Clinical Study Report

Issue Date: 15 September 2009
Prepared by: Johnson & Johnson Pharmaceutical Research & Development
Document No.: EDMS-PSDB-10530025:2.0

Name of Sponsor/Company	Johnson & Johnson Pharmaceutical Research & Development *
Name of Finished Product	To be determined
Name of Active Ingredient	JNJ-17299425

Protocol No.: 17299425TRM2001

Title of Study: An Open-Label Single and Repeat Dose Study to Assess the Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of JNJ-17299425 in Patients With Traumatic Brain Injury.

EudraCT Number: 2007-000280-17.

Principal Investigator: Dr Raf De Jongh, MD. Ziekenhuis Oost Limburg, [redacted], Belgium.

Publication (Reference): None.

Study Period: 02 August 2007 to 12 January 2009. Database lock date was 8 June 2009.

Phase of Development: Phase 2a

OBJECTIVES:

The primary objectives of the study were:

- To determine whether JNJ-17299425 can reduce the increased intracranial pressure (ICP) after traumatic brain injury (TBI). The primary pharmacodynamic (PD) parameter was the reduction of ICP; the percentage reduction was characterized, as well as the absolute reduction, and the reduction below 20 mmHg. The duration of the ICP reduction was also analyzed.
- To determine the safety, tolerability, and maximum safe dose of JNJ-17299425.

The secondary objectives were:

- To determine the effects of JNJ-17299425 on cerebral perfusion pressure (CPP), mean arterial blood pressure (MABP), and clinical scoring assessments (Glasgow Outcome Score [GOS]).
- To investigate the pharmacokinetic (PK) profile of JNJ-17299425.
- To investigate a PK/PD relationship of JNJ-17299425.

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METHODS:

- This was the first exploratory, multi-center, open-label study in humans, with an adaptive design to assess the safety, tolerability, PK, and PD of single and repeat, escalating, intravenous (IV) doses of JNJ-17299425 in subjects with TBI.
- Subjects with a moderately increased ICP, responding to ventricular drainage (ie, having an ICP drop of <20 mmHg after ventricular drainage) and who had not received any specific ICP-lowering therapy, other than ventricular drainage, before being dosed with JNJ-17299425 were enrolled. Study groups were to be adopted on the request of the Data Monitoring Committee (DMC). The first group were to receive 1 mg JNJ-17299425 (the term 'group' referring to the next set of subjects to be studied as requested by the DMC; a group was planned to include up to 3 subjects; a cohort referred to the total number of subjects studied at a given dose, and was made up of one or more groups). The decision for dose changes and trial termination were aided by a Bayesian decision procedure.
- The starting dose was 1 mg (10 mL of a 0.1 mg/mL solution) given as an IV bolus over 2 minutes in a central vein. As long as no relevant plasma drug concentrations of JNJ-17299425 were detected (plasma PK concentrations above the lower limit of quantification (LLOQ) for less than 5 hours), an increased dose could be given after only a cohort of 1 subject. For subsequent cohorts, if there was no toxicity or ICP response, and 10-minute concentration was <40 ng/mL, dose was increased by a factor of 5. If drug related toxicity was observed, or if 10-minute concentration was ≥40 ng/mL, the dose increases were decided on by the DMC, but could not exceed 2-fold. The extent of the dose increase was dependent on the PK, PD, safety and tolerability data obtained from the previous cohorts. The maximal dose permissible was 200 mg. It was expected that around 5 cohorts would be enrolled in this study.
- The study consisted of 2 parts (Part 1 and Part 2). Each part consisted of 2 stages.

Part 1: In Part 1, subjects were given a single dose of JNJ-17299425. The aim of Part 1 was to explore the dose – response curve, tolerability and safety profile, and pharmacokinetics of JNJ-17299425 given as a single dose. The starting dose was selected based on the nonclinical toxicology and toxicokinetic data.

Stage 1: In Stage 1, subjects were managed and treated initially using the standard guidelines of the study center (Refer to Initial management measures in Figure 1). All baseline safety parameters were documented. If the ICP increased to >20 mmHg the subjects were treated with ventricular drainage. For the subjects who responded to the initial treatment (reached an ICP <20 mmHg), the management continued as per site's normal procedures. The subjects who did not respond to the initial treatment were dropped out of the study and were managed according to the standard procedures. Before entering into Stage 2, ventricular drainage could be repeated up to 3 times at the discretion of the investigator.

Stage 2: If the ICP decreased to <20 mmHg after ventricular drainage, and then subsequently increased to >20 mmHg again (and if CPP was ≥60 mmHg), the subject entered Stage 2. These subjects were treated with JNJ-17299425.

The response was monitored for up to 30 minutes. A clinically meaningful response was defined as a relevant reduction of the ICP: a reduction of at least 15% or a value <20 mmHg reached within 30 minutes with the CPP maintained between 65 and 75 mmHg.

