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ORIGINAL RESEARCH

Non-Clinical Safety Pharmacology Evaluations of Trazpiroben (TAK-906), a Novel Dopamine D_2/D_3 Selective Receptor Antagonist for the Management of Gastroparesis

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Background: Gastroparesis is characterized by delayed gastric emptying in the absence of mechanical obstruction. Owing to the potential for serious side effects, current treatments have restrictions on their use and there is a need for novel compounds with favorable safety profiles. Trazpiroben (previously TAK-906) is a peripherally selective dopamine D_2/D_3 receptor antagonist being developed to treat chronic gastroparesis. Effects of trazpiroben on the central nervous system and pulmonary system in rats and on the cardiovascular system in dogs were assessed.

Methods: Functional observational battery and locomotion assessments were conducted in groups of eight female rats receiving 0 (control), 100, 300, or 1000 mg/kg/day oral trazpiroben for 2 days. Assessments were performed at baseline (pre-dosing) and 0.5 hours post-dose on day 2 of dosing. Pulmonary safety: following administration of the same trazpiroben doses, groups of eight male rats underwent heads-out plethysmography at baseline, through 6 hours post-dose, and approximately 24 hours post-dose on day 1. Four telemetry-instrumented male beagle dogs received 0 (control), 1, 10, or 30 mg/kg of oral trazpiroben in a Latin square crossover design on days 1, 4, 8, and 11. Relevant parameters were continuously measured for approximately 18 hours post-dose.

Results: No clinically meaningful effects on central nervous system, pulmonary, or cardiovascular assessments were observed at any trazpiroben dose. Significantly decreased locomotion occurred with increasing dose, including reduced horizontal/vertical ambulation at ≥ 300 mg/kg/day. Small transient decreases in systolic and pulse pressure at ≥ 10 mg/kg/day were observed, with compensatory increases in heart rate at 30 mg/kg/day. No trazpiroben-related effects on cardiovascular parameters (including QT interval corrected for heart rate) or body temperature were noted. No trazpiroben-related qualitative electrocardiogram abnormalities were observed.

Discussion: Our results suggest that trazpiroben has limited central nervous system effects and a favorable cardiac safety profile.

Keywords: dopamine D_2/D_3 selective receptor antagonist, gastroparesis, methods, safety pharmacology

Introduction

Gastroparesis is a motility disorder characterized by delayed gastric emptying in the absence of mechanical obstruction and/or gastric dysrhythmia with reduced coordination of gastric peristalsis.[1–5] Cardinal symptoms, which are chronic with episodic exacerbation, include early satiety, postprandial fullness, nausea, vomiting, and upper abdominal discomfort.[3,6] Symptom pattern and severity may vary and are often determined by the underlying disease etiology, which may be idiopathic, diabetic, iatrogenic, or postsurgical.[3,7] Increasing disease severity can result in greater morbidity and mortality, as well as nutritional deficiencies and other detrimental effects on patients' quality of life.[8,9] Gastroparesis may also be associated with conditions such as Parkinson's disease, or may manifest following a bacterial or viral infection.[3] Owing to an overlap of symptoms with other conditions, diagnosis of gastroparesis can prove challenging, and data on global prevalence are limited.[3,10,11]

The pathophysiology of gastroparesis is poorly understood. Potential mechanisms include a loss of nerve cell bodies and interstitial cells of Cajal, leading to motility and sensory dysfunction, with impaired motor coordination resulting in delayed gastric emptying and gastric dysrhythmias.[12] The relationship between gastric emptying and upper gastrointestinal symptoms remains unclear.[13] Symptoms may stem from a variety of causes, including impaired gastric accommodation, hypomotility of the gastric antrum, and elevated pyloric pressures.[12] Dopamine exerts a direct relaxant effect on the musculature of the gut via activation of muscular dopamine D_2 receptors in the lower stomach and esophageal sphincter, reducing gut motility, as well as stimulating vomiting via the chemoreceptor trigger zone.[14] Correspondingly, D_2 and D_3 receptors in the upper gastrointestinal tract and the area postrema are current therapeutic targets in gastroparesis.[14–16] Therapies that target dopamine receptors without off-target effects are promising options for the treatment of gastroparesis because they can provide benefit by reducing symptoms, increasing gastric emptying, and improving gastric motor coordination and gastric rhythm.[17,18]

Current therapies for gastroparesis are limited. Dietary modification, focusing on reduction of portion size and a lowering of fiber, fat, and solid food intake, is recommended as first-line therapy for patients with mild symptoms. However, in practice these approaches only provide moderate benefit.[19–21] Effective pharmacological therapies, such as metoclopramide and domperidone, are available for managing the symptoms of gastroparesis, but their use is restricted owing to safety concerns. Metoclopramide, a dopamine receptor antagonist that crosses the blood–brain barrier, has been associated with potentially serious central nervous system (CNS) side effects, such as an increased risk of extrapyramidal effects and tardive dyskinesia.[22–25] As a result, both the US Food and Drug Administration and European Medicines Agency recommend limiting exposure to metoclopramide.[22,23,26] Off-target effects also limit the usefulness of domperidone, a peripherally selective dopamine D_2/D_3 receptor antagonist that has been approved in low doses by the European Medicines Agency for short-term treatment of nausea and vomiting (when the benefits are considered to outweigh risks).[27,28] However, domperidone has not received approval from the US Food and Drug Administration owing to the potential for serious cardiac side effects, believed to result from interaction between domperidone and the human ether-à-go-go-related gene (hERG) potassium channel.[29–31] Additionally, domperidone is primarily metabolized via the cytochrome P450 (CYP) 3A4 enzyme, meaning it may not prove to be an appropriate therapy in patients receiving potent CYP3A4 inhibitors.[32,33] Consequently, there is an unmet need for an efficacious treatment for gastroparesis with a favorable safety and metabolic profile.

