INTREPID: INvestigating TREatments for the Prevention of secondary Injury and Disability following TBI

A Randomized, Double-Blind, Placebo-Controlled, Dose-Escalation Study of NNZ-2566 in Patients with Traumatic Brain Injury

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Disclosures

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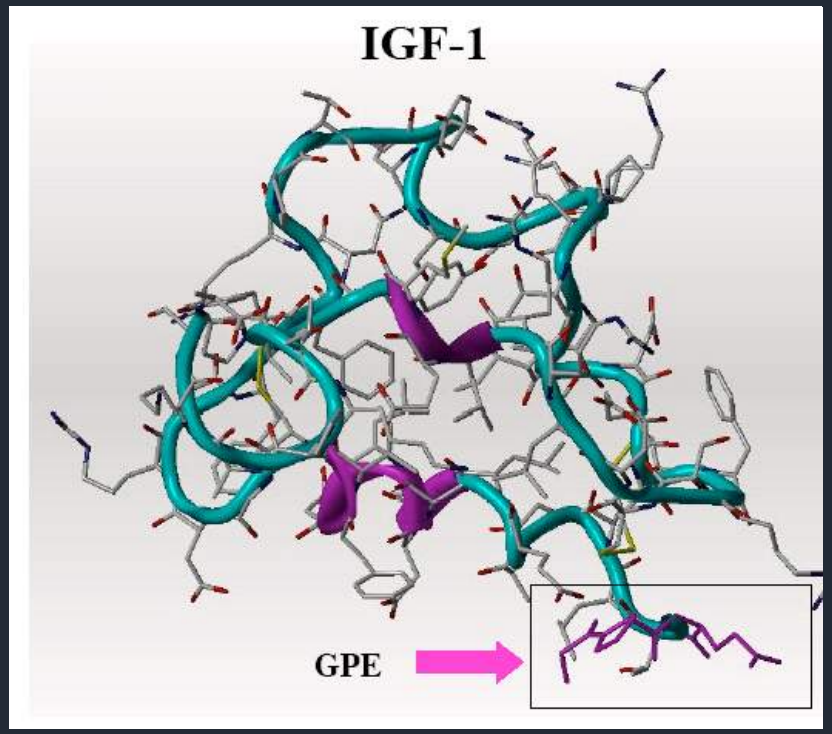
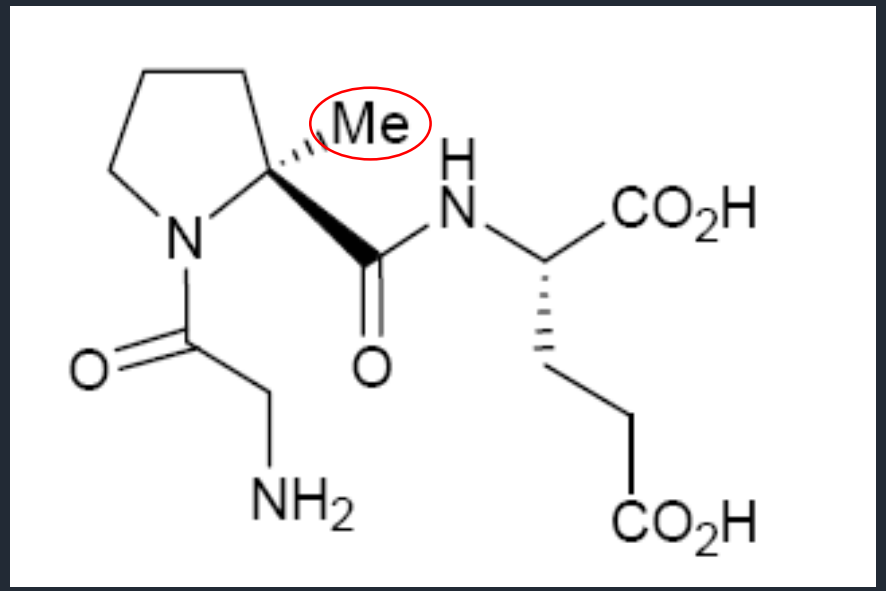
- Opinions, interpretations, conclusions and recommendations are those of the presenter and are not necessarily endorsed by the U.S. Army.

- The presenter is an officer, director and shareholder of Neuren Pharmaceuticals Ltd.

Trofinetide (NNZ-2566)





Primary and Secondary Objectives

- Primary: Evaluate safety and tolerability
  - AEs through 1 month (4-6 wks) or discharge
  - SAEs through 3 months (12-14 wks)
  - C-SSRS: Suicidality assessed at discharge or at 1 and 3 months using the Columbia Suicide Severity Rating Scale
- Secondary: Explore biological activity/efficacy
  - GOS-E *(measure of global function)*
    Glasgow Outcome Scale – Extended
  - MPAI-4 *(measure of activities of daily living)*
    Mayo-Portland Adaptability Inventory – Version 4
  - SURVIVAL *(mortality)*
    at 1 month (4-6 wks) and 3 months (12-14 wks)

Exploratory Objectives

- Biologic Activity/Efficacy
  - Improvement in cognitive and neuropsychological functioning at 1 month (4-6 wks) and 3 months (12-14 wks):

TMT Trail Making Test	**Grooved Peg Board**	**CPT-II** Conner's Continuous Performance Test II
POMS Profile of Mood States	**RPSQ** Rivermead Post-concussion Symptoms Questionnaire	**RBANS** Repeatable Battery for the Assessment of Neuropsychological Status

  - Incidence of convulsive and non-convulsive seizures and epileptiform discharges through to Day 7
  - TBI biomarker (GFAP, UCH-L1) trajectories for the first 120 hrs post infusion

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Exploratory Objectives (continued)

- Pharmacokinetics (PK):
  - Blood concentration of NNZ-2566 in patients with TBI when administered as a 10 minute bolus followed by a 72 hour maintenance infusion at 1, 3 or 6 mg/kg/h

- Explore the relationship between PK and:
  - Biomarker trajectories (GFAP, UCH-L1)
  - Efficacy assessments
  - Safety/tolerability outcomes

Study Design & Dose Escalation

Cohort	N	Loading Dose	Maintenance Dose	Total Dose	Active: Placebo
1	30	20 mg/kg (10–minute infusion)	1 mg/kg/hr for 72 hr	92 mg/kg	2:1
--- DSMC Review ---					
2	30	20 mg/kg (10–minute infusion)	3 mg/kg/hr for 72 hr	236 mg/kg	2:1
--- DSMC Review ---					
3	200	20 mg/kg (10–minute infusion)	6 mg/kg/hr for 72 hr	452 mg/kg	2:1

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Composite Baseline Severity Score (CBSS)

- TBI clinical outcomes are associated with severity of patient condition at baseline as measured by various parameters predictive of outcomes.
- Baseline measures are not available for GOS-E and MPAI-4.
- CBSS was calculated as a composite of baseline predictors of GOS-E, MPAI-4 and Survival:
  - Biomarkers (GFAP and UCH-L1)
  - Injury Severity Score (ISS)
  - Pupil Reaction
  - Rotterdam Score
- Greater CBSS (between 0 and 1) corresponds to greater severity at baseline and higher risk of unfavorable outcome (GOS-E=1-4)
- Imbalance in ISS, GFAP etc. can still impact the outcome, but less than unadjusted

