Antibe Therapeutics: Phase 2B Gastrointestinal Safety Clinical Trial

A Double-Blind, Controlled Study to Compare the Gastrointestinal Safety of a 14 Day Oral Dosing Regimen of ATB-346 to Naproxen in Healthy Male and Female Subjects

Dr. John L. Wallace
Antibe Therapeutics Inc.
Toronto, Canada

ATB-346 is a novel hydrogen sulfide-releasing nonsteroidal anti-inflammatory and analgesic drug. In pre-clinical studies in laboratory animals, it has been found to produce negligible gastrointestinal (GI) damage and bleeding. A Phase 2A efficacy study completed in August 2016 demonstrated that ATB-346 at a daily dose of 250 mg was effective in significantly reducing pain in patients with osteoarthritis of the knee. In August 2017, Antibe commenced the recently completed, substantive endoscopic Phase 2B clinical trial in 240 healthy volunteers to demonstrate an unequivocal GI safety advantage of ATB-346 as compared to naproxen (Alleve; Naprosyn), the most prescribed NSAID in the United States. As reported in a press release issued on March 20, 2018, the GI safety advantage of ATB-346 was profound. Gastric and/or duodenal ulcers of at least 3 mm diameter were observed in 53 of the 126 subjects (42.1%) treated with naproxen for two weeks. Of the 118 subjects treated with ATB-346 for two weeks, ulcers of at least 3 mm diameter were observed in only 3 (2.5%; P<0.0001). This paper provides a more in-depth analysis of the data from this clinical trial, including summaries and discussion of the secondary endpoints. In short, ATB-346 elicited significantly less GI injury with respect to both incidence and severity, while producing comparable suppression of the activity of the key enzyme (cyclo-oxygenase) that is the main target for anti-inflammatory drugs.

I. Introduction

Nonsteroidal anti-inflammatory drugs (NSAIDs) remain one of the most widely used classes of pharmaceuticals due to their proven effectiveness in reducing pain, fever and inflammation. However, it has been recognized for almost a century that their prolonged use can lead to GI damage and bleeding. The key mechanism underlying the ability of NSAIDs to limit the formation of pro-inflammatory substances responsible for pain and inflammation, namely the inhibition of the enzyme cyclo-oxygenase (COX)[1], is also the mechanism that causes gastro-duodenal ulceration. COX enzymes play key roles in the production of a group of mediators, called prostaglandins, that contribute significantly to maintaining the integrity of the lining of the GI tract.[2] There are two forms of COX, referred to as COX-1 and COX-2, which produce exactly the same prostaglandin. Many drugs have been developed with a goal of reducing the incidence and severity of such damage. Selective inhibitors of COX-2 were developed in the 1990s and were promoted as a solution to the NSAID-gastropathy problem.[3] However, use of selective COX-2 inhibitors was found to be associated with significant cardiovascular adverse events, resulting in the withdrawal of most selective COX-2 inhibitors from the market.

Hydrogen sulfide (H_2S) is a gaseous mediator produced throughout the body, and by some of the bacteria that reside within the GI tract.[4] Over the past 20 years, a substantial body of evidence has been generated to demonstrate that H_2S plays key roles in regulating numerous physiological processes.[4] In the GI tract for example, H_2S has been shown to reduce inflammation and accelerate healing of damaged tissue (such as ulcers).[5-10] Hydrogen sulfide has also been shown to exhibit analgesic properties in animal pain models. On the other hand, suppression of H_2S production in the GI tract results in impaired healing of tissue injury and exacerbation of inflammation.[5-10]

Several years ago, Antibe began to experiment with the possibility that linking an H_2S-releasing molecule to an NSAID would reduce the GI toxicity of the NSAID without affecting the ability of the drug to reduce inflammation and pain. Extensive studies in laboratory animals demonstrated that the delivery of H_2S from these experimental drugs did indeed reduce or completely prevent GI ulceration and bleeding while still exerting anti-inflammatory and analgesic effects.[11-13] The GI safety of these H_2S-NSAIDs was maintained even in animal models in which the integrity of the GI tract was intentionally and drastically impaired.[11-13]

ATB-346 is an H_2S-releasing derivative of naproxen, one of the most widely used NSAIDs for treatment of arthritis. A Phase 1 clinical trial performed by Antibe revealed that ATB-346 exhibited greater COX inhibitory potency (~6-fold) than naproxen, a conclusion supported from the equipotent cyclo-oxygenase inhibition by naproxen (500 mg twice daily) and the comparable COX inhibition by a once daily ATB-346 dose containing one-sixth the amount of naproxen. Importantly, ATB-346 exhibited a longer duration of inhibition of COX than was observed with naproxen partially due to its differentiated pharmacokinetic profile.

