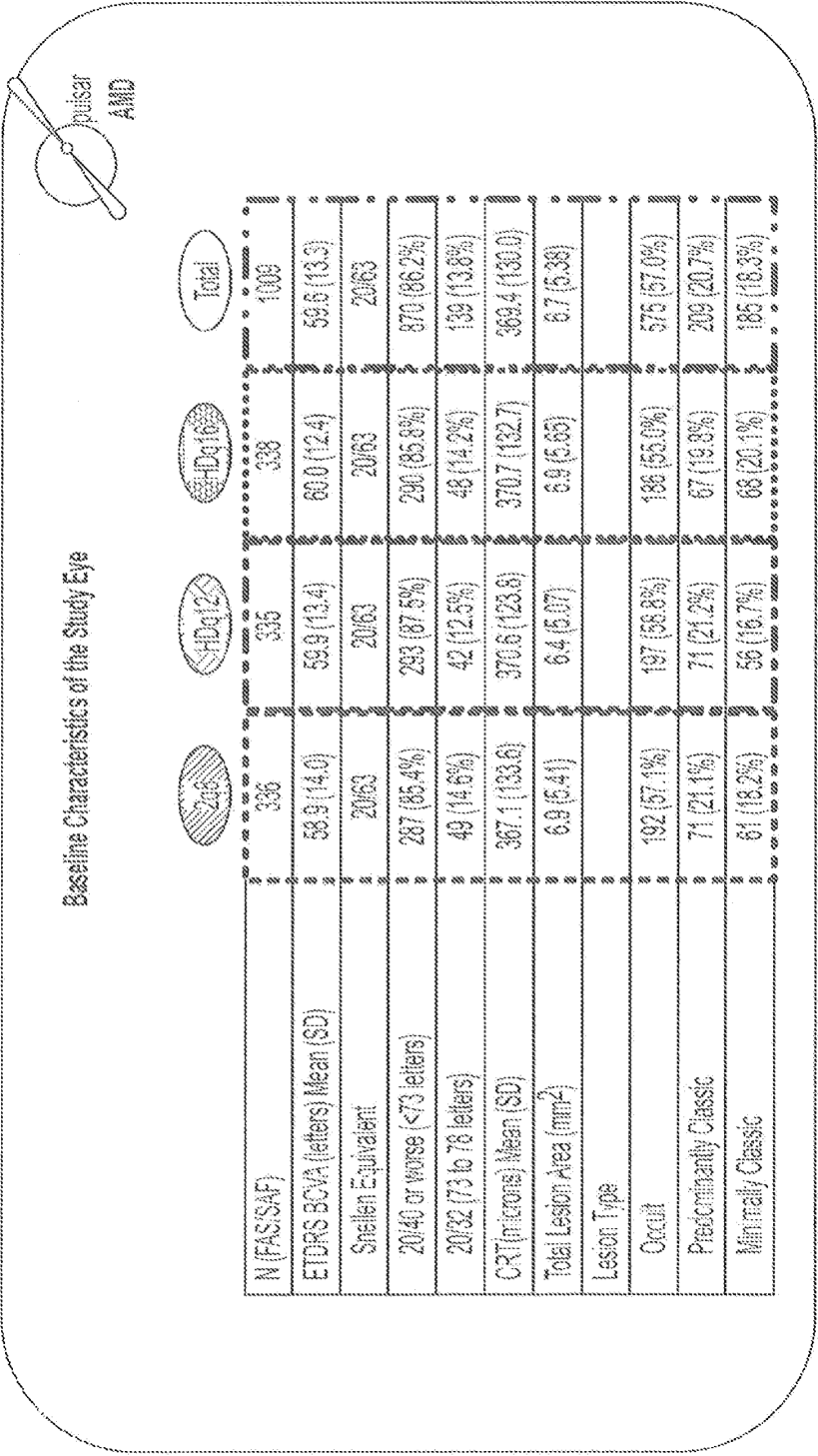


FIG. 47

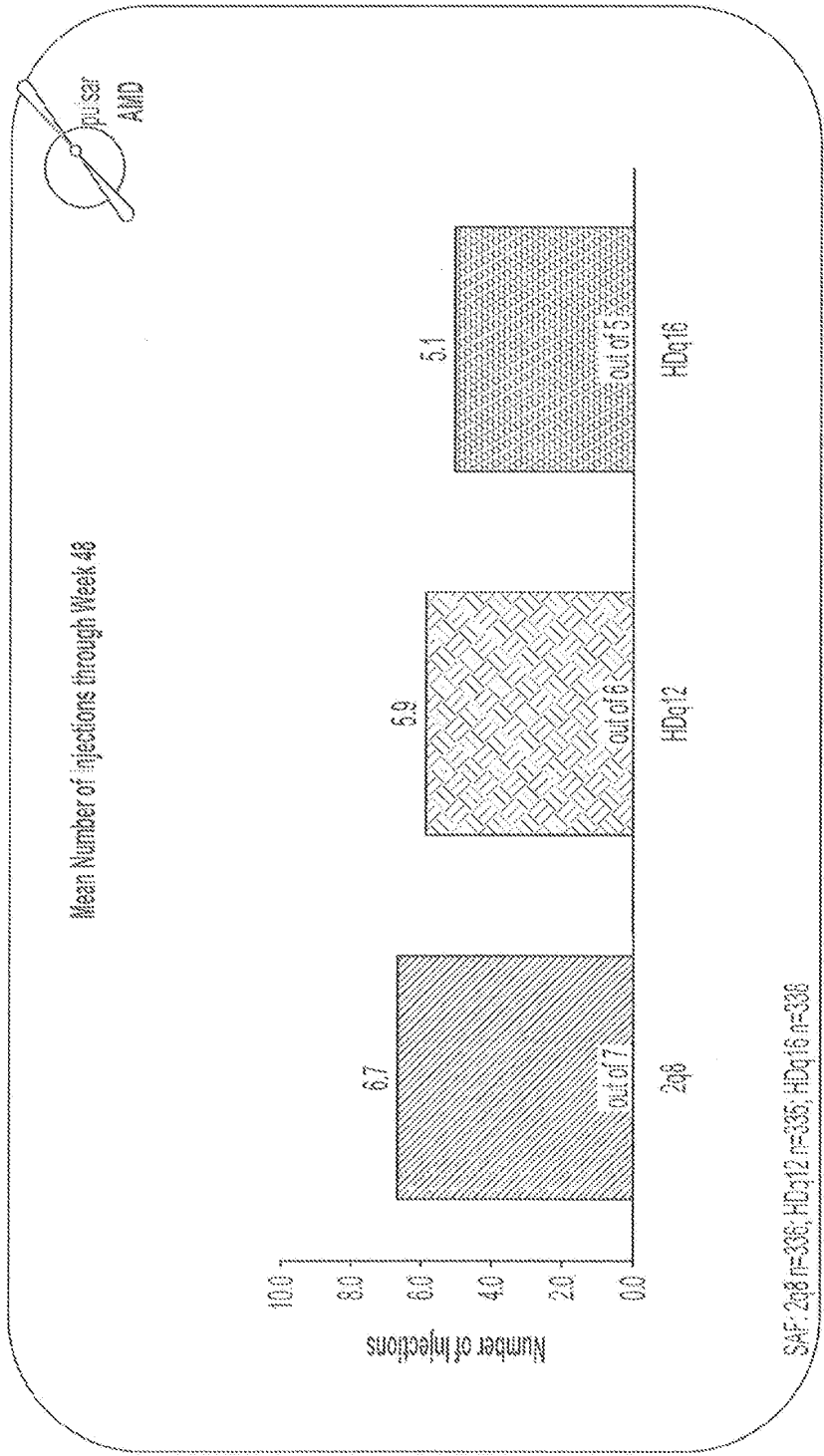


FIG. 48

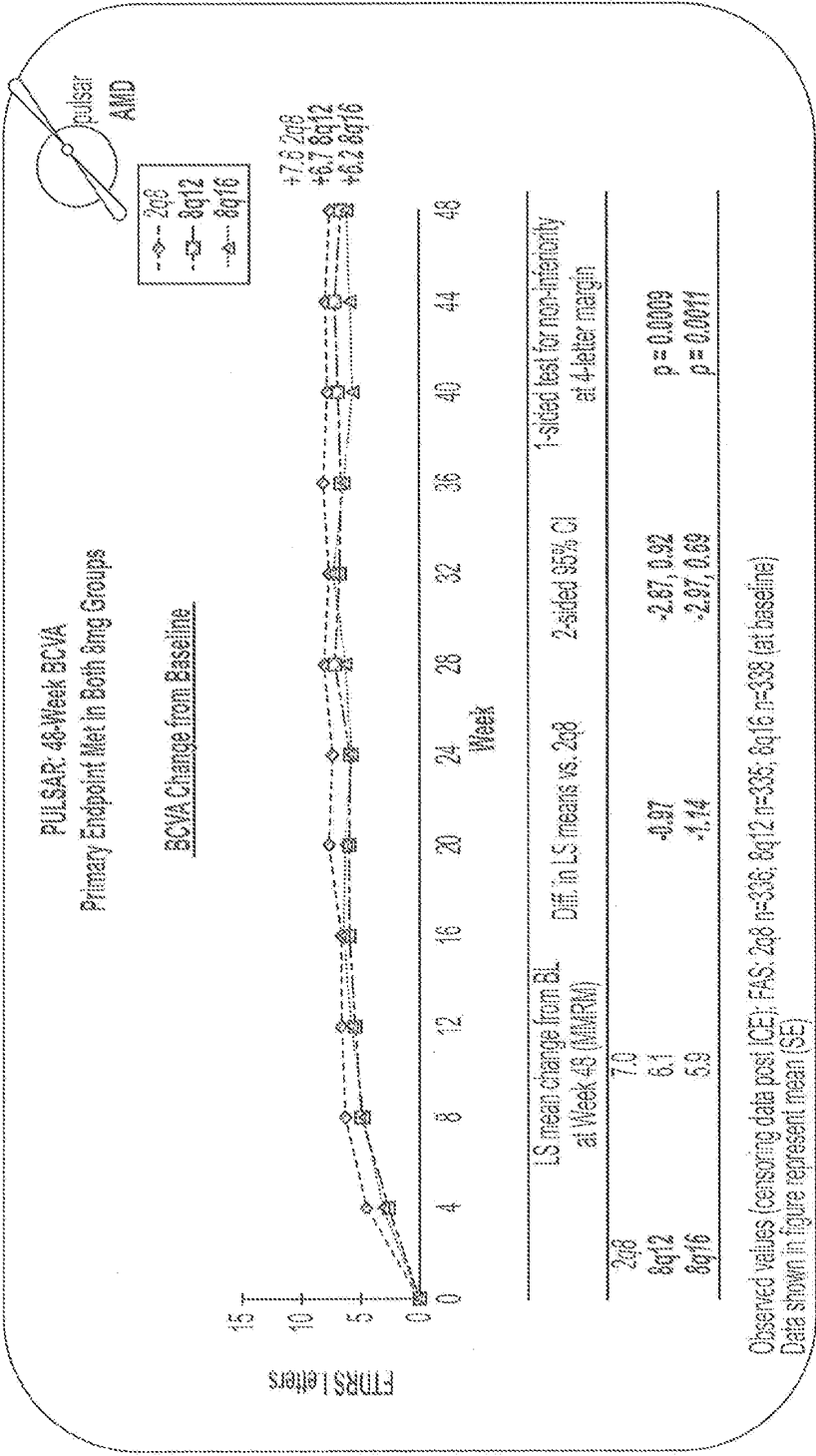


FIG. 49

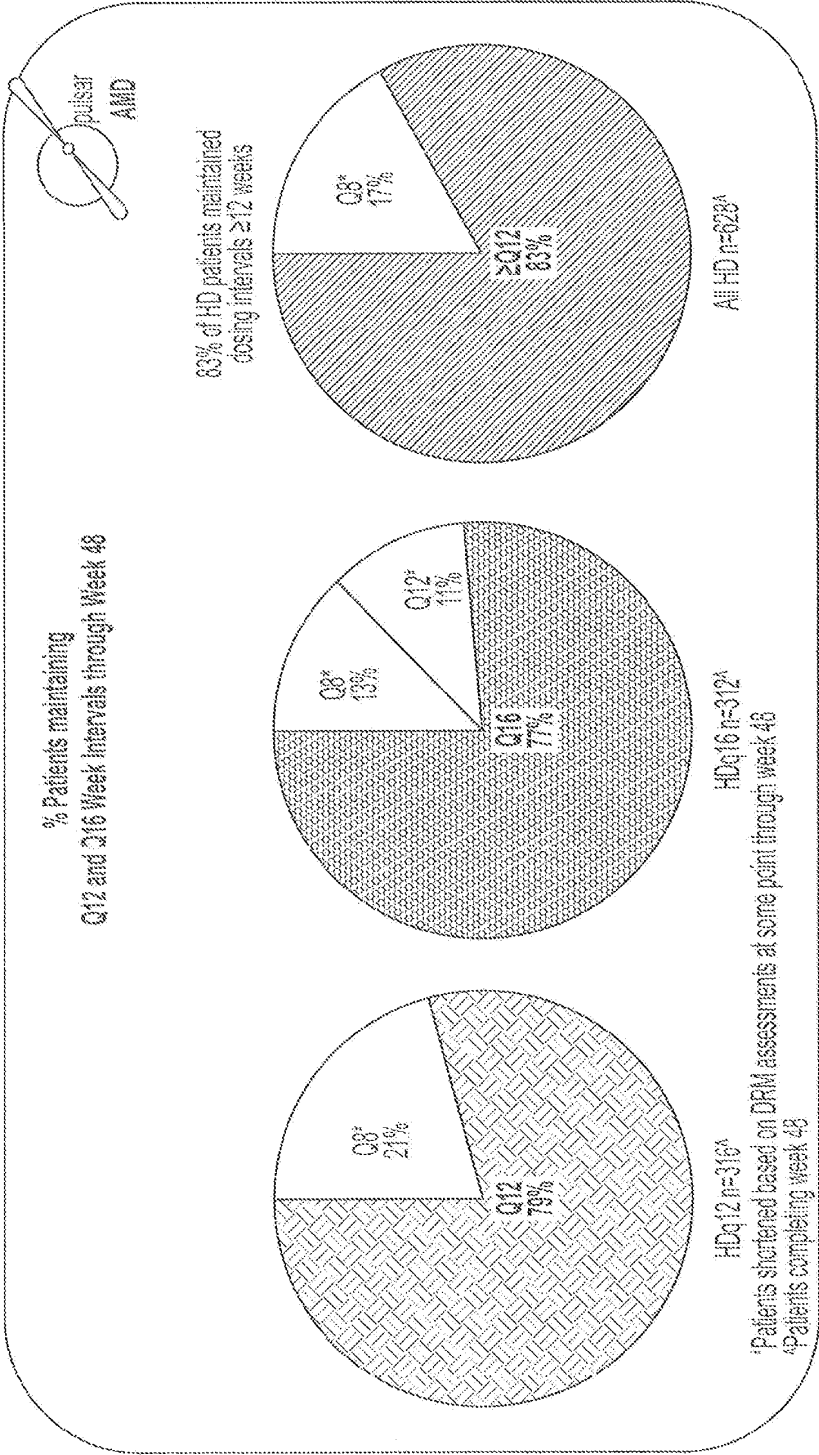


FIG. 50

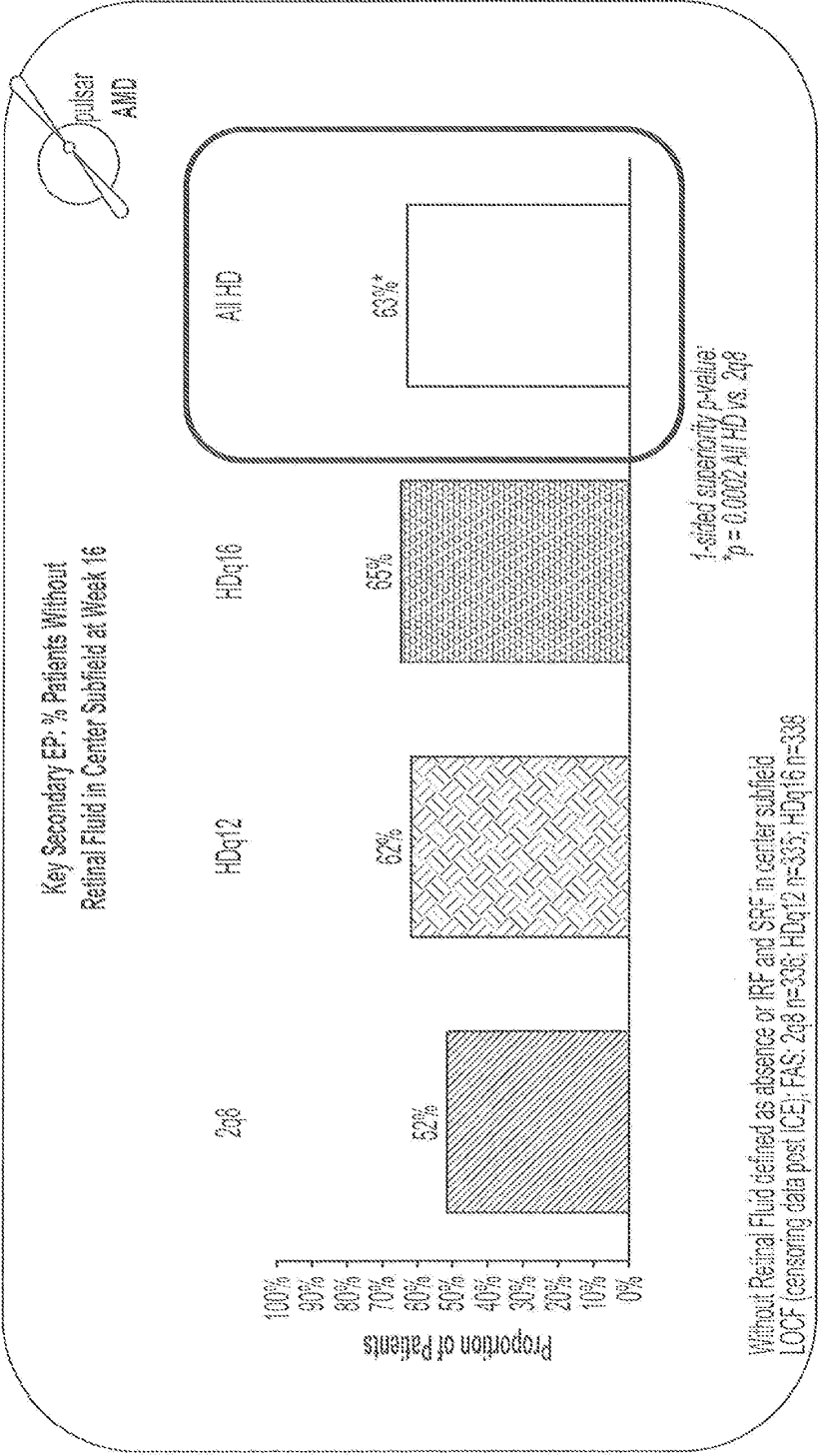


FIG. 51

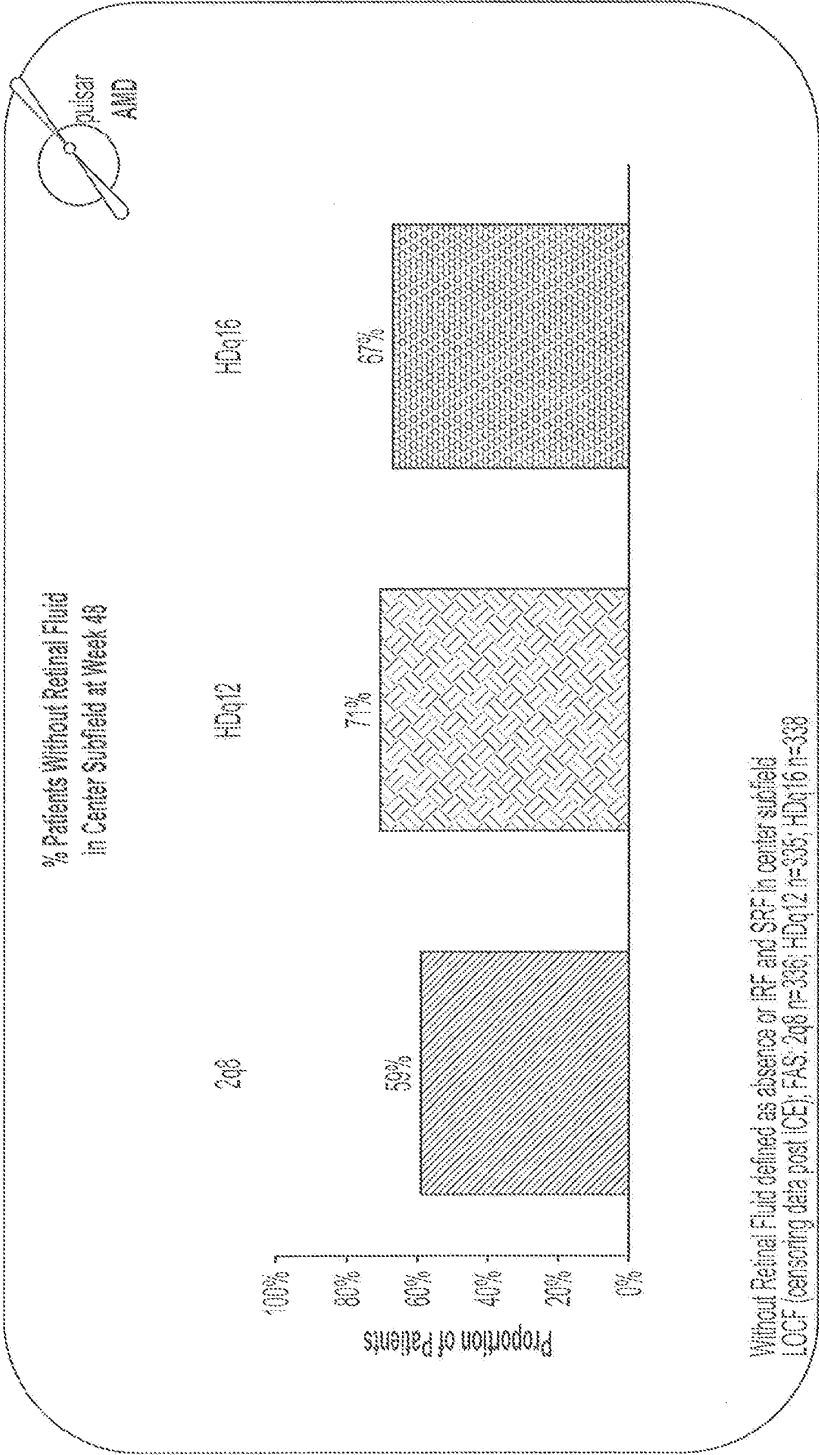
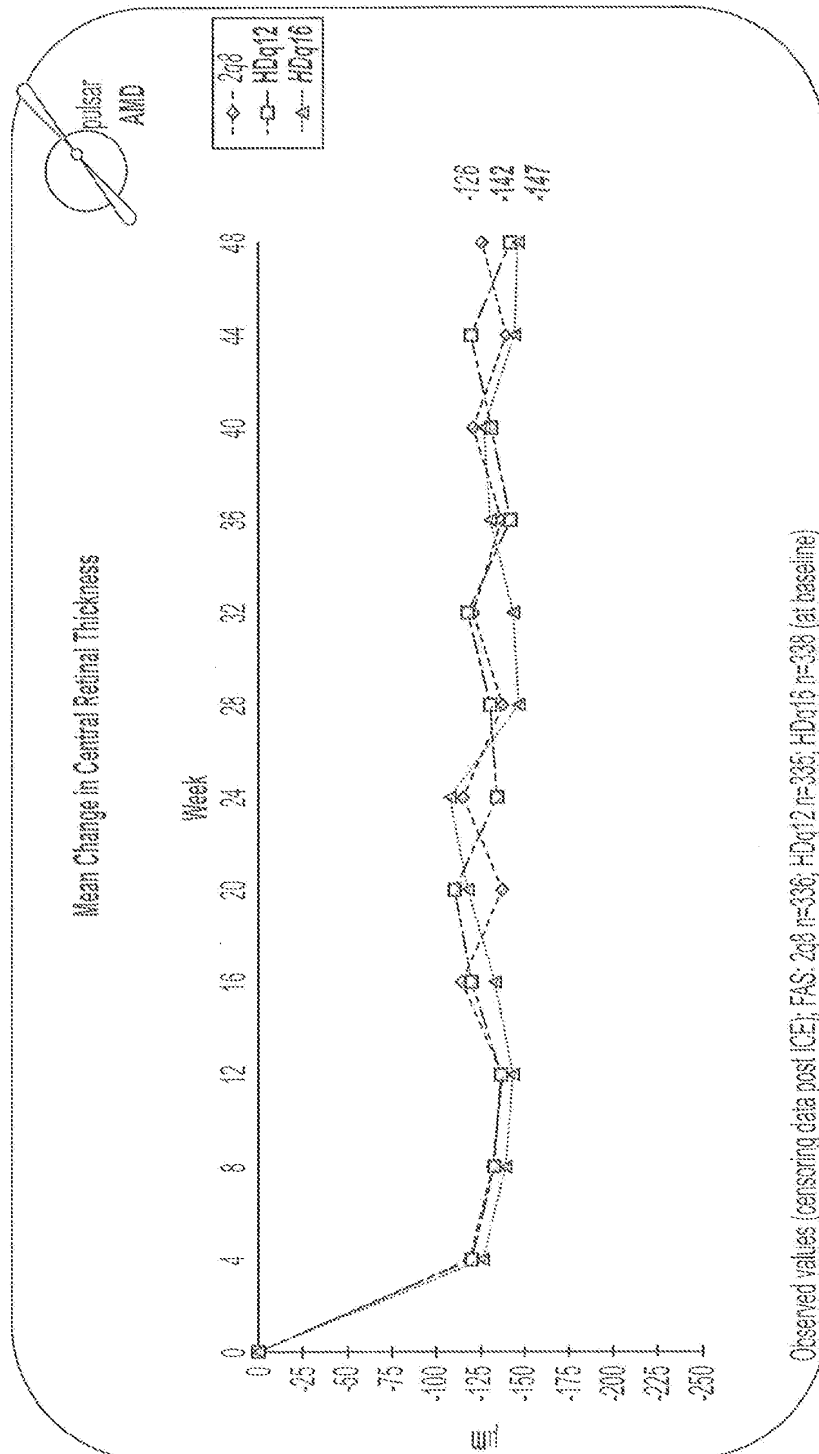
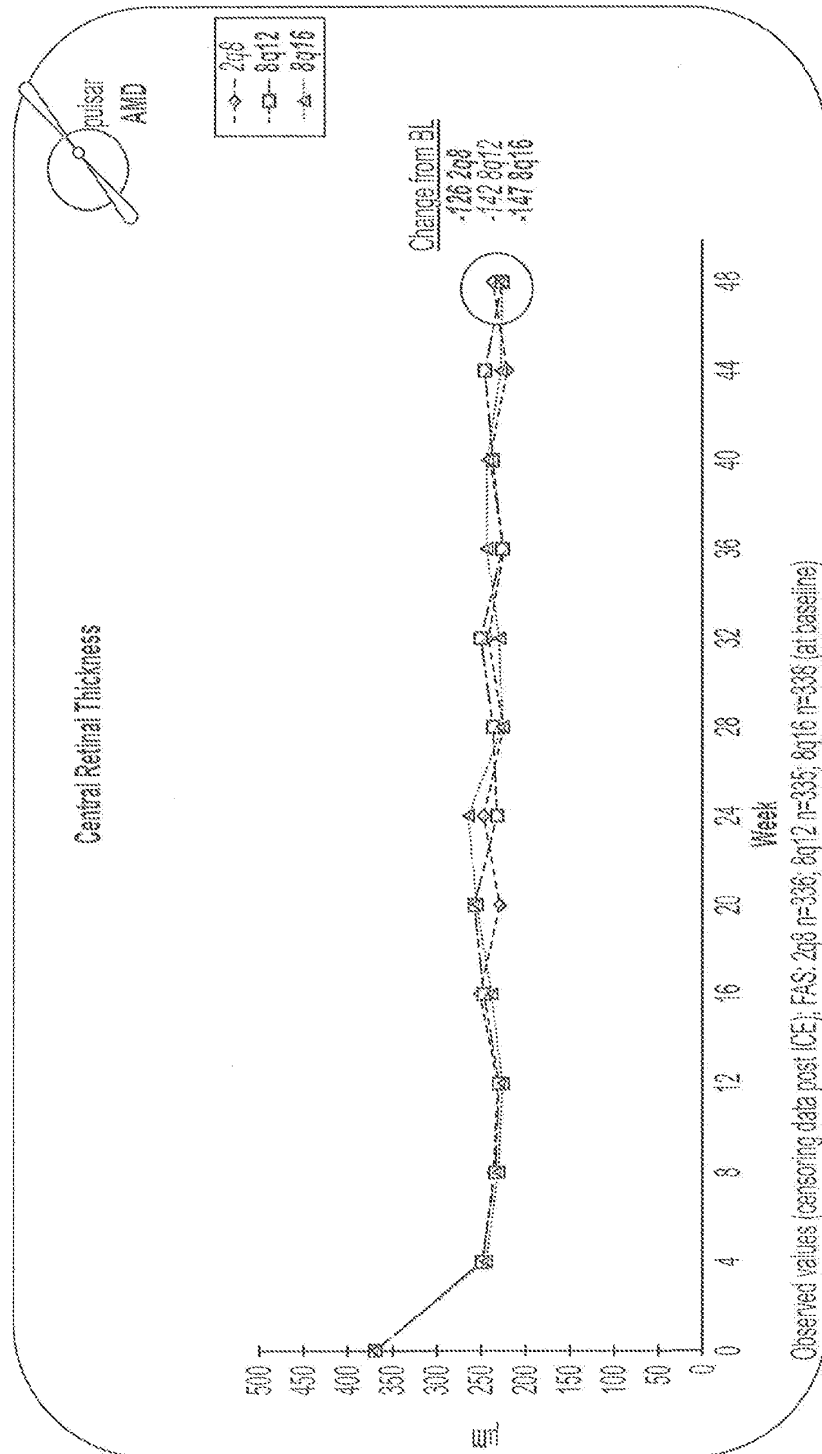