The following decision criteria were used:

Within 30 minutes postdose:

- If there was no meaningful response in ICP and the ICP remained >20 mmHg but <25 mmHg and the CPP remained >65 mmHg → monitoring was continued for 30 minutes.
- If there was no meaningful response in ICP and the ICP remained >20 mmHg but <25 mmHg but the CPP decreased to ≤65 mmHg (or did not sufficiently improve [if CPP was 60 to 65 mmHg at dosing]) → standard treatment was started, and if appropriate ventricular drainage and / or other therapy deemed appropriate by the Investigator, eg, inotropes was given.
- If there was no meaningful response and the ICP remained >25 mmHg → standard treatment (i.e., ventricular drainage) was started.

After 30 minutes postdose:

- If the ICP was still >20 mmHg → standard treatment (ventricular drainage) was started. MABP and CPP were appropriately managed.

After dosing, safety, tolerability, PD and PK assessments were made.

A 10 mL blood sample was collected before the first injection of the study drug from subjects after obtaining written informed consent for the pharmacogenomic component of this study.

The study could proceed to Part 2 only after Part 1 was completed and there was sufficient ICP reduction (mean ≥10% percentage decrease at highest dose, or dose with highest ICP reduction), and safety and tolerability to justify proceeding to Part 2.

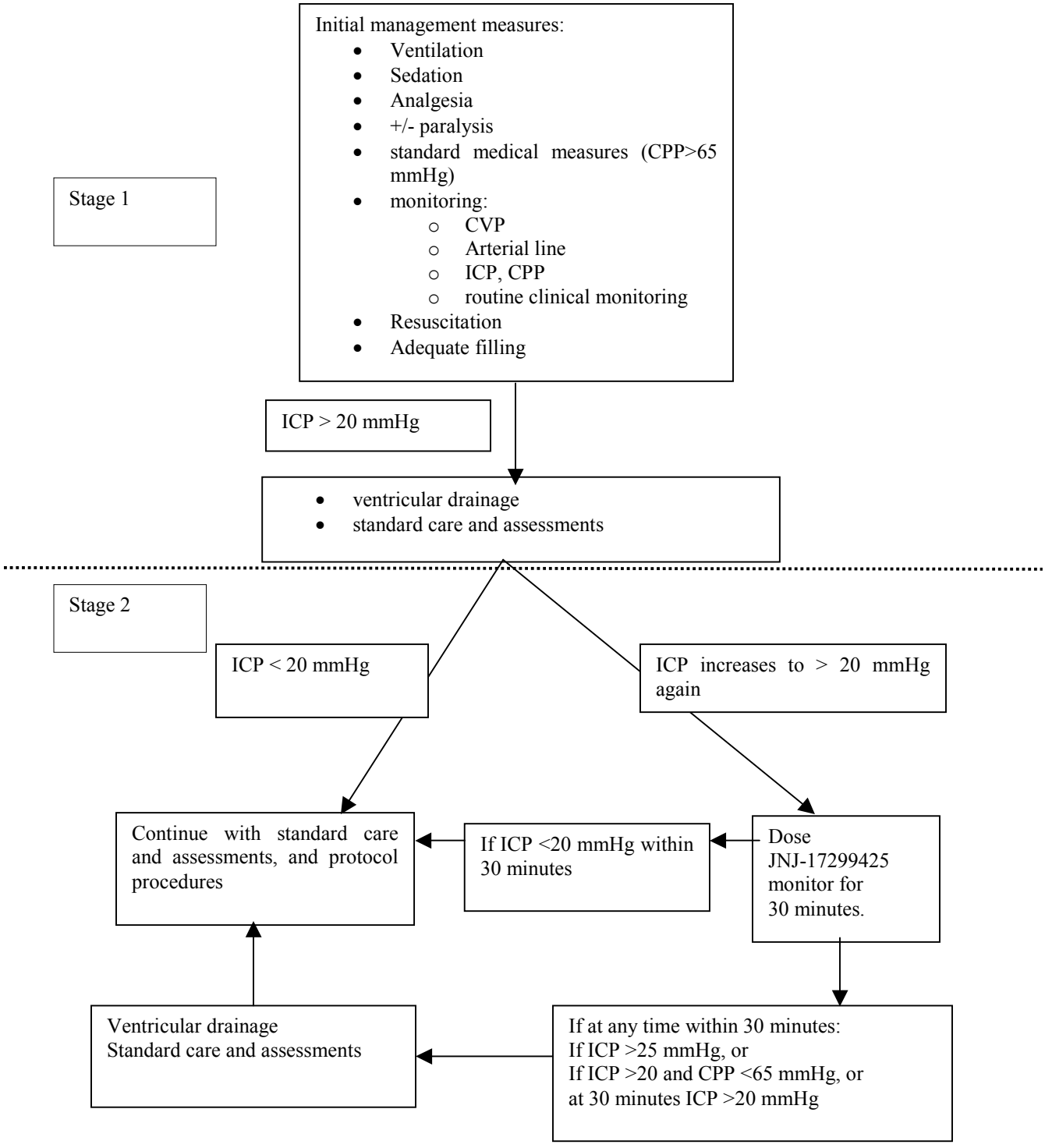
Part 2:

In Part 2, ICP reduction and safety and tolerability were to be assessed as primary endpoints. Secondary endpoints were supposed to be PK, and other clinical parameters.

