

## 2. SYNOPSIS

<p><b>Name of Sponsor/Company:</b> Neurocrine Biosciences, Inc.</p> <p><b>Name of Finished Product:</b> ---</p> <p><b>Name of Active Ingredient:</b> NBI-56418</p>	<p><b>Individual Study Table Referring to Part of the Dossier</b></p> <p><b>Volume:</b></p> <p><b>Page:</b></p>	<p><b>(For National Authority Use Only)</b></p>
<p><b>Title of Study:</b> A Phase 2, Randomized, Double-Blind, Placebo- and Active-Controlled Study to Assess the Efficacy and Safety of NBI-56418 in Subjects with Endometriosis</p>		
<p><b>Study Number:</b> NBI-56418-0703</p>		
<p><b>Study Centers:</b> A total of 27 centers in nine countries in Central Eastern Europe, 21 of which enrolled subjects. [REDACTED]</p>		
<p><b>Publication (reference):</b> None at date of this report.</p>		
<p><b>Study Period (Years):</b> First subject enrolled (randomized) to last subject completed: November 26, 2008 to February 24, 2010.</p>	<p><b>Clinical Phase:</b> 2</p>	
<p><b>Objectives:</b></p> <p><b>Primary:</b> 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.</p> <p><b>Secondary:</b></p> <ul style="list-style-type: none"> <li>• To evaluate the safety of 150 mg and 250 mg once-daily doses of NBI-56418.</li> <li>• To evaluate the effect of 6 months of NBI-56418 treatment on bone mineral density (BMD).</li> <li>• To describe the temporal characteristics of NBI-56418 and leuprorelin acetate in terms of safety and efficacy outcome measures.</li> </ul>		
<p><b>Methodology:</b> This was a Phase 2, multicenter, randomized, double-blind, placebo- and active-controlled study. The study followed a parallel-group design in which the subjects were randomized (1:1:1:1) to one of the following treatment groups for the first 12 weeks of dosing: 150 mg NBI-56418 q.d.; 250 mg NBI-56418 q.d.; placebo; or leuprorelin acetate depot injection 3.75 mg (monthly). Blinding was achieved using a double-dummy design. Following 12 weeks of dosing, subjects continued in the study for an additional 12 weeks; subjects randomized to NBI-56418 continued to receive their assigned dose and subjects randomized to placebo or leuprorelin acetate were re-randomized to receive one of the two doses of NBI-56418 (150 mg q.d. or 250 mg q.d.) for 12 weeks in a double-blind fashion. Six weeks after the last dose of the study drug at the end of Week 24, a follow-up visit was performed (end of Week 30). Subjects whose BMD at the end of Week 24 had decreased more than 3% from screening were required to have an additional dual energy X-ray absorptiometry (DXA) scan at 6 months posttreatment.</p> <p>After providing consent, subjects underwent screening for up to 8 weeks (from start of first screening procedure; Weeks -8 to -1) to ensure eligibility to participate in the study. Subjects who were using</p>		

<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>	

hormonal contraception or other hormonal therapies for endometriosis entered a 1-month wash-out prior to the start of the screening procedures. The Composite Pelvic Signs and Symptoms Score (CPSSS) was administered during screening. Subjects also completed daily symptom assessments of dysmenorrhea and nonmenstrual pelvic pain (NMPP) and a numerical rating scale (NRS) for endometriosis pain via electronic diary (e-Diary) during screening.

Following screening procedures and the onset of spontaneous menstrual bleeding, subjects returned to the study center on Day 1 of Week 1 for collection of baseline assessments and randomization. Day 1 (dosing) started 2 to 5 days (inclusive) after the onset of menstrual bleeding.

Subjects returned to the study center for assessments at 4-week intervals during the treatment (at the end of Weeks 4, 8, 12, 16, 20, and 24). At the end of Week 12 visit, subjects randomized to receive placebo or leuporelin acetate were re-randomized to one of the NBI-56418 treatments, while those subjects who were randomized to NBI-56418 at Week 1 continued with their treatment assignment until the end of Week 24.

A follow-up visit occurred approximately 6 weeks after completion of the 24-week treatment phase (final study visit; end of Week 30 or early termination). If a subject's BMD at the end of Week 24 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 subjects to use daily during screening and for the duration of the study. The e-Diary was used to record dysmenorrhea and nonmenstrual pelvic pain assessments, NRS for rating 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 analgesic medications for endometriosis. The e-Diary also provided prompts to remind subjects to call the site if any unusual signs or symptoms develop and to remind subjects to continue dosing.

