Safety, Tolerability and Pharmacokinetics of GIC-1001 Following Multiple Ascending Dose Administrations Through an Adaptive First-in-Human Study in Healthy Volunteers

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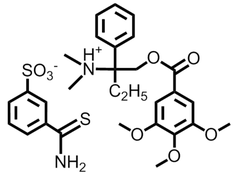
BACKGROUND

GIC-1001 is an innovative single drug intended to be used as an orally-administered alternative to parenteral sedation in order to manage visceral pain in patients undergoing full sedation-free colonoscopy.



GIC-1001 is indeed a salt of trimebutine, a non-centrally-acting opioid agonist bearing a counterion capable of releasing hydrogen sulfide (H_2S) *in vivo*. The exogenous H_2S has been shown *in vivo* to potentialize the colonic analgesic effect provided by the trimebutine moiety.

Trimebutine is marketed as a maleate salt in Canada (registered as Modulon®) and in several EU countries for the treatment of symptoms associated with Irritable Bowel Syndrome. Trimebutine has an analgesic effect through visceral nociception in addition to motility regulation, while its maleate counterion is completely devoid of pharmacological effect. GIC-1001 was shown to be superior to the maleate salt and its innovation resides in the novel counterion with the ability of releasing an active metabolite, H_2S, contributing to the therapeutic effect.

METHODS

OVERVIEW OF THE STUDY

Phase I (FIH), single center, randomized, double-blinded, placebo-controlled, adaptive design study evaluating Single Ascending Doses (SAD), Multiple Ascending Doses (MAD) and food effect.

OBJECTIVES

The objectives of the MAD study portion were to evaluate the safety and tolerability of GIC-1001 compared with placebo and to evaluate the pharmacokinetics (PK) of GIC-1001 following multiple-dose administration in healthy subjects.

INVESTIGATIONAL PRODUCTS

In the MAD study portion, multiple oral doses of 125 up to 500 mg tablets of GIC-1001 or placebo administered tid for 7 consecutive days (total of 19 consecutive doses).

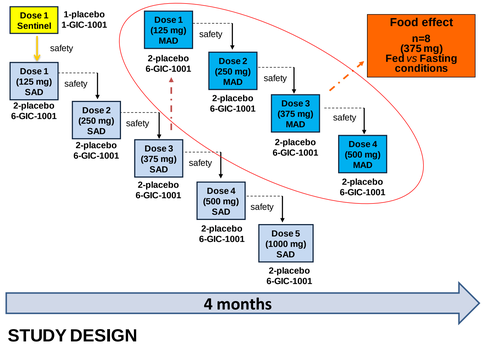
KEY INCLUSION / EXCLUSION CRITERIA

Male and female subjects, non- or ex-smokers, 18-50 years of age with BMI between 18.5 to 30 kg/m^2. Subjects were in good health as determined by a medical history, physical examination (including vital signs), electrocardiogram (ECG) and clinical laboratory tests. Screening of ethyl alcohol, drugs of abuse in urine, and pregnancy test were performed and were to be negative.

SAMPLE SIZE

80 subjects were included in the study and 32 subjects were included in the MAD portion of the study.

FIGURE 1. Schematic Representation of the Study Design



STUDY DESIGN

Multiple Ascending Doses (tid) study portion:

Ascending doses of GIC-1001 (125, 250, 375 or 500 mg) or placebo were orally administered three times daily (8-hour intervals) to 4 cohorts of subjects for 6 consecutive days. The last dose (19th dose) was given on the morning of the 7th day, after a 10-hour overnight fast.

Dose escalation procedure:

Based on the observed safety and tolerability data of GIC-1001 and its pharmacokinetics, the dose escalation was to be approved by a Safety Review Panel (SRP) prior to dosing the next cohort. The 1st multiple dose regimen was initiated only after full SRP review of the 2nd SAD cohort and dosing of the 3rd SAD cohort.

TABLE 1. Analytical Methods

Analyte	Matrix	Method	LLOQ
Trimebutine	human plasma	HPLC with MS/MS detection	2.50 ng/mL
N-monodesmethyl-trimebutine	human plasma		5.00 ng/mL
3-thiocarbamoylbenzene-sulfonate (3-TCBS)	human plasma		5.00 ng/mL

SAFETY

Safety was assessed by clinical and/or statistical review of all safety parameters (adverse events, laboratory tests, vital signs, 12-lead ECG and physical examination).

PHARMACOKINETIC & STATISTICAL ANALYSES

Standard PK parameters were calculated using a non-compartmental approach (Phoenix® WinNonlin®, version 6.3).

Statistical analysis of all pharmacokinetic parameters was based on an ANOVA model. Two-sided 90% confidence intervals of the ratio of geometric LSmeans were obtained from the main pharmacokinetic parameters.

Direct proportional linearity and independence of dose were assessed over all doses of GIC-1001.

Time to reach steady-state was assessed based on ln-transformed C_{pds} and the effect of repeated administrations was also evaluated.

