neuren

pharmaceuticals

INTREPID-2566

NNZ-2566 for Traumatic Brain Injury

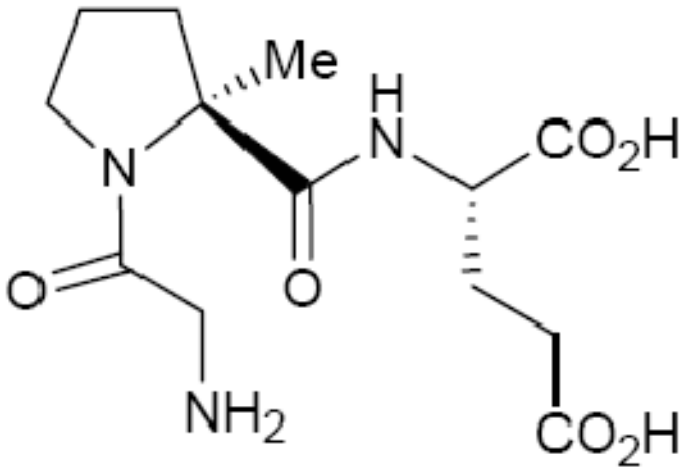
Acknowledgement

- This program is supported by the US Army Medical Research & Materiel Command under assistance agreement award number W81XWH-09-1-0496 to Neuren Pharmaceuticals (FY08 War Supplemental for PH/TBI and FY09 Defense Center of Excellence for PH/TBI) and by the Congressionally Directed Medical Research Program under award number W81XWH-08-2-0014 to The Geneva Foundation.

- Information contained in this presentation does not necessarily reflect the position or the policy of the U.S. Government and no official endorsement should be inferred.

Outline

- Program overview
- Bench to clinic translation
- How different?
- Preclinical efficacy
- Phase I clinical trials
- Phase II clinical trial overview
- Development pathway



Program Overview

Background on the collaboration

- MTA with WRAIR executed in late 2004
- CRADA executed in early 2005
- CRADA amended in mid-2005 to include non-convulsive seizures
- WRAIR focuses on pharmacology and mechanism of action
- Neuren manages safety pharmacology, toxicology, manufacturing, clinical trials and regulatory affairs
- CDMRP award to Geneva in 2008
- USAMRMC award via BAA in 2009 (funds from the FY08 War Supplemental for TBI/PH and the FY09 Defense Center of Excellence for PH and TBI)
- From discovery to Phase II in 5 years for ~$12 million

CRADA rationale

"The ultimate goal of this CRADA is the development and delivery of an efficacious, fieldable drug-based therapy amenable to rapid, far-forward medical application to both brain injured soldiers and civilians." [1]

[1]CRADA W81XWH-05-0074

Program goals

- Drug for acute treatment of TBI that…
  - Reduces neurological damage and sequelae
  - Has a reasonable (2^+ hrs) therapeutic window
  - Can be administered safely to all TBI patients (mild to severe; penetrating and closed-head)
  - Can be administered prior to or without CT or MRI
  - Can be administered by combat medics or EMTs
  - Sufficiently stable for field applications
- Clinical trials that…
  - Maximize opportunities for detecting an effect
  - Accommodate heterogeneity in patients
  - Utilize biologically relevant endpoints
  - Focus on clinically relevant outcomes
  - Accelerate path to marketing approval

Recent Publications

- **J Neurotrauma (2009)**

NNZ-2566, a Glypromate Analog, Improves Functional Recovery and Attenuates Apoptosis and Inflammation in a Rat Model of Penetrating Ballistic-Type Brain Injury

Xi-Chun May Lu, Ren-Wu Chen, Changping Yao, Hans Wei, Xiaofang Yang, Zhilin Liao, Jitendra R. Dave, and Frank C. Tortella

- **J Cerebral Blood Flow and Metabolism (2009)**

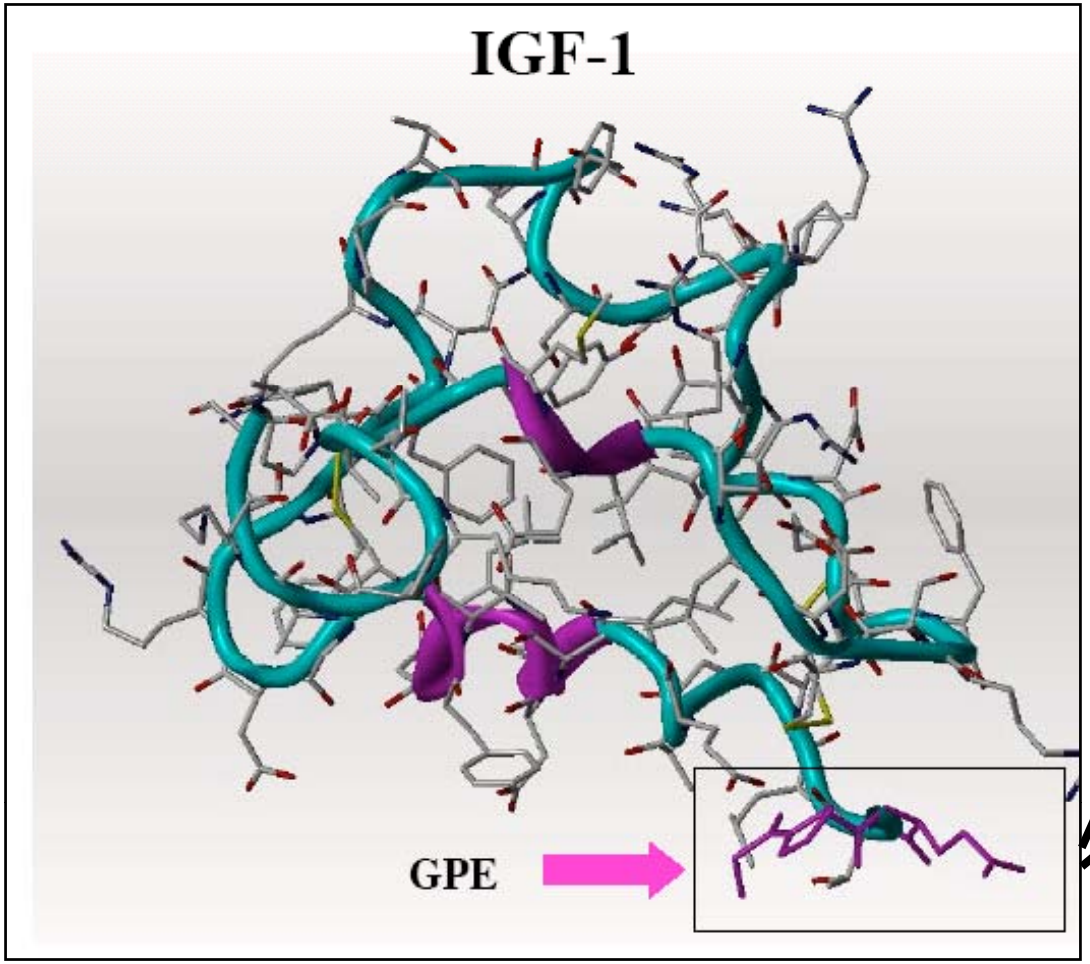
NNZ-2566, a glypromate analog, attenuates brain ischemia-induced nonconvulsive seizures in rats

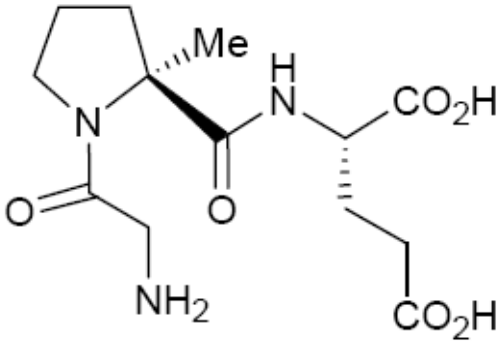
Xi-Chun M Lu, Yuanzheng Si, Anthony J Williams, Jed A Hartings, Divina Gryder and Frank C Tortella

Current status

- Regulatory
  - IND approved in March 2009
  - Fast Track designation granted in June 2009
- Site recruitment
  - 12 sites qualified and committed
  - Predicted enrollment from selected sites: 186 severe; 254 moderate
- IRB review
  - IRB applications submitted to all sites
  - 1 site IRB approval
  - 6 provisional approvals (reviewing updated protocol)
  - 5 reviews ongoing
  - cEEG core lab (UCLA) approved by UCLA IRB

Glypromate → NNZ-2566





Mortality rate in Phase III trial of Glypromate in 325 (mITT) cardiac surgery patients >50 yrs:

- Glypromate: 0.59%
- Placebo: 3.59%

(p=0.067)

NNZ-2566

- Improved pharmacokinetics; orally bioavailable (~35%) and active
- Readily crosses blood-brain barrier with IV and oral administration
- Good stability—4 wks @ 25°C; 50 wks @ 5°C; 36 hrs @ 25°C (reconstituted)
- Good safety profile in preclinical and Phase I studies
- Polypharmacology typical of neuropeptides
- Potent neuroprotection
- Inhibits microglial activation
- Inhibits neutrophil infiltration
- Inhibits pro-apoptotic and inflammatory cytokine gene expression
- Inhibits convulsive and non-convulsive seizures
- Effective in cortical concussive, penetrating brain injury, focal stroke and HI models
- 5+ hour therapeutic time window in stroke models; 2+ hours in PBBI model
- 3 hour therapeutic time window by oral gavage in stroke model

