2. SYNOPSIS

Name of Sponsor/Company: Neurocrine Biosciences, Inc. **Name of Finished Product:** --- **Name of Active Ingredient:** NBI-56418	**Individual Study Table Referring to Part of the Dossier** **Volume:** **Page:**	**(For National Authority Use Only)**
Title of Study: A Phase 2, Randomized, Double-Blind, Placebo-Controlled Study to Assess the Efficacy and Safety of NBI-56418 Na in Subjects with Endometriosis		
Study Number: NBI-56418-0901		
[redacted]		
Study Centers: A total of 37 centers in the United States, 35 of which enrolled subjects. [redacted]		
Publication (reference): None at date of this report.		
Study Period (Years): First subject randomized to last subject completed: October 12, 2009 to September 22, 2010.	**Clinical Phase:** 2	
Objectives: **Primary:** To evaluate the efficacy of 150 mg once-daily dose of NBI-56418 in the treatment of pelvic pain due to endometriosis **Secondary:** To evaluate the safety of repeated daily administration of 150 mg NBI-56418.		
Methodology: This was a Phase 2, multicenter, randomized, double-blind, placebo-controlled parallel group study to assess the efficacy and safety of 150 mg NBI-56418 Na (referred to in this report as NBI-56418) administered once daily (q.d.) for up to 24 weeks. In total, 137 subjects were randomized (1:1) to 150 mg NBI-56418 q.d. or placebo q.d. for the first 8 weeks of dosing. Following 8 weeks of dosing, subjects continued in the study for an additional 16 weeks in an open-label phase where all subjects still enrolled in the study received 150 mg q.d. NBI-56418. Six weeks after the last dose of study drug at the end of Week 24, a follow-up visit was performed (end of Week 30). Screening Phase: After providing informed consent, subjects underwent screening for 4 weeks (Weeks -4 to -1) to ensure eligibility to participate in the study. Screening started 2 to 5 days (inclusive) after the onset of menses. Subjects who were using hormonal contraception or other hormonal therapies for endometriosis entered a 1-month wash-out prior to the start of the screening assessments. The Composite Pelvic Signs and Symptoms Score (CPSSS) and the Endometriosis Health Profile-5 (EHP-5), a Quality of Life (QoL) questionnaire, were administered at the screening visit. During the 4-week screening phase, subjects completed daily assessments of dysmenorrhea, dyspareunia, and nonmenstrual pelvic pain via an electronic diary (e-Diary).		

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Treatment Phase: Subjects returned to the study center at the beginning of Week 1 for the collection of baseline assessments and randomization to one of two treatment groups (150 mg NBI-56418 q.d. or placebo q.d.) provided that they had completed the 4-week screening assessment and it was 2 to 5 days (inclusive) after the onset of menses. Subjects took study drug daily and completed the e-Diary, which included daily assessments of dysmenorrhea, dyspareunia, and nonmenstrual pelvic pain, daily during the 24-week treatment phase.

Subjects returned to the study center for visits at 4-week intervals during treatment (at the end of Weeks 4, 8, 12, 16, 20, and 24). At the end of Week 8, all subjects still enrolled in the study participated in the open-label phase of the study and received 150 mg NBI-56418 q.d. for 16 weeks.

Follow-up Phase: A follow-up visit occurred approximately 6 weeks after completion of the 24-week treatment (final study visit; end of Week 30 or early termination).

An e-Diary was provided to use daily at the start of the screening phase (2 to 5 days after the onset of menses) and for the duration of the study. The e-Diary was used to record on a daily basis dysmenorrhea, dyspareunia, and nonmenstrual pelvic pain assessments based upon modifications to the Biberoglu and Behrman scale. The e-Diary was also used to record vaginal bleeding (menstrual bleeding or bleeding at any other point of the cycle) and use of over-the-counter and prescription analgesics for endometriosis on a daily basis. The e-Diary also provided prompts to remind subjects to call the site if any unusual signs or symptoms developed and to report any changes in medications or taking of new medications. The e-Diary was completed in the morning prior to arrival at the clinic for the monthly visit assessments.

