Single Ascending Dose Pharmacokinetics (PK), Pharmacodynamics (PD), and Tolerability of LP352 in Healthy Subjects

Dolly A. Parasrampuria[1], Ian Mills[2], Gale O'Connell[3], Archana Chaudhary[4], Jon Ruckle[5], Chad Orevillo[1], Phil Perera[1]

[1]Longboard Pharmaceuticals; [2]Mills Medical Ltd; [3]O'Connell Consultancy Services Ltd; [4]Parexel; [5]Pacific Pharma Group, LLC; [1]Longboard Pharmaceuticals

Abstract #1750

BACKGROUND

- LP352 is a 5-HT2C agonist under development for the treatment of developmental and epileptic encephalopathies (DEEs). Primary pharmacology studies indicate that LP352 is a selective 5-HT2C receptor agonist, showing >227-fold selectivity versus 5-HT2A and 5-HT2B receptors and no activity across a wide range of protein targets including those commonly associated with safety considerations and abuse liability.
- A GLP package was conducted to support clinical use of LP352 and included a standard genotoxicity battery, repeat dose toxicity studies in rats and monkeys, and safety pharmacology studies assessing respiratory, cardiovascular, and CNS functions. These studies provided sufficient safety margins and confidence to allow LP352 to be tested in humans.
- 5-hydroxytryptamine (5-HT) plays a stimulatory role in regulating prolactin (PRL) secretion in experimental animals and in healthy human volunteers. Data suggest the possibility that serum PRL levels in humans may represent a useful tool to evaluate the activity of drugs possessing central 5-HT activity (Quattrone 1983, Gustafson 2008, and Mallman 2014). Hence, an objective of this study was to explore the effect of single doses of LP352 on serum prolactin levels.
- Food can impact the PK of an orally administered drug, resulting in a delay in gastric emptying, alteration of drug solubility, or direct interaction with the drug itself (Lentz, 2008). Increases in bioavailability (BA) may produce unwanted AEs, or conversely, if a high fat meal is required to achieve therapeutic drug levels, fasted administration could result in sub-optimal exposures. Therefore, an additional objective of this study was to compare the BA of LP352 administered as powder in capsule under fasted vs fed dosing conditions in order to guide dosing in the multiple ascending dose study.

OBJECTIVES

- To assess the safety and tolerability of single doses of 1 mg, 3 mg, 6 mg, 12 mg, and 24 mg of LP352 in healthy adult female subjects
- To assess PK profile of single doses of 1 mg, 3 mg, 6 mg, 12 mg, and 24 mg LP352 in healthy adult female subjects
- To explore the effect of single doses of LP352 on serum prolactin levels
- To assess the effect of a high fat/high calorie meal on the bioavailability of a 6 mg single dose of LP352

DESIGN/METHODS

Design and Methods (Fasted)

- Randomized, double-blind, placebo-controlled, parallel-group, safety, tolerability, PK and PD assessment of single ascending doses of LP352 or placebo administered orally as powder in capsule (PIC) to healthy adult fasting female subjects in doses of 1 mg, 3 mg, 6 mg, 12 mg, and 24 mg.
- Subjects were initially randomized into 5 sequential cohorts in an ascending dose fashion. Each cohort consisted of 8 new subjects (6 active and 2 placebo), and the first 2 subjects of each cohort (1 active and 1 placebo) were randomized to dosing on Day 1 for sentinel dosing.
- All fasted cohorts, except the cohort which was also later fed, consisted of a Screening period (Day -28 to -2), an Assessment period (Days -1 to 5), and a 9-day post-dosing Follow-up Visit (Day 10 ± 1).

Design and Methods (Fed)

- Randomized, double-blind, placebo-controlled, single-dose design that included subjects from 1 cohort (6 mg) from the fed portion of the study who received LP352 or placebo.
- Subjects from fasting cohort 3 (6 mg dose) undertook a second treatment period prior to their Follow-up Visit. In this second period, subjects received 6 mg LP352 or placebo 6 mg following a high-fat breakfast within 30 minutes prior to dosing.
- For the cohort that participated in both fasting and fed parts, the study consisted of a Screening period prior to the fasting portion of the study (Day -28 to -2), 2 Assessment periods (Days -1 to 5) with dosing separated by a minimum of 10 days, and a 9-day post-dosing Follow-up Visit (Day 10 ± 1) after the fed portion of the study.

