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APPLICATION NUMBER:

205489Orig1s000

CLINICAL REVIEW(S)

CLINICAL REVIEW

Application Type	NDA, 505(b) (2)
Application Number(s)	NDA 205,489 Seq 027
Priority or Standard	Standard
Submit Date(s)	December 19, 2016
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PDUFA Goal Date	June 19, 2017
Division / Office	OND I/DPP
Reviewer Name(s)	Glenn Mannheim, M.D.
Review Completion Date	May 12, 2017
Established Name	Methylphenidate Extended Release Orally Disintegrating 10 mg, 20 mg, and 30 mg Tablets
(Proposed) Trade Name	COTEMPLA XR-ODT
Therapeutic Class	Stimulant
Applicant	Neos Therapeutics, Inc.
Formulation(s)	Extended-Release Orally Disintegrating Tablets
Dosing Regimen	20 mg to 60 mg Per Day
Indication(s)	Attention Deficit Disorder
Intended Population(s)	Attention Deficit Disorder (6 - (b) (4) Years)

I. Benefit-Risk Recommendation

Neos Therapeutics, Inc. originally submitted on January 9, 2015, a 505(b)(2) application for Methylphenidate (MPH) Extended Release Orally Disintegrating Tablets (XR-ODT) for ADHD using Metadate CD (methylphenidate hydrochloride) as the reference listed drug (RLD). A Complete Response was issued on November 6, 2015 based upon differences between the formulations (clinical trial, clinical pharmacology, and commercial scale [to-be-marketed]), used in the different studies. On December 19, 2016, Neos Therapeutics, Inc. submitted the results of Study NT0102.1005, a relative BA/BE (Bioavailability/bioequivalence) study which compared the clinical trial formulation to the commercial scale formulation of MPH XR-ODT. Results of this study indicate that there is an adequate bridge between the clinical trial formulation (Lot: 2E116E), the clinical pharmacology formulation (Lot: 1E101A) and the commercial, to-be-marketed formulation.

The safety data from the previously reviewed three phase 1 studies and a single phase 3 study (Table: Overview of Studies, Appendix), coupled with the present, single phase 1 bridging study suggest that NT0102 is reasonably well tolerated and has a safety profile similar to those of other extended release methylphenidates¹.

From a clinical perspective, there are no objections to this product being approved for the treatment of pediatric and adolescents with ADHD between the ages of 6-17 years. Metadate CD, the reference listed drug (RLD), was previously approved in pediatric and adolescents between the ages of 6-15 years. It is recommended that we approve COTEMPLA XR-ODT for an additional 2 years up to 17 years, so as to provide complete adolescent age spectrum coverage. This would be consistent with the current standard of practice and prescribing regimen of other approved methylphenidate products that includes dosing typically up to and including 17 years (6-12 years, 13-17 years).

Despite there being some well-defined clinical differences between adolescent and pediatric ADHD (co-morbid disorders of oppositional defiance, conduct, substance, mood and anxiety being more common in adolescent ADHD), there is no evidence from the available literature to suggest that COTEMPLA XR-ODT would not also be clinically effective in this 16-17 year age group and that it would substantially be different for the known, labeled risks. The COTEMPLA XR-ODT labeling adequately describes the most commonly known methylphenidate adverse events in this age group and which are not substantially different from the 6-15 year age group.

¹ Common adverse events associated with the methylphenidates include: decreased appetite and weight; nausea, abdominal pain, dyspepsia, dry mouth, vomiting, insomnia, anxiety, nervousness, restlessness, labile affect, agitation, irritability, dizziness, vertigo, tremor, blurred vision; increased blood pressure and heart rate; tachycardia, palpitations, hyperhidrosis, and pyrexia.

II. Background:

Metadate CD Extended-Release Capsules (NDA 21-259), was approved on February 02, 2001, based upon one, 3 week, placebo-controlled clinical study in 321 children, 6-15 years of age, with the combined type hyperactive-impulsive ADHD at doses of 20-60 mg based on the primary endpoint of the teacher's version of the Conner's Global Index Scale, mean changes from baseline to week 3.

Under IND 109,108, Neos Therapeutics had the following meetings and written communication with the Division of Psychiatric Products (DPP):

- a pre-IND meeting on September 14, 2010;
- a Type C Meeting on May 13, 2013 to review and discuss a proposed laboratory classroom study (NT0102) and a pharmacokinetic study;
- and an Information Advice on January 10, 2014 for a proposed initial Pediatric Study Plan (iPSP) to obtain approval of their extended release (XR) orally disintegrating tablet (ODT) formulation of MPH in children, 6-^(b)₍₄₎ years with ADHD using Metadate CD as the Reference Listed Drug.

Neos Therapeutics conducted three pharmacokinetic studies which are summarized in the Appendix (Table: Overview of Studies), and which were previously reviewed in more detail in the original NDA Medical Review from October 11, 2015. These studies were:

- Study NT0102.1001 was a bioequivalent study conducted in 42 healthy adults comparing the rate of absorption and oral bioavailability of two NT0102 formulations to an equivalent oral dose of Metadate CD. This study showed that the MPH XR ODT formulation had a similar release profile to Metadate CD. There were 57 treatment-emergent adverse events (TEAEs) reported by 20 subject (nausea, anxiety and tachycardia). There were no discontinuations. No adverse event was serious.
- Study NT0102.1002 was a food effect study conducted in 24 healthy adults assessing the effect of food on the rate and extent of absorption and the oral bioavailability of a single dose (2 x 30 mg ODTs) of MPH XR-OD, equivalent to 60 mg MPH HCl. This study showed that presence of food did not significantly alter MPH exposure following the administration of MPH XR-ODT (equivalent to 60 mg MPH HCl). There were 34 treatment-emergent adverse events (TEAEs) reported by 14 subjects (anxiety, nausea, tachycardia). No adverse event was serious.
- Study NT0102.1003 was a bioavailability study conducted in 32 children (6-12 years of age) and adolescents (13-17 years of age) with ADHD in which child or adolescent received a single dose of MPH XR ODT after a 4 day washout period and an overnight fast. This study showed that the geometric means for weight-normalized CL/F and Vz/F of total methylphenidate ($d + l$) and the respective 95% confidence intervals about means were within the target range of 60% to 140% for each age group. There were 22 (68.8%) subjects

COTEMPLA XR-ODT: Methylphenidate Extended Release Orally Disintegrating 10 mg, 20 mg, and 30 mg Tablets who experienced 34 treatment-emergent AEs (increased heart rate, decreased, nausea and vomiting. None were serious.

