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Sponsor Novartis
Generic Drug Name AGO178 / agomelatine
Therapeutic Area of Trial Not applicable
Approved Indication Indicated for the treatment of Major Depressive Disorder
Protocol Number CAGO178C2102
Title An open-label, parallel-group study to compare the pharmacokinetics, safety and tolerability of a single sublingual 1 mg dose of AGO178 in subjects with mild and moderate hepatic impairment with that in matched healthy control subjects.

Phase of Development Phase I
Study Start/End Dates 08 Feb to 02 Sep 2011
Study Design/Methodology This study was an open-label, single dose (1 mg single sublingual dose of AGO178) parallel-group, non-randomized study in subjects with mild and moderate hepatic impairment and healthy subjects matched by body mass index, age and gender.
Centre 1 centre in the United States (US).
Publication Not applicable

Outcome measures

Primary outcome measures(s)

- Evaluate Cmax and area under the plasma curve (AUC) of agomelatine after a single sublingual 1mg dose: from predose until 2 min , 5 min , 10 min, 20 min, 30 min, 45 min, 1h, 1.5h, 2h, 3h, 4h, 6h, 12h, 24h, 36h Post dose.

Secondary outcome measures(s)

- Assess the number of patients with adverse events (AEs) from baseline to Day 8.

Test Product (s), Dose(s), and Mode(s) of Administration

Sublingual tablets of agomelatine 1 mg

Statistical Methods

PK parameters AUClast, AUCinf and Cmax of Agomelatine were compared between each hepatically impaired group (mild and moderate) vs. the matched healthy subjects group. Log transformed PK parameters were analyzed separately using a linear mixed effect model. The model included: (1) a random factor for pair (matched pair of subjects); (2) fixed factors for group (mild hepatic (Group 1), moderate hepatic (Group 2), mild-matched healthy volunteer group (Group 3A) and moderate-matched healthy volunteer group (Group 3B)). The geometric means, ratio of geometric means, and the associated 90% CI were derived from the group comparison by back transformation. The matched healthy volunteers Group 3 consisted of a subset of the healthy subjects group of the same size as the Group 1 and Group 2 for matched hepatic impaired groups mild and moderate respectively. The matching by BMI, age and gender was guaranteed that exactly one healthy volunteer is the match to a given hepatically impaired subject.

Similar analysis as mentioned above was done for PK parameters AUClast, AUCinf and Cmax of agomelatine metabolites; trans-3, 4-dihydrodiol metabolite (t-3,4DHDP) and 3-hydroxy-7-desmethylagomelatine- 3-glucuronide (3H7DP3G).

Study Population: Inclusion/Exclusion Criteria and Demographics

Main Inclusion criteria

- Male and female subjects aged from 18 to 70 years with mild and moderate stages of hepatic impairment as well as in healthy volunteers matching their BMI (+/-10%), age (+/-5 years) and gender. Significant inclusion criteria for all subjects included: Body weight: ≥50kg; body mass index (BMI): 17-35 kg/m2 (inclusive) at Screening.

Additional inclusion criteria in patients with hepatic impairment

- Mild and moderate impaired patients with physical signs consistent with a clinical diagnosis of stable liver disease, which has been confirmed by imaging techniques, ultrasound, MRI or CT within 3 months of screening, having glomerular filtration rate ≥ 60 mL/min/1.73 m2 (based on MDRD formula).
- Mild impaired patients: Child-Pugh Class A (5-6 points, mild hepatic impairment, n = 8) Moderate impaired patients: Child-Pugh Class B (7-9 points, moderate hepatic impairment, n = 8).

Additional inclusion criteria in healthy subjects

- Matched to one hepatically impaired subject undergoing study by BMI (± 10%), age (± 5 years) and sex (in that order) with an an estimated eGFR within the normal range ≥ 60 L/min/1.73 m2 (based on MDRD formula) and have had good health as determined by past medical history, physical examination, electrocardiogram, laboratory tests and urinalysis.
- At Screening, and Baseline, vital signs (SBP and DBP and pulse rate) were assessed in the sitting position after the subject had rested for at least three minutes, and again when required after three minutes in the standing position. Sitting vital signs should have been within the normal range: oral body temperature between 35.0-37.5 °C; SBP: 90-150 mm Hg; DBP: 50-90 mm Hg; pulse rate, 40 - 90 bpm.
- When blood pressure and pulse were taken after at least 3 minutes standing, there should have been no more than a 20 mm Hg drop in SBP or 10 mm Hg drop in DBP and increase in heart rate (>20 bpm) (compared to the sitting results) associated with clinical manifestation of postural hypotension. Any subject exhibiting clinical manifestations of postural hypotension should have been excluded.

