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SYM-1219: Oral Single-Dose Safety Pharmacology Studies to Determine Possible Secnidazole Toxicity

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PURPOSE

Purpose SYM-1219, a novel oral granule formulation of secnidazole, an antimicrobial drug in the 5-nitroimidazole class, is under development as a single dose treatment for bacterial vaginosis. Studies were conducted in animals to evaluate the potential cardiovascular, central nervous system (CNS), and respiratory responses to the administration of a single dose of SYM-1219, and to determine the dose at the no observable effect level (NOEL).

Methods Three separate studies were conducted to determine potential pharmacological effects of SYM-1219 (secnidazole). The cardiovascular study was conducted in female Beagle dogs. CNS and respiratory studies were conducted in rats. For the cardiovascular study, dogs (N=4 females) received doses of vehicle granules (control) or SYM-1219 at 20, 60, or 200 mg/kg in a 10 mL/kg volume. Cardiovascular data were collected by use of surgically implanted radiotelemetry. Each dog received each dose in a balanced Latin Square design employing a 3-day washout period between doses. Clinical observations were collected 4 hours post-dose and once on each non-dosing day thereafter. Blood pressure (BP) parameters, heart rate, and ECG parameters were recorded for at least 30 minutes prior to and for 24 hours following each dose. Data were summarized from 30 minutes to 24 hours post-dose. For the study of CNS effects, a total of 80 rats were assigned (10 male and 10 female per group), to receive vehicle, 100, 300, or 1000 mg/kg SYM-1219. A neurobehavioral assessment using a Functional Observational Battery (FOB) and a motor activity test were performed on all animals pre-dose (1-2 hours) and post-dose (24 hours). For the study of respiratory effects, male rats (n=4 per treatment group) received a single dose of the vehicle or SYM-1219 at 100, 300, or 1000 mg/kg, delivered as 10, 30, and 100 mg/mL solutions, respectively, in a 10 mL/kg volume. Respiratory data (respiratory rate, tidal volume, and minute volume) were collected using whole body plethysmographs pre-dose (for a duration of 1 hour) and at 0-6 hours and 24-hours post-dose.

Results No animals died or were deemed moribund during the three studies. In the cardiovascular study, administration of the highest dose of SYM-1219, 200 mg/kg, resulted in significantly lower systolic BP (ranging from 14-24 mmHg lower) compared to control groups at all time points between 0.5 hours-3.75 hours, and again at 5 hours. Mean BP of the 200 mg/kg group was also significantly lower compared to control at many of the observed time points. Administration of SYM-1219 at 200 mg/kg resulted in significantly increased heart rates, which was interpreted to be a baroreflex response to the decreases in BP, and a significantly shorter P-R interval, thought to be related to the increased heart rate. There were no significant cardiovascular responses in animals that received 20 or 60 mg/kg doses. The CNS study in rats revealed that oral administration of 100 or 300, mg/kg SYM-1219 resulted in no test article-related changes for FOB or motor activity parameters. At a dose of 1000 mg/kg, vertical breaks (V1B), vertical counts (V1C), bursts of stereotypic movement were significantly lower in male rats compared to controls, and female rats had significantly lower horizontal counts, V1B and V1C compared to controls. These changes were noted in all rats between 1-2 hours post-dose. The observed neurological signs represented a general decrease in activity and were considered test article related. The study of respiratory effects in rats revealed no changes in respiratory rate, tidal volume, or minute volume for male rats receiving 100, 300, or 1000 mg/kg SYM-1219.

Conclusions In dogs, SYM-1219 at 200 mg/kg produced a degree and duration of decreased BP that was considered drug-related, thus, the NOEL for cardiovascular responses was found to be 60 mg/kg. In rats, a decreased general motor activity at the highest dose tested resulted in a NOEL of 300 mg/kg for neuropharmacological and behavior parameters, and a NOEL of >1000 mg/kg, the highest dose of this study, for respiratory parameters.