Pharmacokinetic Parameters

- Plasma PK samples were collected at predose (within 45 minutes prior to dosing), and up to 96 hours post dose but PK measures most were BQL by 48 h
- Maximum observed plasma concentration (C_{max})
- Time of the maximum observed plasma concentration (T_{max})
- AUC from time zero to the last measurable concentration (AUC_{last})
- AUC from time zero to infinity ($AUC_{0\text{-}inf}$)
- Apparent plasma terminal elimination half-life ($T_{1/2}$)
- Apparent terminal clearance (CL/F)
- Apparent volume of distribution (Vz/F)
- Renal clearance (CL_R)

Plasma LP352 Analysis

- Plasma concentrations of LP352 were determined with a validated method using high performance liquid chromatography with mass spectrometric detection

Statistical Methods

- Determination of Sample Size: The sample size chosen for this study was based on precedent set by other PK studies of similar nature and was not based on power calculations
- **Fasting:** Plasma concentration time data were analyzed using noncompartmental methods to report key PK parameters: C_{max}, T_{max}, AUC_{last}, $AUC_{0\text{-}inf}$, CL/F, Vz/F, $T_{1/2}$, CL_R. Concentration time data and PK parameters were summarized using descriptive statistics. Dose proportionality for C_{max}, AUC_{last} and $AUC_{0\text{-}inf}$ was explored graphically for estimated PK parameters and dose-normalized parameters.
- **Fed:** Plasma concentration time data were analyzed using noncompartmental methods to estimate C_{max}, T_{max}, AUC_{last}, $AUC_{0\text{-}inf}$. Food effect was assessed using geometric mean ratios of Fed/Fasted treatments and percent change in C_{max}, AUC_{last} and $AUC_{0\text{-}inf}$ with food. Concentration time data and PK parameters were summarized using descriptive statistics.

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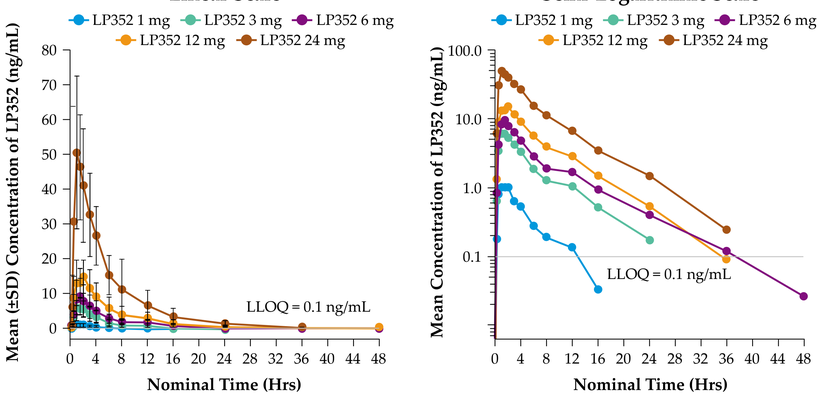
RESULTS

Fasted: Demographics and Baseline Characteristics (Safety Set)

Characteristic, n (%)	LP352 Cohort 1 1 mg (N = 6)	LP352 Cohort 2 3 mg (N = 6)	LP352 Cohort 3 6 mg (N = 6)	LP352 Cohort 4 12 mg (N = 6)	LP352 Cohort 5 24 mg (N = 6)	Pooled Placebo (N = 10)	Overall (N = 40)
Age (years), Mean (SD)	36.0 (5.14)	33.3 (11.60)	40.0 (10.92)	31.5 (7.66)	35.0 (7.56)	34.6 (5.54)	35.0 (8.01)
Sex, n (%)							
Male	0	0	0	0	0	0	0
Female	6 (100)	6 (100)	6 (100)	6 (100)	6 (100)	10 (100)	40 (100)
Ethnicity, n (%)							
Hispanic or Latino	1 (16.7)	1 (16.7)	0	0	1 (16.7)	0	3 (7.5)
Not Hispanic or Latino	5 (83.3)	5 (83.3)	6 (100)	6 (100)	5 (83.3)	10 (100)	37 (92.5)
Race, n (%)							
American Indian or Alaska Native	0	0	0	0	0	0	0
Black or African American	1 (16.7)	1 (16.7)	2 (33.3)	0	0	3 (30.0)	7 (17.5)
Native Hawaiian or Other Pacific Islander	0	0	0	0	0	0	0
White	5 (83.3)	2 (33.3)	3 (50.0)	5 (83.3)	6 (100)	5 (50.0)	26 (65.0)
Asian	0	1 (16.7)	1 (16.7)	0	0	2 (20.0)	4 (10.0)
Other	0	0	0	0	0	0	0
Mixed	0	2 (33.3)	0	1 (16.7)	0	0	3 (7.5)
Height (cm), Mean (SD)	166.8 (5.27)	164.3 (4.13)	162.8 (7.25)	167.8 (4.54)	163.7 (4.59)	164.6 (7.28)	165.0 (5.74)
Weight (kg), Mean (SD)	68.92 (6.640)	69.93 (7.796)	62.78 (7.154)	66.37 (7.599)	60.78 (4.789)	63.44 (5.930)	65.18 (6.996)
BMI (kg/m^2), Mean (SD)	24.80 (2.415)	25.92 (2.880)	23.63 (1.800)	23.60 (3.076)	22.67 (0.991)	23.45 (2.263)	23.96 (2.409)

