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Sponsor Novartis
Generic Drug Name Agomelatine
Therapeutic Area of Trial Renal impairment study
Approved Indication Investigational
Protocol Number CAGO178C2104
Title An open label, non-randomized, parallel-group study to characterize and compare the pharmacokinetics, safety, and tolerability of a single dose of AGO178C in subjects with mild, moderate, severe renal impairment and end-stage renal disease with that in matched healthy control subjects
Phase of Development I
Study Start/End Dates 04-Mar-2011/30-Aug-2011
Study Design/Methodology This study employed a single-dose, open-label, non-randomized, parallel-group design. The study consisted of a screening period of up to 29 days, a baseline period and one treatment period followed by an end of study evaluation.
Centres USA (4 centers)
Publication None

Outcome measures

Primary Outcome Measures:

PK parameters that were determined from plasma and urine concentration-time data of AGO178 and metabolites:

Primary variables (included in statistical analysis):

- Area under the plasma concentration-time curve from time zero to infinity (AUCinf)
- Area under the curve from time zero to the last measurable concentration sampling time (Tlast) [mass x time x volume-1] (AUClast)
- Maximum observed plasma concentration (Cmax)

Secondary Outcome Measures:

Safety and tolerability of AGO178 as assessed by adverse events reports, vital signs, ECGs and safety laboratory tests.

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

The investigational drug was AGO178, 1 mg single sublingual dose.

Statistical Methods

The following PK parameters were considered for statistical analysis:

- Primary PK parameters: Cmax, AUClast, AUCinf,

Log transformed (natural logarithm) primary PK parameters (Cmax, AUClast, AUCinf) of AGO178 were analyzed by a linear mixed effects model with subject group as fixed factor and matching pair as random factor. The estimated difference and corresponding 90% CI were calculated for each of the renal impairment group v/s matching healthy volunteers. These estimates (90% CI) were back transformed to obtain estimate and 90% CI for ratio of geometric means: Renal impairment group / Matched healthy volunteers.

Similar analysis as mentioned above was done for PK parameters AUClast, AUCinf and Cmax of AGO178 metabolites t-3,4DHDP and 3H7DP3G, although they are not pharmacologically active.

The PK parameters were listed by subject group and subject. For these parameters summary statistics were provided by subject group.

The following secondary PK parameters were also calculated but not used in the statistical analysis: Tmax, Tlag, T1/2, CL/F, Vz/F, CLr, Ae

Study Population: Inclusion/Exclusion Criteria and Demographics

Inclusion Criteria:

- Mild, moderate, severe renally impaired or ESRD patients.
- Healthy male or female subjects to match renally impaired patients in BMI (±15%), age (± 7 years) and gender (in this order). Smoking status (yes or no) will also be used as a final criterion, if deemed feasible by the Investigator.

Exclusion Criteria:

- Pregnant or nursing (lactating) women
- Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, unless using effective contraception during the study as defined in the protocol.
- Smokers, smoking 10 cigarettes or more per day from screening to study completion
- Any surgical or medical condition which might significantly alter the absorption, distribution, metabolism, or excretion of drugs, or which may jeopardize the subject in case of participation in the study
- Co-medication for healthy subjects

Other protocol-defined inclusion/exclusion criteria may apply

Participant Flow

Patient disposition (safety analysis set)

	Sublingual 1 mg single dose of AGO178					
	Mild renal impaired patients	Moderate renal impaired patients	Severe renal impaired patients	End-stage renal impaired patients	All renal impaired patients	All healthy subjects
	N=8 n (%)	N=8 n (%)	N=8 n (%)	N=8 n (%)	N=32 n (%)	N=32 n (%)
Subjects Completed	8(100)	8(100)	8(100)	8(100)	32(100)	32(100)