In addition to these 3 pharmacokinetic studies, Neos Therapeutics conducted a single, clinical efficacy and safety phase 3 study:

- *Study NT0102.1004* was a randomized, multicenter, double-blind, placebo-controlled, parallel group study of the MPH XR ODT formulation (equivalent to 20, 30, 40, or 60 mg of methylphenidate hydrochloride) in 87 children (ages 6-12 years) with ADHD. It consisted of a 4 week dose optimization phase, a 1 week dose stabilization period, and a 6 day double blind parallel group phase, culminating in a full-day laboratory classroom setting. Statistical significance was demonstrated on the primary (SKAMP-Combined score average over the duration of the classroom day) and the key secondary endpoints (first and last points, respectively, at which active drug separates from placebo on SKAMP-Combined scores). A total 80.5 % of study subjects experienced TEAE's. The most common TEAE's during the *dose optimization/stabilization phase* were decreased appetite [23 subjects (26.4 %)]; upper abdominal pain [21 subjects (24.1 %)]; headache [19 subjects (21.8 %)]; infections [13 subjects (14.9 %)] with 10 subjects (11.5 %) having upper respiratory infections; insomnia [11 subjects (12.6 %)]; labile affect [9 subjects (10.3 %)]; irritability [7 subjects (8 %)]; vomiting [5 subjects (5.7 %)]; skin/subcutaneous disorders [4 subjects (4.6 %)] with 2 subjects having rash [1: maculopapular rash (1.1 %)], 1 subject alopecia (1.1 %), and pruritus [(1.1 %)]; constipation [3 subjects (3.4 %)]; fatigue [2 subjects (2.3 %)] and tics [2 subjects (2.3 %)]. The most common TEAEs (i.e., >2% incidence) occurring more frequently in subjects on NT0102 than on placebo during the *double-blind phase* were upper respiratory tract infection (4 subjects [9.1%]); second degree burn (1 subject [2.3%]), wound (1 subject [2.3%]); dizziness (1 subject [2.3%]); trichotillomania (1 subject [2.3%]); cough (1 subject [2.3%]); and epistaxis (1 subject [2.3%]).

On February 26, 2015, Neos Therapeutics filed NDA 205, 489, as a 505(b)(2) application using Metadate CD as the RLD for the indication of ADHD. They requested approval of three strengths of MPH XR-ODT (10 mg, 20 mg, and 30 mg). A Complete Response was issued by DPP on November 6, 2015. Several deficiencies precluded approval. The primary deficiencies identified were: 1) lack of an adequate bridge between the clinical trial formulation (Lot: 2E116E), the clinical pharmacology formulation (Lot: 1E101A) and the commercial, to-be-marketed formulation preventing use of the efficacy and safety trial (NT0102.1004) findings to inform the safety and effectiveness of the to-be marketed Product (Table 5, Appendix) ; 2) the weight/weight level of delayed release (b) (4) between the clinical and commercial batches was (b) (4) by (b) (4) % with a need to establish a validated commercial (b) (4) operation and control; 3) the pediatric pharmacokinetic information obtained with the clinical pharmacology formulation (Lot: 1E101A) was insufficient to support extrapolation of efficacy findings; and 4) the food effect findings based on the clinical pharmacology formulation (Lot: 1E101A) could not inform the food effect of the to-be-marketed formulation. Recommendations were to conduct a bioequivalence study bridging the to-be-marketed formulation with the clinical trial formulation (Lot: 2E116E) under fasted and fed conditions; and to do assess the food effect on the to-be-marketed formulation.

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COTEMPLA XR-ODT: Methylphenidate Extended Release Orally Disintegrating 10 mg, 20 mg, and 30 mg Tablets
On December 17, 2015, a Type A meeting between DPP and Neos Therapeutics was held in which their proposed single, three-arm bioavailability, bioequivalence study of the to-be-marketed formulation of Cotempla XR-ODT (Lot 2E116E) was discussed.

III. Materials Reviewed

This submission consisted of a single new study identified below.

- NT0102.1005, Cross Over Bioavailability, Bioequivalence Study under Fasting and Fed Conditions in 48 adults, 18-69 years using 3 formulations.

A clinical review of the following studies was previously reviewed on October 9, 2015, as part of the initial submission.

- Bioequivalence Study NT0102.1001
- Fed Fasted Study NT0102.1002
- Bioavailability Study NT0102.1003
- Study NT0102.1004: Phase 3, Laboratory classroom study in children, 6-12 years with ADHD
- Proposed Labeling
- Financial Disclosure Certification
- Debarment Certification
- Clinical literature included in this submission

IV. Review of Clinical Pharmacology Studies

Study NT0102.1005: A Single-Dose, Three-Period, Three-Treatment, Three-Way Crossover Bioavailability Study of a Commercial Scale Formulation of NT0102 Methylphenidate Extended-Release Orally Disintegrating Tablets (XR-ODT) 60 mg (2 x 30 mg) under Fed and Fasted Conditions and a Clinical Trial Formulation of NT0102 Methylphenidate XR ODT 60 mg (2 x 30 mg) under Fasted Conditions

This was a single-dose, open-label, randomized, three-period, three-treatment crossover study in which 48 healthy adult male (20, [41.7 %]) and female (28, [58.3 %]) subjects (18-69 years, 43 years mean age) received a single dose of the commercial scale formulation of NT0102 60 mg (2 x 30 mg) (formulation 1) under fed conditions in one period (Treatment A), a single dose of NT0102 60 mg (2 x 30 mg) (formulation 1) under fasted conditions in another period (Treatment B), and a single dose of the clinical trial formulation of NT0102 (2 x 30 mg) (formulation 2) under fasted conditions in a different period (Treatment C). Each drug administration was separated by a washout period of at least 7 days. Treatment A was administered after a 10-hour overnight fast followed by ingestion of a Food and Drug Administration (FDA) standard high-fat, high-calorie breakfast beginning 30 minutes before treatment administration. Treatments B and C were administered following a 10-hour overnight fast.

The Schedule of Events is copied and pasted into the Appendix of this review (Table 4).

Study subjects were healthy male or females (postmenopausal or on acceptable birth control), 18 years of age or older, without a history of a clinically significant medical problem, were willing

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Sponsors Conclusion (s): The Clinical Trial Formulation of NT0102 Methylphenidate XR-ODT 60 mg (Treatment C, Formulation 2) was bioequivalent to the Commercial Formulation of NT0102 Methylphenidate XR-ODT 60 mg (Treatment B, Formulation 1) under fasted conditions, as evidenced by the 90% confidence intervals for C_{max}, AUC₀₋₃, AUC₃₋₇, AUC₇₋₁₂, and AUC_{inf} being within the accepted 80% -125% range for establishing bioequivalence for *d+l*-methylphenidate. The rate of absorption of MPH XR-ODT was decreased when administered with a high-fat meal, but overall systemic exposure to methylphenidate was similar under fasted and fed conditions. No significant safety concerns were identified during the study.

OCP's Conclusion³: "Adequate linkages have been established among the three developed formulations (clinical trial formulation, clinical pharmacology formulation, and commercial scale [to-be-marketed] formulation), and to the Listed Drug, Metadate CD, through two relative BA studies in combination with the knowledge that the quantities of release-controlling (b) (4) used in the clinical pharmacology formulation are bracketed by the clinical trial formulation and the to-be-marketed formulation.

