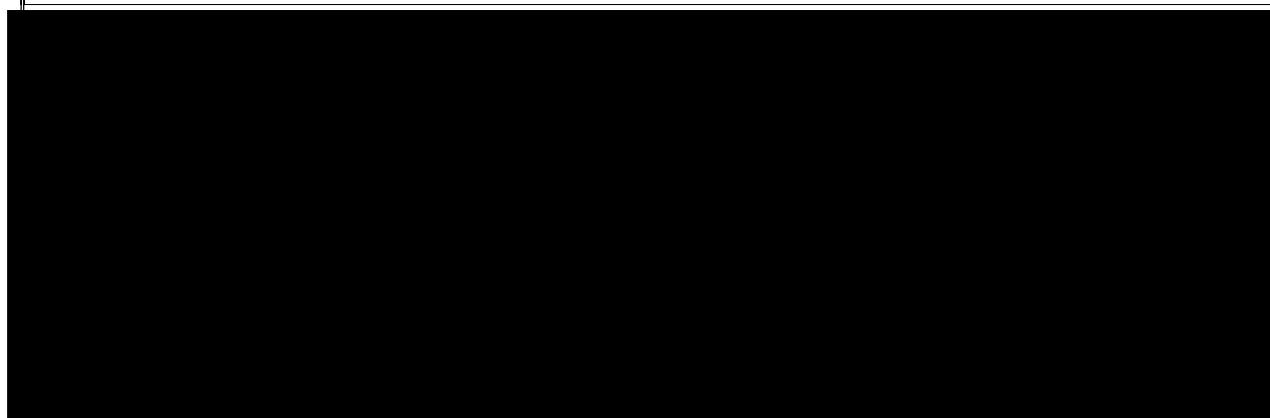


2. SYNOPSIS

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 2, Randomized, Double-Blind, Placebo-Controlled Study to Assess the Efficacy and Safety of NBI-56418 in Subjects with Endometriosis		
Study Number: NBI-56418-0702		



Study Centers: A total of 50 centers in the United States (US) participated in the study, of which 41 centers randomized subjects. [REDACTED]	
Publication (reference): None at date of this report.	
Study Period (Years): First subject enrolled to last subject completed: February 19, 2008 to August 28, 2009.	Clinical Phase: II
Objectives: Primary: To evaluate the efficacy of 150 mg and 250 mg once-daily doses of NBI-56418 in the treatment of pelvic pain due to endometriosis. Secondary: <ul style="list-style-type: none">To evaluate the safety of repeated daily administration of 150 mg and 250 mg NBI-56418.To evaluate the effect of NBI-56418 treatment on bone mineral density (BMD) following 6 months of treatment with NBI-56418.	
Methodology: This was a Phase 2, multicenter, randomized, double-blind, placebo-controlled parallel-group study to assess the efficacy and safety of NBI-56418 at two dose levels (150 mg and 250 mg) administered once daily for up to 6 months. There were 155 subjects randomized (1:1:1) to one of the following treatment groups for the first 12 weeks of dosing: NBI-56418 150 mg q.d.; NBI-56418 250 mg q.d; or placebo q.d. Following 12 weeks of dosing, subjects continued in the study for an additional 12 weeks of dosing; subjects randomized to NBI-56418 continued to receive their assigned dose and subjects randomized to placebo were re-randomized to receive one of the two doses of NBI-56418 (150 mg or 250 mg) for 12 weeks in a double-blind fashion. Blinding was achieved using a double-dummy design. Six weeks after the last dose of study drug at the end of Week 24, a follow-up	

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Name of Finished Product: ---	Volume:	
Name of Active Ingredient: NBI-56418	Page:	

visit was performed (end of Week 30). Subjects whose BMD, as measured by dual energy X-ray absorptiometry (DXA), at the end of Week 24 had decreased more than 3% from screening was required to have an additional DXA scan at 6 months posttreatment.