Bench to clinic translation

- Bolus dosing + infusion → bolus dosing + infusion in Phase II
  - Enhances efficacy in both cortical concussive and PBBI models
  - Extends therapeutic time window
- Non-convulsive and convulsive seizures → continuous EEG in Phase II
  - Dose-dependent effect
  - Reduced mortality in stroke models
- Gene expression → biomarkers in Phase II
  - Inhibits pro-apoptotic and inflammatory cytokine expression
  - Normalizes pro- and anti-apoptotic gene expression
  - Inhibits microglial activation
- Behavioral effects → neuropsychological endpoints in Phase II
  - Improved cognitive performance in cortical concussive model
  - Improved cognitive performance focal stroke and HI models
  - Improved cognitive performance in aged rat model

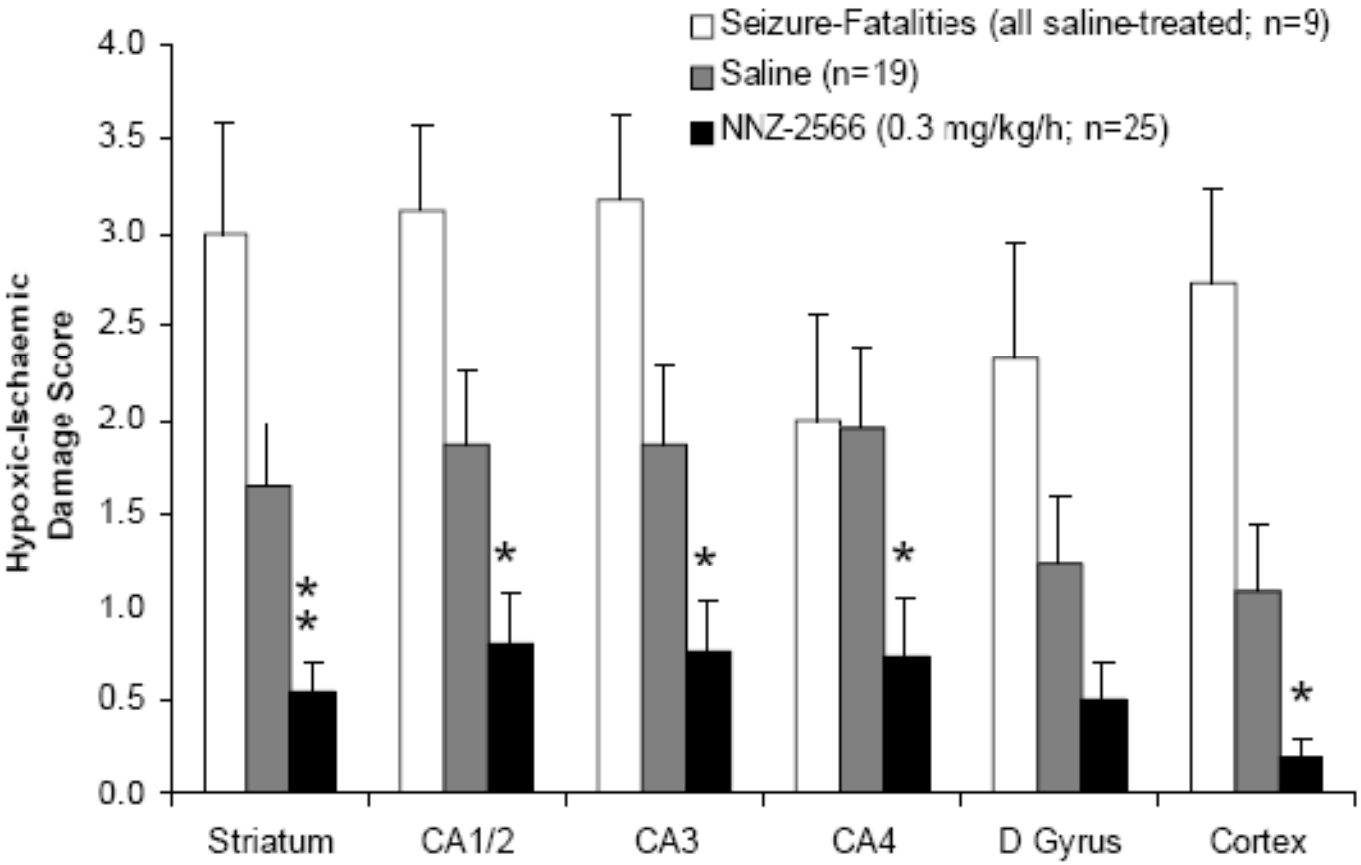
How different is the program?

- Dose-dependent efficacy in all brain injury models
  - Penetrating and concussive TBI, MCAO/NCS, 2 focal stroke and 1 global HI model
  - Models with hemorrhagic, hypoxic, ischemic, reperfusion components
  - Therapeutic time window: 2+ hrs in PBBI; 4+ hrs in stroke/HI models
- Multiplicity of effects
  - Neuroprotection, seizures, gene expression, cell regulation, functional recovery
- Pharmacology
  - Rapid BBB penetration (even when BBB is intact)
  - Oral bioavailability
- Clinical trial design
  - Stratification—2:1 (moderate : severe); randomization—2:1 (active : placebo)
  - Wide range of clinical and physiological endpoints supported by preclinical data
  - Neuropsychological endpoints both approvable and more sensitive than GOS-E
  - Mayo Portland Adaptability Index (ADL) more sensitive than GOS-E
  - Dose escalation—primarily safety but with dose-ranging component
- Regulatory strategy
  - One validated measure + one functional measure = approval
  - No particular endpoint or pre-specified magnitude of effect required by FDA