PK Parameters (Mean ±SD) of (<i>d+l</i>)-MPH Following Administration of 51.8 mg MPH XR-ODT (Clinical pharmacology Formulation) or Metadate CD under Fasting Conditions			
Parameters	Test (T, n=38)	Reference (R, n=38)	Geo mean Ratio (T/R, 90% CI)
C _{max} (ng/mL)	21.2±5.5	17.4 ±5.8	126.0 (119.4, 133.0)
T _{max} (hr)	5.0±1.0	5.0±1.1	--
AUC ₀₋₃ (hr*ng/mL)	22.7±8.1	25.7±9.2	93.5 (85.7, 102.1)
AUC _{0-tmax} (hr*ng/mL)	54.0±17.1	53.1±17.1	104.8 (97.9, 112.2)

Safety: Forty-six (46) of 48 enrolled subjects, received all scheduled doses of NT0102 Methylphenidate XR-ODT 60 mg (2 x 30 mg). Two (2) subjects (4.2 %) were discontinued from the study prior to dosing in Period 3 for protocol non-compliance (positive urine drug screen) at the Period 3 check-in. There were no serious adverse events.

A total of 13 adverse events (AEs) were reported in 9 subjects (Table 3 of Adverse Events-NT0102.1005, Appendix). All were mild except for one (somnolence), which was moderate in intensity. The most commonly reported AEs were palpitations (n=2 subjects, both following Treatment A), decreased appetite (n=2 subjects, both following Treatment A), and hypervigilance (n=2 subjects; 1 following Treatment B and 1 following Treatment C). All were considered as being related to study treatment. No clinically significant observations or changes in safety parameters were identified in the subject population during the study conduct.

None of the TEAEs occurred as the result of abnormal laboratory evaluations (chemistry, hematology, urinalysis, urine for drugs of abuse, urine pregnancy test in females at screening and

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Safety Conclusion: These TEAEs were consistent with other methylphenidate products. Palpitations and hypervigilance occurred more frequently in the commercial scale formulation of NT0102 Methylphenidate XR-ODT 60 mg (2 x 30 mg) (formulation 1) under fed conditions with decreased C_{max}. The significance of this observation is uncertain based upon the small sample size.

V. Review of Clinical Efficacy and Safety Data Conclusion

No new clinical efficacy data was submitted with the current submission. Safety data from the current comparative formulation, bridging PK Study (NT0102.1005) was reviewed (Sec IV).

Medical Reviewer's Overall Safety Conclusion:

The safety data from the previously reviewed three phase 1, and single phase 3 studies², coupled with the present, single phase 1 bridging study suggest that NT0102 is reasonably well tolerated with a safety profile similar to those of other extended release methylphenidates.

VI. OCP Review Conclusion

A preliminary review by Drs. Huixia Zhang, and Hao Zhu³ of the Office of Clinical Pharmacology (OCP)/Division of Clinical Pharmacology I determined that an adequate link was established among the developed formulations (clinical trial formulation, clinical pharmacology formulation, and commercial scale [to-be-marketed] formulation), and to the Listed Drug Metadate CD, through two relative bioavailability studies. Further determinations included: 1) that similar PK properties were demonstrated for children and adolescents with ADHD, and healthy adults; 2) that MPH XR-ODT was *not bioequivalent to Metadate CD*, the Listed Drug, and that approval needed to be based on the results of the efficacy and safety trial; 3) and that a high fat meal decreased C_{max} and increased AUC of MPH following MPH XR-ODT administration. Consequently, they recommended that patients consistently take MPH XR-ODT either with food or on an empty stomach. OCP concluded that there was sufficient clinical pharmacology and biopharmaceutics information provided in the NDA to support a recommendation of approval of MPH XR-ODT.

² Mannheim G, Zhang J. Clinical Review, NDA 205, 489. 505 (b) (2), COTEMPLA XR-ODT: Methylphenidate Extended Release Orally Disintegrating 10 mg, 20 mg, and 30 mg Tablets; pgs. 3-10; October 11, 2015.

³ Zhang H, Zhu H. Office of Clinical Pharmacology (OCP)/Division of Clinical Pharmacology I, Draft Review, May 2017.

VII. Pharmacology/Toxicology Review

A verbal report by Drs. Mathew and Elayan⁴ of Pharmacology and Toxicology identified no Pharmacology/Toxicology issues preventing approval of this NDA. Pregnancy and Lactation Labeling Rule (PLLR) Recommendations were recommended for Section 8, 14 of the label. No review has been finalized at the time of filing of this Clinical Review.

VIII. Quality Assessment Reviews

A combined Draft Executive Summary of the Office of Pharmaceutical Quality Review by Drs. David Claffey, Andrei Ponta, Gene Holbert, Akm Khairuzzaman⁵ concluded that the same batch was used in the clinic as was used in the bridging study and that there do not appear to be any quality related problems with this batch. Data support a 15 month drug product expiry period.

Draft Drug Substance and Drug Product Reviews concluded that the drug substance and bioequivalence study comparing the clinical trial to the to-be-marketed formulation was adequate. They found that the tablet was unstable outside the blister packaging especially when exposed to higher humidity at room temperature and made labeling recommendations for the tablet to be administered immediately after removal from the package.

IX. Proprietary Name Review

A Division of Medication Error Prevention and Analysis (DMEPA) letter by T. Bridges⁶ concluded that the proposed proprietary name, Cotempla XR-ODT was conditionally acceptable.

X. Patient Labeling Review

A Combined Patient Labeling, Medication Guide Review by S. Hutchins and C. Bradshaw⁷ from the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) was completed on May 24, 2017 found the Medication Guide to be acceptable and made various changes which were sent to the sponsor.

XI. Label, Labeling and Packaging Review

A combined Review of Revised Label and Labeling review by Drs. Holmes and White⁸ from The Division of Medication Error Prevention and Analysis (DMEPA) concluded that the revised blister labels and carton labeling for Cotempla XR-ODT were acceptable from a medication

⁴ Mathew S, Elayan I. Office of Clinical Pharmacology, May, 2017.

⁵ Claffey D, Ponta A, Holbert G, Khairuzzaman A. Office of Pharmaceutical Quality. Draft Executive Summary, May 24, 2017.

⁶ Bridges T. Division of Medication Error Prevention and Analysis March 31, 2017

⁷ Hutchins S, Bradshaw C. Division of Medical Policy Programs (DMPP), Office of Prescription Drug Promotion (OPDP); Review of Patient Labeling: Medication Guide (MG); 05/24/2017.

⁸ Holmes L, White L. Division of Medication Error Prevention and Analysis (DMEPA), Review of Revised Label and Labeling, May 26, 2017.

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COTEMPLA XR-ODT: Methylphenidate Extended Release Orally Disintegrating 10 mg, 20 mg, and 30 mg Tablets error perspective. No additional Product Labeling, Medication Guide and/or and Carton/ Container Labeling Comments have been received at the time of filing of this review.