After providing informed consent, subjects underwent screening for up to 8 weeks (Weeks -8 to -1) to ensure eligibility to participate in the study. 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. During screening, a single-blind placebo lead-in of approximately 4 weeks was started 2 to 5 days (inclusive) after the onset of menses. Initial screening assessments were performed before subjects entered the placebo lead-in. 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 placebo lead-in, subjects took placebo daily and completed daily assessments of dysmenorrhea and nonmenstrual pelvic pain and a numerical rating scale (NRS) for endometriosis pain via electronic diary (e-Diary).

Subjects returned to the study center at the beginning of Week 1 for the collection of baseline assessments and randomization to one of three treatment groups (NBI-56418 150 mg q.d., NBI-56418 250 mg q.d, or placebo q.d.) provided that the subject had completed the placebo lead-in and it was 2 to 5 days (inclusive) after the onset of menses. Subjects took the double-blind study drug and completed the e-Diary daily during the 24-week treatment phase. Study drug (including placebo lead-in) was taken on an empty stomach (1 hour before or 2 hours after a meal).

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 12, subjects receiving placebo were-randomized to one of the NBI-56418 treatment groups, while those subjects who were randomized to receive NBI-56418 at Week 1 continued with their current treatment assignment until the end of Week 24.

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). If a subject's BMD at the end of Week 24 had decreased more than 3% from screening, the subject was required to have an additional DXA scan at 6 months posttreatment.

An e-Diary was provided to use daily at the start of the single-blind placebo lead-in (2 to 5 days after the onset of menses) and for the duration of the study. The e-Diary was used to record the dysmenorrhea and nonmenstrual pelvic pain assessments, the NRS for endometriosis pain, vaginal bleeding (menstrual bleeding or bleeding at any other point of the cycle), any occurrence and intensity of hot flashes, and use of over-the-counter and prescription analgesics for endometriosis. The e-Diary also provided prompts to remind subjects to call the site if any unusual signs or symptoms developed and to remind subjects to continue dosing.

Efficacy assessments consisting of dysmenorrhea and nonmenstrual pelvic pain assessments, an NRS specific to endometriosis pain, and analgesic use for endometriosis were completed daily throughout the study (during the placebo lead-in at screening, treatment, and follow-up) using an e-Diary. The EHP-5 was performed at screening, at 4-week intervals during treatment and at the end of Week 30 (or early termination) following treatment. In addition, the dyspareunia component of the CPSSS and a Patient Global Impression of Change (PGIC) questionnaire were completed at 4-week intervals during treatment and at the end of Week 30 (or early termination) following treatment.

Blood samples for pharmacodynamic (PD) and pharmacokinetic (PK) assessments were collected throughout the study. Serum samples for estradiol (E2) were collected at baseline (beginning of