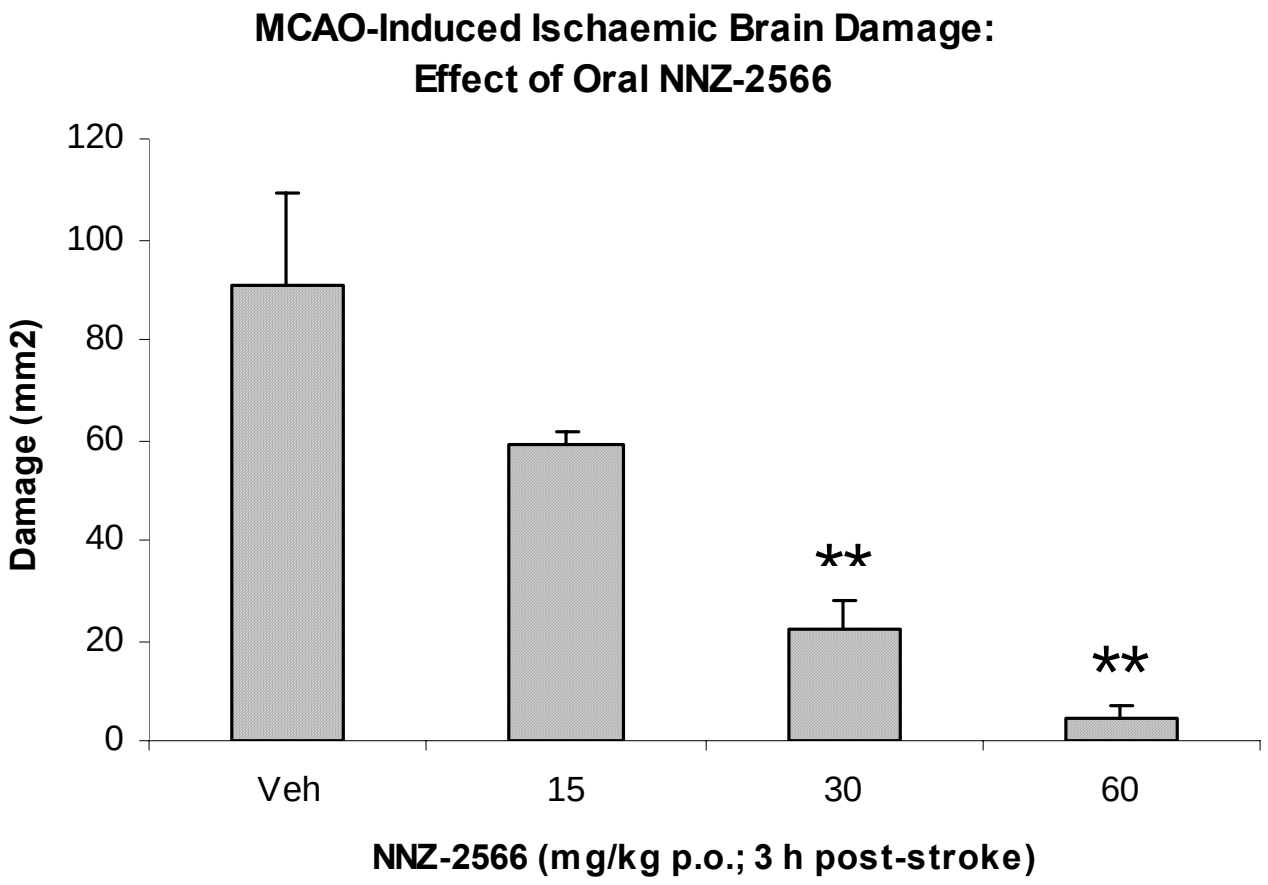
NNZ-2566

Preclinical Efficacy

Neuroprotection in hypoxic-ischemic model



Dose-dependent effect in a stroke model



** P < 0.01, ANOVA with Dunnett's post-hoc test. Group sizes: Veh (9), 15 mg/kg (8), 30 mg/kg (8), 60 mg/kg (7)

Therapeutic time window in a stroke model

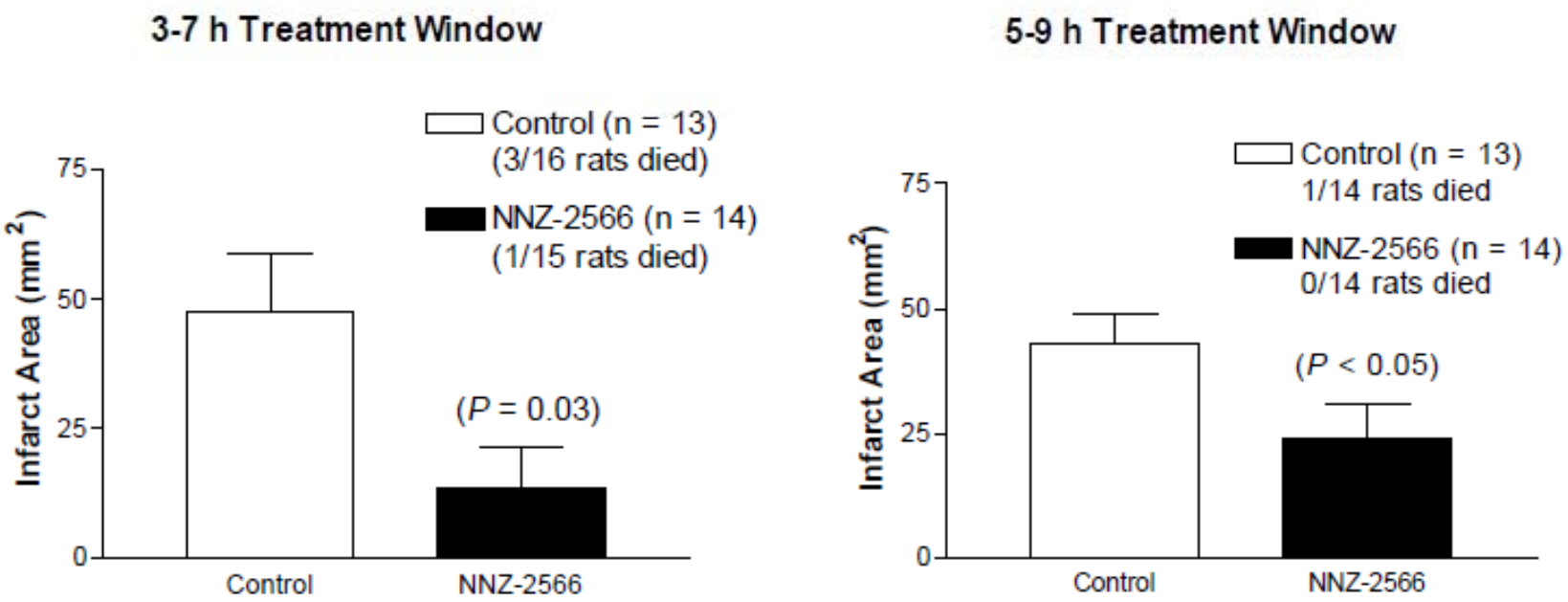
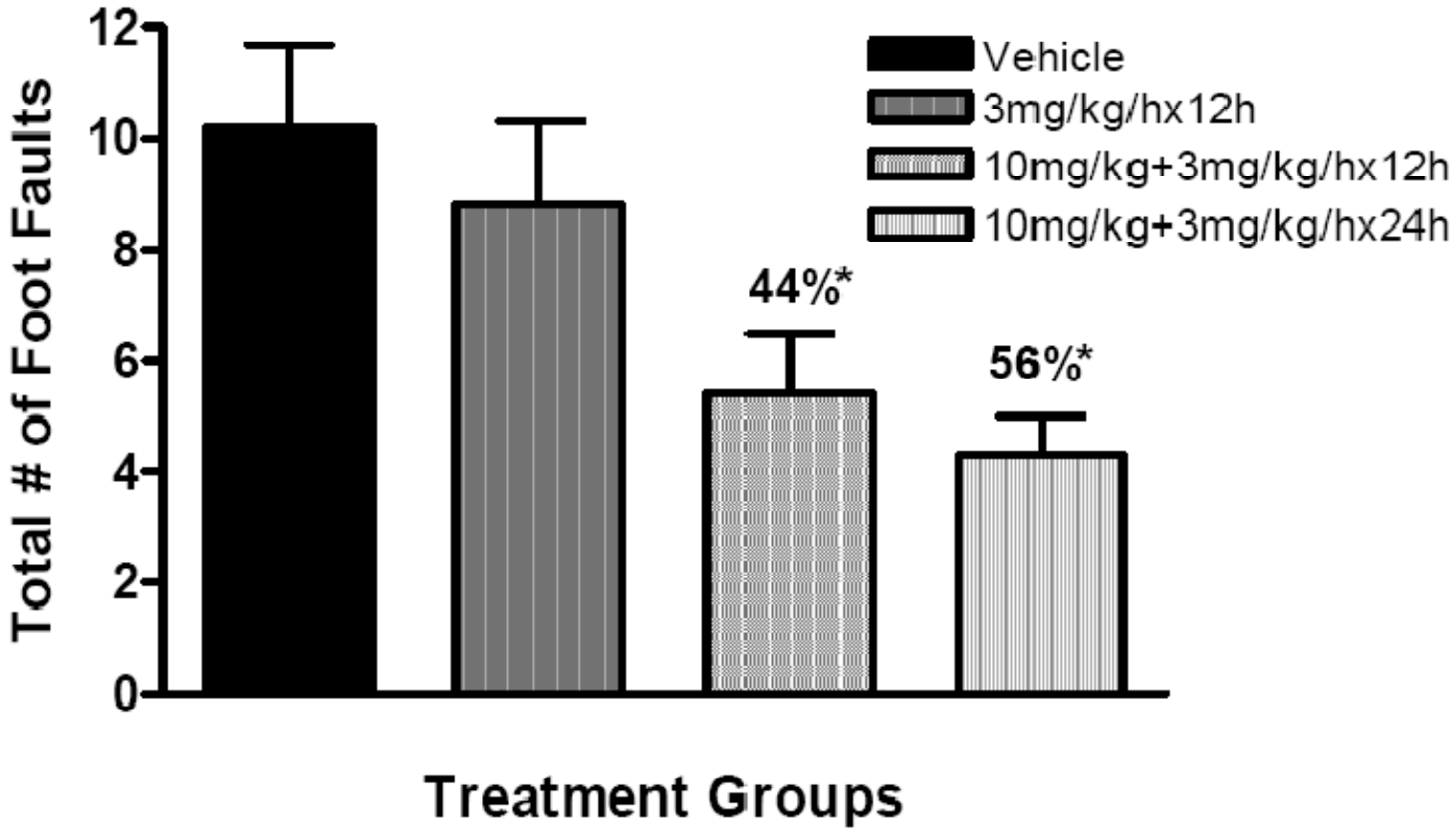
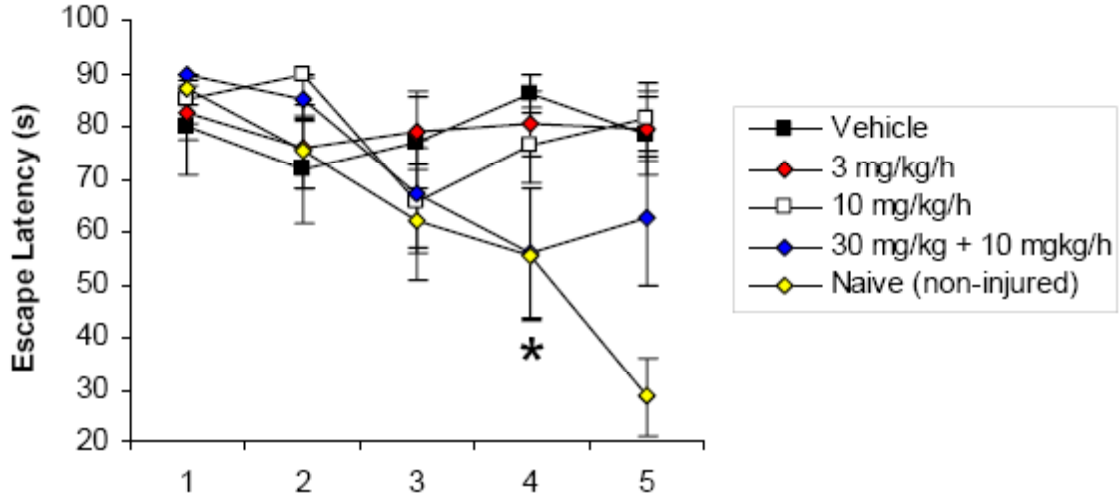


