A Randomized, Double-Blind, Placebo-Controlled, Multiple Ascending Dose Pharmacokinetics (PK), Pharmacodynamics (PD), and Tolerability Study 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

Abstract #1771

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 fasting and fed randomized, double-blind, placebo-controlled, parallel-group, safety, tolerability, PK and PD assessment of LP352 or placebo administered orally to healthy adult female subjects in a single ascending dose of 1 mg, 3 mg, 6 mg, 12 mg, and 24 mg under fasting conditions and a 6 mg dose under fed conditions was completed prior to commencing this multiple ascending dose (MAD) study. LP352 was rapidly absorbed into the systemic circulation following administration of single oral doses. After administration of 1 to 24 mg, the T_{max} range was found to be 1.02 to 1.54 hours and the mean half-life ranged from 4.67 to 6.66 hours. There was no appreciable food effect on systemic exposures. Less than 5% of dose was eliminated by the renal route; a majority of the elimination likely occurred via metabolism.
- Single doses of LP352 1 mg to 24 mg were previously found to be safe and generally well tolerated.
  - Under fasting conditions, the most commonly (≥ 20%) reported TEAEs were headache (LP352 53.3% vs PBO 40%), dizziness postural (LP352 26.7%), and nausea (LP352 20.0%). In subjects receiving LP352 under fed conditions, TEAEs reported in at least 2 subjects included headache (50.0%) and dizziness postural (33.3%). Under fed conditions no TEAE was reported in more than 1 subject in the placebo group. All TEAEs were mild or moderate in severity under fasting and fed conditions. No clinically significant differences were observed between treatment cohorts for the percentage of subjects with shifts from baseline in clinical chemistry, hematology and coagulation, urinalysis (microscopy) or urine chemistry or cardiac troponin values. Mean changes in ECG parameters from baseline were not considered clinically significant.
  - 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 subjects who experienced decreases in SBP and/or DBP, and/or increases in heart rate on standing. There were no serious AEs, and no subjects discontinued or were withdrawn from the study as a result of safety or tolerability related issues.
- 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). The effect of multiple doses of LP352 on serum prolactin levels was also assessed in the MAD study.

OBJECTIVES

Primary: To evaluate the safety and tolerability of oral LP352 administered as:

- Multiple doses (powder in capsule - PIC) given 3 times a day (TID) for 14 days at ascending dose levels in healthy male and female participants.
- Multiple doses of PIC given TID for 14 days as an upward titration in healthy male and female participants.

Secondary: To characterize the plasma and urine pharmacokinetics (PK) of oral LP352 when administered as:

- Multiple doses (powder in capsule - PIC) given 3 times a day (TID) for 14 days at ascending dose levels in healthy male and female participants.
- Multiple doses of PIC given TID for 14 days as an upward titration in healthy male and female participants.

DESIGN/METHODS

Design/Methods - Multiple Ascending Dose (MAD)

- This was a randomized, double-blind, placebo-controlled, parallel-group, multiple ascending dose (MAD) design in healthy male and female subjects ages 18 to 55 years with a body mass index of 18.5-30.0 kg/m^2.
- Subjects were initially randomized into 3 sequential cohorts in an ascending dose (3 mg, 6 mg and 12 mg TID) fashion. One additional cohort (18 mg TID) was added based on emerging data.
  - Each cohort consisted of 8 new subjects (6 active and 2 placebo). Subjects who discontinued, were replaced.
- All subjects were randomized to receive either LP352 or matching placebo TID (i.e., every 8 hours) for 14 consecutive days, with the final dose on the morning of Day 14.
- The morning doses on Days 1, 4, 7, 10, and 14 were administered following an overnight fast of at least 10 hours.

Design/Methods - Dose Titration

- This was a randomized, double-blind, placebo-controlled, multiple dose, upward titrating design in healthy male and female subjects
- The dose titration group started after completion of MAD cohorts. Subjects were randomized into 1 cohort consisting of eight new subjects (6 active and 2 placebo).
  - Two subjects discontinued due to AEs and were replaced and received a modified treatment regimen.
- All subjects were randomized to receive either 12 mg TID LP352 or matching placebo TID for Days 1 to 3, followed by 24 mg TID or placebo from Days 4 to 13, with the final dose of 24 mg on the morning of Day 14.
- The morning doses on Days 1, 4, and 14 were administered following an overnight fast of at least 10 hours.

