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Clinical Trial Synopsis C03-043, NCT# 00220818

Name of Company: TAP Pharmaceutical Products Inc.

Name of Finished Product: Lansoprazole Microgranules Oral Suspension for Pediatric Use

Name of Active Ingredient: Lansoprazole, 2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl]methyl]sulfinyl]benzimidazole

Title of Study: A Phase 1, Single- and Repeated-Dose, Randomized, Open-Label, Multicenter Study to Evaluate the Pharmacokinetics, Pharmacodynamics, and Safety of Lansoprazole in Infants with Clinically Evident Gastroesophageal Reflux Disease

Investigators who Enrolled Subjects: 5 (2 in United States and 3 in Poland)

Study Centers that Enrolled Subjects: 5 (2 in United States and 3 in Poland)

Publications (Reference):

Springer M, Atkinson S, Raanan M, Sutkowski-Markmann D. Symptom relief results in pharmacodynamic/pharmacokinetic studies of lansoprazole in infants and neonates with clinically evident gastroesophageal reflux disease (GERD) [abstract]. *J Pediatr Gastroenterol Nutr.* 2006; 43(4): E18-E19. 16. TAP-08-000257

Springer M, Zhang W, Atkinson S, North J, Raanan M, Witt G. Pharmacokinetic and pharmacodynamic profiles and symptom relief in infants with clinically evident GERD treated with lansoprazole [abstract]. *Ped Research.* 2006. 4811.49. TAP-06-001705

Zhang W, Kukulka MJ, Witt G, Sutkowski-Markmann D, North J, Atkinson S. Substantial differences in lansoprazole pharmacokinetics between older and younger infants and neonates [abstract]. *Gastroenterology.* 2006; 130(4 Suppl 2); A-4. 21. TAP-06-009163

Study Period:

Date of First Dose: 17 January 2005

Date of Last Procedure: 28 July 2005

Phase of Development: 1

Objective(s): The objectives of this study were to characterize the pharmacokinetic (PK) and pharmacodynamic (PD) profiles, and to assess the safety profiles of single and repeated doses of Lansoprazole Microgranules Oral Suspension for Pediatric Use (lansoprazole pediatric suspension) 1.0 or 2.0 mg/kg/day over a 5-day period in infants with clinically evident gastroesophageal reflux disease (GERD).

Methodology: This was a Phase 1, single- and repeated-dose, parallel-group, randomized, open-label, 2-country, multicenter study in 24 infants (1 to 11 months of age) with clinically evident GERD, who were randomly assigned to 1 of 2 treatment groups (1.0 or 2.0 mg/kg/day) of lansoprazole pediatric suspension.

All subjects received the first dose of study drug on Dosing Day 1 after a 30-minute fast. Dosing occurred each day for 5 days (Dosing Days 1 to 5) at approximately 24-hour intervals. Blood samples for PK analyses were drawn

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Methodology (Cont):

from all subjects on Dosing Day 1 (at 0 h [predose] and at 1, 2, 3, 4, 6, 8, 12 h postdose) and on Dosing Day 5 (at 0 h [predose] and at 2 and 6 h postdose). Plasma concentrations of lansoprazole were determined using a validated liquid chromatography assay coupled with tandem mass spectrometry (LC-MS/MS). A buccal sample was obtained from subjects with parent/legal guardian consent to determine CYP2C19 metabolizer status. Intra-gastric and intraesophageal pH monitoring was performed in 6 infants at Baseline (Day -1) and on Dosing Days 1 and 5. The percentage of subjects with GERD symptoms and the numbers of episodes of GERD symptoms were assessed at Baseline and on Dosing Days 1 to 5. Overall GERD symptom relief from Baseline was assessed by the Investigator on Dosing Day 5. Safety was monitored through adverse event (AE) reports, concomitant medication usage, physical examinations, vital sign assessments, and laboratory evaluations.