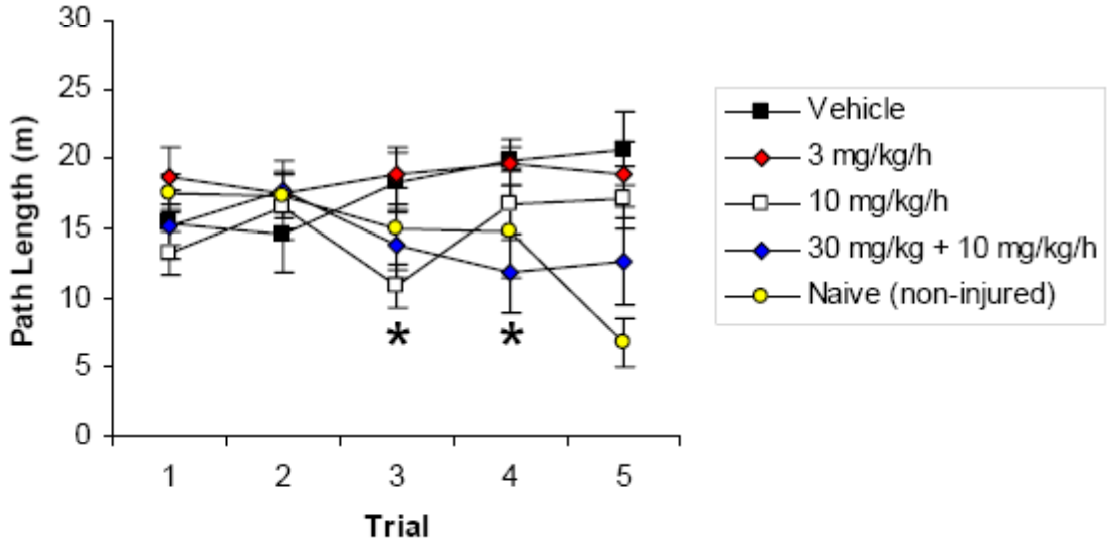
Figure 5. *Effect of 0.3 mg/kg/h NNZ-2566 administered either 3-7 h or 5-9 h after injury on infarct area in the endothelin-induced MCAO rat model.*