Safety and Tolerability Measures (Primary Endpoints) - MAD and Dose Titration

- Nature, frequency, and severity of treatment-emergent adverse events (TEAEs)
- 12-lead electrocardiograms (ECGs)
- Clinical laboratory tests
- Hormone laboratory panel, (prolactin, testosterone, vasopressin, and cortisol)
- Cardiac troponin levels
- Vital signs (including oral temperature, respiratory rate, supine and standing pulse rate, and blood pressure)
- Physical examinations
- Fluid balance (measurement and recording of fluid intake and urine output)
- Urine chemistry (osmolality, sodium, and potassium)
- Visual analogue scales (VAS; Bond-Lader, Nausea, and Appetite)
- Addiction Research Centre Inventory 49-Item Short Form (ARCI-49)
- Columbia Suicide Severity Rating Scale (C-SSRS) responses
- Drug Effects Questionnaire (DEQ) responses

Pharmacokinetic Parameters

- Key plasma PK parameters included: C_{max}, T_{max}, AUC_{tau}, C_{trough}, C_{av}, Vss/F, CL/F, R_{acc}, C_{max}, $R_{acc,AUC}$, $T_{1/2}$.

Pharmacodynamic Measures

- Prolactin serum concentrations

Pharmacokinetics-Pharmacodynamics

- Pharmacokinetics-Pharmacodynamics (PD) relationship between LP352 C_{max} concentrations and prolactin

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.
- Enrolled Population was defined as all subjects who signed informed consent.
- The Safety Analysis Set was defined as all subjects who received at least one dose of study drug after randomization.
- The PK Analysis Set was defined as all subjects who received at least one dose of LP352 and had at least one plasma or urine drug concentration.
- Plasma and urine concentration time data were analyzed using noncompartmental methods to report the following key PK parameters: C_{max}, T_{max}, AUC_{tau}, $R_{acc,AUC}$, renal clearance CLr and amount excreted unchanged in urine as a function of dose (% dose). Concentration time data and PK parameters were summarized using descriptive statistics. Trough plasma concentrations were plotted to visually assess the steady state.
- Prolactin serum concentrations were summarized by timepoint, dose and part. Absolute and percent change from baseline in prolactin value was calculated, with predose value on Day 1 considered as the baseline value. Observed prolactin data, absolute and percent change from baseline versus time were plotted.
- Pharmacokinetics-Pharmacodynamics (PD) relationship between LP352 C_{max} concentrations and prolactin observed and change from baseline as well as percent change from baseline were graphically explored.
- The relationship of AE with concentration time profile was explored graphically.
- Effect of body weight on exposure (C_{max}, AUC_{24}) was explored graphically.
- **Safety:** Continuous data were summarized in terms of the mean, standard deviation (SD), geometric mean, median, minimum, maximum and number of observations. Categorical data were summarized in terms of the number of subjects providing data at the relevant time point (n), frequency counts and percentages. Changes from baseline in categorical data were summarized using shift tables where appropriate. Confidence intervals (CIs) were presented to one more decimal place than the raw data.

A Randomized, Double-Blind, Placebo-Controlled, Multiple Ascending Dose Pharmacokinetics (PK), Pharmacodynamics (PD), and Tolerability Study 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

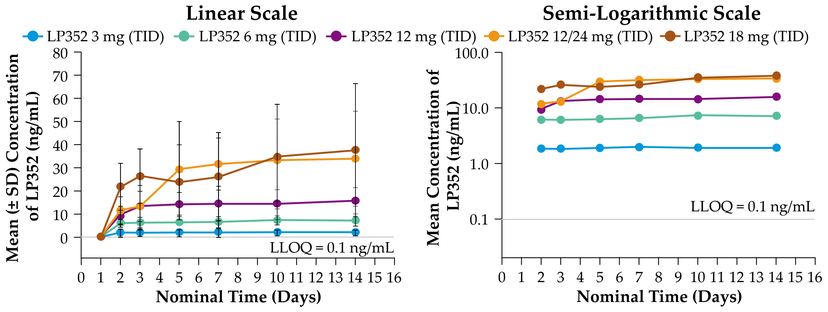
Abstract #1771

RESULTS

Demography, Height, Weight and BMI – MAD (Safety Population)