Part 2 of the study was not performed as the study was prematurely terminated for company reasons.

The treatment schedule for Part 1 is given in Figure 1.

Figure 1: Treatment Schedule for Part 1
Study: 17299425TRM2001



CVP = central venous pressure

Dose Escalation and Dose Increment Guidelines:

- The aim of the study was to find a dose with ICP reduction activity with acceptable safety and tolerability. Thus the dose could be increased until there was:
- Either a clinically meaningful ICP reduction without unacceptable toxicity (success), or unacceptable toxicity without a relevant ICP reduction (failure), or no higher doses were feasible (eg restricted by the formulations available).
- The dose adaptation procedure was based on a procedure described by Ivanova (Ivanova 2003).

For the study endpoint there were:

- $p_{eff,target}$ minimal true response rate that could be considered useful.
- $p_{tox,tol}$ maximal true incidence of acceptable toxicity that could be tolerated.

At the start of the trial, $p_{tox,tol}$ value was set to 0.35 reflecting moderate toxicity of the compound. As the trial progressed and safety information became available, it may be possible to change the value of $p_{tox,tol}$; $p_{eff,target}$ was set to 0.7.

Change in Conduct:

The original protocol was issued on 5 April 2007, and there were 4 amendments to the protocol. The Amendment INT-1 and Amendment INT-2 were considered substantial.

Amendment INT-1 (dated 15 May 2007): A statement to the effect that the maximal dose would not exceed 200 mg was added.

Amendment INT-2 (dated 12 June 2007): The important changes made in this amendment were:

- On the request from Ethics committee, a confirmation of the informed consent was obtained from the subject for the execution of the follow-up visits after he or she had recovered. Similarly, the informed consent for pharmacogenomic research also had to be confirmed by the subject when he or she had recovered.
- Heparin Induced Thrombocytopenia test (HIT) was added. Only if unexpected and severe thrombocytopenia (<50.000 /μL) was observed in a subject, blood would be collected for a HIT test.
- A maximum plasma concentration above which subjects would not be exposed to the study drug, was specified for both parts of the study.

Amendment INT-3 (dated 07 November 2007): The dose escalation guidelines were modified to compare the drug concentrations in animals and humans at the 10-minute timepoint (7-8 minutes after the end of the infusion).

Amendment INT-4 (dated 31 January 2008): Glasgow coma score before ventilation would be documented as baseline value.

Number of Subjects (planned and analyzed):

Planned: A maximum of 54 subjects in about 5 cohorts with escalating doses were planned to be enrolled in the study. Analyzed: Seven subjects were enrolled in the study-2 subjects in 1 mg treatment group, 1 subject in 3 mg treatment group, 2 subjects in 9 mg treatment group and 2 subjects in 18 mg treatment group. Of these, all 7 subjects were analyzed for safety, 5 subjects for PK and 5 subjects for PD.

Diagnosis and Main Criteria for Inclusion:

Male and non-child bearing potential female subjects between 18 to 65 years of age, inclusive and a body mass index (BMI) of 18 to 35 kg/m^2, with traumatic head injury requiring intra-cranial pressure monitoring were included in the study after the informed consent was signed by a close relative or guardian.

Test Product, Dose and Mode of Administration, Batch No.:

JNJ-17299425 was provided in the strengths of 0.1 mg/mL, 1 mg/mL, and 10 mg/mL free base in 22.5% of 2-hydroxypropyl-β-cyclodextrin acidified with 2.5 mg/mL lactic acid to pH 4 for IV injection. The study drug was supplied by the sponsor in vials containing 40 mL. These vials were stored in the refrigerator at 2 to 8 °C in their original packaging.

Batches used during this study:

07C06/F002 = 0.1 mg/mL (expiry: March 2008)

07C06/F003 = 1 mg/ mL (expiry: March 2008)

08B11/F003 = 1 mg/ mL (expiry: February 2009)

The starting dose was 1 mg and the maximal dose did not exceed 200 mg. The study drug was administered using a syringe that is attached to an extension line and a filter connected to the central venous pressure (CVP) catheter using a stopcock. The IV solution given as a bolus over 2 minutes via a central vein using a 3 or 4-lumen central venous pressure (CVP) catheter through a 0.2 micron filter.

Reference Therapy, Dose and Mode of Administration, Batch No.:

Not applicable.

Duration of Treatment:

Since this was a dose finding study, in Part 1, subjects received a single dose of JNJ-17299425. Subjects who entered the Part 2 received 2 doses of JNJ-17299425. Subjects remained in the ITU for 28 days after the administration of the study drug.

CRITERIA FOR EVALUATION:

Pharmacokinetic Evaluation:

Venous blood samples of 3 mL were collected for determination of JNJ-17299425 plasma concentrations at the following time points: predose and 2 (end of bolus), 5, 10, 30 minutes and 1, 2, 3, 4, 6, 9, 12, 24, 36, 48 and 72 hours postdose. The exact dates and times of blood sampling were recorded in the case report form (CRF).