XII. Controlled Substance Review

A combined review from the Controlled Substance Staff recommended that the Dependence section (9.3) in the package insert be modified so as to be consistent with other methylphenidate products which include the full spectrum of MPH withdrawal symptomatology:

‘Withdrawal symptoms after abrupt cessation following prolonged high-dosage administration of CNS stimulants include dysphoric mood; depression; fatigue; vivid, unpleasant dreams; insomnia or hypersomnia; increased appetite; and psychomotor retardation or agitation.’

XIII. Inspection

Shila Nkah⁹ of the Office of Study Integrity and Surveillance (OSIS), Division of New Drug Bioequivalence Evaluation (DNDBE) recommended accepting the data from the study site without an on-site inspection. This was because the clinical or analytical site for the pivotal study 1005 was recently inspected and no issues were identified.

XIV. Pregnancy and Lactation Labeling Review

Dr. Miriam Dinatale and Dr. Lynne Yao¹⁰ of the Division of Pediatric and Maternal Health (DPMH) revised sections 8.1(Pregnancy), 8.2 (Lactation) and 17 (Patient Counseling Information) of Cotempla XR-ODT labeling for compliance with the Pregnancy and Lactation Labeling Rule (PLLR).

XV. Pediatric Plan

Sponsor previously requested a (b) (4). The Division previously informed them that we would grant a Partial Waiver for children age 0-4 years of age with ADHD and a Deferral for ADHD studies in children, 4-6 years old¹¹. Three post-marketing pediatric studies) in 4-6 year olds are required (pharmacokinetic; double blind placebo controlled; and open-label extension.

XVI. Conclusions and Recommendations

The efficacy and safety data from the primary efficacy and safety study (Study NT0102.1004) suggest that NT0102 is effective and well tolerated with a safety profile similar to other extended

⁹ Nkah S, Office of Study Integrity and Surveillance (OSIS), Division of New Drug Bioequivalence Evaluation (DNDBE), Memorandum entitled Recommendation to Accept Data Without an On-Site Inspection; February 17, 2017.

¹⁰ Dinatale M, Yao L. Division of Pediatric and Maternal Health (DPMH). Pregnancy and Lactation Labeling Review. February 06, 2017.

¹¹ Audain G. PeRC Meeting Minutes of September 02, 2015, pg. 4. September 23, 2015.

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COTEMPLA XR-ODT: Methylphenidate Extended Release Orally Disintegrating 10 mg, 20 mg, and 30 mg Tablets release MPH pharmacotherapies. The current bridging study (NT0102.1005) indicates that the commercial scale formulation NT0102.1005 is similar to clinical trial formulation of NT0102.1005 under fasting conditions and that there are no quality related problems with the batch.

From a clinical perspective, there are no objections to COTEMPLA XR-ODT being approved for the treatment of pediatric and adolescents with ADHD between the ages of 6-17 years. Metadate CD, the RLD, was previously approved in pediatric and adolescents between the ages of 6-15 years. It is recommended that we approve COTEMPLA XR-ODT for an additional 2 years up to 17 years, so as to provide complete adolescent age spectrum coverage. This would be consistent with the current standard of practice and prescribing regimen of other approved methylphenidate products that includes dosing typically up to and including 17 years (6-12 years, 13-17 years).

Despite there being some well-defined clinical differences between adolescent and pediatric ADHD (co-morbid disorders of oppositional defiance, conduct, substance, mood and anxiety being more common in adolescent ADHD), there is no evidence from the available literature to suggest that COTEMPLA XR-ODT would not also be clinically effective in this 16-17 year age group and that it would not substantially be different from the already known, labeled risks. The COTEMPLA XR-ODT labeling adequately describes the most commonly known methylphenidate adverse events in this age group and are not substantially different from the 6-15 year age group.

XVII. Appendix

Table 1: Overview of Studies¹²

Study No.	Design	No. of Patients Treated for Each Study Group	Duration	Patient Population
Phase 1 Studies				
NT0102.1001	BA/BE: randomized, active-controlled, crossover	MPH XR-ODT (two 30 mg) Form. 1: 41 MPH XR-ODT (two 30 mg) Form. 2: 39 METADATE CD: 40	Single-dose, 3-period, 3-treatment	Healthy adult volunteers fasted
NT0102.1002	BA: randomized, crossover	MPH XR-ODT (two 30 mg) Fed: 24 MPH XR-ODT (two 30 mg) Fasted: 23	Single-dose, 2-period, 2-treatment	Healthy adult volunteers fed/fasted
NT0102.1003	BA: open label	MPH XR-ODT (two 30 mg): 32	Single-dose, 1-treatment	Children (6-12 years of age) and adolescents (13-17 years of age) with ADHD
NT0102.1005	BA/BE: randomized, crossover	MPH XR-ODT Commercial Scale Formulation Fed: 47 MPH XR-ODT Commercial Scale Formulation Fasted: 48 MPH XR-ODT Clinical Trial Formulation Fasted: 47	Single-dose, 3-period, 3-treatment	Healthy adult volunteers fed/fasted
Phase 3 Study (Optimal Doses Used During Double-Blind Phase)				
NT0102.1004	Randomized, double-blind, placebo-controlled, parallel group	Not Randomized 2 MPH XR-ODT (20-60 mg): 44 Placebo: 41 Overall: 87	5 periods: screening (4 weeks), washout (3-7 days), dose-optimization (4 weeks), dose stabilization (1 week), treatment (1 week) culminating in a classroom testing day)	Children (6-12 years of age) with ADHD

¹² Clinical Overview (Sec 2.5), (Methylphenidate Extended Release Orally Disintegrating Tablet), Table 8: Overview of Studies Included in the Summary of Clinical Safety, pg. 27, December 19, 2016 Submission

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Table 2: List of Investigators: NT0102.1005¹³

George J. Atiee, M.D.	Worldwide Clinical Drug Development Solutions 2455 N.E. Loop, Suite 150 San Antonio, TX 78217	210-635-1500
Elizabeth Camacho, FNP-BV	Worldwide Clinical Drug Development Solutions 2455 N.E. Loop, Suite 150 San Antonio, TX 78217	210-635-1500
Nancy K. Hinit, M.D.	Worldwide Clinical Drug Development Solutions 2455 N.E. Loop, Suite 150 San Antonio, TX 78217	210-635-1500
Steven Hinit, M.D.	Worldwide Clinical Drug Development Solutions 2455 N.E. Loop, Suite 150 San Antonio, TX 78217	210-635-1500
Vanessa Smeberg, M.D.	Worldwide Clinical Drug Development Solutions 2455 N.E. Loop, Suite 150 San Antonio, TX 78217	210-635-1500
Cynthia A. Zamora, M.D.	Worldwide Clinical Drug Development Solutions 2455 N.E. Loop, Suite 150 San Antonio, TX 78217	210-635-1500