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<p>Week 1) and every 4 weeks during the treatment phase and at the follow-up visit (Week 30 or early termination). Serum samples for luteinizing hormone (LH), follicle stimulating hormone (FSH), progesterone, and testosterone were collected at baseline (beginning of Week 1) and at the end of Weeks 12 and 20. Plasma samples for PK were collected at the beginning of Week 1 and during the treatment phase at the end of Weeks 4, 12 and 20.</p> <p>Safety was assessed throughout the study based on monitoring of adverse events (AEs), clinical laboratory tests, vital signs, physical examinations, vaginal bleeding, hot flashes, and electrocardiograms (ECGs). Evidence of ovulation posttreatment was also assessed.</p> <p>To monitor BMD, DXA scans of the femur and spine were acquired at screening and at the end of Weeks 12 and 24 (and 48 as needed). Blood samples for N-telopeptide, a bone resorption biomarker, were collected at screening, during treatment at the end of Weeks 12 and 24, and during follow-up (Week 30 or early termination). Bone-specific alkaline phosphatase was analyzed as part of clinical chemistry at baseline (beginning of Week 1) and at the end of Weeks 12 and 24.</p> <p>At Week 12, an optional transvaginal ultrasound was conducted for subjects who were willing to participate in the assessment. The procedure assessed the total number and size of follicles ≥ 10 mm, endometrial thickness, and volume of the ovaries.</p> <p>A sub-study to evaluate RNA and protein expression was also conducted. Sub-study participation was optional. For subjects who agree to participate, blood samples were obtained at the beginning of Week 1 and at the end of Weeks 12 and 24.</p>		
<p>Number of Subjects (planned and analyzed): This study planned to enroll up to 150 female subjects, and 155 subjects were randomized, including 51 subjects in the NBI-56418 150 mg group, 52 subjects in the NBI-56418 250 mg group, and 52 subjects in the placebo group. All randomized subjects were evaluated for the safety analysis set. The per protocol analysis set included 139 subjects and the intent-to-treat (ITT) analysis set included 154 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 8 years of screening) and with at least mild nonmenstrual pelvic pain and at least moderate dysmenorrhea (≥ 2 for the CPSSS dysmenorrhea CPSSS component and ≥ 1 for the nonmenstrual pelvic pain CPSSS component) at baseline were enrolled.</p>		
<p>Test Products, Doses and Mode of Administration, Batch Number: NBI-56418 is based on the sodium salt and was provided as 100 mg or 150 mg tablets for oral administration (batch numbers for 100 mg are L0108709 and L0201080, and 150 mg are L0108713 and L0201083). The 150 mg q.d. dose (one 150 mg NBI-56418 tablet and one placebo tablet) or the 250 mg q.d. dose (one 150 mg NBI-56418 tablet and one 100 mg NBI-56418 tablet) were administered daily during treatment.</p>		
<p>Duration of Treatment and Study Participation: Subjects were followed for approximately 14 months: up to 8 weeks of screening which includes a 4-week placebo lead-in; a 24-week treatment phase; a 6-week posttreatment phase; and a 24-week posttreatment BMD assessment for subjects who met the criteria.</p>		
<p>Reference Therapy, Dose and Mode of Administration, Batch Number: Matching placebo tablets (batch numbers L0108707 and L0201076) were orally administered in a double-dummy manner on an identical schedule to active drug.</p>		

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:	
Criteria for Evaluation: <u>Efficacy:</u> Efficacy was evaluated using the dysmenorrhea and nonmenstrual pelvic pain assessments, the NRS for endometriosis pain, analgesic use for endometriosis, the EHP-5, the dyspareunia component of the CPSSS, and the PGIC. The primary endpoint for this study is the change from baseline (CFB) in the monthly mean value of the e-Diary-based numerical rating scale (NRS) for endometriosis pain at the Week 12 timepoint. The NRS CFB at other scheduled timepoints will be evaluated as secondary endpoints. Additional efficacy endpoints were based on both e-Diary and case report form (CRF) data collected through Week 30 of the study. These endpoints were defined as follows: <ul style="list-style-type: none">• Monthly peak NRS CFB;• Monthly mean sum of nonmenstrual pelvic pain and dysmenorrhea scores CFB;• Monthly mean nonmenstrual pelvic pain score CFB;• Monthly mean dysmenorrhea score CFB;• Monthly percentage of days with no pain (based on NRS);• Monthly percentage of days with no pain (based on sum of nonmenstrual pelvic pain and dysmenorrhea);• Monthly percentage of days with no pain (based on nonmenstrual pelvic pain);• Monthly percentage of days with no pain (based on dysmenorrhea);• Monthly percentage of days any endometriosis analgesic taken;• Monthly percentage of days prescription endometriosis analgesic taken;• Monthly percentage of days narcotic endometriosis analgesic taken;• 30% decrease from baseline in monthly mean NRS;• 30% decrease from baseline in monthly peak NRS;• 50% decrease from baseline in monthly mean NRS;• 50% decrease from baseline in monthly peak NRS;• Dyspareunia CFB;• PGIC (as a continuous measure);• PGIC response of Minimally Improved, Much Improved, or Very Much Improved (categorical measure);• PGIC response of Much Improved or Very Much Improved (categorical measure);• EHP-5 scores CFB.		
<u>Safety:</u> Safety was evaluated based on AEs, clinical laboratory tests, vital sign measurements, physical examinations, and ECG recordings. Vaginal bleeding, hot flashes, evidence of posttreatment ovulation, confirmation of menses, BMD, and serum N-telopeptide were also assessed.		
<u>Pharmacokinetics:</u> Blood samples to determine the plasma concentration of NBI-56418 were collected and analyzed.		
<u>Pharmacodynamics:</u> Blood samples to determine serum E2, luteinizing hormone, follicle stimulating hormone, progesterone and testosterone concentrations were collected and analyzed.		
Statistical Methods: <u>Efficacy:</u> 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.		