Baseline Characteristics

		Mild renal impaired patients N=8	Moderate renal impaired patients N=8	Severe renal impaired patients N=8	End-stage renal impaired patients N=8	All renal impaired patients N=32	All healthy subjects N=32
Age (years)	Mean (SD)	61.1 (7.74)	62.5 (10.11)	62.4 (7.41)	54.6 (11.78)	60.2 (9.55)	58.8 (9.47)
	Median	61.5	63.5	63.0	58.5	62.0	60.0
	Range	53-76	45-75	51-73	36-71	36-76	40-77
Height (cm)	Mean (SD)	172.2 (8.42)	162.6 (8.45)	162.5 (9.96)	173.1 (7.39)	167.6 (9.65)	167.9 (7.19)
	Median	174.7	160.2	163.6	173.6	168.6	167.3
	Range	158-180	152-175	148-181	158-182	148-182	153-182
Weight (kg)	Mean (SD)	88.81 (17.47)	75.26 (13.15)	68.50 (7.31)	80.06 (15.54)	78.16 (15.20)	77.63 (11.72)
	Median	89.50	78.60	68.05	79.05	78.60	77.35
	Range	54.1-105.7	54.8-96.0	58.2-81.9	59.3-106.0	54.1-106.0	54.5-103.4
BMI (kg/m2)	Mean (SD)	29.77 (4.53)	28.47 (4.53)	26.01 (2.62)	26.57 (3.68)	27.71 (4.03)	27.48 (3.28)
	Median	30.73	30.22	26.03	27.17	27.44	27.33
	Range	21.68-34.69	21.41-33.72	22.63-30.12	19.83-31.90	19.83-34.69	19.66-33.50
Sex - n(%)	Male	5(62.5)	2(25)	2(25)	3(37.5)	12(37.5)	12(37.5)
	Female	3(37.5)	6(75)	6(75)	5(62.5)	20(62.5)	20(62.5)
Race - n(%)	Caucasian	6(75)	5(62.5)	6(75)	2(25)	19(59.4)	28(87.5)
	Black	2(25)	1(12.5)	1(12.5)	6(75)	10(31.3)	4(12.5)
	Asian	0(0.0)	1(12.5)	0(0.0)	0(0.0)	1(3.1)	0(0.0)
	Native American	0(0.0)	1(12.5)	1(12.5)	0(0.0)	2(6.3)	0(0.0)
Ethnicity - n(%)	Hispanic/Latino	2(25)	2(25)	2(25)	1(12.5)	7(21.9)	9(28.1)
	Other	6(75)	6(75)	6(75)	7(87.5)	25(78.1)	23(71.9)

Outcome measures

Primary Outcome Result(s)

Summary statistics for plasma PK parameters of primary interest of AGO178 per subject group

PK parameter (unit)	Statistic	Mild renal	Matched healthy to mild renal	Moderate renal	Matched healthy to moderate renal	Severe renal	Matched healthy to severe renal	ESRD renal	Matched healthy to ESRD renal	all healthy subjects
	n [a]	8	8	8	8	8	8	8	8	32
Cmax	Mean (SD)	14.0 (9.43)	9.84 (4.72)	18.2 (9.01)	12.7 (5.05)	12.1 (8.09)	14.3 (6.42)	11.7 (6.75)	10.8 (4.11)	11.9 (5.19)
(ng/mL)	CV% mean	67.3	48	49.4	39.7	66.6	44.9	57.7	38	43.6
	Geo-mean	12.1	8.8	16.5	11.8	10.3	13.3	9.85	10.2	10.9
AUClast	Mean (SD)	11.4 (8.74)	7.44 (3.08)	11.9 (6.23)	10.1 (4.88)	10.7 (8.69)	10.3 (3.73)	9.57 (5.50)	8.82 (3.23)	9.17 (3.79)
(hr*ng/mL)	CV% mean	76.4	41.4	52.4	48.4	80.9	36.1	57.5	36.6	41.4
	Geo-mean	9.58	6.82	10.8	9.11	8.5	9.87	8.11	8.29	8.44
AUCinf	Mean (SD)	11.7 (8.93)	7.57 (3.12)	12.1 (6.27)	10.2 (4.90)	10.9 (8.78)	10.4 (3.73)	9.73 (5.60)	8.97 (3.30)	9.29 (3.81)
(hr*ng/mL)	CV% mean	76.6	41.2	52	48	80.8	35.7	57.5	36.8	41
	Geo-mean	9.74	6.95	11	9.23	8.62	9.98	8.25	8.42	8.57

Geometric mean ratio (renal patients vs. matched healthy volunteers) and 90% confidence intervals for plasma primary PK parameters