Number of Subjects (Planned and Analyzed): 24 planned (12 each in lansoprazole 1.0 and 2.0 mg/kg/day dose groups); 24 analyzed for PK, GERD symptom assessment, and safety; 20 subjects were analyzed for CYP2C19 genotype (Consent not provided for 4 subjects); 6 subjects were analyzed (as planned) for PD.

Diagnosis and Main Criteria for Inclusion: Male or female subjects with clinically evident GERD who were term (38-42 weeks gestation) or postterm (>42 weeks gestation) infants beyond the neonatal period (>28 days) but <12 months of age, OR a preterm infant with a corrected age of ≥44 weeks but <94 weeks on Dosing Day 1.

Duration of Treatment: All subjects received single daily doses of 1.0 or 2.0 mg/kg/day for 5 consecutive days.

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

Drug Product	Lot Number	Mode of Administration	Drug Product Lot Number	Drug Substance Lot Number
Lansoprazole pediatric suspension – 30 mg (investigational)	1.0 mg/kg/day	intra-oral, oro- or nasogastric tube, or gastronomy tube	040053	HG660
	2.0 mg/kg/day	intra-oral, oro- or nasogastric tube, or gastronomy tube	040053	HG660

Reference Therapy, Dose and Mode of Administration, Batch number: Not applicable.

Criteria for Evaluation

Efficacy:

A primary objective of this study was to assess PK (in all subjects) and PD (in a subset of 6 subjects). GERD symptoms were assessed as secondary efficacy variables. However, this study was not placebo-controlled, and as such, no efficacy conclusions were drawn from these assessments.

Pharmacodynamics:

The PD effect of lansoprazole treatment on intra-gastric pH was evaluated at Baseline (Day -1) and on Dosing Days 1 and 5. Criteria for evaluation included:

1. The mean of the 15-minute median intra-gastric pH values over the entire 24-hour period and for twelve 2-hour time intervals;
2. The percentages of time that intra-gastric pH was >3, >4, >5, and >6 over the entire 24-hour period;
3. The percentage of time intraesophageal pH was <4 over the entire 24-hour period and for twelve 2-hour time intervals; and
4. Integrated gastric acidity (area under the concentration time curve [AUC] of hydrogen ion concentration) over the entire 24-hour period.

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Criteria for Evaluation (Cont):

GERD Symptoms:

The presence of the GERD symptoms of regurgitation/vomiting, apnea, irritability, feeding refusal/crying during feedings, wheezing or stridor, hoarseness, cough, and spells of arching were obtained at Baseline and on each day of dosing (Dosing Days 1 to 5). The number of episodes of each of the a priori-selected symptoms regurgitation/vomiting, apnea, feeding refusal/crying during feedings, and spells of arching per 24-hour period was recorded for each subject at Baseline and on Dosing Days 1 to 5. On the final day of dosing, overall GERD symptom relief was evaluated by the Investigator as Better, Not Changed, or Worse as compared to Baseline.

Pharmacokinetics:

Plasma concentrations of lansoprazole were determined at designated timepoints on Dosing Days 1 and 5. Pharmacokinetic parameters for lansoprazole on Dosing Day 1 were estimated using standard noncompartmental methods. These parameters included the observed peak plasma drug concentration (C_{max}), the time to reach the observed peak plasma drug concentration (t_{max}), the apparent terminal half-life ($t_{1/2z}$), the AUC from time zero to infinity (AUC_{∞}), and the apparent clearance (CL/F).

Safety:

Safety was monitored throughout the study through evaluations of AEs, concomitant medications usage, clinical laboratory assessments, physical examinations, and measurement of vital signs.

Statistical Methods

Efficacy:

Pharmacodynamics:

Median intragastric pH values were calculated using all values obtained within each 15-minute interval for the 24-hour period at Baseline (Day -1) and on Dosing Days 1 and 5. The effect of treatment on intragastric pH was quantified using the mean of the 15-minute median intragastric pH values over the entire 24-hour period following dosing (or entire period following dosing in which pH was recorded) and for each of the twelve 2-hour postdose time intervals over the 24-hour period following dosing. In addition, the percentages of time that the intragastric pH was >3, >4, >5, and >6 over the entire 24-hour period following dosing and the percentages of time that the intraesophageal pH was <4 over the entire 24-hour period following dosing (or over the entire period postdose that pH was recorded) were also determined. Descriptive statistics were generated for each of the twelve 2-hour postdose time intervals over the 24-hour period and for the percentages of time intragastric pH was >3, >4, >5, and >6 on Day -1 and on Dosing Days 1 and 5. Integrated acidity (AUC of hydrogen ion concentration) was evaluated using descriptive statistics.