After the first dose blood PK samples were collected at 30 minutes, 1, 2, 6 and 12 hours postdose. During Part 2 of the study, the PK collection after the first dose was stopped at the second dose of JNJ-17299425. A sample was taken just before the second dose. Blood samples were processed to obtain plasma for measurement of JNJ-17299425 by selective and validated analytical methods under the direction of J&JPRD, Beerse, Belgium.

The following PK parameters were determined using Pharsight's WinNonlin PK analysis software and non-compartmental methodology:

C_0 (plasma concentration at 2 minutes [end of bolus]), AUC_{24} (area under the plasma concentration-time curve from 0 to 24 hours postdose), AUC_t (area under the plasma concentration-time curve from 0 to t hours postdose), AUC_∞ (AUC_t extrapolated to infinity), CL (clearance following IV administration), Vd (volume of distribution following IV administration), λ_z (elimination rate constant), and $t_{1/2}$(terminal half-life, defined as $0.693/\lambda_z$).

Pharmacodynamic Evaluations:

The following PD parameters were to be analyzed:

- Intracranial pressure (ICP): Percentage reduction from predose ICP; absolute ICP reduction defined as difference between pre-dose ICP and lowest ICP value achieved; time that ICP was below 20 mmHg; time to lowest ICP value achieved; time to 50% absolute ICP reduction; time the ICP was below 50% of absolute ICP reduction.
- Cerebral perfusion pressure (CPP): CPP was calculated automatically from ICP and MABP, and clinical scoring assessments. The clinical scoring assessment was to include the GOS.
- ICP derived variables:
  - Minimal ICP value: Lowest ICP value (excluding artifacts - negative and 0 measurements) measured in the interval between the dose administration and moment of the first postdose brain drainage (if performed within 24 hours).
  - Response status (yes/no): Subject was to be considered as a responder if within 30 minutes of drug administration ICP (or between the drug administration and first postdose brain drainage, if first postdose brain drainage occurred within 30 minutes of drug administration) percentage change from baseline was at least 15% or if within the same time minimal ICP value measured was lower then 20 mmHg.

Unacceptable toxicity:

For Part 1 or Part 2, the following observations were considered as unacceptable toxicity in a subject when observed after dosing of the study drug and attributable to the study drug:

- A thrombocytes count <50,000/μL;
- A potassium concentration above 6.0 mmol/L;
- A drop in hemoglobin concentration >30% from predose attributable to the study drug;
- Significant abnormalities in renal function;
- Significant abnormalities in hepatic function;
- Life threatening abnormalities in arterial blood gasses (pH or $PaCO_2$);
- An adverse event (AE) that could jeopardize his/her life as judged by the investigator and for which a relation with drug treatment cannot be excluded;
- If an investigator had any other safety concerns that prohibited any further dosing at the current or higher dose level.

Metabolomic Profiling

In a preclinical study in rats treated with JNJ-17299425, TBI was characterized by decreases in amino acids, lipids, metabolites of energy metabolism, and vitamins, giving a picture of a general slow-down of endogenous metabolism. Except for lipids, JNJ-17299425 led to a reactivation and restoration of metabolic activities. Thus metabolic profiling would be explored in this study, and would only be done in subjects included in Part 2 of the study when ICP reduction was

demonstrated. Timepoints for collection for metabolic profiling were: pre-dose, 30 minutes after the first dose and 30 minutes after the second dose.

Pharmacogenomics:

There were 2 parts to the pharmacogenomic component of this study (unrelated to the 2 parts of the clinical study):

Part 1: This part of pharmacogenomic research allowed for the analysis of genes that were hypothesized to be relevant to JNJ-17299425 or ICP. Only candidate genes were genotyped, as necessary, if it were hypothesized that this could help resolve issues with the clinical data.

Part 2: This part of the pharmacogenomic research allowed for the storage of DNA samples for future genetic research related to JNJ-17299425 or the indications for which it was developed.

Safety Evaluations:

Safety evaluations were made using the standard hospital monitoring procedures for trauma subjects on the ITU from admission until discharge. Adverse events were documented from the time informed consent was signed. The following assessments were made after the administration of study medication:

- Twelve-lead ECG predose and at 1, 2, 3, 4, 6, 9, 12, 18, 24, 36 and 48 hours postdose. Thereafter daily until discharge from the ITU
- Continuous vital signs including systolic blood pressure (SBP), diastolic blood pressure (DBP), pulse rate (PR), MABP, CVP, ventilation parameters, O_2 saturation.
- Frequent clinical laboratory assessments including thromboelastography, clotting screen, full blood count, blood biochemistry, urine safety assessments, platelet and endothelial tests and (optional) platelet function tests.
- Physical examination, body weight and temperature.

STATISTICAL METHODS:

Sample size determination:

As this was a study that followed Bayesian adaptive design algorithm, no formal sample size calculations were appropriate.

