Safety, Tolerability and Pharmacokinetics of GIC-1001 in a Randomized Phase I Integrated Design Study: Single and Multiple Ascending Doses, Effect of Food, with Healthy Volunteers

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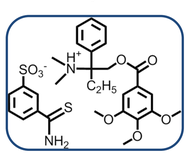
PURPOSE

- 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 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.

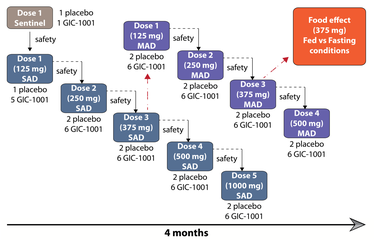


- The objectives of this study were to evaluate the safety, tolerability and pharmacokinetics of GIC-1001 following single ascending doses (SAD), multiple ascending doses (MAD) and to evaluate the influence of food on the pharmacokinetics in healthy volunteers.

METHODS

STUDY DESIGN

- Single-center, randomized, double-blinded, placebo-controlled, integrated Phase I study in healthy subjects.
- The SAD part consisted of five cohorts with dose levels of 125 to 1000 mg administered under fasting conditions.
- The MAD part consisted of four cohorts in which subjects received three times daily (tid) doses of 125 to 500 mg over seven days (19 consecutive doses).
- The food-effect part was a single 375 mg dose of GIC-1001 in a randomized, two-period, crossover design.



PHARMACOKINETIC & STATISTICAL EVALUATION

- Blood samples were collected prior to dosing and up to 36 hours post-dose for the single-dose pharmacokinetic (PK) analysis of trimebutine, N-monodesmethyl-trimebutine (NMT) and 3-thiocarbamoylbenzenesulfonate (3-TCBS). Samples were collected pre-dose and eight hours post-last dose in the MAD part. Plasma samples were assayed through validated analytical methods by using HPLC with MS/MS detection.
- PK parameters were calculated using a non-compartmental approach (Phoenix® WinNonlin®, version 6.3).
- Statistical analyses were performed with ANOVA models to test the Linearity and Proportionality, and to assess steady-state.
- The 90% confidence interval (CI) of the ratio of geometric LSmeans between fed and fasting conditions was calculated for the primary PK parameters.

TOLERABILITY

- Safety endpoints included the occurrence of adverse events (AEs), clinical laboratory test results, measurements of vital signs, 12-lead ECG findings, cardiac monitoring, and physical examination findings.
- A Safety Review Panel approved each dose escalation through a blind review of the safety and PK data.

RESULTS

SUBJECTS

- GIC-1001 or placebo was orally administered to 80 healthy non-smoker male and female subjects, aged between 20 and 50 years.
- Eight subjects were enrolled in each cohort.
- There were six withdrawals in the study: none in the SAD part; three for safety reasons and two for personal reasons in the MAD part; one for personal reasons in the food-effect part.

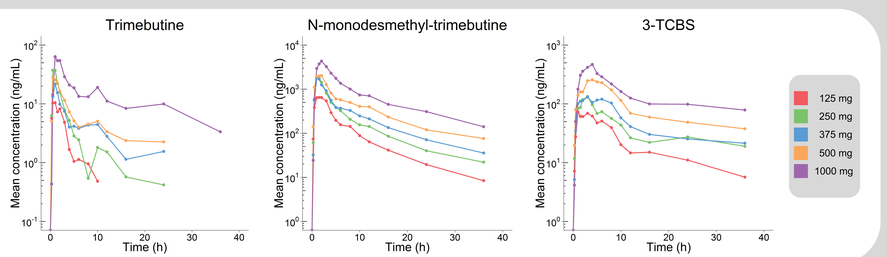
	Study Part		
	SAD (N = 40)	MAD (N = 32)	Food Effect (N = 8)
Age (Years)			
Mean (SD)	30 (8.2)	32 (9.7)	32 (9.2)
Range	20-50	19-50	23-48
Gender			
Male	20	16	5
Female	20	16	3
Race			
White	35	29	6
Black	4	3	0
Other	1	0	2[a]
Weight (kg)			
Mean (SD)	70.2 (11.2)	69.3 (11.7)	76.6 (12.4)
Range	48.2-91.2	49.9-92.2	56.0-93.6
Height (cm)			
Mean (SD)	168.2 (8.4)	167.4 (7.9)	169.6 (9.7)
Range	148.0-181.0	150.0-183.0	153.0-181.5
BMI (kg/m^2)			
Mean (SD)	24.7 (2.7)	24.6 (3.2)	26.5 (2.2)
Range	18.7-29.6	20.1-29.9	22.8-28.7