Characteristic	LP352 Cohort 1 3 mg (N = 6) n (%)	LP352 Cohort 2 6 mg (N = 6) n (%)	LP352 Cohort 3 12 mg (N = 7) n (%)	LP352 Cohort 4 18 mg (N = 6) n (%)	Pooled Placebo (N = 8) n (%)	Overall (N = 33) n (%)
Age (years), Mean (SD)	31.2 (10.30)	36.2 (7.70)	39.1 (8.41)	29.8 (5.95)	35.6 (9.44)	34.6 (8.71)
Sex, n (%)						
Male	3 (50.0)	3 (50.0)	2 (28.6)	0	3 (37.5)	11 (33.3)
Female	3 (50.0)	3 (50.0)	5 (71.4)	6 (100)	5 (62.5)	22 (66.7)
Ethnicity, n (%)						
Hispanic or Latino	1 (16.7)	3 (50.0)	3 (42.9)	4 (66.7)	3 (37.5)	14 (42.4)
Not Hispanic or Latino	5 (83.3)	3 (50.0)	4 (57.1)	2 (33.3)	5 (62.5)	19 (57.6)
Race, n (%)						
American Indian or Alaska Native	0	0	0	0	0	0
Black or African American	4 (66.7)	0	2 (28.6)	1 (16.7)	4 (50.0)	11 (33.3)
Native Hawaiian or other Pacific Islander	0	0	0	0	0	0
White	1 (16.7)	6 (100)	4 (57.1)	5 (83.3)	2 (25.0)	18 (54.5)
Asian	0	0	1 (14.3)	0	1 (12.5)	2 (6.1)
Other	1 (16.7)	0	0	0	1 (12.5)	2 (6.1)
Mixed	0	0	0	0	0	0
Height (cm), Mean (SD)	172.3 (6.62)	171.3 (6.47)	167.0 (10.26)	160.8 (10.07)	168.9 (6.06)	168.1 (8.52)
Weight (kg), Mean (SD)	78.52 (10.624)	76.50 (10.637)	72.53 (10.345)	65.87 (12.630)	72.95 (8.416)	73.23 (10.646)
BMI (kg/m²), Mean (SD)	26.35 (2.521)	26.05 (3.094)	25.93 (2.214)	25.32 (3.277)	25.56 (2.081)	25.83 (2.482)

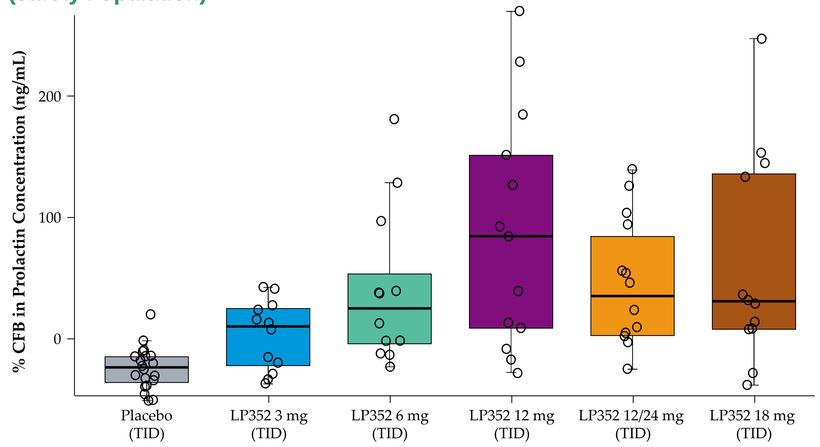
Mean (± SD) LP352 Plasma Trough Concentration Data by Cohort - MAD and Dose Titration (Linear and Semi Log Scale) (PK Analysis Population)



Key Summary of LP352 Pharmacokinetic Parameters by Cohort (Day 14) – MAD and Dose Titration (PK Analysis Population)