Pharmacokinetic analysis:

No statistical analysis of plasma PK parameters was planned.

Pharmacodynamic analysis:

Descriptive statistics (mean, standard deviation, median, and range) for each primary and secondary PD parameter as well as their changes from baseline were calculated. Where feasible, individual subject profile plots as well as summary plots of PD parameters against time were presented graphically for each dose level. Listings of ICP and CPP measurements and changes from baseline were produced. Values of ICP derived variables were calculated and presented in the separate listing.

Pharmacokinetic/Pharmacodynamic Relationships:

No PK/ PD statistical analysis was planned.

Safety analyses:

All treatment emergent AE were tabulated by system organ class using Medical Dictionary for Regulatory Activities (MedDRA). All individual data on physical examination were listed. The data on following laboratory test were listed: hematology, biochemistry, arterial blood gases, urinalysis, urine microscopy and markers for inflammation. Results from thromboelastography test (clotting time, clot formation time, maximum clot firmness and the alpha angle) were listed for each subject. Platelet and haemostasis tests individual results were fully listed. Vital signs (SBP, DBP and PR), together with other Intensive care monitoring parameters (MABP, CVP, O_2 saturation and ventilation parameters) were measured automatically every 30 seconds. The ECG parameters included heart rate, PR interval, QRS interval, QT interval, QTcB (QT corrected for heart rate according to Bazett), QTcF (QT corrected for heart rate according to Fridericia) and QTcL (QT linear correction according to Sagie/Framingham). QTcF was the primary variable. Other Safety Variables included medical history and concomitant treatments of subjects.

RESULTS:

Part 1:

- This trial was prematurely terminated for company strategy reasons and not as a result of any decisions concerning safety.
- Of the 7 subjects enrolled in the study, 4 subjects completed the study. Death occurred in two subjects, but none of them was seen as treatment related and one subject was discontinued due to an AE of intracranial hypertension.
- All subjects were white men aged 18 to 49 years, inclusive. The baseline weight and body mass index were 60 to 85 kg, and 19.1 to 26.2 kg/m^2 respectively.

Part 2:

There were no results for Part 2 of this study as the trial was prematurely terminated for company reasons.

PHARMACOKINETIC RESULTS:

Single Dose Phase (Part 1):

- In 1 subject administered a 1-mg dose and 1 subject administered the 3-mg dose, arterial and venous plasma samples were obtained. These showed similar PK profiles, indicating that either route of blood withdrawal could be used in subsequent subjects. Overlay plots of individual concentration-time profiles of JNJ-17299425 for arterial and venous injections are presented in Figure 2.
- Arterial plasma concentrations versus time curves are shown in Figure 3. At all doses, there was a rapid initial decline in plasma concentration during the first 30 minutes after administration, indicating an extensive distribution into tissues. This was followed by a terminal phase with a long half-life, with low but measurable plasma concentrations up to 72-hours postdose. (Figure 3).
- Blood samples were scheduled to be taken at predose and 2 (end of bolus), 5, 10, 30 minutes and 1, 2, 3, 4, 6, 9, 12, 24, 36, 48 and 72 hours postdose. However, complete PK profiles were only available for 4 (subject ID [redacted]) out of 7 subjects. These PK parameters are presented in Table 1. For the other 3 subjects, plasma samples could only be obtained for a short period after dosing, therefore only a limited number of PK parameters

could be calculated. The PK parameters that could be calculated for all 7 subjects are presented in Table 2.

- C_{max} and AUC_{0-1h} appeared to increase less than proportionally with dose. However, the significance of this observation is unclear, given the limited number of subjects available per dose level.

Table 1: Individual Plasma Pharmacokinetic Parameters of JNJ-17299425 Following Intravenous Administration of 1, 3, 9 or 18 mg in Subjects With Traumatic Brain Injury
(Study JNJ17299425-TRM-2001: Pharmacokinetic Analysis Set)

Treatment		Subject	Pharmacokinetic Parameters					
			t_{last} (h)	AUC_{last} (h.ng/mL)	$t_{1/2}$ (h)	AUC_{∞} (h.ng/mL)	Vd_z (L)	Cl (L/h)
1 mg	Arterial	[redacted]	6.00	10.6	NAs	NAs	NAs	NAs
			9.00	18.6	NAs	NAs	NAs	NAs
	Venous		6.00	9.85	NAs	NAs	NAs	NAs
3 mg	Arterial		72.00	64.8	29.5	74.2	1721	40
	Venous		1.00	26.9	NAs	NAs	NAs	NAs
9 mg	Arterial		72.00	197	(54.6) [a]	(304) [a]	(2334) [a]	(30) [a]
			72.00	182	NAs	NAs	NAs	NAs
18 mg	Arterial		72.00	353	(63.6) [a]	(576) [a]	(2865) [a]	(31) [a]
			1.00	50.2	NAs	NAs	NAs	NAs

[a] Extrapolation of AUC_{∞} exceeds 20%
NAs = Not Assessable; no full time profile was obtained.

