Algorithme Pharma, 575 Armand-Frappier, Laval (Montréal), Québec, Canada
algopharm.com | contact@algopharm.com

A PHASE IB CLINICAL STUDY TO EVALUATE THE ANALGESIC EFFECT OF GIC-1001 AND GIC-1002 ON VISCERAL PAIN UNDER RECTAL DISTENSION USING THE BAROSTAT METHOD IN HEALTHY VOLUNTEERS

J-M. Paquette, M. Iovu Niculita, M. Rufiange, S. Boily, E. Sicard, J. Massicotte, M. Lefebvre; Algorithme Pharma Inc., Laval, QC, Canada. O. Uresandi, P. Colin, M. Ranger; gIcare Pharma Inc., Montreal, QC, Canada.

Overview

Phase 1B, Randomized, Double-Blind (double dummy), Placebo Controlled, Parallel Group Administration Design. GIC-1001 and GIC-1002 are being developed for the management of visceral pain in patients undergoing sedation-free full colonoscopy. This poster will highlight the study design and results of the Phase IB barostat study in healthy volunteers.

Background

GIC-1001 (trimebutine 3-thiocarbamoyl-benzenesulfonate) is an innovative and dual action, single drug substance that gIcare Pharma intends to develop as an orally-administered alternative to parenteral sedation, to manage visceral pain in subjects undergoing full colonoscopy. GIC-1001, a novel drug salt of trimebutine, a non-centrally acting opioid agonist, bears a counterion capable of releasing an active metabolite, hydrogen sulfide (H_2S).

GIC-1002 developed as the active control of GIC-1001. GIC-1002's drug substance is trimebutine tosylate. GIC-1002 is a salt in which the cation is the protonated form of trimebutine and the counterion is tosylate. The counterion is the part of the drug substance which has no ability to release hydrogen sulfide *in vivo*.

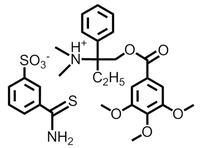

Figure 1. GIC-1001 molecular structure

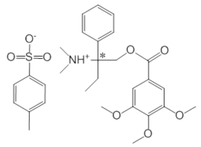

Figure 2. GIC-1002 molecular structure

A double blind, placebo-controlled, parallel design Phase IIA trial was completed in subjects undergoing sedation-free full colonoscopy. While GIC 1001 has been shown to be completely safe in the study subject population, only the mid dose (375 mg tid regimen x 3 days) induced a clinically significant reduction in the overall periprocedural pain experience, as measured with a 100-mm VAS. The apparent U-shaped dose-response curve suggested an interaction between released H_2S and the trimebutine component of GIC-1001. In light of this non-conclusive efficacy evidence, the clinical exploration of the true analgesic effects of GIC-1001, especially at 375 mg tid, gIcare pharma proposed to study the antinociceptive properties of trimebutine as well as the contribution of H_2S in the context of a barostat study.

Rectal and sigmoid distensions have been used to test visceral perception, notably in Irritable Bowel Syndrome (IBS). Predefined and standardized distensions of the bowel wall using a barostat device are widely accepted, and represent the current standard for the assessment of sensorimotor function in experimental trials in healthy and diseased subjects. The barostat is a computer-driven air pump connected to a double-lumen catheter, on which a highly compliant balloon is securely fixed. The balloon is introduced in the rectum and is used to measure the tone, compliance and sensory thresholds. Rectal distension can be done according to a certain protocol, during which different pressures are applied to the rectal wall. The intensity and quality of perception can be measured by means of rating scales (typically VAS). Besides perception scores (pain, urge and discomfort), parameters such as first sensation, minimal distension pressure, and rectal capacity may also be evaluated in these studies.

Method

Objectives

Primary Objective

- To assess the analgesic effect of GIC-1001 via the assessment of visceral pain intensity under rectal distension following the oral administration of a dose regimen of GIC-1001 375 mg TID over three successive days.