Efficacy assessments consisting of dysmenorrhea and nonmenstrual pelvic pain assessments, an NRS specific to endometriosis pain, and use of analgesics for endometriosis were completed daily throughout the study (during screening, treatment, and follow-up) using an e-Diary. In addition, the Endometriosis Health Profile-5 (EHP-5), a Quality of Life (QoL) questionnaire, and a dyspareunia assessment were performed at baseline (beginning of Week 1), every 4 weeks during the treatment phase, and at the follow-up visit (Week 30 or early termination). The Patient Global Impression of Change (PGIC) was performed at the end of Weeks 4, 8, 12, 16, 20, 24 and at early termination (if early termination occurred during the treatment phase). The dysmenorrhea and nonmenstrual pelvic pain components of the CPSSS were performed at the beginning of Week 1 (baseline) and the end of Weeks 12 and 24.

Blood samples for PD assessments were collected throughout the study. Serum samples for E2 were collected at baseline (beginning of Week 1), every 4 weeks during the treatment phase, and at the follow-up visit (Week 30 or early termination). Serum samples for LH, FSH, progesterone, and testosterone were collected at baseline (beginning of Week 1) and at the end of Weeks 12 and 20. Blood samples for PK were collected at the beginning of Week 1 and at the end of Weeks 4, 12 and 20.

Safety was assessed throughout the study based on monitoring of AEs, clinical laboratory tests, vital signs, physical examinations (including a pelvic examination at Week 30 or early termination), vaginal bleeding, hot flashes and ECGs. Evidence of ovulation posttreatment was also assessed.

To monitor BMD, DXA scans of the femur and spine was acquired at screening and at the end of Weeks 12 and 24 (and Week 48 as needed). Subjects whose BMD at the end of Week 24 has decreased more than 3% from screening were required to have an additional DXA scan at 6 months posttreatment (end of Week 48). In addition, blood samples for N-telopeptide, a bone resorption marker, were collected at screening and at the end of Weeks 12 and 24 and during follow-up (Week 30 or early

<p><b>Name of Sponsor/Company:</b> Neurocrine Biosciences, Inc.</p> <p><b>Name of Finished Product:</b> ---</p> <p><b>Name of Active Ingredient:</b> NBI-56418</p>	<p><b>Individual Study Table Referring to Part of the Dossier</b></p> <p><b>Volume:</b></p> <p><b>Page:</b></p>	<p><b>(For National Authority Use Only)</b></p>
<p>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>A sub-study to evaluate RNA and protein expression was also conducted. Sub-study participation was optional. For subjects who agreed to participate, blood samples were obtained at the beginning of Week 1 and at the end of Weeks 12 and 24.</p>		
<p><b>Number of Subjects (planned and analyzed):</b> This study planned to enroll approximately 180 female subjects, and 174 subjects were randomized, including 43 subjects in the NBI-56418 150 mg group, 44 subjects in the NBI-56418 250 mg group, 43 subjects in the placebo group, and 44 subjects in the leuprorelin acetate group. All randomized subjects were evaluated for the safety analysis set. The per protocol analysis set 1 included 171 subjects, the per protocol analysis set 2 included 164 subjects and the intent-to-treat (ITT) analysis set included 174 subjects.</p>		
<p><b>Diagnosis and Main Criteria for Inclusion:</b> Female subjects (aged 18 to 45 years) with a laparoscopically confirmed diagnosis of endometriosis (performed within 5 years of screening) and with at least mild nonmenstrual pelvic pain and at least moderate dysmenorrhea (<math>\geq 2</math> for the CPSSS dysmenorrhea CPSSS component and <math>\geq 1</math> for the nonmenstrual pelvic pain CPSSS component) at baseline were enrolled.</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 100 mg or 150 mg tablets for oral administration (the batch number for 100 mg is 1552.002, and for 150 mg is 1550.001). 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><b>Duration of Treatment and Study Participation:</b> Subjects were followed for approximately 16 months: up to 8 weeks of screening; a 24-week double-blind treatment phase; a 6-week posttreatment phase; and a 24-week posttreatment BMD assessment for subjects who met the criteria.</p>		
<p><b>Reference Therapy, Dose and Mode of Administration, Batch Number:</b> Matching placebo tablets (batch number 1551.001) were orally administered in a double-dummy manner on an identical schedule to active drug. Leuprorelin acetate depot 3.75.mg (Prostap SR, Wyeth) was administered as an intramuscular injection at Weeks 1, 4, and 8. A matching placebo injection of saline solution was administered in a double-dummy fashion on an identical schedule.</p>		