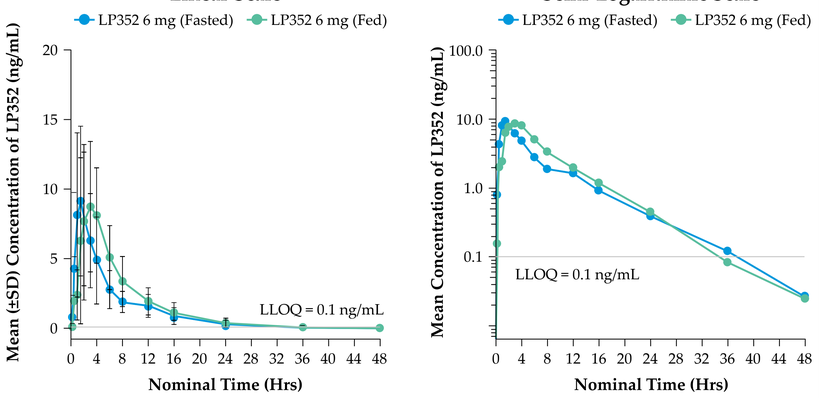
Mean Plasma Concentrations of LP352 (OP352) vs Time up to 48 hours, Linear and Log Linear Scales (PK Set) Under Fasted Conditions



Mean (SD) of PK Parameters Following Single Dose Administration of LP352 Under Fasted Conditions

Statistic	1 mg N = 6	3 mg N = 6	6 mg N = 6	12 mg N = 6	24 mg N =6
C_{max} (ng/mL)	1.08 (0.497)	6.36 (2.12)	9.52 (5.10)	17.0 (5.20)	59.3 (25.5)
T_{max} (h) Median	1.54	1.02	1.50	1.25	1.07
$AUC_{0\text{-}inf}$ (h*ng/mL)	NC	40.9 (19.3)	58.7 (34.0)	101 (46.0)	288 (125)
$AUC_{0\text{-}last}$ (h*ng/mL)	4.9	35.7	57	99.5	285
$T_{1/2}$ (h)	NC	4.94 (1.28)	6.66 (2.88)	4.67 (1.50)	5.09 (0.703)
CL/F (L/h)	NC	92.4 (54.1)	134 (70.3)	150 (87.8)	93.7 (30.6)
Vz/F (L)	NC	608 (236)	1230 (832)	929 (430)	697 (263)
CL_R (L/h)	3.00 (0.572)	3.62 (0.888)	3.42 (0.829)	4.25 (0.755)	3.75 (0.844)

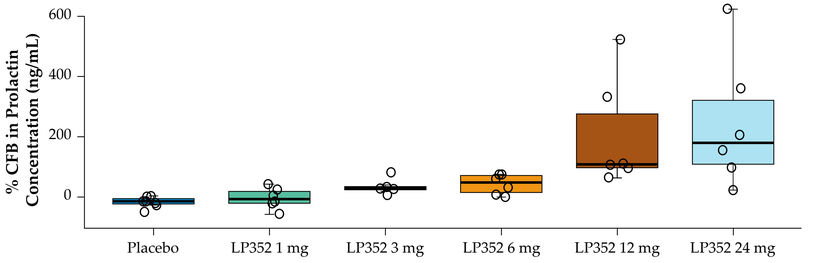
Fed Mean Plasma Concentrations of LP352 (OP-352) vs Time up to 48 hours by Fasted and Fed State, Linear and Log-Linear Scales (PK Set)



Effect of Food on Pharmacokinetic Parameters

Parameter (Unit)	Geometric Mean (95% CI) n	Fed	n	Fasted	% Ratio (Fed/Fasted)	90% Confidence Interval of Ratio	Intra CV%
C_{max} (ng/mL)	6	8.844 [5.129, 15.25]	6	8.474 [4.914, 14.61]	104.37	[84.17, 129.42]	18.7
$AUC_{0\text{-}last}$ (h*ng/mL)	6	61.89 [33.39, 114.7]	6	49.22 [26.55, 91.22]	125.74	[116.05, 136.25]	6.9
$AUC_{0\text{-}inf}$ (h*ng/mL)	6	63.62 [34.73, 116.6]	6	50.97 [27.82, 93.37]	124.83	[115.80, 134.58]	6.5