Efficacy assessments consisting of dysmenorrhea, nonmenstrual pelvic pain, and dyspareunia assessments were completed daily using an e-Diary. Analgesic use for endometriosis was documented daily throughout the study (during screening, treatment, and follow-up) using an e-Diary. The EHP-5 was performed at screening, at the beginning of Week 1, at 4-week intervals during treatment and at the end of Week 30 (or early termination). The Patient Global Impression of Change (PGIC) was performed at 4-week intervals starting at the end of Week 4 through the end of Week 30 (or early termination). In addition, all components of the CPSSS were assessed at screening, during treatment at the end of Weeks 8 and 24, and during follow-up at the end of Week 30 (or at early termination).

Safety was assessed throughout the study based on monitoring of adverse events (AEs), clinical laboratory tests, vital signs, physical examinations, vaginal bleeding, and electrocardiograms (ECGs).

Number of Subjects (planned and analyzed): This study planned to enroll approximately 80 female subjects (this was increased to 120 in Protocol Amendment No. 2, dated October 23, 2009), and 137 subjects were randomized, including 68 subjects in the NBI-56418 150 mg q.d. group and 69 subjects in the placebo group. All randomized subjects were evaluated for the safety analysis set. The intent-to-treat (ITT) analysis set included 132 subjects and the per protocol (PP) analysis set included 129 subjects.

Diagnosis and Main Criteria for Inclusion: Female subjects (aged 18 to 49 years) with a laparoscopically or laparotomically confirmed diagnosis of endometriosis (performed within 8 years of screening) and at least moderate nonmenstrual pelvic pain and dysmenorrhea. Subjects were required to meet all inclusion and exclusion criteria in order to be randomized.

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Test Products, Doses and Mode of Administration, Batch Number: NBI-56418 is based on the sodium salt and was provided as 150 mg tablets for oral administration (batch number 1550.001). The 150 mg q.d. dose was administered daily during treatment.

Duration of Treatment and Study Participation: Subjects were followed for approximately 10 months: up to 8 weeks of screening plus a 1-month wash-out prior to screening for subjects who were using hormonal contraception or other hormonal therapies for endometriosis; a 24-week treatment phase, and a 6-week posttreatment phase.

Reference Therapy, Dose and Mode of Administration, Batch Number: Matching placebo tablets (batch number 1551.001) were orally administered in a double-dummy manner on an identical schedule to active drug.

Criteria for Evaluation:

Efficacy: Efficacy assessments included daily measures of nonmenstrual pelvic pain, dysmenorrhea, and dyspareunia, the CPSSS, analgesic use for endometriosis pain, a QoL assessment as measured by the EHP-5, and PGIC.

The efficacy endpoints for this study were based on both e-Diary and case report form (CRF) data collected through Week 30 of the study.

Safety: Safety was evaluated based on AEs, clinical laboratory tests, vital sign measurements, physical examinations, and ECG recordings. Vaginal bleeding and confirmation of menses posttreatment were also assessed.

Statistical Methods:

Efficacy: Efficacy data were summarized with descriptive statistics and graphs. Comparisons among treatment groups were performed using mixed models, analyses of variance and chi-squared tests. Changes from baseline were tested for significance using t-tests.

Safety: Safety data were summarized with descriptive statistics.

SUMMARY OF RESULTS:

Efficacy Results:

- The monthly means of the daily Dysmenorrhea assessment in both treatment groups at baseline were comparable (2.098 and 2.086 for the placebo and NBI-56418 groups, respectively) and reflected moderate dysmenorrhea. The monthly mean Dysmenorrhea scores decreased from baseline in both treatment groups at Week 8 (-0.37 for placebo and -1.13 for NBI-56418) and this decrease was statistically significantly larger for the NBI-56418 treatment group compared to placebo ($p<0.0001$).
- Monthly means for the daily Dysmenorrhea assessment were lower than baseline in both double-blind treatment groups throughout the open-label treatment phase with the lowest scores observed at Week 16 (0.784) for the placebo group and Week 24 (0.690) for the NBI-56418 groups.
- The monthly mean of the daily Nonmenstrual Pelvic Pain assessment was slightly higher for the NBI-56418 subjects compared to placebo subjects at baseline (1.433 vs. 1.299) but both scores reflect mild to moderate nonmenstrual pelvic pain. Monthly mean Nonmenstrual Pelvic Pain decreased from baseline in both treatment groups at Week 8 (-0.19 for placebo and -0.47 for NBI-56418) and this decrease was statistically significantly larger for the NBI-56418 treatment

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group compared to placebo ($p<0.05$).