[a] Asian

Analyte	Parameter[a]	Dose Level 125 mg	250 mg	375 mg	500 mg	1000 mg
Trimebutine	C_{max} (ng/mL)	18.14 (61.5)	52.29 (38.4)	23.51 (50.4)	38.94 (64.8)	80.83 (50.2)
	T_{max} [b](h)	1.00 (0.50-2.00)	1.00 (0.50-2.00)	1.00 (0.50-3.00)	1.15 (0.50-3.03)	1.50 (1.00-2.00)
	AUC_T (ng*h/mL)	30.33 (64.3)	88.32 (41.1)	89.04 (71.1)	127.70 (74.2)	447.69 (36.5)
	$T_{1/2el}$ (h)	3.25 (83.5)	3.62 (103.9)	8.92 (89.2)	8.48 (68.6)	12.48 (35.9)
NMT	C_{max} (ng/mL)	948.90 (23.7)	2099.02 (34.0)	2064.67 (58.6)	2452.90 (26.1)	4681.64 (26.8)
	T_{max} [b](h)	1.75 (0.50-3.00)	1.03 (1.00-2.00)	1.25 (1.00-3.00)	1.50 (0.80-3.03)	2.00 (1.50-2.00)
	AUC_T (ng*h/mL)	3676.37 (40.6)	7482.51 (38.9)	8825.94 (33.8)	13425.25 (49.4)	28397.48 (25.6)
	$T_{1/2el}$ (h)	8.73 (20.7)	8.40 (23.9)	9.54 (24.2)	12.49 (40.8)	11.07 (31.1)
3-TCBS	C_{max} (ng/mL)	103.25 (66.5)	146.15 (38.2)	173.95 (23.2)	306.69 (27.2)	489.64 (46.8)
	T_{max} [b](h)	5.00 (1.00-8.00)	3.00 (2.00-10.00)	4.00 (1.00-6.00)	4.00 (3.00-6.00)	3.00 (1.50-6.00)
	AUC_T (ng*h/mL)	751.89 (19.7)	1388.03 (21.7)	1740.39 (15.5)	3231.18 (21.1)	5364.18 (26.9)
	$T_{1/2el}$ (h)	23.43 (71.8)	17.59 (58.9)	16.84 (59.7)	21.68 (47.2)	17.16 (30.8)

[a] mean (% CV) [b] median (range)