Analysis Populations

by Cohort & Treatment

Analysis Population	Cohort 1		Cohort 2		Cohort 3		All	
	Placebo	Active	Placebo	Active	Placebo	Active	Not Treated	Total
ITT	10 (100%)	20 (100%)	11 (100%)	17 (100%)	63 (100%)	130 (100%)	10	261 (100%)
mITT	10 (100%)	20 (100%)	11 (100%)	17 (100%)	63 (100%)	130 (100%)		251 (96%)
PA-GOSE	9 (90%)	19 (95%)	11 (100%)	17 (100%)	57 (90%)	114 (88%)		227 (87%)
PP-GOSE 3 months	9 (90%)	19 (95%)	11 (100%)	16 (94%)	54 (86%)	106 (82%)		215 (82%)
PA-MPAI	8 (80%)	19 (95%)	10 (91%)	15 (88%)	50 (79%)	97 (75%)		199 (75%)
PP-MPAI 3 months	8 (80%)	19 (95%)	10 (91%)	14 (82%)	44 (70%)	84 (65%)		179 (69%)

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Baseline Patient Characteristics: PA-GOSE

by Cohort & Treatment

	Cohort 1		Cohort 2		Cohort 3		
	Placebo	Active	Placebo	Active	Placebo	Active	Total
N	9	19	11	17	57	114	227
Sex: M	9 (100%)	19 (100%)	11 (100%)	17 (100%)	52 (91%)	92 (82%)	201 (89%)
F	0 (0%)	0 (0%)	0 (0%)	0 (0%)	5 (9%)	21 (18%)	26 (11%)
Age (yr)	24.19	39.68	35.10	28.85	33.29	36.24	34.70
Height (cm)	176.66	179.42	179.15	177.44	175.54	175.29	176.12
Weight (kg)	80.78	90.79	87.91	81.88	83.75	81.06	82.93
Ethnic.:Hispanic	3 (33%)	3 (16%)	2 (18%)	5 (29%)	10 (18%)	20 (18%)	43 (19%)
Not Hispanic	6 (67%)	16 (84%)	9 (82%)	12 (71%)	47 (82%)	94 (82%)	184 (81%)
Race:White	8 (89%)	10 (53%)	9 (82%)	15 (88%)	42 (74%)	88 (77%)	172 (76%)
Other	1 (11%)	9 (47%)	2 (18%)	2 (12%)	15 (26%)	26 (23%)	55 (24%)

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Baseline CBSS Components (PA-GOSE)

by Cohort & Treatment

		Cohort 1		Cohort 2		Cohort 3		
		Placebo	Active	Placebo	Active	Placebo	Active	Total
GCS	N	9	19	11	17	57	114	227
	Mean	7.0	7.8	6.4	6.8	7.6	7.0	7.2
	Median	7.0	8.0	6.0	7.0	7.0	7.0	7.0
GFAP	N	9	19	11	17	57	114	227
	Mean	7018.47	6576.72	9407.02	9564.11	7383.70	9756.41	8754.59
	Median	4905.20	4920.50	5974.60	5808.80	4291.60	4827.60	4920.50
UCH-L1	N	9	19	11	17	57	114	227
	Mean	988.76	1790.84	2600.73	1754.00	2028.94	2172.43	2046.95
	Median	743.50	1450.10	1339.70	957.55	1515.40	1539.10	1450.10
ISS	N	9	19	11	17	57	114	227
	Mean	19.4	23.6	26.9	21.4	22.9	26.2	24.6
	Median	17.0	22.0	26.0	22.0	22.0	25.0	24.0
Pupil	N	9	19	11	17	57	114	227
	Mean	2.1	1.6	2.5	1.9	1.5	2.0	1.9
	Median	1.0	1.0	3.0	1.0	1.0	1.0	1.0
Rotter.	N	9	19	11	17	57	114	227
	Mean	2.4	2.6	2.6	2.7	3.0	3.1	3.0
	Median	2.0	2.0	3.0	2.0	3.0	3.0	3.0
CBSS	N	9	19	11	17	57	114	227
	Mean	0.4133	0.4590	0.5411	0.4648	0.4897	0.5596	0.5198
	Median	0.3948	0.4799	0.5043	0.3875	0.5039	0.5389	0.5088

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Baseline CBSS Components (PA-MPAI)

by Cohort & Treatment

		Cohort 1		Cohort 2		Cohort 3		
		Placebo	Active	Placebo	Active	Placebo	Active	Total
GCS	N	8	19	10	15	50	97	199
	Mean	7.0	7.8	6.5	7.1	7.6	7.2	7.3
	Median	7.0	8.0	6.5	7.0	7.0	7.0	7.0
GFAP	N	8	19	10	15	50	97	199
	Mean	7608.29	6576.72	9844.16	5968.59	6802.55	8727.21	7841.51
	Median	4905.20	4920.50	7016.60	5783.70	4146.00	4466.90	4590.00
UCH-L1	N	8	19	10	15	50	97	199
	Mean	986.71	1790.84	2541.82	1106.66	1743.62	2032.45	1850.59
	Median	697.35	1450.10	1331.35	872.70	1351.10	1460.80	1323.00
ISS	N	8	19	10	15	50	97	199
	Mean	20.6	23.6	27.5	20.3	22.2	25.3	23.9
	Median	20.5	22.0	27.5	17.0	20.5	24.0	22.0
Pupil	N	8	19	10	15	50	97	199
	Mean	2.0	1.6	2.2	1.8	1.5	2.0	1.8
	Median	1.0	1.0	2.5	1.0	1.0	1.0	1.0
Rotter.	N	8	19	10	15	50	97	199
	Mean	2.5	2.6	2.7	2.3	3.0	2.9	2.8
	Median	2.0	2.0	3.0	2.0	3.0	3.0	3.0
CBSS	N	8	19	10	15	50	97	199
	Mean	0.4387	0.4590	0.5585	0.4042	0.4747	0.5290	0.4971
	Median	0.3985	0.4799	0.5781	0.3853	0.4968	0.5213	0.4991