Parameter	Statistic	MAD 3 mg N = 6	MAD 6 mg N = 6	MAD 12 mg N = 7	MAD 18 mg N = 6	Titration 24 mg N = 8
C_{max} (ng/mL)	N	6	6	6	6	4
	Mean	6.61	20.7	44.9	98.6	107
	SD	2.61	7.21	15.8	49.6	46.2
	CV%	39.5	34.8	35.1	50.3	43.1
T_{max} (h)	N	6	6	6	6	4
	Minimum	1.00	0.50	1.00	1.00	1.00
	Median	1.01	1.78	1.27	2.00	1.04
	Maximum	1.50	2.05	1.50	2.03	2.00
AUC_{tau} (h*ng/mL)	N	6	6	6	6	4
	Mean	27.1	99.8	213	480	480
	SD	13.4	36.5	77.7	276	243
	CV%	49.4	36.6	36.5	57.4	50.5
$AUC_{0\text{-}inf}$ (h*ng/mL)	N	4	6	6	6	4
	Mean	46.1	152	330	775	741
	SD	25.6	55.7	119	421	331
	CV%	55.6	36.6	36.2	54.3	44.6
$AUC_{0\text{-}last}$ (h*ng/mL)	N	6	6	6	6	4
	Mean	38.6	150	327	773	737
	SD	20.4	56.1	118	421	332
	CV%	52.8	37.3	36.1	54.4	45.1
$T_{1/2}$ (h)	N	4	6	6	6	4
	Mean	5.56	4.81	5.96	5.64	6.50
	SD	0.790	0.730	1.34	1.01	2.76
	CV%	14.2	15.2	22.4	18.0	42.4
C_{trough} (ng/mL)	N	6	6	6	6	4
	Mean	1.94	7.02	15.8	37.7	34.0
	SD	1.13	2.17	5.72	28.8	20.4
	CV%	58.2	31.0	36.2	76.3	60.0
C_{av} (ng/mL)	N	6	6	6	6	4
	Mean	3.39	12.5	26.6	60.0	60.1
	SD	1.67	4.56	9.71	34.5	30.4
	CV%	49.4	36.6	36.5	57.4	50.5
CL/F (L/h)	N	4	6	6	6	4
	Mean	125	66.6	63.1	45.9	62.9
	SD	66.4	22.2	23.4	19.0	37.1
	CV%	52.9	33.4	37.0	41.4	59.0
$R_{acc,AUC}$	N	6	6	6	6	4
	Mean	1.75	2.17	2.61	3.79	3.25
	SD	0.300	0.575	0.719	1.01	1.14
	CV%	17.2	26.5	27.5	26.7	35.2

Pharmacodynamics: Boxplot of Percent Change From Baseline in Prolactin Concentration with Dose on Day 1 at 2 Hours – MAD and Dose Titration (Safety Population)



Key Summary Statistics of Urine Pharmacokinetic Parameters for LP352 on Day 14 – MAD and Dose Titration

Parameter	Statistic	MAD 3 mg N = 6	MAD 6 mg N = 6	MAD 12 mg N = 7	MAD 18 mg N = 6	Titration 24 mg N = 8
Cumulative Ae (µg) Amount of Drug Excreted	n	6	6	6	6	4
	Mean	209	968	1900	3880	2950
	SD	88.5	404	894	2140	1520
	CV%	42.4	41.7	47.1	55.1	51.4
% Cumulative Amount Excreted Unchanged (%)	n	6	6	6	6	4
	Mean	20.9	32.3	31.6	32.3	12.3
	SD	8.85	13.5	14.9	17.8	6.32
	CV%	42.4	41.7	47.1	55.1	51.4
CL_R (L/h)	n	6	6	6	6	4
	Mean	5.77	6.58	5.80	5.04	3.91
	SD	1.14	1.74	1.78	0.777	0.303
	CV%	19.7	26.4	30.6	15.4	7.7

A Randomized, Double-Blind, Placebo-Controlled, Multiple Ascending Dose Pharmacokinetics (PK), Pharmacodynamics (PD), and Tolerability Study 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

Abstract #1771

SAFETY

Subject Disposition – MAD (Safety Population)

n (%)	LP352 Cohort 1 3 mg (N = 6)	LP352 Cohort 2 6 mg (N = 6)	LP352 Cohort 3 12 mg (N = 7)	LP352 Cohort 4 18 mg (N = 6)	Pooled Placebo (N = 8)	Overall (N = 33)
Enrolled	-	-	-	-	-	33
Randomized	6	6	7	6	8	33
Subjects dosed	6 (100)	6 (100)	7 (100)	6 (100)	8 (100)	33 (100)
Completed study	6 (100)	6 (100)	6 (85.7)	5 (83.3)	7 (87.5)	30 (90.9)
Withdrawal	0	0	1 (14.3)	1 (16.7)	1 (12.5)	3 (9.1)
Adverse event	0	0	1 (14.3)	0	0	1 (3.0)
Withdrawal by subject	0	0	0	1 (16.7)	1 (12.5)	2 (6.1)