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:	

Changes from baseline were tested for significance using t-tests.

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

SUMMARY OF RESULTS:

Efficacy Results:

- Monthly mean NRS data were typically low across all three treatment groups during the placebo lead-in phase (3.2, 3.4, and 3.0 in the placebo, NBI-56418 150 mg, and 250 mg groups, respectively) and the first 12 weeks of the treatment phase, reflecting low levels of pain as measured by the NRS. Statistically significant decreases from baseline in the monthly mean NRS were observed in all three treatment groups at Week 12. Slightly larger decreases from baseline were observed in the NBI-56418 150 mg (-1.19) and 250 mg (-1.25) groups compared to placebo (-0.88), although the differences were not statistically significant ($p > 0.05$).
- Monthly peak NRS decreased from baseline for all treatment groups at the Weeks 4, 8, and 12 timepoints. Decreases from baseline were larger for the NBI-56418 150 mg and 250 mg groups than for placebo, especially at Week 12 (-2.45 [NBI-56418 150 mg] and -2.74 [250 mg] versus -1.30 [placebo]).
- The percentage of days with no pain based on the NRS increased in all three initial randomization treatment groups during Weeks 1-12 of the treatment phase compared to the placebo lead-in.
- Responder rates based on monthly peak NRS were higher at Week 12 for NBI-56418 150 mg and 250 mg subjects compared to placebo using either definition 1 (30% decrease from baseline; 36.8, 47.7, and 57.8 in the placebo, 150 mg, 250 mg groups, respectively) or definition 2 (50% decrease from baseline; 23.7, 34.1, and 42.2 in the in the placebo, 150 mg, 250 mg groups, respectively).
- The monthly means for the Dysmenorrhea and NMPP e-Diary daily assessments, as well as the Total Score, were decreased from baseline for all treatment groups at Weeks 4, 8, and 12. There was a larger decrease from baseline in monthly mean dysmenorrhea at Weeks 8 and 12 in the NBI-56418 groups compared to placebo, although monthly means were generally low, reflecting mild pain, throughout the study.
- During Weeks 1-12, prescription analgesic use showed a modest decrease from baseline for all treatment groups, with slightly greater decreases from baseline observed for the NBI-56418 treatment groups compared to placebo (Week 12: -2.6 [150 mg] and -3.3 [250 mg] versus -2.1 [placebo]). A similar trend was observed for the percentage of days with narcotic analgesic use during Weeks 1 through 12 (although at Week 12 the decrease from baseline was only greater in the NBI-56418 250 mg [-3.6] compared to placebo [-1.7]).
- There was a modest decrease from baseline indicating improvement of dyspareunia in all three treatment groups during Weeks 1-12 of the treatment phase, with slightly greater improvement in the NBI-56418 treatment groups compared to placebo (CFB Week 12: -0.67 [150 mg] and -0.49 [250 mg] versus -0.29 [placebo]).
- Mean PGIC scores decreased (indicating improvement) from Week 1 for all treatment groups with slightly greater decreases observed for the NBI-56418 treatment groups compared to placebo (Week 12 mean scores: 2.2 [both NBI-56418 150 mg and 250 mg] versus 3.2 [placebo]).
- The percentage of subjects with PGIC responses of Much Improved or Very Much Improved was

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:	

typically higher for the NBI-56418 treatment groups compared to placebo.