FIG. 52



430



Б
С
С
С
С

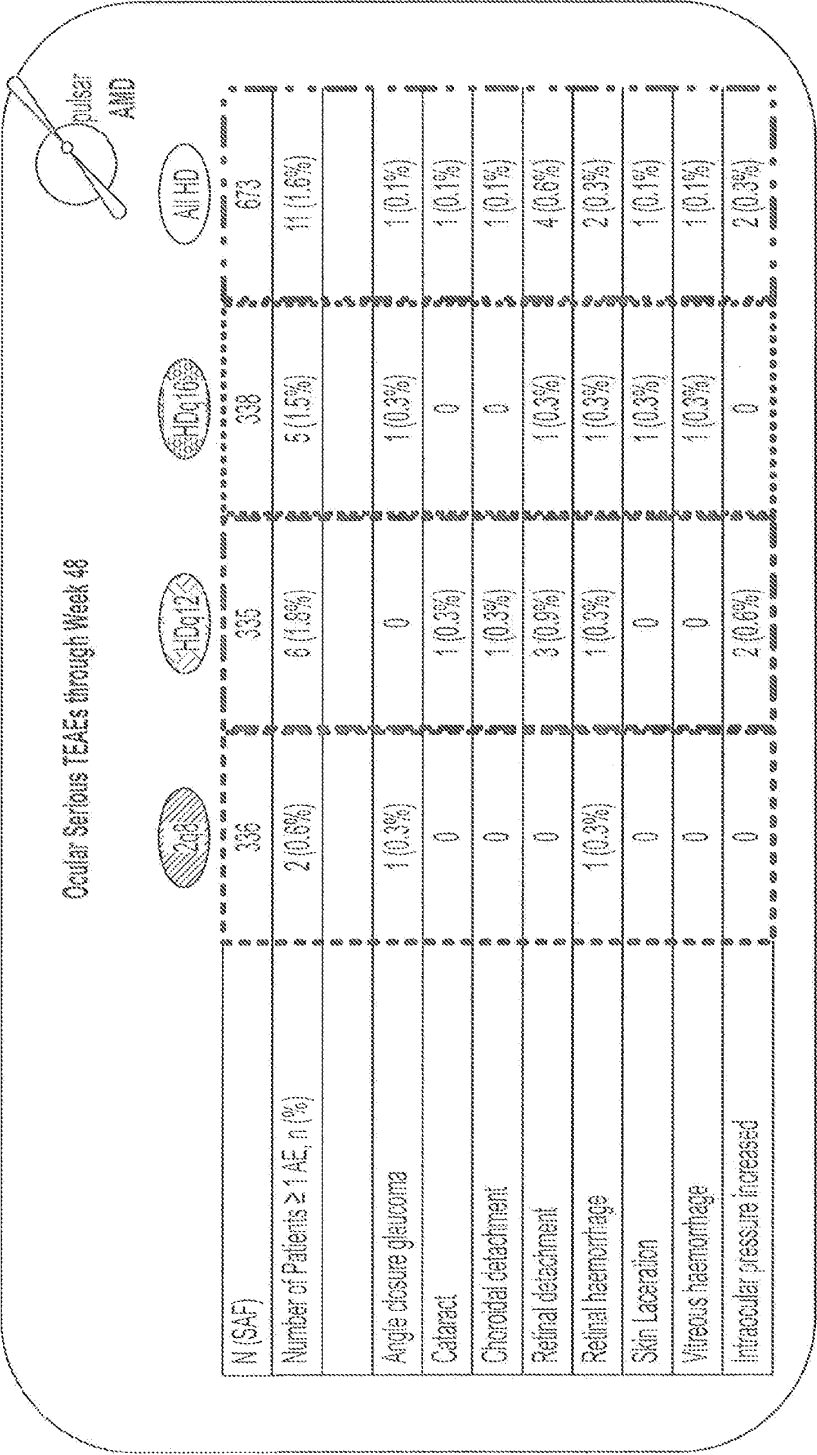


FIG. 54A

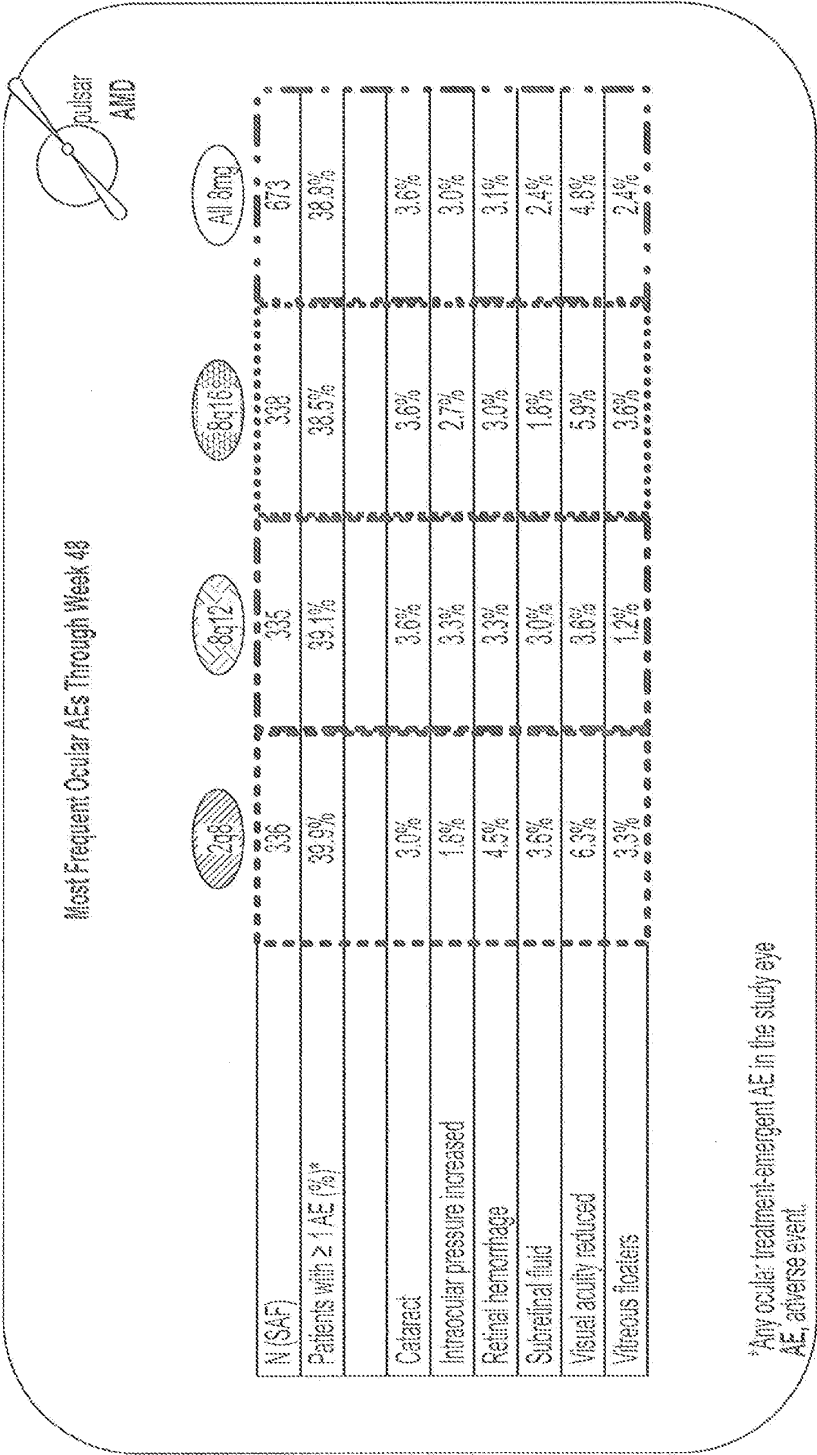


FIG. 54B



FIG. 55

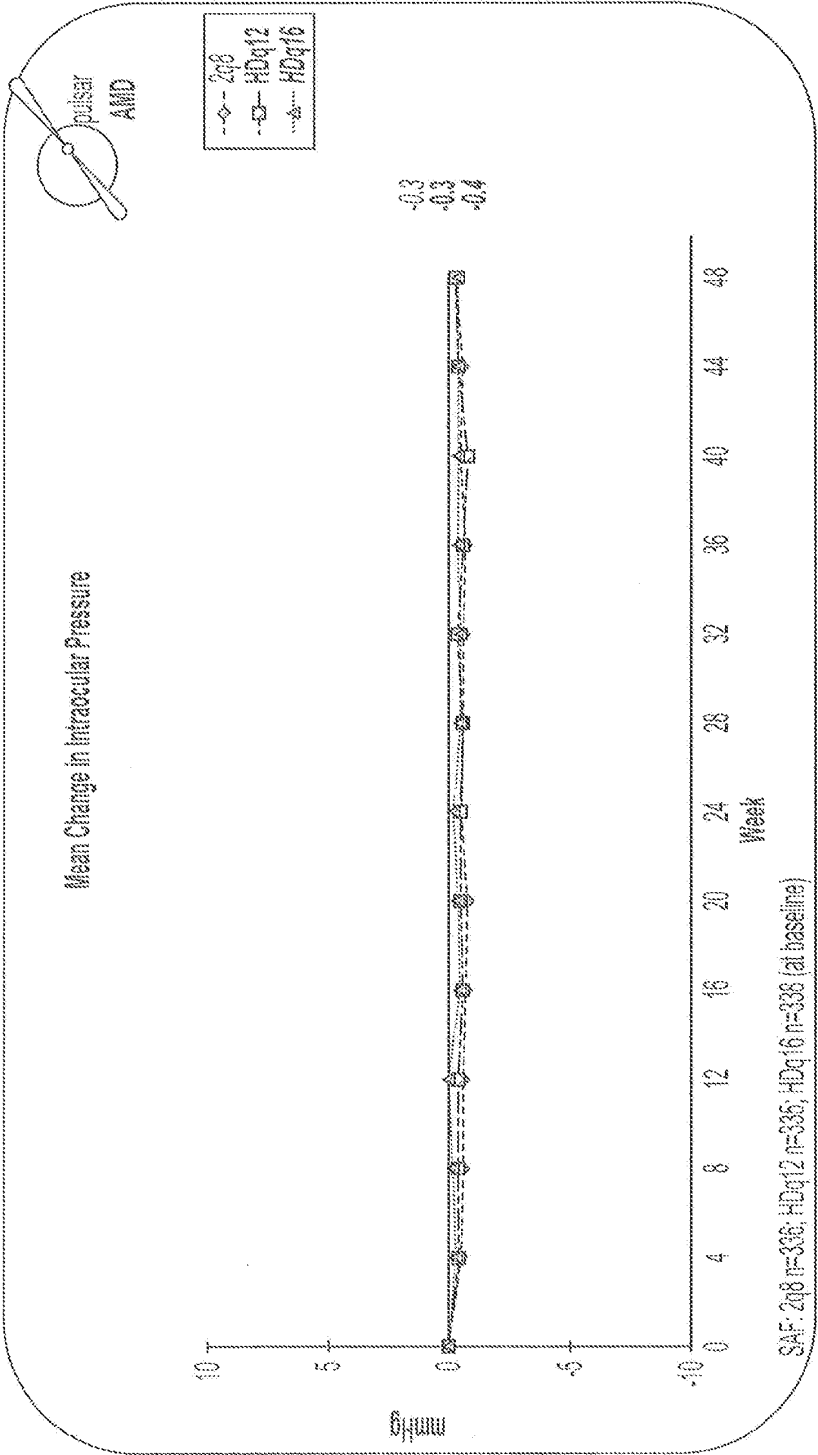


FIG. 56

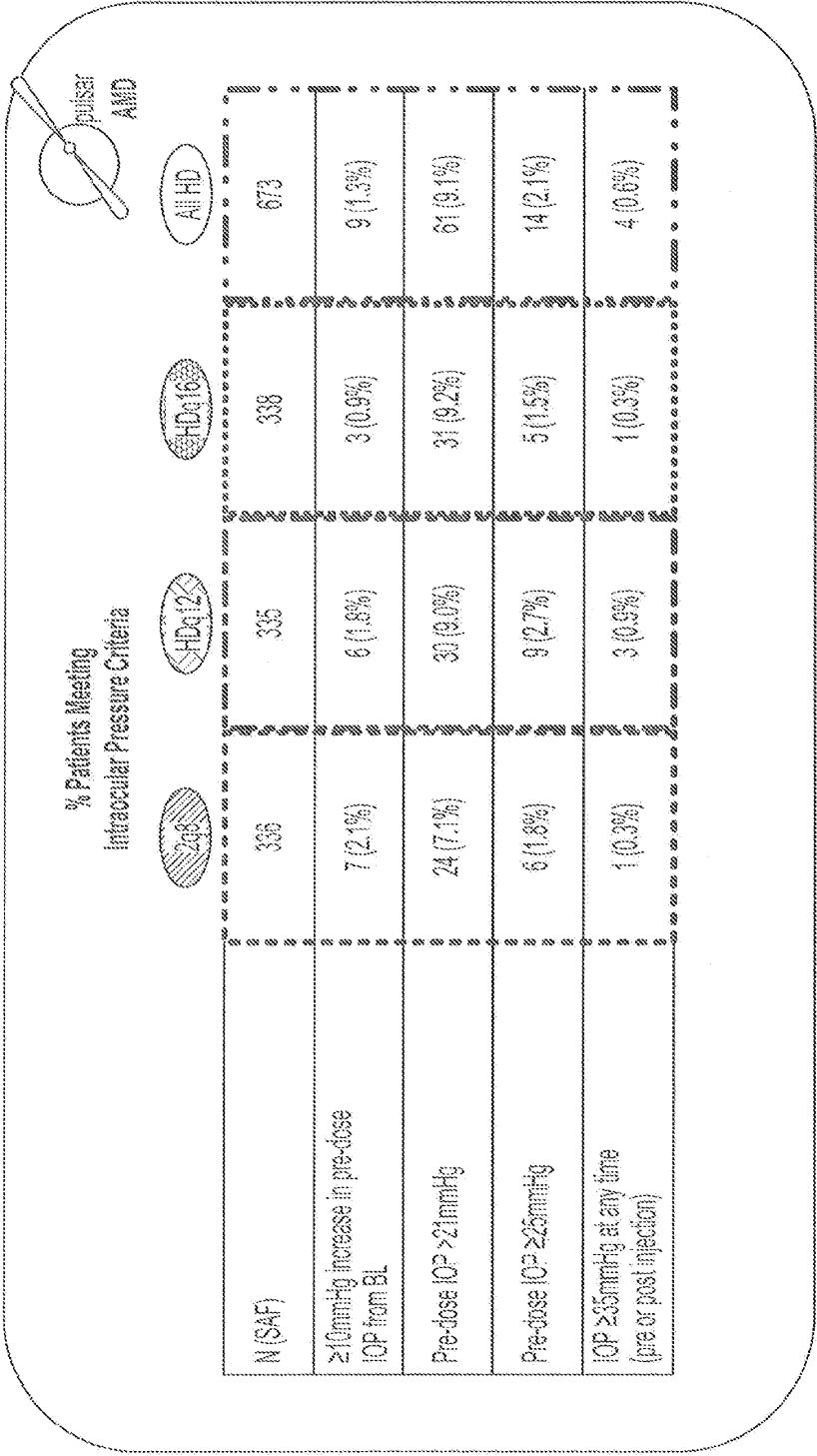


FIG. 57

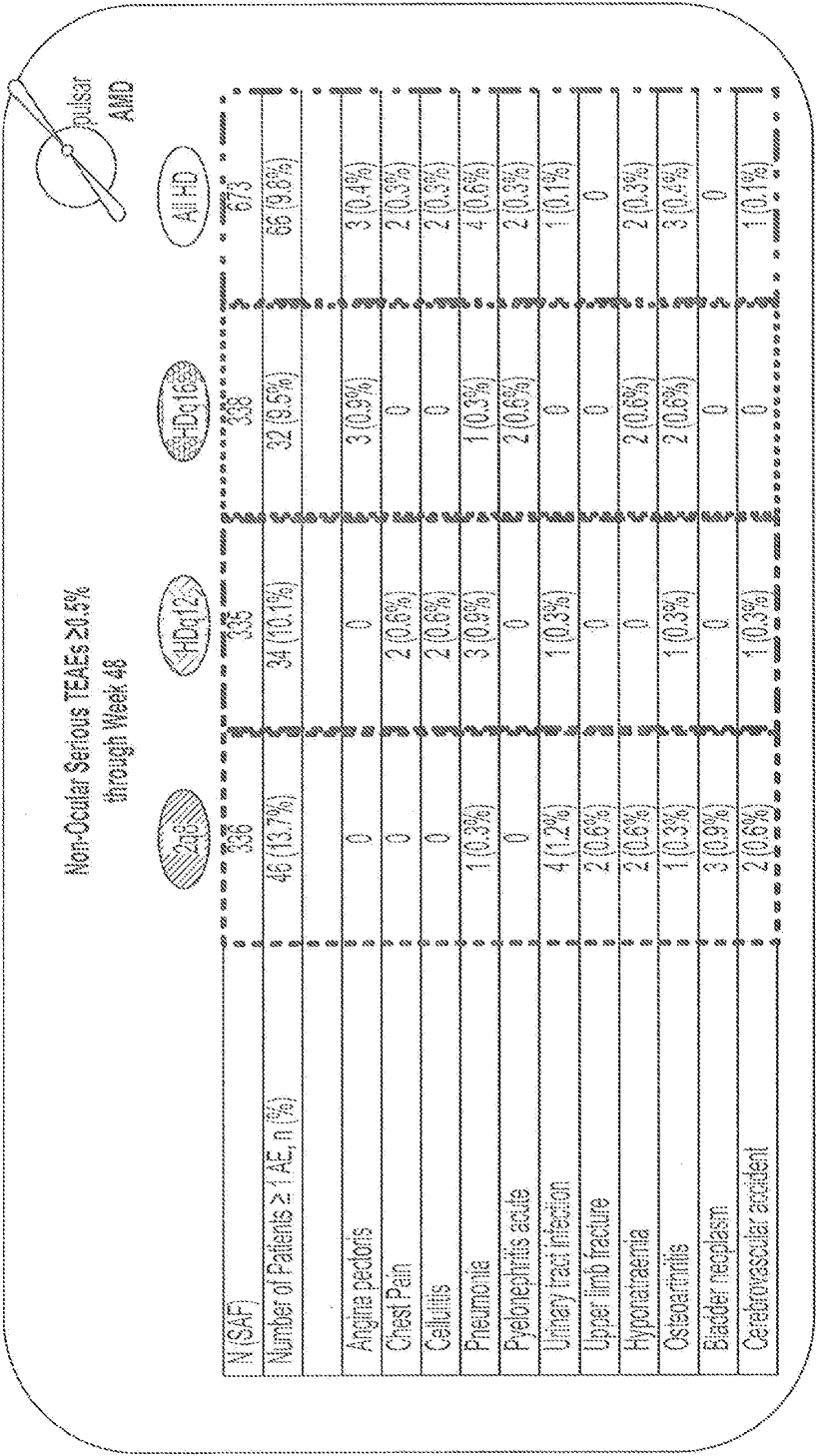