<p><b>Name of Sponsor/Company:</b> Neurocrine Biosciences, Inc.</p> <p><b>Name of Finished Product:</b> ---</p> <p><b>Name of Active Ingredient:</b> NBI-56418</p>	<p><b>Individual Study Table Referring to Part of the Dossier</b></p> <p><b>Volume:</b></p> <p><b>Page:</b></p>	<p><b>(For National Authority Use Only)</b></p>
<p><b>Criteria for Evaluation:</b></p> <p><u>Efficacy:</u> Efficacy was evaluated using the NRS for endometriosis pain, the dysmenorrhea and nonmenstrual pelvic pain assessments, analgesic use for endometriosis, the EHP-5, the dyspareunia, dysmenorrhea, and nonmenstrual pelvic pain components of the CPSSS, and the 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. These endpoints were defined as follows:</p> <ul style="list-style-type: none"> <li>• Monthly mean NRS for endometriosis pain score change from baseline (CFB)</li> <li>• Monthly peak NRS for endometriosis pain score CFB</li> <li>• Monthly mean nonmenstrual pelvic pain score CFB</li> <li>• Monthly mean dysmenorrhea score CFB</li> <li>• Monthly mean sum of nonmenstrual pelvic pain and dysmenorrhea scores CFB</li> <li>• Monthly percentage of days any endometriosis analgesic taken</li> <li>• Monthly percentage of days prescription endometriosis analgesic taken</li> <li>• Monthly percentage of days narcotic endometriosis analgesic taken</li> <li>• Dyspareunia (CPSSS component) CFB</li> <li>• Dysmenorrhea (CPSSS component) CFB</li> <li>• Nonmenstrual pelvic pain (CPSSS component) CFB</li> <li>• PGIC (as a continuous measure)</li> <li>• PGIC response of Minimally Improved, Much Improved, or Very Much Improved (categorical measure)</li> <li>• PGIC response of Much Improved or Very Much Improved (categorical measure)</li> <li>• EHP-5 scores CFB</li> </ul>		
<p><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 N-telopeptide were also assessed.</p>		
<p><u>Pharmacokinetics:</u> Blood samples to determine the plasma concentration of NBI-56418 were collected and analyzed.</p>		
<p><u>Pharmacodynamics:</u> Blood samples to determine serum E2, luteinizing hormone, follicle stimulating hormone, progesterone and testosterone concentrations were collected and analyzed.</p>		
<p><b>Statistical Methods:</b></p> <p><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. Changes from baseline were tested for significance using t-tests.</p> <p><u>Pharmacokinetics, Pharmacodynamics, and Safety:</u> Safety, PK, and PD data were summarized with descriptive statistics.</p>		

<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>	

**SUMMARY OF RESULTS:**

Efficacy Results:

