## 2.0 SYNOPSIS

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| **Company:** IMPAX Pharmaceuticals<br>**Finished Product:** IPX056 capsules (extended-release baclofen)<br>**Active Ingredient:** baclofen | Individual Study Table Referring to Part of the Dossier<br>VOLUME:<br>PAGE: | *For National Authority Use Only* |
| **Title of Study:** A Double-blind, Randomized, Placebo- and Active Comparator-controlled, Parallel Group, Multinational Study to Evaluate the Pharmacokinetics and Pharmacodynamics of IPX056 in Subjects with Established Spasticity Resulting from Multiple Sclerosis | | |
| **Protocol Number:** IPX056-B06-03 | | |
| **Investigator(s):** multicenter | | |
| **Study Center(s):** multicenter | | |
| **Publication (reference):** none | | |
| **Study Period:**<br>Date of first enrollment: 27 June 2007<br>Date of last completed: 07 May 2008 | | |
| **Phase of Development:** 3 | | |
| **Objectives:**<br>***Part 1****:* The primary objective of the study was to demonstrate that IPX056 reduces spasticity, measured by Ashworth score, in subjects with multiple sclerosis (MS).<br>The secondary objectives of the study were: (1) To assess the correlation between the pharmacokinetic (PK) and pharmacodynamic (PD) endpoints (Ashworth score); and (2) to quantify the duration of PD effects for IPX056 as well as commercial immediate-release (IR) baclofen tablets in subjects with MS after a single dose.<br>***Part 2****:* In the open-label extension, the objectives were to assess exploratory efficacy parameters including frequency of nighttime awakenings (due to spasm), morning stiffness score, frequency of spasm, spasticity control rating, Multiple Sclerosis Impact Scale (MSIS)-29, and Global Assessment of Efficacy and Tolerability rated by the subject.<br>The safety objective was to monitor the safety of IPX056 throughout the study. | | |

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**Methodology:** This study consisted of 2 parts: Part 1 was a single-dose, double-blind, randomized, placebo- and active comparator-controlled, parallel group (4 dose groups) design containing a single 12-hour evaluation period, and Part 2 was an optional, approximately 9-week open-label extension study which began immediately after the Part 1 procedures were completed.

***Part 1***: Qualified subjects were washed out of antispasticity medications or devices before enrolling into the study. Eligible subjects were randomized to receive 1 of 4 single-dose treatments (placebo, IR baclofen 20 mg, IPX056 20 mg, IPX056 40 mg,). Subjects underwent hourly PD procedures (Ashworth assessments) for 12 hours after dosing. PK blood samples were collected predose and at 1, 2, 3, 4, 5, 6, 7, 8, 10, and 12 hours after dosing on Day 1. Blood samples for safety lab assessments were collected any time after 5 hours postdose. Upon completion of all Part 1 procedures, the subjects had the option to exit the study or to enroll into the open-label extension (Part 2).

***Part 2***: After signing the optional Part 2 ICF, IPX056 was titrated to effect for each subject over an approximately 3-week period. At the end of the 4-week maintenance phase, study treatment was down-titrated or converted to commercial IR baclofen treatment.

**Number of Subjects (planned and analyzed):** A total of 160 subjects were planned and 173 subjects were actually enrolled and randomized in Part 1, the double-blind portion of this study. All 173 subjects were included in the efficacy and safety analyses for Part 1. Of the 173 subjects enrolled in the double-blind portion of the trial, 147 (85%) were treated in Part 2, the open-label extension portion of the study.

**Diagnosis and Main Criteria for Inclusion:** Subjects must have been at least 18 years old with stable MS (no exacerbation within 3 months) and moderate to severe spasticity, defined as Ashworth scores of 2 or more for at least 1 of the 3 lower extremity muscle groups (hip adductor, knee flexor and knee extensor) in the most affected limb, and a total minimum score of 6 for 4 muscle groups (the above 3 plus plantar flexor) on both limbs (maximum total score is 32) during screening and predose on Day 1. The subjects may or may not have been previously treated with IR baclofen or other antispasticity medications, but all such medications were to be washed out prior to study treatment at Visit 1. Detailed inclusion and exclusion criteria are described in the protocol.