Secondary Objectives Included

- To assess visceral pain intensity under rectal distension following the oral administration of GIC-1001 and GIC-1002 at any studied dosing regimen.
- To assess the contribution of H_2S to the colonic analgesic activity of GIC-1001 by comparison to that of GIC-1002.

Key Inclusion and Exclusion Criteria

Ninety healthy male or female subjects aged between 18 and 65 years with a BMI between 18.5 and 35 kg/m^2 and having a normal anorectal area as confirmed by digital rectal examination were included in this Phase IB study. Subjects with diagnosis of IBS or any other functional bowel disorder were to be excluded. Subjects with a history of abdominal or rectal surgery, including gynaecological surgery for females subjects, were also to be excluded.

Study Design

This study was designed as a single center, Phase Ib, randomized, double-blind, placebo controlled, parallel group administration design. Fully blinded for both GIC-1001 and GIC-1002, with double dummy technique. Subjects were randomized in five treatment arms (n =18); GIC-1001 (375 or 500 mg), equimolar doses of GIC-1002 (345 or 460 mg) or matching placebo.

Ten administrations of GIC-1001, GIC-1002 and/or matching placebo were administered as follows:

- One administration tid on an empty stomach for 3 consecutive days prior to barostat procedure, last administration on the 4th day in the morning at least 1 hour prior to beginning of the procedure (Barostat rectal insertion)
- Bowel preparation to be performed using Fleet enema following the last administration (approximately 2 hours before the barostat procedure)

In the morning of Day 4, subjects completed a barostat procedure comprised of 4 different stages in about one hour:

I. Balloon Unfolding: single distension at a balloon pressure of 20 mmHg for 60 sec.

II. Rectal Conditioning Distension: staircase distension protocol with pressure steps of 4 mmHg with a duration of 30 seconds each and a range from 0 to 40 mmHg.

III. Compliance, Sensory Thresholds and Ratings: staircase distension protocol with pressure steps of 4 mmHg with a duration of 60 seconds each and a pressure range of 0–60 mmHg

IV. Visceral Pain Perception: automatic distensions from 0 to a maximal pressure limit of 60 mmHg. Distensions were randomly increased by increments of 6 mmHg with an isobar duration of 60 seconds. Randomization of pressures were split into two series: (a) 6 to 42 mmHg and (b) 48 to 60 mmHg. The balloon was deflated down to 6 mmHg for a period of 60 seconds after each distension.

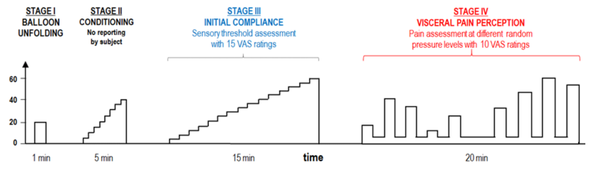

Figure 3. Schematic Representation of the Four Barostat Stages

Study Endpoints

Primary Endpoint

- Mean visceral pain intensity score in millimeters (mm) on a 100-mm Visual Analog Scale (VAS) based on seven measurements collected at increasing rectal distension pressures from 24 to 60 mmHg following the oral administration of the GIC-1001 375 mg TID x 3 days regimen, and comparing it to placebo.

Secondary Endpoints Included

- Mean visceral pain intensity score in mm on a 100-mm VAS based on seven measurements collected at increasing rectal distension pressures from 24 to 60 mmHg following the oral administration of the GIC-1001 500 mg TID, GIC-1002 345 mg TID and 460 mg TID x 3 days regimens, compared to placebo.
- Contribution of H_2S to GIC-1001 analgesic effects in terms of mean VAS scores differences between GIC-1001 and GIC-1002 at equimolar doses.

