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Prescribing decisions should be made based on the approved package insert.*

Proprietary Drug Name:

Intuniv™

Generic Drug Name:

Guanfacine Hydrochloride

Therapeutic area and FDA approved indications: Intuniv is indicated for the treatment of Attention Deficit Hyperactivity Disorder (ADHD)

Name of Sponsor/Company:

Shire Development Inc.

Title of Study:

A Phase I, Randomized, Gender Stratified, Double-Blind, Placebo- and Positive-Controlled, Three Period Crossover Trial to Assess the Effect of Guanfacine Hydrochloride on QT/QTc Interval in Healthy Men and Women

Study Center(s):

1 - United States

Studied period:

08 April 2008 to 07 August 2008

Phase of Development:

1

Objectives:

Primary

To assess the effect of immediate-release guanfacine hydrochloride (HCl) on QT/QTc interval as a marker for ventricular repolarization following a therapeutic and suprathreshold dose of immediate-release guanfacine HCl when compared to placebo and the positive control, moxifloxacin HCl.

Secondary

To assess the safety and tolerability of immediate-release guanfacine HCl and assess the pharmacokinetic (PK) profile for each subject and investigate any relationship between plasma concentration (i.e., maximum plasma concentration [C_{max}]) and any observed electrocardiogram (ECG) changes.

Methodology:

Subjects were randomly assigned to one of six treatment regimens: G/P/M, M/G/P, P/G/M, M/P/G, or G/M/P, where P=placebo; M=moxifloxacin HCl; G=guanfacine HCl. Subjects were stratified by gender.

Subjects were screened up to 28 days prior to first dose of study drug. On Day -2 of each of the three treatment periods, subjects were admitted to the clinic. On Day -1 of each treatment period, baseline vital signs and continuous, digital, 12-lead ECGs were obtained. Each treatment period consisted of 9 days on which doses were administered. Days 1 and 6 were important for dose administration as subjects received therapeutic and suprathreshold doses of immediate-release guanfacine HCl, first and second doses of moxifloxacin, or placebo. There was a minimum 5-day and maximum 18-day washout period between the last down-titration dose and the subject's return for the next dose period.

Number of Patients (planned and analyzed):

72 subjects planned, 83 subjects enrolled, 83 subjects analyzed for safety, 58 subjects analyzed for pharmacodynamics, and 76 subjects analyzed for pharmacokinetics.

Diagnosis and Main Criteria for Inclusion:

Healthy subjects between 18 and 45 years of age, with a body mass index (BMI) of 20-29.9kg/m²

Test Product, Dose and Mode of Administration:

Immediate-release guanfacine HCl (heretofore referred to as guanfacine HCl) was administered in ascending doses of 4mg once daily on Day 1, 4–6mg twice daily on Days 2–5, 8mg once daily on Day 6, and descending doses from 6mg twice daily to 2mg once daily on Days 7–9.

Duration of Treatment:

Subjects were treated in three 9-day Periods with 72-hours of safety follow-up for each period.

Reference Therapy, Dose and Mode of Administration:

On Days 1 and 6, 400mg of moxifloxacin HCl was administered as a positive control. Placebo was administered on Days 1–9 of the placebo period and on Days 2-5 and 7-9 of the moxifloxacin period. Moxifloxacin HCl batch numbers were 54012JR and 5401332.

Criteria for Evaluation:

Subjects with no major protocol deviations who received guanfacine HCl on Days 1 and 6 were included in the pharmacodynamic analyses. All subjects with evaluable concentration-time data were analyzed for pharmacokinetics.

Statistical Methods:

The primary analysis examined the primary endpoints of heart rate (HR), PR interval (PR), QRS interval (QRS), QT, and QT corrected using the Fridericia (QTcF), and the subject-specific (QTcNi) methods, and their corresponding changes from baseline. Baseline was defined as the average of all timepoints on the run-in day for each period for all analyses including the repeated-measures analysis and categorical analysis, but not the time-matched analysis where time-matched baselines were used. These data were analyzed using two methods: time-matched and repeated-measures.

The time-matched analysis examined the baseline-adjusted, largest time-matched drug-placebo difference in QTc intervals from Hours 1-12 post-dose on Days 1 (therapeutic dose) and 6 (supratherapeutic dose). Drug-placebo differences for individual subjects on Days 1 and 6 were computed and mean value of the individual differences from time-matched baselines at each given timepoint were examined within an analysis of covariance framework using a mixed effects model.

The repeated-measures analysis equalized the variances across all timepoints and examined change from baseline in HR, PR, QRS, QT, QTcF, and QTcNi interval between Hours 1-12 on Days 1 and 6 and was subjected to an analysis of covariance using a mixed effects model using restricted maximum likelihood estimates of variance components.

The secondary analyses of the primary endpoints included a 'time-averaged' analysis and an analysis at subject-specific t_{max} using an analysis of covariance framework.

The time-averaged analysis over Hours 1-5 corresponded to the Holter bin analysis over the same period of maximal concentrations between Hours 1-5.

The analyses at subject specific t_{max} (time of subject-specific C_{max}) examined HR and intervals PR, QRS, QT, QTcF, and QTcNi on Day 6 (and Day 1) and were analyzed by a mixed effects model.

Secondary analyses examined QT data via a Holter bin method of three Holter bin endpoints. QT changes, for each subject and each RR bin, between treatment period (Days 1 and 6) and run-in baseline (Day -1) were calculated on a 4-hour time interval (over the 1-5 hour period corresponding to the period of expected maximal drug concentrations of guanfacine HCl and moxifloxacin HCl).