- During the open-label treatment phase, monthly means for the daily Nonmenstrual Pelvic Pain assessment were lower than baseline in both double-blind treatment groups with the lowest mean scores observed at Week 24 (0.754 and 0.648 for the placebo and NBI-56418 groups, respectively).
- The monthly mean of the Cumulative Pain score, which includes all daily Dysmenorrhea and Nonmenstrual Pelvic Pain scores, was slightly higher for the NBI-56418 subjects compared to placebo subjects at baseline (1.57 vs. 1.47). The monthly mean Cumulative Pain score decreased from baseline in both treatment groups at Week 8 (-0.21 for placebo and -0.55 for NBI-56418) and this decrease was statistically significantly larger for the NBI-56418 treatment group compared to placebo ($p<0.05$).
- During the open-label treatment phase, monthly means for the Cumulative Pain score were lower than baseline in both double-blind treatment groups with the lowest mean scores observed at Week 24 (0.813 and 0.697 for the placebo and NBI-56418 groups, respectively).
- The monthly mean of the daily Dyspareunia assessment was slightly higher at baseline for the NBI-56418 group compared to the placebo group (1.581 vs. 1.335). Monthly mean Dyspareunia scores decreased from baseline in both treatment groups at Week 8 (-0.23 for placebo and -0.61 for NBI-56419) and these decreases were statistically significantly larger for the NBI-56418 treatment group compared to placebo ($p<0.05$).
- The percentage of days with any analgesic use was comparable at baseline between the placebo and NBI-56418 groups. Decreases from baseline were observed for both groups at Week 8 (-9.19 for placebo and -21.63 for NBI-56418); the decrease was statistically significantly larger for the NBI-56418 group compared to placebo ($p<0.05$). Similar trends were observed with the percentage of days of prescription and narcotic analgesic use during the double-blind treatment phase.
- The Total CPSSS and the CPSSS components were similar between the placebo and NBI-56418 groups at screening. At the end of the double-blind treatment phase (Week 8), the Total CPSSS decreased 4.45 points from baseline in the NBI-56418 group compared to a decrease of 2.19 points in the placebo group, a statistically significant difference ($p<0.0001$). Among the CPSSS components, the largest difference between placebo and NBI-56418 was observed at Week 8 for dysmenorrhea (-1.05; $p<0.001$).
- Scores for the PGIC were statistically significantly lower ($p<0.5$) in the NBI-56418 group compared to placebo at Week 8 and were consistent with much improvement to minimal improvement.
- The percentage of subjects with PGIC responses of Much Improved or Very Much Improved was approximately two-fold higher in the NBI-56418 subjects (60.3%) compared to placebo subjects (30.2%) at Week 8 during the double-blind treatment phase.
- Baseline EHP-5 scores were slightly higher in the NBI-56418 group compared to the placebo group for each core dimension. During the double-blind treatment phase, there were decreases from baseline for each EHP-5 core dimension in both treatment groups, but the decreases were approximately 1.7- to 3.3-fold larger for the NBI-56418 treatment group compared to placebo.
- Statistical comparisons between the NBI-56418 150 mg q.d. and placebo treatment groups EHP-5 Pain core dimension CFB scores indicated that improvement from baseline was statistically significantly larger for the NBI-56418 treatment group compared to placebo at the

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end of the double-blind treatment phase (Week 8) (-28.25 vs.-13.02; p<0.001).