GERD Symptom Assessment:

The number and percentage of subjects who experienced each GERD symptom (regurgitation/vomiting, apnea, feeding refusal/crying during feeding, arching, irritability, wheezing/stridor, hoarseness, and cough) were summarized at Baseline (Day -1) and on Dosing Days 1 to 5, overall, by dosing regimen, and by concomitant prokinetic drug use. The percent change from Baseline in the percentage of subjects with each GERD symptom was determined on Dosing Days 1 to 5 for each dosing regimen. The numbers of episodes per 24-hour period of a subset of a priori-selected symptoms (regurgitation/vomiting, apnea, feeding refusal/crying during feedings, and spells of arching) were determined for each subject at Baseline and on Dosing Days 1 to 5. Mean changes in the number of episodes for each symptom from Baseline to each of the 5 dosing days (Dosing Days 1 to 5) was summarized overall, by dosing regimen, and by concomitant prokinetic drug use. The numbers and percentages of subjects within each category of overall GERD symptom relief (Better, Not Changed, or Worse from Baseline) were summarized overall, by dosing regimen, and by concomitant prokinetic drug use.

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Statistical Methods (Cont):

Pharmacokinetics:

For each dosing regimen, lansoprazole concentration in plasma at each scheduled timepoint on Dosing Days 1 and 5, and each PK parameter value on Dosing Day 1 were tabulated and descriptive statistics were computed. Descriptive statistics including n, mean, standard deviation, median, minimum and maximum values, and %CV are provided. Additionally, the harmonic mean was determined for the terminal phase elimination half-life ($t_{1/2z}$). The relationships of AUC and C_{max} with body weight and with age were explored.

Safety:

Adverse events (AEs) were summarized using descriptive statistics. The numbers and percentages of subjects reporting an AE were summarized overall and by dosing regimen, severity level, and relatedness to study drug.

Results

Demographics:

Gender: Female 10 (41.7%), Male 14 (58.3%); Race: Black 12 (50.0%), White 12 (50.0%);

Ethnicity: Hispanic or Latino 1 (4.2%), Not Hispanic/ Latino 23 (95.8%); Country: Poland 6 (25%), US 18 (75%);

Mean Chronological Age 24.1 ± 13.22 (range 6 to 54) weeks; Mean Corrected Age 59.7 ± 12.22 (range 46 to 84) weeks;

Mean Body Weight: 6378.8 ± 1517.01 (3270 to 8540) g; Mean Body Length: 62.2 ± 7.05 (50 to 75) cm;

Mean Body Head Circumference: 40.5 ± 3.35 (35 to 46) cm.

Efficacy Results:

Efficacy was not the primary objective in this Phase 1 study; however, GERD symptom relief was assessed as a secondary endpoint. Pharmacodynamic, GERD symptom relief, and PK results are presented.

Pharmacodynamic Results:

Pharmacodynamic results are based on data obtained, in accordance with the protocol, from 6 subjects (n=3 and n=3 for lansoprazole 1.0 and 2.0 mg/kg/day dose groups, respectively).

Overall, an increase in 24-hour mean intragastric pH was observed from Baseline (3.94) on Dosing Day 1 (4.75) and Day 5 (5.76).