Building upon these pharmacodynamic and pharmacokinetic findings, Antibe performed a Phase 2A

clinical trial to evaluate the pain management effectiveness and relief of disease associated symptoms in patients with osteoarthritis of the knee. The study involved 12 patients taking ATB-346 once-daily at a dose of 250 mg for 10 days, and measurements of the patients' level of pain during that period. The study demonstrated that ATB-346 produced a substantial and statistically significant reduction of pain as measured by the standard WOMAC assessment.[14] The degree of pain relief observed after 4 days of treatment was comparable to what has been observed in clinical trials of naproxen and celecoxib in osteoarthritis patients, and pain relief was further reduced after 10 days of treatment with ATB-346.[15,16] Additional WOMAC measures of joint stiffness and ability to perform daily activities were also markedly improved in patients taking ATB-346. Importantly, COX enzyme activity following administration of ATB-346 was substantially inhibited and comparable to published data for naproxen and celecoxib.[17, 18]

Having established that once-daily administration of ATB-346 at a dose of 250 mg could produce substantial pain relief in osteoarthritis patients, Antibe then undertook a large Phase 2B clinical study to validate the GI-protective properties of its H_2S technology. Specifically, the Phase 2B study was designed to determine if there was a significant improvement in GI safety among subjects taking 250 mg of ATB-346 once-daily versus the standard prescription dose of naproxen (500 mg twice-daily). GI safety was determined by pre- and post-study endoscopic examination of the incidence of gastroduodenal ulcers and erosions. Additional safety measures (cardiovascular, liver and central nervous system) as well as comparative levels of COX inhibition were also assessed.

II. OBJECTIVES

A. Primary Objective

The primary objective of the study was to show unequivocal superiority of ATB-346 in GI safety compared to naproxen. Thus, the primary endpoint was the incidence of endoscopically-observed gastric and/or duodenal ulcers of at least 3 mm diameter with unequivocal depth, considered the gold standard in assessing the GI safety of NSAIDs.

B. Additional Objectives

The additional objectives of the study were to evaluate other indices of GI safety, tolerability and effectiveness of ATB_346 versus naproxen. Accordingly, the study included the following secondary endpoints:

- Incidence of gastric or duodenal ulcers of at least 5 mm diameter with unequivocal depth;
- Number of gastric and/or duodenal erosions and/or ulcers;
- Incidence of dyspepsia leading to discontinuation of study treatment;
- Changes from baseline in hematocrit levels; and
- Changes from baseline in ex vivo whole blood thromboxane B2 (TXB2) synthesis.

III. CLINICAL TRIAL DESIGN

Healthy volunteers were recruited initially to a single clinic, but later expanded to three additional clinics to increase the rate of recruitment. The study consisted of three phases: (1) a screening, pre-treatment phase of 21 days, (2) a blinded treatment phase of 14 days, and (3) a follow-up visit 14 days after end of treatment. Due to the participation of such a large number of healthy volunteers the study was run as a Phase 2 safety trial rather than as a standard Phase 1 study. The study was conducted by Topstone Clinical Research Ltd. in Ontario, Canada. Healthy subjects are routinely used preferentially over OA patients to gauge intestinal damage caused by NSAIDS.[19, 20]

During the pre-treatment period, subject eligibility was determined and those who consented to participate in the study underwent medical history and physical examinations, clinical laboratory evaluations and a screening endoscopy to confirm the absence of erosions and ulcers in the gastroduodenal mucosa.

The main criteria for inclusion in the trial were:

- Healthy male or female subjects (≥18 to ≤65 years of age) in otherwise good health and with no prior history of significant GI disease, arthritis or bleeding disorders; and
- Body mass index ≤35 kg/m^2.

The main exclusion criteria were:

- Subjects with abnormal baseline laboratory values deemed to be clinically significant by the Investigator;
- Subject-reported past history of gastrointestinal ulcer or bleeding, or any clinically significant gastrointestinal disease;
- Use of NSAIDS, aspirin or naproxen-containing medications within 14 days prior to study entry;
- Subjects taking gastroprotective drugs or drugs affecting GI motility; and
- Subjects positive for *Helicobacter pylori*.

Those subjects meeting the above inclusion/exclusion criteria were randomized to one of the two groups:

1. ATB-346 (250 mg) in the morning and placebo in the evening; and
2. Sodium naproxen (550 mg) in the morning and evening.

