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 II, Randomized, Double-Blind, Active-Controlled Study to Assess the Safety and Efficacy of NBI-56418 in Subjects with Endometriosis		
Study Number: NBI-56418-0603		
[redacted]		
Study Centers: A total of 78 centers in the United States (US) participated in the study, of which 58 centers randomized subjects. [redacted]		
Publication (reference): None at date of this report.		
Study Period (Years): First subject enrolled to last subject completed: December 11, 2006 to November 24, 2008.		**Clinical Phase:** II

Objectives:

Primary: To assess the effects of two dose regimens of NBI-56418 (75 mg twice daily [b.i.d.] or 150 mg once daily [q.d.]) and subcutaneous medroxyprogesterone acetate (DMPA-SC, depo-subQ provera 104™, Pfizer) on bone mineral density (BMD) using dual energy X-ray absorptiometry (DXA) following 24 weeks of treatment.

Secondary:

- To demonstrate noninferiority of at least one dose regimen of NBI-56418 (150 mg q.d. or 75 mg b.i.d.) to DMPA-SC in the reduction of dysmenorrhea and nonmenstrual pelvic pain scores from the Composite Pelvic Signs and Symptoms Score [CPSSS]) following 24 weeks of treatment.
- To evaluate the safety and tolerability of NBI-56418.
- To evaluate the effect of NBI-56418 on BMD following discontinuation of treatment (at Weeks 48 and 72).

Methodology: This was a Phase II, multicenter, randomized, double-blind, active-controlled study. The study followed a parallel-group design in which 252 subjects were randomized (1:1:1) to one of the

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following treatment groups: NBI-56418 150 mg once daily (q.d.); NBI-56418 75 mg twice daily (b.i.d.); or DMPA-SC.

NBI-56418 and/or placebo were administered daily for 24 weeks. DMPA-SC or placebo injections were administered twice during the study, at Weeks 1 and 12. Blinding was achieved using a double-dummy design. After the last dose at the end of Week 24, follow-up visits continued every 4 weeks for another 24 weeks up to the final study day at the end of Week 48. Subjects were asked to return at Week 72 to complete additional BMD assessments.

After providing informed consent, subjects underwent screening evaluations to ensure suitability to participate in the study together with the acquisition of data for up to 60 days to provide baseline data. Subjects who were using hormonal contraception or other hormonal therapies for endometriosis entered a 1-month wash-out prior to the start of screening procedures. The CPSSS and the Endometriosis Health Profile-5 (EHP-5) questionnaire were administered during screening. Subjects also completed a visual analog scale (VAS) for pelvic pain daily during screening.

Following screening procedures and the onset of menstrual bleeding, subjects returned to the study center on Day 1 of Week 1 for collection of baseline assessments and randomization. Dosing started 2 to 7 days (inclusive) after the onset of menstrual bleeding.

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). Upon completion of the 24-week treatment period, subjects returned to the study center for follow-up visits every 4 weeks for an additional 24 weeks (at the end of Weeks 28, 32, 36, 40, 44, and 48).

Efficacy assessments using CPSSS and the EHP-5 were performed at 4-week intervals during treatment and at the end of Weeks 28, 36, and 48 (or at early termination) following treatment. A VAS specific to pelvic pain was completed daily throughout the study (during screening, treatment, and follow-up).

Blood samples for pharmacokinetics (PK) were collected (before and after dosing) at the beginning of Week 1 and at the end of Weeks 4, 12 and 20. Blood samples for pharmacodynamic (PD) assessments were collected at screening and every 4 weeks during the treatment phase and during the posttreatment follow-up phase. Estradiol (E2) was assessed at all collection points. Luteinizing hormone [LH], follicle stimulating hormone [FSH], progesterone, and testosterone were assessed at Weeks 1 (baseline), 12, and 20.

Safety was assessed throughout the study based on monitoring of adverse events (AEs), clinical laboratory tests, vital signs, physical examinations, and electrocardiograms (ECGs). Bone mineral density monitoring was done using DXA scans of the femur and spine that were acquired at screening and at the end of Week 24, and a single DXA scan was acquired at the end of Weeks 12 and 48 (or at early termination). In addition, blood samples for N-telopeptide, a bone resorption marker, were collected at screening and at the end of Weeks 12, 24, and 48 (or at early termination).

