

2. SYNOPSIS

Name of Sponsor/Company: Neurocrine Biosciences, Inc.	Individual Study Table Referring to Part of the Dossier	(For National Authority Use Only)
Name of Finished Product: ---	Volume:	
Name of Active Ingredient: NBI-56418	Page:	
Title of Study: A Phase II, Randomized, Double-Blind, Placebo-Controlled Study of NBI-56418 in Endometriosis		
Study Number: NBI-56418-0501		
Study Centers: A total of 18 centers in the United States participated in the study, of which, 16 centers randomized subjects. [REDACTED]		
Publication (reference): None at date of this report.		
Study Period (Years): First subject enrolled to last subject completed: April 22, 2005 to June 5, 2006.		Clinical Phase: II
Objectives: Primary: To explore the effect of NBI-56418 on Composite Pelvic Signs and Symptoms Score (CPSSS) following 12 weeks of treatment. Secondary: <ul style="list-style-type: none">• To evaluate the safety, tolerability and pharmacodynamic (PD) effects of repeated administrations of NBI-56418.• To explore the effect of NBI-56418 on Quality of Life and a Visual Analog Scale (VAS) specific to pelvic pain.• To explore the effect of NBI-56418 on a bone resorption biomarker (N-telopeptide).		
Methodology: This was a Phase II, multicenter, randomized, double-blind, placebo-controlled, parallel-group study conducted in 76 subjects randomized to one of three treatment groups, placebo, 75-mg NBI-56418, and 150 mg NBI-56418 in a 1:1:1 ratio. Study drug was administered once daily (q.d.) for 12 weeks. After the last dose at the end of Week 12, follow-up continued every 4 weeks for 12 weeks. After providing informed consent, subjects underwent screening within 30 days prior to the first dose of study drug. The onset date of menstrual bleeding for the cycle prior to the screening visit was recorded. Subjects completed a VAS for pelvic pain daily, and collected samples of first morning-void urine for analysis of pregnanediol glucuronide/creatinine (PdG/Cr) beginning 4 days before expected onset of menses. Following the onset of menstrual bleeding, subjects returned to the clinic for completion of the baseline assessments, randomization, and initial dosing, which occurred anytime during Days 2 to 7 after the onset of menstrual bleeding. Efficacy assessments using the CPSSS and the Endometriosis Health Profile-5 (EHP-5, a Quality of Life questionnaire) were performed at 4-week intervals. A VAS specific to pelvic pain was also completed daily.		

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<p>Methodology (continued):</p>		
<p>Blood samples for PD assessments (i.e., levels of estradiol [E2]) were collected every 2 weeks during the treatment phase and every 4 weeks during the posttreatment follow-up. In addition, blood samples for N-telopeptide, a bone resorption biomarker, were collected at the beginning of Week 1 and at the end of Weeks 12 and 24.</p>		
<p>Safety assessments, including adverse event (AE) monitoring, clinical laboratory tests, vital signs, physical examinations, e-Diary recording of vaginal bleeding, and electrocardiograms (ECGs), were conducted throughout the study. Evidence of ovulation and onset of menstrual bleeding were assessed upon completion of treatment.</p>		
<p>An electronic diary was provided to subjects to use daily at screening and for the duration of the study. It was used to monitor dosing, any AEs, any hot flashes, any concomitant medication taken, the start and end date of pre- and posttreatment vaginal bleeding (menstrual bleeding or bleeding at any other point of the cycle), and to complete a daily VAS for pelvic pain.</p>		
<p>Number of Subjects (planned and analyzed): This study was to enroll up to 72 female subjects; 76 were randomized (placebo, N=28; NBI-56418 75 mg, N=25; NBI-56418 150 mg, N=23). All randomized subjects were evaluated for the safety and intent-to-treat (ITT) analysis sets. The per protocol (PP) analysis set included 71 subjects.</p>		
<p>Diagnosis and Main Criteria for Inclusion: Female subjects (aged 18 to 49 years) with a laparoscopically confirmed diagnosis of endometriosis (performed within 5 years of screening) and with pelvic pain and dysmenorrhoea (CPSSS \geq 6) were enrolled in this study. Subjects must not have been currently receiving a gonadotropin-releasing hormone (GnRH) agonist or antagonist, or have received these agents within 6 months of screening. In addition, subjects must not have been using steroids or hormonal therapy including the oral contraceptive pill within 3 months of screening.</p>		
<p>Test Products, Doses and Mode of Administration, Batch Number: NBI-56418 is based on the sodium salt and was provided as 25 mg tablets for oral administration (batch numbers KD2004023 and KK2004009). The doses that were used in the study were 75 mg (3 tablets) and 150 mg (6 tablets).</p>		
<p>Duration of Treatment and Study Participation: Subjects were followed for approximately 28 weeks (up to 30 days of screening, 12 weeks of treatment, and approximately 12 weeks of follow-up).</p>		
<p>Reference Therapy, Dose and Mode of Administration, Batch Number: Matching placebo tablets (batch number KK2004011) were orally administered in a double-dummy manner on an identical schedule to those receiving active drug.</p>		
<p>Criteria for Evaluation:</p> <p><u>Efficacy:</u> Efficacy was evaluated based on the CPSSS, the VAS for pelvic pain, and EHP-5. The primary efficacy endpoint was the change from baseline in the Total CPSSS at Week 12. Secondary endpoints included (but were not limited to): change from baseline in the Total CPSSS at Weeks 4 and 8, in Total CPSSS excluding dyspareunia, and in individual CPSSS components (dysmenorrhea, dyspareunia, pelvic pain, pelvic tenderness, pelvic induration); moderate to severe Total CPSSS and for dysmenorrhea, absence of dysmenorrhea at Week 12, change from baseline in monthly peak and monthly mean VAS for pelvic pain, change from baseline in EHP-5 core and modular dimensions, and CPSSS during posttreatment.</p>		