Analysis Population

The analysis populations were as follows: 1) full analysis population: all randomized subjects who received at least one dose of study medication, had a baseline VAS measurement, reached stage IV of the barostat experiment, and had at least one VAS measurement at stage IV, 2) Per-protocol population: all randomized subjects who completed the study, had at least 80 % drug compliance, provided mean visceral pain intensity score VAS on seven measurements (out of a total of 10) from 24 to 60 mmHg at stage IV, and had no major deviation and 3) safety population: all randomized subjects who took at least one dose of study drugs.

Safety & Efficacy Evaluation

Safety was evaluated through assessment of adverse events, the measurement of clinical laboratory parameters, concomitant medication, vital signs, physical examination and 12-lead electrocardiogram (ECG). Clinical events were classified by system organ class and preferred term using the Medical Dictionary for Regulatory Activities (MedDRA), version 17.0.

For the analysis of efficacy data, subjects reported visceral pain on a 100-mm VAS scale, where 0 mm meant no discomfort or pain at all, and 100 mm meant severe pain. The adapted 'last observation carried forward' (adapted LOCF) was used to extrapolate any missing data. The rationale of LOCF method is that pain experienced by a subject at a given pressure should be at least equal or even greater at a higher pressure level. Therefore, after having reclassified pressures in ascending order, the VAS value collected at the lower pressure was applied to the next pressure if the VAS score was not reported by the subject for a given pressure. The average of mean VAS difference between treatments was assessed using an analysis of variance (ANOVA) model. This model included the treatment as a fixed factor. Results are presented as mean VAS value difference between treatments, with statistical significance (with a significance level of $\alpha = 0.05$). Descriptive statistics were used to summarize pressure and VAS results. Statistical analyses were generated with SAS version 9.4.

Results

Demographic

A total of 90 subjects were included in this study and after randomization 18 subjects received one of the five treatment regimens. All subjects received all 10 doses of the allocated study product.

Table 1. Demographic Summary – Safety Population

		Overall (n=90)	Placebo (n=18)	GIC-1001 375 mg (n=18)	GIC-1001 500 mg (n=18)	GIC-1002 345 mg (n=18)	GIC-1002 460 mg (n=18)
Age (years)	Mean (SD)	41 (13)	40 (13)	41 (13)	43 (11)	40 (12)	41 (15)
Gender [n]	Male	59	10	11	14	10	14
	Female	31	8	7	4	8	4
Weight (kg)	Mean (SD)	74.6 (13.5)	74.1 (15.0)	74.9 (15.9)	76.4 (13.4)	72.3 (11.2)	75.2 (13.1)
BMI (kg/m^2)	Mean (SD)	25.63 (3.58)	25.91 (3.61)	25.68 (3.66)	25.83 (4.42)	25.04 (3.09)	25.70 (3.32)
	<25	39	6	7	9	10	7
	25-30	36	9	7	4	7	9
	≥30	15	3	4	5	1	2

Safety

No deaths or serious adverse events (AEs) occurred during the study. Forty-three of the 90 (48%) subjects enrolled in this study reported 87 AEs, of which 92% were mild and 7% were moderate in severity. One severe AE (1%) was reported by one subject following the administration of 500 mg GIC-1001. The most frequently reported AEs by subjects were procedural complication (placebo 6%, 500 mg GIC-1001 17%, 345 mg GIC-1002 28%, and 460 mg GIC-1002 33%), nausea (placebo 17%, 375 mg GIC-1001 11%, 500 mg GIC 1001 6%, 345 mg GIC-1002 6%, and 460 mg GIC-1002 6%), headache (placebo 11%, 375 mg GIC-1001 6%, 345 mg GIC-1002 11%, and 460 mg GIC-1002 6%), and somnolence (375 mg GIC-1001 17%, 345 mg GIC-1002 11%, and 460 mg GIC-1002 6%). The incidence of AEs was similar between GIC-1001 / 375 mg, 500 mg and GIC-1002 / 345 mg whereas a higher incidence of AEs was observed in the placebo and in the GIC-1002 / 460 mg groups.

