SYNOPSIS

Name of Sponsor:
Abbott Healthcare Products

Individual Study Table:

(For National Authority Use only)

Name of Finished Product:
SLV334

Name of Active Ingredient:
SLV334

Study Title:
A Randomized, Double-Blind, Placebo-Controlled Dose Escalation Study to Investigate the Safety and Pharmacokinetics after Single and Multiple Doses of SLV334 in Sequential Cohorts of Patients with Moderate and Severe Traumatic Brain Injury

Principal Investigator:
M Ross Bullock

Study Centers:
Fifteen study centers screened subjects and 14 study centers randomized subjects in Spain, Israel, Italy and the United States of America

Publication (Reference):
Not Applicable

Study Period:
24 APR 2009 (first subject first visit) to
16 AUG 2010 (last subject last visit)

Phase of Development:
IIa

Objectives:

Primary Objective

To determine the safety and tolerability of SLV334 after a single intravenous dose of 1000 mg SLV334 and after multiple intravenous doses of 1000 mg SLV334 and 2000 mg SLV334 (up to 3 days, twice daily [b.i.d.]) compared to placebo in subjects with moderate or severe traumatic brain injury (TBI).

Secondary Objectives

To determine the pharmacokinetics (PK) of SLV334 after a single dose of 1000 mg SLV334 and after multiple doses of 1000 mg SLV334 and 2000 mg SLV334 (up to 3 days, b.i.d) in subjects with moderate or severe TBI.

To assess the effect of SLV334 on clinical assessments such as intracranial pressure (ICP), cerebral perfusion pressure (CPP) and therapy intensity level (TIL).

To assess in a sub-sample of subjects (those with a ventricular catheter or microdialysis), SLV334 levels in the cerebrospinal fluid (CSF) and/or microdialysis compared to systemic levels.

To assess in a sub-sample of subjects (those with a ventricular catheter or microdialysis), the influence of single and multiple intravenous doses of SLV334 on neurohormone activities/concentrations related to the mode of action (neutral endopeptidase [NEP] and endothelin converting enzyme [ECE] and markers for apoptosis, necrosis and neural damage in the CSF and/or microdialysis) compared to placebo and compared to systemic (plasma) levels.

Methodology:

This was a multi-center, randomized, double-blind, placebo-controlled, dose escalation study to be conducted in four sequential cohorts. The following dose levels were to be administered intravenously:

Cohort 1: 1000 mg SLV334 as a single dose (n = 12) or placebo (n = 6)

Cohort 2: 1000 mg SLV334 b.i.d. for 1 day (n = 12) or placebo (n = 6)

Cohort 3: 2000 mg SLV334 b.i.d. for 1 day (n = 12) or placebo (n = 6)

Cohort 4: 2000 mg SLV334 b.i.d. for 3 days (n = 12) or placebo (n = 6)

Subjects were to be monitored for 14 days after the first dose for safety purposes and early outcome indications. A Data Safety Monitoring Board (DSMB) was to evaluate the safety after the first 15 subjects in each cohort had completed the first 14 days. If no safety concerns were identified by the DSMB, recruitment of subjects for the next dose cohort was to proceed. The DSMB could recommend adjusting the dose to be administered in the next cohort.

This study was prematurely terminated after Cohort 3 and subsequently the dose regimen planned for Cohort 4 (2000 mg SLV334 b.i.d. for 3 days) was not investigated. All subjects dosed in Cohort 3 at the time of termination were monitored and completed the study as per the Clinical Study Protocol. The decision to prematurely terminate the study was due to strategic considerations and not based on safety concerns as the DSMB recommendation after dosing in Cohort 3 was to allow the continuation of the study to Cohort 4.

Number of Subjects (Planned, Consented, Randomized and Analyzed):

Planned: 72 subjects

Consented: 58 subjects

Randomized: 57 subjects (All Subjects Randomized subject sample)

Analyzed: 54 subjects (Safety subject sample)

Diagnosis and Main Criteria for Inclusion:

Male or female subjects aged 16 to 70 years, both inclusive, diagnosed with TBI by history or by a clinical examination with a Glasgow Coma Score (GCS) of 12 or less and confirmed by abnormalities on a computed tomography (CT) scan. Subjects were to have a clinical indication to monitor ICP.