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Criteria for Evaluation (continued): <u>Safety:</u> Safety was evaluated based on AEs, clinical laboratory tests, vital sign measurements, physical examinations, and ECG tracings. Hot flashes, vaginal bleeding, evidence of posttreatment ovulation, and bone resorption biomarker (N-telopeptide) were also assessed. <u>Pharmacodynamics:</u> Serum E2 concentrations were collected.		
Statistical Methods: <u>Efficacy:</u> The change from baseline in the CPSSS (i.e., total and individual sign/symptom scores), monthly peak and mean VAS score, and EHP-5, were analyzed using a repeated measures analysis of covariance (ANCOVA) and/or analysis of variance (ANOVA) model. The purpose of applying these statistical models was to provide point estimates of the change from baseline in CPSSS score (and other listed endpoints) at Week 12 for each treatment group, including placebo, and their corresponding 95% confidence intervals (CIs). The analyses also included the calculation of point estimates, and their corresponding 95% CIs, of the mean difference in the change from baseline in the CPSSS total score (and other endpoints) between each of the NBI-56418 treatment groups and placebo. <u>Safety and Pharmacodynamics:</u> Safety and PD data were summarized with descriptive statistics.		
SUMMARY OF RESULTS: <u>Efficacy Results:</u> For the primary efficacy endpoint, the change from baseline for the Total CPSSS at Week 12 was -3.7, -3.8, and -5.2 for the placebo, NBI-56418 75 mg, and 150 mg groups, respectively, and the improvement in the 150 mg group was different than placebo based on the 95% CI (CI did not span zero). Similarly, the change from baseline for the Total CPSSS excluding dyspareunia at Week 12 and the change from baseline for the Total CPSSS at Week 4 were more improved in the 150 mg group relative to placebo and this improvement was different than placebo based on the 95% CI. A >4 point reduction was observed in the NBI-56418 150 mg group for the measures noted above, which has been established as corresponding to a clinically significant reduction in endometriosis signs and symptoms. Other differences than placebo for secondary efficacy endpoints included: reduction for dysmenorrhea at Week 8 in the 75 mg group and at Weeks 4, 8, and 12 in the 150 mg group, reduction for pelvic induration at Week 8 in the NBI-56418 75 mg group, improvement in pain in the monthly peak VAS for the NBI-56418 75 mg group at Week 4 and the 150 mg group at Weeks 8 and 12, improvement in pain in mean VAS for the NBI-56418 75 mg group at Week 8 and the 150 mg group at Weeks 8 and 12. There were fewer subjects (based on %) with moderate to severe Total CPSSS and dysmenorrhea in the NBI-56418 dose groups at each timepoint relative to placebo, with the exception of Week 8 for Total CPSSS in the 75 mg group. There was a dose-related increase in the percentage of subjects with an absence of dysmenorrhea in NBI-56418 subjects compared to placebo at Week 12. There was a greater improvement in the EHP-5 pain core component in subjects receiving NBI-56418 150 mg compared to placebo.		