Study medication was administered in capsules that were physically identical so that neither the subject nor the physicians had knowledge of which drug the subject was taking. The subjects took the drug they were assigned for 14 days. A final endoscopy was performed on the 14th day of the study. The endoscopist (blind to which drug the subject was taking) looked for ulcers in the stomach and duodenum. The number of ulcers with a diameter of greater than 3 mm and 5 mm were recorded (see Figure 1), as was the number of gastric or duodenal erosions.

Prior to the first dose of study medication, plasma samples were obtained from eligible subjects for thromboxane and hematocrit analyses. Measuring thromboxane synthesis provides an index of the amount of inhibition of cyclo-oxygenase (COX) activity by the treatment drug. Hematocrit is a measure of red blood cell volume. Decreases in hematocrit can be an indicator of gastrointestinal bleeding and is often used as a proxy for significant ulceration and bleeding in the lower GI tract.

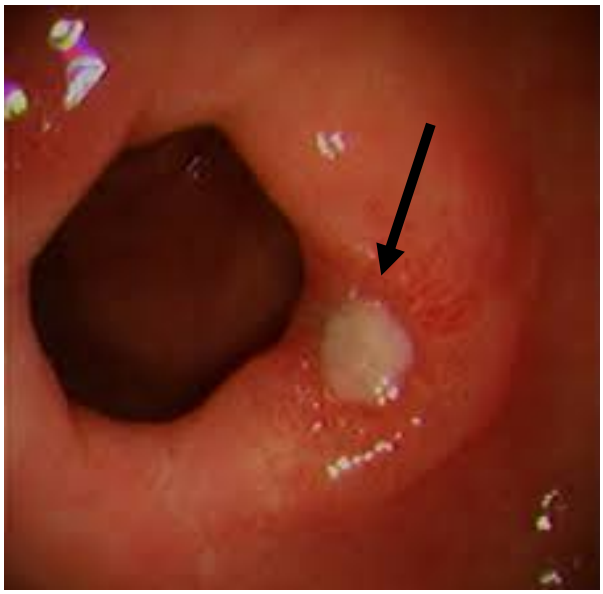

Figure 1. Image of an ulcer (white lesion) at the junction between the stomach and duodenum.

IV. Statistical Methods

The sample size was powered to obtain a significant difference in endoscopically observed gastric or duodenal ulcers between the two study groups (n=120 subjects/group) at the end of 2 weeks of daily treatment. The study was "powered" based on a conservatively-predicted incidence of ulceration in 30 (25%) of the naproxen-treated subjects based on a review of several similar endoscopic clinical trials of naproxen that have been published.[19-26]

The primary endpoint was analyzed using the conventional Chi-square test with a significance level of $P<0.05$ to determine any difference between naproxen and ATB-346 in the incidence of endoscopically detected gastric or duodenal ulcers of at least 3 mm diameter with unequivocal depth.

V. Results & Discussion

Of the 258 subjects enrolled in the study, 244 (94.6%) completed the study: 126 subjects in the naproxen group and 118 subjects in the ATB-346 group. The mean age of trial subjects was 41.7 years: 54.7% were female and 53.1% of the subjects were Caucasian.

A. GI Safety

The primary objective for the study was to assess the comparative incidence of gastric or duodenal ulcers of at least 3 mm diameter with unequivocal depth, considered the gold standard in assessing the GI safety of NSAIDs. The study also included the following secondary measures to evaluate overall GI safety: (i) incidence of larger gastric or duodenal ulcers (> 5 mm diameter with unequivocal depth); and (ii) number of gastric and/or duodenal erosions and/or ulcers.

Profound reduction in ulcers with ATB-346

Of the 126 subjects treated with naproxen, 53 (42.1%) had at least one ulcer greater than 3 mm in diameter. Of the 118 subjects treated with ATB-346, 3 (2.5%) had at least one ulcer greater than 3 mm in diameter. The difference in incidence of ulcers between the two groups reached an exceptionally high level of statistical significance ($P<0.0001$) (Figure 2).

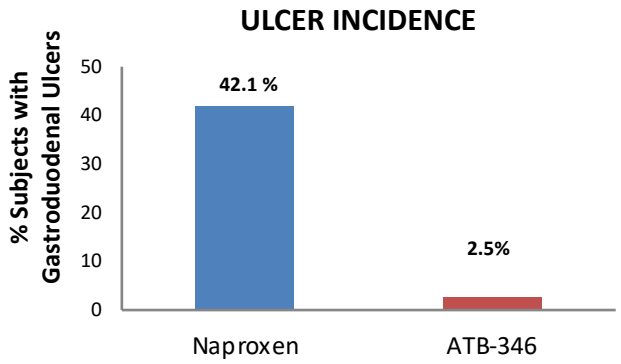

Figure 2. The primary endpoint of the study: incidence of gastric and/or duodenal ulcers of more than 3 mm diameter.