Trazpiroben (previously referred to as TAK-906 or ATC-1906M) is a D_2/D_3 receptor antagonist under development for the chronic treatment of moderate to severe idiopathic and diabetic gastroparesis. In non-clinical in vitro pharmacology studies, trazpiroben has been shown to be selective for D_2/D_3 receptors and to antagonize these receptors to a similar degree to domperidone.[34,35] The zwitterionic structure of trazpiroben restricts the potential for brain penetration, as well as lowering affinity for the hERG potassium channel, thus avoiding the CNS or cardiovascular safety concerns observed with metoclopramide and domperidone, respectively. This limited CNS penetration has previously been demonstrated during rotarod testing in rats, during which no trazpiroben-related effects were observed following administration of the compound at doses up to 30 mg/kg.[35] Additionally, further investigation has shown that trazpiroben weakly blocks the hERG potassium channel (half maximal inhibitory concentration [IC_{50}] = 15.6 μM), exhibiting a 10,000-fold difference in affinity when compared with the compound affinity for the intended D_2/D_3 receptor targets (1.5 and 3.2 nM, respectively).[35] Trazpiroben has also demonstrated limited potential for CYP enzyme induction or inhibition,[36,37] and has been classified as a non-sensitive CYP3A4 substrate following a Phase I drug–drug interaction study conducted in healthy volunteers (NCT03161405). The safety of trazpiroben has been evaluated in a first-in-human Phase I clinical trial,[38] and further investigation of the compound's safety, tolerability, pharmacokinetics, and pharmacodynamics was conducted in a Phase IIa study (NCT03268941). Both studies demonstrated that trazpiroben was well tolerated and possessed a favorable safety profile, with no CNS or cardiac safety concerns observed. Trazpiroben, therefore, represents a potentially effective therapy for gastroparesis, with an advantageous safety profile compared with current pharmacological treatments.

Three separate nonclinical safety pharmacology studies were conducted to assess the potential effects of trazpiroben on the CNS and pulmonary system in rats and on the cardiovascular system in dogs. These studies were conducted prior to the human clinical trials. Nevertheless, they provide compelling data on the clinical translation of non-clinical safety

pharmacology models, thus acting as an adjunct to the human studies to demonstrate the favorable safety profile of trazpiroben.

Materials and Methods
Rat Study
Study Design

Safety pharmacology evaluations of trazpiroben were conducted in 64 Sprague Dawley rats (32 male, 32 female; Figure 1). Rats were 11–12 weeks old at initiation of dosing (Charles River Laboratories, Portage, MI, USA), with body weights for female and male rats ranging between 217–290 g and 325–474 g, respectively. Rats were group housed (≤ 3 rats/sex/cage) and food and water were freely available, except when undergoing plethysmography evaluation. A 12-hour light/12-hour dark cycle was maintained and interrupted only for study-related activities. Rats were acclimatized to the study environment for at least 1 week during the pre-dose phase, with any rats not used in the study removed from the study room.

Rats were divided into four groups (eight rats/sex/group) and dosed via oral gavage with 0 mg/kg/day (Group 1; vehicle control, 5% [v/v] dimethyl sulfoxide, 40% [v/v] polyethylene glycol 400, and 55% [v/v] 0.9% sodium chloride, USP [sterile saline]), 100 mg/kg/day (Group 2), 300 mg/kg/day (Group 3), or 1000 mg/kg/day (Group 4) of trazpiroben at a dose volume of 10 mL/kg. The doses of trazpiroben chosen for this study were based on results of a previous 7-day, repeat-dose, range-finding study conducted in Crl:CD(SD) rats.[39] As standard in safety pharmacology studies, single sexes of rats were used for CNS and pulmonary assessments, which also served to minimize the overall number of animals tested and preserved animal welfare as far as possible. Trazpiroben and vehicle control formulations were prepared, with dose concentrations of trazpiroben being based on the maleate salt of the compound as supplied with no correction. Vehicle control and trazpiroben formulations were refrigerated at 2–8°C and protected from light until dosing.

Functional Observational Battery Assessments

In all, eight female rats per group were dosed on days 1 and 2 and underwent functional observational battery (FOB) assessments and evaluation of locomotor activity. Female rats were examined once during the pre-dose phase and at approximately 0.5 hours post-dose on day 2, with all examinations completed at the same time of day (± 2 hours). Assessments were conducted while rats were in their home cage (home-cage observations, eg evaluations of posture and activity), during handling (hand-held observations, eg evaluations of respiration and muscle tone), and in an open-field
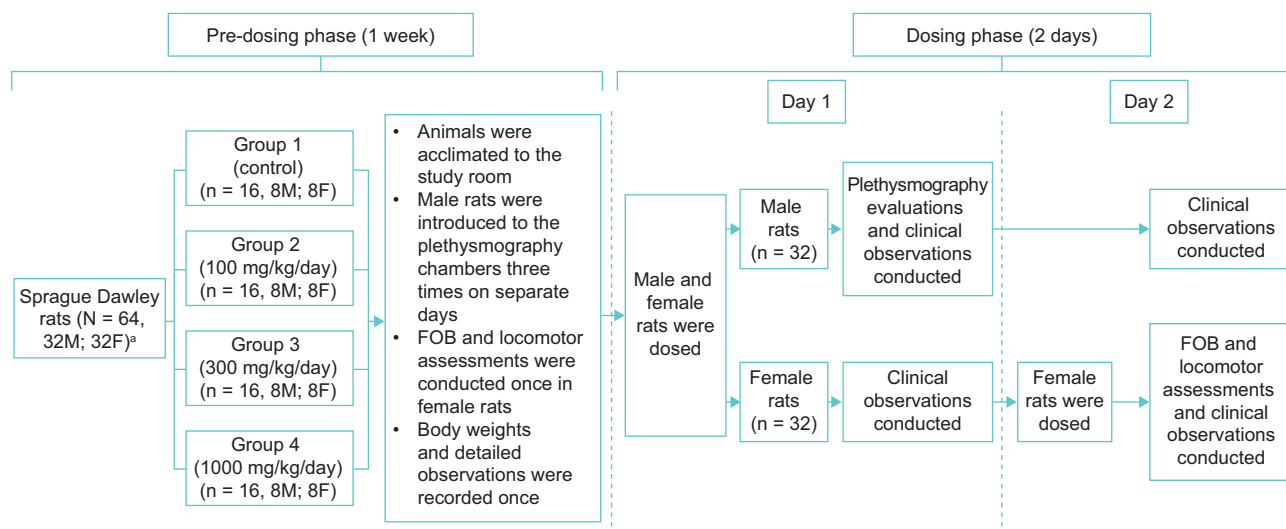
Figure 1 Study schematic for the safety pharmacology evaluations conducted in rats. Animals were assigned to the study using a computerized procedure designed to achieve body weight balance with respect to subgroup assignment. Eight males (M) per group underwent plethysmography evaluation and eight females (F) per group underwent FOB and locomotor activity assessments. Dose levels and concentrations were expressed as the maleate salt and based on trazpiroben as supplied with no correction. Group 1 received the control formulation only. Day 1 of the dosing phase is defined as the first day of dosing for each sex.

environment (open-field observations, eg the number of grooms or rears; Table 1). Rats were also assessed for sensory reactivity to stimuli (elicited behaviors, eg approach response and righting reflex), grip strength, foot splay, and body temperature (further information in Table 1). All observations were assessed and recorded.