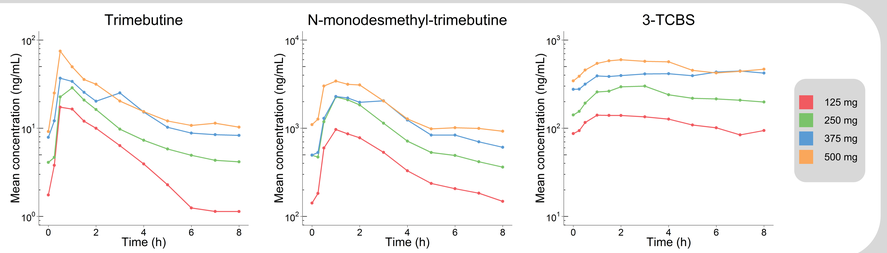
Single Ascending Doses



Analyte	Parameter[a]	Dose Level 125 mg	250 mg	375 mg	500 mg	1000 mg
Trimebutine	C_{max} (ng/mL)	21.51 (77.2)	30.36 (35.8)	52.95 (64.5)	74.85 (44.9)	-
	T_{max} [b](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)	-
	Fluctuation (%)	392.73 (42.6)	258.12 (18.2)	255.12 (24.0)	296.74 (16.1)	-
NMT	C_{max} (ng/mL)	1061.93 (25.0)	2558.26 (28.6)	3133.64 (18.0)	3624.19 (9.2)	-
	T_{max} [b](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)	-
	Fluctuation (%)	233.80 (28.6)	238.19 (14.4)	205.98 (8.7)	166.37 (11.2)	-
3-TCBS	C_{max} (ng/mL)	158.19 (18.1)	360.65 (34.7)	514.99 (4.0)	658.26 (34.7)	-
	T_{max} [b](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)	-
	Fluctuation (%)	73.08 (38.8)	94.50 (39.3)	66.01 (45.3)	62.81 (75.4)	-

[a] mean (% CV) [b] median (range)

Multiple Ascending Doses



PHARMACOKINETIC

- Following a single dose administration, C_{max} and AUC_T were linear (non-linearity p> 0.05) and proportional (p≤0.05) over the 125 to 1000 mg dose range. $T_{½el}$ was independent of dose (p ≥ 0.05) over the same dose range for NMT and 3-TCBS; however the statistical analysis indicated that $T_{½el}$ of trimebutine was dependant of dose (p < 0.05).
- Following multiple dosing, C_{max} and AUC_{Tau} were linear (p ≥ 0.05) and proportional (p < 0.05) over the 125-500 mg dose range for trimebutine and 3-TCBS. For NMT, only AUC_{Tau} was linear and proportional.
- Consumption of food tended to increase peak concentration and systemic exposure of trimebutine; it had no significant effect on the profile of NMT, and tended to decrease peak concentration and systemic exposure of 3-TCBS. T_{max} and $T_{½el}$ were not significantly affected.

Analyte	Parameter	Geometric LSmeans Treatment-1 (fed)	Treatment-2 (fast)	Ratio (%)	90% Confidence Limits Lower	Upper
Trimebutine	C_{max} (ng/mL)	63.95	45.63	140.16	84.00	233.87
	AUC_T (ng*h/mL)	174.70	100.16	174.41	137.73	220.86
	AUC_∞ (ng*h/mL)	190.93	116.34	164.11	123.39	218.29
NMT	C_{max} (ng/mL)	3360.34	2860.44	117.48	94.57	145.94
	AUC_T (ng*h/mL)	16342.37	13758.98	118.78	101.27	139.31
	AUC_∞ (ng*h/mL)	16615.57	14004.64	118.64	101.08	139.25
3-TCBS	C_{max} (ng/mL)	154.16	203.37	75.80	44.15	130.15
	AUC_T (ng*h/mL)	1598.93	2039.58	78.40	70.00	87.80
	AUC_∞ (ng*h/mL)	2164.36	2436.11	88.84	80.20	98.42

TOLERABILITY

- No deaths or serious AEs were reported during the study.
- The most common AEs included headache, somnolence, nausea, and dizziness. The majority of AEs reported during the study were of mild or moderate severity. Nausea and increased transaminases were the only two severe AEs and were reported following single drug administration.
- There were no apparent trends or clinically important changes in the serum biochemistry, hematology, or urinalysis.

CONCLUSION

- GIC-1001 is a new molecular entity that was found safe and well-tolerated when first administered to humans. The safety profile was similar under fed and fasting conditions.
- The PKs of GIC-1001 (trimebutine, NMT and 3-TCBS) were shown to be mainly linear and proportional over the studied dose range following single and multiple doses.
- Steady-state was generally considered to be reached after three days of administration.
- A food-effect was reported. Considering the different impact on each analyte, it is difficult to know if GIC-1001 should be taken on an empty stomach. However, because the intended use of GIC-1001 is for colonoscopy and the patient should be fasted before the procedure, administration of GIC-1001 should be oral and in fasting conditions.

REFERENCES

- Paquette JM et al. (2014) *Clinical Therapeutics*, article in press, available online: http://dx.doi.org/10.1016/j.clinthera.2014.08.005