The group treated with naproxen not only had a much higher incidence of ulcers than the ATB-346 group (Fig. 2), but and a much larger number of total ulcers as well (Fig. 3).

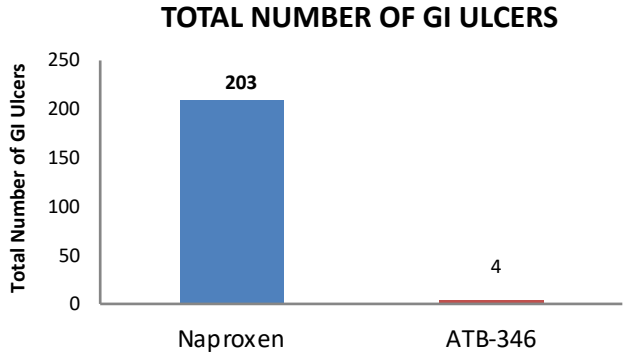

Figure 3. Total number of ulcers in the stomach and/or duodenum of at least 3 mm diameter among study participants in whom ulcers were endoscopically confirmed [Naproxen (N=53/126) and ATB-346 (N=3/118)].

More severe gastric ulcers with naproxen

Large ulcers in the GI tract pose a clinically significant risk of bleeding. Fully 24% of the naproxen-treated subjects had gastric ulcers larger than 5 mm in diameter (an average of 3.2 large ulcers/subject). There were no large gastric ulcers in the ATB-346 group (Figure 4).

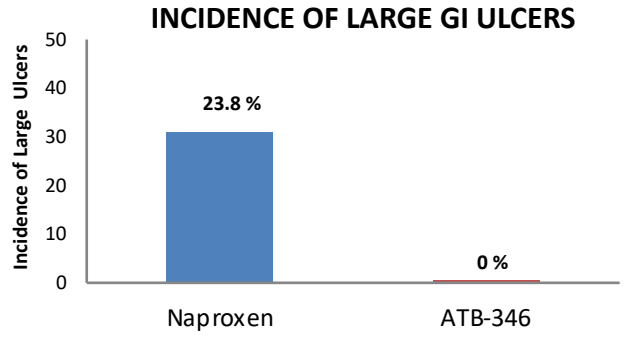

Figure 4. Incidence of large ulcers (⩾5mm in diameter) in the stomach and/or duodenum.

Multiple duodenal ulcers with naproxen

A total of 24 duodenal ulcers were observed in the 7 subjects treated with naproxen that had duodenal ulcers, representing an average of 3.4 duodenal ulcers per subject. No duodenal ulcers were observed in subjects treated with ATB-346.

Significantly higher number of erosions with naproxen

Erosions are superficial lesions which are less clinically significant than ulcers. In the ATB-346 group there was an average of 1.7 erosions per subject, versus 12.7 erosions per subject in the naproxen group (Figure 5).

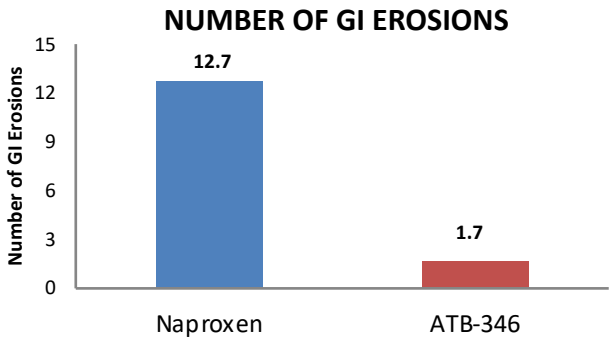

Figure 5. Average number of erosions per subject in the stomach and/or duodenum. Erosions were endoscopically observed in 49/118 (41.5%) ATB-346 dosed subjects and in 109/126 (86.5%) Naproxen dosed subjects.

B. Other Endpoints

No dyspepsia events led to study withdrawal

There was a greater incidence of dyspepsia events with naproxen versus ATB-346 (Table 1). No dyspepsia events led to study withdrawal in either group

	Naproxen	**ATB-346**
Abdominal pain/distension:	6.2%	1.6%
Gastro-esophageal reflux disease:	4.7%	0%
Nausea	3.1%	0%

Table 1. Incidence of dyspepsia events during the study.

No significant change in hematocrit levels

There were no significant differences in change from baseline of hematocrit between the two treatment groups at the end of the two-week treatment period. The mean values of hematocrit in the naproxen-treated and ATB-346-treated groups were the same at the beginning and end of the trial (0.41 ± 0.04 L/L).