Locomotor Activity Assessments

Locomotor activity assessments were conducted once during the pre-dose phase and following dosing on day 2. Each female rat was placed in a sound-attenuated, dark locomotor assessment chamber within 10 minutes of completing the FOB assessments, and activity was recorded for 40 minutes using an automated photocell-activity recording device. Intervals for reporting and data presentation were in 20 chambers for 2 minutes each. Basic movement, vertical and horizontal ambulation, fine movement, and rearing activity were assessed.

Pulmonary Assessments (Plethysmography)

In total, eight male rats in each group were evaluated for pulmonary function on day 1 of the dosing phase. Male rats were acclimated to the facility for 4 days before plethysmography acclimation, and then introduced to the head-out plethysmography chambers three times on separate days. Males were dosed on day 1 of the dosing phase in protocol-specified order (Groups 3, 1, 4, and 2) and placed immediately in a plethysmography chamber. Assessments were conducted in block order (the first rat from Group 1 followed by the first rat from Group 2 etc), and chambers were arranged in the same order. Rats were monitored for at least 1 hour after the last rat was placed in a chamber and thereafter at intervals of ≤ 75 minutes. If abnormal behavior was observed, the rat was adjusted in or removed from the chamber, the time the abnormal behavior occurred was recorded, and the study director or the pharmacologist was notified. The rat in question could subsequently be returned to the chamber at the discretion of the study director, contributing scientist, or veterinary staff.

Bioanalytical and Toxicokinetic Analysis

For toxicokinetic assessments, 60 rats (30 male), separate to those used for FOB, locomotor, or plethysmography assessments, received trazpiroben on day 1 of the dosing phase at 0, 100, 300, and 1000 mg/kg. Plasma analyses of trazpiroben were performed using liquid chromatography with tandem mass spectrometric detection. On day 1, blood samples were collected post-dose within acceptable timeframes (± 2 minutes for the 0.5-hour collection, ± 4 minutes for the 1-hour collection, ± 5 minutes for the 2-hour collection, and ± 10 minutes for the 4- and 6-hour collections; Table 2) from the jugular vein of non-fasted rats undergoing toxicokinetic evaluations. If an animal assigned to a specific time point died before its scheduled toxicokinetic collection, another animal in the same dose group was used. Toxicokinetic analysis included maximum observed concentration (C_{max}), time to peak concentration (T_{max}), and area under the concentration–time curve (AUC).

Table 1 FOB Assessments Conducted in Female Rats During the Pre-Dose Phase and Approximately 0.5 Hours Post-Dose on Day 2 of the Dosing Phase

Observation	Factors Evaluated
Home-cage observations	Posture, activity, gait abnormalities, or any other unusual behavior
Hand-held observations	Reactivity to handling, vocalization, palpebral closure, exophthalmos, excessive lacrimation, excessive salivations, respiration, appearance of fur, piloerection, muscle tone, and pupillary status
Open-field observations	Latency to the first step, number of grooms and rears, number of urine pools and fecal boli, locomotor activity, posture, gait abnormalities, and other unusual behavior
Elicited behavior evaluations	Auditory reactivity, approach response, proprioception, nociceptive response, pinna response, papillary status, papillary response, corneal response to touch, and righting reflex

Table 2 Blood Sampling Schedule for Bioanalytical and Toxicokinetic Analyses of Trazpiroben in Rats During the Dosing Phase

| Group	Set	Time Points on Day 1[a]
1	First three/sex/group	1 hour post-dose
2, 3, 4	First three/sex/group	2 hours post-dose
2, 3, 4	Second three/sex/group	0.5 and 4 hours post-dose
2, 3, 4	Third three/sex/group	1 and 6 hours post-dose

Note: [a]Blood collection times were approximate. If an animal assigned to a specific time point died before its scheduled toxicokinetic collection, another animal in the same dose group was used for sample collection.

Clinical Observations and Examinations

Rats were checked twice daily for mortality, abnormalities, and indications of pain or distress. Ophthalmic examinations and body weight assessments were conducted and recorded once for all rats during the pre-dose phase.

Dog Study

Study Design

Four purebred male beagle dogs (Covance Research Products Inc., Cumberland, VA, USA) were chosen from a pool of five non-naive and four naive animals and dosed in a Latin square design to ensure all dose levels were represented on each dosing day, and to control for bias (Figure 2). At dosing initiation, the dogs were 17–18 months old, and weighed 9.9–12.8 kg at the final pre-dose collection. Animals were co-housed in stainless steel cages, except during cardiovascular monitoring (≤ 4 hours before and after telemetry collections), during which the dogs were individually housed. Food was available ad libitum for ≥ 6 hours a day, whereas water was freely available at all times. A 12-hour light/12-hour dark cycle was maintained. Dogs were distinguished using a tattoo, implantable microchip identification device, and/or cage card. All animals were prequalified for the study and acclimated to the study room for 2 weeks before dosing on day 1.
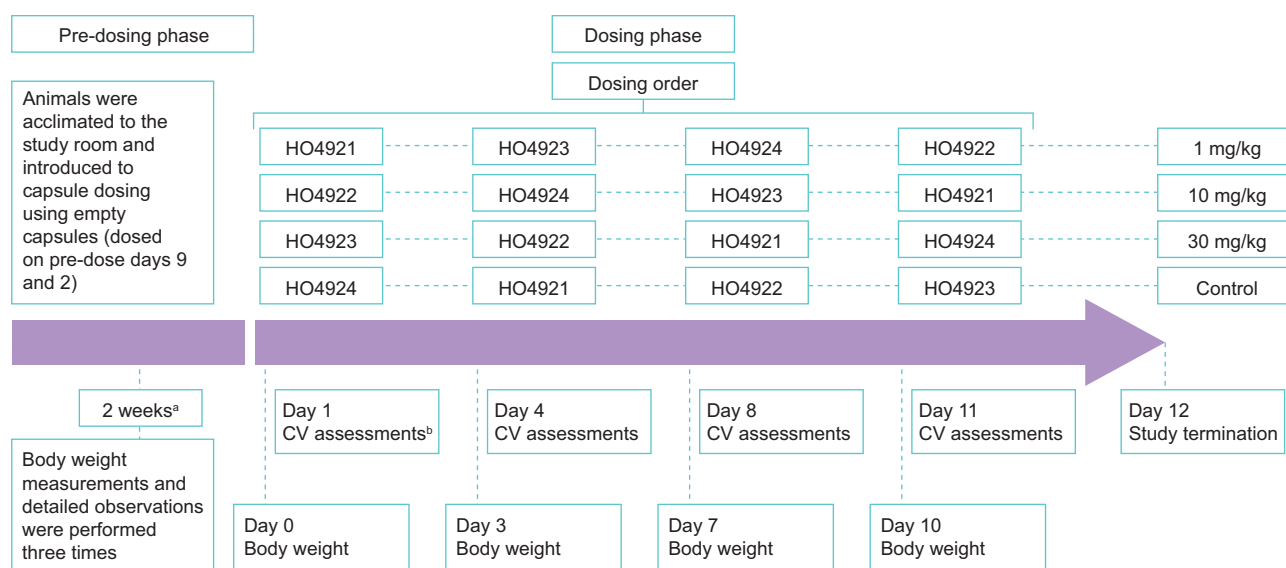
Figure 2 Study schematic for the safety pharmacology evaluations conducted in male dogs. Animals were dosed in ascending order based on dose level and received each dose once in a unique dosing sequence. Washout periods of 2 days were included between dosing. Animals in the control group received the same amount of control article in capsules as the number of trazpiroben capsules administered to the animal in the high-dose level designation at each interval. [a]Dogs were abdominally implanted with an ECG, blood pressure, and body temperature transmitter ≥ 2 weeks before study initiation. [b]Cardiovascular (CV) assessments in the dosing phase were recorded for at least 90 minutes before dosing.