Percent Change From Baseline in 2-Hour Prolactin Concentration Across All Dose Groups (OP352 = LP352) Under Fasted Conditions



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SAFETY

Fasted: Overview of Treatment-Emergent Adverse Events (Safety Set)

Category, n (%) E	LP352 Cohort 1 1 mg (N = 6) n (%) E	Cohort 2 3 mg (N = 6) n (%) E	Cohort 3 6 mg (N = 6) n (%) E	Cohort 4 12 mg (N = 6) n (%) E	Cohort 5 24 mg (N = 6) n (%) E	Pooled Placebo (N = 10) n (%) E	Pooled LP352 (N = 30) n (%) E
Subjects with at least 1 TEAE	3 (50.0) 5	4 (66.7) 12	5 (83.3) 29	5 (83.3) 12	6 (100) 36	5 (50.0) 10	23 (76.7) 94
TEAE related to study drug	2 (33.3) 3	4 (66.7) 8	4 (66.7) 22	4 (66.7) 10	6 (100) 35	5 (50.0) 6	20 (66.7) 78
Severe TEAE	0	0	0	0	0	0	0
TEAE leading to study discontinuation	0	0	0	0	0	0	0
SAE	0	0	0	0	0	0	0

E = number of events; n = number of subjects.

Fed: Overview of Treatment-Emergent Adverse Events (Safety Set)

Category, n (%)	LP352 6 mg (Fasted) Active (N = 6) n (%) E	LP352 6 mg (Fasted) Placebo (N = 2) n (%) E	LP352 6 mg (Fed) Active (N = 6) n (%) E	LP352 6 mg (Fed) Placebo (N = 2) n (%) E	Pooled LP352 (N = 6) n (%) E
Subjects with at least 1 TEAE	5 (83.3) 29	1 (50.0) 1	5 (83.3) 10	2 (100) 2	5 (83.3) 39
TEAE related to study drug	4 (66.7) 22	1 (50.0) 1	5 (83.3) 8	2 (100) 2	5 (83.3) 30
Severe TEAE	0	0	0	0	0
Severe TEAE related to study drug	0	0	0	0	0
TEAE leading to study discontinuation	0	0	0	0	0
SAE	0	0	0	0	0

E = number of events; n = number of subjects.

Fasted: Treatment-Emergent Adverse Events by Preferred Term Occurring in ≥ 2 Subjects in Any Treatment Group (Safety Set)

Preferred Term, n (%) E	LP352 Cohort 1 1 mg (N = 6) n (%) E	Cohort 2 3 mg (N = 6) n (%) E	Cohort 3 6 mg (N = 6) n (%) E	Cohort 4 12 mg (N = 6) n (%) E	Cohort 5 24 mg (N = 6) n (%) E	Pooled Placebo (N = 10) n (%) E	Pooled LP352 (N = 30) n (%) E
Subjects with at least 1 TEAE	3 (50.0) 5	4 (66.7) 12	5 (83.3) 29	5 (83.3) 12	6 (100) 36	5 (50.0) 10	23 (76.7) 94
Headache	0	2 (33.3) 2	3 (50.0) 3	5 (83.3 5)	6 (100) 6	4 (40.0) 7	16 (53.3) 16
Dizziness postural	0	2 (33.3) 2	1 (16.7) 1	1 (16.7) 1	4 (66.7) 9	0	8 (26.7) 13
Nausea	1 (16.7) 1	1 (16.7) 1	1 (16.7) 1	1 (16.7) 1	2 (33.3) 2	0	6 (20.0) 6
Paresthesia	0	0	2 (33.3) 2	2 (33.3) 3	0	0	4 (13.3) 5
Burning sensation	0	0	0	1 (16.7) 1	2 (33.3) 2	0	3 (10.0) 3
Feeling cold	0	0	1 (16.7) 1	0	2 (33.3) 2	0	3 (10.0) 3
Micturition urgency	0	0	0	0	2 (33.3) 2	0	2 (6.7) 2
Neck pain	0	2 (33.3) 2	0	0	0	0	2 (6.7) 2

E = number of events; n = number of subjects.