No statistical difference in thromboxane inhibition

Thromboxane is a substance produced mainly by blood platelets via the COX enzyme. COX is the target enzyme for the anti-inflammatory and analgesic effects of NSAIDs; thus, measuring the effects of naproxen and ATB-346 on thromboxane levels in the blood is a meaningful index of the extent of COX inhibition that has been achieved. While the analgesic and anti-inflammatory effects of naproxen are due only to inhibition of COX activity, ATB-346 inhibits COX and releases H_2S, a moiety shown to exert a range of anti-inflammatory and analgesic effects.[6, 8, 27-29] Also, previous

studies have demonstrated that ATB-346 is longer acting than naproxen with respect to suppression of COX activity.[13]

As shown in Figure 6, both ATB-346 and naproxen substantially suppressed COX activity (>94%) at the end of one and two weeks of treatment.

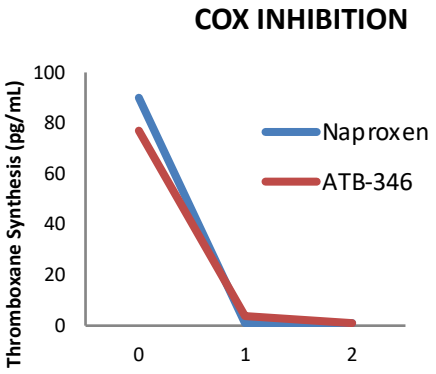

Figure 6. Thromboxane synthesis was substantially suppressed after one and two weeks of treatment with naproxen or ATB-346.

C. Pharmacokinetics

Differentiated metabolic profile for ATB-346

After one and two weeks of administration of naproxen to healthy subjects, the mean plasma naproxen concentrations were 59.7 and 52.1 µg/mL, respectively. At the same time points in the group treated with ATB-346, the mean plasma naproxen concentrations were 16.9 and 14.2µg/mL, respectively. Such a difference was anticipated since the 250 mg dose of ATB-346 contains approximately one-sixth the amount of naproxen as the 550 mg, twice daily dose of naproxen. Also, the pharmacokinetics of naproxen released from ATB-346 differs substantially from that when naproxen itself is administered, specifically, a much longer plasma half-life. Importantly, these results together with the COX inhibition data (Figure 6) indicate an increased potency and duration-of-activity of ATB-346 compared to naproxen. This differentiated pharmacokinetic profile allows for once-daily dosing, a favorable commercial characteristic due to its positive impact on patient compliance.

It should be noted that ongoing analyses of ATB-346 metabolism in humans have revealed the presence of several naproxen-like structures with possible cyclo-oxygenase inhibitory potential. These metabolites are either absent from or present at much lower concentrations in the plasma of naproxen-dosed individuals. Such observed differences in the occurrence or concentration of these NSAID structures resulting from the metabolism of ATB-346 and naproxen may contribute to the equipotent cyclo-oxygenase inhibition seen between ATB-346 and naproxen and are currently being studied.

D. Safety and Tolerability

Overall safety profile is favorable

This study demonstrated superior gastrointestinal outcomes and comparative safety of ATB-346 to naproxen in healthy subjects. Specifically, there were significantly fewer ulcers and erosions in subjects receiving ATB-346, as well as less gastrointestinal treatment-related adverse events compared to those who received naproxen. Review of non-GI safety parameters including cardiovascular, liver and general nervous system disorders revealed no effect of ATB-346 on systolic/diastolic blood pressure, comparable low incidence of headache and dizziness between the ATB-346 and naproxen study groups and mild transient elevations of liver transaminases that were not of clinical concern. ATB-346 was seen as safe and well tolerated. These results support further investigation of ATB-346 in future clinical studies as a viable treatment option for the safer and gastroprotective management of osteoarthritic pain.

Liver-related effects comparable to existing NSAIDs

Blood levels of liver enzymes (including alanine transaminase (ALT) and aspartate transaminase (AST)) were measured on days 7 and 14 of treatment and at two-weeks post-treatment (day 28). Over the 14 day treatment course non-clinically significant treatment-related transient elevations in liver transaminases were observed in up to 7% of subjects receiving ATB-346 and up to 7% of subjects receiving naproxen. One subject receiving ATB-346 (0.8%) had clinically significant treatment-related transient transaminase elevations. At the two week post treatment follow up assessment 5.4% of the ATB-346-treated subjects had clinically significant, treatment-related, transient transaminase elevations that had resolved or were resolving. Cumulative data now obtained from three clinical trials in which ATB-346 has been dosed at 250 mg once daily for 10-14 days reveal a 4.7% overall incidence of clinically significant, transient liver transaminase increase; this can be contrasted to diclofenac, the most prescribed NSAID globally, where the incidence of clinically-significant liver transaminase elevations is up to 4%.[30]

No significant effect on blood pressure

High blood pressure (hypertension) is an important risk factor for stroke and cardiovascular disease and subjects were monitored at various points throughout the study period. No clinically significant changes in blood pressure were noted among subjects in either treatment group at any of the physical assessment visits.