Subjects were asked to return to the study center at the end of Week 72 (approximately 12 months after the last dose) to acquire a single DXA scan to assess BMD, collect a blood sample for N-telopeptide, and record medications, surgeries, and additional therapies for endometriosis from the time of the final study day (Week 48) until Week 72.

An electronic diary (e-Diary) was provided to subjects to use daily at screening and for the duration of the study. The e-Diary was used to record the VAS for pelvic pain, any vaginal bleeding (menstrual bleeding or bleeding at any other point of the cycle), and any occurrence of hot flashes. The e-Diary

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provided prompts to remind subjects to call the site if any unusual signs or symptoms develop and to remind subjects to continue dosing.

A substudy to evaluate gene expression, protein expression and complement activation was 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 24 and 48.

Number of Subjects (planned and analyzed): This study planned to enroll up to 240 female subjects, and 252 subjects were randomized, including 84 subjects in the NBI-56418 150 mg q.d. group, 84 subjects in the NBI-56418 75 mg b.i.d. group, and 84 subjects in the DMPA-SC group. All randomized subjects were evaluated for the safety analysis set. The per protocol BMD analysis set included 204 subjects, the intent-to-treat (ITT) analysis set included 251 subjects, and the per protocol efficacy analysis set included 227 subjects.

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 moderate nonmenstrual pelvic pain and dysmenorrhea (Total CPSSS $\geq$ 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.

Test Products, Doses and Mode of Administration, Batch Number: NBI-56418 is based on the sodium salt and was provided as 75 mg tablets for oral administration (batch numbers KC2006063 and KH2006012). The 75 mg b.i.d. dose (one 75 mg NBI-56418 tablet and one placebo tablet b.i.d.) and the 150 mg q.d. dose (two 75 mg NBI-56418 tablets in the morning and two placebo tablets in the evening) were studied. DMPA-SC or saline solution (placebo) was provided for injection in a sterile aqueous suspension in a prefilled syringe with a strength of 160 mg/mL for subcutaneous injections at the beginning of Week 1 and the end of Week 12.

Duration of Treatment and Study Participation: Subjects were followed for approximately 20 months (up to 60 days of screening, 24 weeks of treatment, 24 weeks of posttreatment follow-up, and after an additional 24 weeks a return visit at Week 72 for a final BMD assessment).

Reference Therapy, Dose and Mode of Administration, Batch Number: Matching placebo solution (batch numbers 33-362 DK and 50-483-DK) or DMPA-SC (depo-subQ provera 104™, Pfizer, 104 mg/0.65 mL per syringe, batch number MC1083 and MF0676) was provided for injection in a sterile aqueous suspension in a prefilled syringe with dose strength of 160 mg/mL. Matching placebo tablets (batch numbers KC2006057 and KF2006021 and) were orally administered in a double-dummy manner on an identical schedule to active drug.

Criteria for Evaluation:

Efficacy: Efficacy was evaluated based on the CPSSS, VAS for pelvic pain, and EHP-5. The key efficacy endpoint was defined by a 1-point or greater decrease from baseline in each of the dysmenorrhea and nonmenstrual pelvic pain scores of the CPSSS at the end of Week 24.

Additional endpoints included: Change from Baseline (CFB) in the Total CPSSS, in Total CPSSS excluding dyspareunia, and in individual CPSSS components (dysmenorrhea, dyspareunia, pelvic pain, pelvic tenderness, pelvic induration); CFB in monthly peak and monthly mean VAS for pelvic pain, CFB in EHP-5 core and modular dimensions, use of analgesics, and CPSSS during posttreatment.

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Safety: 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.

Pharmacokinetics: Blood samples to determine the plasma concentration of NBI-56418 were collected and analyzed.

Pharmacodynamics: Blood samples to determine serum E2, LH, FSH, progesterone and testosterone concentrations were collected and analyzed.