FIG. 58

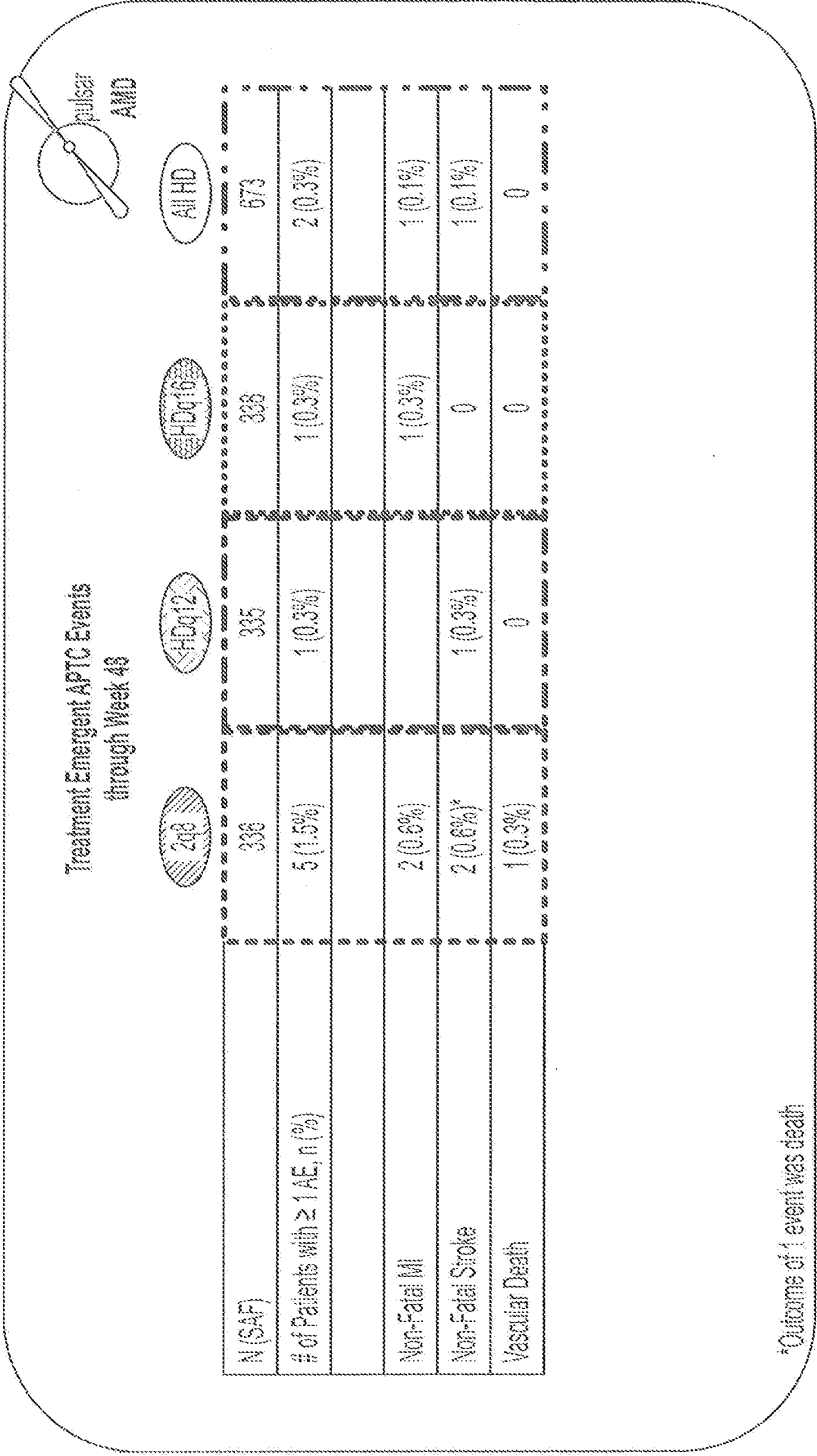


FIG. 59A

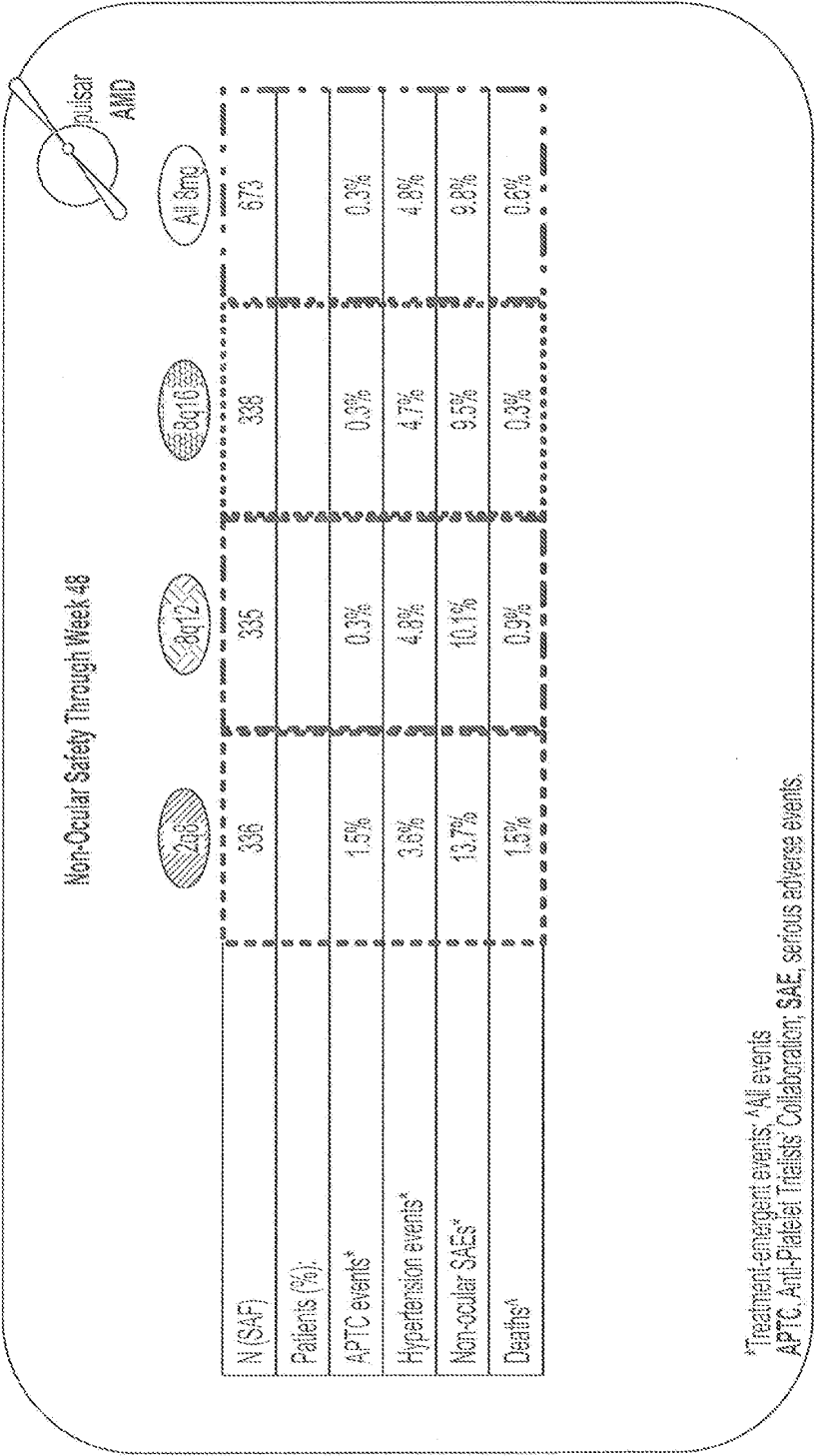


FIG. 59B

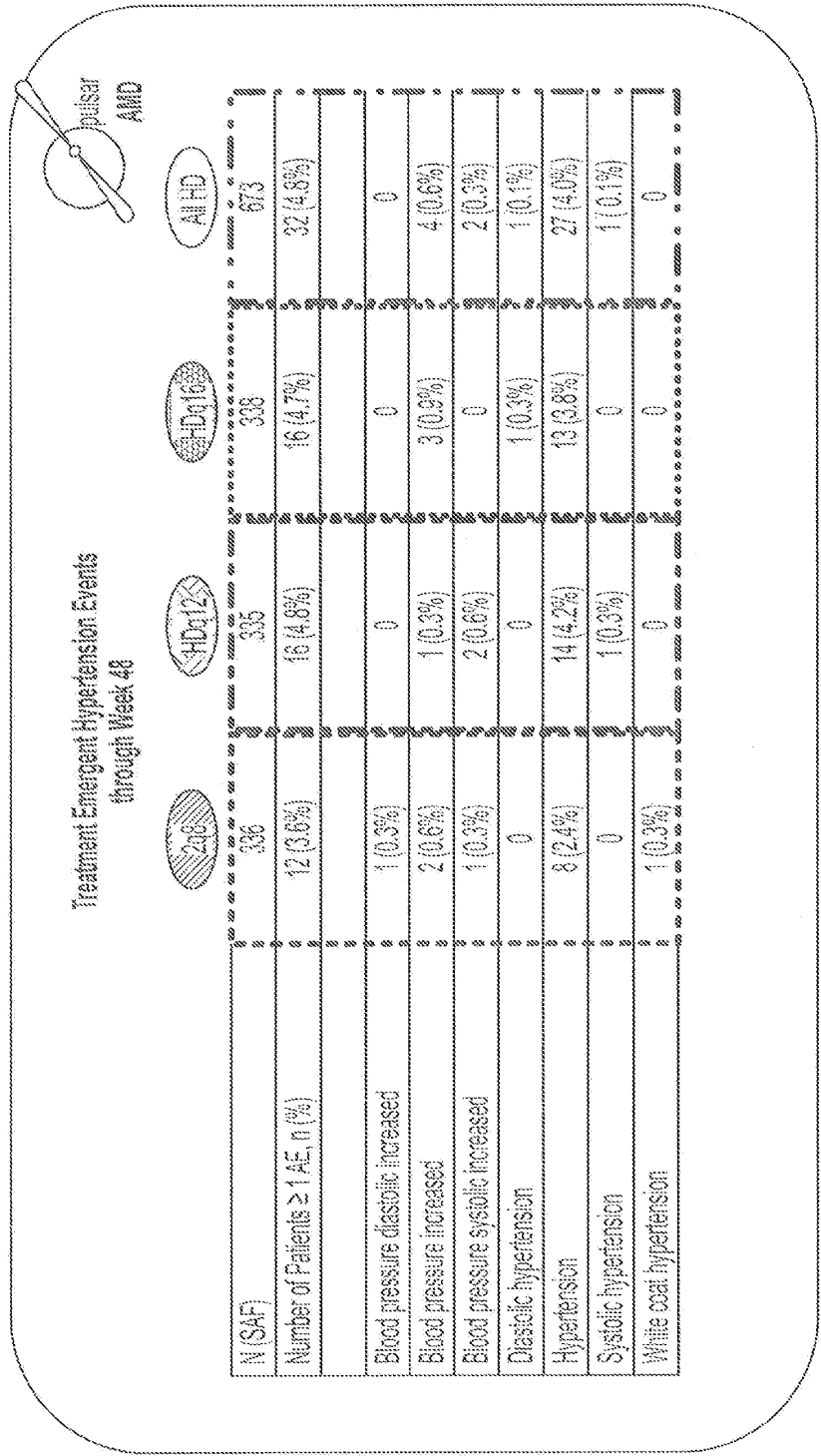


FIG. 60

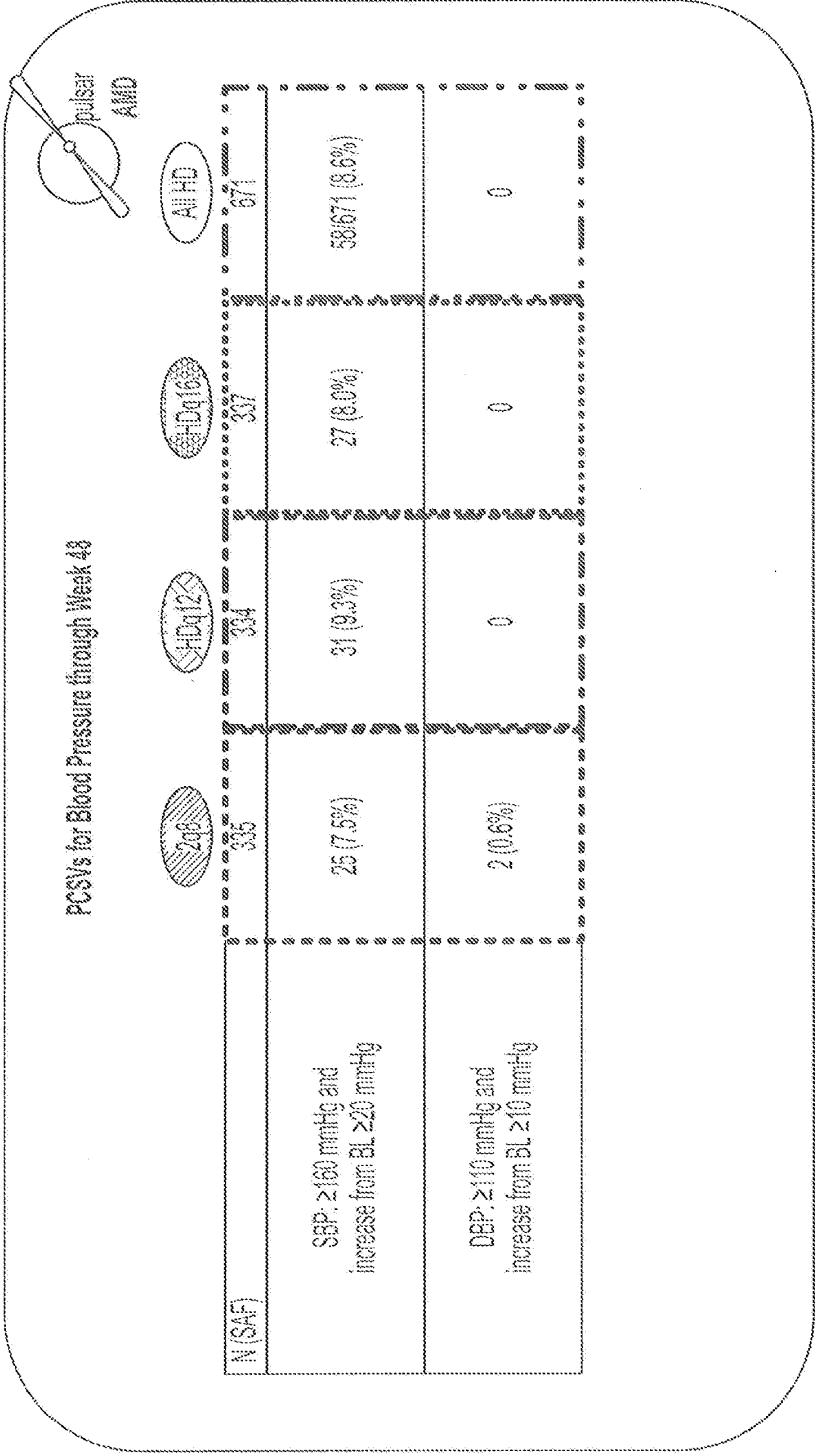
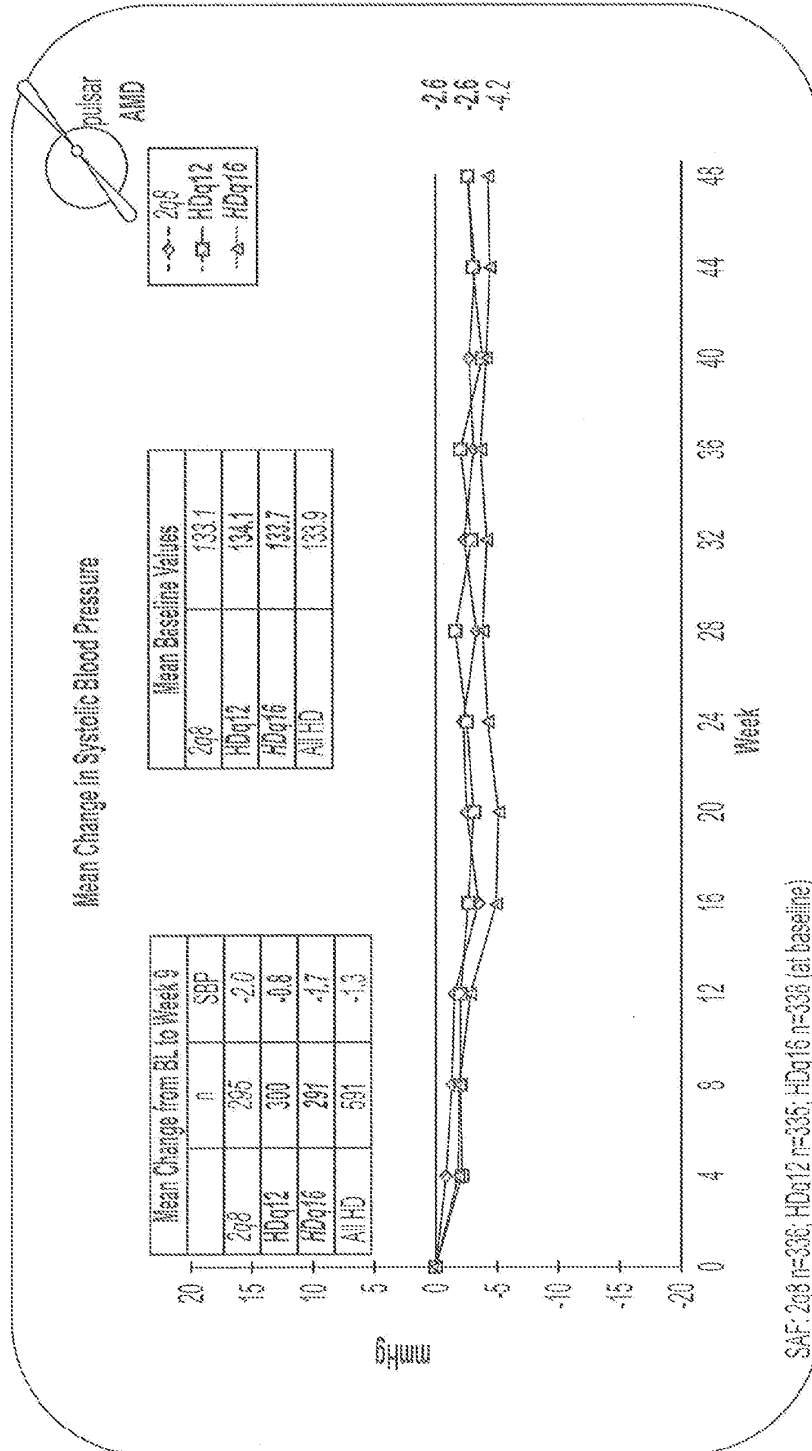
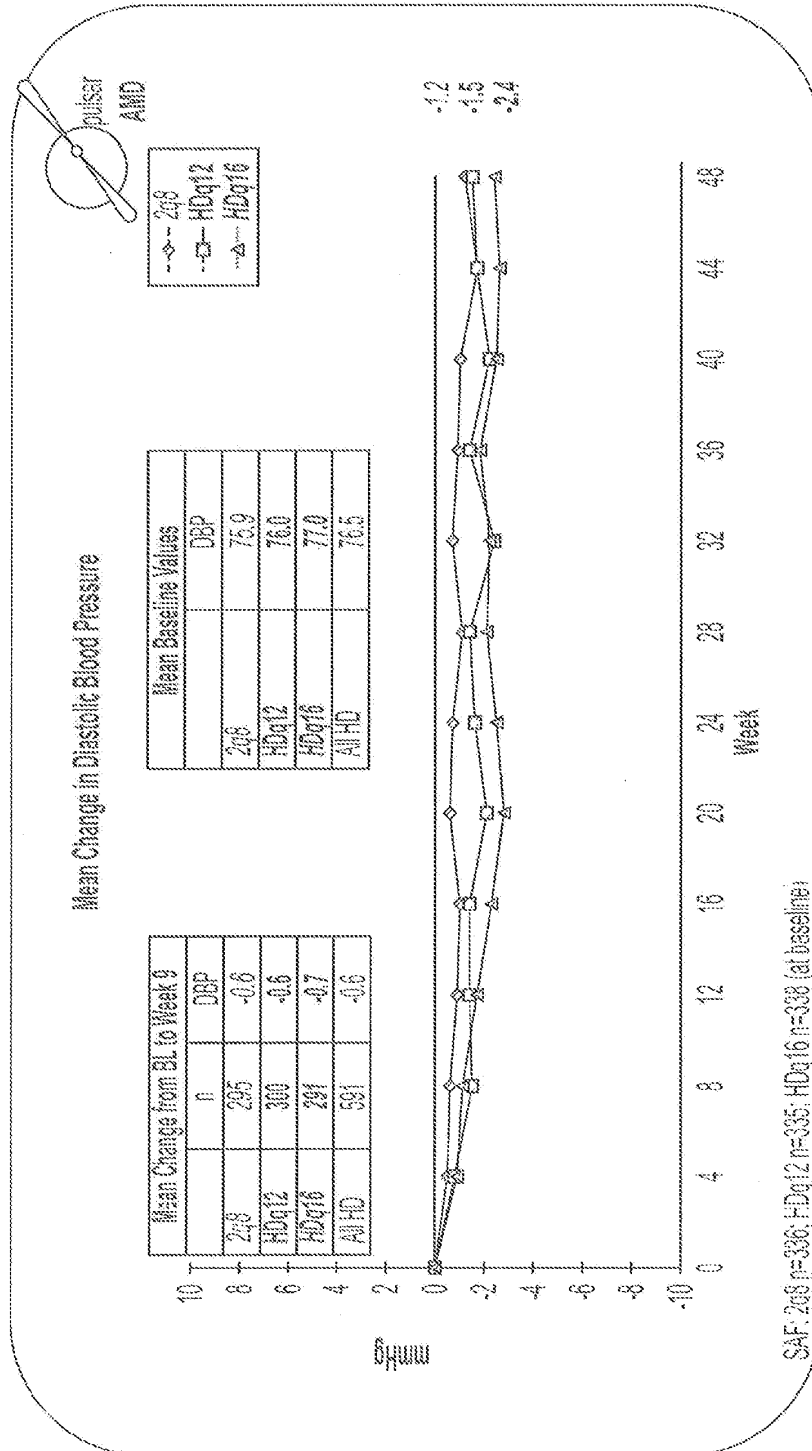


