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A PHASE 1B, 3-DOSE ARM STUDY TO ASSESS PHARMACOKINETICS AND SAFETY OF OTENAPROXESUL, A NON-ABUSABLE, NOVEL ANTI-INFLAMMATORY COMPOUND IN HEALTHY MALE AND FEMALE SUBJECTS UNDER FASTING CONDITIONS

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INTRODUCTION

- Non-steroidal anti-inflammatory drugs (NSAIDs), although widely used in the acute pain setting for their ability to reduce pain, fever, and inflammation, are known to cause gastrointestinal (GI) damage and bleeding
- Hydrogen sulfide (H_2S), a gaseous molecule produced in the body and by GI-colonizing bacteria, has been shown to reduce inflammation and accelerate healing of the GI tract[1-3]
- Otenaproxesul is a novel chemical entity comprising an H_2S-releasing moiety coupled to a naproxen-derivative intended to enhance the analgesic effects of naproxen while minimizing the GI ulcerating effects typical of NSAIDs[3-5]
- In this study, otenaproxesul amorphous dispersion was administered to healthy participants to determine its pharmacokinetic (PK) properties, safety, and tolerability

METHODS

Study Design

- This open-label, phase 1b study recruited 36 healthy participants aged 18-59 years who were randomly assigned to 1 of 3 treatment groups, each comprising 4 males and 8 females
- The treatment schedule is shown for Groups A-C in **Table 1**
  - Participants in each group fasted 10 hours before and 4 hours after the first dose administration and, in Groups B and C, 2 hours before and after each subsequent treatment administration

Table 1. Otenaproxesul Treatment Schedule by Group

Treatment Group	Time	Day 1	Day 2	Day 3	Day 4	Day 5
Group A	08:00	600 mg	ND	ND	ND	ND
	20:00	ND	ND	ND	ND	ND
Group B	08:00	200 mg	100 mg	50 mg	25 mg	25 mg
	20:00	100 mg	100 mg	50 mg	25 mg	25 mg
Group C	08:00	400 mg	200 mg	100 mg	50 mg	50 mg
	20:00	200 mg	200 mg	100 mg	50 mg	50 mg

Patients received the appropriate number of otenaproxesul 100 mg or 25 mg amorphous dispersion tablets to achieve the proper dose.
ND, no drug.

Outcomes

- The primary objectives were:
  - To measure blood levels of H_2S and the naproxen-like metabolite of otenaproxesul (M25) during treatment
  - To evaluate hepatic function via clinical laboratory testing at 72 hours post-dose and at Day 11±1 follow-up (FU)/end-of-study (EOS) for Group A and at 120 hours post-dose for Groups B and C after first administration of otenaproxesul and at Day 13±1 FU/EOS
- The secondary objective was to evaluate the safety and tolerability of otenaproxesul in each group by monitoring treatment-emergent adverse events (TEAEs)

Pharmacokinetics

- Blood sampling schedules for each treatment group are shown in **Figures 1A** and **1B** for M25 and **Figures 2A** and **2B** for H_2S
- M25 plasma samples were prepared by centrifugation in 3- or 4-mL anticoagulant/sodium heparin tubes within 30 minutes of whole blood collection
  - Plasma samples were stored at -25 °C (-80 °C was acceptable) in 2 aliquots within 40 minutes from the start of centrifugation
- For H_2S determination, whole blood samples in 3.5 mL of clot-activator/gel, serum separator tubes were allowed to stand for 30 minutes after collection to allow clotting
  - Serum samples were prepared by centrifugation and stored at -80 °C in 2 aliquots within 30 minutes from the start of centrifugation
- In Groups B and C, all samples starting at 12 hours post-dose administration were collected prior to receiving the next dose
- Descriptive PK parameters were estimated with WinNonlin (Cetera)

RESULTS

- All 36 participants completed the study; 80.6% of study participants were Caucasian (**Table 2**)

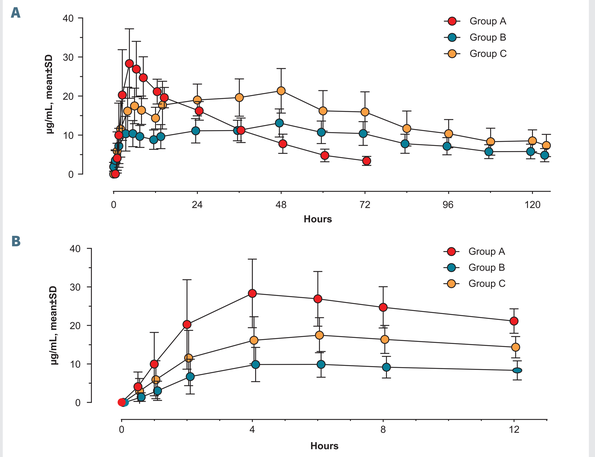
Table 2. Patient Demographics and Characteristics

	Total N=36
Sex, n (%)	
Female	24 (66.7)
Male	12 (33.3)
Age, years	
Mean±SD	46±11
Median	50
Range	22-59
Weight, kg	
Mean±SD	73.0±12.0
Median	70.9
Range	48.9-96.4
Race, n (%)	
Asian	1 (2.8)
Black or African American	6 (16.7)
White	29 (80.6)
Ethnicity, n (%)	
Hispanic or Latino	15 (41.7)
Non-Hispanic or Latino	21 (58.3)

SD, standard deviation.