RESULTS

SAFETY RESULTS

Twenty-five (25) of the 32 subjects (78.1%) reported 144 adverse events; 19 of those subjects received GIC-1001 (79.2%) and 6 received the placebo (75%).

The most frequently reported adverse event in subjects receiving GIC-1001 was in the nervous system disorders class, i.e. headache (14.4%). Somnolence (8.5%), nausea (8.5%) and dizziness (7.6%) were also reported in subjects receiving the active product.

TABLE 2. Summary of Adverse Events

Adverse Event (AE) Monitoring	Dose Level				
	Placebo	125 mg	250 mg	375 mg	500 mg
Nº (%) of subjects who experienced at least 1 AE	6 (75.0%)	5 (83.3%)	6 (100%)	3 (50.0%)	5 (83.3%)
Nº of AE reported	26	17	25	36	40

PHARMACOKINETIC RESULTS

TABLE 3. Summary of Main Pharmacokinetic Results

Analyte	Parameter[1]	Dose Level				Linear[3] / Proportional
		125 mg	250 mg	375 mg	500 mg	
Trimebutine	C_{max} (ng/mL)	21.51 (77.2)	30.36 (35.8)	52.95 (64.5)	74.85 (44.9)	Yes (p: 0.4693) / Yes (p: 0.0060)
	T_{max} [2](h)	0.75 (0.50-2.00)	1.00 (1.00-2.00)	2.00 (0.50-3.00)	0.50 (0.50-0.57)	-
	AUC_{Tau} (ng*h/mL)	44.90 (67.2)	81.33 (31.8)	134.80 (44.5)	176.71 (33.8)	Yes (p: 0.7608) / Yes (p: 0.0002)
N-mono-trimebutine	C_{max} (ng/mL)	1061.93 (25.0)	2558.26 (28.6)	3133.64 (18.0)	3624.19 (9.2)	No (p: 0.0319) / N/AP
	T_{max} [2](h)	1.25 (1.00-2.00)	1.00 (1.00-2.00)	2.00 (1.00-3.00)	1.00 (1.00-2.00)	-
	AUC_{Tau} (ng*h/mL)	3347.16 (30.8)	7654.00 (31.8)	10360.91 (11.1)	13930.23 (14.1)	Yes (p: 0.4611) / Yes (p< 0.0001)
3-TCBS	C_{max} (ng/mL)	158.19 (18.1)	360.65 (34.7)	514.99 (4.0)	658.26 (34.7)	Yes (p: 0.4689) / Yes (p< 0.0001)
	T_{max} [2](h)	1.00 (0.50-2.00)	3.00 (1.00-6.00)	6.50 (3.00-7.00)	1.50 (1.50-4.00)	-
	AUC_{Tau} (ng*h/mL)	924.96 (21.1)	1889.41 (27.4)	3218.21 (15.1)	4010.44 (21.5)	Yes (p: 0.8846) / Yes (p< 0.0001)

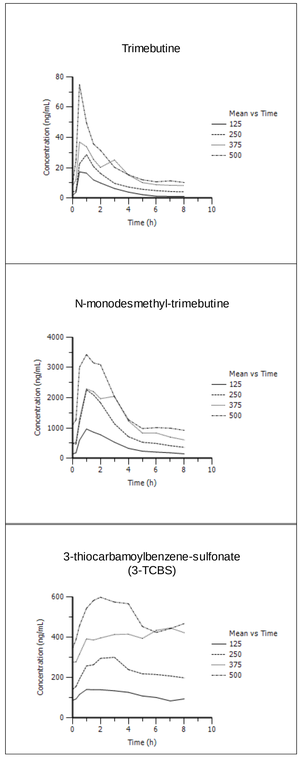
1. Mean (CV%) are presented.
2. Median (Range) are presented.
3. If the p-value of the non-linearity test was higher than 0.05, linearity was assumed.

Twenty-one (21) subjects were included in the pharmacokinetic and statistical analysis (4-6 subjects per cohort).

Steady-state was considered to be reached after 3 days of a tid administration of GIC-1001, except for trimebutine at the highest dose level (500 mg) which reached steady-state after 5 days of administration.

The fluctuation ranged from 255.12 – 392.73% for trimebutine, from 166.37 – 238.19% for n-monodesmethyl-trimebutine and from 62.81 – 94.50% for 3-TCBS.

FIGURE 2. Linear Profile of the Mean



CONCLUSION

No clinically significant effects on vital signs or ECGs were noted and no serious adverse events or deaths were reported during the multiple dose portion of this study.

Multiple ascending oral doses of 125 mg through 500 mg over 7 days were generally safe, non sedative and well tolerated by the subjects included in this study. There was no pattern of increasing number or severity of adverse events with increasing doses. Based on the ANOVA models and the linear regression models, the pharmacokinetics of GIC-1001 was shown to be mainly linear and proportional following multiple doses administration over the studied dose range. In light of these findings, GIC-1001 warrants further clinical evaluation as a novel colonic analgesic drug, in patients undergoing full colonoscopy.

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