Efficacy

Eighty-eight subjects were included in the full analysis population. Excluded subjects 503 and 704 received the placebo. These subjects did not complete stage III and/or stage IV due to equipment malfunction/technical difficulty.

VAS score collection for visceral pain intensity was performed during stage IV of the barostat procedure, in which a series of randomized rectal distension pressures were applied. There was no statistically significant difference between the mean visceral pain intensity VAS scores of active treatment groups and placebo groups during the application of a rectal distension pressure ($p > 0.05$).

A large variability was observed (SD ranging between 17.8 and 25.0 over 100 mm). VAS results were re-assessed using sensitivity tests that used a "censored" method instead of the adapted LOCF. With the "censored" method, the arithmetic mean of all VAS scores was calculated. Results of the sensitivity analysis confirmed the non-significant results of the LOCF analysis.

Table 2. Mean VAS Score (24-60 mmHg) – Between Treatment Comparisons

		Placebo (N=16)	GIC-1001 375 mg (N=18)	GIC-1001 500 mg (N=18)	GIC-1002 345 mg (N=18)	GIC-1002 460 mg (N=18)
Mean Visceral Pain Intensity Score (mm)	n	14	18	16	18	16
	Mean (SD)	60.8 (20.1)	63.7 (23.3)	55.0 (25.0)	53.0 (21.5)	66.5 (17.8)
	Median	59.7	72.1	64.3	55.7	72.2
	Min, Max	11.4, 88.4	2.7, 92.6	12.9, 90.9	0.4, 81.9	26.7, 90.9
Difference in LSmeans with Placebo (mm)			2.9	-5.8	-7.7	5.7
95% CI			-12.76,18.55	-21.85,10.31	-24.93, 9.48 [1]	-11.94,23.40 [1]
P-value			0.714	0.477	0.526 [1]	0.714 [1]

CI: Confidence Interval, [1] Pairwise treatment comparisons were assessed using Tukey-Kramer's procedure of adjustment for multiple comparisons for GIC-1002. Only subjects who had at least three measurements with pressure between 24 and 60 mmHg are included in the analysis. The adapted LOCF was used to extrapolate any missing data.

Discussion and Conclusion

High variability was expected while planning the barostat study. In order to control/decrease this variability, different measures were implemented as part of the study design. First, thorough explanations about the procedures were provided and explained to subjects at the study initiation in order to ensure their full understanding of the procedures. In addition to regular informed consent forms, participants were handed study guides that provided them further information on barostat procedures and the different ratings that would be required during the study. The personnel in charge of the study clarified all procedures required at screening and before study procedures' initiation. Most importantly, the barostat procedure contained a conditioning phase for participants to familiarize themselves with the procedure (stage II). Stage II was performed in all subjects and was planned as a sensitization step prior to the compliance and perception measurements in order to increase reproducibility of subsequent measurements. Hammer et al. confirmed that a conditioning distension phase reduced and stabilized basal tone. This additional phase was to help subjects familiarize themselves with the procedure and reduce response bias for the reporting of sensations. The same authors also confirmed that the initial inflation (step I) induced a change in basal tone of the rectum that could possibly contribute to sensitivity.[1] The final stage of the barostat experiment was planned to provide more accurate results by randomization of pressure levels and separation of the pressures by controlled pressure drop.[2]

The barostat experiment using intra-rectal balloon distensions was well tolerated by the subjects, as evaluated by the assessment of adverse events, the measurement of clinical laboratory parameters, concomitant medication, vital signs, physical examination, and 12-lead ECG. The assessment of visceral pain intensity under rectal distension following the oral administration of four different dose regimens of GIC-1001 and GIC-1002 over three successive days failed to show a significant analgesic effect of the investigational products, as measured with a 100-mm VAS. The large intra- and inter-subject variability of VAS values observed might have contributed to this lack of apparent efficacy.

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