- For the Dysmenorrhea, Nonmenstrual Pelvic Pain, and Dyspareunia assessments the percentage of responders was higher in the NBI-56418 group compared to the placebo group at nearly every responder threshold evaluated. For the Nonmenstrual Pelvic Pain assessment, response rates were higher in the NBI-56418 group compared to the placebo group for response rate thresholds ranging from 10% to 40%. The percentage of subjects with ≥50% decrease from baseline was relatively low and comparable in both groups.
- Mean decreases from baseline at Week 8 (indicating improvement) were greater for every assessment in NBI-56418 subjects compared to placebo subjects, regardless of previous study status; however, greater decreases were consistently observed in the subjects with previous NBI study participation.

Safety Results:

- No deaths were reported during the study. There were treatment-emergent SAEs reported for six subjects during the study: depression suicidal in a placebo subject; abortion spontaneous in a placebo subject, abortion spontaneous in a placebo/NBI-56418 subject, abdominal pain lower in a placebo/NBI-56418, bipolar disorder in a placebo/NBI-56418 subject, and convulsion in a placebo/NBI-56418 subject (SAE occurred during placebo treatment).
- Seven subjects discontinued from the study due to a treatment-emergent adverse event (TEAE). One placebo subject (due to depression suicidal) and three NBI-56418 subjects discontinued due to a TEAE during the double-blind treatment phase (one due to abdominal pain upper; one due to fatigue and hot flush; and one due to nausea and vomiting). Two NBI-56418 subjects (one due to nausea and one due to fatigue, headache, and weight gain) and one placebo/NBI-56418 subject (due to headache, nausea, and vaginal mycosis) discontinued due to a TEAE during the open-label treatment phase.
- During the double-blind treatment phase, the incidence of TEAEs was nearly the same between the placebo (49.3%) and NBI-56418 (51.5%) treatment groups. The most commonly reported TEAEs in the NBI-56418 group were hot flush (10.3%), nausea (7.4%), and upper respiratory infection (7.4%).
- During the 24-week treatment phase, the most common TEAEs in subjects who received NBI-56418 (double-blind and open-label) were nausea, headache, and hot flush, each occurring in 9.9% of subjects.
- Clinical laboratory results, vital sign measurements, and ECG readings throughout the study were unremarkable, and in general, there were no important differences between the treatment groups. Mean values generally remained relatively constant throughout the study, and there were no clinically significant changes from baseline.
- In the NBI-56418 group, the percent of days with any vaginal bleeding decreased from approximately 23% during screening to approximately 14% during the double-blind treatment phase. In contrast, the mean percent of days with any vaginal bleeding was nearly identical during the screening and double-blind treatment phases (approximately 24%) for subjects randomized to receive placebo. The decrease in the percent of days with any vaginal bleeding observed in the NBI-56418 group was due primarily to reductions in the percent of days with moderate bleeding to 3.13% during Weeks 1-8 from 6.29% during screening and in the percent of days with heavy bleeding to 2.36% during Weeks 1-8 from 5.83% during screening.

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- Five subjects became pregnant during the study. Three subjects (two NBI-56418 and one placebo) became pregnant during the treatment phase: one subject (placebo) experienced a spontaneous abortion, and two subjects (both NBI-56418) delivered healthy infants. Two subjects became pregnant during the posttreatment phase: one subject (placebo/NBI-56418) experienced a spontaneous abortion and one (NBI-56418) delivered a healthy infant.

CONCLUSIONS:
The conclusions of this study are the following:

- The daily efficacy assessments of dysmenorrhea and nonmenstrual pelvic pain used in this study reflected moderate pain at baseline. During the double-blind treatment phase, the NBI-56418 150 mg group experienced statistically significantly greater improvement from baseline for these measures compared to the placebo group.
- Multiple measures of endometriosis symptoms including a daily assessment of dyspareunia, endometriosis analgesic use, the CPSSS, the PGIC, and EHP-5 showed improvement in subjects receiving NBI-56418 150 mg compared to placebo during the double-blind treatment phase.
- NBI-56418 was generally well-tolerated when administered as 150 mg q.d. for 24 weeks with few subjects experiencing SAEs or discontinuing due to a treatment-emergent AE.

Date of the Final Report: June 7, 2011