FIG. 61

26
U



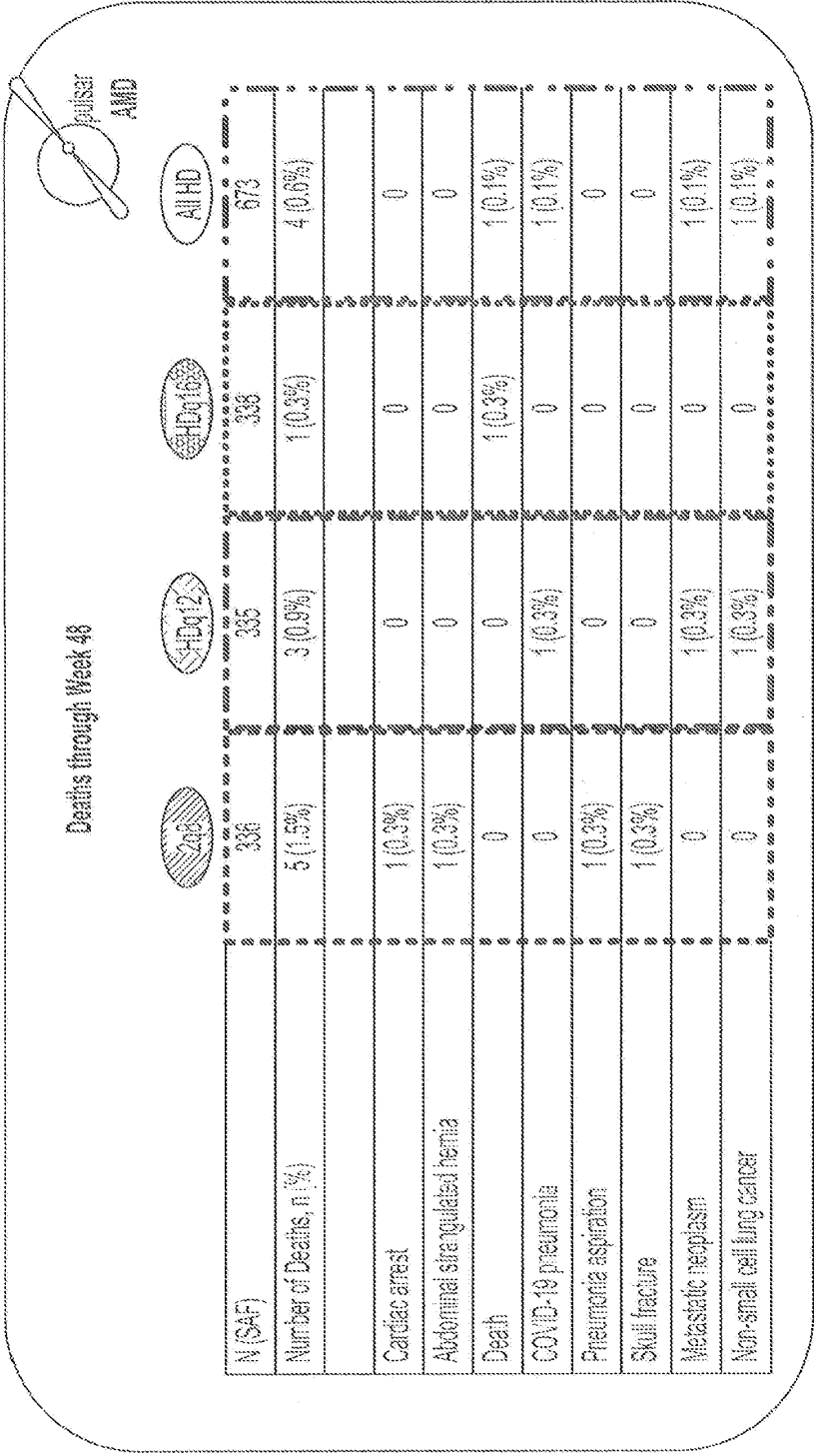
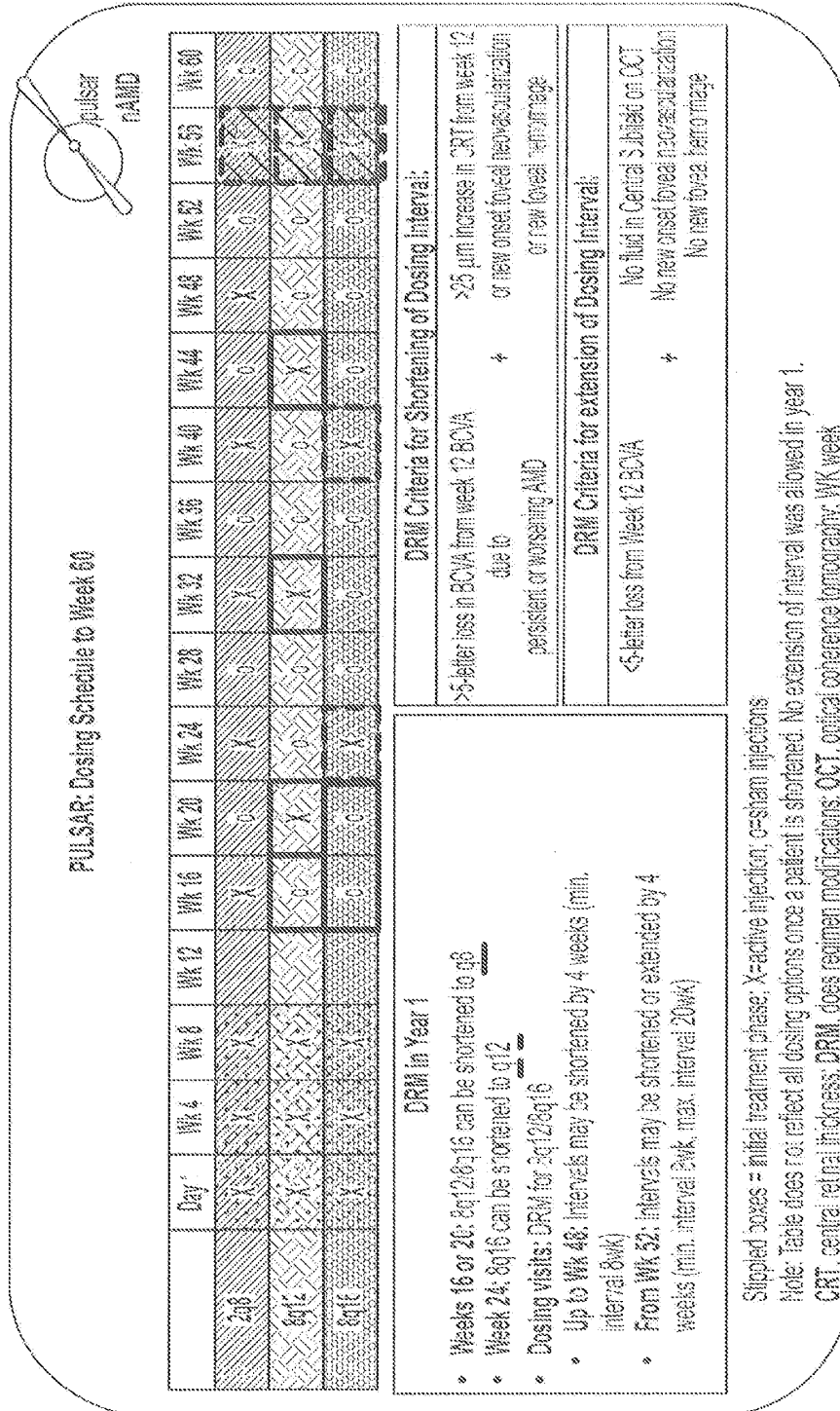
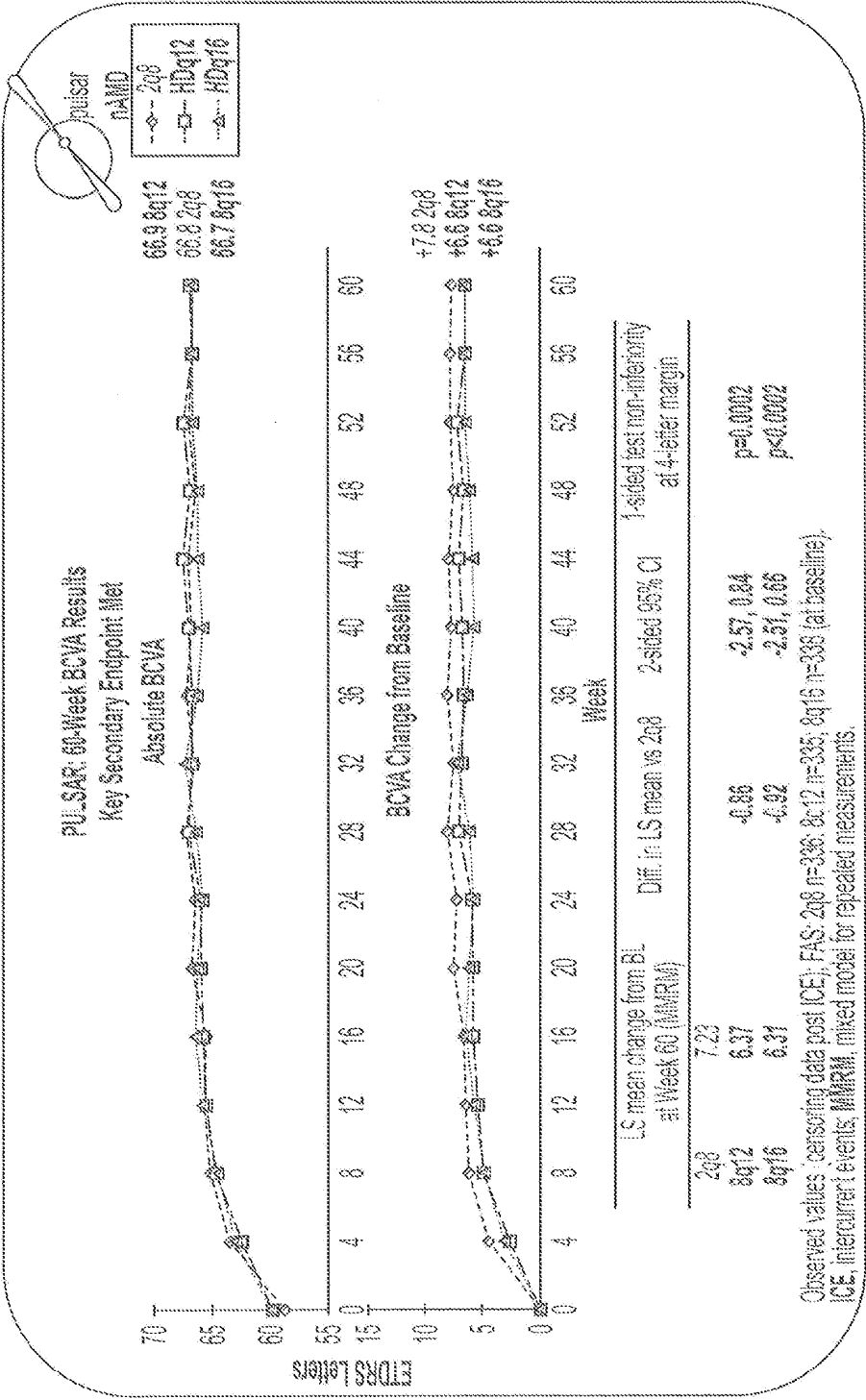


FIG. 64





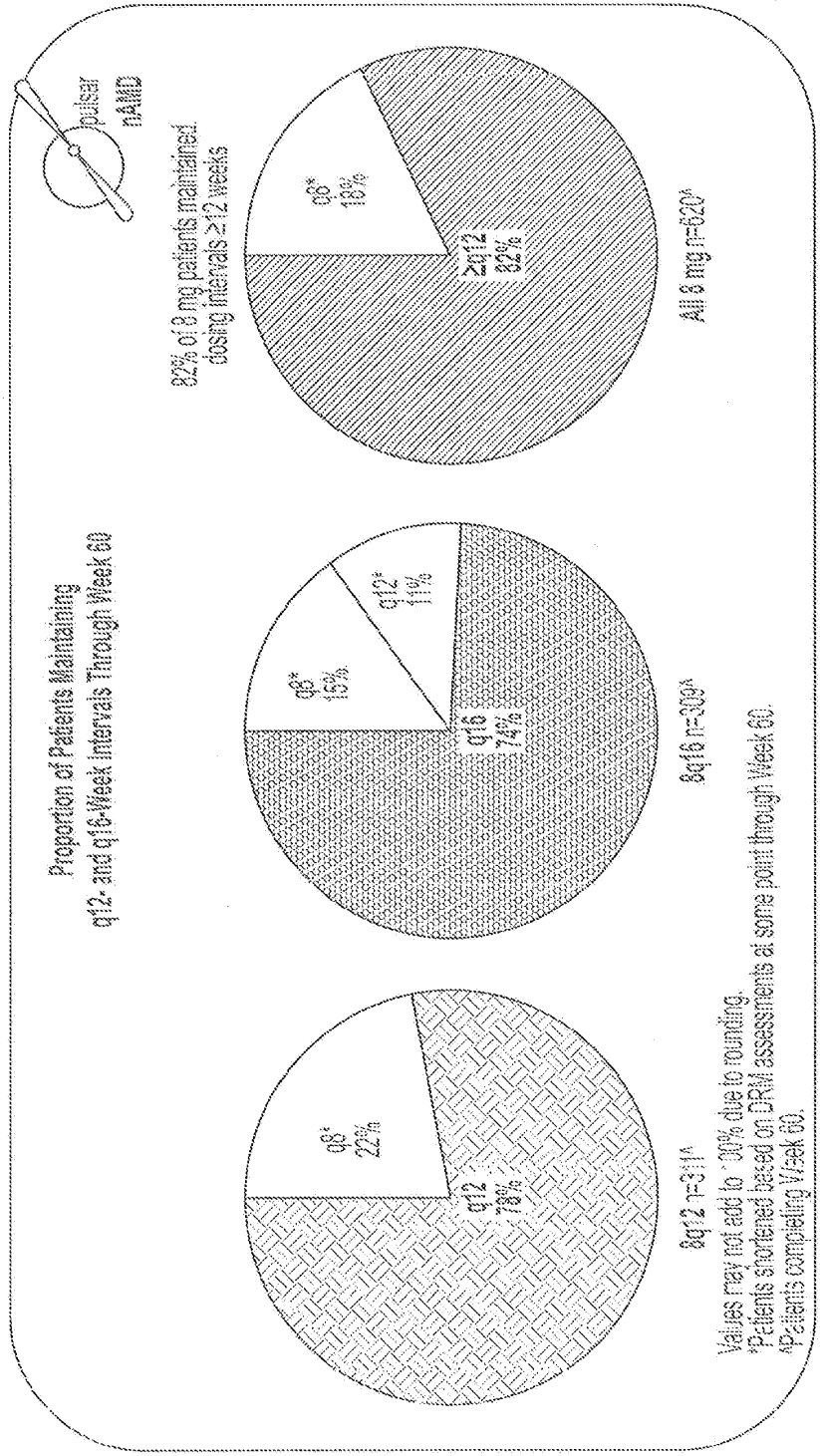


FIG. 67

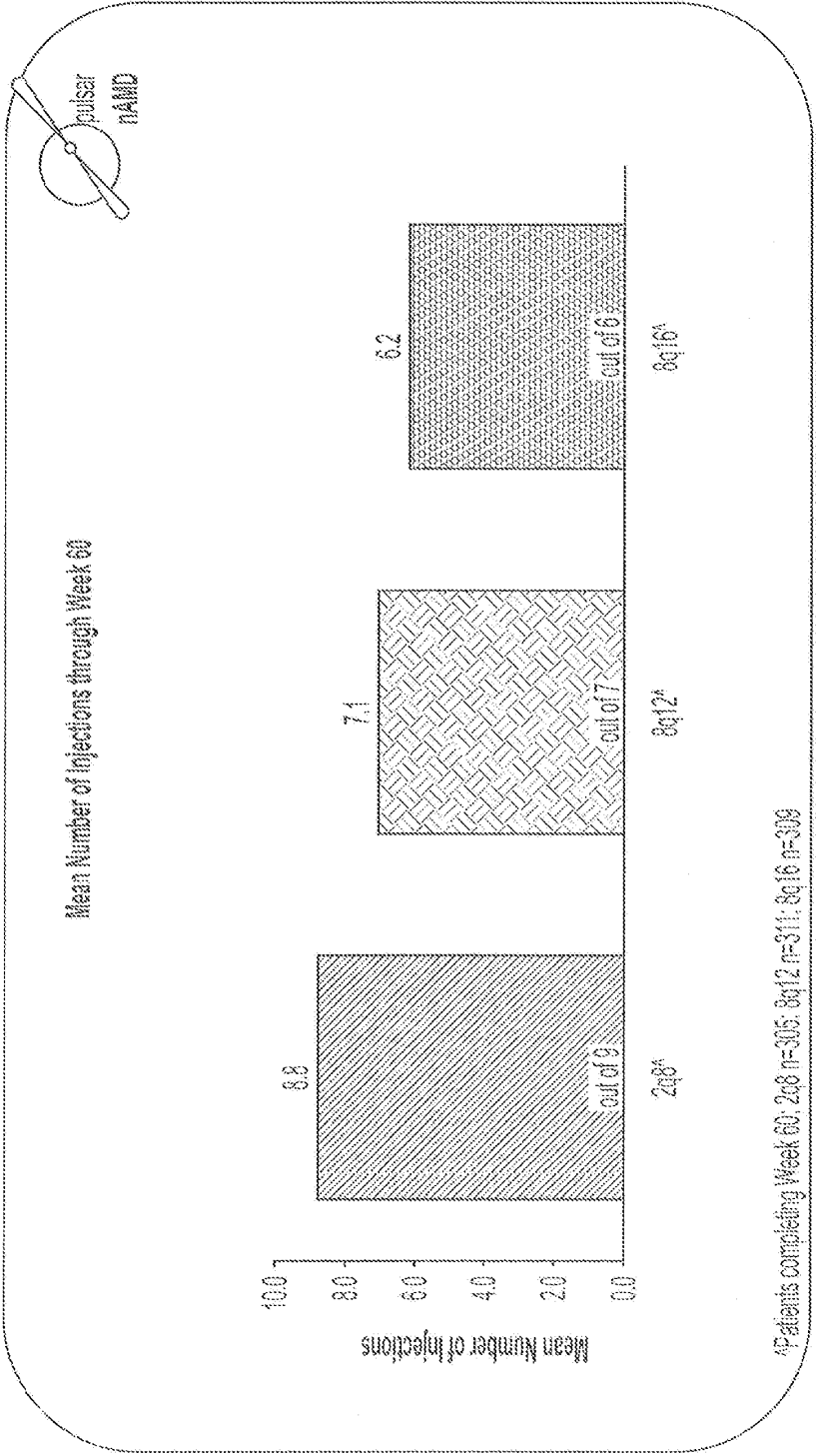
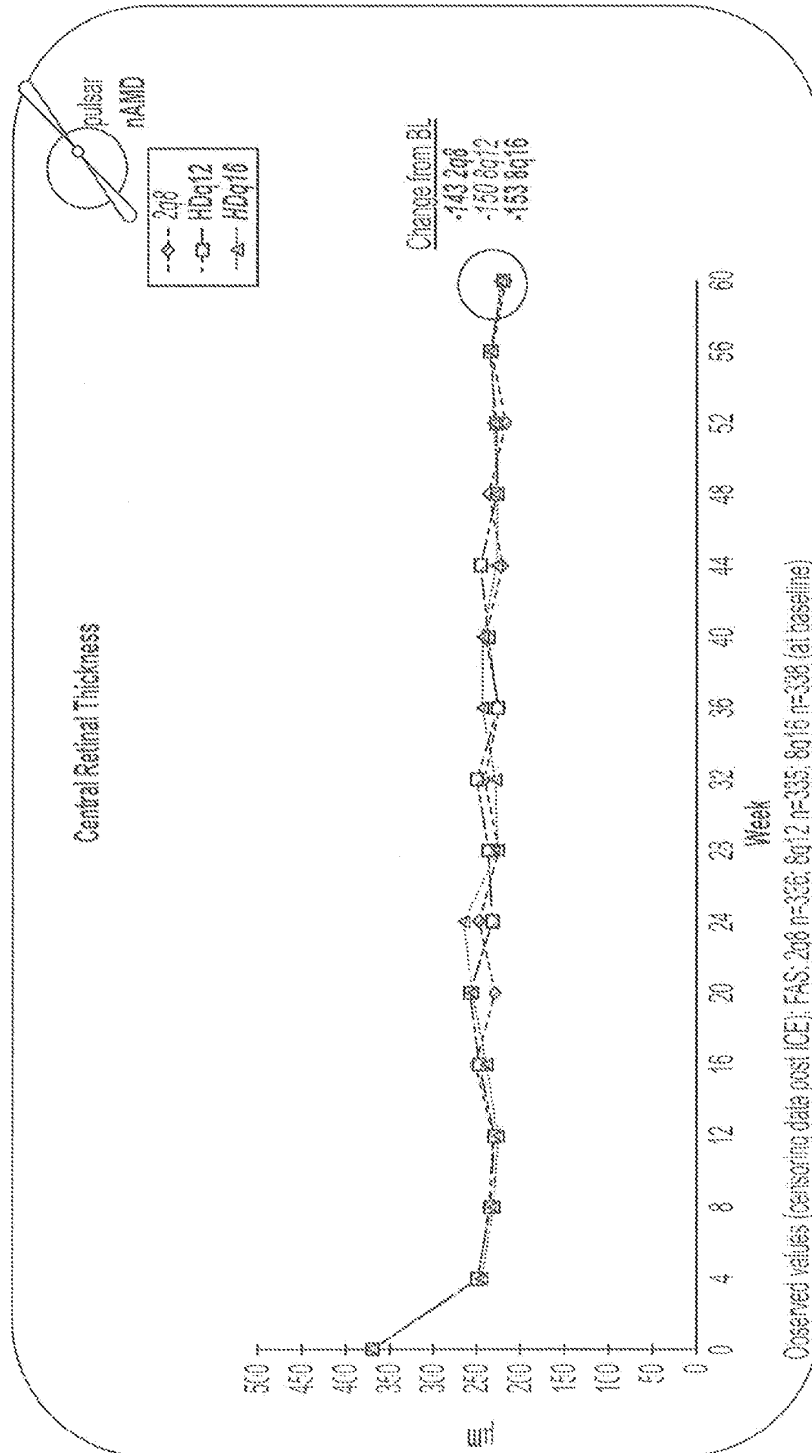