METHODS

Cardiovascular Study SYM-1219 or vehicle was administered once per day with a minimum of a 3-day washout between doses until all doses were administered to each animal. Four female dogs were included in this study and each animal received each dose level (0, 20, 60, 200 mg/kg) over the course of the study according to a balanced Latin Square Design. Doses were administered orally.

All animals were observed once each morning and afternoon throughout the study for viability. For all animals, physical examinations were conducted at 3 and 4 hours postdose (at the time of feeding and feed removal) on the days of dose administration and once per day on nondosing days. Animals appearing to be in pain or distress were brought to the attention of the Study Director and a staff veterinarian. Each animal was weighed prior to each dose administration.

The dogs for this study were previously surgically implanted with Data Sciences International (DSI) transmitters (TL11M2-D70-PCT). The transmitter was used to record ECG, arterial blood pressures, and body temperature. Animals were unrestrained within their home cage during collection of the selected cardiovascular parameters. Arterial blood pressure, ECG, and body temperature were recorded by telemetry for at least 12 hours prior to the first dosing event to establish the function of each telemetry unit.

Data collected from a minimum 30-minute pre-dose period on the day of dosing were used to generate a single baseline mean value for each parameter. Data were collected continuously for at least 24 hours post-dose and recorded as mean values of 60 second time bins. Further data summarization (e.g. means of 15 minute time bins) was determined by Study Director and/or Study Physiologist as appropriate for purpose of characterizing any test article effects. Times of any entry into the room during radiotelemetry monitoring were documented.

Respiratory Study A total of 16 male rats were assigned to four groups. The animals were not fasted overnight prior to dosing. Animals were acclimated for a minimum of 5 days prior to initiation of dosing.

SYM-1219 (100, 300, 1000 mg/kg) or vehicle control was administered by oral gavage once at a dose volume of 10 mL/kg body weight. The actual volume/weight to be administered to each animal was calculated based on the most recent body weight of each animal. Formulations were stirred during dosing. Animals were observed for viability at least once in the morning and once in the afternoon, at least 4 hours apart, throughout the study. Body weights were measured prior to dose administration.

Animals were placed in a plethysmograph chamber and data were collected for 1 hour before dose administration, for at least 6 hours immediately following dose administration, and for approximately 1 hour around the 24-hour postdose time point (~23.5 to 24.5 hours postdose). The following parameters were recorded and reported: respiratory rate (breath/minute), tidal volume (TV, mL/breath), and minute volume (MV, mL/minute).

Two 15-minute predose intervals were calculated and averaged together to be used as the baseline value. Postdose data were summarized as means of 15-minute intervals throughout the 6 hour data collection period, and for approximately 1 hour around the 24-hour postdose time point (~23.5 to 24.5 hours postdose).

Central Nervous System Study A total of 80 animals (10/sex/group) were assigned to and received 100, 300 or 100 mg/kg. The animals were not fasted overnight prior to dosing. SYM-1219 was administered once, orally by gavage, at a dose volume of 10 mL/kg body weight. Animals were observed for viability at least once in the morning and once in the afternoon, at least 4 hours apart, throughout the study. Body weights were measured prior to dose administration.

The neurobehavioral assessment included a Functional Observational Battery (FOB) and a motor activity test. The FOB and motor activity tests were performed on all animals once predose and postdose at 1 to 2 hours, and between 23.5 to 24.5 hours. The anticipated T_{max} is approximately 1 hour postdose. Animals were randomized prior to the predose neurobehavioral evaluation to allow “blinded” FOB testing throughout the study.

This battery was comprised of 4 sets of observations. The battery included home cage observations, handling observations, open-field observations and handling/specific testing of the animal.

A motor activity test was performed. Each rat was placed in an Opto-Varimex Animal Chamber designed to measure motor activity. Measurements were recorded every minute during a 15-minute session. A white noise generation system (WNGS) was used during each evaluation to produce approximately 70 dB of background noise in order to keep the variation of sound level to a minimum during the test.

RESULTS

Cardiovascular Study There were no test article related observations. Administration of SYM-1219 orally at 200 mg/kg resulted in significantly lower systolic blood pressure by 14-24 mmHg compared to control at each individual time point from 30 minutes to 3.75 hours and at the 5 hour time point.