VI. SUMMARY

Clinically significant GI bleeding and ulceration continues to be the major limitation to the use of NSAIDs for treatment of pain and inflammation associated with a number of

disorders, including osteoarthritis, rheumatoid arthritis, gout, etc. Despite the introduction of drugs that suppress gastric acid secretion (e.g., proton pump inhibitors, histamine H2-receptor antagonists) and NSAIDs that have selectivity for the COX-2 enzyme, NSAID gastroenteropathy remains the most common adverse effect of this class of drugs. In addition, there are significant polypharmacy issues surrounding the use of NSAIDs with low-dose aspirin and drugs that suppress gastric acid secretion.[31-33] A growing body of evidence now suggests that while acid suppressing agents marginally improve the extent of gastric ulceration, the incidence of duodenal damage (erosions and ulcers) appears to be an unintended and potentially even more severe consequence. This is exacerbated by the relative reduction in pain sensing mechanisms in duodenal versus gastric tissues.

ATB-346 is a novel anti-inflammatory drug developed by Antibe that combines two key actions: suppression of COX activity and the release of H_2S.[12] The latter provides GI protection from the adverse effects of suppression of COX, as well as contributing to the analgesic effects of the compound.[27-29] The ability of ATB-346 to inhibit COX without causing significant GI damage has been demonstrated in extensive laboratory studies.[5,7-13] Importantly, the GI-safety of ATB-346 was demonstrated in several models of impaired GI mucosal defence, which more closely approximates the susceptibility of patients to the GI-damaging effects of NSAIDs. However, until now, the GI-safety of ATB-346 had not been directly examined in humans.

Overall, this Phase 2 endoscopy trial has demonstrated a dramatic reduction in upper GI ulcer formation in healthy subjects taking ATB-346 versus naproxen, one of the most commonly used drugs for treatment of osteoarthritis and other painful conditions. The remarkably low incidence of gastroduodenal ulcers among individuals taking once daily ATB-346 as well as the significant reduction in ulcerogenic mucosal erosions and lack of ulcers, not only those ≥3mm in diameter but also the more clinically significant ulcers ≥5mm in diameter, highlight the gastroprotective effects of ATB-346 derived hydrogen sulfide. In addition, suppression of COX activity (a biomarker for pain relief and reduced inflammation) was comparable between the two drugs. As well, the measured inhibition of cyclo-oxygenase in the current study was virtually identical to the COX inhibition measured in the earlier referenced Antibe Phase 2A osteoarthritis patient trial confirming the high and sustained suppression of pro-inflammatory mediators by once daily dosing of 250 mg ATB-346

Review of non-GI safety parameters including cardiovascular, liver and general nervous system disorders revealed no effect of ATB-346 on systolic/diastolic blood pressure, comparable low incidence of headache and dizziness between the ATB-346 and naproxen study groups and mild transient elevations of liver transaminases that were not of clinical concern. Clinically, 250 mg once daily doses of ATB-346 were seen as safe and well tolerated.

Ongoing studies are investigating and characterizing the metabolic pathway of ATB-346. Several naproxen-like structures with possible cyclo-oxygenase inhibitory potential that are either absent from or present at much lower concentrations in the plasma of naproxen-dosed individuals have been found in blood samples taken from subjects treated with ATB-346. Such observed differences in the metabolism of ATB-346 and naproxen coupled with the analgesic properties of H_2S may account for the equipotent COX inhibition seen between ATB-346 and naproxen. In the near future, studies will investigate the potential of lower doses (150 mg and 200 mg) of ATB-346 to manage pain and associated symptoms of osteoarthritis and to select a commercial dose(s) for Phase 3 safety and efficacy studies.

In conclusion, a dose of 250 mg ATB-346 once daily has been shown to be clinically safe, effective and well tolerated in several clinical studies. Further advancement of this novel NSAID for the safer and gastroprotective management of osteoarthritic pain is warranted.

REFERENCES

[1] Vane JR. Inhibition of prostaglandin synthesis as a mechanism of action for aspirin-like drugs. Nat New Biol 1971; 231: 232-235.

[2] Wallace JL. Prostaglandins, NSAIDs, and gastric mucosal protection: why doesn't the stomach digest itself? Physiol Rev 2008; 88: 1547-1565.

