040

Single-dose, Multiple-dose, and Population Pharmacokinetics of SUN13837 Injection, a Basic Fibroblast Growth Factor Mimic in Healthy Subjects

B Shah[1], PhD, I Darling[2], PhD, E Ludwig[2], PhD, H Zahir[3], PhD, K Duchin[1], PhD

[1]Asubio Pharmaceuticals, Inc, [2]Cognigen Corporation, [3]Daiichi Sankyo Pharma Development

ABSTRACT

SUN13837, a novel small molecule in development for the treatment of acute spinal cord injury and stroke with biological activities similar to basic fibroblast growth factor (bFGF) promotes cellular differentiation including angiogenesis and axonal outgrowth and provides neuronal protection without stimulating cell proliferation.

A first-in-human, randomized, double-blind, placebo-controlled study was conducted to assess safety, tolerability, and pharmacokinetics (PK) of SUN13837 in healthy subjects (escalating single intravenous [IV] dose of SUN13837: 0.04 to 1.92 mg/kg; 8 dose groups; 6 active and 2 placebo per dose group; 64 subjects). In a multiple-dose study, a daily IV dose of SUN13837 was administered for 7 days (0.25, 0.50, 1.00, and 1.50 mg/kg; 6 active and 2 placebo per group; 32 subjects). Interim population PK models were developed with pooled data from these Phase 1 studies and one additional Phase 1 PK study of SUN13837, administered 1 mg/kg intravenously to 28 healthy subjects.

SUN13837 was safe and well tolerated. In general, C_{max} and AUC for SUN13837 increased in a dose-proportional manner. Mean $t_{1/2}$ values after single doses ranged between 12.0-17.9 hours. With multiple doses, steady state appears to be achieved by Day 5 and accumulation was minimal (20% based on AUC). Urinary recovery of SUN13837 ranged from 31.7%-60.9% after multiple doses. SUN13837 metabolites in plasma were identified. Three metabolites were measured with a validated LC/MS method after single and multiple doses.

Three-compartment base structural PK models with linear elimination best described the SUN13837 and metabolite ASB15490 data. SUN13837 estimated clearance (15.5 L/h) and total volume of distribution (112.5 L) were similar to ranges obtained previously using noncompartmental analysis methods. Age was the most significant covariate; SUN13837 exposure increased modestly with advancing age.

SUN13837 showed linear PK and minimal accumulation with once-daily regimen. Initial population PK models provide a starting basis for dose selection and optimization in the target population.

BACKGROUND

- SUN13837 is a novel small molecule in development for the treatment of acute spinal cord injury (ASCI) and stroke
- Biological activities are similar to basic fibroblast growth factor which promotes cellular differentiation including angiogenesis and axonal outgrowth
- Provides neuronal protection without stimulating cell proliferation

OBJECTIVES

- Evaluate safety, tolerability, and PK of SUN13837 after single and multiple IV doses of SUN13837 in adult healthy subjects
- Identify and evaluate PK of SUN13837 metabolites – ASB15490, ASB15491, and ASB16628
- Develop a population PK model of SUN13837 and metabolite ASB15490 in healthy subjects

METHODS

Single-dose Study

Design: Phase 1, single-center, placebo-controlled, double-blind, randomized, sequential single-escalating dose study

Type and number of subjects

- Healthy male/female subjects (64) aged 18-50 years
- Groups 1-8 of 8 subjects each – 6 active and 2 placebo

Dose levels and dosing conditions

- 0.04, 0.08, 0.16, 0.32, 0.64, 0.96, 1.28, and 1.92 mg/kg
- Single bolus IV administration in the fasted state
- IV push did not exceed approximately 1 minute

Pharmacokinetic blood sample collection

- Blood samples collected in tubes containing sodium heparin at: pre-dose and at 0.08 (5 minutes), 0.25, 0.5, 1, 1.5, 2, 4, 6, 8, 12, 18, 24, 36, 48, 60, and 72 hours postdose
- Urine samples collected at: pre-dose at -12 to 0 and at 0-4, 4-8, 8-12, 12-24, 24-48, and 48-72 hours postdose

Multiple-dose Study

Design: Phase 1, single-center, placebo-controlled, double-blind, randomized, sequential escalating multiple-dose study