Dose-dependent effects in PBBI model

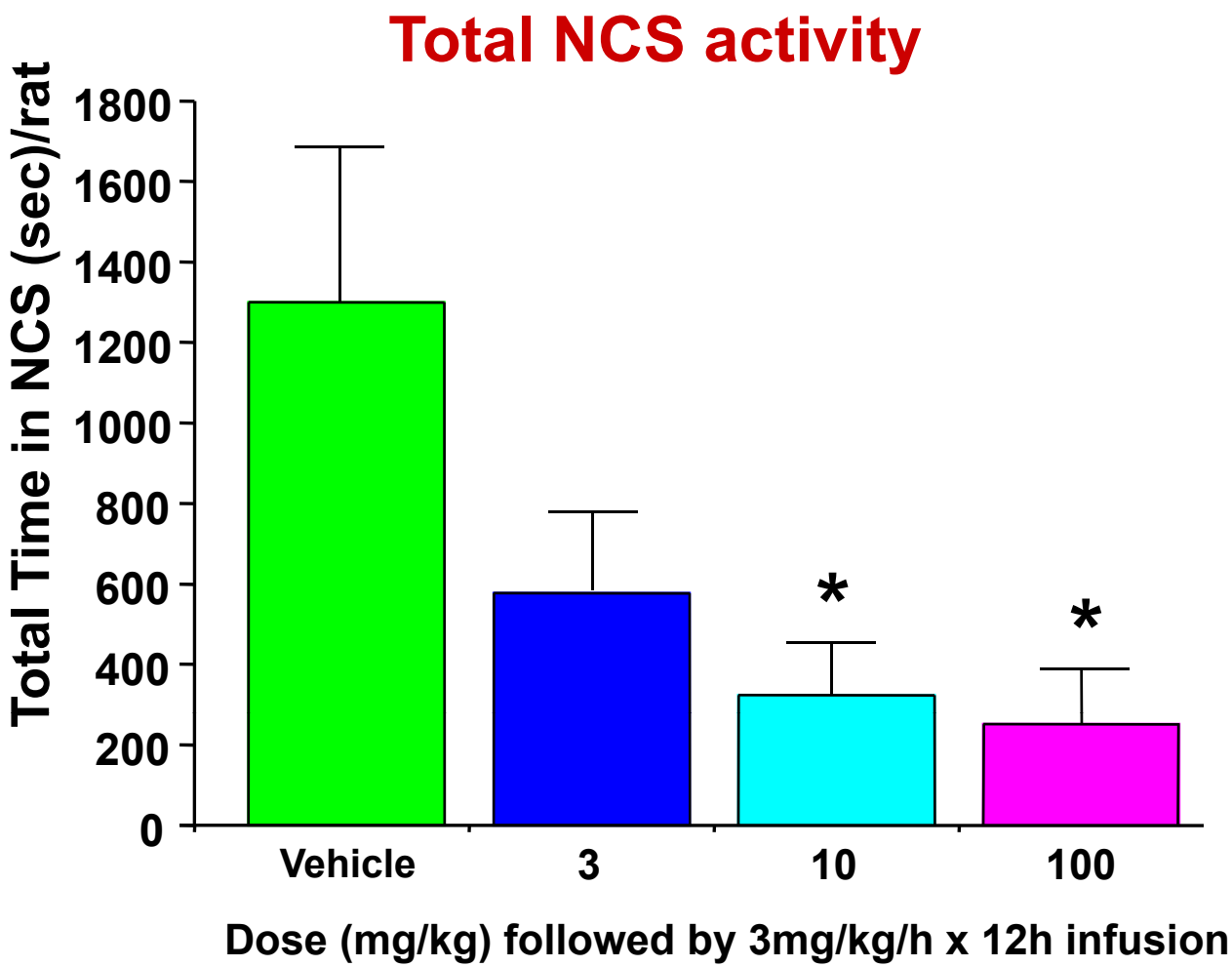


Dose-dependent effect in cortical concussive injury model

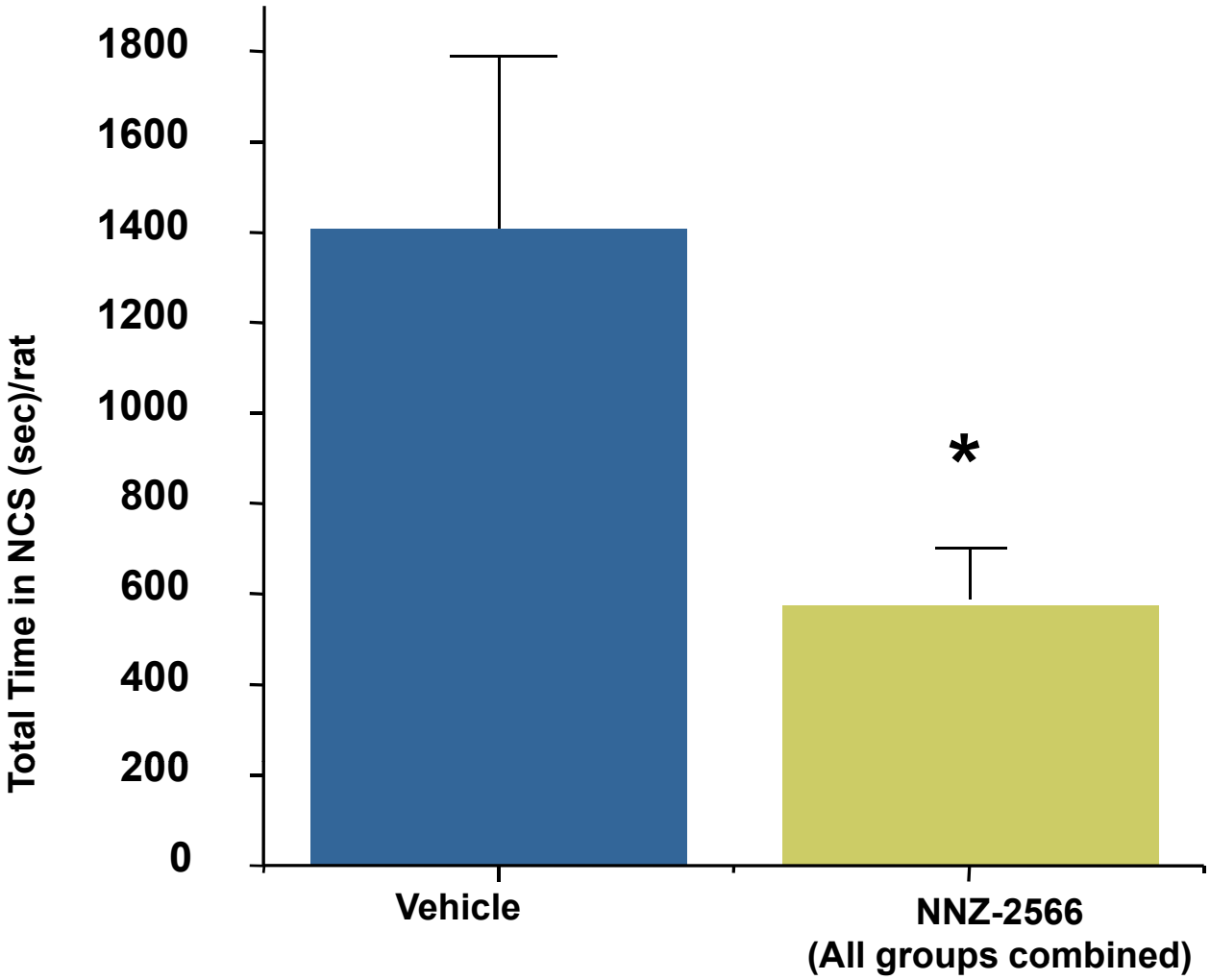




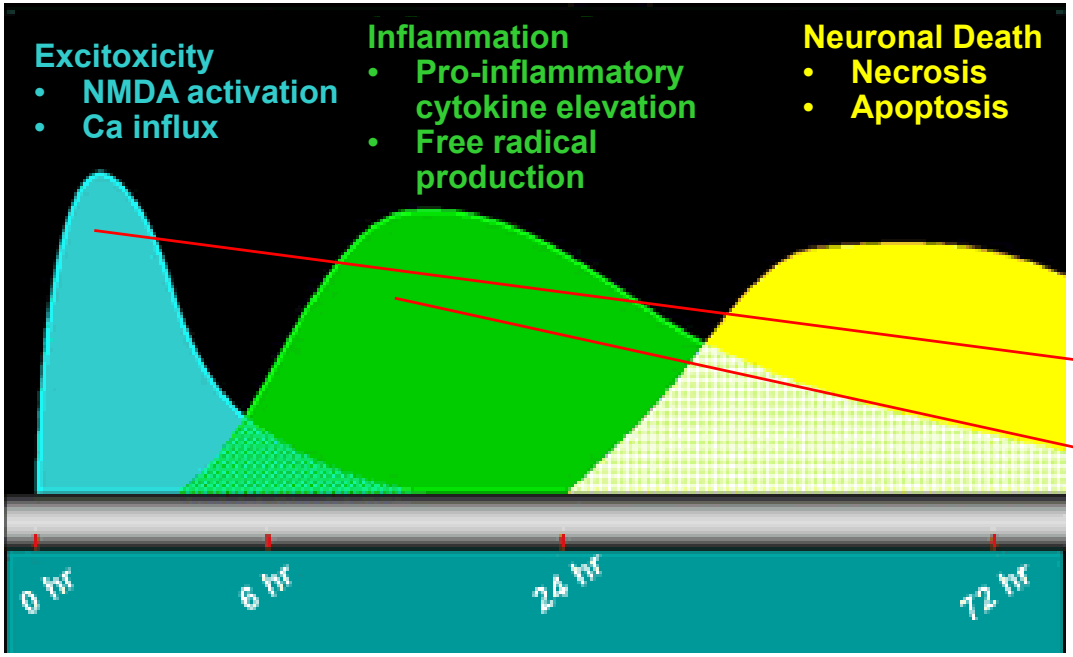
Dose-dependent effect in NCS model