Mean Blood Pressure was also significantly lower for the dogs receiving 200 mg/kg from 30 minutes to 1.75 hours, and at the 2.5 and 3.25 hour time points. Both parameters were generally lower than control during the 30 minute to 6-hour postdose period.

A significant increase in diastolic pressure at 22 hours postdose for the 200-mg/kg group was considered incidental and not test article related.
Heart rate was significantly increased from 45 minutes to 1.25 hours and at 2 hours postdose for dogs receiving 200 mg/kg SYM-1219.

Significantly lower P-R interval means were observed from 45 minutes to 1.25 hours, 2 to 3.25 hours, and 3.75 to 4 hours postdose for the high dose group. The increased heart rate was interpreted to be a baroreflex response to the drop in systolic and mean blood pressure, whereas the shorter PR interval was related to the increased heart rate. P-R interval mean values were significantly lower in dogs receiving 60 mg/kg at 1, 3, and 3.25 hour postdose, and at 6, 9, and 22 hours postdose for the 200-mg/kg group; however, these occurrences were not dose or time related and not considered test article related.

Other incidental but statistically significant changes for dogs receiving SYM-1219 at 200 mg/kg included higher QRS at 7 hours, lower QT at 1, 1.25, and 3.75 hours, lower QTcV at 3.25 hours, and higher QTcV at 11 and 18 hours postdose. QTcV for dogs receiving SYM-1219 at 60 mg/kg was higher at 11 hours postdose. This was also considered incidental as there were no other corresponding changes in ECG parameters.

There were no abnormalities in the electrocardiographic data that were considered related to test article administration.

Respiratory Study Rats receiving 100 mg/kg SYM-1219 had no test article-related changes in respiratory rate, tidal volume, or minute volume.

Rats receiving 1000 mg/kg SYM-1219 had significantly lower than control minute volume at 0.25 hours postdose. Rats receiving 300 mg/kg SYM-1219 had significantly higher than control tidal volume at 23.5 hours postdose. These findings were not considered test article-related as there were no clear correlations to dose level or trends following dose administration. Respiratory rate, tidal volume or minute volume had no significant changes between dose groups at these time points.

Central Nervous System Study Rats receiving 100, 300, or 1000 mg/kg SYM-1219 had no test article-related changes in FOB parameters at 1 to 2 hours or 23.5 to 24.5 hours postdose.

Rats receiving 100, 300, or 1000 mg/kg SYM-1219 had no test article-related changes in motor activity parameters at 23.5 to 24.5 hours after dose administration.

Rats receiving 100, or 300 mg/kg SYM-1219 had no test article-related changes in motor activity parameters at 1 to 2 hours after dose administration.

Male rats receiving 1000 mg/kg SYM-1219 had Bursts of Stereotypic Movement (BMS), Vertical Breaks (V1C), and Vertical Counts (V1B) that were significantly lower than control at 1 to 2 hours postdose, and were considered test article-related.

Female rats 1000 mg/kg SYM-1219 had Horizontal Counts (HC), Vertical Breaks (V1C), and Vertical Counts (V1B) that were significantly lower than control at 1 to 2 hours postdose, and were considered test article-related.

CONCLUSIONS

Cardiovascular Study SYM-1219 at 200 mg/kg po produced a degree and duration of reduced blood pressure that was considered adverse. Based on the effects on blood pressure, the NOEL in the cardiovascular safety study was 60 mg/kg.

Respiratory Study There were no changes in respiratory rate, tidal volume, or minute volume for male rats receiving 100, 300, or 1000 mg/kg SYM-1219 by oral administration. The NOEL on respiratory parameters in the rat was >1000 mg/kg, the high dose of this study, when given as a single oral dose.

Central Nervous System Study Based on the changes in motor activity changes for the 1000 mg/kg group males and females, the NOEL on the neuropharmacological and behavior parameters in rats was considered to be 300 mg/kg.

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