FIG. 68



400

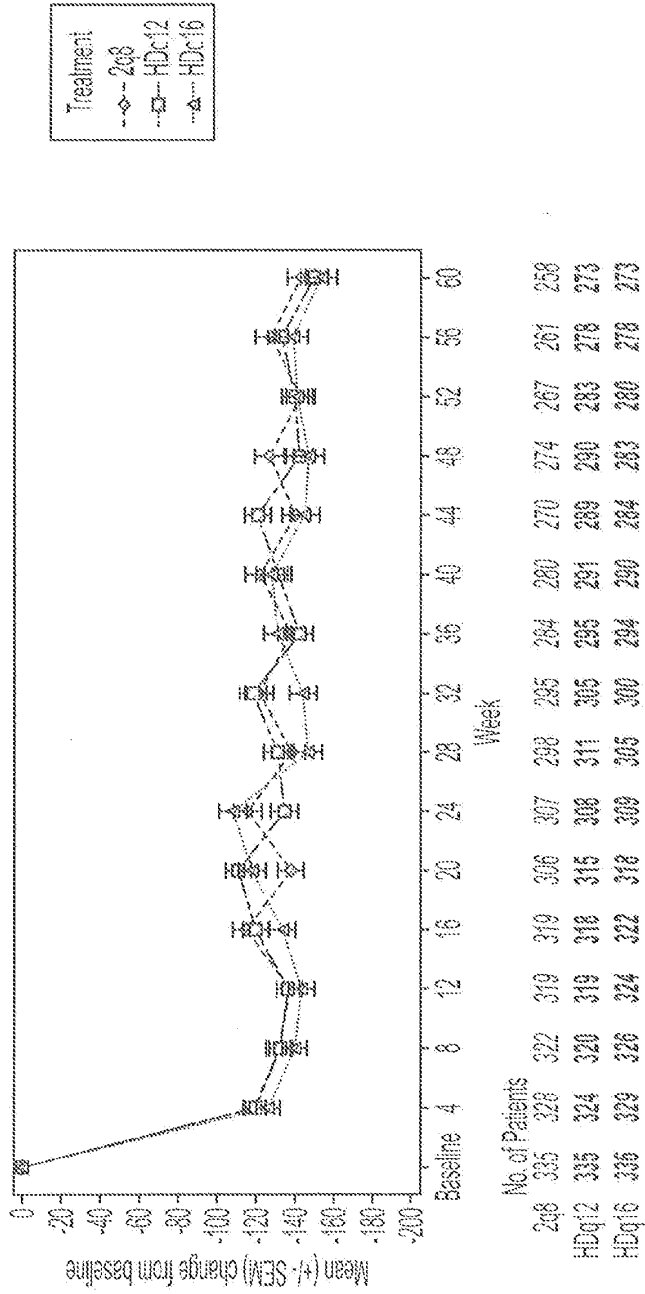


FIG. 69B

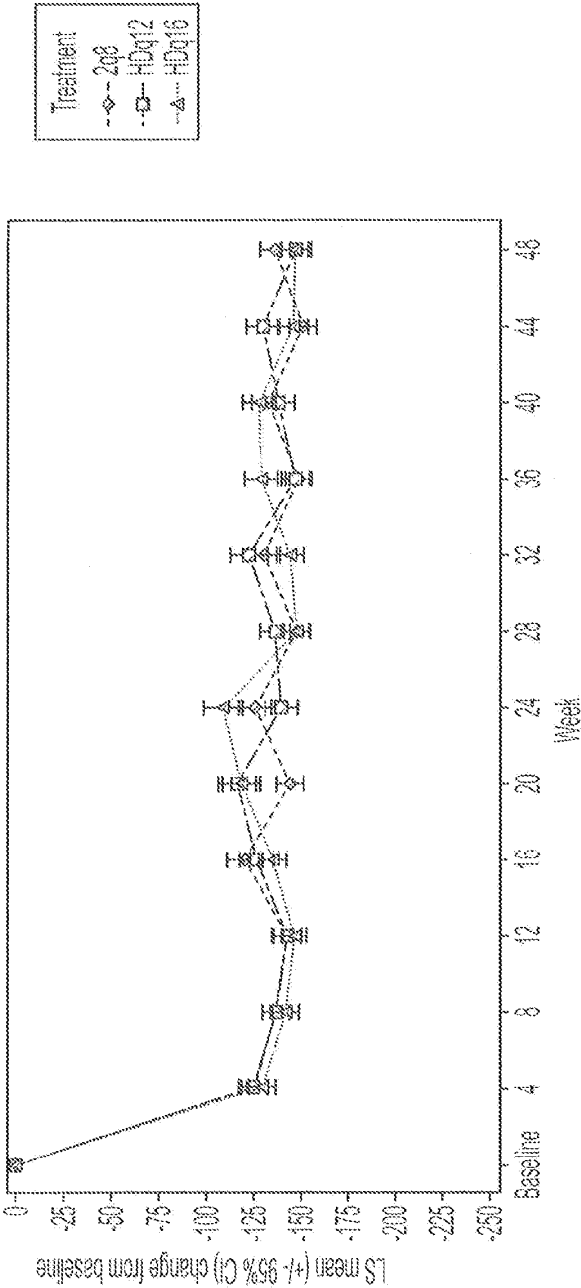


FIG. 69C

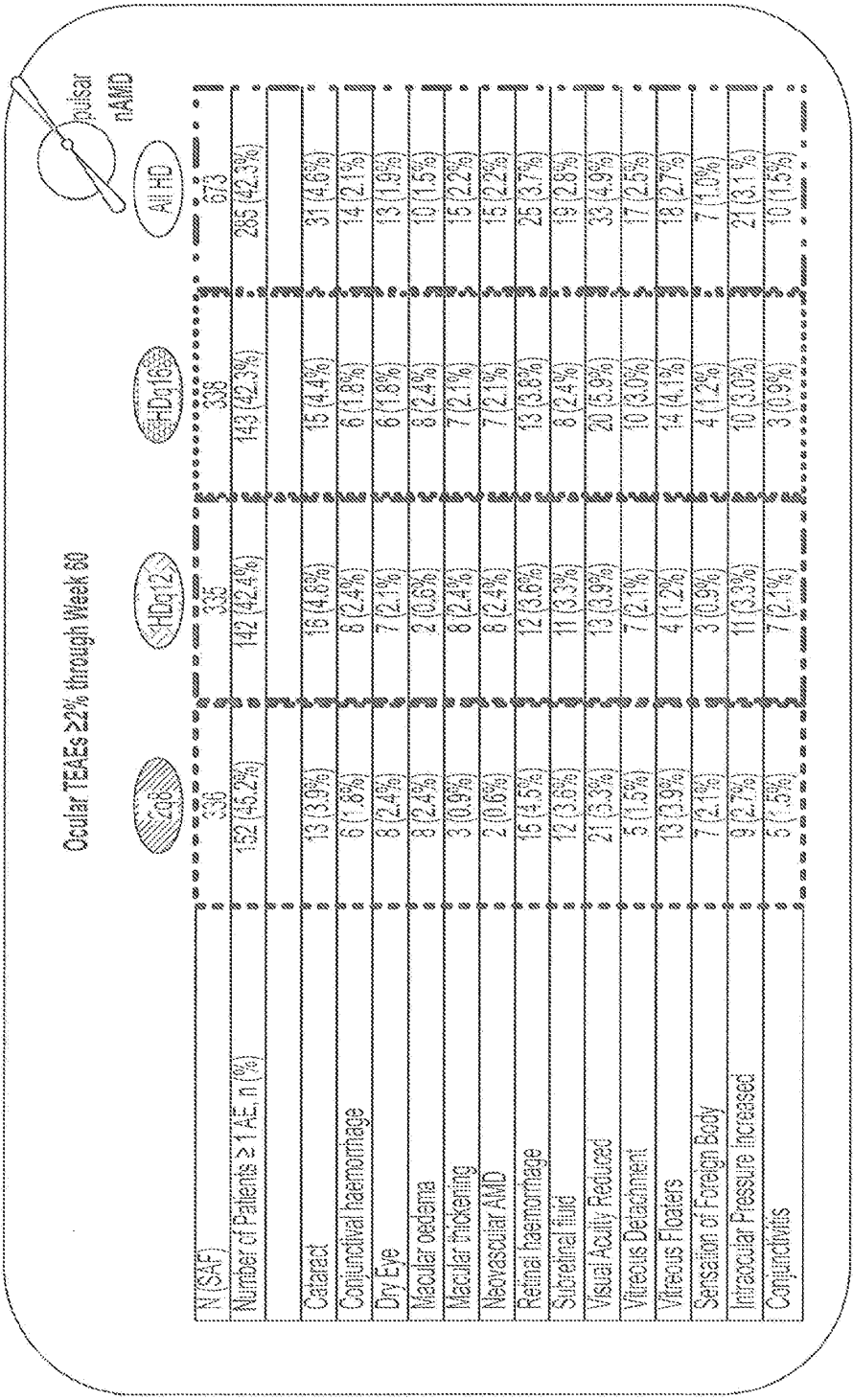


FIG. 70A

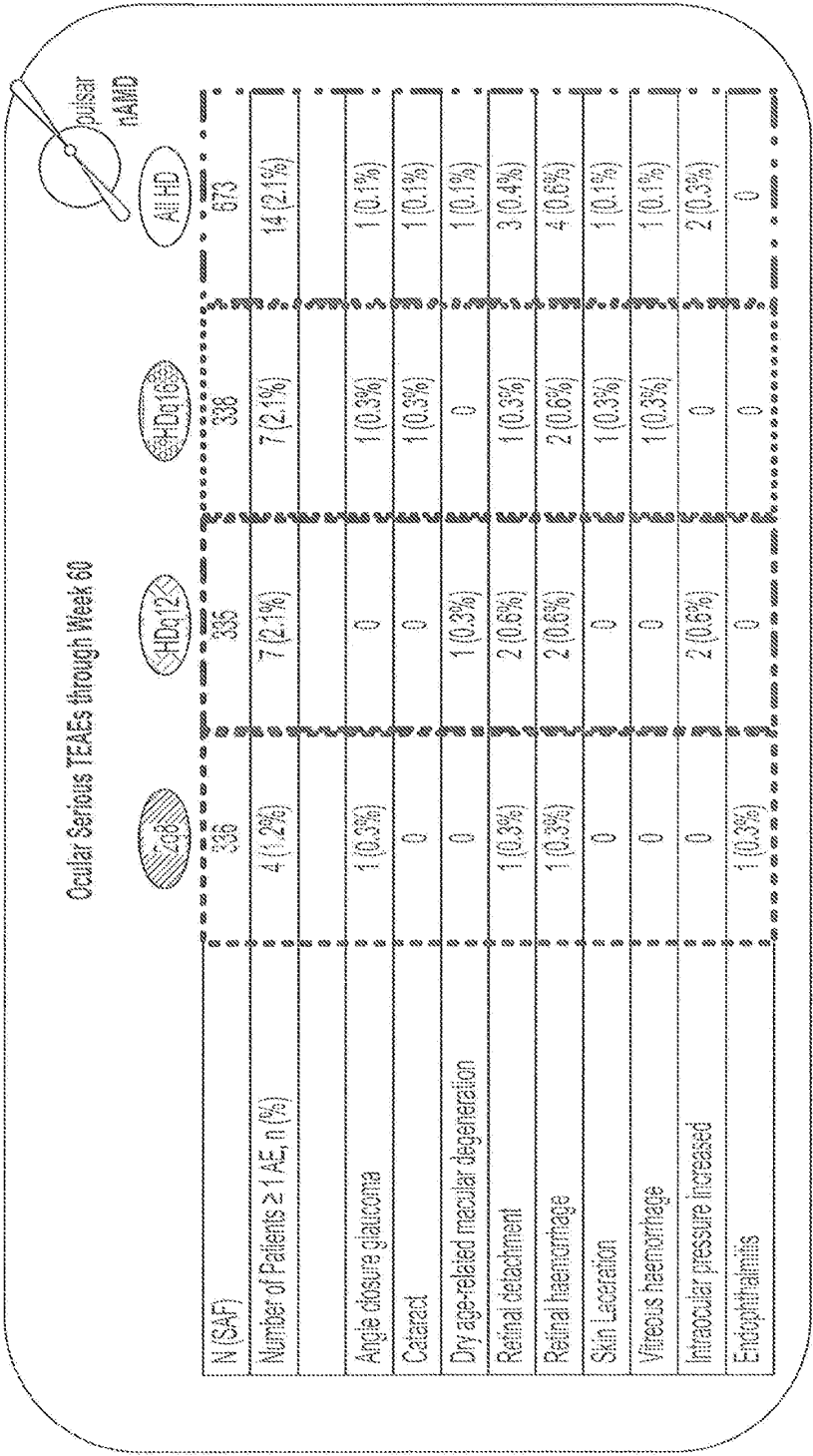


FIG. 70B

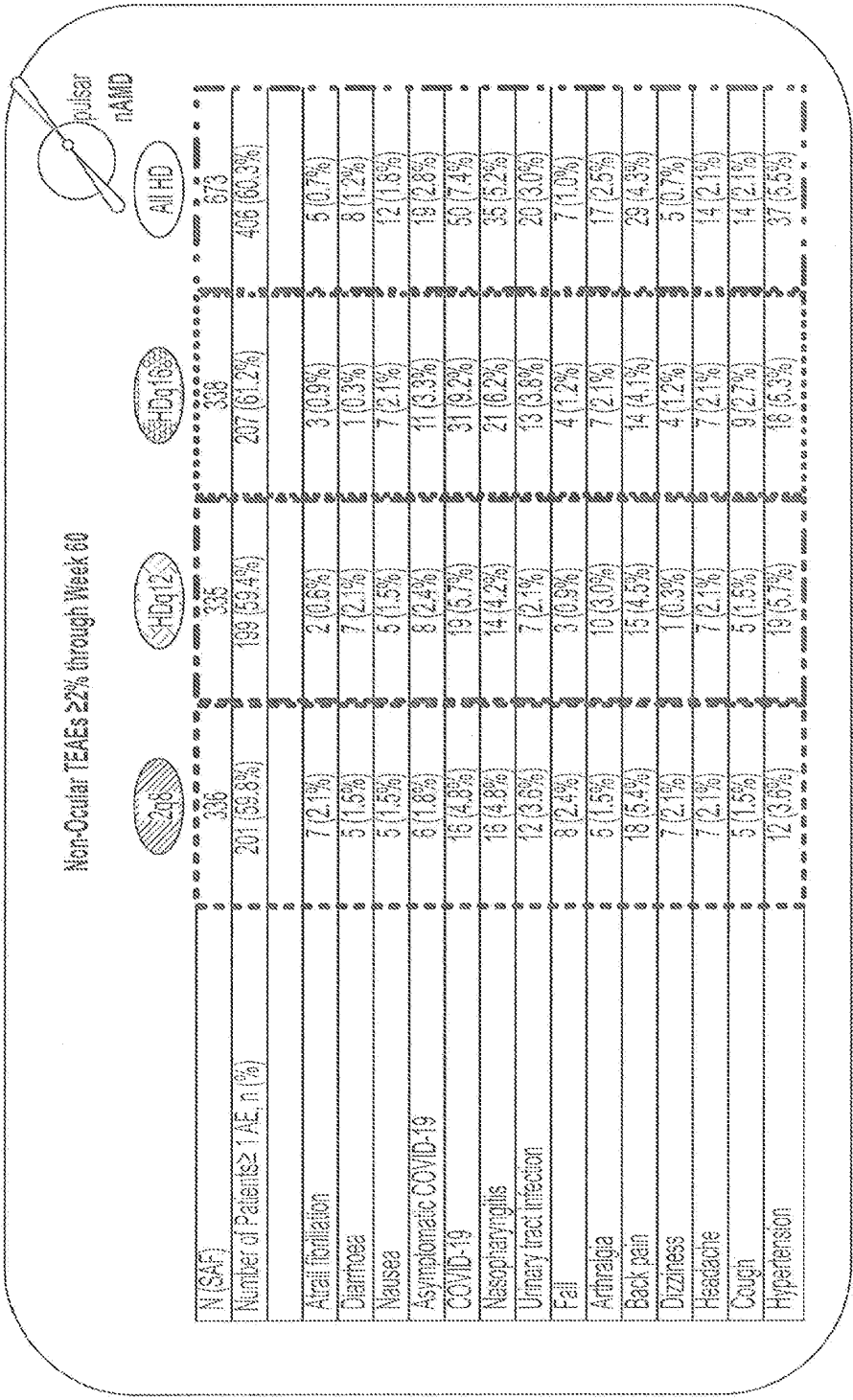


FIG. 70C

Non-Ocular Serious TEAEs ≥0.5% through Week 60

	200	HDq12	SHDq100	All HD
(N(SAF))	336	336	336	673
Number of Patients ≥ 1 AE, n (%)	53 (15.8%)	41 (12.2%)	41 (12.1%)	82 (12.2%)
Asthenia	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
Hypotension	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. 70D