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Pharmacodynamic Results:

At baseline (Week 1), median serum E2 concentrations were generally comparable between the placebo (44.3 pg/mL), 75 mg (55.9 pg/mL), and 150 mg (33.7 pg/mL) treatment groups, though some modest baseline differences were observed. In the placebo group, median serum E2 concentrations exhibited an increase at Week 2 (127 pg/mL), consistent with the late follicular/early luteal phase of the menstrual cycle, followed by a nadir at Week 4 (53.5 pg/mL), consistent with the late luteal/early follicular phase. This general pattern was also still somewhat evident at later timepoints, though non-synchronized menstrual cycles among individual placebo treated subjects would be expected particularly by Month 3 and thereafter (Weeks 10 to 24). Median serum E2 concentrations ranged from 53.5 to 127 pg/mL across Weeks 2 to 24 in the placebo group.

In the 150 mg treatment group, median serum E2 concentrations were constrained within a relatively narrow range (37.2 to 48.5 pg/mL) from Weeks 2 to 12. In the 75 mg group, median serum E2 concentrations were less constrained and fell within a relatively wider range (37.3 to 84.9 pg/mL) from Weeks 2 to 12. At Weeks 16 to 24, median serum E2 concentrations ranged from 80.1 to 92.9 and 42.2 to 97.5 pg/mL in the 150 mg and 75 mg treatment groups, respectively, suggesting the return of a normal range of E2 values.

Safety Results:

No deaths were reported during the study and two subjects (both in the NBI-56418 150 mg group) experienced a serious AE (SAE) during the study (anaphylactoid reaction in one subject and calculous cholelithiasis and dehydration in the other subject). One subject (NBI-56418 150 mg) reported an SAE (gastroschisis [of fetus]) detected by ultrasound two months after study completion; conception occurred approximately one month after discontinuation of dosing. Eight subjects were discontinued from the study due to an AE including one subject in the placebo group, six subjects in the NBI-56418 75 mg group, and one subject in the NBI-56418 150 mg group.

The percentage of subjects experiencing AEs was similar among treatment groups. The most common AEs during the treatment phase included headache (24.0%), nausea (20.0%), upper respiratory tract infection (20.0%), and nasopharyngitis (16.0%) in the NBI-56418 75 mg group, and nausea (34.8%), headache (26.1%), diarrhea (17.4%), and fatigue (13.0%) in the NBI-56418 150 mg group. Most AEs were mild or moderate in intensity and considered unlikely or not related to study drug.

The percentage of subjects who reported a hot flash during the treatment phase was similar among treatment groups, although the median of the average number of hot flashes per day was somewhat higher in the NBI-56418 75 mg and 150 mg groups during the treatment phase.

During the treatment and posttreatment phases, there was a dose-related decrease in the number of days with any bleeding in subjects receiving NBI-56418 compared to placebo. There was posttreatment evidence of ovulation within 4 weeks in 88.2% of placebo subjects, 85.7% of NBI-56418 75 mg subjects, and 88.2% of NBI-56418 150 mg subjects with adequate urine samples to detect evidence of ovulation.

Clinical laboratory results, vital sign measurements, and ECG readings throughout the study were unremarkable. Mean values generally remained within normal ranges, and there were no clinically significant changes from baseline. Mean N-telopeptide values were within the normal range for all treatment groups throughout the study and no clinically significant changes were noted.

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CONCLUSIONS: The conclusions of this study are the following: <ul style="list-style-type: none">• Multiple measures of pain including CPSSS (Total CPSSS and dysmenorrhea component score), VAS for pelvic pain, and the EHP-5 pain core component showed improvement in subjects receiving NBI-56418 compared to placebo subjects. More improvement was seen with the 150 mg dose than with the 75 mg dose.• In the placebo group, a relatively wide range of serum E2 concentrations was observed across Weeks 1 to 24, consistent with the normal pattern of menstrual cycles in placebo-treated subjects during the study.• In the 150 mg treatment group, serum E2 concentrations were typically constrained within a relatively narrow range from Weeks 2 to 12. However, in the 75 mg treatment group, serum E2 concentrations were typically less constrained indicating dose-dependent effects. After drug discontinuation in both groups, observed serum E2 concentrations suggested a return of normal cycling.• NBI-56418 was generally well-tolerated at doses of 75 mg and 150 mg when administered as a single daily dose over 12 weeks.• During the treatment and posttreatment phases, there was a dose-related decrease in the number of days with any bleeding in subjects receiving NBI-56418 compared to placebo, and ovulation was detected in >85% of subjects in all treatment groups in the posttreatment phase.• Mean N-telopeptide values were within the normal range for all treatment groups throughout the study, and there were no clinically significant changes noted.		
Date of the Report: August 2, 2007 (Final)		