Subject Disposition – Dose Titration (Safety Population)

n (%)	LP352 (N = 8)	Placebo (N = 2)	Total (N = 10)
Enrolled	-	-	10
Randomized	8	2	10
Subjects dosed	8 (100)	2 (100)	10 (100)
Completed study	6 (75.0)	2 (100)	8 (80.0)
Withdrawal	2 (25.0)	0	2 (20.0)
Adverse event	2 (25.0)	0	2 (20.0)

Overview of Treatment-emergent Adverse Events – MAD (Safety Population)

Category, n (%) E	LP352 Cohort 1 3 mg (TID) (N = 6)	LP352 Cohort 2 6 mg (TID) (N = 6)	LP352 Cohort 3 12 mg (TID) (N = 7)	LP352 Cohort 4 18 mg (TID) (N = 6)	Pooled Placebo (TID) (N = 8)	Pooled LP352 (N = 25)
Subjects with at least 1 TEAE	5 (83.3) 9	6 (100) 29	6 (85.7) 39	6 (100) 55	4 (50.0) 8	23 (92.0) 132
TEAE related to study drug	3 (50.0) 5	5 (83.3) 23	6 (85.7) 36	6 (100) 49	3 (37.5) 4	20 (80.0) 113
Severe TEAE	0	0	1 (14.3) 1	1 (16.7) 1	0	2 (8.0) 2
Severe TEAE related to study drug	0	0	1 (14.3) 1	1 (16.7) 1	0	2 (8.0) 2
TEAE leading to study drug interruption	0	0	0	0	0	0
TEAE leading to study discontinuation	0	0	1 (14.3) 3	0	0	1 (4.0) 3
SAE	0	0	0	0	0	0

Overview of Treatment-emergent Adverse Events – Dose Titration (Safety Population)

Category, n (%) E	LP352 12/24 mg (TID) (N = 8)	Placebo (TID) (N = 2)
Subjects with at least 1 TEAE	8 (100) 87	2 (100) 6
TEAE related to study drug	8 (100) 80	2 (100) 6
Severe TEAE	1 (12.5) 3	0
Severe TEAE related to study drug	1 (12.5) 3	0
TEAE leading to study drug interruption	0	0
TEAE leading to study discontinuation	2 (25.0) 2	0
SAE	1 (12.5) 1	0
SAE related to study drug	1 (12.5) 1	0

Treatment-emergent Adverse Events by Preferred Term Occurring in ≥ 2 Subjects in Any Treatment Group – MAD (Safety Population)

Preferred Term, n (%) E	LP352 Cohort 1 3 mg (TID) (N = 6)	LP352 Cohort 2 6 mg (TID) (N = 6)	LP352 Cohort 3 12 mg (TID) (N = 7)	LP352 Cohort 4 18 mg (TID) (N = 6)	Pooled Placebo (TID) (N = 8)	Pooled LP352 (N = 25)
Subjects with at least 1 TEAE	5 (83.3) 9	6 (100) 29	6 (85.7) 39	6 (100) 55	4 (50.0) 8	23 (92.0) 132
Headache	2 (33.3) 2	2 (33.3) 4	2 (28.6) 5	4 (66.7) 5	1 (12.5) 1	10 (40.0) 16
Somnolence	1 (16.7) 1	1 (16.7) 1	4 (57.1) 4	3 (50.0) 5	0	9 (36.0) 11
Dizziness	0	3 (50.0) 3	2 (28.6) 3	2 (33.3) 2	0	7 (28.0) 8
Micturition urgency	1 (16.7) 1	0	1 (14.3) 1	5 (83.3) 5	0	7 (28.0) 7
Dizziness postural	0	0	1 (14.3) 1	5 (83.3) 5	0	6 (24.0) 6
Diarrhoea	1 (16.7) 1	4 (66.7) 4	1 (14.3) 1	0	0	6 (24.0) 6
Orthostatic hypotension	0	0	2 (28.6) 2	4 (66.7) 4	0	6 (24.0) 6
Constipation	1 (16.7) 1	1 (16.7) 1	2 (28.6) 2	1 (16.7) 1	1 (12.5) 1	5 (20.0) 5
Nausea	1 (16.7) 1	0	1 (14.3) 2	2 (33.3) 3	1 (12.5) 1	4 (16.0) 6
Paraesthesia	0	1 (16.7) 1	2 (28.6) 2	1 (16.7) 1	0	4 (16.0) 4
Chills	0	0	1 (14.3) 1	3 (50.0) 3	0	4 (16.0) 4
Anxiety	0	2 (33.3) 2	0	2 (33.3) 2	0	4 (16.0) 4
Orthostatic heart rate response increased	0	0	0	3 (50.0) 3	1 (12.5) 1	3 (12.0) 3
Dysmenorrhoea	1 (16.7) 1	0	0	2 (33.3) 2	1 (12.5) 1	3 (12.0) 3
Fatigue	0	2 (33.3) 2	0	0	0	2 (8.0) 2
Vessel puncture site bruise	0	0	0	2 (33.3) 2	0	2 (8.0) 2
Hypotension	0	2 (33.3) 2	0	0	0	2 (8.0) 2

