

## 2. SYNOPSIS

<b>Name of Sponsor/Company:</b> Neurocrine Biosciences, Inc.	<b>Individual Study Table Referring to Part of the Dossier</b>	<b>(For National Authority Use Only)</b>
<b>Name of Finished Product:</b> ---	<b>Volume:</b>	
<b>Name of Active Ingredient:</b> NBI-56418	<b>Page:</b>	
<b>Title of Study:</b> A Phase II, Randomized, Double-Blind, Placebo-Controlled Twice-Daily Dosing Study of NBI-56418 in Endometriosis		
<b>Study Number:</b> NBI-56418-0504		

**Study Centers:** A total of 29 centers in the United States (US) participated in the study, of which, 23 centers randomized subjects. [REDACTED]

**Publication (reference):** None at date of this report.

**Study Period (Years):** First subject enrolled to last subject completed: December 21, 2005 to February 1, 2007.

**Clinical Phase:** II

**Objectives:**

**Primary:**

To explore the effect of 12 weeks of twice-daily (b.i.d.) treatment of NBI-56418 on Composite Pelvic Signs and Symptoms Score (CPSSS) in subjects with endometriosis.

**Secondary:**

- To evaluate the safety, tolerability and pharmacodynamic (PD) effects of repeated administrations of NBI-56418.
- To assess the effect of NBI-56418 on Quality of Life (QoL) and a Visual Analog Scale (VAS) specific to pelvic pain.
- To assess the effect of NBI-56418 on a bone resorption biomarker (N-telopeptide).

**Methodology:** This was a Phase II, multicenter, randomized, double-blind, placebo-controlled study. The study followed a parallel-group design in which 68 subjects were randomized to one of three treatment groups: placebo, NBI-56418 50 mg b.i.d. or NBI-56418 100 mg b.i.d. in a 1:1:1 ratio. Study drug was administered orally b.i.d. for 12 weeks during the treatment phase. After the last dose of study drug (Week 12), follow-up visits continued every 4 weeks for another 12 weeks (Weeks 13 to 24) during the posttreatment phase.

After providing informed consent, subjects underwent screening procedures within 30 days prior to the first dose of study drug. The onset date of menstrual bleeding for the cycle prior to screening was recorded. Subjects completed a VAS for pelvic pain daily during the screening phase. Following screening procedures and the onset of menstrual bleeding, subjects contacted the study center to schedule completion of the baseline assessments and randomization and initial dosing of study drug,

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<p>which occurred anytime during Days 2-7 (inclusive) after the onset of menstrual bleeding.</p>		
<p>At baseline (Day 1 before the first dose of study drug), at Weeks 4, 8, 12 during the treatment phase, and at Weeks 16, 20, and 24 during the posttreatment phase, efficacy, safety, and tolerability were assessed.</p>		
<p>Efficacy assessments using the CPSSS and the Endometriosis Health Profile-5 (EHP-5, a QoL questionnaire) were performed at 4-week intervals. A VAS specific to pelvic pain was completed daily.</p>		
<p>Blood samples for the PD measurement, estradiol (E2), were obtained every 2 weeks beginning at baseline (Day 1 predose) during the treatment phase and every 4 weeks during posttreatment follow-up. In addition, blood samples for N-telopeptide, a bone resorption biomarker, were collected at baseline (Day 1 predose), Week 12 (end of treatment phase), and Week 24 (end of posttreatment phase).</p>		
<p>Safety assessments (clinical safety laboratory tests, vital sign measurements, physical examinations, return to menses and ovulation, and electrocardiograms [ECGs] recordings) were conducted at scheduled times throughout the study. Adverse events (AEs) and the use of concomitant medications were monitored from the time of informed consent through the final visit (Week 24). Posttreatment menses and ovulation were further assessed upon completion of treatment.</p>		
<p>An electronic diary (e-Diary) was provided to subjects to use daily at screening and for the duration of the study. It was used for the collection of pain score information (VAS), to record any vaginal bleeding (menstrual bleeding or bleeding at any other point of the cycle), and to record the occurrence of hot flashes experienced. Additionally the diary reminded the user to take their study drug, report AEs, and to report the use of any concomitant medication.</p>		
<p><b>Number of Subjects (planned and analyzed):</b> This study planned to enroll up to 72 female subjects, and 68 subjects were randomized, including 20 subjects in the placebo group, 23 subjects in the NBI-56418 50 mg b.i.d. group, and 25 subjects in the NBI-56418 100 mg b.i.d. group. All randomized subjects were evaluated for the safety analysis set. The intent-to-treat (ITT) analysis set included 65 subjects and per protocol (PP) analysis set included 63 subjects.</p>		
<p><b>Diagnosis and Main Criteria for Inclusion:</b> Female subjects (aged 18 to 49 years) with a laparoscopically confirmed diagnosis of endometriosis (performed within 7 years of screening) and with pelvic pain and dysmenorrhea (CPSSS <math>\geq</math> 6) were enrolled. Subjects were not concurrently receiving a gonadotropin-releasing hormone (GnRH) agonist or antagonist, and had not received these agents within 6 months of screening. In addition, subjects were not using steroids or hormonal therapy including oral contraceptives within 3 months of screening.</p>		
<p><b>Test Products, Doses and Mode of Administration, Batch Number:</b> NBI-56418 is based on the sodium salt and was provided as 50 mg tablets for oral administration (batch number KE2005028). The 50 mg b.i.d. dose (one 50 mg NBI-56418 tablet and one placebo tablet b.i.d.) and the 100 mg b.i.d. dose (two 50 mg NBI-56418 tablets b.i.d.) were studied.</p>		
<p><b>Duration of Treatment and Study Participation:</b> Subjects were followed for approximately 28 weeks (up to 30 days of screening, 12 weeks of treatment, and 12 weeks of posttreatment follow-up).</p>		
<p><b>Reference Therapy, Dose and Mode of Administration, Batch Number:</b> Matching placebo tablets (batch number KE2005030) were orally administered in a double-dummy manner on an identical schedule to active drug.</p>		