SUMMARY – CONCLUSIONS:

PHARMACODYNAMIC RESULTS:

Time-matched analysis:

- For moxifloxacin HCl, the lower confidence bound (LCB) was greater than 5msec at the majority of timepoints in the maximal concentration window (Hours 1-5) for both QTcNi and QTcF. At the 12-hour timepoint, where both QTcNi and QTcF for guanfacine HCl had the largest 95% one-sided upper confidence bound (UCB), the largest 95% one-sided LCB for moxifloxacin was >0msec, thus indicating assay sensitivity. Furthermore, at the majority of timepoints for QTcNi and QTcF, the UCB for moxifloxacin HCl was >10msec (the largest being 17.64msec at Hour 5 on Day 6).
- In the QTcNi analysis for guanfacine HCl, the largest 95% one-sided UCB was 1.94msec and the largest mean difference was -1.18msec (Day 6 suprathereapeutic dose of 8mg) at the 12-hour timepoint.
- For the QTcF analysis of guanfacine HCl, the largest 95% one-sided UCB was slightly >10msec (10.34msec); the largest mean difference (7.61msec) for the suprathereapeutic dose (8mg) occurred at the 12-hour timepoint.
- For both QTcNi and QTcF, guanfacine HCl and moxifloxacin HCl had no overlapping confidence intervals at the timepoints of maximal concentrations (Hours 2-5).

Repeated-measures analysis

- For moxifloxacin HCl, the LCB was greater than 5msec at all timepoints in the maximal concentration window (Hours 2-5) for both QTcNi and QTcF. At the 12-hour timepoint, where both QTcNi and QTcF for guanfacine HCl had the largest 95% one-sided UCB, the largest 95% one-sided LCB for moxifloxacin was >0msec (4.8msec for QTcNi and 3.93msec for QTcF), thus indicating assay sensitivity. Furthermore, at the majority of timepoints for QTcNi and QTcF, the UCB for moxifloxacin HCl was >10msec (the largest being QTcNi of 17.39msec at Hour 5).
- For the QTcNi analysis of guanfacine HCl, the largest 95% one-sided UCB was 2.79msec. The largest mean difference (-0.46msec) for the guanfacine HCl suprathereapeutic dose (8mg) occurred at the 12-hour timepoint.
- For the QTcF analysis of guanfacine HCl, the largest 95% one-sided UCB was 10.54msec, and the largest mean difference (7.82msec) for the suprathereapeutic dose (8mg) occurred at the 12-hour timepoint (the only occurrence >10msec).

Analysis at subject-specific t_{max}

- For guanfacine HCl, QTcNi had an UCB of <10msec at t_{max} on Days 1 and 6 (-0.34 and -4.78msec, respectively).
- For guanfacine HCl, QTcF also had an UCB of <10msec at t_{max} on Days 1 and 6 (3.03 and 4.27msec, respectively).
- For both QTcNi and QTcF, moxifloxacin HCl had an UCB >10msec on Day 1 (16.29 and 13.24msec, respectively) and Day 6 (16.93 and 13.97msec, respectively).

PHARMACOKINETIC RESULTS:

- Overall, guanfacine HCl plasma concentrations on Day 6 (suprathereapeutic dose, 8mg) were approximately threefold higher than those on Day 1 (therapeutic dose, 4mg)
- Following oral administration of guanfacine HCl on Day 1 and Day 6, maximum plasma concentrations were attained at a median 3.1 and 5.0 hours post-dose, respectively
- Overall, plasma concentrations for moxifloxacin HCl were similar on Days 1 and 6 (400mg dose on both days)
- Following oral administration of moxifloxacin HCl on Day 1 and Day 6, maximum plasma concentrations were attained at a median 2 hours post-dose for both doses.

SAFETY RESULTS:

- No subjects died during the study
- All subjects receiving guanfacine HCl had at least one treatment-emergent adverse event (TEAE)
- The majority of TEAEs were mild. Severe TEAEs were reported in two subjects
- Adverse events seen were generally consistent with the known pharmacology of guanfacine HCl.
- Five subjects reported six serious adverse events (constipation, ileus, syncope (2), syncope vasovagal, orthostatic hypotension)
- Six subjects had TEAEs leading to discontinuation (dry mouth, asthenia, dizziness, presyncope, syncope, hot flush, hypotension)
- No clinically important laboratory abnormalities occurred
- One subject had a clinically significant abnormality upon physical examination
- There were no outliers of clinical significance for 12-lead ECG results. No subjects had a QTcNi or QTcF of >500msec or an increase of >60msec from baseline. Among guanfacine HCl-treated subjects, no subjects had a prolonged QTcNi or QTcF. Among subjects receiving moxifloxacin HCl, two subjects had a prolonged QTcNi.

Overall Summary:

- This study was valid and showed assay sensitivity using moxifloxacin HCl.
- At concentrations approximately twice the steady state C_{max} of the highest recommended therapeutic dose in pediatric ADHD, guanfacine HCl did not prolong the QT interval after correcting for HR using the individualized correction method, QTcNi.
- Adverse events seen were consistent with the known pharmacology of guanfacine HCL and likely associated with a rapid titration to a supratherapeutic dose of guanfacine HCl.

Date of Report: 14 January 2008