**Test Product, Dose and Mode of Administration, Lot Number:** The investigational product in this study was IPX056, an extended-release oral capsule formulation of baclofen. IPX056 was provided in 5 strengths: 10, 20, 30, 35, and 40 mg per capsule. All study medications were taken orally with approximately 240 mL of water.

***Part 1***: In the double-blind portion of the study (Part 1), each subject randomized to IPX056 was administered a single dose of 20 or 40 mg IPX056. The lot number for IPX056 20 mg and 40 mg capsules was 0630021R1.

***Part 2***: During the open-label extension (Part 2), IPX056 was titrated to effect for each subject using a total daily dose of 20 to 105 mg IPX056 per day (10, 20, 30, or 40 mg twice per day, or 30 or 35 mg three times per day). Lot numbers for IPX056 40 mg, 35 mg, 30 mg, 20 mg, and 10 mg capsules were RB06029, PB06306, PB06406, PB06606, and RB06031B-30, respectively.

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**Duration of Treatment:** The total study duration for Part 1 and Part 2 was a maximum of 9 weeks (excluding the predose washout period). The duration for Part 1 (excluding washout period) was 1 day, during which the subject received a single dose of study medication. The treatment period for Part 2 was up to 9 weeks, including a 3-week up-titration period, a 4-week maintenance period, and a down-titration period of up to 11 days.

**Reference Therapy, Dose and Mode of Administration, Lot Number:**

***Part 1***: A single dose of IR baclofen 20 mg was administered orally as the active comparator during Part 1 (the double-blind portion of the study). The commercial IR baclofen tablets, manufactured by IVAX Pharmaceuticals, were over-encapsulated in gelatin capsules to match the investigational product (IPX056) capsules. The lot number for over-encapsulated IR baclofen used in this study was PB00207.

For blinding purposes, each subject simultaneously took three capsules (IR baclofen 20 mg tablet or placebo, IPX056 20 mg or placebo, and IPX056 40 mg or placebo) at Visit 1. Lot numbers for placebos matching IR baclofen, IPX056 20 mg, and IPX056 40 mg were PB00107, PB04106, and PB04006, respectively.

***Part 2***: There was no reference therapy during the Part 2 open-label extension.

**Criteria for evaluation**:

***Part 1:*** Plasma baclofen concentrations were assessed for PK predose and 1, 2, 3, 4, 5, 6, 7, 8, 10, and 12 hours postdose on Day 1. The PD parameter, as well as the primary efficacy parameter, was the total Ashworth score, which was defined as the sum of the Ashworth scores of the four lower extremity muscle groups (hip adductors, knee flexors, knee extensors, and plantar flexors) of both lower limbs. Ashworth score was assessed at 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, and 12 hours after dosing on Day 1. The total Ashworth score was also used for secondary efficacy analyses, including the duration of effect, defined as the number of postdose hourly assessments at which the total Ashworth score was better than the predose score.

***Part 2:*** Exploratory efficacy parameters included: frequency of nighttime awakenings (due to spasm), morning stiffness score, frequency of spasm, spasticity control rating, MSIS-29, and Global Assessment of Efficacy and Tolerability rated by the subject and by the investigator.

***Safety***: Parameters for Parts 1 and 2 included adverse events (AEs), laboratory results, electrocardiograms (ECGs), vital signs, physical exams, and concomitant medication usage.

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**Statistical Methods:**

This trial was planned to have 160 subjects complete Part 1 of the study. Determination of the sample size was based on 90% power, alpha=0.05, and an estimated true mean improvement in total Ashworth score of 0.10 and 1.72 (SD=2.2) for the placebo group and the IPX056 40 mg group, respectively.