- Monthly mean NRS for endometriosis pain scores were typically low across all four treatment groups during screening (3.3, 3.7, 3.3, and 3.1 in the placebo, NBI-56418 150 mg, 250 mg, and leuprorelin acetate groups, respectively) and the first 12 weeks of the treatment phase, reflecting low levels of pain as measured by the NRS. Decreases from baseline in the monthly mean NRS were observed in all four treatment groups at Week 12. Slightly larger decreases were observed in the NBI-56418 and leuprorelin acetate groups compared to the placebo groups; however, these differences were not statistically significant.
- Monthly peak NRS for endometriosis pain scores decreased from baseline for all treatment groups at the Weeks 4, 8, and 12 timepoints. These decreases were statistically significantly larger than those observed in the placebo group for the NBI-56418 250 mg and leuprorelin acetate groups at Weeks 4, 8, and 12 and for the NBI-56418 150 mg group at Week 4.
- Dysmenorrhea and NMPP daily scores were typically low (<1.4) at baseline reflecting mild to moderate pain. Decreases from baseline were observed for all treatment groups at Weeks 4, 8, and 12 for both Dysmenorrhea and NMPP assessments. Although small, the decreases for the monthly mean Dysmenorrhea assessment were statistically significantly larger than those observed in the placebo group for the NBI-56418 and leuprorelin acetate groups at Weeks 4, 8, and 12 (p<0.001 for NBI-56418 250 mg and leuprorelin acetate at all three timepoints and for NBI-56418 150 mg at Weeks 4 and 8, p=0.0005 for NBI-56418 150 mg at Week 12).
- The percentage of days with any analgesic use or prescription analgesic use was low overall and comparable during screening across the treatment groups. The percentage of days with any analgesic use decreased from screening at Weeks 4, 8, and 12 in all treatment groups. The percentage of days with prescription analgesic use showed little change overall. Few subjects in any treatment group used narcotic analgesics for endometriosis at any time during the study.
- Dyspareunia CPSSS component scores (monthly) were comparable across all treatment groups at screening and baseline (Week 1), ranging from 1.6 to 1.9. There was a modest but statistically significant decrease from baseline indicating improvement of dyspareunia in all four treatment groups during Weeks 4-12 of the treatment phase.
- Dysmenorrhea and NMPP CPSSS component scores (monthly) were comparable across treatment groups at both screening and baseline and were consistent with moderate dysmenorrhea and mild NMPP.
- All four treatment groups showed a mean decrease of ≥1 point from baseline in the Dysmenorrhea CPSSS component at Week 12 with the largest decrease observed in the leuprorelin acetate group (-1.75) and the smallest decrease observed in the placebo group (-1.03).
- All four treatment groups showed modest decreases from baseline at Week 12 in the NMPP CPSSS component with the largest decrease observed in the leuprorelin acetate group (-0.79) and the smallest decrease observed in the NBI-56418 250 mg group (-0.48).
- Scores for the PGIC were comparable across treatment groups at the Week 4 timepoint, ranging from 2.9 to 3.4 consistent with minimal improvement. Mean scores were lower (indicating additional improvement) beyond Week 4 for all treatment groups, ranging from 2.1 to 2.6 at Week 12.

<p><b>Name of Sponsor/Company:</b> Neurocrine Biosciences, Inc.</p> <p><b>Name of Finished Product:</b> ---</p> <p><b>Name of Active Ingredient:</b> NBI-56418</p>	<p><b>Individual Study Table Referring to Part of the Dossier</b></p> <p><b>Volume:</b></p> <p><b>Page:</b></p>	<p><b>(For National Authority Use Only)</b></p>
<ul style="list-style-type: none"> <li>The percentage of subjects with PGIC responses of Much Improved or Very Much Improved increased approximately 2 to 3-fold from Week 4 to Week 8 and remained relatively consistent for the rest of treatment phase for all treatment groups. The percentage of responders was higher in the NBI-56418 and leuprorelin acetate groups at Weeks 4, 8, and 12 compared to placebo.</li> <li>Baseline scores were similar across treatment groups for each core dimension of the EHP-5. In general for all treatment groups, there were decreases (indicating improvement) from baseline to Week 12 for all five core dimensions. The magnitudes of the decreases were similar across treatment groups for each core dimension except Pain, for which the leuprorelin acetate group had a larger decrease than placebo.</li> </ul> <p><u>Pharmacokinetic and Pharmacodynamic Results:</u></p> <ul style="list-style-type: none"> <li>In general, subjects receiving NBI-56418 had measurable NBI-56418 plasma concentrations postdose, with higher levels in the 250 mg group compared to the 150 mg group.</li> <li>Baseline median serum E2 values were comparable among the placebo (39.1 pg/mL), NBI-56418 150 mg (43.4 pg/mL), 250 mg (47.5 pg/mL), and leuprorelin acetate (46.2 pg/mL) treatment groups, reflecting that subjects were synchronized to Day 2-5 of menses at baseline. During Weeks 4-12 of the treatment phase, median serum E2 concentrations ranged from approximately 49.50 to 87.90 pg/mL across visits in the placebo group compared to 36.40 to 39.60 pg/mL in the NBI-56418 150 mg group and 22.00 to 26.20 pg/mL for the NBI-56418 250 mg group. As expected, median serum E2 concentration were very low (&lt;10 pg/mL) during Weeks 4-12 in the leuprorelin acetate group.</li> <li>After drug discontinuation (measured at Week 30 during the posttreatment phase), median serum E2 concentrations increased compared to those observed during the treatment phase in all treatment groups.</li> <li>Median serum LH and FSH concentrations were similar at baseline and remained relatively constant at Week 12 for the placebo and NBI-56418 treatment groups. As expected based on the mechanism of action of leuprorelin acetate, reductions from baseline in LH and FSH were observed at Week 12 in the leuprorelin acetate group. Median progesterone and testosterone were low at baseline in all treatment groups, reflecting normal physiologic levels, and remained so during the course of treatment, with the exception of increased progesterone in the NBI-56418 150 mg and placebo groups at Week 12 (reflecting some subjects with luteal phase elevations) and decreased progesterone (to the LLOQ value of 0.21 ng/mL) in the leuprorelin acetate group. Testosterone at Week 12 remained the same as baseline or was lower in all groups except placebo where testosterone increased from 20.00 ng/dL (LLOQ) at baseline to 29.35 ng/dL at Week 12.</li> </ul>		