Statistical Methods:

Bone Mineral Density: The %CFB for BMD at Week 24 for the spine and femur were analyzed using a one-way analysis of variance (ANOVA) model and summarized using 95% two-sided confidence intervals (CIs) for the treatment group mean values.

The absence of significant bone loss for a given NBI-56418 dose regimen was considered to be supported only if the CI bounds for both spine and femur mean BMD %CFB were equal to or above the specified threshold value of -2.2% at Week 24.

Efficacy: A responder analysis using the dysmenorrhea and nonmenstrual pelvic pain components of the CPSSS as variables was performed. For both of these variables (which were analyzed separately), a subject was classified as a "responder" (or, equivalently, "improved") at a given postbaseline study visit if she reported a 1-point (or greater) decrease from baseline, with Week 24 considered as the primary timepoint. A noninferiority analysis was conducted comparing response rates between each NBI-56418 dose and DMPA-SC. Statistical noninferiority for dysmenorrhea and nonmenstrual pelvic pain was demonstrated when the lower bound of the 95% two-sided CI for the difference between an NBI-56418 dose regimen and DMPA-SC in the response rate was no less than -20% at Week 24. 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) model.

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

SUMMARY OF RESULTS:

Bone Mineral Density Results:

The primary safety endpoint for this study was the %CFB in mean BMD at Week 24 as measured by DXA scans. The active comparator (DMPA) assured that there was assay sensitivity.

- The lower bound of the 95% CI for the BMD mean %CFB was above the prespecified threshold of -2.2% for the spine and femur in the treatment groups at Week 24 and Week 48. In subjects randomized to receive NBI-56418 150 mg q.d., the mean %CFB in total BMD at Week 24 was -0.11% for the spine and -0.47% for the femur. The mean %CFB for the NBI-56418 75 mg b.i.d. group at Week 24 was -1.29% for the spine and -1.02% for the femur. The mean %CFB for DMPA-SC at Week 24 was -0.99 for the spine and -1.29 for the femur.
- At Week 48, the mean %CFB for the NBI-56418 150 mg q.d. group was +0.20% for the spine and -0.38% for the femur. The mean %CFB at Week 48 for the NBI-56418 75 mg b.i.d group was -0.49% for the spine and -0.86% for the femur. The mean %CFB for DMPA-SC at Week 48 was -0.56 for the spine and -0.76 for the femur.
- In the subjects that returned for Week 72 DXA scans, the mean %CFB in Total BMD for the

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NBI-56418 150 mg q.d. group was 0.75% (N=28) for the spine and 0.17% (N=29) for the femur. The mean %CFB at Week 72 for the NBI-56418 75 mg b.i.d group was -0.42% (N=42) for the spine and -0.91% (N=42) for the femur. The mean %CFB for the DMPA-SC group at Week 72 was -0.18% (N=27) for the spine and -0.22% (N=27) for the femur. These data are consistent with the lack of significant posttreatment effects of NBI-56418 on BMD.

Efficacy Results:

Efficacy measures were considered secondary endpoints.