Type and number of subjects

- Healthy male/female subjects (32) aged 18-53 years
- Groups 1-4 of 8 subjects each – 6 active and 2 placebo

Dose levels and dosing conditions

- 0.25, 0.50, 1.00, and 1.50 mg/kg
- Daily bolus IV administration in the fasted state for 7 consecutive days
- IV push did not exceed approximately 1 minute

Pharmacokinetic blood sample collection

- Blood samples collected in tubes containing sodium heparin at: Day 1 – pre-dose and at 0.08 (5 minutes), 0.25, 0.5, 1, 2, 4, 6, and 12 hours postdose
- Trough samples – Days 2 through 6, Day 7 - 0.08 (5 minutes), 0.25, 0.5, 1, 2, 4, 6, 12, 24, 36, 48, and 72 hours postdose and Day 13 or 14 (~168 hours postdose)
- Urine samples collected at: Day 1 – pre-dose at -24 to 0, and at 0-4, 4-8, 8-12, 12-24 hours postdose, Day 6 – 0-24 hours postdose, Day 7 – 0-4, 4-8, 8-12, 12-24, 24-48, and 48-72 hours postdose

Formulation

- SUN13837: 20 mL of 5 mg/mL in a sterile vial (100 mg/vial)

Bioanalytical methods

- Validated LC-MS/MS method for the analysis of SUN13837 in plasma and urine with a lower limit of quantitation (LLOQ) of 0.01 ng/mL
- Validated LC-MS/MS method for the analysis of ASB15490, ASB15491, and ASB16628 in plasma with LLOQ of 1 ng/mL

Pharmacokinetic analysis

- Noncompartmental analysis of plasma concentration-time profile for each subject using WinNonlin® Professional, Version 5.2

Metabolite Identification

- Exploratory analyses of possible SUN13837 metabolites in plasma were performed using LC-MS method

Structural Population Pharmacokinetic Model

Data Sources

- Pooled SUN13837 plasma concentration data from a single-dose study, multiple-dose study, single 1-mg/kg IV dose in middle aged (N = 14) and elderly (N = 14) healthy subjects
- Pooled ASB15490 plasma concentration data from multiple-dose study and single 1-mg/kg IV dose in middle aged (N = 14) and elderly (N = 14) healthy subjects

METHODS, CONT'D.

Structural Population Pharmacokinetic Model

Pharmacokinetic analysis

- Compartmental analysis of plasma concentration-time profile for each subject using NONMEM, Version 7.1.2

Demographics

- See **Table 1**

Table 1. Demographics

Characteristics	Total Subjects (N = 100)
Dose Range	0.043 to 1.929 mg/kg
Sex, N (%)	100 (100)
Male	84.0 (84.0)
Female	16.0 (16.0)
Age (y)	
Mean (SD)	38.0 (17.5)
Median	29.0
(Min - Max)	(18.0 - 80.0)
Race, N (%)	100 (100)
Caucasian	91.0 (91.0)
African-American	9.0 (9.0)
Others	0.0
Weight (kg)	
Mean (SD)	77.7 (12.3)
Median	76.8
(Min - Max)	(54.0 - 117)

RESULTS

Single-dose Study

- A rapid initial distribution phase within the first 15 minutes with an apparent biphasic disposition after the rapid distribution phase between 15 minutes and 72 hours after IV administration (**Figure 1**)
- In general, SUN13837 mean exposure increased with increasing dose (**Table 2**)
- The mean terminal $t_{1/2}$ for all treatment groups ranged between 12 and 18 hours
- Minimal accumulation ratio of approximately 1.05 was predicted from single-dose data
- Urinary recovery was variable among dose groups with the mean percent of dose excreted unchanged in the urine ranging between 30.2% and 81.5%

Figure 1. Mean (SD) SUN13837 Plasma Concentration-Time Profiles After Single Intravenous Administration of SUN13837 to Healthy Subjects (Logarithmic Y-Axis Scale)