¹³ Protocol NT0102.1005, Appendix 16.1.4, pgs 1-47, December 19, 2016 Submission

Table 3: Adverse Events by System Organ Class and Preferred Term: NT0102.1005¹⁴

System Organ Class\ Preferred Term	NT0102 Methylphenidate XR-ODT 60 mg (Formulation 1) (Fed)		NT0102 Methylphenidate XR-ODT 60 mg (Formulation 1) (Fasted)		NT0102 Methylphenidate XR-ODT 60 mg (Formulation 2) (Fasted)	
	# Reports	# Subjects	# Reports	# Subjects	# Reports	# Subjects
Number of Subjects Dosed		47		48		47
<i>Cardiac disorders</i>	2	2 (4.3%)	0	0 (0.0%)	0	0 (0.0%)
Palpitations	2	2 (4.3%)	0	0 (0.0%)	0	0 (0.0%)
Mild	2	2 (4.3%)	0	0 (0.0%)	0	0 (0.0%)
<i>Gastrointestinal disorders</i>	1	1 (2.1%)	0	0 (0.0%)	1	1 (2.1%)
Dry mouth	1	1 (2.1%)	0	0 (0.0%)	0	0 (0.0%)
Mild	1	1 (2.1%)	0	0 (0.0%)	0	0 (0.0%)
Nausea	0	0 (0.0%)	0	0 (0.0%)	1	1 (2.1%)
Mild	0	0 (0.0%)	0	0 (0.0%)	1	1 (2.1%)
<i>General disorders and administration site conditions</i>	0	0 (0.0%)	2	2 (4.2%)	0	0 (0.0%)
Energy increased	0	0 (0.0%)	1	1 (2.1%)	0	0 (0.0%)
Mild	0	0 (0.0%)	1	1 (2.1%)	0	0 (0.0%)
Vessel puncture site pain	0	0 (0.0%)	1	1 (2.1%)	0	0 (0.0%)
Mild	0	0 (0.0%)	1	1 (2.1%)	0	0 (0.0%)
<i>Metabolism and nutrition disorders</i>	2	2 (4.3%)	0	0 (0.0%)	0	0 (0.0%)
Decreased appetite	2	2 (4.3%)	0	0 (0.0%)	0	0 (0.0%)
Mild	2	2 (4.3%)	0	0 (0.0%)	0	0 (0.0%)
<i>Nervous system disorders</i>	1	1 (2.1%)	1	1 (2.1%)	0	0 (0.0%)
Dizziness	0	0 (0.0%)	1	1 (2.1%)	0	0 (0.0%)
Mild	0	0 (0.0%)	1	1 (2.1%)	0	0 (0.0%)
Somnolence	1	1 (2.1%)	0	0 (0.0%)	0	0 (0.0%)
Moderate	1	1 (2.1%)	0	0 (0.0%)	0	0 (0.0%)
<i>Psychiatric disorders</i>	0	0 (0.0%)	1	1 (2.1%)	2	2 (4.3%)
Agitation	0	0 (0.0%)	0	0 (0.0%)	1	1 (2.1%)
Mild	0	0 (0.0%)	0	0 (0.0%)	1	1 (2.1%)
Hypervigilance	0	0 (0.0%)	1	1 (2.1%)	1	1 (2.1%)
Mild	0	0 (0.0%)	1	1 (2.1%)	1	1 (2.1%)

¹⁴ Protocol NT0102.1005, Clinical Study Report: Table 3, MedDRA Summary of Treatment Emergent Adverse Events by Primary System Organ Class, Preferred Term and Severity, pgs. 52-53, December 19, 2016 Submission

Table 4: Events Schedule: NT0102.1005, Cross Over Bioavailability, Bioequivalence Study under Fasting and Fed Conditions in 48 adults, 18-69 years using 3 formulations

PROCEDURE	Screening	Periods 1, 2, and 3			End-of-Study/ Early Termination
		Check-in	Day 1	Day 2	
Informed consent	X				
Medical and medication histories	X	X			
ECG	X				X
Vital signs ¹	X		X	X	X
Physical examination	X				X
Oral cavity examination	X	X			
Biochemistry, hematology, urinalysis	X				X
Serology	X				
Urine drug and cotinine screen	X				
FSH test (postmenopausal females) subjects	X				
Pregnancy test (female subjects) ²	X	X			
Suicidality assessment	X	X			
Urine drug and alcohol screen		X			
Drug administration			X		
Blood sample collection for pharmacokinetic analysis ³			X	X	
Outpatient visit ⁴				X	X
Adverse events		X	X	X	X

1. A full set of vital signs (blood pressure, pulse rate, respiration rate, and temperature) were measured at screening, at 0 hour (predose), at 24 hours postdose, and at 36 hours postdose (last visit) in each study period. Blood pressure and pulse rate only were measured at 4 and 8 hours postdose in each study period.
2. All female subjects underwent a serum pregnancy test at screening and a urine pregnancy test at each check-in.
3. Blood samples (1 x 6 mL) were collected at 0 (predose) and at 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 5.5, 6, 6.5, 7, 8, 10, 12, 18, 24, and 36 hours after dosing.
4. Subjects remained in the research center until completion of the 24-hour procedures and returned for an outpatient visit at approximately 36 hours postdose in each study period.

Table 5: Differences in Release Control Components of MPH XR-ODT Formulations

(b) (4)		Function	Clinical Trial Formulation	Clinical Pharmacology Formulation	Commercial Scale Formulation
Extended Release/ Delayed Release (ER/DR)	Lot#	--	2E116E	1E101A	6P081
(b) (4)					

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/s/

GLENN B MANNHEIM

06/02/2017

JASMINE C GATTI

06/05/2017

Correction on Cover Sheet of age of intended population: Intended Population(s) Attention Deficit Disorder (6 -17 Years)

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: 5 November 2015

FROM: Mitchell V. Mathis, M.D.
Director
Division of Psychiatry Products, HFD-130

TO: File NDA 205489

SUBJECT: Complete Response (CR) Decision for Methylphenidate (MPH) Extended-Release (ER) Orally Disintegrating Tablet (ODT) for the Treatment of Attention-Deficit Hyperactivity Disorder (ADHD)

Background and Summary

Cotempla XR-ODT is an extended-release (ER) orally disintegrating tablet (ODT) formulation of a well-known drug to treat attention-deficit hyperactivity disorder (ADHD). ODT formulations are developed to facilitate swallowing, which is the purpose of this formulation which would be used in pediatric patients. Many different MPH products are approved to treat ADHD; one of these products is a transdermal patch and another is a liquid suspension, but the rest require swallowing a capsule or tablet. No ODT formulation of MPH has been approved.

This application is a 505(b)(2) citing Metadate CD as the reference listed drug (RLD) and requests three strengths (10 mg, 20 mg, and 30 mg) be approved for marketing. The Offices of Product Quality (OPQ) and Clinical Pharmacology (OCP) have recommend a Complete Response (CR) action secondary to a product formulation change that results in bioinequivalence from the clinical drug product used in the safety/efficacy study. The primary difference from the clinical drug product formulation is a (b) (4) in the delayed release and extended release (b) (4) in the to-be-marketed formulation; this difference is approximately (b) (4) % (b) (4) for both components, and the pharmacokinetic (PK) and pharmacodynamic (PD) properties of this drug in this disease are so closely related that the team feels the change requires a bridging study to the clinical drug formulation prior to recommending approval. OCP has also asked that a food effect study with the to-be-marketed formulation be conducted with the to-be-marketed formulation.