- M25 concentration-time curves are shown in **Figure 1A**
  - In Groups B and C, tapered dosing after 48 hours led to a gradual decline in M25 concentration compared with Group A
- M25 plasma concentrations increased rapidly in the first 4 hours after administration (**Figure 1B**)

Figure 1. Mean M25 Plasma Concentration-Time PK Profile for the Duration of the Study (A) and 0-12 Hours (B)



PK, pharmacokinetic; SD, standard deviation.
Points are offset slightly along the x-axis for clarity.

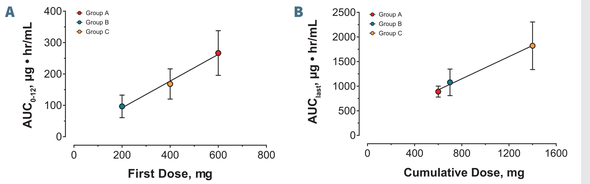
- M25 exposure as estimated by AUC was proportional to dose in the first 12 hours and cumulatively (**Table 3; Figure 2**)

Table 3. Summary of M25 PK Parameters

Treatment Group	T_{max} (h)	C_{max} (μg/mL)	AUC_{last} (μg·hr/mL)	$AUC_{0\text{-}12}$ (μg·hr/mL)
Group A	5.0±3.1	30.1±8.0	889.3±111.9	266.8±71.3
Group B	27.7±23.8	13.9±3.0	1078.1±271.0	96.6±36.1
Group C	34.7±18.6	23.9±5.3	1821.0±483.5	168.2±48.3

Mean±SD.
AUC, area under the curve (at specified time points); C_{max}, maximum concentration; N/A, not applicable; T_{max}, time to maximum concentration.

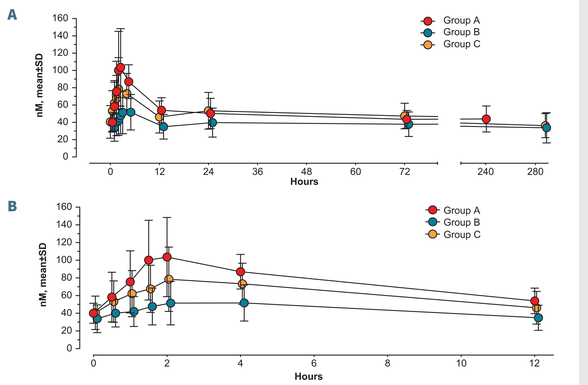
Figure 2. M25 Exposure is Linear in the First 12 Hours Post-First Dose Administration (A) and Cumulatively (B)



AUC is presented as mean±SD.

- H_2S serum concentrations exhibited dose-proportional behavior in all groups over the first 12 hours and over 288 hours for Groups B and C (**Figure 3A**)
- Mean H_2S serum concentrations peaked at 2 hours in all groups (**Figure 3B**)
  - In Group A, H_2S concentration increased 2.6-fold within 2 hours of drug administration

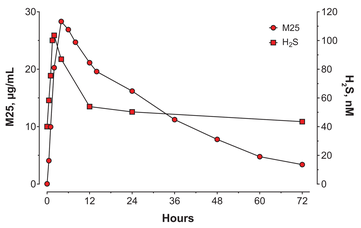
Figure 3. Mean H_2S Serum Concentration-Time PK Profile for the Duration of the Study (A) and 0-12 Hours (B)



nM, nanomolar; PK, pharmacokinetic; SD, standard deviation.
Points are offset slightly along the x-axis for clarity.

- **Figure 4** shows the relationship between M25 and H_2S PK profiles following a single 600 mg dose

Figure 4. Mean M25 Plasma Concentration-Time and Mean H_2S Serum-Time PK Profile for Group A



nM, nanomolar; PK, pharmacokinetic.

- Safety data are shown in **Table 4**; no serious adverse events were observed during the study

Table 4. Summary of TEAE Incidence

	Group A n=12	Group B n=12	Group C n=12	Total N=36
Any TEAE, subjects, n (%)	4 (33.3%)	4 (33.3%)	4 (33.3%)	12 (33.3%)
Constipation*	0	0	2 (16.7%)	2 (5.6%)
TEAE severity				
Mild	4 (33.3%)	4 (33.3%)	4 (33.3%)	12 (33.3%)
Moderate	0	0	0	0
Severe	0	0	0	0
Relationship to treatment				
Possible	2 (16.7%)	1 (8.3%)	1 (8.3%)	4 (11.1%)
Probable	0	0	0	0
Unlikely	0	2 (16.7%)	0	2 (5.6%)
Unrelated	2 (16.7%)	1 (8.3%)	4 (33.3%)	7 (19.4%)

*No other TEAE was reported in >1 patient in a single group.
TEAE, treatment emergent adverse event.

CONCLUSIONS

- Otenaproxesul was shown to be safe and well-tolerated across all treatment regimens
- Mean M25 plasma concentrations and AUC plasma exposures were linear and dose-proportional and exhibited the expected characteristics of the amorphous dispersion formula
- The well-behaved and predictable PK characteristics afford flexibility for the design of safe acute pain treatment regimens
- Investigation of otenaproxesul's efficacy in patients undergoing abdominoplasty or bunionectomy is planned

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DISCLOSURES

JWS, AS, AF, SK, and DV: Employee and shareholder of Antibe Therapeutics Inc.

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