<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>	

**Safety Results:**

- No deaths were reported during the study. There were SAEs reported for three subjects during the study: diabetes mellitus non-insulin dependent in Subject [REDACTED] (NBI-56418 150 mg) during the treatment phase; paranasal sinus benign neoplasm in Subject [REDACTED] (NBI-56418 250 mg) during the posttreatment phase; and appendicitis in Subject [REDACTED] (placebo/NBI-56418 250 mg) during the posttreatment phase.
- Three subjects discontinued early from the study due to adverse events during the treatment phase: Subject [REDACTED] (NBI-56418 150 mg) due to hot flash; Subject [REDACTED] (NBI-56418 250 mg) due to rash; and Subject [REDACTED] (leuprorelin acetate/NBI-56418 150 mg) due to arthralgia (pain in knee and pelvic joints).
- During Weeks 1-12, the incidence of TEAEs was higher in the NBI-56418 150 mg and 250 mg (44.2% and 36.4%, respectively) and leuprorelin acetate (29.5%) groups compared to the placebo (18.6%). The most commonly reported TEAEs in both NBI-56418 treatment groups were headache (18.6% in the NBI-56418 150 mg group and 9.1% in the 250 mg group), nausea (7.0% in the NBI-56418 150 mg group and 4.5% in the 250 mg group) and vertigo (7.0% in the NBI-56418 150 mg group and 2.3% in the 250 mg group).
- During Weeks 1-24 in NBI-56418 150 mg and 250 mg groups (including data from placebo and leuprorelin acetate subjects re-randomized to either NBI-56418 150 mg or 250 mg), the incidence of TEAEs was nearly identical between the two dose groups (40.0% and 40.2% in the NBI-56418 150 mg and NBI-56418 250 mg groups, respectively). The most commonly reported TEAE in both groups was headache (11.8% and 11.5% in the NBI-56418 150 mg and NBI-56418 250 mg groups respectively). Nausea was the only other TEAE that occurred in ≥5% of subjects in both NBI-56418 treatment groups (5.9% and 5.7% of NBI-56418 150 mg and 250 mg subjects, respectively).
- Seven subjects became pregnant during or after completion of the study. Three subjects (one placebo, one NBI-56418 250 mg, and one leuprorelin acetate/NBI-56418 150 mg) became pregnant during the treatment phase of the study. Four subjects (one placebo/NBI-56418 150 mg, one NBI-56418 250 mg, one leuprorelin acetate/NBI-56418 150 mg, and one leuprorelin acetate/NBI-56418 250 mg) became pregnant after completing the Week 30 study visit. All seven subjects gave birth to healthy infants with no major complications or congenital anomalies.
- 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. Sporadic increases from baseline in mean creatine kinase were observed during the study in the NBI-56418 150 mg, 250 mg, and leuprorelin acetate treatment groups; however, these increases appear to be due in part to a few subjects with very high creatine kinase values due to events unrelated to the study (e.g., strenuous exercise).
- Bone mineral density of the femur and spine, as measured by DXA scan, showed only small decreases in all four treatment groups at Week 12 with the largest decreases observed in the leuprorelin acetate group (1.122% and 1.633% decrease from baseline in the femur and spine, respectively). Mean decreases in BMD were slightly greater at Week 24 than Week 12 in subjects who received NBI-56418 for 24 weeks and mean decreases in BMD were slightly greater in the NBI-56418 250 mg group compared to 150 mg at both Weeks 12 and 24.