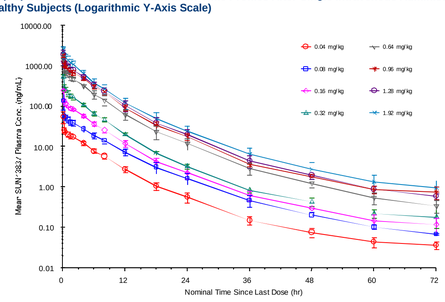


Table 2. Plasma Pharmacokinetic Parameters of SUN13837 After Single Intravenous Administration of SUN13837 to Healthy Subjects (n = 6/group)

Parameters Mean (%CV)	SUN13837 Injection (mg/kg)							
	0.04	0.08	0.16	0.32	0.64	0.96	1.28	1.92
C_{max} (ng/mL)	55.4 (32.1)	139 (42.1)	247 (23.7)	540 (13.2)	1457 (20.2)	1809 (10.4)	1896 (30.4)	2545 (17.4)
C_0 (ng/mL)	77.9 (41.3)	204 (54.3)	322 (34.8)	683 (15.8)	1927 (24.1)	2210 (12.7)	2319 (36.6)	3029 (18.2)
$AUC_{0\text{-}1h}$ (ng·h/mL)	145 (12.2)	347 (15.9)	678 (8.7)	1307 (9.6)	3767 (14.4)	5571 (9.4)	6142 (16.5)	7950 (21.1)
$AUC_{0\text{-}72h}$ (ng·h/mL)	152 (12.6)	367 (16.2)	705 (9.1)	1346 (9.4)	3898 (14.6)	5760 (9.4)	6353 (16.9)	8229 (21.3)
$AUC_{0\text{-}\infty}$ (ng·h/mL)	153 (12.6)	368 (16.1)	708 (9.1)	1350 (9.4)	3904 (14.5)	5778 (9.4)	6364 (16.8)	8247 (21.3)
CL (L/h)	19.8 (15.4)	17.8 (16.8)	17.7 (9.2)	17.2 (4.0)	13.6 (8.5)	14.7 (14.8)	14.7 (13.0)	17.0 (19.4)
Vd_{ss} (L)	135 (12.9)	127 (13.9)	110 (9.1)	95.7 (12.7)	77.5 (14.1)	87.8 (14.7)	85.4 (15.1)	93.5 (12.4)
$t_{1/2}$ (h)	17.9 (20.1)	13.7 (20.9)	14.7 (22.4)	15.8 (24.3)	12.0 (24.7)	15.9 (24.5)	13.0 (26.2)	12.7 (11.4)

Multiple-dose Study

- The Day 1 plasma-concentration-time profiles were consistent with those observed in the single-dose study (**Figure 2**)
- Steady-state conditions for SUN13837 were achieved by Day 5 of the study (**Figure 3**)
- Dose proportionality over the 0.25- to 1.50-mg/kg dose range was observed (**Table 3** and **Table 4**)
- With repeated administration intersubject variability for C_{max} and AUC was relatively low (10.7-24.6 %CV)
- Accumulation ratios were approximately 20% for AUC
- 31.7% to 60.9% of the dose was excreted unchanged in urine
- Steady-state metabolite to parent ratios (in %) for AUC_{tau} for ASB15490, ASB15491, and ASB16628 were 4.4%, 13.8%, and 12.9%, respectively (**Figure 4**)

RESULTS, CONT'D.

Figure 2. Day 1 and Day 7 Mean SUN13837 Plasma Concentration-Time Profiles After Multiple Daily Intravenous Administration of SUN13837 to Healthy Subjects (Logarithmic Y-Axis)