- In general for all three treatment groups, there was a decrease from baseline to Week 12 for the core dimensions of the EHP-5 questionnaire, with the greatest decrease observed in the NBI-56418 150 mg group, indicating improvement.

Pharmacokinetic and Pharmacodynamic Results:

In general, subjects receiving NBI-56418 had measurable NBI-56418 plasma concentrations postdose. Baseline median serum E2 values were comparable among the placebo (28.4 pg/mL), NBI-56418 150 mg (31.7 pg/mL), and 250 mg (32.7 pg/mL) treatment groups. During Weeks 4-12 of the treatment phase, median serum E2 concentrations ranged from approximately 38 to 77 pg/mL across visits in the placebo group compared to 29 to 38 pg/mL in the NBI-56418 150 mg group and 20 to 33 pg/mL for the NBI-56418 250 mg group. After drug discontinuation (Week 30 during the posttreatment phase), median serum E2 concentrations increased for all treatment groups, consistent with a return to a normal range of E2 concentrations.

The median value of subject average serum E2 concentrations during the treatment phase was lower in the NBI-56418 150 mg (47.3 pg/mL) and 250 mg (33.2 pg/mL) groups compared to the placebo group (61.9 pg/mL). The percentage of subjects in the average serum E2 concentration category <10 pg/mL was higher for the NBI-56418 250 mg group (16.3%) compared to 150 mg (9.3%) or placebo (0%).

Median serum LH, FSH, testosterone, and progesterone concentrations remained relatively constant at baseline, Week 12 and Week 20 for all treatment groups. None of the minor fluctuations in gonadotropins reflects sustained or profound suppression or hyperstimulation of the hypothalamic-pituitary-gonadal axis.

Safety Results:

No deaths were reported during the study. Three subjects experienced treatment emergent SAEs: one NBI-56418 250 mg subject experienced an SAE of spontaneous abortion [a suspected ectopic pregnancy treated with methotrexate] approximately 1 week after discontinuing from the study during the treatment phase; one NBI-56418 150 mg subject experienced an SAE of pelvic pain during the posttreatment phase; and a NBI-56418 150 mg subject gave birth approximately 7.5 months after her last dose of study drug to an infant who experienced SAEs of tracheo-oesophageal fistula, patent ductus arteriosus, tricuspid valve incompetence, pneumothorax, and atelectasis. The infant may have been exposed in utero to NBI-56418 150 mg for approximately 2 weeks.

Seven subjects discontinued from the study due to an AE: one placebo/NBI-56418 150 mg subject (during the treatment phase), two NBI-56418 150 mg subjects (one during treatment and one during posttreatment), and four NBI-56418 250 mg subjects (all during treatment).

During Weeks 1-12, the incidence of TEAEs was higher in the NBI-56418 250 mg group (67.3%) compared to the NBI-56418 150 mg (54.9%) and placebo (50.0%) groups. The most commonly reported TEAEs in both NBI-56418 treatment groups that occurred at a much higher incidence than placebo were headache (9.8% in the NBI-56418 150 mg and 7.7% in the 250 mg groups versus 1.9% in the placebo group), nausea (9.8% in the NBI-56418 150 mg and 5.8% in the 250 mg groups versus 1.9% in the placebo group), and anxiety (5.9% in the NBI-56418 150 mg and 5.8% in the 8 250 mg groups versus 0% in the placebo group). Nausea, headache, upper respiratory tract infection and urinary tract infection were the most common TEAEs observed in NBI-56418 subjects during Weeks 1-24.