Treatment-emergent Adverse Events by Preferred Term Occurring in ≥ 2 Subjects in Any Treatment Group – Dose Titration (Safety Population)

Preferred Term, n (%) E	LP352 12/24 mg (TID) (N = 8)	Placebo (TID) (N = 2) n (%) E
Subjects with at least 1 TEAE	8 (100) 87	2 (100) 6
Headache	6 (75.0) 6	0
Somnolence	4 (50.0) 4	1 (50.0) 1
Feeling cold	4 (50.0) 5	0
Dizziness	3 (37.5) 4	0
Dizziness postural	3 (37.5) 4	0
Nausea	3 (37.5) 4	0
Paraesthesia	2 (25.0) 3	0
Vomiting	2 (25.0) 2	0
Feeling hot	2 (25.0) 2	0
Sluggishness	2 (25.0) 2	0
Abnormal dreams	2 (25.0) 2	0
Anxiety	2 (25.0) 2	0
Insomnia	2 (25.0) 2	0
Pollakiuria	2 (25.0) 2	1 (50.0) 1
Hot flush	2 (25.0) 2	0
Orthostatic hypotension	2 (25.0) 2	0
Vision blurred	2 (25.0) 2	0
Hyperhidrosis	2 (25.0) 3	0

A Randomized, Double-Blind, Placebo-Controlled, Multiple Ascending Dose Pharmacokinetics (PK), Pharmacodynamics (PD), and Tolerability Study 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

Abstract #1771

PK CONCLUSIONS

- LP352 was rapidly absorbed into systemic circulation following administration of first dose and after multiple oral dose administrations of LP352. The peak plasma concentrations after the first and last dose occurred at a median T_{max} between 1.00 and 2.00 hours.
- Most subjects were at steady state after 10 days of dosing in the MAD cohorts.
- Multiple dosing with a TID regimen resulted in dose dependent accumulation. Accumulation ratio for AUC_{tau} increased from 1.75 to 3.79 from 3 to 18 mg in MAD and was 3.25 for 12/24 mg dose titration regimen. Accumulation ratio for C_{max} increased from 1.55 to 3.37 from 3 to 18 mg in MAD and was slightly less at 2.79 with 12/24 mg with the dose titration regimen (as this regimen did not reach steady-state during the dosing period).
- Note: In the dose titration regimen, 24 mg TID was dosed for a shorter duration of 10 days versus 14 days in MAD.
- LP352 mean half-life at steady state was consistent among all dose groups and ranged from 4.81 to 6.50 hours.
- At steady state, 20.9% to 32.3% of the dose was eliminated by the renal route in 48 hours across doses of 3 to 18 mg TID. In the 12/24 mg TID titration regimen, only 12.3% of the dose was eliminated by the renal route in 48 hours.

PD CONCLUSIONS

- The mean percent change from baseline prolactin level at 2 hours increased with increasing doses from 3 mg to 12 mg and plateaued thereafter. The data were highly variable.