Trazpiroben was administered orally on days 1, 4, 8, and 11 in a gelatin capsule at 0 (control; 10:1 dispersion of Avicel PH102 [microcrystalline cellulose]:Explotab [sodium starch glycolate]), 1, 10, or 30 mg/kg. Trazpiroben and control doses were prepared either the day before or on the day of dosing. Dose levels and dose concentrations were expressed as the maleate salt. Dose levels for capsules containing trazpiroben were corrected for batch-specific drug content at a ratio of 1:9:1 (trazpiroben:Avicel PH102:Explotab), and capsules containing the control and trazpiroben formulations were protected from light and stored at room temperature (15–30°C) before dosing. Each dog received each dose once in a unique dosing sequence. Doses were administered in ascending order based on dose level (control to high dose), with 2-day washout intervals between dosing. All animals received the same number of capsules, following acclimation to capsule dosing (twice during the pre-dose phase, using empty capsules). The doses of trazpiroben selected for use in this study were based on a prior 7-day, repeat-dose, range-finding study conducted in dogs.[40,41]

Study Procedures
Telemetry
At least 2 weeks before study initiation, an electrocardiogram (ECG), pressure, and temperature transmitter was implanted into the abdomen of each dog and sutured to the abdominal wall. The ECG leads of the transmitter were arranged in an approximate Lead II configuration (negative electrode on the right front limb, positive electrode on the left rear limb). The negative ECG lead was placed into the right jugular vein and advanced towards the heart. The positive lead was sutured to the abdominal side of the diaphragm close to the apex of the heart. The pressure catheter was placed in the aorta via the femoral artery to assess aortic pressure. Dataquest® OpenART® telemetry equipment (Data Sciences International, St Paul, MN, USA) was used to generate and to acquire data input.

During the pre-dose phase, all implanted telemetry devices were checked for signal consistency and to confirm the telemetry signal was acceptable for analysis. Telemetry data (ECG, blood pressure, and body temperature) were recorded continuously for at least 22 hours and were reviewed to confirm that an animal qualified for the study. On each dosing day, ECG, blood pressure, and body temperature measurements were recorded for at least 90 minutes before dosing and continuously through the end of the first post-dose 12-hour dark cycle (~18 hours post-dose).

Analysis of Telemetry Data
Post-dose telemetry data were divided for analysis based on photoperiod (before room entry [baseline], during the first post-dose light cycle and during the first post-dose dark cycle). Human activity in the room was minimized to limit the effect on cardiovascular outcomes. Telemetry data were excluded if affected by room disturbances, were of poor quality, were outside of physiological ranges, or were > 3 standard deviations from the mean of each variable for each dog on each dosing day. Data collected during the light/dark cycle transition times at 04:00–06:00 and 16:00–18:00 were also excluded. Corrected QT (QTc) intervals were determined using an individual animal correction factor (IACF) generated by fitting a linear regression line to 1-minute means of QT versus heart rate (time from one R wave to the next R wave [HR_{RR}]) based on data collected on the day of control dose. QTc values were calculated for each 1-minute interval according to the formula:

$$QTc = QT - (IACF \times [HR_{RR} - 75])$$

HR_{RR} is denoted in beats per minute. The IACF was applied for all doses administered in the same animal. Common heart rate correction formulae developed for use in humans (eg, Bazett's or Fridericia's) have been shown to be sub-optimal for use in the lab animal species typically used to screen for potential cardiovascular liabilities (eg, dogs).[42] Individual animal-based methods for heart rate correction of QT interval introduce significantly less error into QTc calculation.

Qualitative and Quantitative ECG Evaluations
For qualitative evaluation of ECG, 1–1.5 minutes of continuous ECG recordings for each dog were isolated before dosing, and at 1, 2, 4, 8, 12, and 18 hours post-dose. ECG segments selected for qualitative analysis post-dose were used to generate a collection of representative ECG waveforms for each dog, which was then used to quantify ECG waveforms for the dog in question.

Hemodynamic and Body Temperature Measurements

Data regarding hemodynamic parameters (systolic, diastolic, and mean arterial pressures; arterial pulse pressure, and heart rate) and body temperature were collected and analyzed.

Clinical Observations and Examinations

Dogs were checked twice daily, except on the day of transfer on or off the study (checked once daily), for mortality, abnormalities, and indications of pain or distress. Cage-side observations were conducted once daily on each day of dosing and made continuously for each dog ≥ 2 hours after the final dog had completed dosing. Detailed observations were performed three times during the pre-dose phase, the day before each day of dosing, and on the last day before telemetry data collection. Body weights were recorded three times during the pre-dose phase and the day before each day of dosing.

Statistical Analysis
Rat Study

Plethysmography data from the first eight males per group were analyzed by repeated measures analysis of covariance.[43,44] For post hoc analyses, if applicable, group comparisons (100, 300, and 1000 mg/kg vs 0 mg/kg) were evaluated by Dunnett–Hsu adjusted t-test.[45–47] All analyses were performed using SAS version 9.2 (2002–2008; SAS Institute, Cary, NC, USA).