Statistical analysis results

PK Parameter	Mild renal vs. Matched healthy to mild renal	Moderate renal vs. Matched healthy to moderate renal	Severe renal vs. Matched healthy to severe renal	End-stage renal vs. Matched healthy to End-stage renal
AGO178				
Cmax (ng/mL)	1.38 (0.92,2.07)	1.40 (0.93,2.10)	0.77 (0.51,1.16)	0.96 (0.64,1.45)
AUClast (hr*ng/mL)	1.40 (0.91,2.16)	1.19 (0.77,1.83)	0.86 (0.56,1.33)	0.98 (0.63,1.51)
AUCinf (hr*ng/mL)	1.40 (0.91,2.16)	1.19 (0.78,1.83)	0.86 (0.56,1.33)	0.98 (0.64,1.51)
3H7DP3G metabol.				
Cmax (ng/mL)	1.02 (0.84,1.24)	1.23 (1.01,1.50)	1.48 (1.22,1.80)	1.47 (1.21,1.78)
AUClast (hr*ng/mL)	1.83 (1.26,2.66)	4.15 (2.85,6.03)	5.81 (4.00,8.45)	37.26 (25.63,54.16)
AUCinf (hr*ng/mL)	2.05 (1.26,3.33)	4.24 (2.61,6.88)	6.01 (3.70,9.76)	95.65 (52.84,173.13)
t-3,4-DHDP metabol.				
Cmax (ng/mL)	1.19 (0.79,1.80)	1.39 (0.92,2.10)	1.10 (0.73,1.65)	1.17 (0.78,1.77)
AUClast (hr*ng/mL)	1.46 (0.99,2.16)	1.66 (1.12,2.46)	1.62 (1.09,2.39)	2.44 (1.65,3.60)
AUCinf (hr*ng/mL)	1.47 (1.00,2.17)	1.65 (1.12,2.43)	1.60 (1.09,2.36)	2.36 (1.58,3.52)

Secondary Outcome Result(s)

Safety results

Adverse events overall and most frequent events - n (%) of subjects (Safety analysis set)

	Sublingual 1 mg single dose of AGO178					
	Mild renal impaired patients	Moderate renal impaired patients	Severe renal impaired patients	End-stage renal impaired patients	All renal impaired patients	All healthy subjects
	N=8	N=8	N=8	N=8	N=32	N=32
	n(%)	n(%)	n(%)	n(%)	n(%)	n(%)
Subjects with AE(s)	8(100.0)	6(75.0)	4(50.0)	5(62.5)	23(71.9)	23(71.9)
Preferred term						
Dysgeusia	7(87.5)	4(50.0)	4(50.0)	3(37.5)	18(56.3)	18(56.3)
Nausea	0(0.0)	1(12.5)	0(0.0)	2(25.0)	3(9.4)	0(0.0)
Paraesthesia oral	2(25.0)	1(12.5)	0(0.0)	0(0.0)	3(9.4)	0(0.0)
Dizziness	0(0.0)	0(0.0)	1(12.5)	1(12.5)	2(6.3)	1(3.1)
Glossodynia	1(12.5)	0(0.0)	0(0.0)	0(0.0)	1(3.1)	2(6.3)
Headache	0(0.0)	0(0.0)	0(0.0)	1(12.5)	1(3.1)	2(6.3)
Diarrhoea	0(0.0)	0(0.0)	0(0.0)	1(12.5)	1(3.1)	1(3.1)
Oral discomfort	0(0.0)	0(0.0)	0(0.0)	1(12.5)	1(3.1)	1(3.1)
Oral pain	0(0.0)	1(12.5)	0(0.0)	0(0.0)	1(3.1)	1(3.1)
Abnormal faeces	1(12.5)	0(0.0)	0(0.0)	0(0.0)	1(3.1)	0(0.0)
Faeces discoloured	1(12.5)	0(0.0)	0(0.0)	0(0.0)	1(3.1)	0(0.0)
Tooth disorder	0(0.0)	1(12.5)	0(0.0)	0(0.0)	1(3.1)	0(0.0)
Epistaxis	0(0.0)	0(0.0)	0(0.0)	1(12.5)	1(3.1)	0(0.0)
Ecchymosis	0(0.0)	1(12.5)	0(0.0)	0(0.0)	1(3.1)	0(0.0)
Petechiae	1(12.5)	0(0.0)	0(0.0)	0(0.0)	1(3.1)	0(0.0)
Somnolence	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	2(6.3)
Dyspepsia	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	1(3.1)
Administration site reaction	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	1(3.1)
Feeling jittery	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	1(3.1)
Oral herpes	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	1(3.1)
Muscle spasms	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	1(3.1)
Rash papular	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	1(3.1)

AEs by preferred term are presented in descending order of overall frequency.

All AEs were of mild to moderate severity and none of these were SAEs

Overall, no clinically significant changes in laboratory parameters (hematology, blood chemistry, and urinalysis), vital signs and ECG were observed during the study.

Other Relevant Findings

None

Date of Clinical Trial Report 23-Apr-2012
Date Inclusion on Novartis Clinical Trial Results Database 29 Aug 2012
Date of Latest Update