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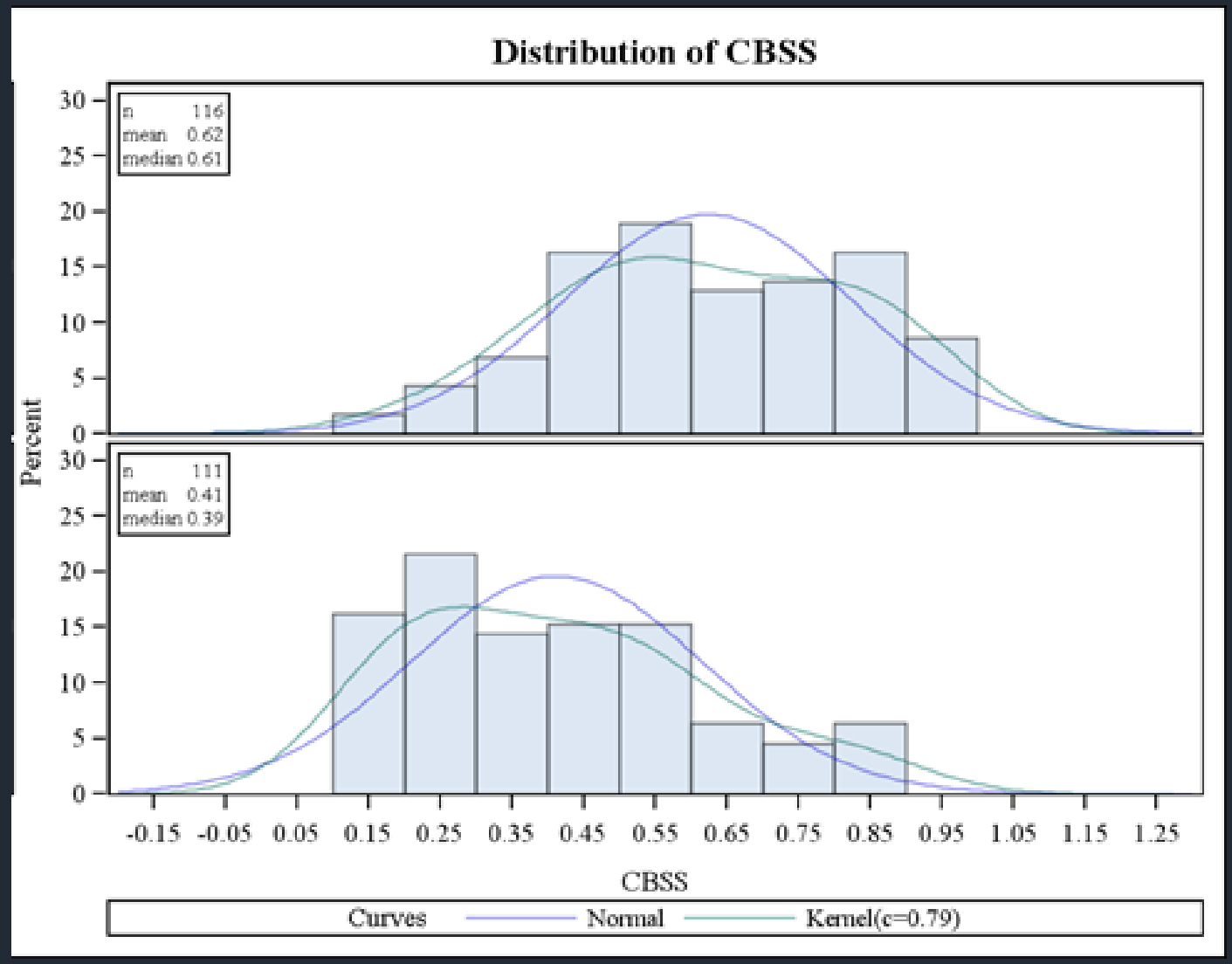
Baseline CBSS by Dichotomized 3 month GOS-E

(PA-GOSE)

GOS-E (1-4) Unfavorable

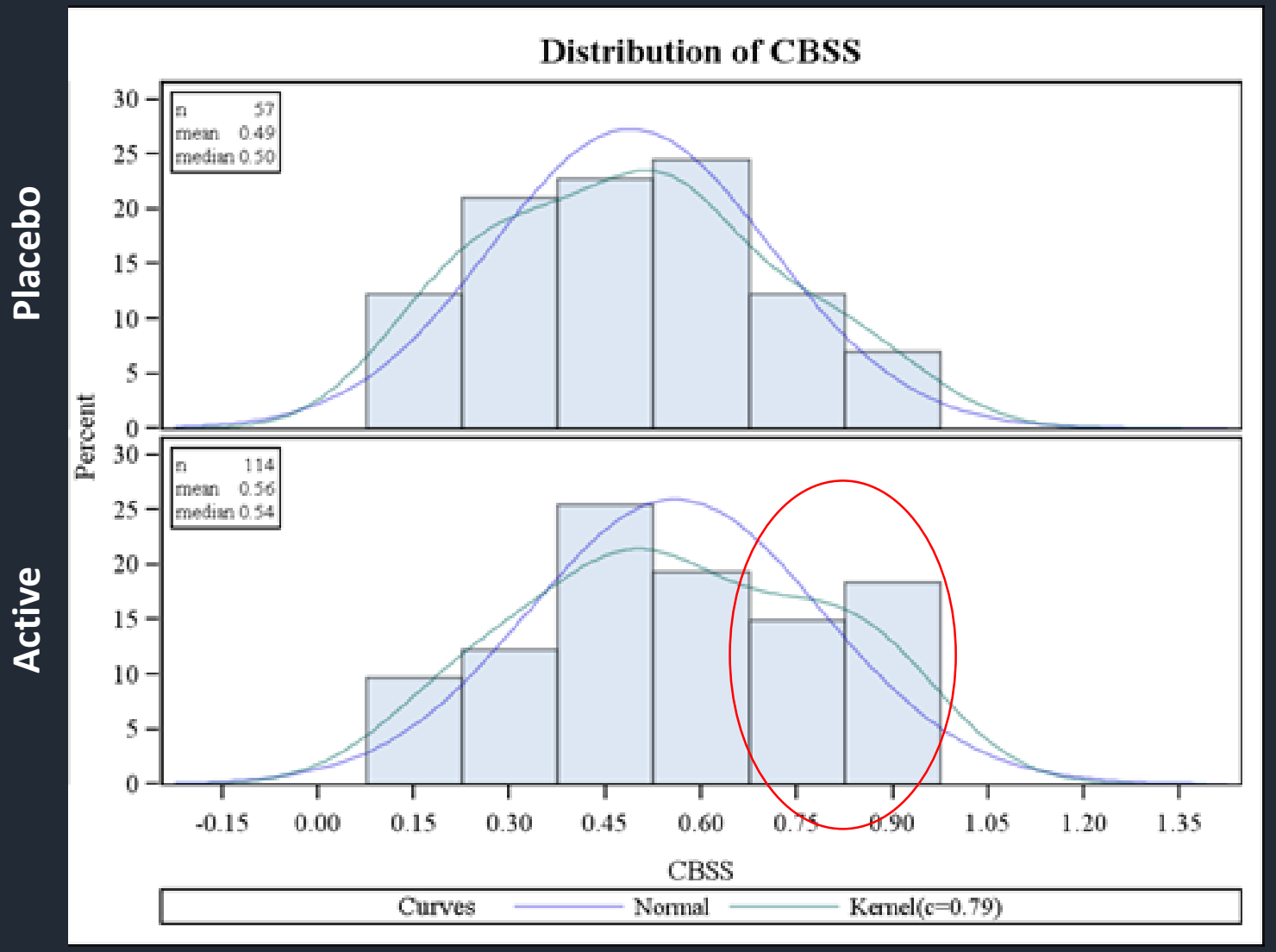
GOS-E (5-8) Favorable



Baseline CBSS by Treatment

Cohort 3

(PA-GOSE)