The clinical review team agrees with the assessments and recommendations made by OPQ and OCP, and I agree that we must issue a Complete Response Letter to resolve the deficiencies in this application.

Clinical/Statistical

Glenn Mannheim, M.D. was the clinical reviewer for this application. Dr. Thomas Birkner was the statistical reviewer for this application. The single study submitted to support his claim (NT0102.1004, a laboratory classroom study in children 6-12 years old with ADHD) was reviewed and found to be positive on difference in combined score Swanson, Kotkin, Agler, M-Flynn, and

Pelham (SKAMP) rating scale for ADHD, a commonly accepted measure of ADHD symptomatology. The secondary endpoints were designed to identify time of onset and duration of effect.

Eighty-seven children (ages 6-12 years) with ADHD were randomized to receive test drug in different doses, which were compared to placebo. The SKAMP combined scores were collected each hour for 13 hours after dosing and then averaged and compared to placebo. The primary analysis used an Analysis of Covariance (ANOVA) model and the treatment difference was -11 (lower is less ADHD symptoms) with a p-value less than 0.0001) for the primary endpoint. The onset of efficacy (first separation of drug from placebo) was at Hour 1 (first measurement) and the duration of effect (last separation of drug from placebo) was at Hour 12.

No new safety issues were identified with the trial formulation of test drug. As noted above, the formulation used for this study was meaningfully different than the to-be-marketed formulation, and the applicant has not conducted a bridging study, and so Dr. Mannheim's recommendation is to issue a CR Letter, and I agree with him.

Pharmacology/Toxicology

Dr. Mathew reviewed this submission. She did not identify any issues precluding approval from her perspective. No new impurities, degradants, or novel excipients were identified that would require additional toxicological characterization.

Clinical Pharmacology/Biopharmaceutics

Dr. Balimane reviewed this application. He determined that the information in the application does not support approval for the following reasons:

1. No adequate link established between the clinical trial formulation and the to-be-marketed formulation (see above).
2. No adequate link established between the to-be-marketed formulation and the RLD.
3. Pediatric PK information obtained with the clinical pharmacology formulation insufficient to support extrapolation of efficacy findings from children into adolescents (b) (4) for the to-be-marketed formulation.
4. Food effect from the prior formulation may not inform the food effect for the to-be-marketed formulation.

OCP has recommended the sponsor conduct a bioequivalence study to link the to-be-marketed formulation with the clinical trial formulation under fasted conditions and conduct a food effect study on the to-be marketed formulation prior to approval, and I agree with them.

Office of New Drug Quality Assessment (ONDQA)

Dr. Claffey was the Technical Lead for this application. He concluded that the commercial drug product would have substantially (about (b) (4) %) delayed/extended release (b) (4) than the product used to conduct the relevant studies, and that changes in drug product (b) (4) would require bioequivalence studies. He has recommended a CR action, and I agree with him.

Advisory Committee

There were no issues with this application that required the input of an advisory committee.

Labeling/Medication Guide

Labeling was not negotiated for this CR action.

CONCLUSIONS

The Division will issue a Complete Response Letter and outline the deficiencies for the applicant. This action will be completed by the PDUFA date.

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/s/

MITCHELL V Mathis
11/05/2015

MEMORANDUM **DEPARTMENT OF HEALTH AND HUMAN
SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND
RESEARCH**

DATE: October 25, 2015

FROM: Jing Zhang, MD. PhD.
Medical Team Leader, Division of Psychiatry Products
HFD-130

SUBJECT: Cross Discipline Team Leader Review

NDA/Supp#: 205489

**Proprietary/
Established name:** Cotempla XR-ODT/Methylphenidate extended release oral
disintegrating tablet

**Dosage forms/
Strength:** Oral Tablets: 8.7 mg, 17.3 mg, and 25.9 mg (equivalent to 10, 20,
and 30 mg methylphenidate HCl salt, respectively)

Indication: Attention deficit/hyperactivity disorder in children aged 6 to (b) (4)
years old

Recommendation: Complete Response

I. Introduction and Background

Neos Therapeutics, Inc. has submitted a New Drug Application (NDA) for Methylphenidate (MPH) Extended Release Orally Disintegrating Tablets (XR-ODT), trade name Cotempla XR-ODT, for the treatment of ADHD via a 505 (b) (2) route using Metadate CD[®] as the reference listed drug (RLD). Metadate CD[®] (methylphenidate hydrochloride) Extended-Release Capsules (NDA 21-259) is an extended release methylphenidate, which was approved on February 02, 2001 for indication of ADHD in children 6 (b) (4) years old.

Under IND 109,108, Neos Therapeutics had a pre-IND meeting with the Division on September 20, 2010 to discuss this program. FDA suggested an efficacy study. On May 21, 2013, the Division met with the sponsor (a Type C Meeting) and provided feedback on the Phase 3 efficacy study protocol. A pre-NDA meet was held on Jan. 31, 2013. FDA indicated that the current MPH XR-ODT would support filing.

The clinical program of MPH XR-ODT consists of three phase 1 clinical pharmacology trials, relative bioavailability (NT0102.1001), food-effect (NT0102.1002), and pediatric pharmacokinetic trials (NT0102.1003) and a single clinical efficacy and safety trial (NT0102.1004). Neos is requesting marketing approval for three strengths of Cotempla XR-ODT, 10 mg, 20 mg, and 30 mg (equivalent to methylphenidate hydrochloride).

II. Summary of Conclusions and Recommendations from Review Teams

1. CMC

The CMC review team identified a major deficiency that affects the approvability of this drug product and recommended a Complete Response (CR) action. David Claffey, PhD., is the technical lead for CMC review team.

(b) (4)

In vitro data were provided to support this. The CMC review team discussed the issue with the biopharm review team and determined that such a relatively large change (b) (4) cannot be supported by in vitro data only – and that bioequivalence studies would be required. There is more discussion regarding this issue in the clinical pharmacology review section of this document.

Due to this major deficiency, the CMC review team had the following comments to be conveyed to the sponsor in the CR letter:

- Bridge the clinical and commercial drug product formulations with a bioequivalence study.
- Establish, validate and fully justify an unequivocal commercial operation and control. (b) (4)

2. Nonclinical Pharmacology/Toxicology

Shiney V. Mathew, PhD, is the pharmacology/toxicology reviewer for this submission. For nonclinical studies to support the current application, the Sponsor is relying on the Agency's previous findings of safety (and efficacy) for METADATE CD®. Dr. Mathew felt that the previous findings of safety (and efficacy) for METADATE CD® are adequate to support the clinical doses of methylphenidate in COTEMPLA XR®, and no impurities, degradants, or novel excipients in COTEMPLA XR® that would require additional toxicological characterization at this time. She concluded that there are no Pharmacology/Toxicology issues that would prevent the approval of this NDA.