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**Criteria for Evaluation:**

Efficacy: Efficacy was evaluated based on the CPSSS, VAS for pelvic pain, and EHP-5. The primary efficacy endpoint was the change from baseline (CFB) in the Total CPSSS at Week 12 (end of the treatment phase). Secondary endpoints included (but were not limited to): CFB 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, CFB in monthly peak and monthly mean VAS for pelvic pain, CFB in EHP-5 core and modular dimensions, and CPSSS during posttreatment.

Safety: Safety was evaluated based on AEs, clinical laboratory tests, vital sign measurements, physical examinations, and ECG recordings. Vaginal bleeding, evidence of posttreatment ovulation, and bone resorption biomarker (N-telopeptide) were also assessed.

Pharmacodynamics: Serum E2 concentrations were collected.

**Statistical Methods:**

Efficacy: The CFB in the CPSSS (i.e., total and individual sign/symptom scores), monthly peak and mean VAS score for pelvic pain, 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 CFB 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 CFB in the CPSSS total score (and other endpoints) between each of the NBI-56418 treatment groups and placebo.

Safety and Pharmacodynamics: Safety and PD data were summarized with descriptive statistics.

**SUMMARY OF RESULTS:**

Efficacy Results:

For the primary efficacy endpoint, the CFB for the Total CPSSS at Week 12 was -4.5, -4.4, and -5.9 for the placebo, NBI-56418 50 mg b.i.d., and 100 mg b.i.d. groups, respectively. Although all three treatment groups demonstrated a clinically meaningful improvement over baseline in Total CPSSS (reduction in mean value from baseline of at least 4 points based on literature references) the NBI-56418 100 mg b.i.d. group had a nearly 1.5 point improvement compared to placebo. Similarly, the CFB in Total CPSSS excluding dyspareunia at Week 12 and the CFB in Total CPSSS at Week 4 were more improved in the NBI-56418 100 mg b.i.d. group relative to placebo at these timepoints.

A smaller percentage of subjects with moderate to severe dysmenorrhea were in the NBI-56418 100 mg b.i.d. group compared to placebo at Weeks 4, 8, and 12. There was a dose-related increase in the percentage of subjects with an absence of dysmenorrhea in the NBI-56418 groups compared to the placebo group at Week 12. The negative CFB in monthly peak VAS for pelvic pain observed for the NBI-56418 100 mg b.i.d. group was greater than the placebo group CFB by 17.6, 22.4, and 12.9 points (based on difference in Least Squares means [LS means]) at Weeks 4, 8, and 12, respectively.

Pharmacodynamic Results:

Baseline values were generally comparable among the placebo (41.0 pg/mL), NBI-56418 50 mg b.i.d. (44.45 pg/mL), and NBI-56418 100 mg b.i.d. (31.1 pg/mL) treatment groups. In the placebo group,