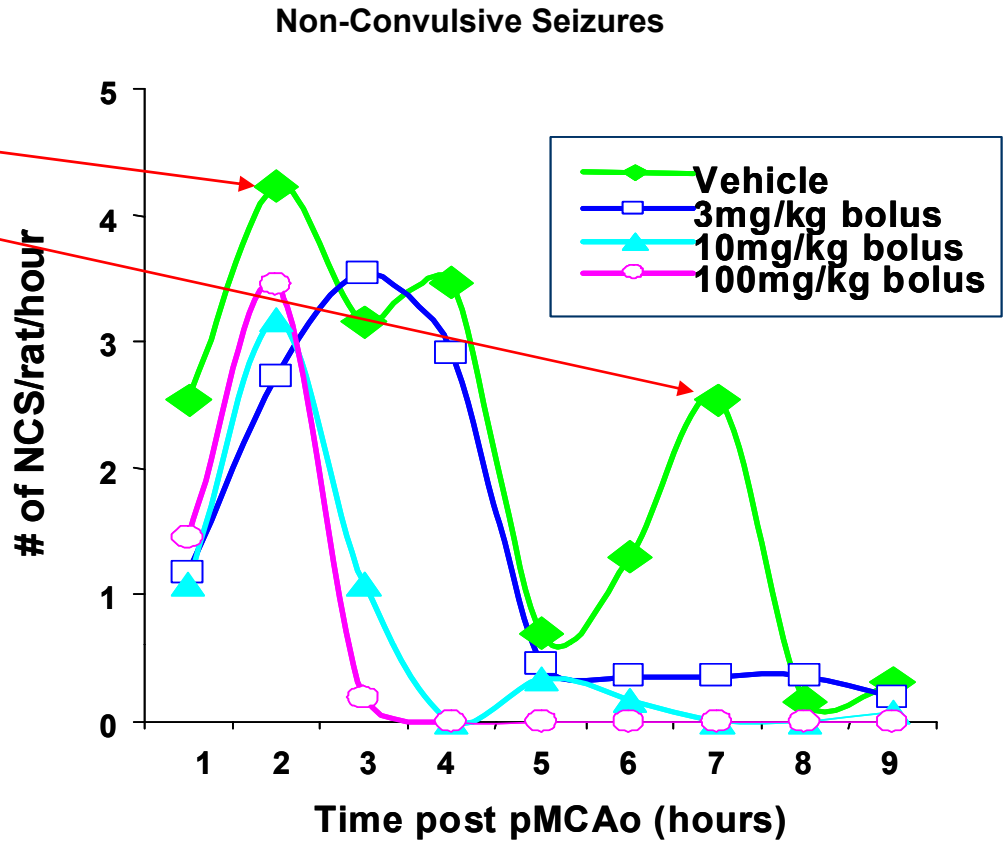


Attenuation of seizures after onset

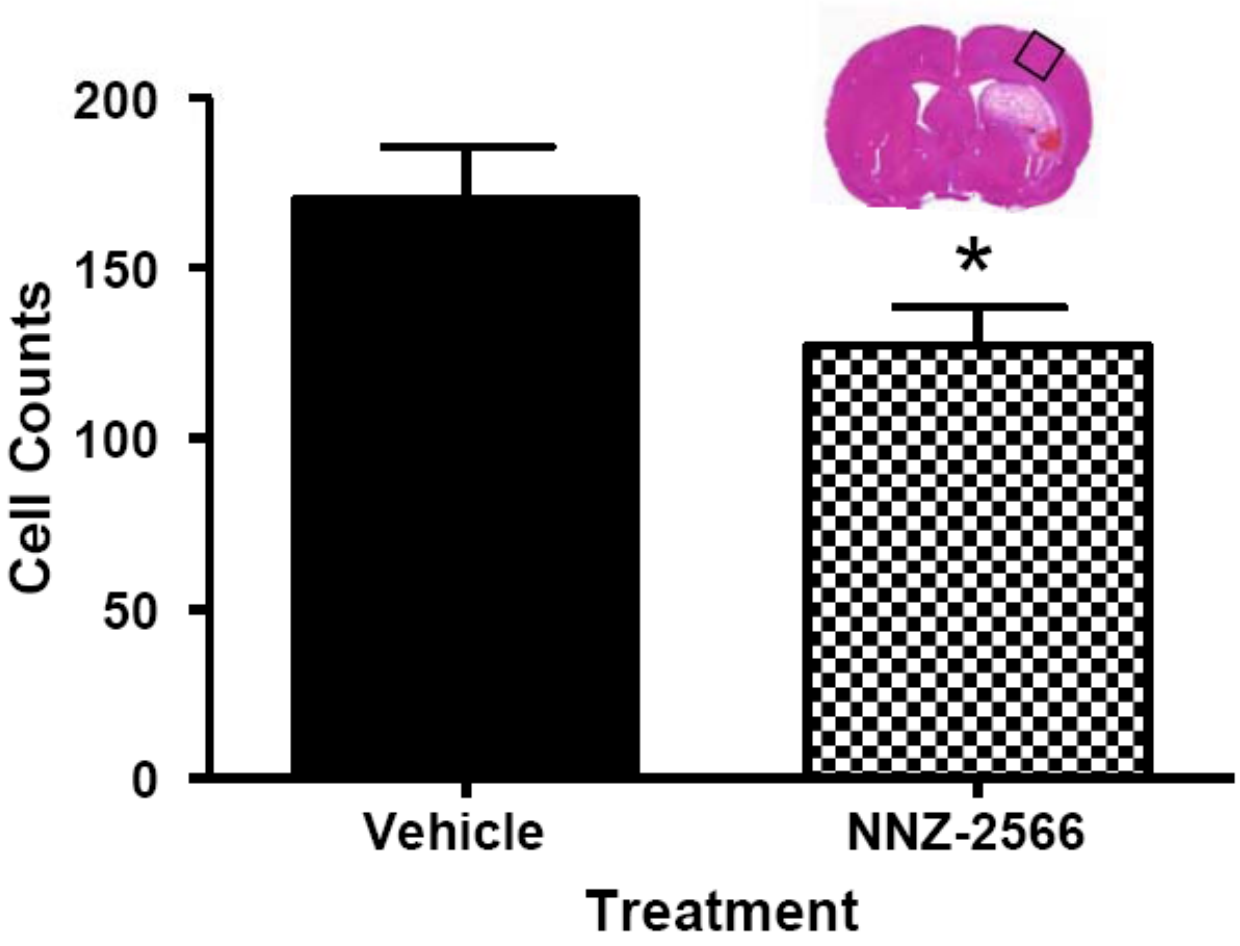


NCS time course

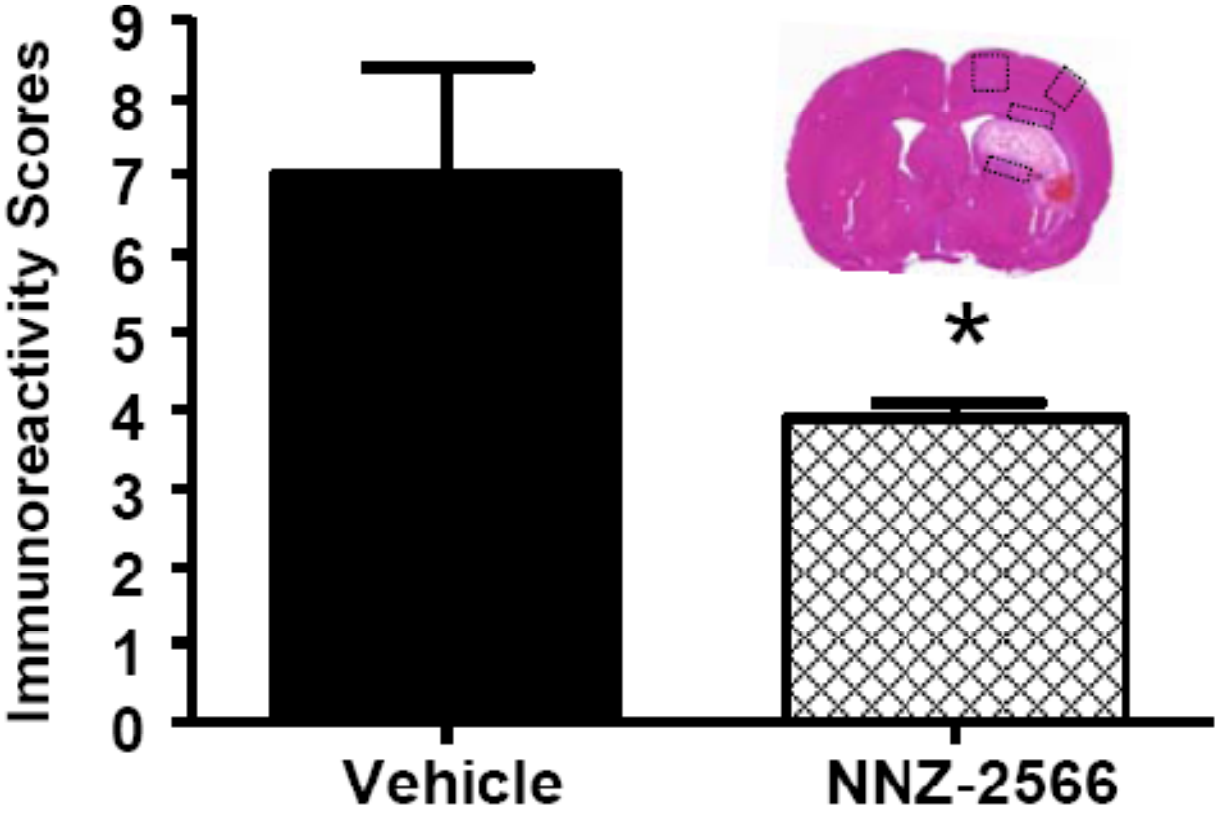




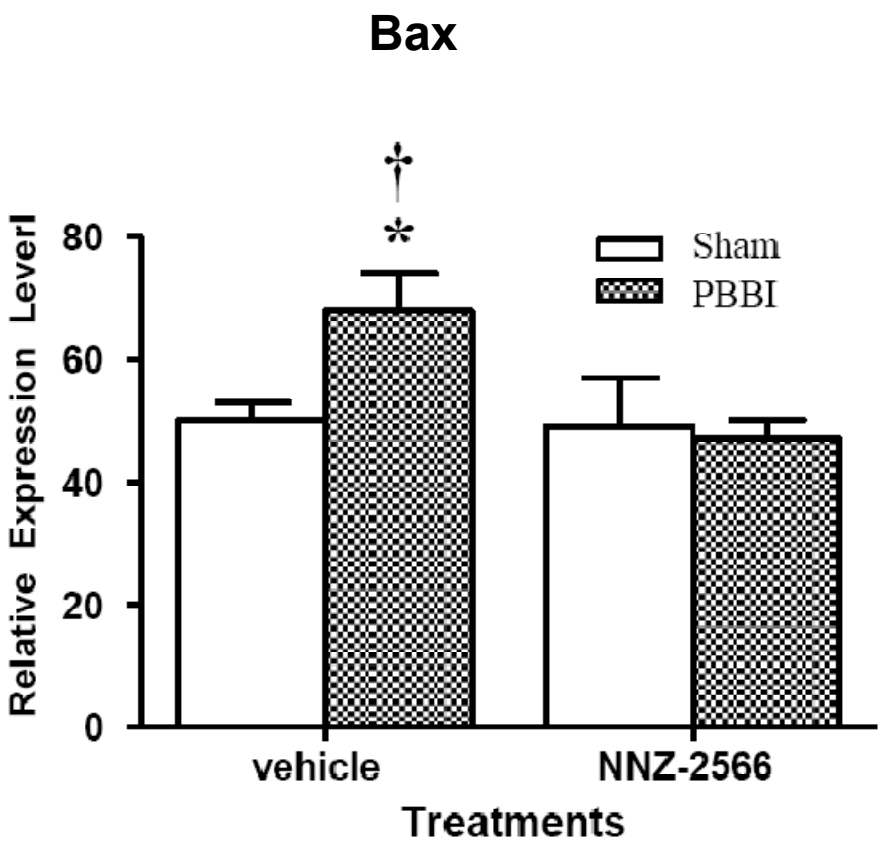
Inhibition of microglial activation in PBBI model