[3] Silverstein FE, Faich G, Goldstein JL, Simon LS, Pincus T, Whelton A, Makuch R, Eisen G, Agrawal NM, Stenson WF, Burr AM, Zhao WW, Kent JD, Lefkowith JB, Verburg KM, Geis GS. Gastrointestinal toxicity with celecoxib vs nonsteroidal anti-inflammatory drugs for osteoarthritis and rheumatoid arthritis: the CLASS study: A randomized controlled trial. Celecoxib Long-term Arthritis Safety Study. JAMA 2000; 284: 1247-1255.

[4] Wallace JL, Wang R. Hydrogen sulfide-based therapeutics: exploiting a unique but ubiquitous gasotransmitter. Nat Rev Drug Discov. 2015; 14: 329-345.

[5] Wallace JL, Dicay M, McKnight W, Martin GR. Hydrogen sulfide enhances ulcer healing in rats. FASEB J 2007; 21: 4070-4076.

[6] Wallace JL, Vong L, McKnight W, Dicay M, Martin GR. Endogenous and exogenous hydrogen sulfide promotes resolution of colitis in rats. Gastroenterology. 2009; 137: 569-578.

[7] Blackler R, Syer S, Bolla M, Ongini E, Wallace JL. Gastrointestinal-sparing effects of novel NSAIDs in rats with compromised mucosal defence. PLoS One 2012; 7(4): e35196.

[8] Flannigan KL, Ferraz JG, Wang R, Wallace JL. Enhanced synthesis and diminished degradation of hydrogen sulfide in experimental colitis: a site-specific, pro-resolution mechanism. PLoS One 2013; 8(8): e71962.

[9] Blackler RW, Motta JP, Manko A, Workentine M, Bercik P, Surette MG, Wallace JL. Hydrogen sulphide protects against NSAID-enteropathy through modulation of bile and the microbiota. Br J Pharmacol 2015; 172: 992-1004.

[10] Motta JP, Flannigan KL, Agbor TA, Beatty JK, Blackler RW, Workentine ML, Da Silva GJ, Wang R, Buret AG, Wallace JL. Hydrogen sulfide protects from colitis and restores intestinal microbiota biofilm and mucus production. Inflamm Bowel Dis 2015; 21: 1006-1117.

[11] Blackler RW, De Palma G, Manko A, Da Silva GJ, Flannigan KL, Bercik P, Surette MG, Buret AG, Wallace JL. Deciphering the pathogenesis of NSAID enteropathy using proton pump inhibitors and a hydrogen sulfide-releasing NSAID. Am J Physiol Gastrointest Liver Physiol 2015; 308: G994-G1003.

[12] Wallace JL, Caliendo G, Santagada V, Cirino G. Markedly reduced toxicity of a hydrogen sulphide-releasing derivative of naproxen (ATB-346). Br J Pharmacol 2010; 159: 1236-1246.

[13] Wallace JL, Vaughan D, Dicay M, MacNaughton WK, de Nucci G. Hydrogen sulfide-releasing therapeutics: translation to the clinic. Antioxid Redox Signal. 2018; 28: 1533-1540.

[14] Bellamy N, Buchanan WW, Goldsmith CH, Campbell J, Stitt LW. Validation study of WOMAC: a health status instrument for measuring clinically important patient relevant outcomes to antirheumatic drug therapy in patients with osteoarthritis of the hip or knee. J Rheumatol. 1988 Dec;15(12):1833-40.

[15] Wittenberg RH, Schell E, Krehan G, Maeumbaed R, Runge H, Schlüter P, Fashola TOA, Thurston HJ, Burger KJ, Trechsel U. First-dose analgesic effect of the cyclo-oxygenase-2 selective inhibitor lumiracoxib in osteoarthritis of the knee: a randomized, double-blind, placebo-controlled comparison with celecoxib [NCT00267215]. Arthritis Research & Therapy 2006, 8(2): 1-9.

[16] Boucher M. A Bayesian Meta-Analysis of Longitudinal Data in Placebo Controlled Studies with Naproxen. PAGE 17 (2008) Abstr 1353 [www.page-meeting.org/?abstract=1353].

[17] Patrignani P, Tacconelli, Capone ML. Risk management profi le of etoricoxib:an example of personalized medicine. Therapeutics and Clinical Risk Management 2008:4(5) 983–997.

[18] Schwartz JI, Dallob AL, Larson PJ, Laterza OF, Miller J, Royalty J. Comparative Inhibitory Activity of Etoricoxib, Celecoxib, and Diclofenac on COX-2 vwesus COX-1 in healthy subjects. J Clin Pharm 2008; 48(6):745-754.