***Part 1***: To meet the primary study objective, the total Ashworth score was analyzed in a number of different ways, including a repeated measures analysis of the change from baseline for the 12 hourly total Ashworth score measurements, and the average total Ashworth score over the 12-hour postdose period, adjusted for baseline. This adjustment was done both by analysis of covariance (ANCOVA) with baseline as the covariate, and by analysis of variance (ANOVA) on the change from baseline. For secondary efficacy analysis, the duration of antispasticity effects for each subject was defined as the total number of timepoints at which the total Ashworth score was lower than the baseline (predose) total Ashworth score.

***Part 2***: The exploratory efficacy parameters collected during Part 2 were compared with the values at screening (before washout) and predose on Day 1. All testing was done using paired comparison t-tests.

***Safety:*** Results were tabulated.

**Summary and Conclusions, Part 1:**

*Efficacy:*

- Both IPX056 doses were significantly superior to placebo in reducing the signs and symptoms of spasticity as measured by total Ashworth score.
- The positive control in this study, IR baclofen, was also significantly superior to placebo in reducing symptoms of spasticity as measured by the total Ashworth score.
- Differences from placebo in antispasticity effect appeared to be sustained up to 12 hours after dosing for all three active treatments (i.e., little evidence of active treatments wearing off).

*Safety:*

- The majority of adverse events during Part 1 in the IR baclofen and IPX056 treatment groups were mild or moderate and were either known symptoms of MS or AEs associated with baclofen use. There was no consistent relationship between AE incidence and dose of either IR baclofen or IPX056. No clinically relevant safety laboratory abnormalities or changes in ECG parameters or vital signs were identified, and no substantial differences among treatment groups were observed.

*Pharmacokinetics:*

- The PK of IPX056 in subjects with spasticity resulting from MS was approximately dose-proportional and comparable to those in healthy volunteers.
- Peak plasma concentrations of baclofen were noted later with the 20 mg dose level of IPX056 ($t_{max}$ = 3 hours) compared with the 20 mg dose of IR baclofen ($t_{max}$ = 2 hours), consistent with the extended-release performance of the IPX056 formulation.

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*Pharmacodynamics:*

- There is a correlation between plasma baclofen concentration and its antispasticity effect with an $EC_{50}$ of 209 ng/mL.
- The time course of baclofen PD, as measured using total Ashworth score, has a temporal lag with the measured baclofen PK. The maximum PD effect is noted at approximately 6 hours, later than the time of the peak plasma baclofen concentration (2 to 3 hours) for IR baclofen or IPX056.
- When the data are modeled by parsing the total PD response into a placebo response and a drug effect response, the effect compartment concentration-drug effect relationship is similar for all three drug treatment groups.

**Summary and Conclusions, Part 2:**

*Efficacy:*

- There was a significant improvement from screening to maintenance in the symptoms associated with spasticity for all subjects in the Part 2 open-label extension study.
- Significant improvement was also observed in Part 2 for the subset of subjects who were taking oral IR baclofen prior to enrollment.
- While Part 2 was not conducted as a double-blind comparison, these results are supportive of the efficacy of IPX056 in alleviating the signs and symptoms of spasticity resulting from MS.

*Safety:*

- During the maintenance phase of Part 2, the median daily dose of IPX056 was 50 mg, and 80% of subjects used IPX056 once or twice per day. Adverse events in Part 2 were generally mild or moderate and were either known symptoms of MS or AEs associated with baclofen use. No clinically-relevant patterns of laboratory abnormalities or changes in ECG parameters or vital signs were identified.

**Conclusions:** The IPX056 extended-release oral capsule formulation of baclofen is generally well tolerated in subjects with spasticity resulting from MS. IPX056 appears to provide an extended duration of action as compared with commercially available immediate-release baclofen, which may translate into reduced dosing frequency and sustained relief of spasticity for MS patients.

**Date of Report: 22 April 2009**