Main Exclusion criteria

- Significant illness within the two weeks prior to the dosing.
- In this context, diseases in subjects with hepatic impairment that were the cause of the hepatic disease (such as ascites orencephalopathy) in the medical history were acceptable when they were under medical / therapeutic control and in a stable state.
- History of malignancy of any organ system (other than localized basal cell carcinoma of the skin), treated or untreated, within the past five years, regardless of whether there was evidence of local recurrence or metastases.

Additional exclusion criteria in patients with hepatic impairment

- Patients with hepatic impairment could continue treatments that were required to keep their hepatic disease status stable or control the effects of hepatic impairment and/or were required to control the medical condition being the underlying etiology of the hepatic disease.

However the dosing regimen should have been stable for at least 30 days before dosing. Drugs known to interfere with AGO178 metabolism (CYP1A2 inhibitors or inducers) were prohibited during the study and should have been washed-out before to enter the study

- Patients with grade 2 or higher encephalopathy, clinical evidence of severe ascites, Child-Pugh alterations due to a non-liver disease (e.g. cancer or treatment related weight loss), patients who had a previous surgical porto-systemic shunt.
- History of drug or alcohol abuse within 3 months prior to Screening, or evidence of such abuse as indicated by the laboratory assays conducted during Screening and Baseline.
- A past medical history of clinically significant ECG abnormalities or any clinically relevant ECG abnormalities in the ECG obtained at Screening or at Baseline, according to the following ranges: PR > 220 msec; QRS complex > 120 msec; QTc > 500 msec (Bazett's correction applied)

Participant Flow

	Mild		Moderate		
	Hepatic impaired patients	Matched healthy subjects	Hepatic impaired patients	Matched healthy subjects	All healthy subjects
	N=8 n (%)	N=8 n (%)	N=8 n (%)	N=8 n (%)	N=16 n (%)
Subjects Completed	8 (100)	8 (100)	8 (100)	8 (100)	16 (100)

Baseline Characteristics

		Mild		Moderate		
		Hepatic impaired patients – Group 1	Matched healthy subjects – Group 3A	Hepatic impaired patients – Group 2	Matched healthy subjects – Group 3B	All healthy subjects
		N=8	N=8	N=8	N=8	N=16
Age (years)	Mean (SD)	53.6 (3.34)	51.8 (4.37)	55.8 (3.88)	54.1 (3.60)	52.9 (4.06)
	Median	53.5	51.0	55.0	53.0	51.5
	Range	49-60	45-60	51-62	51-60	45-60
Gender - n(%)	Male	7(87.5)	7(87.5)	5(62.5)	5(62.5)	12(75.0)
	Female	1(12.5)	1(12.5)	3(37.5)	3(37.5)	4(25.0)
Race - n(%)	Caucasian	3(37.5)	6(75.0)	6(75.0)	7(87.5)	13(81.3)
	Black	2(25.0)	2(25.0)	1(12.5)	1(12.5)	3(18.8)
	Other	3(37.5)	0(0.0)	1(12.5)	0(0.0)	0(0.0)
Ethnicity - n(%)	Hispanic/Latino	3(37.5)	0(0.0)	0(0.0)	2(25.0)	2(12.5)
	Indian (Indian subcontinent)	0(0.0)	0(0.0)	1(12.5)	0(0.0)	0(0.0)
	Other	5(62.5)	8(100)	7(87.5)	6(75.0)	14(87.5)
Weight (kg)	Mean (SD)	87.00 (14.65)	94.24 (11.62)	72.58 (13.44)	74.05 (13.79)	84.14 (16.14)
	Median	90.30	96.50	70.85	73.90	85.00
	Range	65.1-111.0	72.5-106.5	53.5-90.9	53.0-97.5	53.0-106.5
Height (cm)	Mean (SD)	172.89 (5.883)	177.13 (6.802)	167.94 (8.902)	170.13 (8.676)	173.63 (8.354)
	Median	172.90	178.50	165.00	169.50	173.50
	Range	164.5-181.0	167.5-188.0	159.0-184.0	156.0-186.0	156.0-188.0
BMI (kg/m^2)	Mean (SD)	29.07 (4.29)	30.09 (3.77)	25.62 (3.45)	25.44 (3.29)	27.76 (4.18)
	Median	30.30	31.47	25.29	25.20	26.63
	Range	21.81-33.89	23.63-33.52	20.90-30.37	21.21-31.84	21.21-33.52