For both dose groups, an increase from Baseline was noted in the percentage of time that the intragastric pH was >3, >4, >5, and >6 over the 24-hour period following dosing on Dosing Days 1 and 5 are presented below:

Study Day	Lansoprazole 1.0 mg/kg/day (n=3)				Lansoprazole 2.0 mg/kg/day (n=3)			
	% Time Above				% Time Above			
	pH >3	pH >4	pH >5	pH >6	pH >3	pH >4	pH >5	pH >6
Day -1	62.5	50.0	27.4	12.2	67.0	52.4	34.0	24.0
Dosing Day 1	81.1	71.5	60.2	34.0	64.2	60.0	55.1	41.7
Dosing Day 5	89.8	84.9	76.5	53.8	88.8	83.9	75.9	53.2

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GERD Symptom Relief Results:

The percentages of subjects with GERD Symptoms by drug regimen are presented in the following table.

GERD Symptom ^a	Day -1	Dosing Day 1	Dosing Day 2	Dosing Day 3	Dosing Day 4	Dosing Day 5
Lansoprazole 1.0 mg/kg/day^b						
Regurgitation/Vomiting	92	92	83	75	75	83
Feeding Refusal/Crying	33	33	42	33	8	17
Spells of Arching	50	50	42	42	25	17
Irritability	50	50	58	50	17	33
Cough	42	25	17	25	25	33
Lansoprazole 2.0 mg/kg/day^b						
Regurgitation/Vomiting	75	92	83	83	83	67
Feeding Refusal/Crying	50	25	17	8	17	0
Spells of Arching	50	25	42	8	17	0
Irritability	50	25	25	25	8	17
Cough	75	42	42	33	25	0
All Subjects^c						
Regurgitation/Vomiting	83	92	83	79	79	75
Feeding Refusal/Crying	42	29	29	21	12	8
Spells of Arching	50	37	42	25	21	8
Irritability	50	37	42	37	12	25
Cough	58	33	29	29	25	17

Note: There were no reported episodes of apnea for any subject.

a Symptoms present in $\geq 40\%$ of subjects at Baseline are included.

b Days -1 to Dosing Day 4 (n=12); Dosing Day 5 (n=6).

c Days -1 to Dosing Day 4 (n=24); Dosing Day 5 (n=12).

The mean number of episodes of GERD Symptoms in subjects by drug regimen is presented in the following table.

GERD Symptom	Day -1	Dosing Day 1	Dosing Day 2	Dosing Day 3	Dosing Day 4	Dosing Day 5
Lansoprazole 1.0 mg/kg/day^a						
Regurgitation/vomiting	5.1	3.1	4.8	2.1	2.7	2.2
Feeding Refusal/Crying	2.3	0.9	1.7	1.6	0.2	0.3
Spells of Arching	2.6	1.7	2.4	1.3	0.9	0
Lansoprazole 2.0 mg/kg/day^b						
Regurgitation/vomiting	4.0	3.0	2.1	1.8	2.4	0.8
Feeding Refusal/Crying	1.7	0.8	0.6	0.3	0.4	0
Spells of Arching	2.6	0.5	0.8	0.3	0.7	0
All Subjects^c						
Regurgitation/vomiting	4.5	3.0	3.4	2.0	2.5	1.5
Feeding Refusal/Crying	2.0	0.8	1.1	0.9	0.3	0.2
Spells of Arching	2.6	1.1	1.6	0.8	0.8	0

Note: There were no reported episodes of apnea for any subject.

a Days -1 to 4 (n=12) and Day 5 (n=5).

b Days -1 to 4 (n=12) and Day 5 (n=6).

c Days -1 to 4 (n=24) and Day 5 (n=11).

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Results (Cont):

GERD Symptom Relief Results (Cont):

On Dosing Day 5, overall GERD symptom relief was assessed as Better in 83% (10/12) and 92% (11/12) of subjects in the lansoprazole 1.0 and 2.0 mg/kg/day groups, respectively.