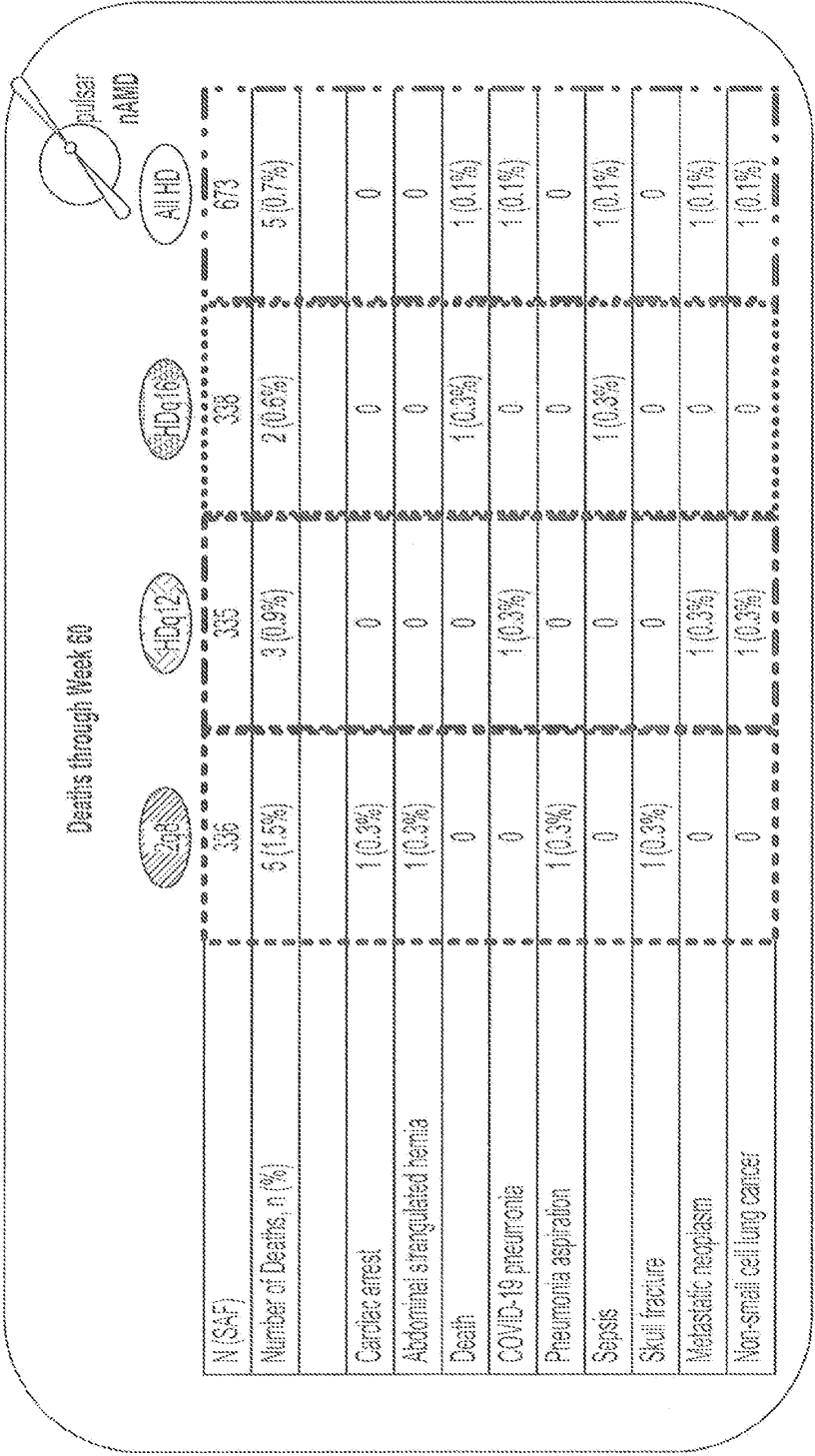


FIG. 70E

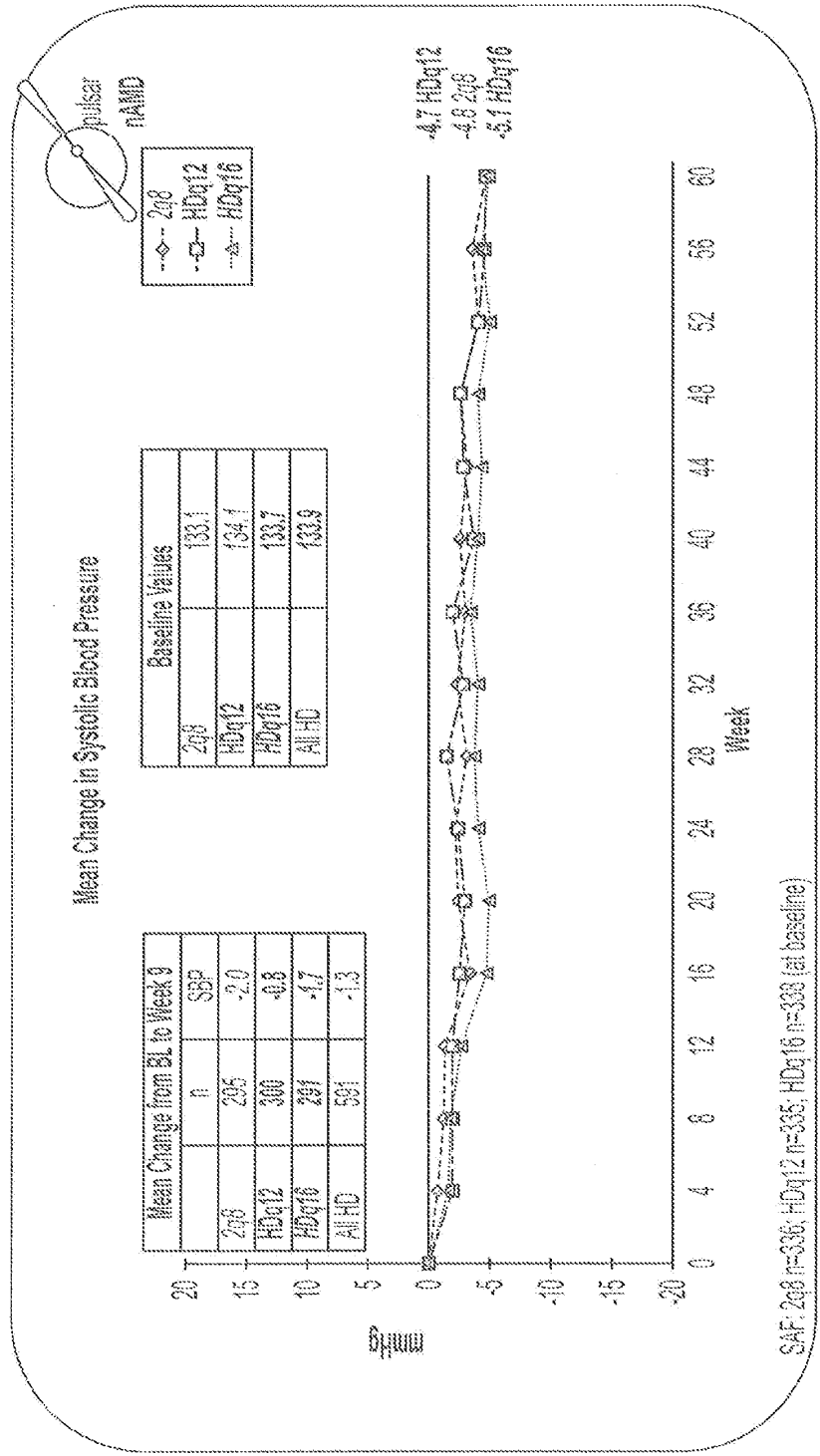


FIG. 70F

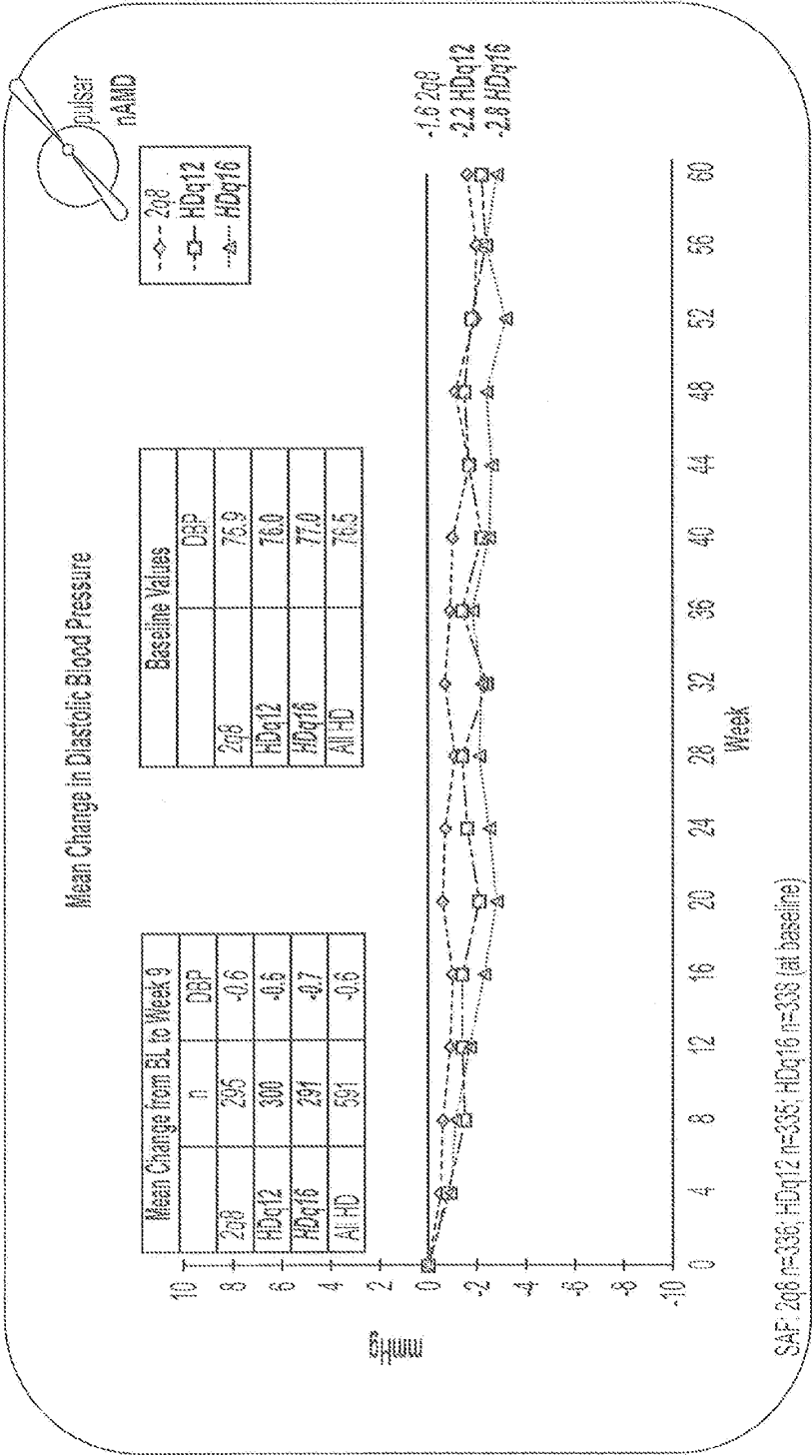


FIG. 70G

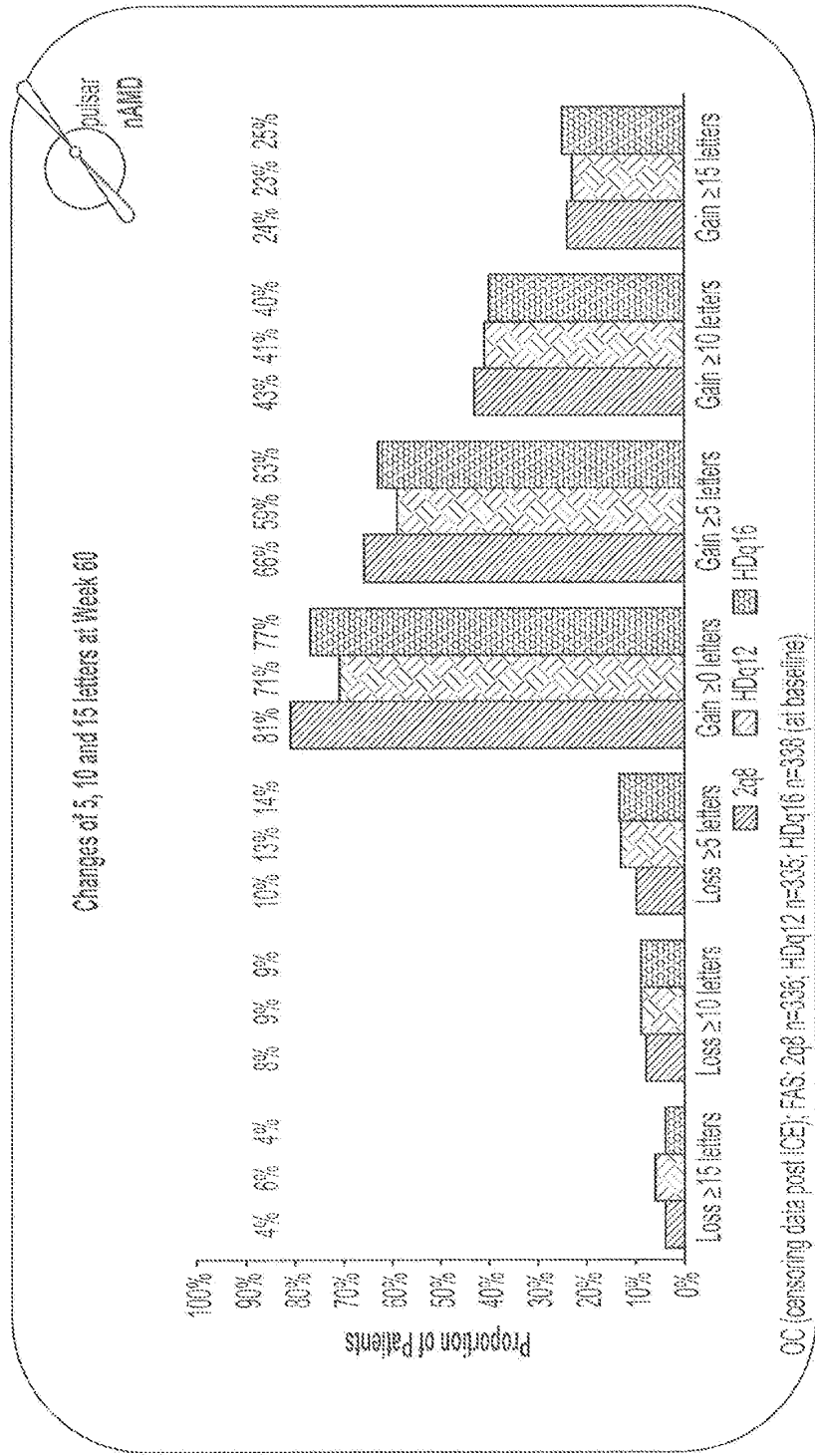


FIG. 71

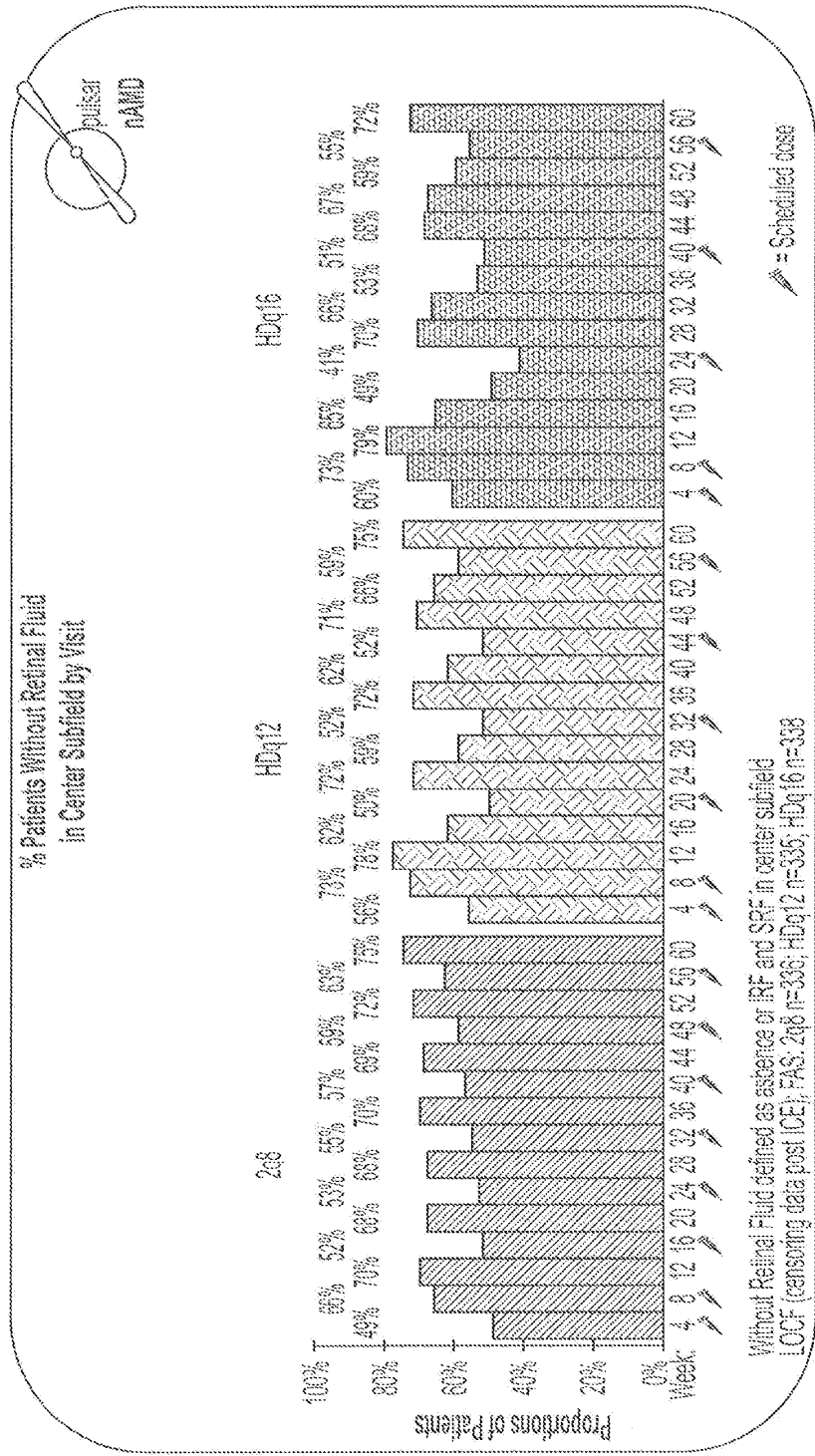


FIG. 72

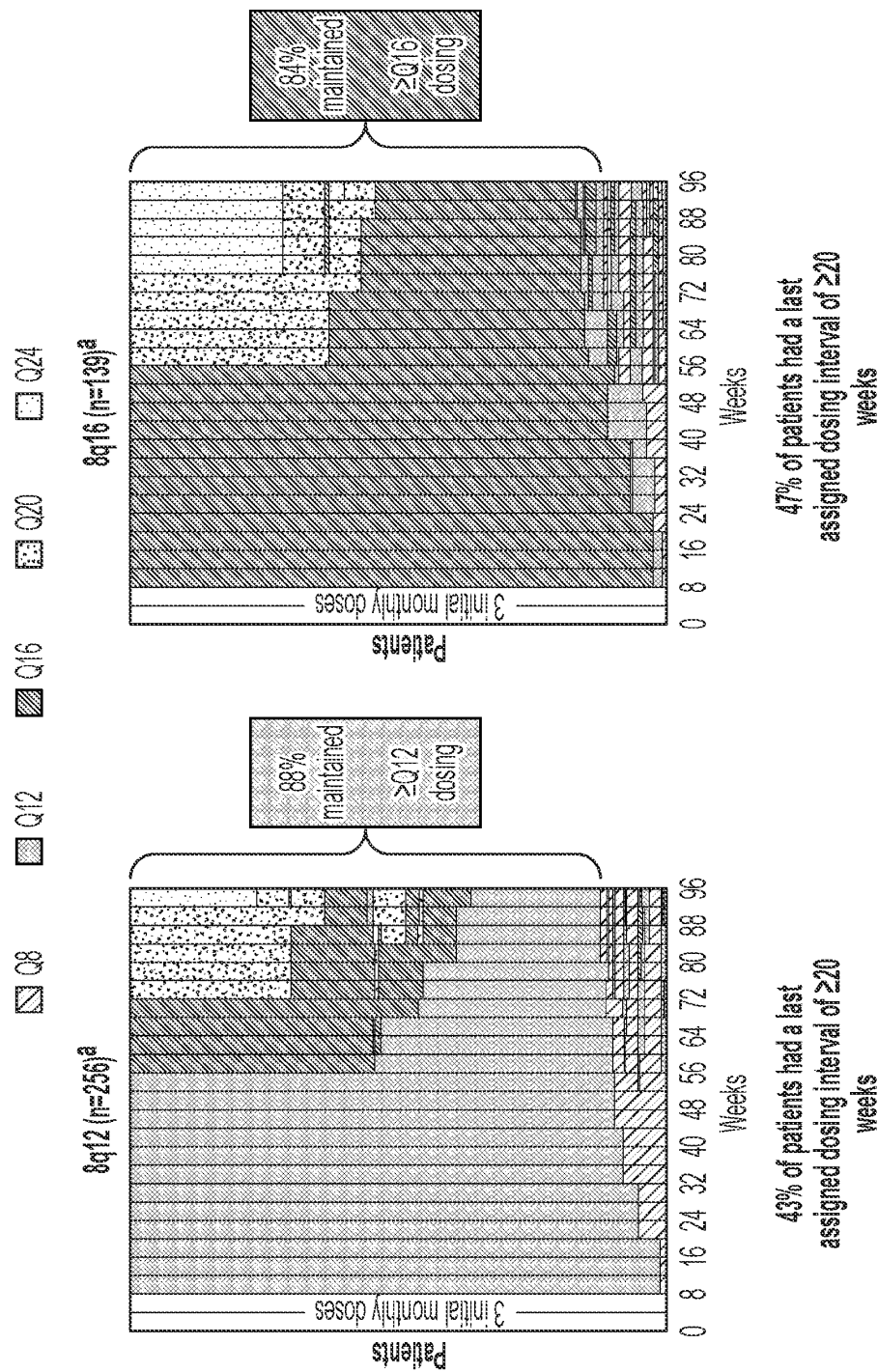


FIG. 73

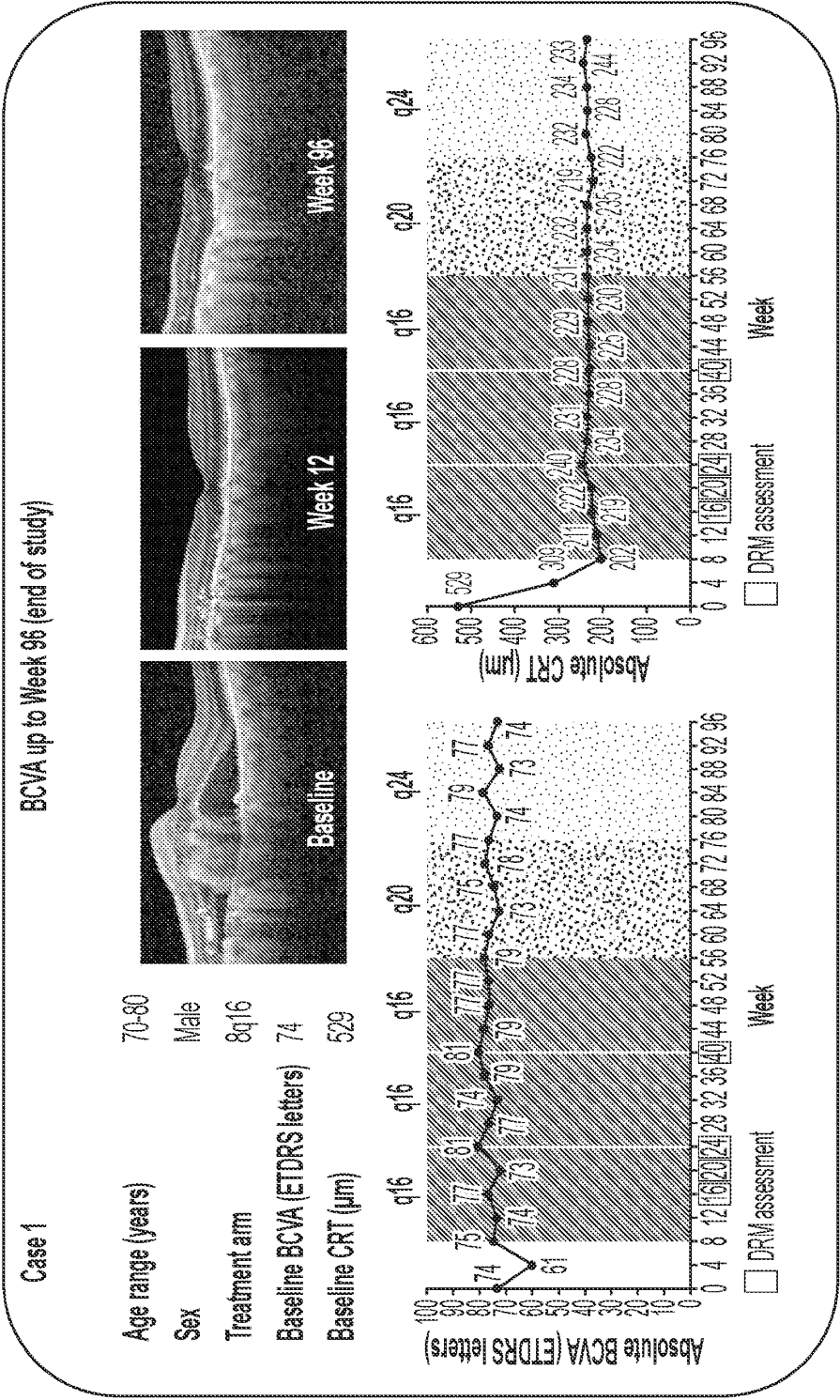


FIG. 74A

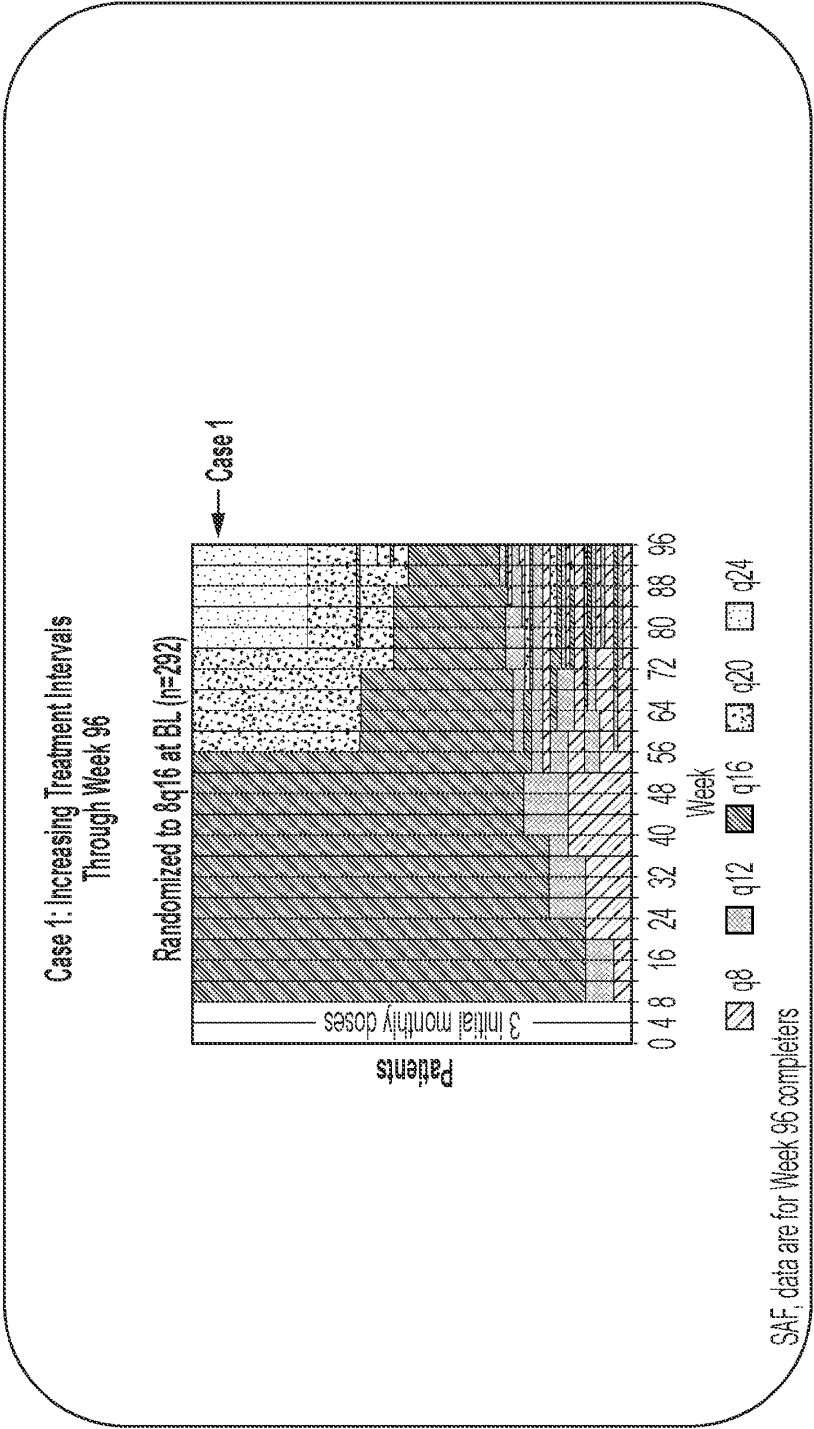


FIG. 74B

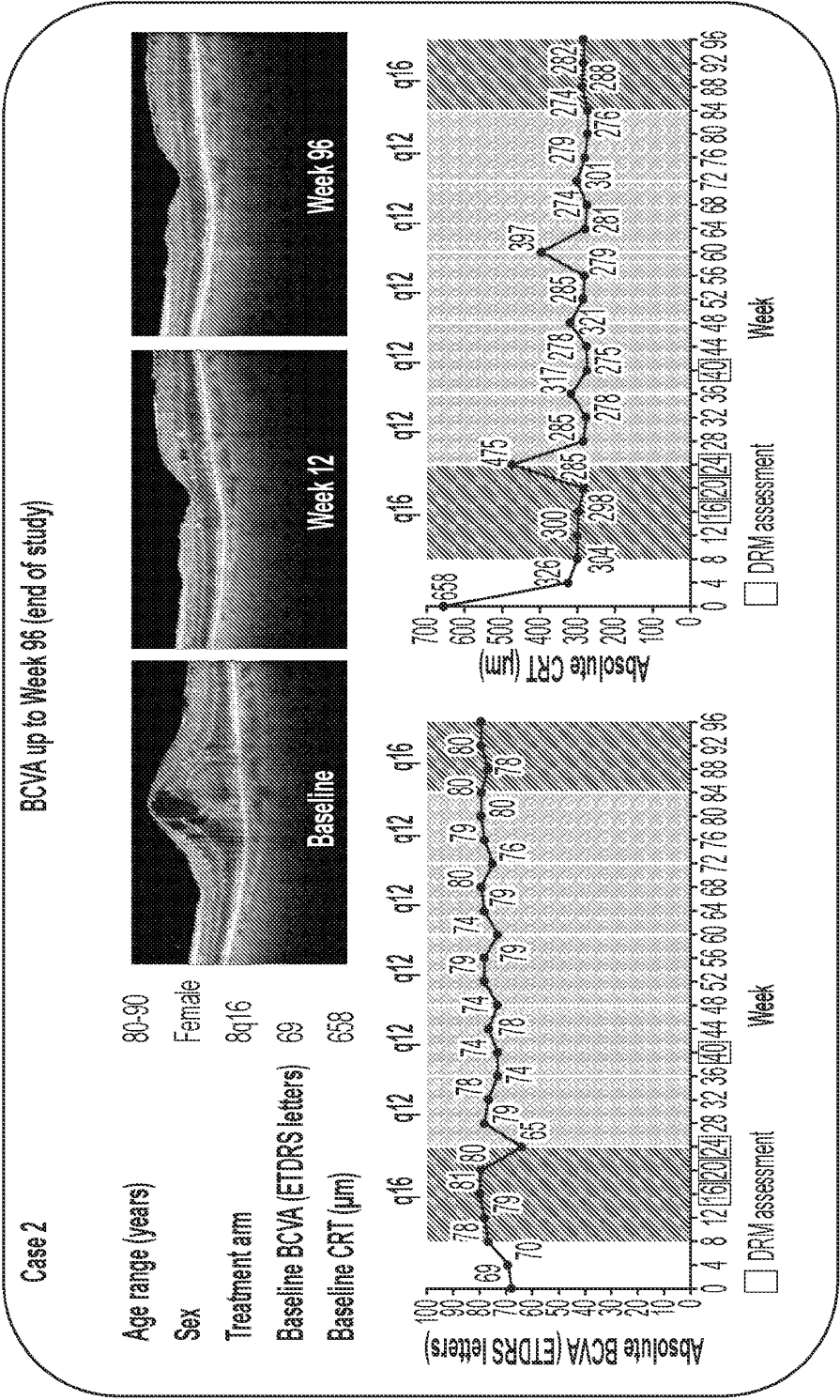


FIG. 75A

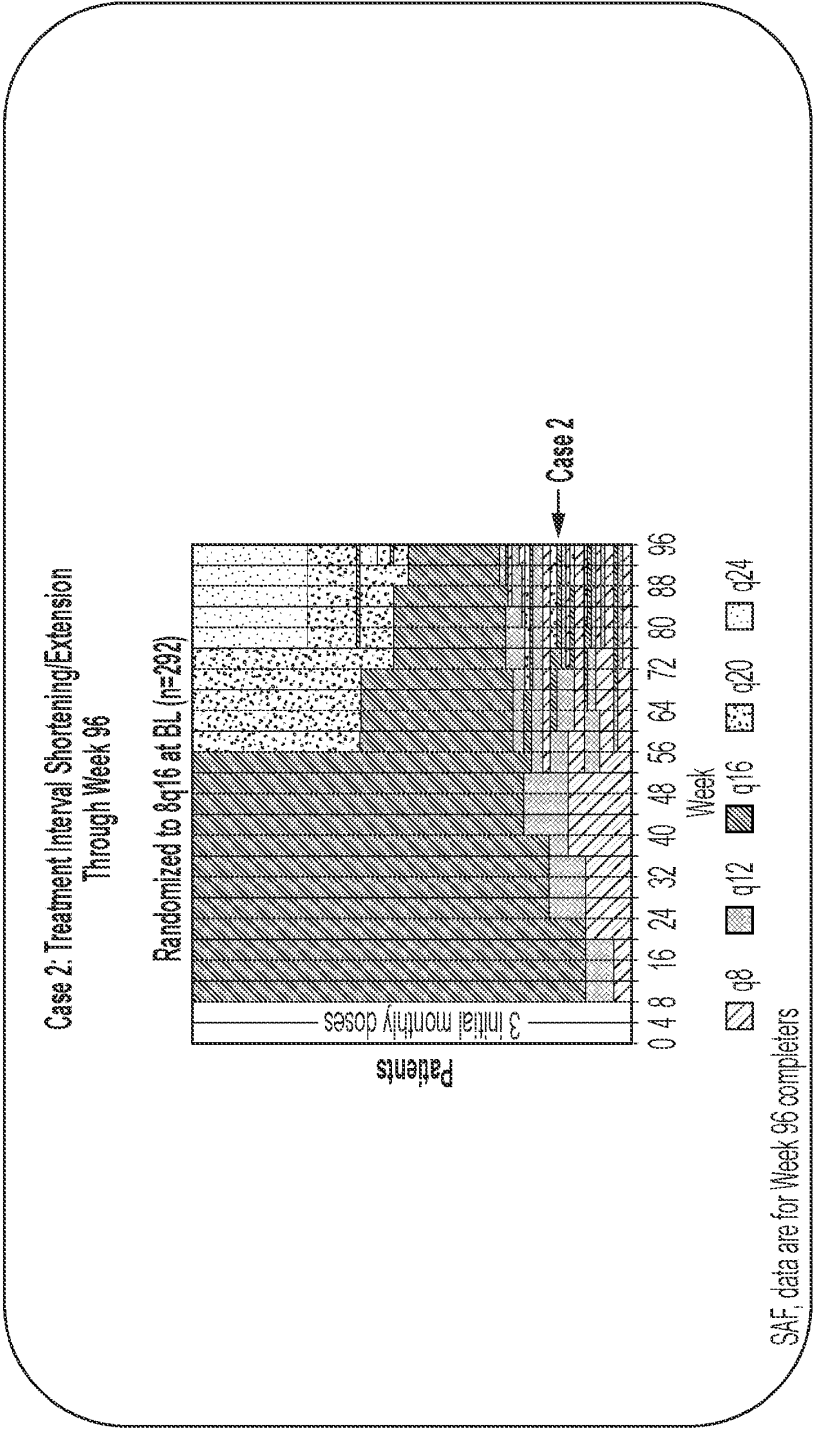


FIG. 75B

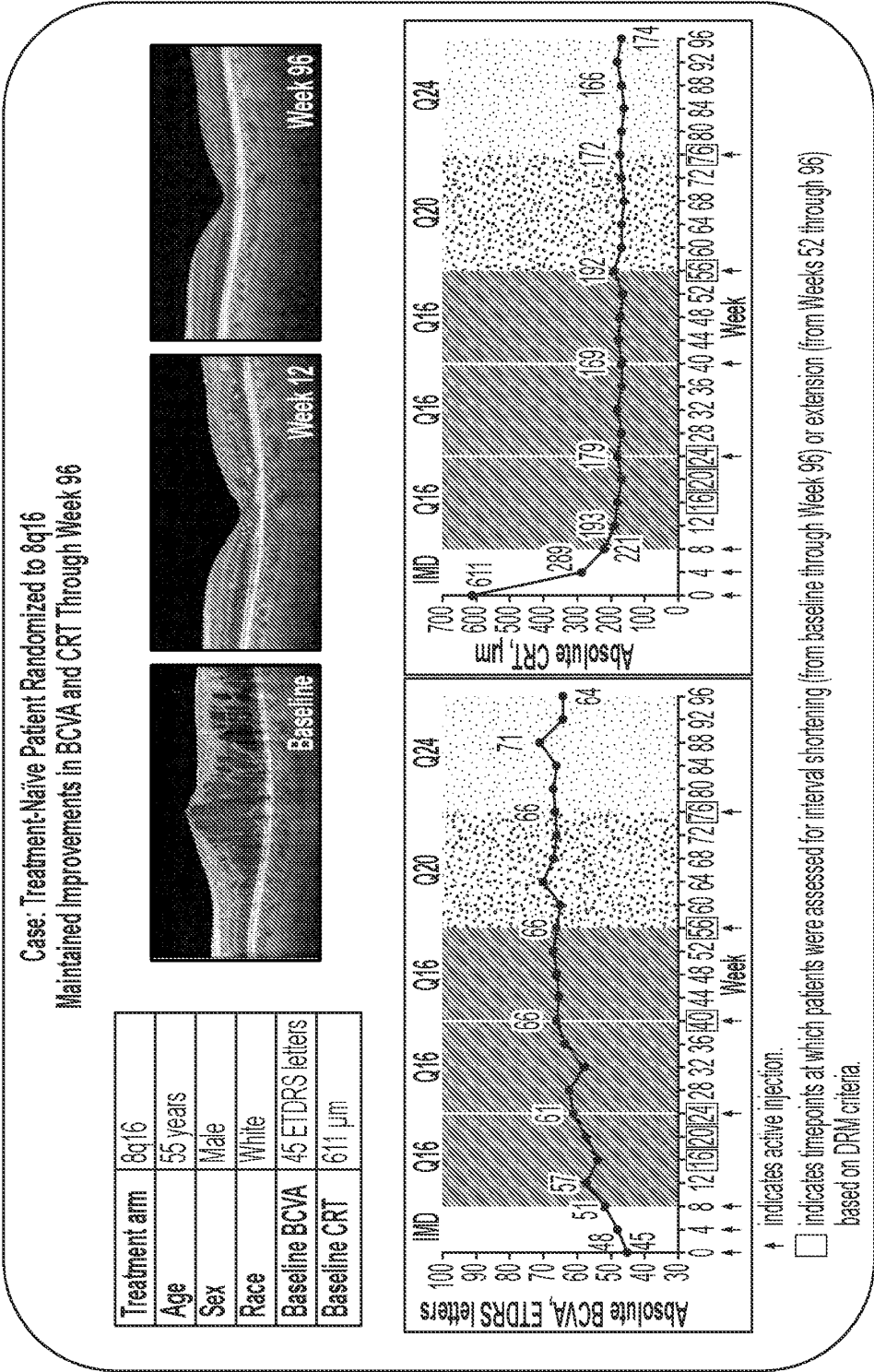


FIG. 76

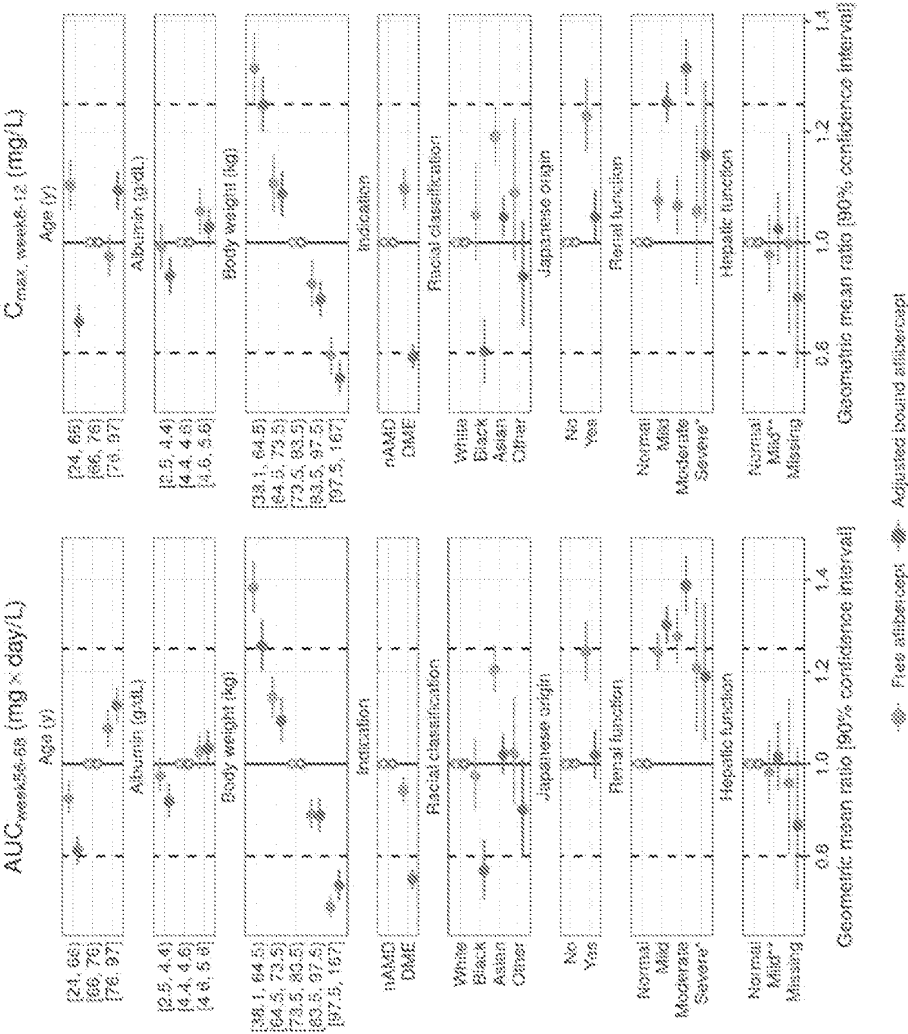


FIG. 77

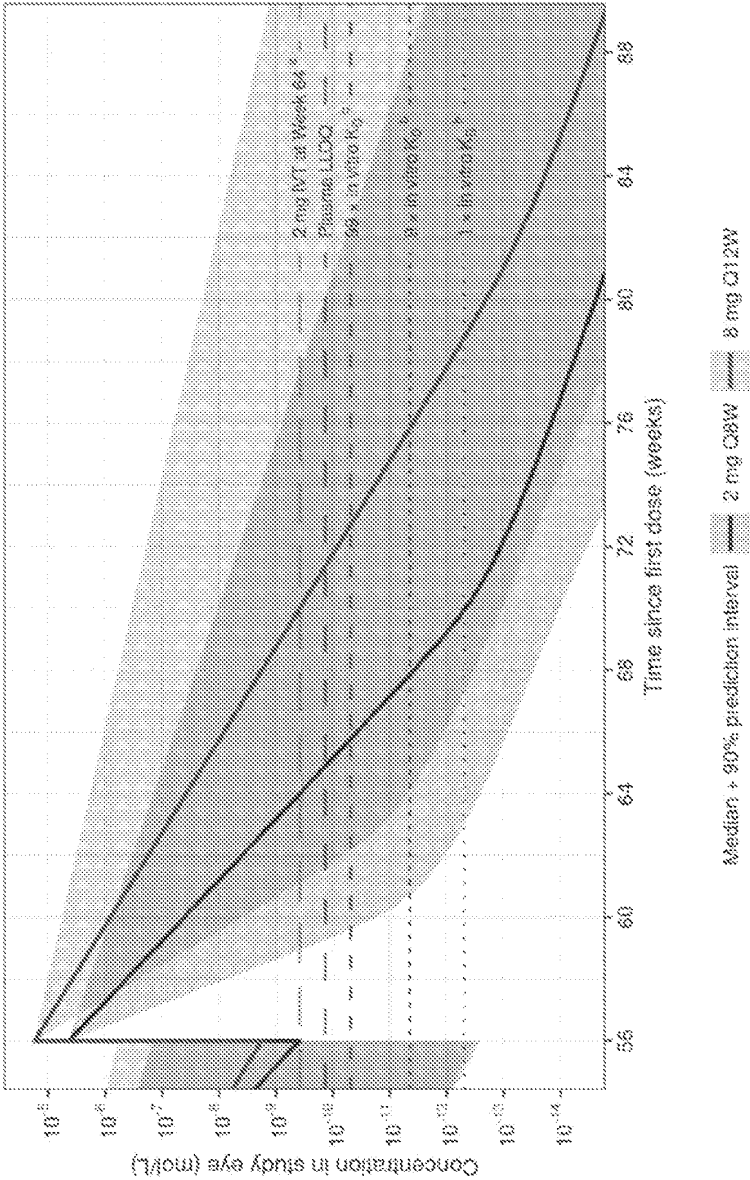


FIG. 78

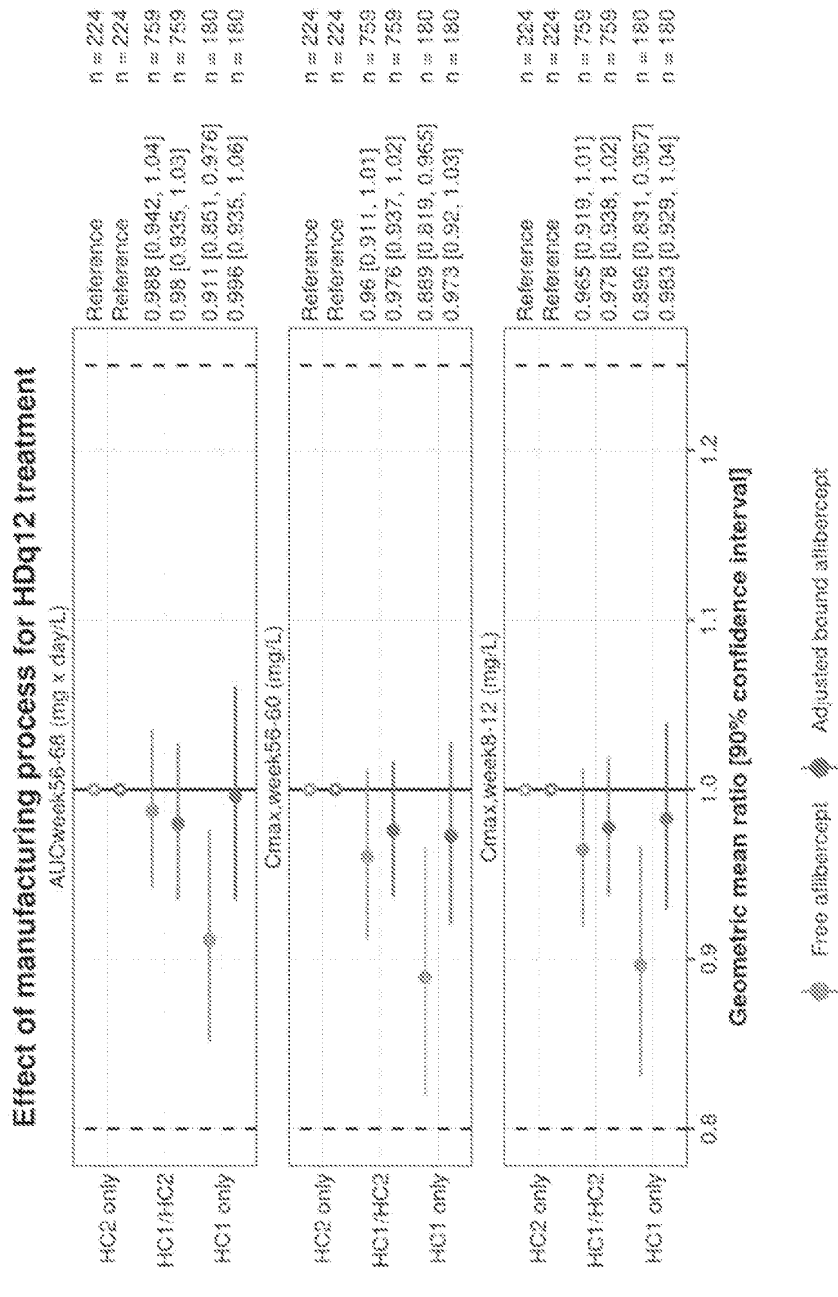
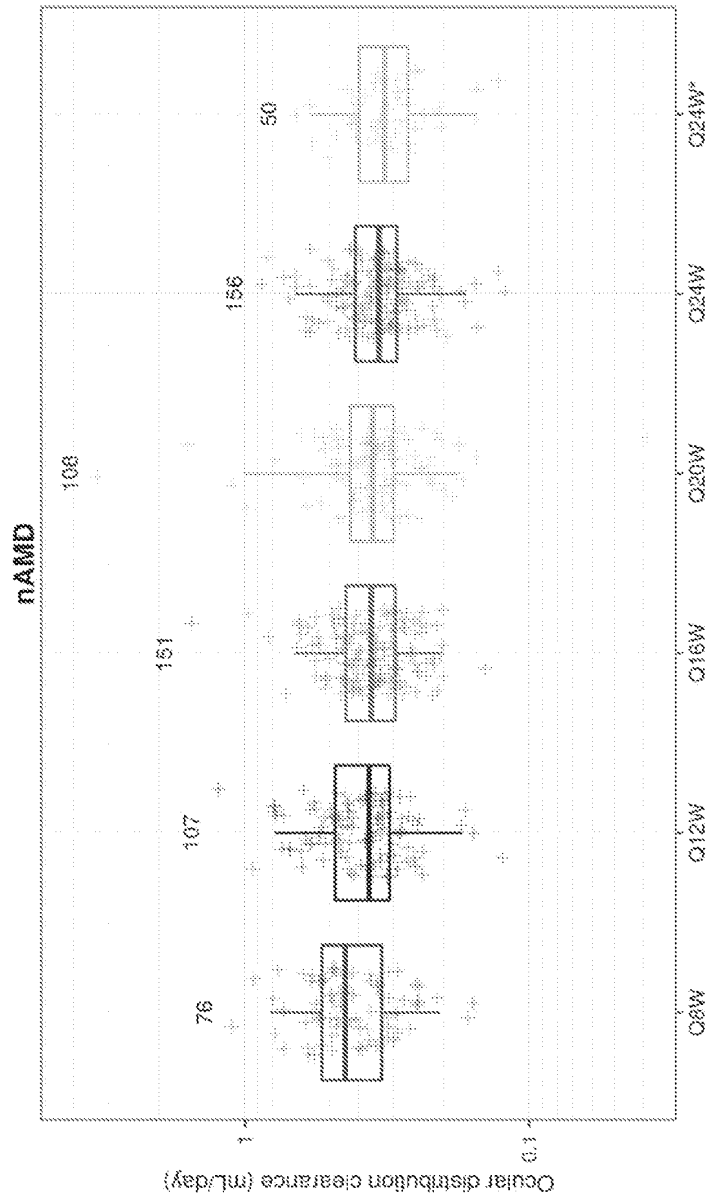
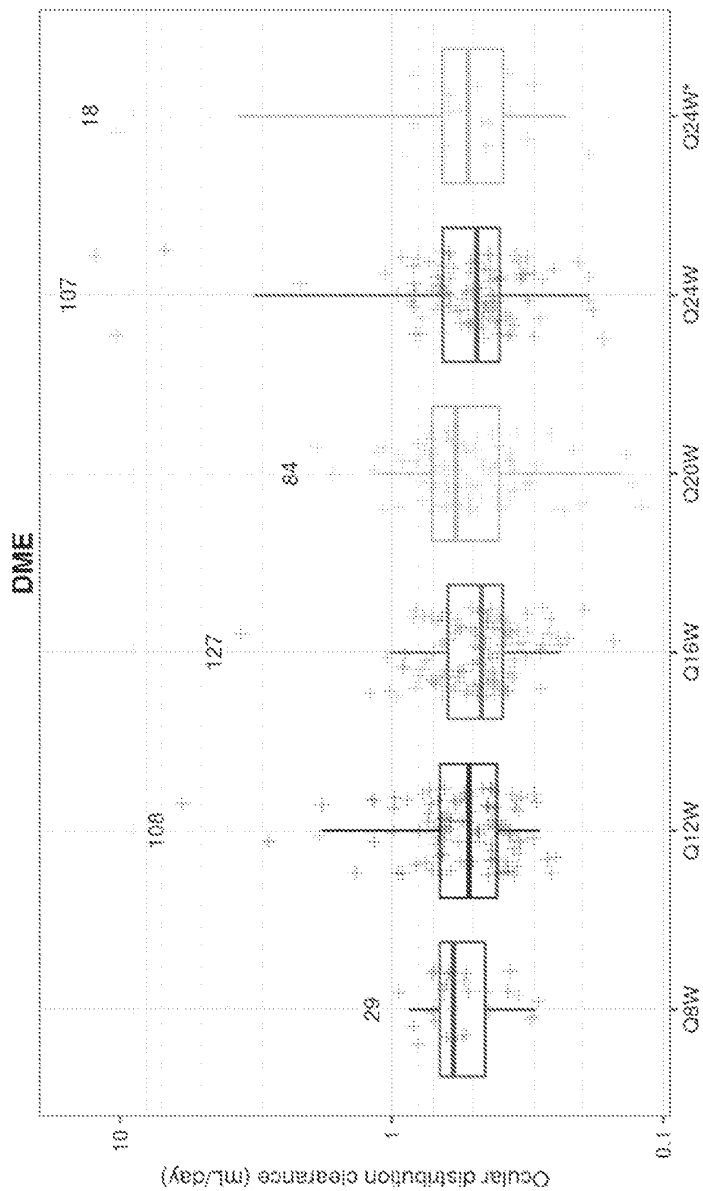


FIG. 79



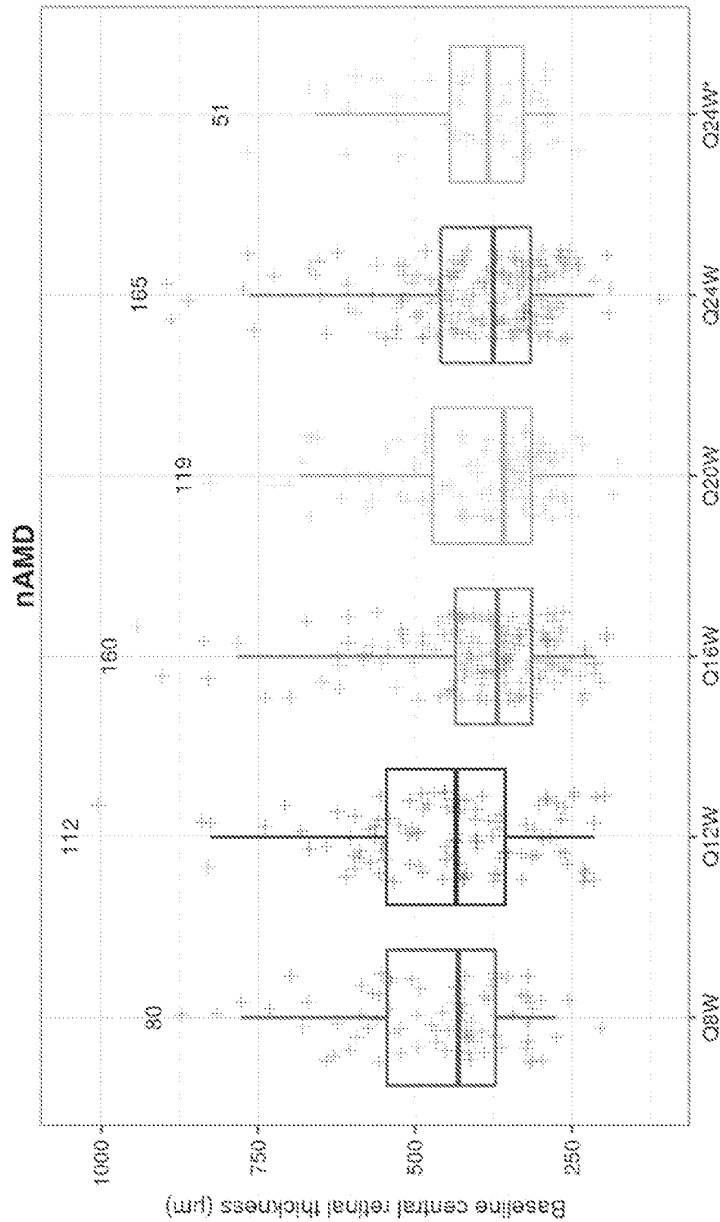
QxW = Every X weeks; nAMD = Neovascular age-related macular degeneration
Q24W* is a subset of the Q24W group and includes patients who were extended to and completed a 24-week interval without shortening. The boxes and whiskers delimit the interquartile range and 95% confidence interval of the data, respectively. The lines inside the boxes represent the medians. The number of data points associated with each group is shown above each box.

FIG. 80



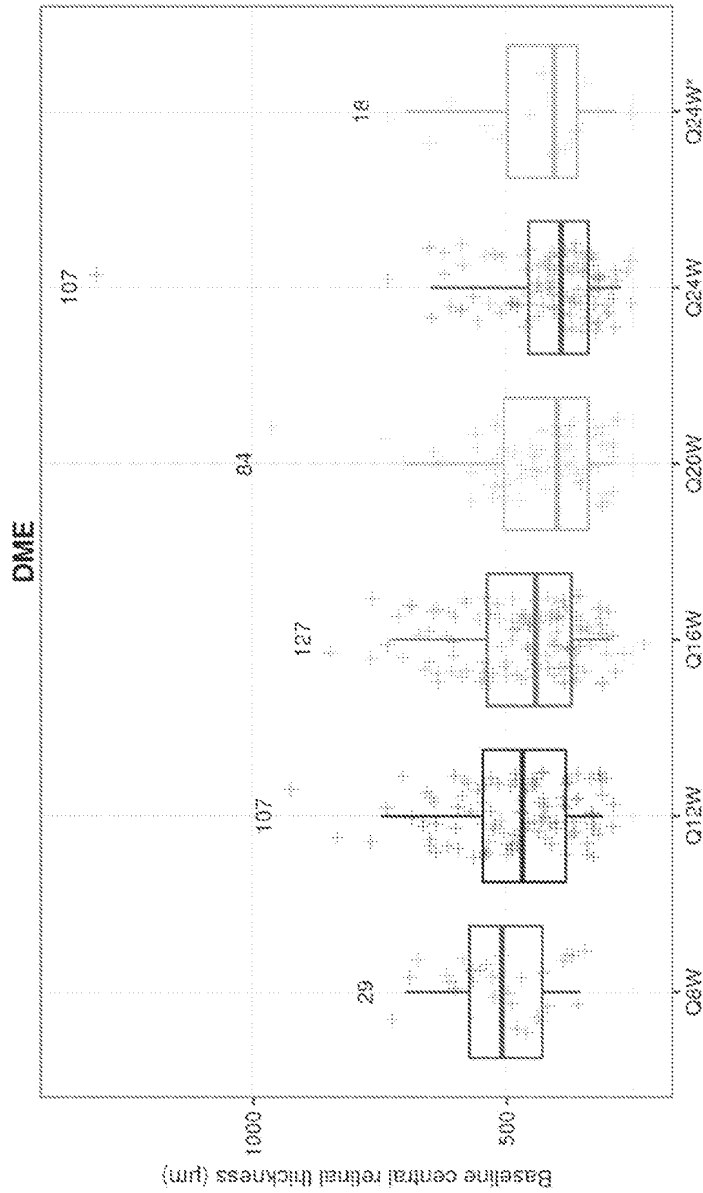