PK-PD CONCLUSIONS

- There appeared to be a weak positive PK-prolactin relationship in that an increase in C_{max} leads to an increase in 2-hour post-dose prolactin levels.
- With limited data available, no relationship was observed between LP352 concentration and QTcF

SAFETY CONCLUSIONS

- Multiple ascending doses of LP352 3 mg to 18 mg (MAD) were generally tolerated but not in in all subjects. Similarly, LP352 12/24 mg TID as an upward titration was generally tolerated but not in all subjects.
- In MAD cohorts and in dose titration cohorts most TEAEs were experienced as mild or moderate.
- In the dose titration regimen, 1 SAE of anxiety was reported on Day 16 (after stopping study drug) by 1 subject receiving LP352 12/24 mg (TID) and was considered related to study drug.
- In MAD, at least 1 TEAE was reported by 23/25 (92.0%) subjects receiving LP352 and 4/8 (50.0%) subjects receiving placebo. TEAEs related to study drug were reported by 20/25 (80.0%) subjects receiving LP352 and 3/8 (37.5%) subjects receiving placebo. Two severe TEAEs were reported by 2 subjects: 1 subject receiving LP352 12 mg and 1 subject receiving the 18 mg dose. Both severe TEAEs were considered related to study drug.
- With dose titration, at least 1 TEAE was reported by 8/8 (100%) subjects receiving LP352 12/24 mg (TID) and 2/2 (100%) subjects receiving placebo. In subjects receiving LP352 12/24 mg (TID), 80 out of 87 TEAEs were related to the study drug, while in subjects receiving placebo, 6 out of 6 TEAEs were related. Three severe TEAEs were reported by 1 subject receiving LP352 12/24 mg (TID) and were considered related to the study drug.
- In the LP352 MAD cohorts, the most commonly (≥ 20%) reported TEAEs were headache (40.0%), somnolence (36.0%), dizziness (28.0%), micturition urgency (28.0%), dizziness postural (24.0%), diarrhoea (24.0%), orthostatic hypotension (24.0%), and constipation (20.0%). In placebo group, no TEAE was experienced by more than 1 subject.
- In the dose titration group, overall, the most commonly (≥ 30%) reported TEAEs seen in subjects receiving LP352 12/24 mg (TID) were headache (75.0%), somnolence (50.0%), feeling cold (50.0%), dizziness (37.5%), dizziness postural (37.5%), and nausea (37.5%).
- In MAD, overall, 20 subjects (80.0%) receiving LP352 reported 113 TEAEs related to study drug. The most commonly (≥ 20%) reported TEAEs related to study drug were somnolence (36.0%), headache (28.0%), dizziness (28.0%), micturition urgency (28.0%), dizziness postural (24.0%), orthostatic hypotension (24.0%), diarrhoea (20.0%), and constipation (20.0%).
  - In the placebo group, 3 subjects (37.5%) reported 4 TEAEs related to study drug. The most commonly (12.5% each) reported TEAEs related to study drug in subjects receiving placebo were presyncope, constipation, nausea and orthostatic heart rate response increased.
- In the dose titration group, overall, all subjects receiving LP352 12/24 mg (TID) and placebo reported TEAEs related to study drug. In the LP352 group, the most commonly (≥ 30%) reported TEAEs related to study drug were headache (75.0%), somnolence (50.0%), feeling cold (50.0%), dizziness (37.5%), dizziness postural (37.5%) and nausea (37.5%).
  - In the placebo group, no TEAEs related to study drug were reported in more than 1 subject.
- In MAD, 3 TEAEs leading to study discontinuation were reported on Day 5 by 1 subject in the LP352 12 mg dose group. TEAEs were reported to be recovered/resolved by the end of the study. In the dose titration group, 2 subjects receiving LP352 (12 mg) experienced TEAEs leading to study discontinuation on Day 1. TEAE in 1 subject was reported to be recovered/resolved by the end of the study. Outcome in the other subject was unknown.
- In the dose titration group, 1 subject receiving LP352 12/24 mg (TID) had low potassium (3.2 mmol/L; nonserious AE of hypokalaemia) and low sodium (132 mmol/L; nonserious AE of hyponatraemia) at Day 16. This subject also experienced an SAE of anxiety. Otherwise, there was no clinically significant abnormal value found for clinical laboratory parameters (clinical chemistry, hematology and coagulation, urinalysis, urine chemistry, or serum cardiac troponins) in MAD cohorts or in the dose titration group.