Table 2: Plasma Pharmacokinetic Parameters Estimates (Mean) of JNJ-17299425 Following Intravenous Administration of 1, 3, 9 and 18 mg in Subjects With Traumatic Brain Injury
(Study JNJ17299425-TRM-2001: Pharmacokinetic Analysis Set)

Treatment		Pharmacokinetic Parameters					
		N	C_{max} (ng/mL)	DN_C_{max} (ng/mL) [c]	t_{max} (h) [a]	AUC_{0-1h} (h.ng/mL)	DN_AUC_{0-1h} (h.ng/mL) [c]
1 mg	Arterial	2	127	127	0.06	11.9	11.9
	Venous	1 [b]	100	100	0.03	7.73	7.73
3 mg	Arterial	1 [b]	414	138	0.03	27.3	9.1
	Venous	1 [b]	367	122	0.03	26.9	9.0
9 mg	Arterial	2	632	70	0.03	56.4	6.3
18 mg	Arterial	2	858	48	0.03	64.5	3.6

[a] t_{max}: mean
[b] represent the individual PK parameters of one subject
[c] dose normalized to 1 mg
DN = dose normalized

Figure 2: Individual Plasma Concentration-Time Profiles After Sampling Arterial or Venous Blood (Study JNJ-17299425-TRM-2001: Pharmacokinetics Analysis Set)

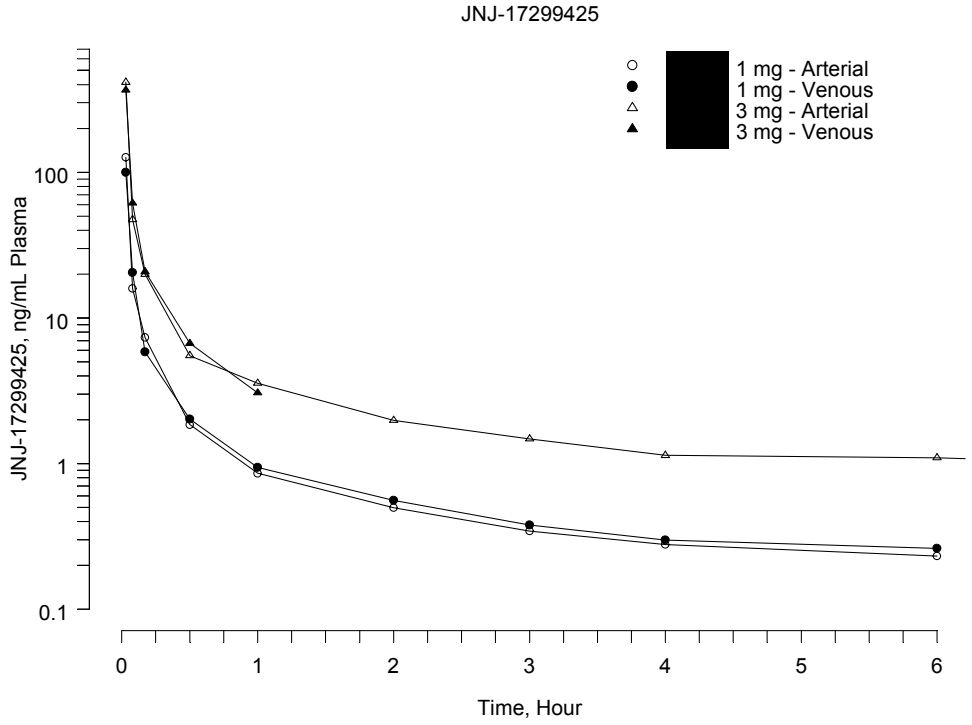
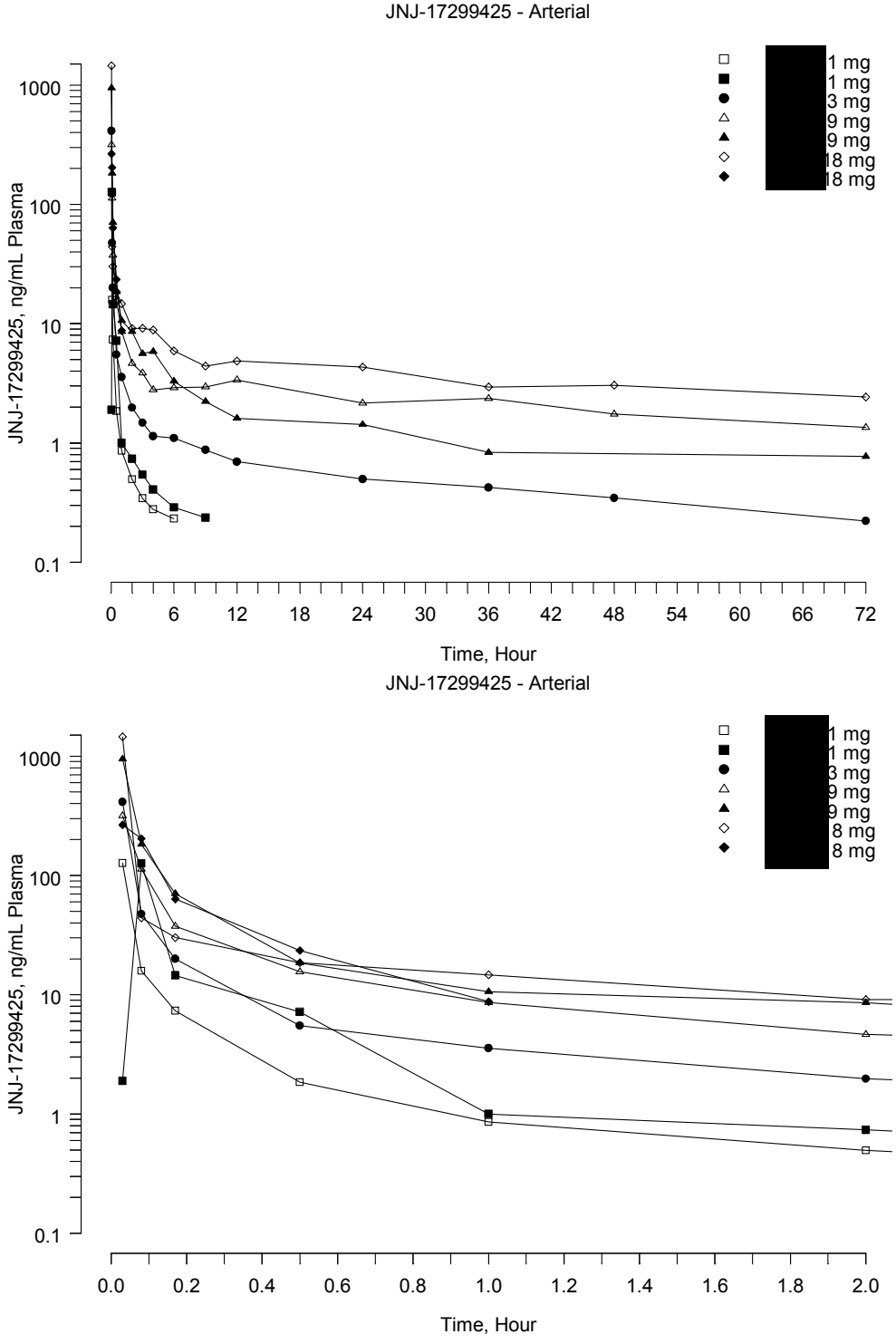