DME = Diabetic macular edema; QxW = Every X weeks
Q24W* is a subset of the Q24W group and includes patients who were extended to and completed a 24-week interval without shortening. The boxes and whiskers define the interquartile range and 95% confidence interval of the data, respectively. The lines inside the boxes represent the medians. The number of data points associated with each group is shown above each box.

FIG. 81



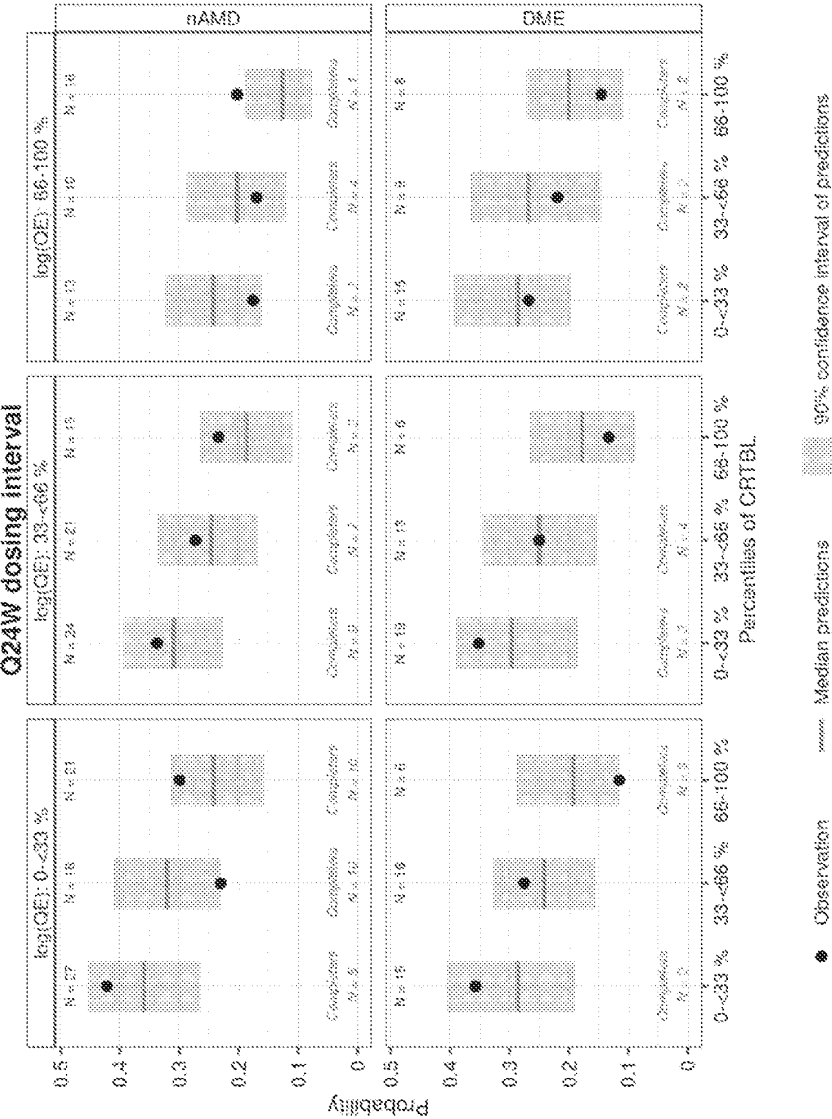
QxW = Every X weeks; nAMD = Neovascular age-related macular degeneration
Q24W* is a subset of the Q24W group and includes patients who were extended to and completed a 24-week interval without shortening. The boxes and whiskers delimit the interquartile range and 95% confidence interval of the data, respectively. The lines inside the boxes represent the medians. The number of data points associated with each group is shown above each box.

FIG. 82



DME = Diabetic macular edema. QxW = Every X weeks.
Q24W* is a subset of the Q24W group and includes patients who were extended to and completed a 24-week interval without shortening. The boxes and whiskers define the interquartile range and 95% confidence interval of the data, respectively. The lines inside the boxes represent the medians. The number of data points associated with each group is shown above each box.