Summary of top-line safety and efficacy results

- No treatment-related or dose-dependent trends in adverse events or laboratory results
- No significant difference between active and placebo assessed by the 3 core efficacy measures: GOS-E, MPAI-4 and survival
  - Overall and within each Cohort
  - In sub-groups with CBSS below and above the median
- In Cohort 3, the sub-group with CBSS above the median, active was significantly better than placebo assessed by RBANS at 3 months

GOS-E, MPAI-4 and RBANS at 3 months

Primary Analysis Populations (PA) Cohort 3 Adjusted for CBSS

		GOS-E		MPAI-4		RBANS	
		Placebo	Active	Placebo	Active	Placebo	Active
CBSS ≤ median	N	32	56	29	51	27	44
	LSmean	5.6	5.4	23.0	31.6	81.5	81.0
	SE	0.38	0.29	5.33	4.01	2.55	2.00
	Median	6.0	6.0	20.0	33.0	79.0	80.0
	Min - Max	1 – 8	1 – 8	-30 – 142	-30 – 142	50 – 110	50 – 106
	p-value	*p=0.747*		*p=0.203*		*p=0.872*	
CBSS > median	N	25	58	20	43	12	31
	LSmean	3.9	3.9	46.8	41.7	71.6	84.0
	SE	0.46	0.29	6.33	4.30	3.71	2.31
	Median	3.0	3.0	43.0	37.0	73.0	82.0
	Min - Max	1 – 8	1 – 8	14 – 142	3 – 142	45 – 90	53 – 111
	p-value	*p=0.930*		*p=0.512*		*p=0.007*	

Incidence of Treatment Emergent AEs and SAEs

(ITT Population)

Treatment Emergent AEs

	Cohort 1		Cohort 2		Cohort 3		
	Placebo	Active	Placebo	Active	Placebo	Active	Total *
Reported at least one event	10 (100%)	20 (100%)	10 (91%)	15 (88%)	54 (86%)	102 (78%)	211 (81%)

Treatment Emergent SAEs

	Cohort 1		Cohort 2		Cohort 3		
	Placebo	Active	Placebo	Active	Placebo	Active	Total *
Reported at least one event	2 (20%)	5 (25%)	2 (18%)	4 (24%)	20 (32%)	42 (32%)	75 (29%)

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Incidence of Out of Range ECG Parameters

(ITT Population)

	Cohort 1		Cohort 2		Cohort 3		
QTc>450ms	**Placebo**	**Active**	**Placebo**	**Active**	**Placebo**	**Active**	**Total ***
Screening	**0**	**1** (5%)	**0**	**0**	**1** (2%)	**0**	**3** (1%)
QTc>480ms							
Day 1-2					**1** (2%)	**2** (2%)	**3** (1%)
Day 2-3					**1** (2%)	**1** (<1%)	**2** (<1%)
Day 3-4					**1** (2%)	**4** (3%)	**5** (2%)
Day 4					**1** (2%)	**3** (2%)	**4** (2%)
Abnormal ECG							
Screening	**4** (40%)	**7** (35%)	**4** (36%)	**7** (41%)	**32** (51%)	**61** (47%)	**119** (46%)
Day 1-2					**25** (40%)	**67** (52%)	**92** (35%)
Day 2-3					**32** (51%)	**66** (51%)	**98** (38%)
Day 3-4					**36** (57%)	**67** (52%)	**103** (39%)
Day 4					**33** (52%)	**57** (44%)	**90** (34%)