Figure 3: Individual Arterial Plasma Concentration-Time Profiles of JNJ-17299425 up to 72 (Top) or 2 (Bottom) Hours
(Study JNJ-17299425-TRM-2001: Pharmacokinetics Analysis Set)



PHARMACODYNAMICS RESULTS:

- ICP and CPP values from baseline were measured and listings were generated accordingly.
- The minimal ICP values for Subjects [redacted] and [redacted] were 22, 28 2, 21 and 19 respectively.
- Of the 5 subjects, 4 subjects (Subjects [redacted] and [redacted] were non-responders and 1 subject (Subject [redacted] was a responder.

SAFETY RESULTS:

- Death occurred in 2 subjects with TBI which were considered to be unrelated to study drug administration by the Investigator.
- There were 3 serious adverse events (SAE) of intracranial pressure increased, cardiac arrest and brain edema in Subjects [redacted] and [redacted] respectively. Subject [redacted] was discontinued from the study and death occurred in Subjects [redacted] and [redacted] All SAE were of severe intensity and were considered by the Investigator to be not related to study drug.
- All subjects reported at least 1 treatment emergent adverse event.
- The most commonly reported treatment-emergent AE by system organ class (SOC) in subjects receiving JNJ-17299425 were anemia (3 subjects), ECG QT prolonged (2 subjects), intracranial pressure increased (2 subjects) and diabetes insipidus (2 subjects) (Table 3).
- Most of the AE reported were moderate [20 (57%)] in severity.
- The majority of AE reported were considered by the Investigator not to be related to the study drug. Subject [redacted] reported treatment–emergent AE of bradycardia and QT prolongation that were considered by the Investigator to be possibly related to study drug. All other AEs were considered by the Investigator to be not related to study drug.
- No clear or consistent relationship with the incidence, type or duration of any AEs was observed with respect to dosing with JNJ-17299425.