Locomotor activity was analyzed using one-way analysis of variance (ANOVA). If the group effect of the ANOVA was significant ($p < 0.05$), Dunnett's t-test was used for pairwise comparisons between each treated and control group.[45,46] If the group effect of the ANOVA was not significant ($p > 0.05$), no further analyses were conducted.

Dog Study

Telemetry data were analyzed using repeated measures analysis of covariance. A Dunnett or Dunnett–Hsu t-test was used for comparing treatment groups to control when required.[45,46]

Results
Rat Study
FOB and Locomotor Activity Assessments

No effects were observed on FOB assessment results following administration of trazpiroben. Elicited behaviors, hand-held, home-cage, and open-field observations were unremarkable following dosing of trazpiroben at ≤ 1000 mg/kg/day (data not shown).

No clinically meaningful changes in locomotion parameters were observed following trazpiroben dosing (Figure 3). Minimal effects were observed, which were short-lived and that did not correlate with T_{max} exposure. Locomotion assessment outcomes are presented in Figure 3. Significant reductions in basic movements were seen in female rats given 300 and 1000 mg/kg/day of trazpiroben at 4–6 minutes post-commencement of the locomotor activity assessment (199 and 171 basic movements in 2 minutes, respectively) on day 2 of the dosing phase compared with rats receiving control (375 movements in 2 minutes; $p ≤ 0.05$). As shown in Figure 3, fine movements were significantly decreased in rats receiving 1000 mg/kg/day at 4–6 minutes post-commencement of the locomotor activity assessment, with 134 movements recorded in 2 minutes compared with 273 movements for the control group. Counts of horizontal and vertical ambulation were also significantly decreased in rats given ≥ 300 mg/kg/day at 2–6 minutes post-dose. Significantly reduced rearing activity was noted in rats receiving 100, 300, and 1000 mg/kg/day of trazpiroben at 4–8 minutes post-commencement of the locomotor activity assessment (100 mg/kg/day: 3 counts of rearing [9 counts for controls]; 300 mg/kg/day: 2 and 4 counts of rearing [10 and 9 counts for controls, respectively]; 1000 mg/kg/day: 2 and 3 counts of rearing [10 and 9 counts for controls, respectively]).

Pulmonary Evaluations

Adjusted mean tidal volume values were greater in rats receiving 1000 mg/kg/day trazpiroben than for the control group at all post-dose time points. Significant differences occurred in rats receiving 1000 mg/kg/day (+0.26 mL; 17%) and 300 mg/kg/day (+0.29 mL; 19%) at 6 hours post-dose ($p ≤ 0.05$; Figure 4). Because changes in tidal volume were small
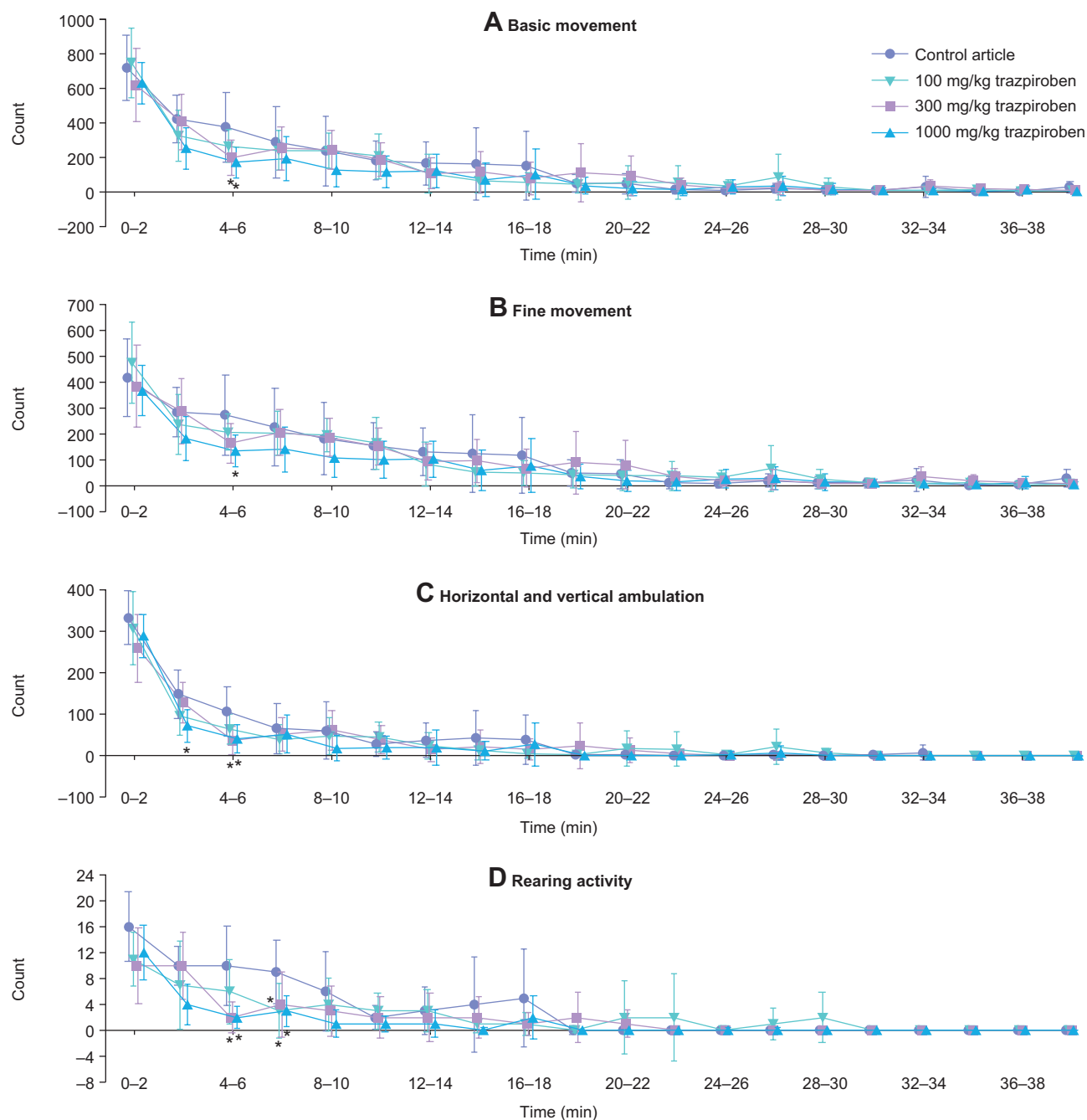
Figure 3 Mean locomotion parameters. (**A**) Basic movement, (**B**) Fine movement, (**C**) Horizontal and vertical ambulation, and (**D**) Rearing activity, as measured in female rats following receipt of trazpiroben during the dosing phase. FOB assessments were conducted at approximately 30 minutes post-dose. Locomotor activity was assessed within 10 minutes following the end of the FOB assessment for each animal and was measured for a total of 40 minutes. *Statistical significance was determined at $p \leq 0.05$.

and late in onset relative to dosing, the observed higher tidal volumes were not considered biologically meaningful (Supplementary Table 1). No biologically relevant effect on respiration rate or minute volume was observed at any trazpiroben dose level (Supplementary Tables 2 and 3).