- For the key efficacy endpoint, the responder rate on the dysmenorrhea and nonmenstrual pelvic pain components of the CPSSS at Week 24 was 86% (both components) for the NBI-56418 150 mg q.d. group, 74% (dysmenorrhea) and 77% (nonmenstrual pelvic pain) for the NBI-56418 75 mg b.i.d. group, and 86% (dysmenorrhea) and 77% (nonmenstrual pelvic pain) for the DMPA-SC group based on the definition of an improvement of greater than or equal to 1 point.
- The NBI-56418 150 mg q.d. dose regimen demonstrated statistical noninferiority to DMPA-SC for dysmenorrhea and nonmenstrual pelvic pain components at Week 24. For the NBI-56418 150 mg q.d. regimen, the lower bounds of the 95% CIs for the difference between the dose regimen and DMPA response rates were no less than the prespecified margin of -20%. The difference in response rates at Week 24 was -0.3% for NBI-56418-150 mg q.d. and -12.4% for NBI-56418 75 mg b.i.d. for the dysmenorrhea component and 9.5% for NBI-56418-150 mg q.d. and 0.5% for NBI-56418 75 mg b.i.d. for the nonmenstrual pelvic pain component.
- The least squares (LS) mean CFB for the Total CPSSS was -3.9, -3.7, and -3.8 at Week 4 and -5.5, -5.4, and -4.6 at Week 16 for the NBI-56418 150 mg q.d., 75 mg b.i.d., and DMPA-SC groups, respectively. While scores were similar for all groups at Week 24, there was a greater improvement from baseline relative to DMPA-SC in the NBI-56418 150 mg q.d. group at Week 16 and in the NBI-56418 75 mg b.i.d. group at Week 12.
- The LS mean CFB for the Total CPSSS at Week 24 was -5.5, -5.2, and -5.3 for the NBI-56418 150 mg q.d., NBI-56418 75 mg b.i.d., and DMPA-SC groups, respectively. Both NBI-56418 treatment groups demonstrated a clinically meaningful improvement over baseline in Total CPSSS. Posttreatment, the mean CFB for the Total CPSSS at Week 48 was -4.1, -3.6, and -4.4 for the NBI-56418 150 mg q.d. and NBI-56418 75 mg b.i.d., and DMPA-SC groups, respectively.
- At Week 48 Total CPSSS remained improved for all treatment groups. A modest increase in Total CPSSS at Weeks 28 and 36 in the NBI-56418 groups compared to the DMPA group reflects the return of menses (and associated dysmenorrhea). The depot treatment (DMPA) is associated with suppression of menses for an average of 10 months post injection in contrast to the rapid return to ovulation and menses following discontinuation of NBI-56418. By Week 48 the treatment groups had comparable scores.
- All treatment groups showed improvement from baseline (negative change representing a decrease in reported pain) in monthly peak and mean VAS for pelvic pain throughout the treatment phase including Week 24.
- The percentage of subjects at baseline who responded “never” or “rarely” to the pain component of the EHP-5 questionnaire (“During the last 4 weeks, how often because of your endometriosis have you found it difficult to walk because of the pain?”) was 25.0%, 22.6%, and 22.9% for the NBI-56418 150 mg q.d, NBI-56418 75 mg b.i.d., and DMPA-SC groups, respectively. At Week 24, the percentage of subjects who responded “never” or “rarely” was 82.4%, 78.4%, and 72.6% for the

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NBI-56418 150 mg q.d, NBI-56418 75 mg b.i.d., and DMPA-SC groups, respectively. The increase from baseline in the percentage of subjects who responded "never" or "rarely" was similar among all three treatment groups at Week 24, approximately 50% to 57%.

Pharmacokinetic and Pharmacodynamic Results:

- In general, subjects receiving NBI-56418 had measurable NBI-56418 plasma concentrations postdose. With a few minor exceptions, concentrations 0 to 2 hours after dosing were higher than predose at Weeks 1, 4, 12 and 20. Median NBI-56418 plasma concentrations 0 to 2 hours postdose at Weeks 4, 12, and 20 were somewhat lower than those at Week 1 for both dosing regimens. This is likely due to widely ranging sampling times (0 to 2 hours) after dosing, which resulted in variability in concentrations. In a previous study (NBI-56418-0405) where full PK curves were generated in healthy premenopausal women; there was no meaningful difference in Day 1 versus Day 42 NBI-56418 pharmacokinetic parameters.
- Baseline median E2 values were comparable among the NBI-56418 150 mg q.d. (41.1 pg/mL), NBI-56418 75 mg b.i.d. (39.1 pg/mL), and the DMPA-SC (39.3 pg/mL) treatment groups. During the treatment phase (Weeks 4 to 24), median E2 serum concentrations ranged from 36 to 63 pg/mL across visits in the NBI-56418 150 mg q.d. group compared to a range of approximately 23 to 31 pg/mL for the NBI-56418 75 mg b.i.d. group and 19 to 37 pg/mL for the DMPA-SC group. After drug discontinuation (Weeks 28 to 48 during the posttreatment phase), median serum E2 concentrations increased in both NBI-56418 groups starting at Week 28 (71 pg/mL, NBI-56418 150 mg q.d., and 55 pg/mL, 75 mg b.i.d.) suggesting a return to a near normal range of E2 concentrations. The median value of subject average E2 concentrations during the treatment phase was higher in the NBI-56418 150 mg q.d group (61.9 pg/mL) compared to the NBI-56418 75 mg b.i.d. (34.8 pg/mL) and DMPA-SC (34.8 pg/mL) groups.
- Median serum LH concentrations increased nominally from baseline to Week 12 for all treatment groups and decreased from Week 12 to Week 20 for the NBI-56418 150 mg q.d. and DMPA-SC groups. These values reflect the transition from synchronized menses at baseline (Days 2-7) to variable, nonsynchronized days during the treatment phase. Median serum FSH and testosterone concentrations remained relatively constant at baseline, Week 12 and Week 20 for all treatment groups. None of the fluctuations in gonadotropin reflects sustained or profound suppression or hyperstimulation of the Hypothalamic-Pituitary-Gondal axis. Median progesterone concentrations decreased slightly from baseline to Week 12 and increased from Week 12 to Week 20 for the NBI-56418 75 mg b.i.d. and DMPA-SC groups, while remaining similar during the same period for the NBI-56418 150 mg q.d. group, reflecting cycle desynchronization for both NBI-56418 groups and remained relatively constant for the same period of the DMPA-SC group.