Test Product, Dose and Mode of Administration, Batch Number:

Test product: SLV334

Strength: 25 mg/mL

Mode of administration: intravenously

Batch numbers: 1060100-71163; 1060100-71208; 1060100-610161

Duration of Treatment:

Cohort 1: one 1-hour infusion

Cohorts 2 and 3: two 1-hour infusions separated by 12 hours

Reference Therapy, Dose and Mode of Administration, Batch Number:

Test product: Placebo

Strength: 0.9% NaCl

Mode of administration: intravenously

Batch numbers: 1060101-71164; 1060101-610290; 1060101-610291

Criteria for Evaluation

Pharmacokinetics and Pharmacodynamics:

The PK parameters assessed from plasma SLV334 concentrations were terminal elimination rate constant (λ_z [/h]), elimination half life ($t_{1/2}$) area under the plasma concentration-time curve from zero to infinity (AUC) and systemic clearance (CL) for Cohort 1 only and area under plasma concentration-time curve from zero to 12 hours ($AUC_{0-\tau}$), area under the plasma concentration-curve from zero to the last measurable time point (AUC_{0-t}), observed maximal plasma concentration (C_{max}), time to reach maximum plasma concentration (t_{max}) for Cohorts 1 to 3.

No PK parameters were estimated from the CSF or microdialysis concentrations of SLV334.

The pharmacodynamic (PD) markers in plasma were endothelin (ET) (1-21), big-ET-1, pro-brain natriuretic peptide (BNP), atrial natriuretic peptide (ANP), cyclic guanosine monophosphate (cGMP), ubiquitin C-terminal hydrolase (UCH-L) 1, and microtubule associated protein 2 (MAP-2). The observed and change from pre-dosing values were reported.

Safety:

Safety was assessed by adverse event (AE) monitoring, laboratory tests (hematology, biochemistry, coagulation and urinalysis), vital signs and electrocardiogram (ECG).

Furthermore, neuroworsening, ICP, CPP and TIL, CT scans, therapeutic procedures and surgical therapy, the use of vasopressor and hyperosmolar agents, fluids and arterial blood gases were assessed.

The long-term outcome was assessed with a Barthel Activities of Daily Living (ADL) Index, extended Glasgow Outcome Scale (GOS-E) and Short Form (SF)-36.

Other:

Total duration in the intensive care unit (ICU), the Day 14 status of subjects and the survival time from first dosing.

Statistical Methods:

Subject disposition, major protocol deviations, demographics, Baseline characteristics, GCS, medical history and concomitant medication were listed by subject and summarized.

The data analysis was descriptive in nature by cohort and treatment group as well as combining all cohorts and treatment groups.

Pharmacokinetics

Plasma SLV334 concentrations and PK parameters were summarized in tables, listings and figures. Cerebrospinal fluid concentrations for SLV334 were summarized descriptively and presented in listings. Microdialysis SLV334 concentrations were only listed.

Pharmacodynamics

For plasma PD markers, the concentrations were summarized as observed concentrations and baseline-adjusted concentrations for the PD markers. For all the PD markers, Day 1 pre-dose levels served as the baseline value. The CSF concentrations of the PD markers will be listed by-subject. The microdialysate concentrations of the PD markers will be listed by-subject. In order to explore the potential effect of placebo or the different doses from SLV334 on the PD markers, a repeated measures analysis was conducted using a mixed effect model on log concentrations.

Safety

Incidence, related and maximum severity of treatment-emergent AEs (TEAEs), serious adverse events (SAEs) and treatment-emergent SAEs (TESAEs) were listed by subject and summarized. All AEs starting after the first dosing, but within the Monitoring Period (13 days after the last dosing) were regarded as TEAEs. All AEs were listed by subject. Quantitative, qualitative, clinically significant and shifts in laboratory measurements were listed by subject and summarized. Vital signs and clinically significant abnormalities of vital signs were listed by subject and summarized. Quantitative, marked abnormalities, overall and ECG diagnoses were listed by subject and summarized.

Neuroworsening, ICP, TILs, CT scans, vasopressor and hyperosmolar agents, GCS, fluids and arterial blood gases were listed by subject and summarized. Therapeutic procedures and surgical therapy were listed by subject.

Barthel ADL Index, GOS-E and SF-36 scores were listed by subject and summarized.

Other

Total duration in ICU, Day 14 status and survival time from first dosing were listed by subject and summarized.