Toxicokinetics and Clinical Observations

In Table 3, results from day 1 of the dosing phase are presented to reflect the acute timeframe of the safety pharmacology evaluations. Following administration and absorption of trazpiroben, T_{max} values ranged from 1.00 to 4.00 hours on day 1 of dosing. Exposure, as measured by C_{max} and AUC_{0-6} values, was found to increase with trazpiroben dose level from
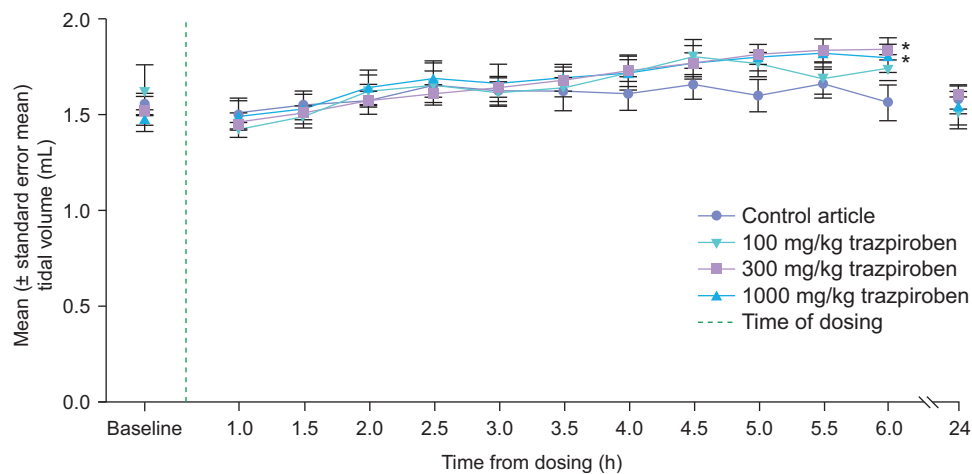
Figure 4 Mean (± standard error mean) tidal volume in male rats undergoing plethysmography evaluations during the dosing phase. *Statistically significantly different from data from animals given 0 mg/kg at $p < 0.05$.

100 to 1000 mg/kg/day. Increases in these parameters were roughly dose-proportional in both male and female rats, with differences generally less than twofold greater in females. Elimination phase half-life could not be estimated owing to an indistinct elimination phase.

Clinical Observations and Examinations

No unexpected clinical observations or changes in ophthalmic or body weight parameters were observed in rats treated with trazpiroben, and no trazpiroben-related mortality was noted (data not shown).
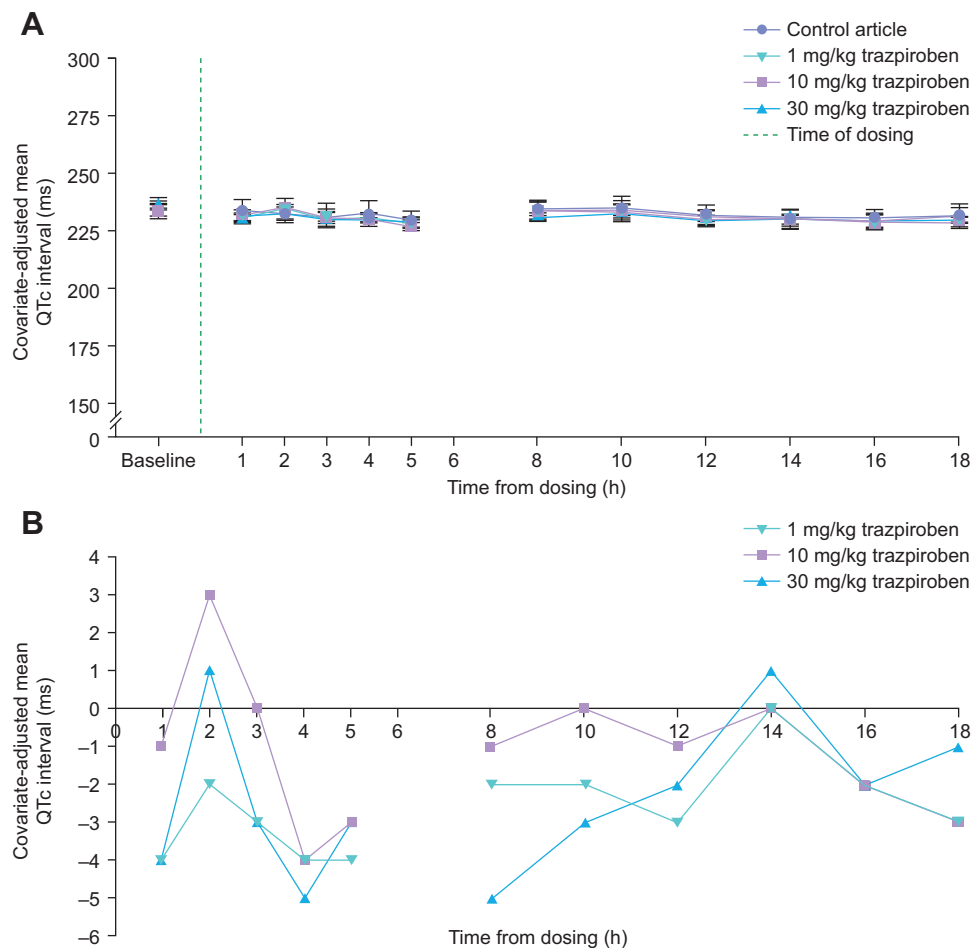
Dog Study

Telemetry

No abnormal ECG waveforms or arrhythmias were recorded following administration of trazpiroben (data not shown). In dogs receiving 30 mg/kg trazpiroben, QT and PR interval values were lower than those recorded in the control group during the first light cycle. The maximal effect on the PR interval occurred 3 hours after administration of 30 mg/kg trazpiroben, when the adjusted PR interval mean was 12% lower than control (90 vs 102 msec, respectively [data not shown]). With respect to the QT interval, consistent decreases from control values occurred throughout the first light cycle in dogs receiving 30 mg/kg and correlated with higher heart rates in dogs receiving trazpiroben throughout this period (data not shown). However, differences were relatively small (≤ 6% lower than control) and not significant at any dose of trazpiroben (data not shown). All changes to the QT and PR intervals were considered secondary to trazpiroben-related changes in heart rate, and no trazpiroben-related effects on QRS duration or the QT interval corrected for heart rate (QTc) were recorded (Figure 5A). Changes in mean QTc interval versus time-matched controls are shown in Figure 5B.