- In MAD, no mean change from baseline of > 20 mmHg, > 10 mmHg, > 30 bpm in values was found in any of the LP352 dose groups for supine SBP, DBP, and heart rate, respectively. Dose dependent effect for decrease from baseline in 1 minute and 3 minutes standing SBP was observed with the highest decrease in the 18 mg dose group. More than 10 mmHg mean decrease from baseline in values of standing 1 minute and 3 minutes DBP was found at occasional time points for all the dose groups. Maximum decrease was observed for the 18 mg dose group at 3 minutes standing and at 1 minute standing. There was no > 30 bpm mean change from baseline in heart rate at 1 minute and 3 minutes standing for all dose groups except for 3 minutes standing on Day 16 (48 hours post-dose) in the 18 mg dose group.
  - In MAD, there was no > 20 mmHg and > 10 mmHg mean orthostatic decrease (from supine) in SBP and DBP, respectively, upon 1 minute and 3 minutes standing at any time point in all LP-352 dose groups. Significant orthostatic change (≤ -20 mmHg SBP and ≤ -10 mmHg DBP) at 1 minute and 3 minutes standing was observed in either 1 or 2 subjects receiving 12 mg and 18 mg dose at various time points. Orthostatic change in heart rate of ≥ 30 bpm at 1 minute and 3 minutes standing was observed at majority of the time points in at least 1 subject to a maximum of 4 subjects of all LP352 dose groups.
- In the 12/24 mg TID dose group, in the supine position, no mean change from baseline of > 20 mmHg, > 10 mmHg, > 30 bpm was observed at any time point in SBP, DBP, heart rate, respectively in LP352. The mean decrease from baseline of > 20 mmHg was observed at various time points between Day 7 and Day 14 at 1 minute and 3 minutes standing SBP in LP352 group. The mean decrease from baseline of > 10 mmHg fin DBP was observed at various time points between Day 4 to Day 16 at 1 minute standing and between Day 2 to Day 23 at 3 minutes standing. No > 30 bpm mean change from baseline was observed for 1 minute and 3 minutes standing heart rate at all time points in LP352 group (except Day 16 [50 hours post-dose] at 1 minute standing.
  - In the 12/24 mg TID dose group, mean orthostatic increase in heart rate was between 30 to 40 bpm at majority of timepoints for subjects of LP352 12/24 mg dose group. Mean orthostatic decrease in 1 minute and 3 minutes SBP and DBP versus Day for majority of morning predose time points from Day 4 (start of dose 24 mg) onwards was more pronounced as compared to Day 1 to Day 3 (12 mg). Significant orthostatic change (≤ -20 mmHg SBP, ≤ -10 mmHg DBP) at 1 minute and 3 minutes standing was observed in at least 1 subject to a maximum of 3 subjects of LP-352 12/24 mg dose group at various time points. Orthostatic change in 1 minute and 3 minutes standing heart rate was ≥ 30 bpm at majority of time points in at least 1 subject to a maximum of 6 subjects receiving LP-352 titration doses.
- There were no significant mean changes in ECG data in any treatment cohort and categorical analysis of QTcF interval values measured at all time points was not clinically significant in MAD or the 12/24 mg TID dose group.
- The C-SSRS data did not show the study drug to affect subject's suicidal ideation and/or behavior in MAD or the 12/24 mg TID dose group.

REFERENCES

Gustafson A, King C, Rey JA. Lorcaserin (Belviq): A Selective Serotonin 5-HT2C Agonist In the Treatment of Obesity. *PT.* 2013;38(9):525-534. Lentz, K. Current methods for predicting human food effect. *AAPS Journal.* 2008; 10(2):282-288. Mallmann ES, Paixão L, Ribeiro MF, Spritzer PM. Serotonergic 5-HT2A/2C receptors are involved in prolactin secretion in hyperestrogenic rats. *Neurosci Lett.* 2014 Oct 17;582:71-4. Quattrone A, Tedeschi G, Aguglia U, Scopacasa F, Direnzo GF, Annunziato L. Prolactin secretion in man: a useful tool to evaluate the activity of drugs on central 5-hydroxytryptaminergic neurones. Studies with fenfluramine. *Br J Clin Pharmacol.* 1983 Nov;16(5):471-5.