FIG. 83



CRTBL = Baseline central retinal thickness; DME = Diabetic macular edema; N = Number of patients; nAMD = Neovascular age-related macular degeneration; OE = Ocular distribution clearance; QxW = Every X weeks
Probabilities are calculated across assigned dosing intervals within a disease population, tertile of OE, and tertile of CRTBL.
Limits of OE and CRTBL tertiles are specific to the nAMD and DME populations

FIG. 84

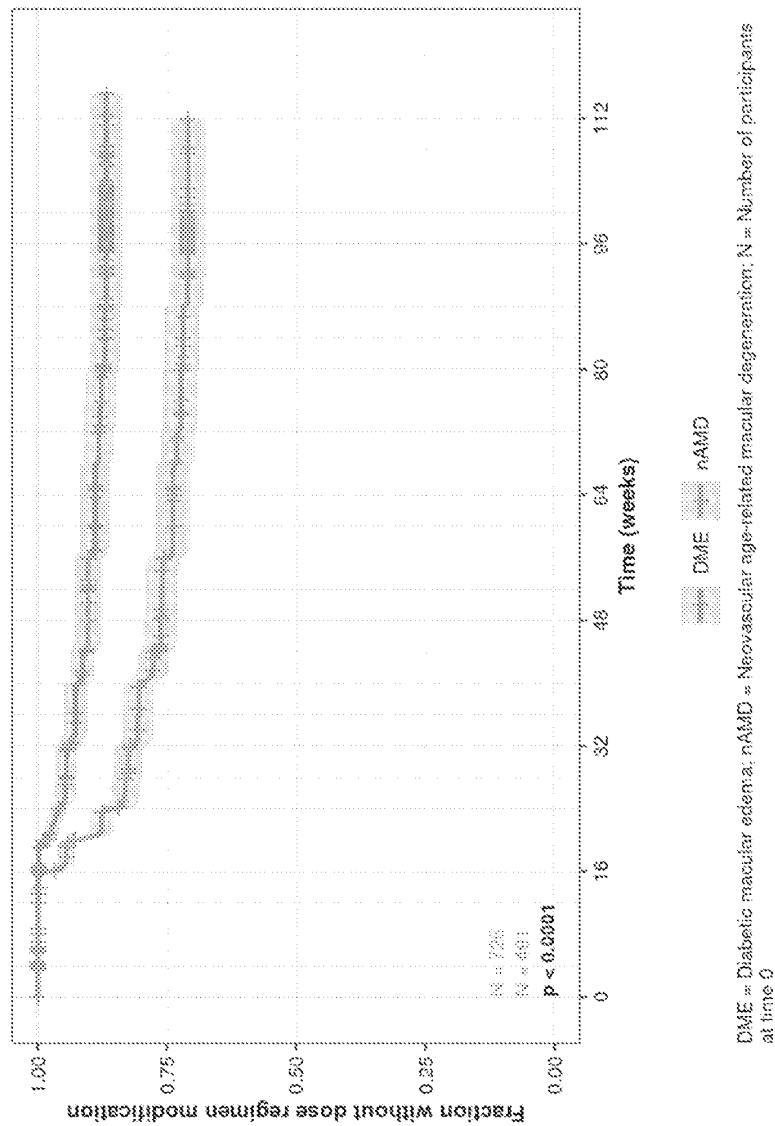


FIG. 85

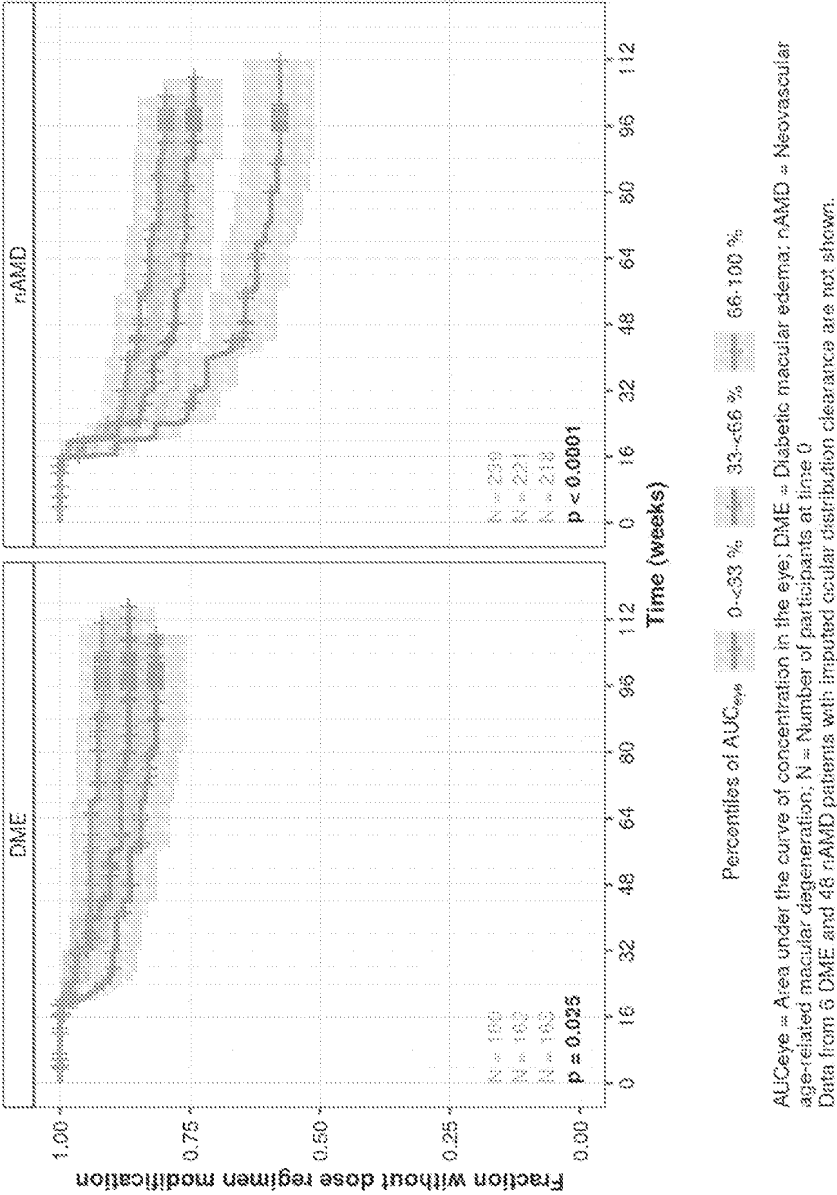


FIG. 86

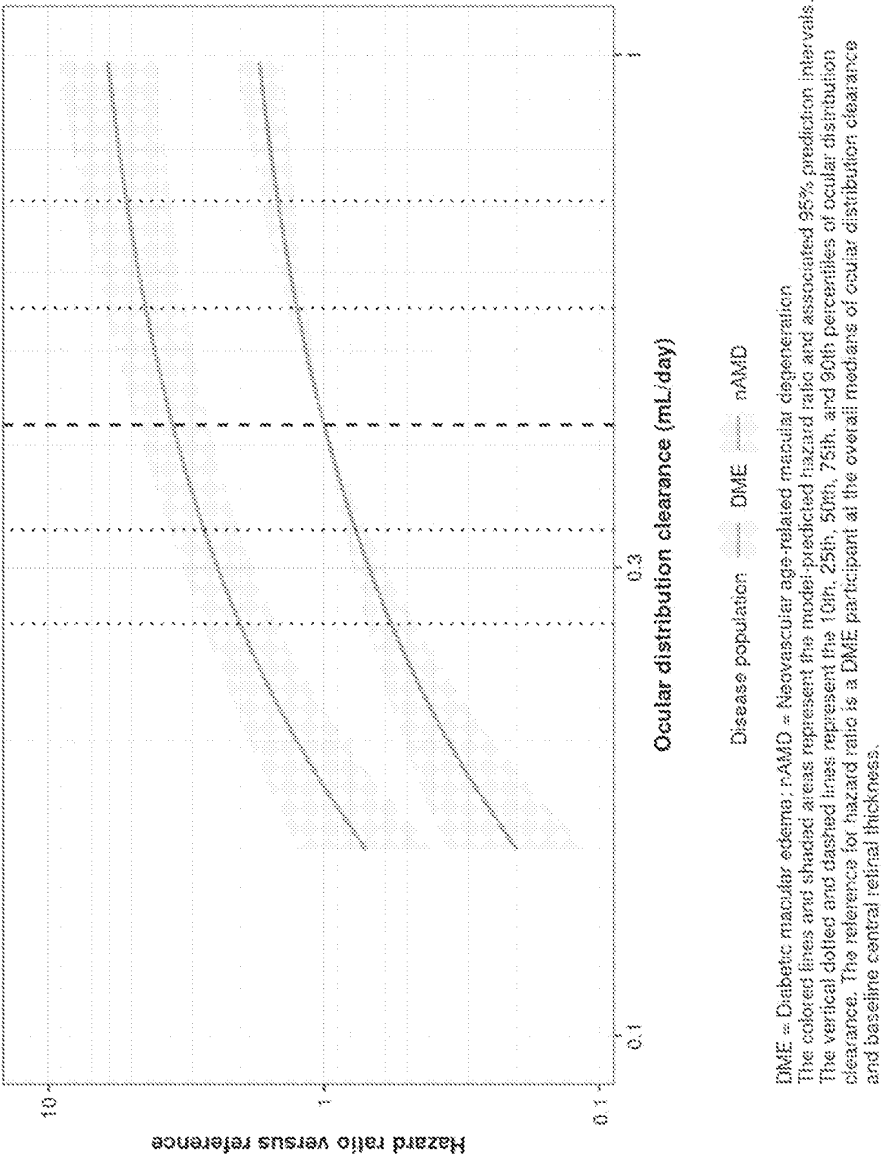


FIG. 87

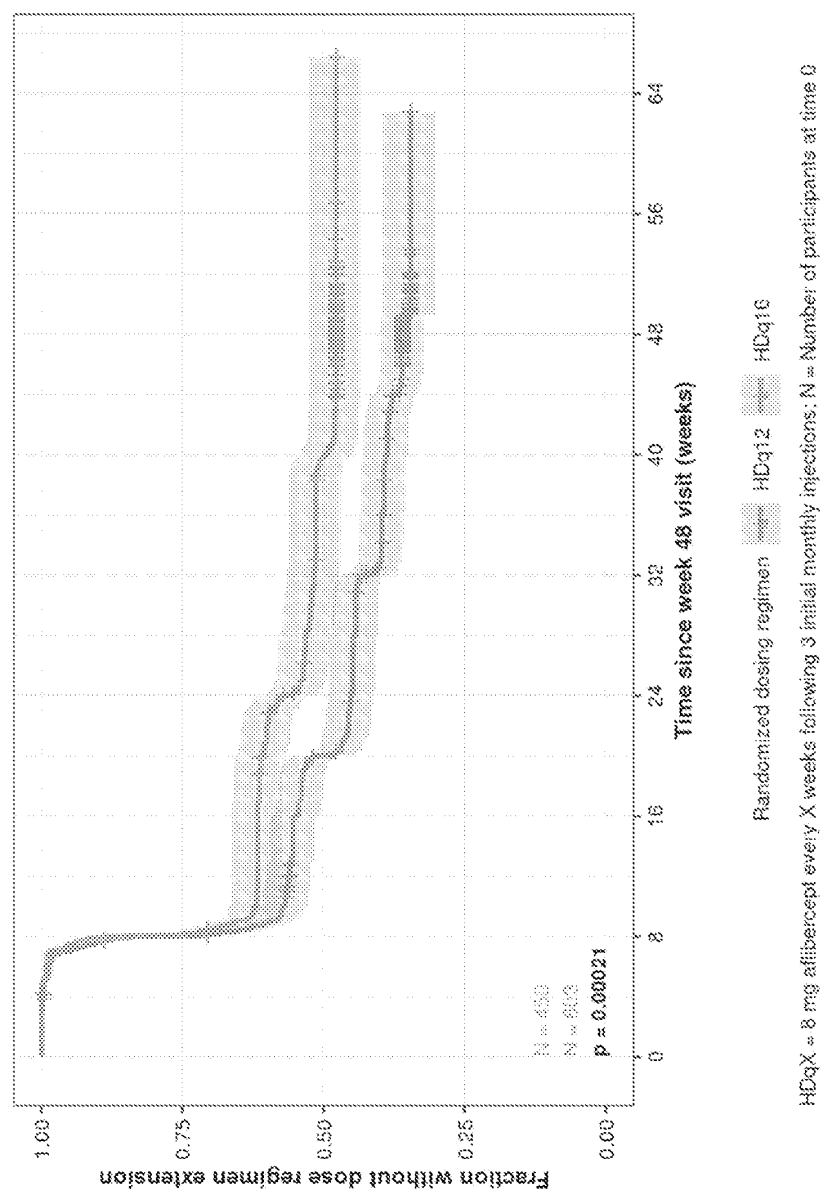


FIG. 88

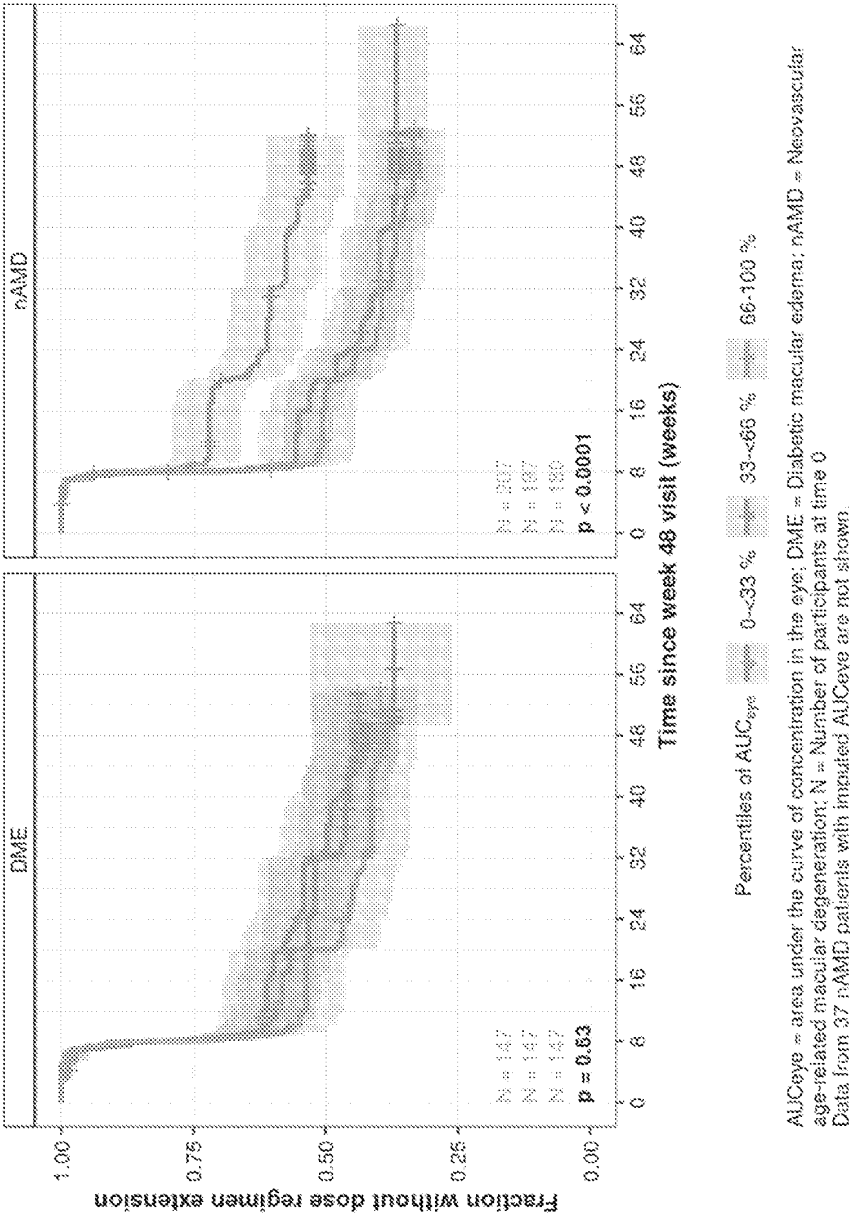
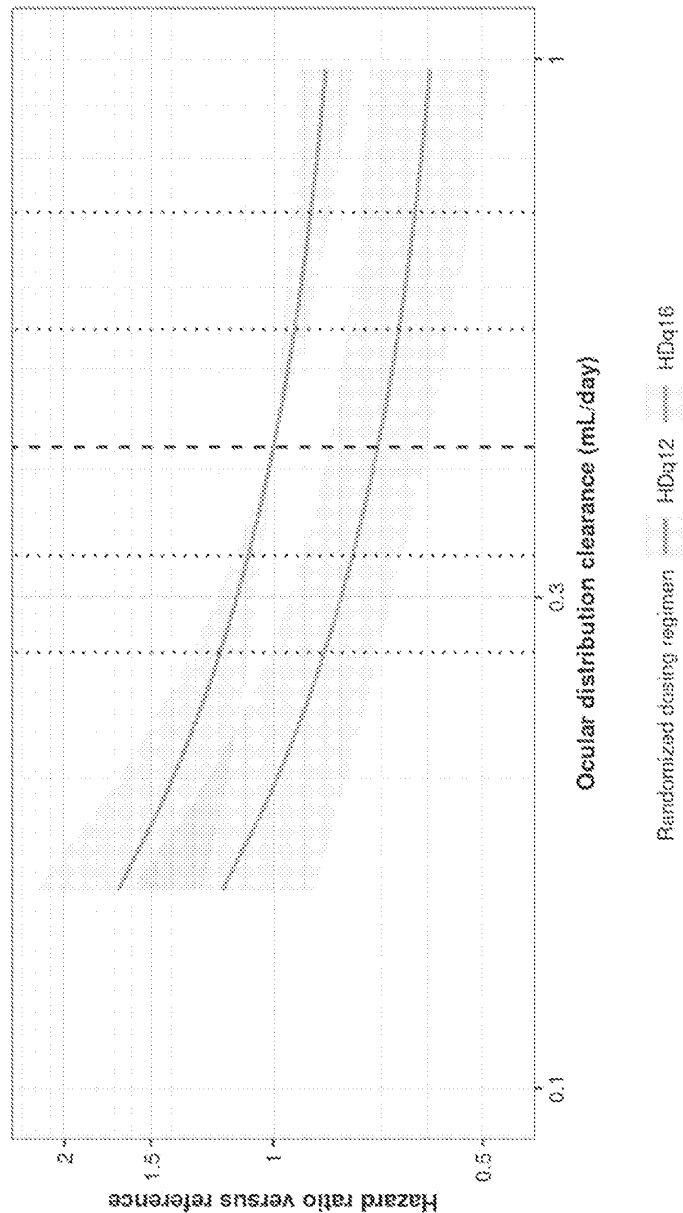
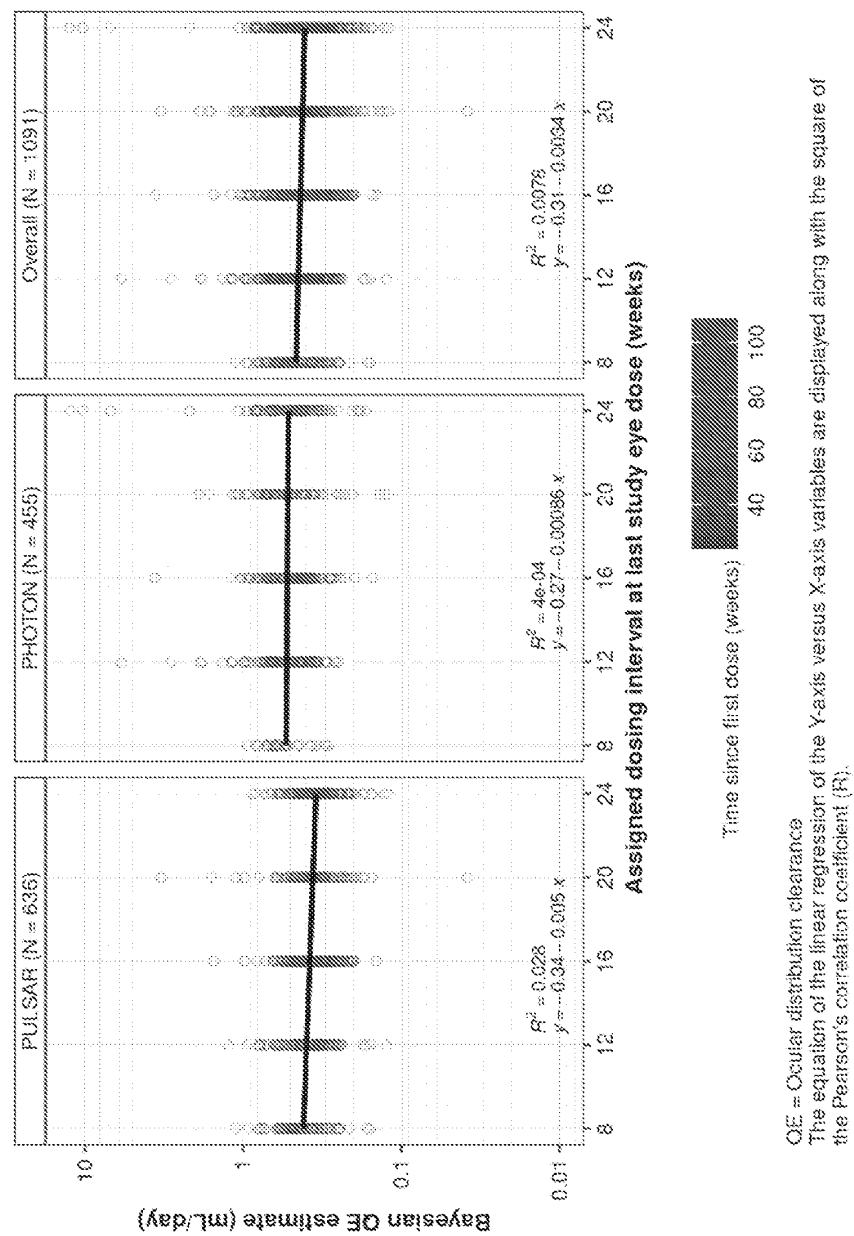


FIG. 89



HDqX = 8 mg aflibercept every X weeks following 3 initial monthly injections
The colored lines and shaded areas represent the model-predicted hazard ratio and associated 95% prediction intervals.
The vertical dotted and dashed lines represent the 10th, 25th, 50th, 75th, and 90th percentiles of ocular distribution clearance.
The reference for hazard ratio is a patient randomized to HDq12 and at the overall medians of ocular distribution clearance and baseline central retinal thickness.

FIG. 90



OE = Ocular distribution clearance
The equation of the linear regression of the Y-axis versus X-axis variables are displayed along with the square of the Pearson's correlation coefficient (R^2).

FIG. 91

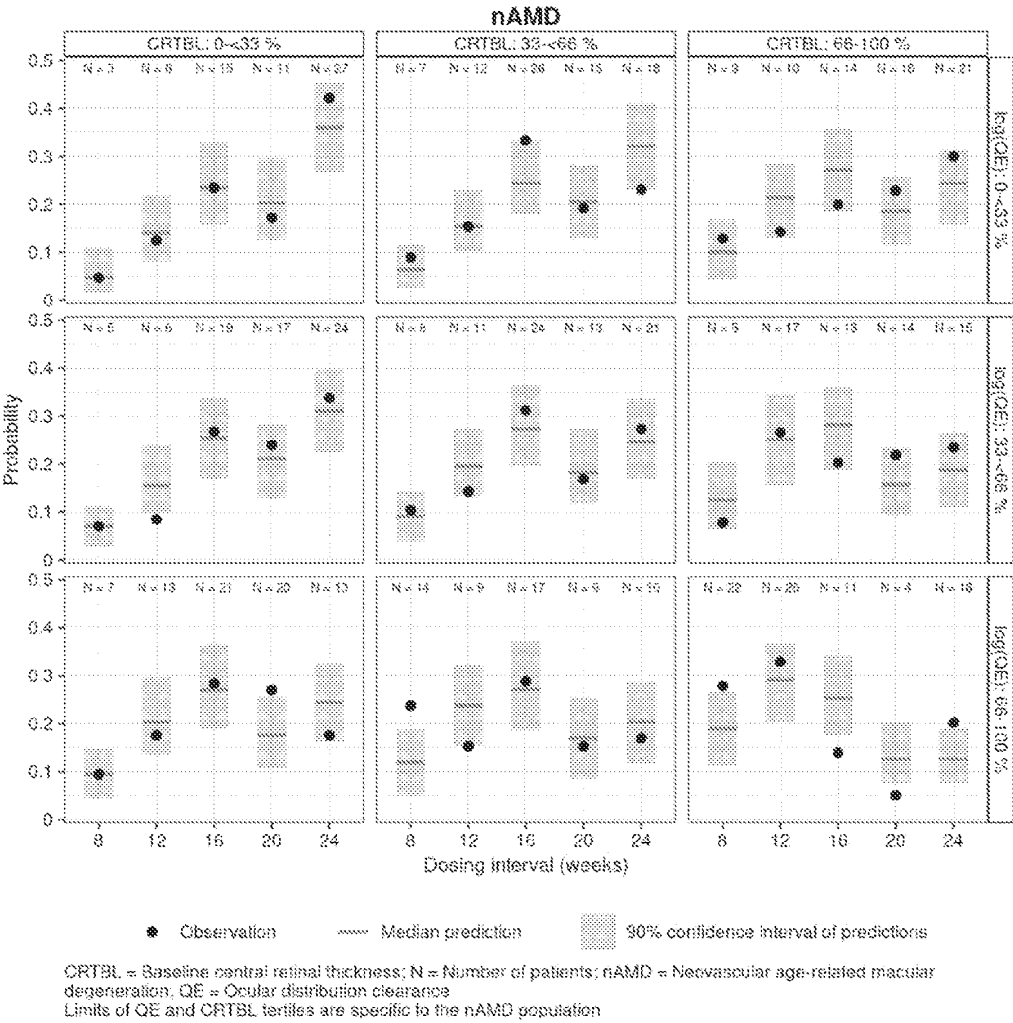


FIG. 92

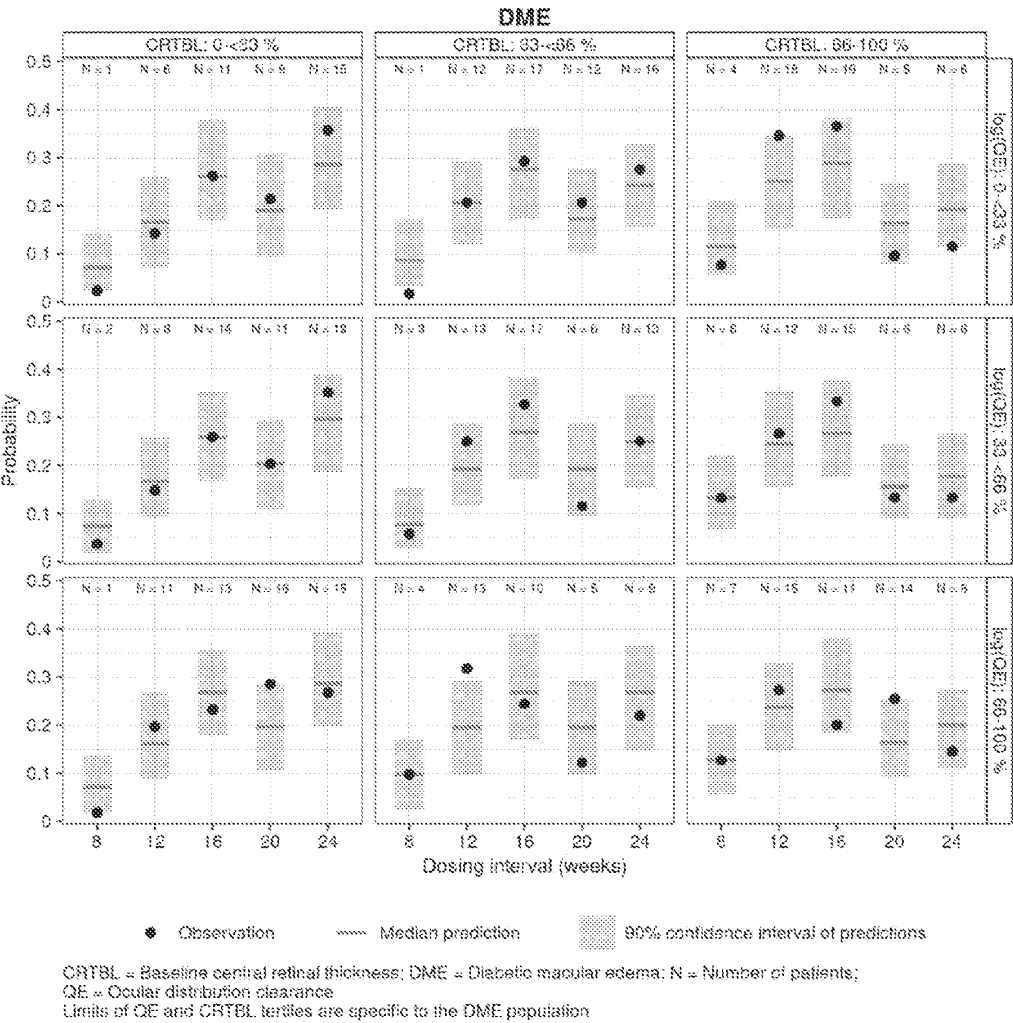


FIG. 93