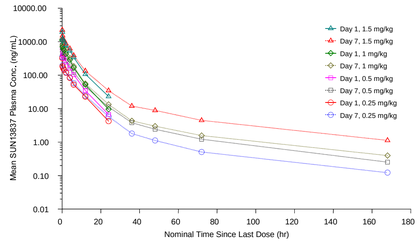


Figure 3. Mean (SD) SUN13837 Pre-dose Plasma Concentrations From Day 1 to Day 7

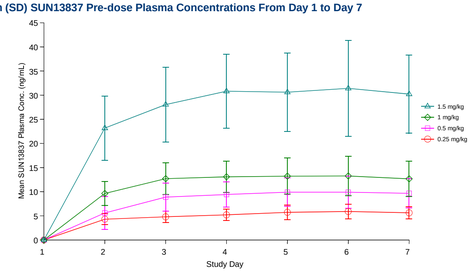


Table 3. Mean (%CV) Day 1 Plasma Pharmacokinetic Parameters of SUN13837

PK Parameter (unit)	Dose Level of SUN13837 Injection (mg/kg)			
	0.25 (n = 5)[a]	0.50 (n = 5)[b]	1.00 (n = 6)	1.50 (n = 6)
C_0 (ng/mL)	441 (22.5)	801 (20.0)	1410 (30.2)	2358 (36.4)
C_{max} (ng/mL)	327 (17.8)	634 (19.1)	1096 (26.9)	1952 (32.1)
C_{min} (ng/mL)	4.25 (29.6)	6.71 (34.0)	9.63 (26.1)	23.2 (28.7)
$AUC_{0\text{-}24}$ (ng·hr/mL)	1049 (13.7)	2057 (15.3)	3436 (14.8)	6504 (22.9)
C_{max}/Dose (ng/mL/mg)	16.0 (20.0)	18.2 (17.0)	14.7 (29.7)	14.9 (36.0)
$AUC_{0\text{-}24}$/Dose (ng·hr/mL/mg)	51.1 (11.7)	59.3 (16.1)	46.0 (18.0)	49.0 (22.1)

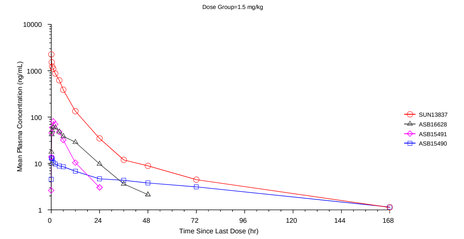
[a] Subject 104 was excluded from Day 1 only because the profile was not consistent with IV dosing;
[b] Subject 202 was excluded from Day 1 only because SUN13837 was not administered on that day.

Table 4. Mean (%CV) Day 7 Plasma Pharmacokinetic Parameters of SUN13837

PK Parameter (unit)	Dose Level of SUN13837 Injection (mg/kg)			
	0.25 (n = 6)	0.50 (n = 6)	1.00 (n = 6)	1.50 (n = 6)
C_0 (ng/mL)	470 (26.2)	953 (18.9)	1440 (31.6)	2787 (31.3)
$C_{max,ss}$ (ng/mL)	350 (24.1)	748 (13.8)	1185 (24.6)	2254 (24.0)
$C_{min,ss}$ (ng/mL)	5.83 (16.6)	11.2 (37.4)	13.4 (19.9)	34.7 (24.3)
C_{trough} (ng/mL)	46.8 (11.8)	100 (18.0)	160 (10.7)	314 (18.3)
$C_{max,ss}$/Dose (ng/mL/mg)	17.1 (22.6)	21.5 (16.3)	15.6 (21.3)	17.0 (22.8)
$t_{1/2}$ (hr)[a]	36.0 (40.4)	35.8 (21.3)	39.0 (25.9)	38.9 (25.9)
AUC_{tau} (ng·hr/mL)	1125 (11.8)	2401 (18.0)	3829 (10.7)	7530 (18.3)
AUC_{tau}/Dose (ng·hr/mL/mg)	55.1 (7.9)	69.2 (23.4)	51.3 (15.4)	57.0 (18.8)
CL_{ss} (L/hr)	18.2 (7.5)	15.1 (21.7)	19.9 (17.2)	18.1 (19.9)
Vd_{ss} (L)	148 (16.8)	113 (17.0)	129 (18.3)	140 (13.7)

[a] The long elimination half-life compared with single dose (ASBI601) was calculated from the terminal elimination phase after the Day 7 drug administration using time points to 168 hours.

Figure 4. Mean SUN13837 and Metabolite Plasma Concentration-Time Profiles on Day 7 in the Highest Dose Group (Logarithmic Y-Axis)



SUN13837 Structural Population Pharmacokinetic Model

- 3-compartment model with linear elimination (**Figure 5**)
- Estimated CL (15.5 L/h) and total volume of distribution (112.5 L) were similar to ranges of 13.6-19.9 L/h and 77.5-148 L obtained using noncompartmental methods (**Table 5**)
- Age and weight are significant covariates: CL, Vc, Q2, and Q3 decrease with increasing age, and CL increases with increasing weight (power functions)
- All parameters were precisely estimated (%SEMs generally < 30%)
- The goodness-of-fit plots indicate a reasonable fit of the model to the data (**Figure 6**)

RESULTS, CONT'D.