<p><b>Name of Sponsor/Company:</b> Neurocrine Biosciences, Inc.</p> <p><b>Name of Finished Product:</b> ---</p> <p><b>Name of Active Ingredient:</b> NBI-56418</p>	<p><b>Individual Study Table Referring to Part of the Dossier</b></p> <p><b>Volume:</b></p> <p><b>Page:</b></p>	<p><b>(For National Authority Use Only)</b></p>
<p>Subjects with a &gt;3% decrease in BMD at Week 24 were required to have a follow-up DXA scan at Week 48. In these subjects, BMD as measured at the femur remained relatively unchanged from Week 24 to Week 48, while the decrease from baseline in BMD as measured at the spine was smaller at Week 48 than Week 24.</p> <ul style="list-style-type: none"> <li>• Only small changes from baseline in serum N-telopeptide measurements were observed during the treatment phase; however, increases at Week 12 were larger in the leuprorelin acetate (3.18 nM BCE) and NBI-56418 250 mg (2.04 nM BCE) groups compared to the placebo (0.62 nM BCE) and NBI-56418 150 mg (0.77 nM BCE) treatment groups. No important differences in mean serum N-telopeptide were noted among the treatment groups. Mean serum N-telopeptide values remained within the normal range at all timepoints.</li> <li>• The percentage of subjects who reported hot flashes via the e-Diary during screening ranged from 38.6% in the NBI-56418 250 mg group to 20.5% in the leuprorelin acetate group. During the treatment phase, the percentage of subjects with hot flashes increased at least 2-fold compared to screening in all four study groups and ranged from 65.1% in the placebo group (for Weeks 1-12) to 93.2% in the NBI-56418 250 mg group (for Weeks 1-24). The percentage of subjects who reported a hot flash during the posttreatment phase was lower compared to the treatment phase in all treatment groups but still higher than screening.</li> <li>• In the NBI-56418 and leuprorelin acetate treatment groups, the percent of days with any vaginal bleeding decreased almost 50% during the treatment phase compared to screening. In contrast, the percent of days with any vaginal bleeding was nearly identical during the screening and treatment phases (Weeks 1-12) for placebo subjects. The decrease in the percent of days with any vaginal bleeding observed in the NBI-56418 and leuprorelin acetate groups was due primarily to a reduction of the percent of days with moderate or heavy bleeding during the treatment phase compared to screening.</li> <li>• Among subjects with adequate urine samples to detect evidence of ovulation, ovulation was detected posttreatment in a high percentage of subjects in all treatment groups (&gt;94%). Median time to ovulation posttreatment ranged from 8 to 14.5 days across the treatment groups.</li> </ul>		



<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>CONCLUSIONS:</b> The conclusions of this study are the following: <ul style="list-style-type: none"><li>• Baseline values for the daily NRS for endometriosis pain and daily dysmenorrhea, and nonmenstrual pelvic pain scales were low, reflecting mild pain for these particular scales. Despite low baseline values, a consistent trend of improvement from baseline was observed for these daily assessments for all four treatment groups during the 12-week placebo- and active-controlled treatment phase with a greater magnitude of improvement observed in the NBI-56418 and leuprorelin acetate groups compared to placebo.</li><li>• Multiple measures of endometriosis signs and symptoms including the dyspareunia, dysmenorrhea, and nonmenstrual pelvic pain components of the CPSSS, the PGIC, and EHP-5 showed improvement in subjects receiving NBI-56418 150 mg or 250 mg. This improvement was typically greater than that observed for placebo and similar in magnitude to that observed in subjects receiving leuprorelin acetate during the 12-week placebo- and active-controlled treatment phase.</li><li>• Small decreases from baseline in bone mineral density, as measured by DXA scan of the femur and spine, were observed at Weeks 12 and 24 in subjects receiving NBI-56418. Bone mineral density decreases from baseline at Week 12 in subjects receiving either dose of NBI-56418 were typically smaller than those observed in subjects receiving leuprorelin acetate. No important differences were noted among the treatment groups for mean serum N-telopeptide values at any timepoint throughout the study.</li><li>• 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.</li></ul>		
<b>Date of the Final Report: April 15, 2011</b>		