Other Safety Results:

- There were no deaths reported in this study. Fifteen subjects experienced serious adverse events (SAEs), including one subject in the NBI-56418 150 mg q.d. group, two subjects in the NBI-56418 75 mg b.i.d group and three subjects in the DMPA-SC group during the treatment phase, and two subjects in the NBI-56418 150 mg q.d. group, one in the NBI-56418 75 mg b.i.d and three in the DMPA-SC during the posttreatment phase. Three additional subjects experienced SAEs following study completion at Week 48 (or discontinuation); two were from the NBI-56418 150 mg q.d. group and one was from the NBI-56418 75 mg b.i.d group.
- Of the subjects who were discontinued from the study due to an AE, five were from the NBI-56418 150 mg q.d. group (four during treatment and one during posttreatment), seven were from the

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NBI-56418 75 mg b.i.d. group (all during treatment) and 15 were from the DMPA-SC group (14 subjects during treatment and one during posttreatment).

- The incidence of treatment-emergent adverse events (TEAEs) during the treatment phase was similar across all treatment groups. The most commonly occurring TEAE was headache with a higher incidence in the NBI-56418 groups than DMPA-SC (21.4% in the 150 mg q.d. group, 26.2% in the 75 mg b.i.d. group versus 15.5% in the DMPA-SC group). Nausea was also commonly reported in all treatment groups with similar incidence among them; 16.7%, 13.1%, and 14.3% in the NBI-156418 150 mg q.d., NBI-56418 75 mg b.i.d., and DMPA-SC groups respectively. There was a slightly higher incidence of TEAEs in the NBI-56418 75 mg b.i.d. group compared to the NBI-56418 150 mg q.d. and DMPA-SC groups during the posttreatment phase (72.6% subjects in the NBI-56418 75 mg b.i.d versus 57.1% and 60.8% in the NBI-56418 150 mg q.d. and DMPA-SC groups respectively). Most AEs were mild or moderate in intensity.
- The percentage of subjects who reported one or more episodes of hot flash at screening was 47.6%, 39.3%, and 46.4% in the NBI-56418 150 mg q.d., NBI-56418 75 mg b.i.d., and DMPA-SC groups respectively. The percentage of subjects who reported a hot flash during the treatment phase was 71.1%, 82.1%, and 75.9% in the NBI-56418 150 mg q.d., NBI-56418 75 mg b.i.d., and DMPA-SC groups respectively. The percentage of subjects who reported a hot flash during the posttreatment phase was somewhat higher in the NBI-56418 75 mg b.i.d (67.2%) than the NBI-56418 150 mg and DMPA-SC groups (52.1% for both). The average number of hot flashes per day was similar in the NBI-56418 150 mg q.d. and DMPA-SC groups, approximately 0.1 per day, and slightly higher in the NBI-56418 75 b.i.d. group, 0.2 per day.
- Clinical laboratory results, vital sign measurements, and ECG readings throughout the study were unremarkable, and in general, there were no important difference among the treatment groups. Mean values generally remained relatively constant throughout the study, and there were no clinically significant changes from baseline. An exception was mean creatine kinase, which increased from baseline by at least 20 U/L for subjects in all three groups (NBI-56418 150 mg q.d. at Week 12 and NBI-56418 75 mg b.i.d. and DMPA-SC at Week 36) most likely related to the double-dummy or DMPA-SC injections. The group means were within normal range at all timepoints during the study. There were 17 subjects who had clinical laboratory findings that were reported as AE's, 15 subjects from the NBI-56418 groups and two from the DMPA-SC group. Seventeen subjects in the NBI-56418 groups and seven subjects in the DMPA-SC group had abnormal physical examination findings reported as TEAEs during the treatment phase.
- During the treatment phase, subjects who received NBI-56418 150 mg q.d. or 75 mg b.i.d. had fewer days with any vaginal bleeding compared to subjects in the DMPA-SC group. The median percent of days with any bleeding were 16%, 12%, and 26% during treatment, and 20%, 20%, and 14% during posttreatment in the NBI-56418 150 mg q.d., NBI-56418 75 mg b.i.d. and DMPA-SC groups, respectively.
- Among subjects with adequate urine samples to detect evidence of ovulation, ovulation was detected posttreatment in 94.2% of subjects in the NBI-56418 150 mg q.d. group, 91.7% of subjects in the NBI-56418 75 mg b.i.d. group, and 56.3% of subjects in the DMPA-SC group. Median time to ovulation was 9, 12, and 68 days for the NBI-56418 150 mg q.d., NBI-56418 75 mg b.i.d. and DMPA-SC groups, respectively. The median number of days to first posttreatment menses was less for subjects in the NBI-56418 groups (26 days in the 150 mg q.d. group and 24 days in 75 mg b.i.d. group) compared to subjects in the DMPA-SC group (60 days). The median length of the