3. Clinical Pharmacology/Biopharmaceutics

Praveen Balimane, PhD is the clinical pharmacology reviewer for this submission. The clinical pharmacology review team recommended a CR action because the sponsor did not provided adequate information to support this NDA approval.

The sponsor developed three formulations including a clinical pharmacology formulation (Lot: 1E101A), a clinical trial formulation (Lot: 2E116E), and a to-be-marketed formulation (Proposed). The clinical pharmacology formulation (Lot: 1E101A) was used in the relative bioavailability trial, food effect trial, and pediatric pharmacokinetic trial. The clinical trial formulation (Lot: 2E116E) was used in the single efficacy and safety trial. It was identified in the review cycle that all three formulations are significantly different from each other (see Table 1). The to-be-marketed formulation will have (b) (4) (w/w) delayed release and (b) (4) (w/w) (b) (4) extended release (b) (4) than the clinical trial formulation. In addition, there is about (b) (4) % change on the release controlling (b) (4) between the clinical pharmacology formulation and the clinical trial formulation. No additional bioequivalence study was conducted to bridge the three formulations.

Table 1. Summary of the Differences among the Three Different Formulations

Component	Function	Quantity per 30 mg Strength Tablet (mg)		
		1E101A	2E116E	Proposed
(b) (4)				(b) (4)
(b) (4)				
Crospovidone				
Sucralose				
Citric Acid				(b) (4)
(b) (4) Grape				(b) (4)
(b) (4)				
Natural Masking Type Powder				
(b) (4)				
Lake Blend Purple				(b) (4)
Magnesium Stearate				

1E101A: clinical pharmacology formulation

2E116E: clinical trial formulation

Proposed: to-be-marketed formulation

The clinical pharmacology review team summarized the following deficiencies:

1. No adequate link has been established between the clinical trial formulation and the to-be-marketed formulation. Due to the lack of adequate link, the findings from the efficacy and safety trial based on the clinical trial formulation may not inform the effectiveness of the product intended to be marketed.
2. No adequate link has been established between the to-be-marketed formulation (clinical trial formulation), and the RLD (Metadate CD). Hence, the agency's

findings on efficacy and safety of the RLD may not be used to support the approval of the product intended to be marketed.

3. Pediatric pharmacokinetic information obtained with the clinical pharmacology formulation is insufficient to support extrapolation of efficacy findings (based on clinical trial formulation) from children into adolescents (b) (4) for the to-be-marketed formulation.
4. Food effect findings based on the clinical pharmacology formulation may not inform the food effect on the to-be-marketed formulation. The to-be-marketed formulation contains the (b) (4) amount of release controlling (b) (4) among the three formulations. Because the level of interaction between food and the release controlling (b) (4) is unclear, it may not be appropriate to extrapolate the food effect findings from the clinical pharmacology formulation to the to-be-marketed formulation.

The clinical pharmacology review team recommended the following remedy actions:

- The sponsor should conduct a bioequivalence study to link the to-be-marketed formulation with the clinical trial formulation under fasted condition.

It has been shown that the release controlling (b) (4) of the clinical pharmacology formulation is bracketed by the clinical trial formulation and the to-be-marketed formulation. Therefore, should bioequivalence be demonstrated between these two formulations i.e. an adequate link established between the to-be-marketed formulation and clinical trial formulation, it will also be sufficient to bridge between the clinical pharmacology formulation and the to-be-marketed formulation. Hence deficiency 1 through 3 can be resolved.

- Food effect on the to-be-marketed formulation should be assessed to address deficiency 4.

Food effect on the to-be-marketed formulation can be evaluated by adding one more arm (i.e. to be marketed formulation in fed state) in the above bioequivalence study.

5. Clinical Review

The sponsor submitted only one Phase 3 clinical study, study NT0102.1004, to support a NDA submission. The clinical data from this application was reviewed by Glenn Mannheim, MD, a medical reviewer. Thomas Birkner, PhD, is the statistical reviewer and his review was focused on efficacy review only. Please refer to their reviews for more detailed review information.

Study NT0102.1004

Study Design

A randomized, multicenter, double-blind, placebo-controlled, parallel group study of MPH polistirex XR-ODT (equivalent to 20-, 30-, 40-, or 60 mg of MPH HCl) in children (6-12 years of age) with ADHD conducted in a laboratory classroom setting. The study was conducted in 4 US site.

The study enrolled male and female children, 6 to 12 years of age, with a diagnosis of ADHD (inattentive, hyperactive-impulsive, or combined types) based on DSM-IV-TR criteria, taking a stable dose of 20-60 mg of Metadate CD or comparable dose of another XR or IR formulation of MPH at screening.

There were 5 periods in this study: screening, washout (3-7 days), open-label stepwise dose optimization (4 weeks), dose stabilization (1 week), and a 1 week double-blind parallel group treatment period culminating in a laboratory classroom session.

In the open-label, dose optimization period, the eligible subjects started at 20 mg/day of MPH XR-ODT, and increased each week (from 20- to 30- to 40- to 60 mg of MPH XR-ODT per day) until an optimal dose, defined as a reduction of $\geq 30\%$ on the ADHD-RS-IV and a CGI-I score of 1 or 2, was reached followed by a 1 week stabilization period. No dose adjustments were permitted during stabilization period.

In the 1-week, double-blind treatment period, patients were randomized in a 1:1 ratio to either the optimized daily dose of MPH XR-ODT or placebo. The last day of the double-blind treatment period (Day 7), was the classroom test day comprised of classroom sessions arranged at baseline, and 1, 3, 5, 7, 10, 12, and 13 hours post-dose with each session lasting about 30 minutes. The SKAMP rating scale was completed by trained classroom raters. Different versions of the PERMP at the same level were administered across the multiple classroom sessions.

The primary endpoint is the average of the SKAMP-Combined (Attention and Deportment) scores over the test day (not including baseline assessment) with assessments taken at baseline, and 1, 3, 5, 7, 10, 12, and 13 hours post-dose. The key secondary endpoints are 1) onset of effect of MPH XR-ODT, and 2) duration of effect of MPH XR-ODT.

Other secondary endpoints include the average of the SKAMP-Attention scores over the test day, the average of the SKAMP-Deportment scores over the test day, the average of the PERMP-A scores over the test day, and the average of PERMP-C scores over the test day.

The primary analysis was carried out using an analysis of covariance (ANCOVA) model with factors for treatment and site with a covariate for pre-dose SKAMP-Combined Score. Analyses were performed using both the Full Analysis Set (FAS) and the Per Protocol Set (PPS), with the FAS considered the primary population. A mixed model repeated measures (MMRM) approach was used to assess whether the effect of treatment on the SKAMP-Combined Score post-dose was dependent on the time of assessment post-dose. Terms for treatment, site, pre-dose SKAMP-Combined Score at the classroom testing session, time of

assessment post-dose, and treatment-by-time interaction were included in this model as fixed effects and subject was included as a random effect. In addition, this model was used to estimate the differences in the SKAMP-Combined Score between treatments at each post-dose assessment. An unstructured covariance matrix was used to model the covariance of within-subject scores; and the Kenward-Roger approximation to estimate denominator degrees of freedom.