Pharmacokinetic Results:

The PK profile of lansoprazole was determined in 24 infants with chronological ages 6 to 54 weeks (corrected ages of 46 to 84 weeks) following oral administration of 1.0 or 2.0 mg/kg/day lansoprazole pediatric suspension. Mean PK parameter estimates for lansoprazole on Dosing Day 1 are presented below:

Lansoprazole Dose Group		t _{max} (h)	C _{max} (ng/mL)	AUC _∞ (ng·h/mL)	t _{1/2} (h)	CL/F (L/hr/kg)
1.0 mg/kg/day (n=12)	Mean	1.83	959.08	2202.83	0.83 ^a	0.71
	SD	1.19	472.10	2301.02	NA	0.40
2.0 mg/kg/day (n=12)	Mean	1.76	2086.83	5794.35	0.79 ^a	0.61
	SD	1.06	1558.39	5618.94	NA	0.38

a harmonic mean; NA = not applicable.

An approximate dose-proportional increase in mean C_{max} values was noted for the 1.0 and 2.0 mg/kg/day dose groups (from 959 ng/mL to 2087 ng/mL, respectively). However, a greater than dose-proportional increase was noted for mean AUC values (from 2203 ng h/mL to 5794 ng h/mL, respectively). The apparent clearance was 0.71 L/hr/kg for the 1.0 mg/kg/day dose group and 0.61 L/hr/kg for the 2.0 mg/kg/day dose group. Mean dose-normalized C_{max} and AUC values for the three CYP2C19 heterozygous extensive metabolizers (EM) were up to 1.3 and 1.2 times higher, respectively, than those for the 17 homozygous EM, while the mean apparent clearance for the homozygous EM was 1.8 times higher than that for the heterozygous EM.

The mean lansoprazole plasma concentrations for samples collected at the same time points on Day 1 and Day 5 are presented below:

Lansoprazole Dose Group	Dose Day		Lansoprazole Plasma Concentration (ng/mL)		
			0 hr Sample	2 hr Sample	6 hr Sample
1.0 mg/kg/day (n=12)	1	Mean	0.00	510.62	85.11
		SD	0.00	488.13	183.92
	5	Mean	0.00	484.18	186.64
		SD	0.00	453.31	528.04
2.0 mg/kg/day (n=12)	1	Mean	0.00	1482.58	195.41
		SD	0.00	1387.53	278.13
	5	Mean	0.00	1190.59	241.91
		SD	0.00	1013.72	355.40

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Results (Cont):

GERD Symptom Relief Results (Cont):

No accumulation was observed following either the 1.0 mg/kg/day or 2.0 mg/kg/day lansoprazole microgranules suspension as indicated by lansoprazole concentrations below the lower limit of quantitation at the 0 hour time point on Day 5 for all infants.

There was an apparent age effect on the PK of lansoprazole, with 3 subjects (chronological age of 6 weeks; 1 subject in the 1.0 mg/kg/day dose group and 2 in the 2.0 mg/kg/day dose group) having a substantially lower mean apparent clearance (0.11 L/hr/kg) and higher mean dose-normalized C_{max} (2215 ng/mL/mg/kg) and AUC (8837 ng·h/mL/mg/kg) values compared to the mean CL/F, dose-normalized C_{max} and AUC values for the other 21 subjects who had a chronological age of >10 weeks (0.74 L/hr, 828 ng/mL/mg/kg, and 1652 ng·h/mL/mg/kg, respectively).

Safety Results:

During the Dosing Period, 42% (5/12) of subjects in the lansoprazole 1.0 mg/kg/day and 2.0 mg/kg/day groups experienced at least one AE; all were of mild or moderate severity. The most frequently reported AEs (Hepatic Enzyme Increased and Vomiting) were each experienced by 2 subjects. One treatment-related AE (Hepatic Enzyme Increased) was reported on Dosing Day 5 in the lansoprazole 2.0 mg/kg/day group, was mild in severity, considered probably related to study drug by the investigator, and resolved with treatment during the Postdosing Period. No other treatment-related AEs were reported during the dosing period. One subject in the lansoprazole 2.0 mg/kg/day group experienced a serious AE (SAE) of Pneumonia Viral (MedDRA PT). This SAE was severe but was not considered to be related to study drug by the investigator. No subject died during the study. No subjects prematurely discontinued from this study.

Date of Synopsis: 06 March 2008