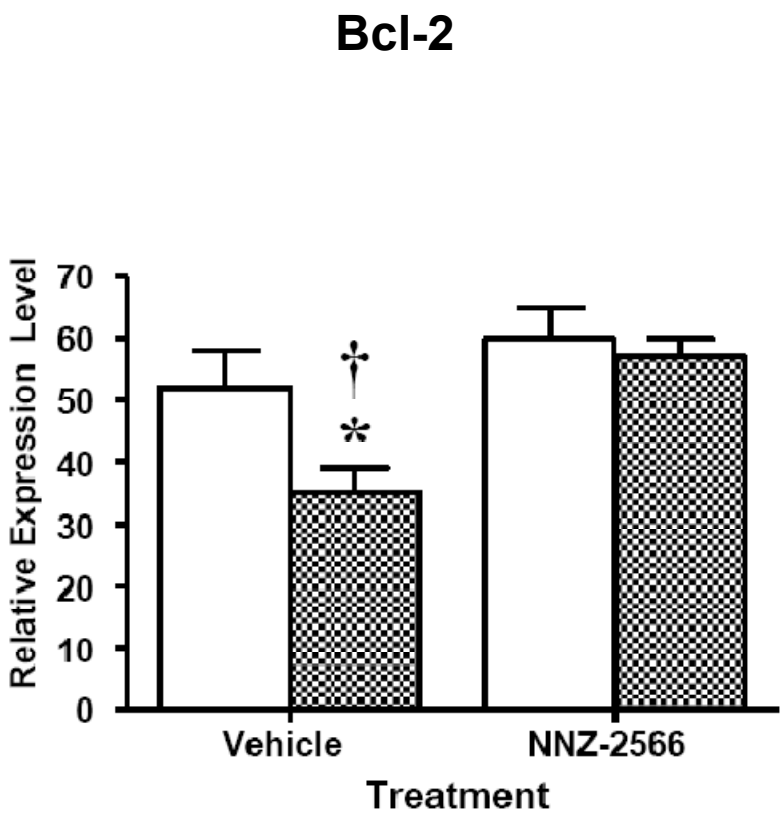


Inhibition of neutrophil infiltration in PBBI model

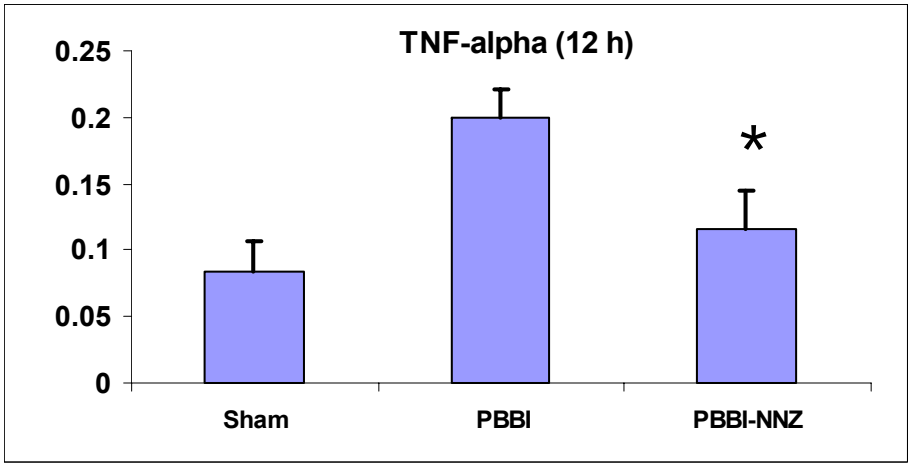


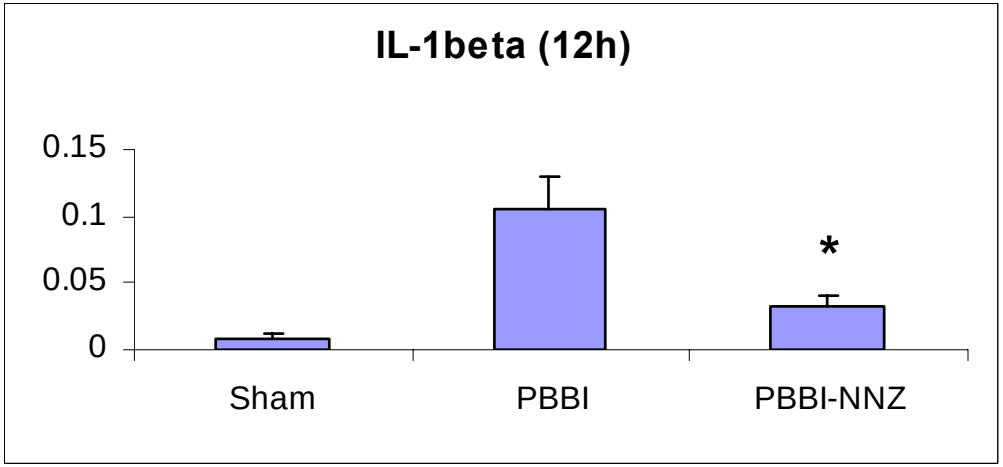
Bax and Bcl-2 expression in PBBI model

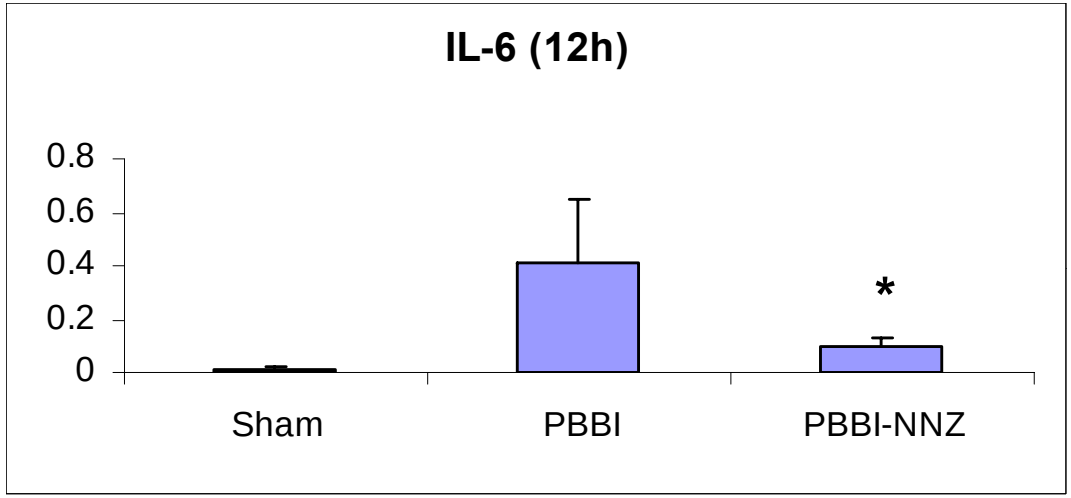




Inflammatory cytokine expression in PBBI model







NNZ-2566

Phase I Clinical Trials

Three Phase I Clinical Studies

- **Neu-2566-HV-001 (bolus)**
  - 4 cohorts, randomized 5:2 (drug:placebo)
  - 0.1, 1.0, 10.0, 20.0 mg/kg bolus IV infused over 10 minutes
- **Neu-2566-HV-002 (infusion)**
  - 1 cohort, randomized 5:2 (drug:placebo)
  - 1mg/kg/hr infused IV over 12 hours
  - Study terminated in favor of bolus + infusion
- **Neu-2566-HV-002 (bolus + infusion)**
  - 4 cohorts, randomized 5:2 (drug:placebo)
  - 20mg/kg IV infusion over 10 minutes then infusion:
    - 1 mg/kg/hr 12 hours
    - 3mg/kg/hr 24hours
    - 3mg/kg/hr 48 hours
    - 6mg/kg/hr over 72 hours

Adverse Events

- No SAEs
- Dose dependent cannula site reactions
- 4 subjects: dizziness
  - 2 in 001, spontaneous recovery
  - 2 in 003, I at 4.5 hours after 1mg/kg/hr; withdrawn and recovered
  - 1 after 2 minutes of planned 72 hour infusion; vasovagal; recovered, infusion continued for full 72 hours
- 2 subjects: ECG changes
  - 1 with transient minor T wave changes, also seen pre-dosing
  - 1 with transient tachycardia
  - Both reviewed by cardiologist
- 1 subject: rise in serum amylase
  - 12 hrs into 24 hr 3mg/kg/hr infusion, almost normal by 24 hours. Nil else, no pancreatitis

Monitoring AEs based on preclinical observations

- **Thyroid Function**
  - No changes
- **ECG and QTc**
  - Digitally read ECGs from 003 (Covance Safety Services; Reno, NV)
  - Heart rate data inconsistent—in pooled cohorts, mild 8 bps increase at 10 minutes and 5 hours only, resolved by 12 hours
  - No significant within cohort QTc changes
  - Pooled cohort data: 7 msec prolongation 5 to 10 minutes after 20 mg/kg bolus, not thereafter

NNZ-2566

Phase II Clinical Trial Overview

Phase II Dose Selection

- Efficacy
  - Efficacy range in rats: 3 – 30 mg/kg/h IV infusion
  - Improved efficacy in TBI models with bolus dose (10 – 30 mg/kg)
  - Exposure at efficacious infusion rate: 3 – 30 µg/mL
  - Human doses expected to produce exposure in this range
- Safety
  - Exposure levels in toxicity studies exaggerate expected clinical exposure (based on Phase I PK data)
- Prior human experience
  - Top dose (20 mg/kg bolus + 6 mg/kg/h infusion for 72 h) was well tolerated in a Phase I human volunteer study
- Conservative approach on safety
  - Dose escalation protocol for cohorts 1 – 3 increases safety of trial and provides some opportunity for dose-ranging on efficacy

Phase II Dose Selection

Phase II Exposure Comparison with Preclinical Efficacy and Safety Data:

	Efficacy	Phase II TBI Trial [1]			Preclinical Safety	
	Rat	*Cohort 1*	*Cohort 2*	*Cohort 3*	*Rat*	*Dog*
Bolus dose (mg/kg)	10-30	20	20	20	350	350
Infusion dose (mg/kg/h)	3-30	1	3	6	231 [2]	20 [3]
Infusion duration	24 h	72 h	72 h	72 h	168 h	672 h
Cmax from Bolus (µg/mL)	25-80 [4]	60	60	60	900 [4]	1850
Cmax during Infusion (µg/mL)	3-30	6	18	35	260	39
Daily Drug Exposure (µg.h/mL)	70-700	240	505	905	5640	920
Total Drug Exposure (µg.h/mL)	-	505	1300	2500	38000	25800

1 Trial PK values are estimates, extrapolated from Phase I trial data
2 MTD in rat 7 day continuous infusion toxicity study
3 LoAEL in dog 28 day continuous infusion toxicity study (only drug related effect was slight, reversible, thyroid hyperplasia in 4/6 dogs, unaccompanied by clinical signs)
4 Estimated from infusion data

The dose escalation regime in Phase II spans the drug exposure range necessary for efficacy while remaining below preclinical exposure in key toxicity studies

Phase II protocol overview (moderate – severe)