Table 3 Toxicokinetic Parameters for Trazpiroben in Rat Plasma for Day 1

Dose Group	Trazpiroben Dose (mg/kg/Day)	Sex	C_{max} (ng/mL)	T_{max} (h)	AUC_{0-6} (ng ħ/mL)
2	100	M	1450	2.00	5450
2	100	F	2680	1.00	12,700
3	300	M	6890	2.00	24,500
3	300	F	14000	1.00	60,900
4	1000	M	18300	4.00	65,100
4	1000	F	23700	1.00	85,400

Abbreviations: AUC_{0-6}, area under the concentration–time curve 0–6 hours; C_{max}, peak concentration; T_{max}, time to peak concentration.

Figure 5 Heart rate-corrected QT (QTc) intervals of instrumented male beagle dogs during study dosing phase: (**A**) Mean (± standard error mean) QTc interval; (**B**) Change in mean QTc interval versus time-matched control article.

Hemodynamics

Small decreases in systolic and pulse pressures were noted in dogs receiving 10 and 30 mg/kg of trazpiroben versus control (data not shown). Adjusted mean systolic pressure values were generally lower than control throughout the first light cycle, although differences were not significant (data not shown). The greatest change occurred 3 hours post-dose, which fell within the previously established range for T_{max} exposure for trazpiroben in beagle dogs, but did not correlate with the previously established median T_{max} (median T_{max}: approximately 1 hour post-dose, range: 1–4 hours post-dose), when adjusted mean systolic pressure values were 6% (10 mg/kg trazpiroben) and 9% (30 mg/kg trazpiroben) lower than controls.[41] Notably, these differences still did not reach significance. With respect to pulse pressure, the effect of trazpiroben was also greatest at 3 hours post-dose, when adjusted mean values were 15% (10 mg/kg trazpiroben) and 23% (30 mg/kg trazpiroben) lower than in controls (data not shown). Adjusted mean values for diastolic pressure were lower at 1 hour post-dose for all doses of trazpiroben (5% lower at 10 mg/kg [$p \leq 0.05$] and 8% lower at 30 mg/kg [$p \leq 0.01$] vs control) and significantly higher at 4 hours post-dose at $\geq$ 1 mg/kg (6%, 8%, and 5% higher at 1, 10, and 30 mg/kg, respectively; [$p \leq 0.05$]) and 5 hours post-dose at $\geq$ 10 mg/kg (6% higher at both 10 and 30 mg/kg [$p \leq 0.01$]). An increased heart rate was noted in dogs receiving 30 mg/kg trazpiroben during the first light cycle, with the greatest effect at 3 hours post-dose (28% higher than control). Owing to their small and inconsistent nature, the changes observed in mean arterial or diastolic pressure were considered incidental and unrelated to trazpiroben.

Clinical Observations, Body Weight, and Body Temperature

No clinical observations were deemed related to trazpiroben and all dogs survived to study termination on day 12. Administration of the study drug at doses ≤ 30 mg/kg was not associated with effects on body weight or temperature (data not shown).

Discussion

Gastroparesis is a poorly understood motility disorder with limited treatment options. Current therapies come with restrictions for use, owing to the potential for serious side effects. Therefore, there remains a need for efficacious therapies for gastroparesis with a favorable safety profile. Trazpiroben is a selective D_2/D_3 receptor antagonist under development for the chronic treatment of moderate to severe idiopathic and diabetic gastroparesis. The three safety pharmacology studies described here assessed the potential effects of trazpiroben on the CNS and pulmonary system (conducted in rats), as well as on the cardiovascular system (conducted in dogs). These standard non-clinical safety pharmacology models provide additional data for translation to predicted clinical effects (or lack of effects) of novel drugs in humans.

CNS, Pulmonary and Toxicokinetic Evaluations of Trazpiroben in Rats

One current issue with contemporary therapies for gastroparesis is the potential for penetration of the CNS. Trazpiroben is zwitterionic in its neutral form and demonstrates limited CNS penetration, as well as acting as a substrate for the efflux transporter P-glycoprotein (P-gp).[48–51] In contrast, the properties of metoclopramide (2-methoxy-4-amino-5-chloro-N, N-[dimethylaminoethyl]benzamide) allow relatively efficient transport into the CNS and, because it acts as only a weak substrate for P-gp, it is not extensively transported back out of these tissues.[52–55] The central penetration of metoclopramide gives rise to the risk of potentially irreversible CNS side effects, such as tardive dyskinesia. As a result, the compound has restrictions for use recommended by several regulatory bodies.[22] To confirm the absence of clinically meaningful CNS penetration of trazpiroben, FOB and locomotor activity assessments were conducted in rats on day 2. While delaying these assessments until day 2 risks missing a CNS effect that presents upon first exposure to trazpiroben, this risk is quite minimal compared with the potential loss in sensitivity of conducting the assessment on day 2 when many other study activities were being conducted (eg toxicokinetic analysis, blood sampling, etc.); such activities result in increased staff activity (and attendant noise) in the animal room, which can negatively impact FOB and locomotor activity assessments. Following administration of trazpiroben at doses of ≤ 1000 mg/kg/day, no trazpiroben-related effects were noted during FOB assessments at any dosing level. Equally, no biologically meaningful changes were observed in horizontal/vertical ambulation, rearing activity, or basic and fine movements, with minimal effects on horizontal and vertical ambulation seen at ≥ 300 mg/kg/day and decreased fine movements at 1000 mg/kg/day. While there were statistically significant differences in some of the motor activity parameters, the differences were of very short duration (2–4 minutes) and were not corroborated by effects on any of the locomotion-related end points within the more comprehensive FOB assessments. These data indicate that trazpiroben has limited penetration across the blood–brain barrier and exerts negligible effect on central dopaminergic receptors, thus avoiding a key concern of metoclopramide therapy. These data are additionally encouraging as the doses of trazpiroben evaluated in this study substantially exceed those required for D_2/D_3 receptor engagement in rats by more than 300-fold. Maximal D_2 receptor engagement in rats, gauged using prolactin release as a pharmacodynamic biomarker, has previously been observed to occur at a dose of 1 mg/kg trazpiroben.[56] This demonstrates that even with far higher doses than required for this pharmacological effect, CNS penetration, as determined by locomotor assessment, is minimal.[56] The current findings are further supported by the results of rotarod testing in rats following oral administration of trazpiroben, which demonstrated that doses of up to 30 mg/kg did not affect motor coordination[35] or the minimal brain penetration of trazpiroben observed in rats and dogs following administration of 100 mg/kg and 50 mg/kg of trazpiroben, respectively.[51] Importantly, these observations from preclinical studies reflect the clinical experience of CNS effects to date. In humans, maximal D_2 receptor engagement was observed to occur at a 10 mg dose of trazpiroben during the first-in-human Phase I trial, with no CNS effects noted at any dose of trazpiroben administered up to the maximum of 300 mg.[38,57] Overall, trazpiroben has displayed a favorable safety profile in both the first-in-human Phase I trial[38] and Phase IIa clinical trial.[58]