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<p>median serum E2 concentrations exhibited an increase at Week 2 (96.2 pg/mL), consistent with the late follicular/early luteal phase of the cycle, followed by a nadir at Week 4 (35.1 pg/mL), consistent with the late luteal/early follicular phase. This general pattern was also evident at later timepoints in the placebo group (median serum E2 concentrations ranged from 35.1 to 107 pg/mL across Weeks 2 to 24), though synchronized menstrual cycles among individual placebo-treated subjects would not be expected particularly by Month 3 and thereafter (Weeks 10 to 24).</p> <p>During the treatment phase (Weeks 2 to 12) median E2 serum concentrations were maintained in the range of approximately 30 to 45 pg/mL in the NBI-56418 50 mg b.i.d. group and 13 to 23 pg/mL in the 100 mg b.i.d. group. During the posttreatment phase (Weeks 16 to 24), median serum E2 concentrations ranged from 99.7 to 66.8 pg/mL in the NBI-56418 50 mg b.i.d. group suggesting the return of a normal range of E2 levels. Median E2 serum concentrations in the NBI-56418 100 mg b.i.d. group increased during the posttreatment phase relative to the treatment phase, ranging from 36.3 to 61.8 pg/mL.</p>		
<p><u>Safety Results:</u></p> <p>There were no deaths in this study. Overall, three subjects had an SAE during the study, including one subject in the NBI-56418 100 mg b.i.d. group (endometriosis; reported term: endometriosis pain total abdominal hysterectomy) during the treatment phase and one subject in the placebo group (appendicitis) and one subject in the NBI-56418 100 mg b.i.d. group (endometriosis; reported term: worsening of endometriosis pain leading to hysterectomy) during the posttreatment phase.</p> <p>Five subjects discontinued the study due to an AE, including two subjects in the NBI-56418 50 mg b.i.d. group and two subjects in the NBI-56418 100 mg b.i.d. group during the treatment phase and one subject in the NBI-56418 100 mg b.i.d. group during the posttreatment phase.</p> <p>The incidence of treatment emergent AEs (TEAEs) during the treatment phase was similar across all treatment groups, with 85.0%, 91.3%, and 88.0% of subjects experiencing a TEAE in the placebo, NBI-56418 50 mg b.i.d., and NBI-56418 100 mg b.i.d. groups, respectively. Most AEs were reported in the Infections and Infestations, Nervous System Disorders, and Gastrointestinal Disorders system organ classes. The most commonly occurring TEAE was headache in the placebo, NBI-56418 50 mg b.i.d., and NBI-56418 100 mg b.i.d. groups (15.0%, 34.8%, and 36.0%, respectively). Additional common events that occurred more frequently in the NBI-56418 50 mg b.i.d. group than placebo included pain (8.7% versus no subjects). In the NBI-56418 100 mg b.i.d. group, these events included dizziness (20.0% versus 5.0%), nausea (16.0% versus 10.0%), and nasopharyngitis (12.0% versus 5.0%). There was a slightly higher incidence of AEs in the NBI-56418 groups compared to placebo during the posttreatment phase (70.0% and 66.7% for 50 mg b.i.d. and 100 mg b.i.d., respectively, versus 52.9% for placebo), although no AE was experienced by more than two subjects within any treatment group.</p> <p>The percentage of subjects reporting at least one hot flash in response to daily e-Diary questioning during treatment or posttreatment was 60.0%, 73.9%, and 76.0% for the placebo, NBI-56418 50 mg b.i.d., and NBI-56418 100 mg b.i.d. groups, respectively. The median of the average number of hot flashes per day was slightly higher in the NBI-56418 50 mg b.i.d. and 100 mg b.i.d. groups compared to placebo during the treatment phase, but similar among treatment groups during the posttreatment phase.</p> <p>During the treatment phase, there was a dose-related decrease in the median number of days with any bleeding in subjects receiving NBI-56418 vs. placebo. There was posttreatment evidence of ovulation</p>		

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<p>within 4 weeks in 93.3% of subjects in the placebo group, 93.8% in the NBI-56418 50 mg b.i.d. group, and 81.3% in the NBI-56418 100 mg b.i.d. group with adequate urine samples to detect evidence of ovulation.</p> <p>Clinical laboratory results, vital sign measurements, and ECG recordings throughout the study were unremarkable, and in general, there were no important differences among the treatment groups for these safety parameters. Mean values generally remained constant throughout the study, and there were no clinically significant changes from baseline, with the exception of elevated creatine kinase at various timepoints. Overall, these elevations were asymptomatic and self-limited. No important differences were noted among the treatment groups for mean N-telopeptide values at any timepoint throughout the study, and there was no biomarker evidence suggestive of bone loss up to 12 weeks posttreatment.</p>		
<p><b>CONCLUSIONS:</b> The conclusions of this study are the following:</p> <ul style="list-style-type: none"><li>• 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 100 mg b.i.d. compared to placebo.</li><li>• In subjects who received placebo, a relatively wide range of serum E2 concentrations was observed across Weeks 1 to 24, consistent with the normal pattern of menstrual cycles.</li><li>• In the NBI-56418 50 mg b.i.d. and 100 mg b.i.d. treatment groups, median serum E2 concentrations were typically constrained within a relatively narrow range from Weeks 2 to 12 during the treatment phase. Median serum E2 concentrations in the NBI-56418 100 mg b.i.d. group were lower compared to the 50 mg b.i.d. group indicating dose-dependent effects of NBI-56418. After drug discontinuation in both groups during the posttreatment phase (Weeks 16 to 24), median serum E2 concentrations increased, suggesting a return to a near normal range of E2 concentrations.</li><li>• NBI-56418 was generally well-tolerated when administered as 50 mg b.i.d. or 100 mg b.i.d. over 12 weeks.</li><li>• During the treatment phase, there was a dose-related decrease in the median number of days with any bleeding in subjects receiving NBI-56418 compared to placebo, and ovulation was detected within 4 weeks posttreatment in &gt;80% of subjects in all treatment groups with adequate urine samples to detect evidence of ovulation.</li><li>• No important differences were noted among the treatment groups for mean N-telopeptide values at any timepoint throughout the study, and there was no biomarker evidence suggestive of bone loss up to 12 weeks posttreatment.</li></ul>		
<b>Date of the Report:</b> November 25, 2008		