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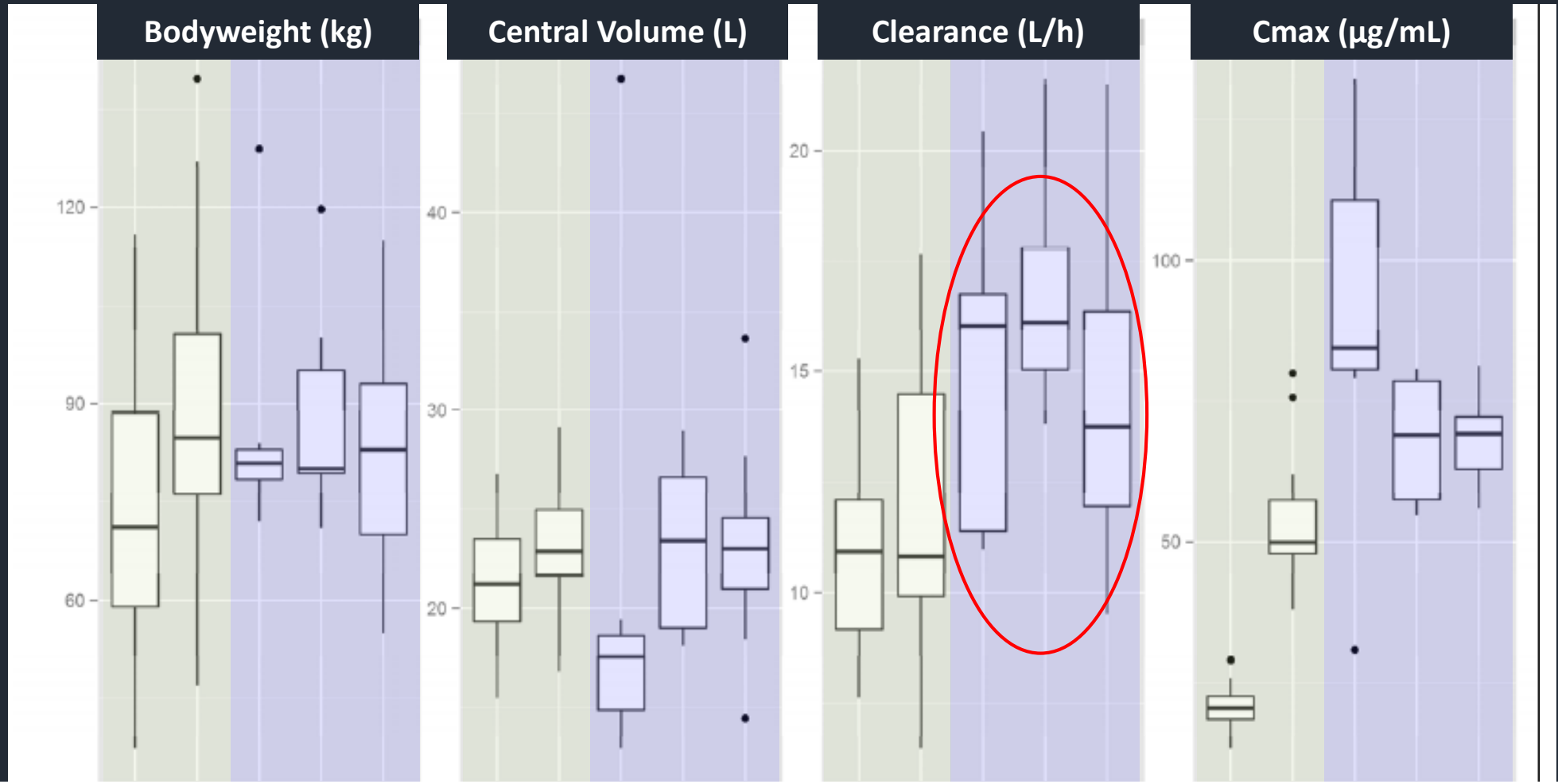
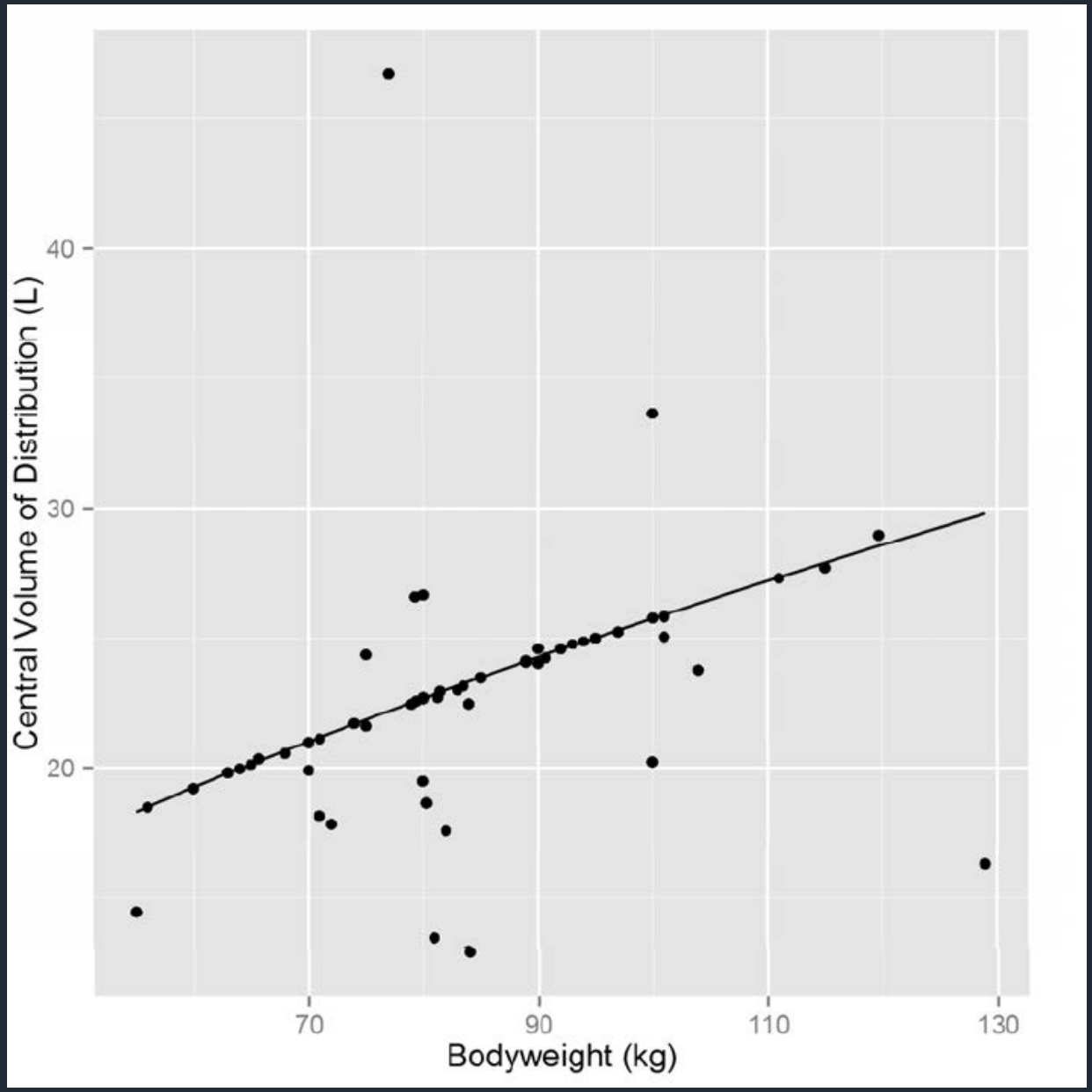
Difference in drug distribution in Fragile X Syndrome and TBI Patients



Effect of body weight on exposure



Pharmacokinetic conclusions

- NNZ-2566 showed linear pharmacokinetics across the dose range evaluated in TBI patients
- No accumulation, metabolic inhibition or induction was observed during the course of treatment
- Body weight has a significant effect on clearance and volume of distribution and consequently on the overall systemic exposure to NNZ-2566
- **Clearance in TBI subjects is ~24% higher than the dose-specific average for healthy volunteers, Rett and Fragile X subjects**
- **$AUC_{(24h)}$ in TBI subjects is ~20% lower than the dose-specific average for healthy volunteers, Rett and Fragile X subjects**
- Higher inter-individual and residual variability in the pharmacokinetics of NNZ-2566 appear to reflect the heterogeneity of the patient population (CV = 42.7%)

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PK/PD Analysis

- Hypotheses:
  - Exposure to NNZ-2566 (dose, duration or both) was not sufficient to demonstrate clinical benefit vs. placebo
  - Noise level at baseline due to highly variable severity impacted treatment effect detection
- Methodology: evaluate high dose treatment response adjusted for AUC and baseline severity
  - If hypothesis is correct this analysis is not likely to produce definitive outcomes, only trends
  - Concordant trends will support the hypotheses and next study design consideration