Outcome measures

Primary Outcome Result(s)

Agomelatine summary of pharmacokinetic parameters of primary interest per subject group

PK parameter (unit)	Statistic	Mild hepatic impairment patients	Matched healthy subjects to mild hepatic impairment	Moderate hepatic impairment patients	Matched healthy subjects to moderate hepatic impairment	All healthy subjects
	n	8	8	8	8	16
Cmax (ng/mL)	Mean (SD)	15.7 (3.14)	12.3 (4.60)	21.3 (5.94)	12.5 (1.98)	12.4 (3.42)
	CV% mean	20	37.4	27.9	15.8	27.6
	Geo-mean	15.4	11	20.5	12.4	11.7
AUClast (hr*ng/mL)	Mean (SD)	12.0 (3.00)	7.95 (3.01)	25.5 (23.4)	8.10 (2.96)	8.02 (2.88)
	CV% mean	24.9	37.9	91.6	36.5	35.9
	Geo-mean	11.7	7.16	18.6	7.7	7.43
AUCinf (hr*ng/mL)	Mean (SD)	12.2 (3.06)	8.08 (3.05)	25.7 (23.5)	8.16 (2.95)	8.12 (2.90)
	CV% mean	25.1	37.7	91.5	36.2	35.7
	Geo-mean	11.8	7.31	18.8	7.77	7.54

Secondary Outcome Result(s) / Safety Results

Adverse Events by System Organ Class

	Sublingual 1 mg single dose of AGO178					
	Mild		Moderate		All	
	Hepatic impaired patients	Matched healthy subjects	Hepatic impaired patients	Matched healthy subjects	Hepatic impaired patients	Matched healthy subjects
	N=8	N=8	N=8	N=8	N=16	N=16
	n(%)	n(%)	n(%)	n(%)	n(%)	n(%)
Subjects with AE(s)	8(100)	6(75.0)	8(100)	8(100)	16(100)	14(87.5)
System organ class						
Nervous system disorders	7(87.5)	6(75.0)	8(100)	8(100)	15(93.8)	14(87.5)
Gastrointestinal disorders	4(50.0)	1(12.5)	2(25.0)	0(0.0)	6(37.5)	1(6.3)
Infections and infestations	0(0.0)	0(0.0)	1(12.5)	0(0.0)	1(6.3)	0(0.0)
Injury, poisoning and procedural complications	0(0.0)	1(12.5)	0(0.0)	0(0.0)	0(0.0)	1(6.3)
Respiratory, thoracic and mediastinal disorders	0(0.0)	0(0.0)	0(0.0)	1(12.5)	0(0.0)	1(6.3)

10 Most Frequently Reported AEs Overall by Preferred Term n (%)

	Sublingual 1 mg single dose of AGO178					
	Mild		Moderate		All	
	Hepatic impaired patients	Matched healthy subjects	Hepatic impaired patients	Matched healthy subjects	Hepatic impaired patients	Matched healthy subjects
	N=8	N=8	N=8	N=8	N=16	N=16
	n(%)	n(%)	n(%)	n(%)	n(%)	n(%)
Subjects with AE(s)	8(100)	6(75.0)	8(100)	8(100)	16(100)	14(87.5)
Preferred term						
Dysgeusia	7(87.5)	6(75.0)	8(100)	8(100)	15(93.8)	14(87.5)
Paraesthesia oral	3(37.5)	1(12.5)	0(0.0)	0(0.0)	3(18.8)	1(6.3)
Oral discomfort	0(0.0)	0(0.0)	2(25.0)	0(0.0)	2(12.5)	0(0.0)
Salivary hypersecretion	0(0.0)	0(0.0)	1(12.5)	0(0.0)	1(6.3)	0(0.0)
Tongue pruritus	1(12.5)	0(0.0)	0(0.0)	0(0.0)	1(6.3)	0(0.0)
Upper respiratory tract infection	0(0.0)	0(0.0)	1(12.5)	0(0.0)	1(6.3)	0(0.0)
Procedural dizziness	0(0.0)	1(12.5)	0(0.0)	0(0.0)	0(0.0)	1(6.3)
Sinus congestion	0(0.0)	0(0.0)	0(0.0)	1(12.5)	0(0.0)	1(6.3)

Serious Adverse Events and Deaths

No subjects died or experienced Serious Adverse Events during this study.

Other Relevant Findings

There were no other relevant findings in this study.

Date of Clinical Trial Report 25 April 2012
Date Inclusion on Novartis Clinical Trial Results Database *02 July 2012*
Date of Latest Update