<p>Name of Sponsor/Company: Neurocrine Biosciences, Inc.</p> <p>Name of Finished Product: ---</p> <p>Name of Active Ingredient: NBI-56418</p>	<p>Individual Study Table Referring to Part of the Dossier</p> <p>Volume:</p> <p>Page:</p>	<p>(For National Authority Use Only)</p>
<p>Clinical laboratory results, vital sign measurements, and ECG readings throughout the study were unremarkable, and in general, there were no important differences among the treatment groups. Mean values generally remained relatively constant throughout the study, and there were no clinically significant changes from baseline. The group means were within normal range at all timepoints during the study. There were sporadic increases in mean CK in the NBI-56418 treatment groups (both initially randomized and re-randomized) of <15 U/L; however, at all timepoints during the study, the group means were within normal range.</p> <p>Bone mineral density of the femur and spine, as measured by DXA scan, showed only small changes from baseline in all three treatment groups at Week 12. Minor decreases from baseline in BMD at the femur and spine (approximately 1.6% decrease from baseline or less) were observed at Week 24 for the initially randomized NBI-56418 treatment groups with a larger decrease observed in the 250 mg group compared to 150 mg. No important differences were noted among the treatment groups for mean serum N-telopeptide values throughout the study and values remained within the normal range at all timepoints.</p> <p>The mean endometrium thickness at Week 12 was comparable between the three treatment groups (5.54, 6.68, and 4.61 mm for placebo, NBI-56418 150 mg, and 250 mg, respectively). In general, parameters assessed fell within normal ranges and there was no evidence of ovarian hyperstimulation based on the Week 12 transvaginal ultrasound findings.</p> <p>The percentage of subjects who reported hot flashes during the placebo lead-in phase was approximately 77% in the placebo group, approximately 63% in the NBI-56418 150 mg group, and approximately 52% in the 250 mg group. During Weeks 1-12 of the study, the percentage increased compared to the placebo lead-in across all three study groups and ranged from approximately 85% to 92%. The percentage of subjects who reported a hot flash during the posttreatment phase was lower compared to the treatment phase in both NBI-56418 groups (60.5% and 38.9% in the 150 mg and 250 mg groups, respectively).</p> <p>During the treatment phase, subjects who received NBI-56418 150 mg or 250 mg had a smaller percentage of days with any vaginal bleeding compared to subjects in the placebo group. This decrease was due primarily to a >50% decrease in the percent of days with heavy bleeding (median percent of days approximately 3.12%, 1.39%, and 0.65% in the placebo, NBI-56418 150 mg, and 250 mg groups, respectively).</p> <p>The majority of subjects in all treatment groups had evidence of ovulation within 4 weeks of completing the treatment phase</p>		

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Name of Finished Product: ---	Volume:	
Name of Active Ingredient: NBI-56418	Page:	
CONCLUSIONS: The conclusions of this study are the following: <ul style="list-style-type: none">• The primary endpoint of the study, the change from baseline (CFB) in the monthly mean value of the daily e-Diary-based numerical rating scale (NRS) for endometriosis pain at the Week 12 timepoint, was not statistically significantly different in the NBI-56418 treatment groups compared to placebo, although larger decreases from baseline were observed in the NBI-56418 groups.• Multiple measures of endometriosis signs and symptoms including endometriosis analgesic use, the dyspareunia component of the CPSSS, the PGIC, and EHP-5 showed improvement in subjects receiving NBI-56418 150 mg or 250 mg and this improvement was typically greater than that observed for placebo during the 12-week placebo-controlled treatment phase.• Only small changes from baseline were observed at Weeks 12 and 24 for bone mineral density of the femur and spine, as measured by DXA scan. No important differences were noted among the treatment groups for mean serum N-telopeptide values at any timepoint throughout the study.• NBI-56418 was generally well-tolerated when administered as 150 mg or 250 mg for 24 weeks with few subjects experiencing SAEs or discontinuing due to a treatment-emergent AE.		
Date of the Final Report: November 29, 2010		