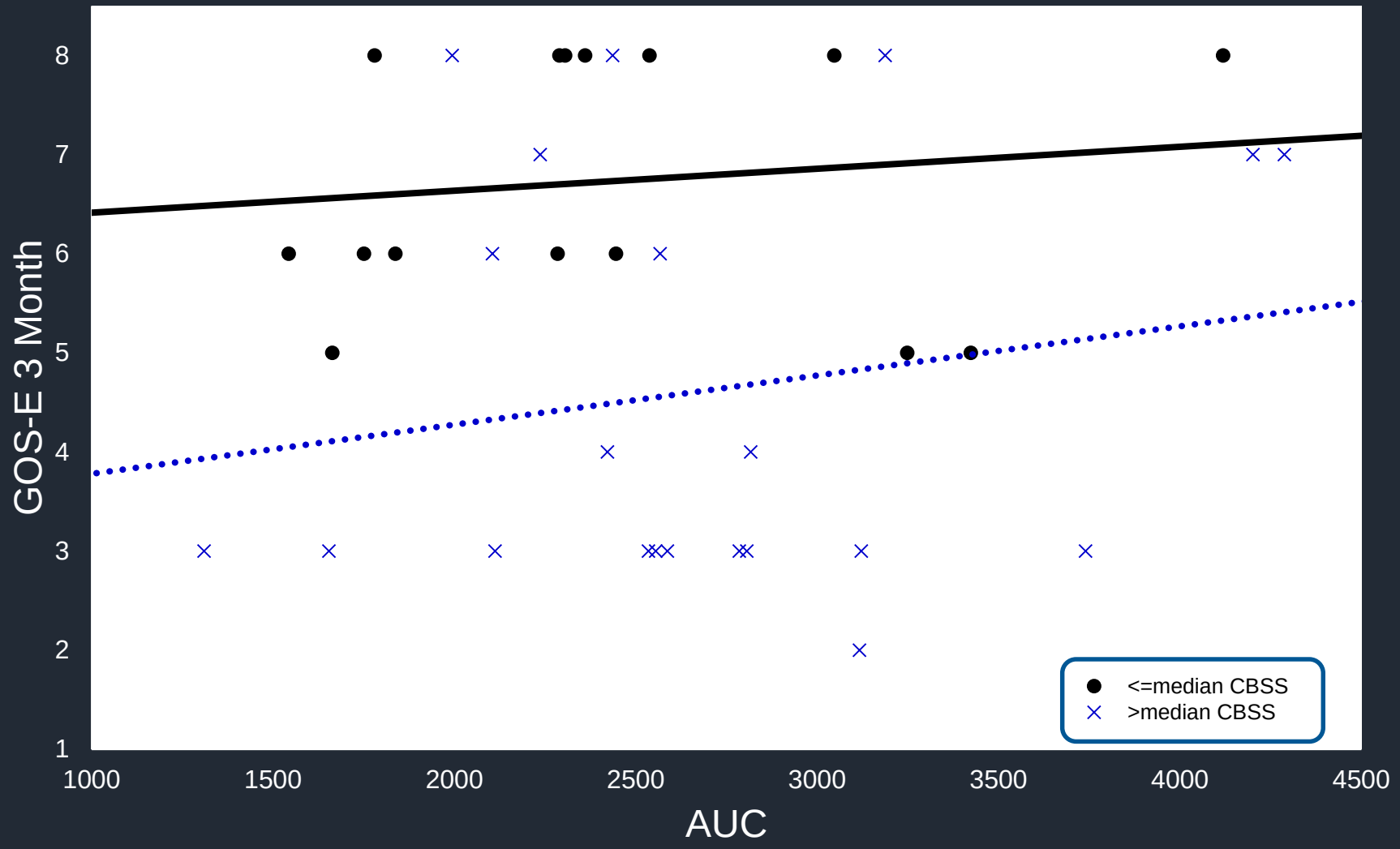
PK/PD Analysis Details

- For high dose group, evaluate association between GOS-E, MPAI4, and RBANS and AUC stratified by baseline severity (CBSS)
  - Descriptive evaluation
  - Selected quantitative evaluation
- For RBANS responders evaluate relationship between RBANS, GOS-E, and MPAI4

3 Month GOS-E vs. AUC

Cohort 3 - Active

(PA-GOSE)

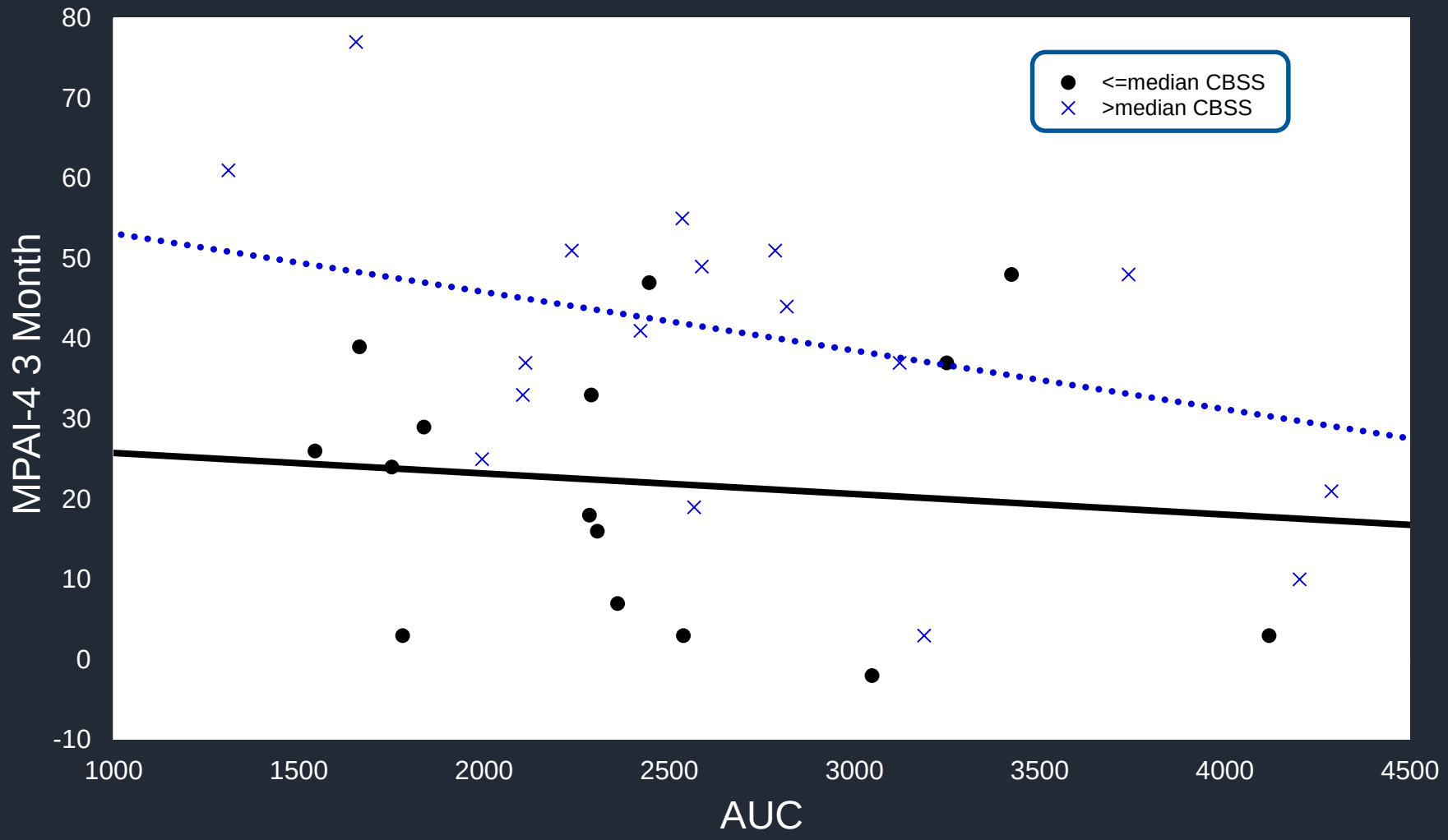


Note: For subjects alive at 3 months. Excludes GOS-E of 1 (dead).