Fed: Treatment-emergent Adverse Events by Preferred Term Occurring in ≥ 2 Subjects in Any Treatment Group (Safety Set)

System Organ Class/ Preferred Term, n (%) E	LP352 6 mg (Fasted) Active (N = 6) n (%) E	LP352 6 mg (Fasted) Placebo (N = 2) n (%) E	LP352 6 mg (Fed) Active (N = 6) n (%) E	LP352 6 mg (Fed) Placebo (N = 2) n (%) E	Pooled LP352 (N = 6) n (%) E
Subjects with at least 1 TEAE	5 (83.3) 29	1 (50.0) 1	5 (83.3) 10	2 (100) 2	5 (83.3) 39
Headache	3 (50.0) 3	0	3 (50.0) 3	1 (50.0) 1	3 (50.0) 6
Dizziness postural	1 (16.7) 1	0	2 (33.3) 2	0	2 (33.3) 3
Paresthesia	2 (33.3) 2	0	0	0	2 (33.3) 2

E = number of events; n = number of subjects.

PK CONCLUSIONS

- LP352 was rapidly absorbed into the systemic circulation following administration of a single oral dose of LP352 PIC formulation. Peak plasma concentrations were observed at a median T_{max} range of 1.02 to 1.54 hours after administration of 1 to 24 mg as a single oral dose.
- With increasing dose, there appears to be a slightly greater than proportional increase in exposures at higher doses; however, data were highly variable.
- There was no appreciable food effect on systemic exposures. There was less than 5% increase in mean C_{max} and about a 25% increase in mean $AUC_{0\text{-}inf}$ in the Fed state as compared to the Fasted state. Median T_{max} doubled to about 3 hours in the Fed state from 1.5 hours.
- LP352 mean half-life ranged from 4.67 to 6.66 hours across 1 to 24 mg dose groups.
- Since less than 5% of dose was eliminated by the renal route, a majority of the elimination likely occurred via metabolism.

PK-PD CONCLUSIONS

- Following administration of a single oral dose of LP352 PIC, the prolactin concentrations at 2 hours post dose for doses of 3 to 24 mg increased in a dose-dependent manner. Exploratory graphical analysis of PK-PD showed a relationship between dose-related change in prolactin and peak concentration of LP352, with a positive correlation between % change from baseline in prolactin at 2 hours post-dose and C_{max} of LP352.
- Although there was high variability and considerable overlap across doses in prolactin levels for subjects on LP352, the mean % CFB at 2 hours increased in a dose-dependent manner, with a greater than dose proportional increase between 6 mg and 12 mg doses. By 24-hour postdose, prolactin levels returned to baseline for only the 6 mg dose level. Placebo and 1 mg dose groups showed an initial decline at 2 hours, followed by higher prolactin concentrations at 24 hours, but this could be the result of diurnal variation together with variability in data.
- No relationship was observed between C_{max} or $AUC_{0\text{-}inf}$ and body weight.
- No relationship was observed between LP352 concentration and CFB in QTcF.

SAFETY CONCLUSIONS

Safety

- Single doses of LP352 1 mg to 24 mg (fasted) were safe and generally well tolerated. Similarly, single doses of LP352 6 mg (fed) were safe and generally well tolerated.
- Overall, in the fasted cohorts, the most commonly (≥ 20%) reported TEAEs were headache (LP352 53.3% vs placebo 40%), dizziness postural (LP352 26.7%), and nausea (LP352 20.0%). Dose-dependent increases in frequency of events of headache were observed. In subjects receiving LP352 in fed cohorts, TEAEs reported in at least 2 subjects included headache (50.0%) and dizziness postural (33.3%). In the fed placebo cohort, no TEAE was reported in more than 1 subject.
- All TEAEs were mild or moderate in severity in fasted and fed cohorts.
- No clinically significant differences were observed between fasted and fed treatment cohorts for the percentage of subjects with shifts from baseline in clinical chemistry, hematology and coagulation, urinalysis (microscopy) or urine chemistry.
- Single doses of LP352 caused dose-related increases in serum prolactin which were most evident at 2 hours following dosing. None of these increases was associated with symptoms of hyperprolactinemia, and none was considered clinically significant.
- No clinically significant mean changes from baseline in any serum cardiac troponin values were observed in any treatment cohort.
- Mean changes from baseline in vital signs were not considered clinically significant in any treatment cohort. Categorical analysis for orthostatic change in SBP and DBP also did not show any trend across treatment cohorts. Individual clinically significant orthostatic changes were observed in 3 fasted subjects who experienced decreases in SBP and/or DBP, and/or increases in heart rate on standing.
- Mean changes in ECG parameters from baseline were not considered clinically significant in any treatment cohort.
- There were no serious AEs, and no subjects discontinued or were withdrawn from the study as a result of a safety or tolerability related issue.

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