Summary

Pharmacokinetic Results:

SLV334 Plasma PK

Maximal plasma SLV334 concentrations were observed at the end of the infusion (approximately 1 hour) in all the cohorts [redacted] The geometric mean C_{max} was 2.75 (Cohort 3 versus Cohort 1) and 2.67 (Cohort 3 versus Cohort 2) folds higher with the 2000 mg dose as compared to the 1000 mg dose whereas the geometric mean $AUC_{0-\tau}$ was 3.5 (Cohort 3 versus Cohort 1) and 2.1 (Cohort 3 versus Cohort 2) folds higher with the 2000 mg dose as compared to the 1000 mg dose. The summary of key PK parameters of SLV334 for all cohorts is presented below. In addition, at the same dose level of 1000 mg, the geometric mean $AUC_{0-\tau}$ following the first dose in Cohort 2 was approximately 1.7 fold that of Cohort 1 in which a single dose was administered. The high variability in

$AUC_{0-\tau}$ estimates for Cohorts 2 and 3 likely contributed to the differences in Cohort 1 versus Cohort 2 geometric mean $AUC_{0-\tau}$ at the 1000 mg dose level and the higher ratio of geometric mean $AUC_{0-\tau}$ for Cohort 3 (2000 mg) / Cohort 1 (1000 mg) compared to Cohort 3 (2000 mg) / Cohort 2 (1000 mg).

Parameter (unit)	Cohort 1 (n=11)	Cohort 2 (n=12)	Cohort 3 (n=11)
C_{max} (µg/mL)	111 (43.9)	108 (20.7)	299 (92.8)
	104	107	286
C_{min} (µg/mL)	NC	4.96 (11.3)	17.6 (31.4)
	NC	ND	3.06
t_{max} (h)	1.00 (0.50-1.00)	1.02 (0.50 – 3.85)	1.00 (0.50-1.53)
$AUC_{0-\tau}$ (µg*h/mL)	180 (82.8)	325 (245)	778 (576)
	163	271	572
AUC (µg*h/mL)	238 (154)	NC	NC
	198	NC	NC
CL (L/h)	6.06 (3.95)	NC	NC
	5.05	NC	NC
$t_{1/2}$ (h)	2.46 (1.49)	NC	NC
	1.99	NC	NC

Note: Treatments are Cohort 1- 1000 mg SLV334; Cohort 2-1000 mg SLV334 bid; Cohort 3- 2000 mg SLV334 bid; Data are presented as mean (standard deviation) and geometric mean, respectively, except for t_{max} which is presented as median (range). In Cohort 1, n=10 for $AUC_{0-\tau}$ and n=8 for each of the following parameters: AUC, CL, $t_{1/2}$. NC: not calculated; ND: not determined

SLV334 CSF and Microdialysis PK

Seven CSF samples were collected from 6 subjects (treated with SLV334) in which concentrations of SLV334 in the CSF were measurable in 6 samples, ranging from 11.8 to 605 ng/mL.

Only one microdialysis sample was obtained for Subject [redacted] in Cohort 1 and the SLV334 concentration in the microdialysis sample was 19.0 ng/mL.

Pharmacodynamic Results:

Plasma PD variable

There were no statistically significant differences in least-squares means of ANP, ET (1-21), UCH-L1, and MAP-2 plasma concentrations though the ANP concentrations were higher with SLV334 treatment as compared to placebo. Plasma big-ET-1 was approximately 26 ($p = 0.0407$), 29 ($p = 0.0236$), and 64% ($p < 0.0001$) higher for SLV334 treatment in Cohorts 1, 2 and 3, respectively, as compared to the placebo.

Mean plasma concentration of cGMP was approximately 56% ($p = 0.0108$) higher for SLV334 treatment in Cohort 3 compared to placebo whereas Cohort 1 and 2 were not statistically significantly different from the placebo.

Mean plasma concentration of pro-BNP was approximately 58% ($p = 0.0495$) lower for SLV334 treatment in Cohort 2 as compared to the placebo whereas Cohorts 1 and 3 were not statistically significantly different from the placebo, however the Cohort 3 pro-BNP

concentration was 42% higher than placebo.

CSF PD Variables

There were no statistically significant differences in least-squares means of ANP CSF concentrations (combined across all time points) between Cohorts 1 and 2 SLV334 treatments as compared to placebo.

The mean MAP-2 CSF concentration for Cohort 1 was not statistically significantly different from the mean of the placebo group. The mean MAP-2 CSF concentration, combined was statistically significantly different from the mean concentration of the placebo group ($p = 0.0253$, approximately 119% higher versus placebo).