3 Month MPAI-4 vs. AUC

Cohort 3 - Active

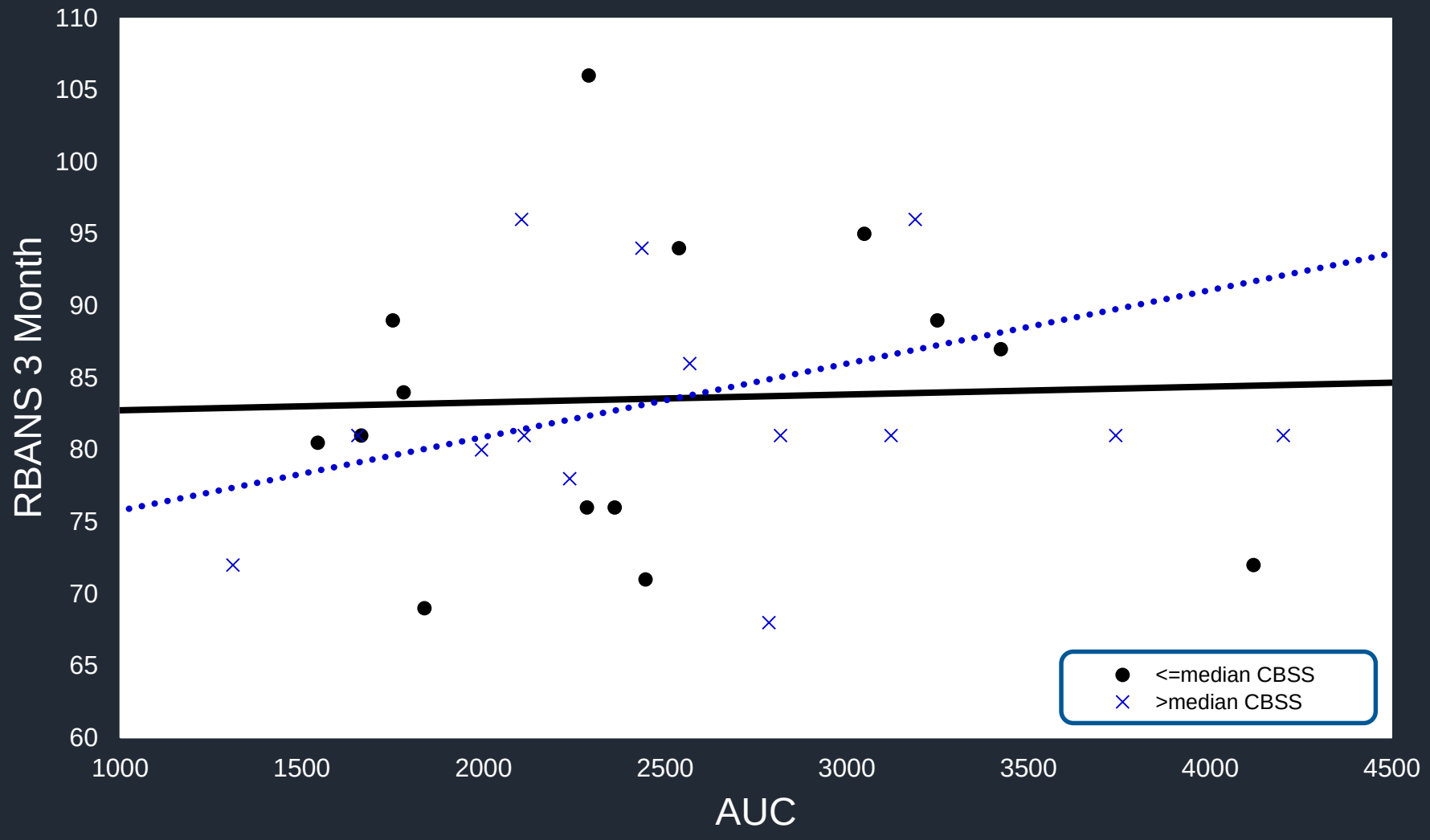
(PA-MPAI)



3 Month RBANS vs. AUC

Cohort 3 – Active

PA (RBANS)



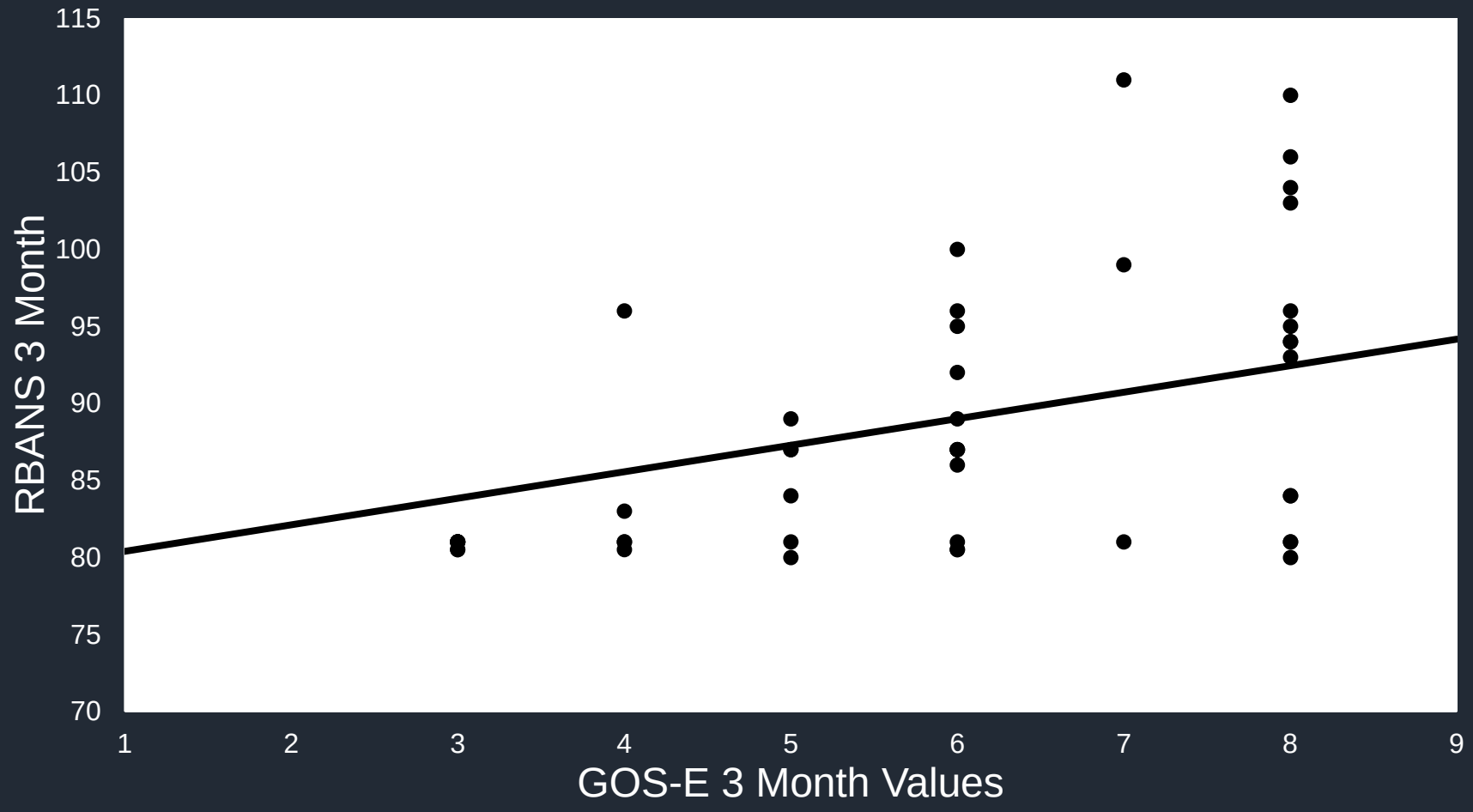
GOS-E: Analysis Adjusted for AUC and CBSS