- 260 acute, non-penetrating TBI patients (Glasgow Coma Scale 4-12)
- Males 18-70 years old (females to be added following Phase I PK/safety study)
- Stratified 2:1 moderate (GCS 9-12) to severe (GCS 4-8 with one reactive pupil)
- Randomized 2:1 drug to placebo, 3 cohort dose-escalation study
- Administration of drug within 8 hours of injury (earlier strongly encouraged)
- 20 mg/kg IV bolus followed by 1, 3 or 6 mg/kg/h IV infusion for 72 hrs
- Endpoints
  - Primary: safety (SAEs thru to 3 months, AEs thru to Day 30 or discharge)
  - Secondary
    - Efficacy: Glasgow Outcome Scale-Extended (GOS-E); ADL; neurocognitive function; mood; intracranial pressure
    - Biological effect: continuous EEG; serum biomarkers
    - Pharmacokinetics
- Interim analysis for safety between each cohort and on data from first 30 patients in cohort 3 (6 mg/kg/h)
- Interim efficacy analysis on collective data from first 100 patients

Efficacy measures (moderate – severe)

- Global outcomes (1 and 3 months)
  - GOS-E
  - ADL (Mayo-Portland Adaptability Inventory-4)
- Neuropsychological outcomes (1 and 3 months)
  - speed of information processing, choice reaction time, attention, verbal learning/memory, visuospatial learning/ memory, mental flexibility, response inhibition, fine motor speed and coordination
  - Rivermead Post-Concussion Symptom Questionnaire (RPSQ)
  - Profile of Mood States (POMS)
- Physiological outcomes
  - Biomarkers (Banyan Biomarkers, Inc.) (baseline through 72 hours)
    - UCHL-1 (neuronal)
    - SDBP145 (axonal)
    - GFAP (glial)
  - Continuous EEG (between groups and within patients; days 1-3 and days 4-7)
    - Incidence of non-convulsive & convulsive seizures
    - Epileptiform activity
    - Mean global percent alpha variability (PAV)
  - ICP

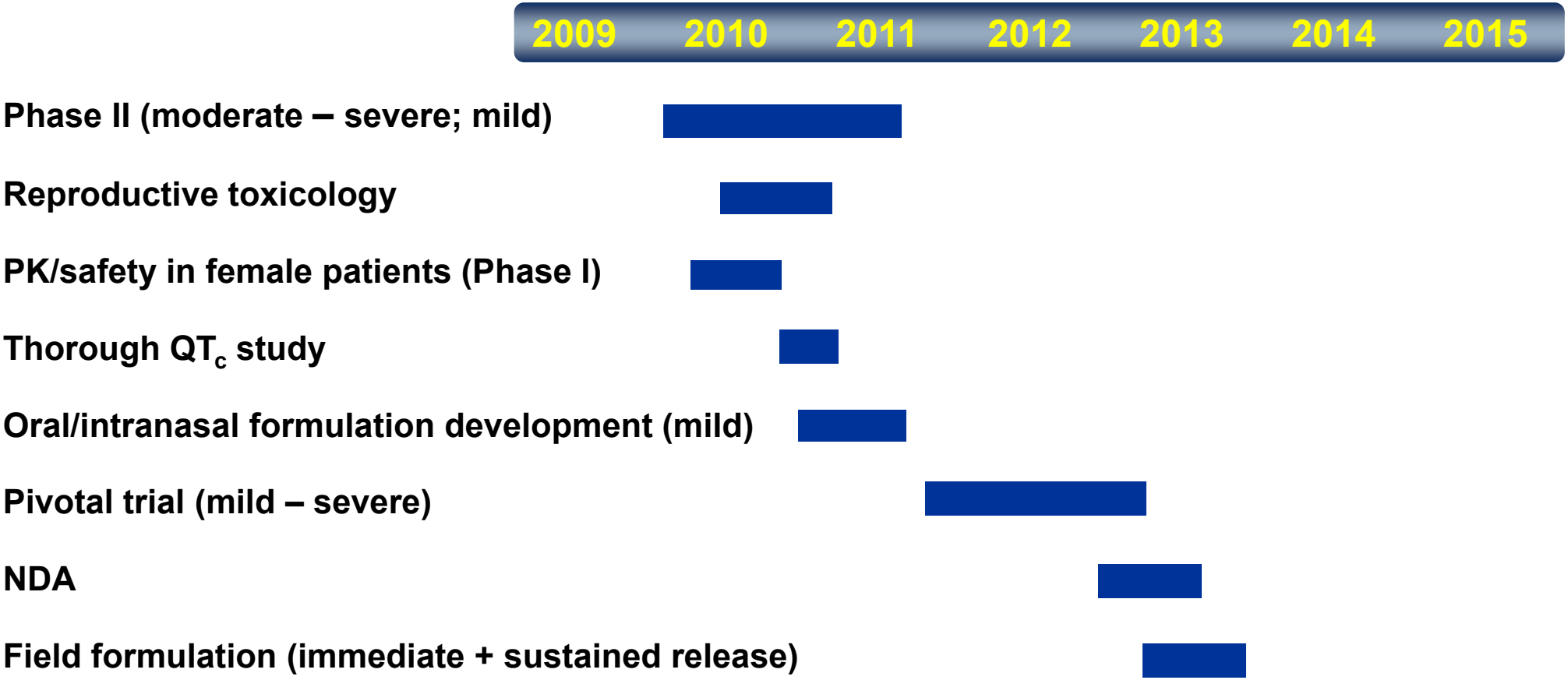
Phase IIa protocol overview (mild)

- 40 evaluable acute, non-penetrating TBI patients (GCS 13-15)
- Patients 18-70 years old
- Randomized 1:1 drug to placebo
- Administration of drug within 4 hours of injury
- 20 mg/kg bolus followed by 6 mg/kg/h infusion for 24 hrs
- Endpoints
  - Primary: effect on cognitive functioning at 3 months (speed of information processing, choice reaction time, attention, verbal learning/memory, visuospatial learning/ memory, mental flexibility, response inhibition, fine motor speed and coordination)
  - Secondary:
    - Safety: SAEs thru to 3 months, AEs thru to Day 30 or discharge
    - Change in concussive symptoms within first 96 h, 1 month, 3 month
    - Change in psychological sequelae within first 96 h, 1 month, 3 month
    - Change in PTSD related sequelae at 1 month, 3 month
    - Change in functional problems at 1 month, 3 month
    - Biological effect: serum biomarkers thru to discharge or 72 h

Efficacy measures (mild)

- Primary Endpoints (<96 h, 1 and 3 months)
  - CVLT-II (California Verbal Learning Test-II)
  - D-KEFS Trail Making Test (Delis-Kaplan Executive Function Scale)
  - CPT-II (Connors' Continuous Performance Test-II)
  - WAIS-III Digit Span (Wechsler Adult Intelligence Scale –III)
  - D-KEFS Verbal Fluency
  - WAIS-III Digit Symbol-Coding
- Secondary Endpoints (1 and 3 months)
  - RPSQ (Rivermead Post-Concussion Symptom Questionnaire) (also at < 96 h)
  - POMS (Profile of Mood States) (also at < 96 h)
  - PCL-C (Post-traumatic Stress Disorder Questionnaire – Civilian version)
  - MPAI-4 (Mayo-Portland Adaptability Inventory-4)
- Other measures
  - GOAT (Galveston Orientation and Amnesia Test) daily until PTA resolved
  - TOMM (Test of Memory Malingering) at 1 and 3 months
  - WTAR (Wechsler Test of Adult Reading) (IQ) at 3 months
  - Biomarkers (Banyan Biomarkers, Inc.): UCHL-1 (neuronal), SDBP145 (axonal), GFAP (glial)

Product Development Plan Overview: Best Case



Best case rationale and assumptions

- Additional studies required for pivotal trial initiated with positive clinical signal from interim analysis
- Oral/intranasal formulation development for mild TBI in parallel with additional pharmacology/toxicology studies for inclusion in pivotal trial
- Assumes single pivotal trial required for approval; to be negotiated under Special Protocol Assessment procedures
- Assumes rolling NDA submission under Fast Track
- Application for oral/intranasal form for mild TBI would be submitted simultaneously with IV form for moderate – severe
- Field formulation for single administration of bolus plus sustained release would be developed following completion of pivotal trial

On the horizon

- Formulation for mild TBI—intranasal versus oral
  - Intranasal typically results in higher and faster C_{max}, faster BBB penetration
  - Intranasal formulations tend to have better bioavailability than oral
  - Intranasal will have fewer bridging tox requirements than oral
  - Delivery of an effective dose (volume) will be the key issue
- Field formulation
  - Simulate bolus + 4 hour infusion with single injection
  - Combination of protected and unprotected drug reconstituted for immediate use
  - Delivery of an effective dose (volume) will the key issue
- Penetrating
  - More data on PBBI than any other drug in clinical development
  - Major cause of mortality and morbidity for warfighters and civilians
  - Feasibility, trial design and implementation will be challenging
- Blast
  - Relevance of NNZ-2566 mechanism(s) to blast mechanism(s) of injury?
  - Feasibility, trial design and implementation will be challenging