Comparison of Cohort 3 (SLV334 2000 mg b.i.d. 1 day) versus placebo was not performed because there were only 6 observations in the Cohort 3 group for MAP-2 and none for ANP.

Safety Results:

Two treatment-emergent deaths (10.0%) were reported in the placebo treatment group. Treatment-emergent SAEs were reported for 10 subjects (29.4%) in the SLV334 treatment group and 5 subjects (25.0%) in the placebo treatment group and other SAEs were reported for 11 subjects (32.4%) in the SLV334 treatment group and 4 subjects (20.0%) in the placebo treatment group.

Most TEAEs were considered to be unlikely related or unrelated to the study medication and mild by the investigator.

At least one TEAE was reported for all subjects. There were 102 events reported for 11 subjects in the SLV334 treatment group and 89 events reported for 7 subjects in the placebo treatment group in Cohort 1; 102 events reported for 12 subjects in the SLV334 treatment group and 68 events reported for 6 subjects in the placebo treatment group in Cohort 2; and 149 events reported for 11 subjects in the SLV334 treatment group and 72 events reported for 7 subjects in the placebo treatment group in Cohort 3.

The most frequently reported TEAE was pyrexia (18 subjects [52.9%] in the SLV334 treatment group and 12 subjects [60.0%] in the placebo treatment group). The following high level terms (HLTs) were reported for ≥ 10% more subjects in the SLV334 treatment group than in the placebo treatment group: hyperglycemic conditions nec, potassium imbalance, headaches nec, increased ICP disorders, neurological signs and symptoms nec, vascular hypertensive disorders nec and vascular hypotensive disorders.

The proportion of subjects in the SLV334 treatment group (38.2%) with hypotension was more than double that of subjects in the placebo treatment group (15.0%). However, the number of clinically significant abnormal vital signs measurements was lower and evenly distributed between the two treatment groups.

Variation in laboratory measurements was seen over time and was similar for the two treatment groups. Shift changes from normal at Baseline to high/low at Endpoint were observed for most variables. All subjects had at least one markedly abnormal laboratory measurement at any time point other than at Baseline.

Variation in vital signs was seen over time and between treatment groups. A decrease in mean and median systolic blood pressure (SBP) values was noted after the second dose. The change from Baseline was larger in the SLV334 treatment group than in the placebo treatment group.

Variation in ECG data, but no obvious trend, was observed over time and between treatment groups.

Most of the neuroworsening that were reported lasted 1 day and the proportion of subjects was similar in the two treatment groups (26.5% in the SLV334 treatment group and 30.0% in the placebo treatment group). No neuroworsening longer than 3 days was reported. Life-threatening critical events reported were hypoxemia and hypotension.

The mean duration of treatments used, ICP, CT scan evaluation results, the use of vasopressors and hyperosmolar agents and arterial blood gases were similar in both treatment groups. The proportion of subjects who received fluids was larger in the SLV334 treatment group than in the placebo treatment group.

The long-term outcome of subjects treated with SLV334, as assessed by the Barthel ADL Index, GOS-E and SF-36, did not indicate worsening as compared to subjects treated with placebo.

Other Results:

The mean and median duration from time of injury to the end of the ICU stay was longer in the SLV334 treatment group than in the placebo treatment group in all cohorts.

Overall, 3 subjects (15.0%) in the placebo treatment group died before the Day 14 assessments could be performed, while no subjects in the SLV334 treatment group died before the Day 14 assessments.

Most of the subjects discharged at the time of the Day 14 assessments were in the SLV334 treatment group.

The difference in the time from first dosing to death between the two treatments was not statistically significant.

Conclusion:

- In this exploratory study, SLV334 can be considered safe and well tolerated in males and females with moderate to severe TBI when administered intravenously as a 1000 mg single dose, 1000 mg b.i.d. for 1 day and 2000 mg b.i.d. for 1 day, with a recommendation to closely monitor blood pressure and ICP.
- In subjects with moderate to severe TBI, peak and total exposures of SLV334 increased in a greater than dose-proportional manner following single dosing (Day 1) over the 1000 to 2000 mg dose range. Geometric mean SLV334 C_{max} increased by 2.67 to 2.75-fold and $AUC_{0-\tau}$ increased by 2.1 to 3.5-fold.
- An apparent dose related statistically significant increase (26 to 64%) in big-ET-1 was seen with SLV334 treatments compared to placebo. cGMP plasma levels significantly increased (58% increase) with the highest dose (2000 mg SLV334 b.i.d.). None of the other biomarkers showed any meaningful differences.