- The mean treatment effect versus placebo evaluated for high dose at 1 month
  - If not adjusted for AUC and CBSS p=0.96
  - When adjusted for AUC and CBSS
    - High dose 4.3 vs. 2.5 on placebo
    - p= 0.14
  - Significance of each covariate in determining outcome
    - AUC: p=0.07
    - CBSS: p=0.006

3 Month RBANS vs. 3 Month GOS-E

Cohort 3 – Active RBANS Responder

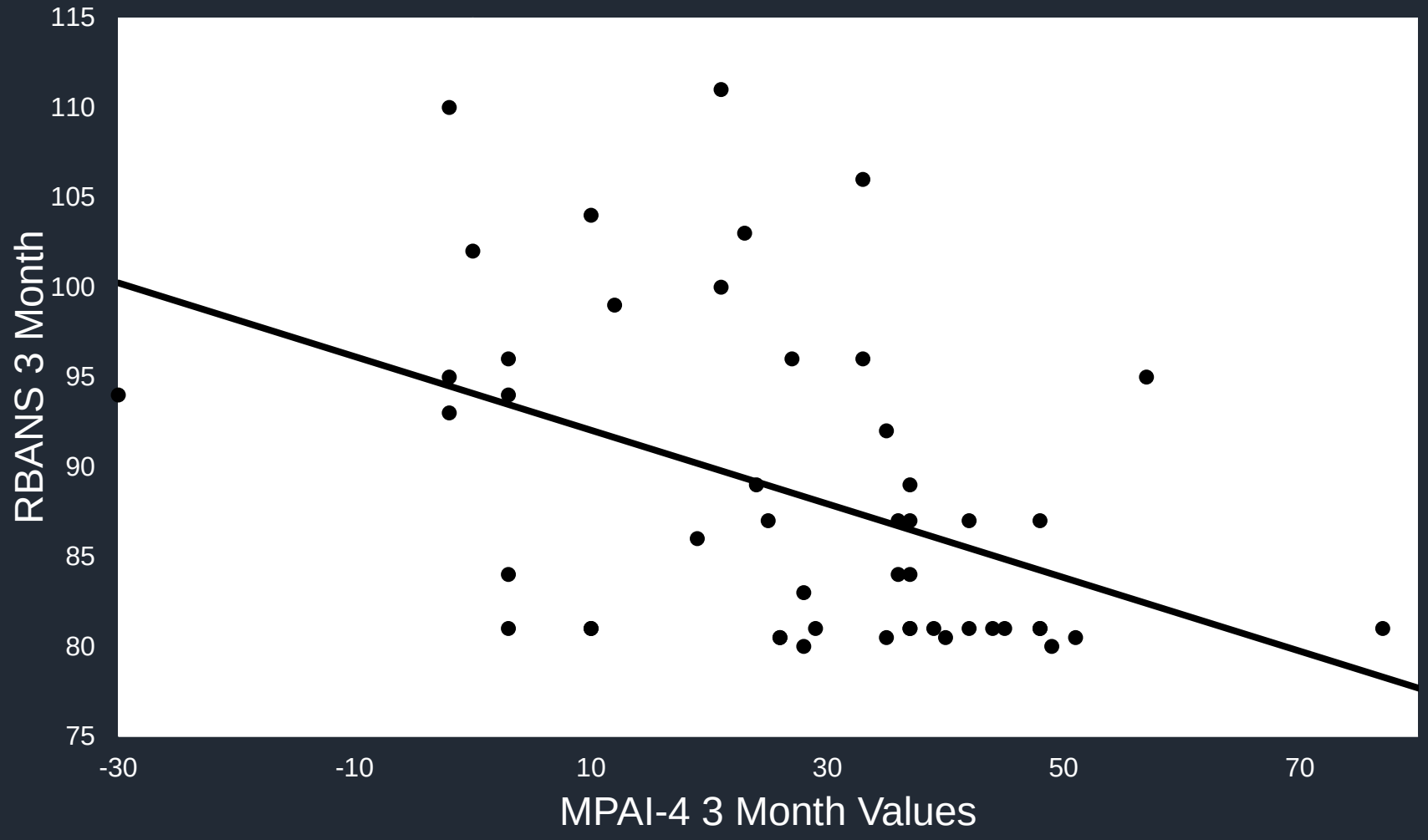
PA (RBANS)



3 Month RBANS vs. 3 Month MPAI-4

Cohort 3 – Active RBANS Responder

PA (RBANS)



PK/PD analysis: Conclusions

- There appears to be an association of GOS-E, MPAI-4 and RBANS with AUC and CBSS
- The association with AUC is stronger for patients with greater severity at baseline (higher CBSS)
- The association with CBSS is very strong
- For RBANS responders, RBANS is correlated with both GOS-E and MPAI4

Study conclusions from top-line results(1)

- NNZ-2566 has a favorable safety profile
- Baseline severity as measured by CBSS was strongly associated with all primary outcomes
- Significant imbalance in baseline severity between active and placebo in all cohorts
- No evidence of dose-response or consistent pattern of improvement for drug vs. placebo in GOS-E or MPAI-4

Study conclusions from top-line results(2)

- Overall mortality rate was lower than reported in comparable TBI clinical trials, but difference between drug and placebo was not significant
- Evidence of improvement for drug versus placebo in RBANS for patients with CBSS above the median
- Higher drug clearance rate (+24%) in this study compared to prior study populations resulted in lower than predicted drug exposure (-20%)
- Evidence of positive PK/PD associations

Next Steps

- Responder analysis
- Biomarker trajectory analysis as a component of PK/PD
- Explore adjustment of the analysis for covariates not included in CBSS (e.g., location of lesion, focal vs diffuse injury, comorbidities)
- Evaluate utility of secondary endpoints for future trials
- Subscale analysis for MPAI and RBANS
- Feasibility of second trial:
  - enriched population based on responder analysis
  - enrollment criteria exclusion of high ISS
  - randomization stratified by GFAP
  - substantially higher doses and longer treatment based on PK/PD analysis

INTREPID Investigators

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