When considering the pulmonary and toxicokinetic assessments of trazpiroben, further evidence of a favorable safety profile for the compound was observed. Administration at doses ≤ 1000 mg/kg/day was not associated with any biologically relevant changes in tidal volume, respiration rate, or minute volume. Trazpiroben was rapidly absorbed and demonstrated dose-proportional increases in toxicokinetic parameters in rats, in line with results seen in the first-in-human, randomized, double-blind, placebo-controlled, single and multiple ascending dose study of trazpiroben.[38,57] Maximal D_2 receptor engagement was inferred, again using prolactin release, to occur at an average C_{max} in plasma of ~11 ng/mL trazpiroben in humans, again much lower than the observed C_{max} for each group of rats receiving trazpiroben (≥ 1450 ng/mL). This further indicates that, despite the presence of trazpiroben at concentrations far higher than those required for therapeutic effect, no safety concerns arise.

Cardiovascular Evaluations of Trazpiroben in Dogs

With respect to the cardiovascular assessments conducted in dogs, trazpiroben was noted to cause small decreases in systolic and pulse pressures when administered at doses of ≥ 10 mg/kg, relative to control values. All changes in diastolic pressure were small ($\leq 8\%$ different from control) and inconsistent over time, and so were considered incidental and not related to trazpiroben. Additionally, administration of trazpiroben at 30 mg/kg was associated with an increase in mean heart rate that was considered to have been compensatory for decreases in blood pressure, and correlated with lower QT and PR interval values, which were also deemed due to increased heart rate. Notably, no trazpiroben-related effects on QRS duration, QTc interval, diastolic or mean arterial pressure, or body temperature occurred, and no qualitative ECG abnormalities were attributed to administration of trazpiroben. The lack of an effect on QT interval observed with trazpiroben is consistent with the low affinity of the compound for the hERG potassium channel ($IC_{50} = 15.6$ μM).[59] This is in contrast to domperidone, which is characterized by its propensity to block the hERG potassium channel ($IC_{50} = 0.057$ μM) at clinically relevant concentrations, leading to delayed ventricular repolarization and QT interval prolongation, with the risk of sudden cardiac death.[31,60,61] Previous preclinical studies have unambiguously demonstrated the ability of domperidone to produce action potential prolongation, as well as suggesting proarrhythmic potential.[61] Our results indicate that trazpiroben offers a viable alternative with a favorable cardiac safety profile and minimal potential for prolongation of the QT interval, supporting clinical evidence from the associated Phase I[38] and Phase IIa trials.[58]

Conclusion

These data indicate that trazpiroben is not associated with CNS, pulmonary, or cardiovascular safety concerns in the preclinical setting. The absence of abnormalities in FOB assessment results as well as the absence of any biologically meaningful effects on locomotion, even at doses greatly increased from those needed for compound efficacy, indicates limited penetration of the CNS by trazpiroben and, thus, a reduced risk of extrapyramidal symptoms. Trazpiroben also demonstrated no effects on QRS duration, QTc interval, and ECG outcomes, indicating a favorable cardiac safety profile. Trazpiroben thus represents a promising potential therapy for the treatment of chronic gastroparesis, without the risk of serious side effects associated with currently available treatments.

Abbreviations

ANOVA, analysis of variance; AUC, area under the concentration–time curve; C_{max}, maximum observed concentration; CNS, central nervous system; CYP, cytochrome P450; ECG, electrocardiogram; FOB, functional observational battery; hERG, human ether-à-go-go-related gene; HR_{RR}, Heart rate (the time interval from one R wave to the next R wave); IC_{50}, half maximal inhibitory concentration; QTc, QT interval corrected for heart rate; T_{max}, time to peak concentration.

Data Sharing Statement

Due to the nature of this research, data supporting the results reported in this manuscript will not be shared owing to Intellectual Property considerations.

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Ethics Approval

Both studies complied with the National Institutes of Health Guide for the Care and Use of Laboratory Animals, (NIH Publications No. 8023, revised 1978) the 'Animal Research: Reporting of in vivo Experiments' guidelines, and applicable animal welfare acts. Both studies were approved by the Covance Animal Care and Use Committee. Covance Laboratories is fully accredited by the Association for Assessment and Accreditation of Laboratory Animal Care. No specific approval or permit numbers were applicable for these studies.

Consent for Publication

Not applicable

Author Contributions

All authors made substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; took part in drafting the article or revising it critically for important intellectual content; agreed to submit to the current journal; gave final approval of the version to be published; and agree to be accountable for all aspects of the work.

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Disclosure

Laura Kreckler: Study director for the cardiovascular safety study conducted at Covance Laboratories Inc., Madison, WI, United States of America, at the time of the study and currently at AbbVie, North Chicago, IL, USA. Mark Osinski and Scott Williams were employees of Covance Laboratories Inc., Madison, WI, USA at the time of the study and currently at Labcorp Drug Development, Madison, Wisconsin 53704-2523, USA. Roger Whiting is a former shareholder of Altos Therapeutics LLC; Dr Whiting will benefit from any future payments by Takeda Pharmaceutical Company Ltd. with respect to certain clinical development and commercial milestones for TAK-906. Dr Whiting has not received consulting fees from Takeda Pharmaceutical Company Ltd since 2017. The authors report no other conflicts of interest in this work.

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