[19] Goldstein GL, Aisenberg J, Zakko SF, Berger MF, Dodge WE. Endoscopic Ulcer Rates in Healthy Subjects Associated with Use of Aspirin (81 mg q.d.) Alone or Coadministered with Celecoxib or Naproxen: A randomized, 1-Week Trial. Dig Dis Sci (2008) 53:647–656.

[20] Moberly JB, Harris SI, Riff DS, Dale JC, Breese T, McLaughlin P, Lawson J, Wan Y, Xu J, Truitt KE. A Randomized, Double-Blind, One-Week Study Comparing Effects of a Novel COX-2 Inhibitor and Naproxen on the Gastric Mucosa. Dig Dis Sci (2007) 52:442–450.

[21] Simon LS, Lanza FL, Lipsky PE, Hubbard RC, Talwalker S, Schwartz BD, Isakson PC, Geis GS. Preliminary study of the safety and efficacy of SC-58635, a novel cyclooxygenase 2 inhibitor: efficacy and safety in two placebo-controlled trials in osteoarthritis and rheumatoid arthritis, and studies of gastrointestinal and platelet effects. Arthritis Rheum. 1998; 41: 1591-1602.

[22] Goldstein JL, Kivitz AJ, Verburg KM, Recker DP, Palmer RC, Kent JD. A comparison of the upper gastrointestinal mucosal effects of valdecoxib, naproxen and placebo in healthy elderly subjects. Aliment Pharmacol Ther. 2003; 18: 125-132.

[23] Scheiman JM, Cryer B, Kimmey MB, Rothstein RI, Riff DS, Wolfe MM. A randomized, controlled comparison of ibuprofen at the maximal over-the-counter dose compared with prescription-dose celecoxib on upper gastrointestinal mucosal injury. Clin Gastroenterol Hepatol 2004; 2: 290-295.

[24] Bias P, Buchner A, Klesser B, Laufer S. The gastrointestinal tolerability of the LOX/COX inhibitor, licofelone, is similar to placebo and superior to naproxen therapy in healthy volunteers: results from a randomized, controlled trial. Am J Gastroenterol 2004; 99: 611-618.

[25] Goldstein JL, Lowry SC, Lanza FL, Schwartz HI, Dodge WE. The impact of low-dose aspirin on endoscopic gastric and duodenal ulcer rates in users of a non-selective non-steroidal anti-inflammatory drug or a cyclo-oxygenase-2-selective inhibitor. Aliment Pharmacol Ther. 2006; 23: 1489-1498.

[26] Wilder-Smith CH, Jonzon B, Fornstedt-Wallin B, Hedman A, Karlsson P. Dose-effect comparisons of the CINOD AZD3582 and naproxen on upper gastrointestinal tract mucosal injury in healthy subjects. Scand J Gastroenterol 2006; 41: 264-273.

[27] Wallace JL, Blackler RW, Chan MV, Da Silva GJ, Elsheikh W, Flannigan KL, Gamaniek I, Manko A, Wang L, Motta JP, Buret AG. Anti-inflammatory and cytoprotective actions of hydrogen sulfide: translation to therapeutics. Antioxid Redox Signal 2015; 22: 398-410.

[28] Fiorucci S, Orlandi S, Mencarelli A, Caliendo G, Santagada V, Distrutti E, Santucci L, Cirino G, Wallace JL. Enhanced activity of a hydrogen sulphide-releasing derivative of mesalamine (ATB-429) in a mouse model of colitis. Br J Pharmacol 2007; 150: 996-1002.

[29] Cenac N,Castro M, Desormeaux C, Colin P, Sie M, Ranger M, Vergnolle N. A novel orally administered trimebutine compound (GIC-1001) is anti-nociceptive and features peripheral opioid agonistic activity and hydrogen sulphide-releasing capacity in mice. Eur J Pain 2016 20:723-730.

[30] National Institute of Health: LiverTox Database: Retrieved from https://livertox.nlm.nih.gov/Diclofenac.htm

[31] Wallace JL. Polypharmacy of osteoarthritis: the perfect intestinal storm. Dig Dis Sci 2013; 58: 3088-3093.

[32] Wallace JL, Syer S, Denou E, et al. Proton pump inhibitors exacerbate NSAID-induced small intestinal injury by inducing dysbiosis. Gastroenterology 2011;141:1314–1322.

[33] Lanas A, Sekar MC, Hirschowitz BI. Objective evidence of aspirin use in both ulcer and non-ulcer upper and lower gastrointestinal bleeding/perforation. Gastroenterology 1992;103:8629–8637.