Figure 5. 3-Compartment Pharmacokinetic Model

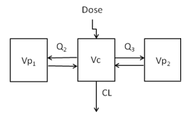
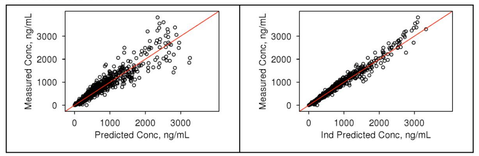


Table 5. SUN13837 Population Pharmacokinetic Estimates

Parameter	Final Parameter Estimate		Inter-individual and Residual Variability (%CV)	
	Typical Value	%SEM	Final Estimate	%SEM
CL (L/h)	15.5	1.95	15.6	20.0
Age effect on CL	-0.360	13.9		
Weight effect on CL	0.386	23.3		
Vc (L)	31.5	6.32	34.8	18.5
Age effect on Vc	-0.518	18.2		
Q_2 (L/h)	0.637	3.94	22.9	30.1
Age effect on Q_2	-0.355	24.4		
Vp_2 (L)	25.2	7.08	57.0	12.7
Q_3 (L/h)	109	5.84	NE	NA
Age effect on Q_3	-0.864	9.25		
Vp_3 (L)	55.8	4.16	21.6	16.9
Proportional RV	NA	NA	15.6	9.57

Abbreviations: %CV, coefficient of variation; NA, not applicable; NE, not estimated; RV, residual variability; %SEM, (standard error / parameter estimate × 100)

Figure 6. SUN13837 Goodness-of-fit Plots



Metabolite ASB15490 Structural Population Pharmacokinetic

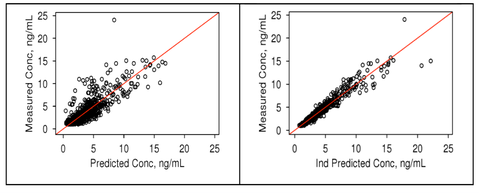
- 3-compartment model with linear elimination; ASB15490 formation was described by a first-order process (ka, **Table 6**)
- Age was a significant covariate: CL, Vc, Q2, and Vp2 decrease with increasing age
- Fixed effect parameters were precisely estimated (most %SEMs < 23%); random error parameters were estimated less precisely (most %SEMs < 40%)
- The goodness-of-fit plots indicate a reasonable fit of the model to the data (**Figure 7**)

Table 6. Metabolite ASB15490 Population Estimates

Parameter	Final Parameter Estimate		Inter-individual and Residual Variability (%CV)	
	Typical Value	%SEM	Final Estimate	%SEM
CL (L/h)	670	19.5	57.3	39.0
Age Effect on CL	-1.05	49.5		
Vc (L)	13700	12.0	40.9	25.4
Age Effect on Vc	-0.825	20.9		
Q_2 (L/h)	9560	22.0	35.3	60.8
Age Effect on Q_2	-1.25	22.8		
Vp_2 (L)	7500	8.86	NE	NA
Q_3 (L/h)	1170	17.4	64.7	40.2
Vp_3 (L)	32400	22.6	42.3	70.8
Age Effect on Vp_3	-0.458	109		
ka (1/h)	22.6	9.08	NE	NA
Proportional RV	NA	NA	14.2	4.9

Abbreviations: NA, not applicable; NE, not estimated; RV, residual variability; %SEM, (standard error / parameter estimate × 100)

Figure 7. Metabolite ASB15490 Goodness-of-fit Plots



CONCLUSIONS

- SUN13837 was well tolerated
- SUN13837 showed linear PK and minimal accumulation with once-daily regimen
- The initial population PK model provides a starting basis for dose selection and optimization in the target population

ACKNOWLEDGEMENT

Authors sincerely thank Alex Vandell, PharmD, PhD, Daiichi Sankyo Pharma Development for presenting the poster at American College of Clinical Pharmacology Annual Meeting, September 2015, San Francisco, CA, USA.