Table 3: Incidence of Treatment-Emergent Adverse Events by System Organ Class and Preferred Term
(Study JNJ17299425-TRM-2001: Safety Analysis Set)

Body System or Organ Class Dictionary-Derived Term	JNJ17299425 1 mg (N=2) n (%)	JNJ17299425 3 mg (N=1) n (%)	JNJ17299425 9 mg (N=2) n (%)	JNJ17299425 18 mg (N=2) n (%)	Total (N=7) n (%)
Total no. subjects with adverse events	2 (100)	1 (100)	2 (100)	2 (100)	7 (100)
Infections and infestations	1 (50.0)	1 (100)	2 (100)	1 (50.0)	5 (71.4)
Bacterial infection	0	1 (100)	0	0	1 (14.3)
Bronchitis	0	0	1 (50.0)	0	1 (14.3)
Bronchopneumonia	1 (50.0)	0	0	0	1 (14.3)
Catheter sepsis	0	0	0	1 (50.0)	1 (14.3)
Central nervous system infection	0	1 (100)	0	0	1 (14.3)
Clostridium colitis	0	0	0	1 (50.0)	1 (14.3)
Infection	0	0	0	1 (50.0)	1 (14.3)
Lower respiratory tract infection	0	1 (100)	0	0	1 (14.3)
Lung infection pseudomonal	0	0	0	1 (50.0)	1 (14.3)
Pneumonia	0	0	1 (50.0)	0	1 (14.3)
Blood and lymphatic system disorders	1 (50.0)	0	1 (50.0)	1 (50.0)	3 (42.9)
Anaemia	1 (50.0)	0	1 (50.0)	1 (50.0)	3 (42.9)
Cardiac disorders	2 (100)	0	1 (50.0)	0	3 (42.9)
Bradycardia	0	0	1 (50.0)	0	1 (14.3)
Cardiac arrest	1 (50.0)	0	0	0	1 (14.3)
Tachycardia	1 (50.0)	0	0	0	1 (14.3)
Investigations	1 (50.0)	0	2 (100)	0	3 (42.9)
Electrocardiogram QT prolonged	1 (50.0)	0	1 (50.0)	0	2 (28.6)
Blood potassium decreased	0	0	1 (50.0)	0	1 (14.3)
Nervous system disorders	1 (50.0)	0	0	2 (100)	3 (42.9)
Intracranial pressure increased	1 (50.0)	0	0	1 (50.0)	2 (28.6)
Brain oedema	0	0	0	1 (50.0)	1 (14.3)
Endocrine disorders	0	0	1 (50.0)	1 (50.0)	2 (28.6)
Diabetes insipidus	0	0	1 (50.0)	1 (50.0)	2 (28.6)
Gastrointestinal disorders	0	1 (100)	1 (50.0)	0	2 (28.6)
Constipation	0	1 (100)	0	0	1 (14.3)
Gastritis	0	0	1 (50.0)	0	1 (14.3)
General disorders and administration site conditions	0	0	0	1 (50.0)	1 (14.3)
Oedema peripheral	0	0	0	1 (50.0)	1 (14.3)
Injury, poisoning and procedural complications	0	0	0	1 (50.0)	1 (14.3)
Brain contusion	0	0	0	1 (50.0)	1 (14.3)
Diffuse axonal injury	0	0	0	1 (50.0)	1 (14.3)
Metabolism and nutrition disorders	0	0	0	1 (50.0)	1 (14.3)
Hypernatraemia	0	0	0	1 (50.0)	1 (14.3)
Vascular disorders	0	1 (100)	0	0	1 (14.3)
Hypertension	0	1 (100)	0	0	1 (14.3)

Note: Incidence is based on the number of subjects, not the number of events
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Clinical Laboratory Tests

- There were no clinically significant changes in the clinical laboratory values except in Subject [redacted] This subject who received 1 mg JNJ17299425, had incidences of increased blood sodium on Day 3 (151.6 mmol/L) and Day 4 (152.9 mmol/L), and increase in the values of C reactive protein on Day 1 (194.4 mg/L), Day 2 (243.2 mg/L), Day 3 (265.4 mg/L) and Day 4 (243.8 mg/L). None of the above events were reported as AE.

Vital Signs

- There were no clinically meaningful changes from baseline pulse, blood pressure, and body temperature in any treatment group.

- None of the subjects had clinically significant abnormal vital signs values.

ECG Results

- High QTc and QRS values were flagged for all subjects. High HR values were flagged for Subjects [redacted] and [redacted] QT values were high for Subjects [redacted] and [redacted] Subjects [redacted] had low QRS and PR values. Low HR values were flagged for Subjects [redacted] and [redacted] None of these events was considered clinically significant by the Investigator.
- QT Prolongation was reported for Subject [redacted] and recorded as an AE. The event was considered by the Investigator to be not related to study drug
- Overall, there were no clear consistent treatment or time related changes to any clinical laboratory parameters, vital signs, or ECG measurements in any dose group.

Other Tests

- Thromboelastography and clotting tests were performed to assess thrombocyte function, as a slight decrease in platelet count, considered to be possibly due to mechanical injury of platelets, had been seen in dogs. No significant effects on platelet function were observed in this study.

STUDY LIMITATIONS:

No notable study limitations were identified by the sponsor.

CONCLUSION:

- In this prematurely terminated study of 7 subjects with traumatic brain injury, JNJ-17299425 appeared to be well tolerated with no severe treatment related adverse events.

REFERENCES

Ivanova A. A new dose-finding design for bivariate outcomes. Biometrics. 2003 Dec;59(4):1001-1007.

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