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posttreatment menstrual cycle (i.e., number of days from the start of first posttreatment menses to the start of the second posttreatment menses) was similar among the two NBI-56418 groups (28 days) and slightly higher in the DMPA-SC group (35 days).

- Mean N-telopeptide (a bone resorption biomarker) values were within the normal range for all treatment groups throughout the study and there were no clinically significant changes noted. The mean CFB values for N-telopeptide were 0.2, -0.3, and -0.2 nM bone collagen equivalent (BCE) at Week 24 and -1.3, -1.5, and -1.4 nM BCE at Week 48 for the NBI-56418 150 mg q.d., NBI-56418 75 mg b.i.d., and DMPA-SC groups, respectively. At Week 72, mean CFB values were -2.7, -2.7, and -2.6 for the NBI-56418 150 mg q.d., NBI-56418 75 mg b.i.d., and DMPA-SC groups, respectively.

CONCLUSIONS:

The conclusions of this study are the following:

- The primary endpoint of the study was met; the lower bounds of the 95% CI for the BMD mean %CFB was above the prespecified -2.2% for spine and femur in the treatment groups at Week 24. The active comparator (DMPA) served to assure assay sensitivity (DXA).
- Multiple measures of pain including CPSSS (Total CPSSS and components), VAS for pelvic pain, and the EHP-5 pain core component showed improvement in subjects receiving NBI-56418 150 mg q.d. and 75 mg b.i.d. during 24 weeks of treatment.
- Statistical noninferiority was demonstrated between the NBI-56418 150 mg q.d. dose and DMPA-SC for dysmenorrhea and nonmenstrual pelvic pain responder analyses.
- During the treatment phase, there was a decrease in the median percent of days with any bleeding in subjects receiving NBI-56418 in contrast to DMPA-SC, which was associated with an increase in the percentage of days with vaginal bleeding (light flow).
- Evidence of ovulation was detected posttreatment in >90% of subjects randomized to NBI-56418 among subjects with adequate urine samples.
- No important differences were noted among the treatment groups for mean N-telopeptide values at any timepoint throughout the study.
- NBI-56418 was generally well-tolerated at doses of 150 mg q.d. and 75 mg b.i.d. administered for 24 weeks.

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