EFFICACY RESULTS

A total of 87 subjects were enrolled in the study. There were more males (n=54, 65.9 %) enrolled, which is consistent with the epidemiology distribution of this disease. Age, race, ethnicity, height, weight, and body mass index (BMI) were similar in both groups. The mean age in years was 9.2 across both groups. The majority of the subjects were White (79.3%) followed by Black or African American (12.2%). There were 34.1% of subjects who were Hispanic or Latino. The average height was 138 cm (108 to 169 cm) and the average weight was 36.3 kg (15.4 to 82.6 kg).

A total of 83 subjects completed dose stabilization. The FAS comprised of 82 subjects (One did not have baseline SKAMP score).

The most frequent optimal dose level used during the double-blind phase was 60 mg (33.3%), followed by 40 mg (27.6%), 30 mg (24.1%), and 20 mg (12.6%). Distribution was similar across treatments.

Primary Endpoint

The primary efficacy endpoint is the average of all post-dose SKAMP-Combined scores assessed at 1, 3, 5, 7, 10, 12, and 13 hours post-dose during the classroom testing day on Visit 8.

Our statistician, Dr. Birkner, pointed out in his review that the SKAMP pre-dose score at the laboratory classroom day (Visit 8, after one week of double-blind treatment) for the MPH XR-ODT group was numerically worse at each optimized dose level compared to placebo (26.8 vs. 19.1, respectively) even though the SKAMP scores were similar between treatments at Visit 7 (the practice classroom session before the double-blind treatment). He thought the SKAMP score difference at Visit 8 might be caused by withdrawal effect (24 hours post previous dose) from MPH XR-ODT treatment.

Table 2 summarizes the differences in least squares means (LS means) between MPH XR-ODT and placebo treatment groups for SKAMP-Combined scores. There was no significant site-level effect for the SKAMP-Combined Score (p-value = 0.1216 [FAS]). The study showed a treatment effect of -11.0 (95% CI: -13.9, -8.2) at a significance level of $p < 0.0001$ in the FAS.

Table 2. Primary Analysis Results for the SKAMP-Combined Scores Averaged Over the Classroom Testing Day

	SKAMP-Combined (Full Analysis Set) N=82 (Primary Endpoint Analysis)	SKAMP-Combined (Per Protocol Set) N=80 (Primary Endpoint Sensitivity Analysis)	SKAMP-Attention (Full Analysis Set) N=82	SKAMP- Department (Full Analysis Set) N=82
LS Mean (95% CI)				
NT0102	14.3 (12.2, 16.4)	14.6 (12.4, 16.7)	7.7 (6.7, 8.7)	6.7 (5.2, 8.1)
Placebo	25.3 (23.0, 27.6)	25.9 (23.5, 28.3)	12.2 (11.1, 13.4)	12.8 (11.3, 14.3)
Difference	-11.04 (-13.9, -8.20)	-11.29 (-14.2, -8.42)	-4.49 (-5.91, -3.08)	-6.13 (-7.97, -4.28)
P-value	<0.0001	<0.0001	<0.0001	<0.0001
Baseline Pre-dose				
P-value	<0.0001	<0.0001	<0.0001	<0.0001
Site Main Effect				
P-value	0.1216	0.1338	0.0098	0.6299

Abbreviations: CI= confidence interval, LS Mean=least squares mean, SKAMP=Swanson, Kotkin, Agler, M-Flynn, and Pelham (Source: Study Report p. 44; Results [SKAMP-Combined, SKAMP-Attention, and SKAMP-Department] for FAS replicated by reviewer [Primary_Analysis_1004.sas and SKAMP_Deport_Att_1004.sas])

The sensitivity analyses for the primary endpoint include 1) Per Protocol Set; and 2) Non-parametric Model. The results from both analyses were consistent with the result of primary analysis.

Key Secondary Efficacy Endpoint:

The key secondary endpoints are 1) onset of effect of MPH XR-ODT, and 2) duration of effect of MPH XR-ODT. Onset of efficacy was met at the first post-dose assessment of 1 hour, and duration of efficacy was consecutively observed through Hour 12, but not at Hour 13 (see Table 3).

Table 3. Least Squares Mean SKAMP-Combined Scores at All Time Points - FAS

Time Point (Hour)	Placebo LS Mean (SE)	NT0102 LS Mean (SE)	Difference LS Mean (SE)	95% CI	P Value
1	21.2 (1.19)	10.5 (0.993)	-10.7 (1.44)	(-13.6, -7.86)	<0.0001
3	23.4 (1.43)	7.28 (0.831)	-16.1 (1.55)	(-19.2, -13.0)	<0.0001
5	25.5 (1.52)	9.86 (1.16)	-15.7 (1.82)	(-19.3, -12.1)	<0.0001
7	24.8 (1.51)	12.1 (1.42)	-12.7 (1.99)	(-16.7, -8.77)	<0.0001
10	25.6 (1.80)	18.5 (1.48)	-7.11 (2.25)	(-11.6, -2.61)	0.0024
12	27.1 (1.48)	22.7 (1.42)	-4.46 (1.97)	(-8.37, -0.542)	0.0262
13	25.2 (1.60)	26.0 (1.52)	0.817 (2.13)	(-3.42, 5.06)	0.7022

Abbreviations: CI= confidence interval, LS Mean=least squares mean, SKAMP=Swanson, Kotkin, Agler, M-Flynn, and Pelham (Source: Study Report p. 46; Key secondary results replicated by reviewer [Key_Second_Analysis_1004.sas])

Other secondary endpoints:

Both PERMP endpoints (Attempted and Correct) showed significant treatment effects in the FAS based on the ANCOVA model.

Our statistical reviewer, Dr. Birkner, confirmed the sponsor's analysis results aforementioned. He also performed exploratory analyses on normality assumption

underlying primary analysis, effect on SKEPM deportment vs. attention score, efficacy by optimized dose, appropriateness of weight based dosing, baseline weight vs. optimized dose, and baseline BMI vs. optimized dose. He found that the normality assumption underlying the ANCOVA appears to hold; there is a numerically stronger impact on the deportment score compared to the attention score; the SKAMP raw mean scores are fairly similar within treatment groups (with the exception of the optimized dose of 20 mg in the placebo group) regardless of optimized dose; and there is no correlation between baseline weight, BMI, and optimal dose.

Dr. Birkner also did analyses on race, age, gender and region. He stated in his review that no firm conclusion can be drawn from those exploratory subgroup analyses due to limited sample size.

Discussion of Primary Reviewers' Comments and Conclusions

In summary, both Drs. Thomas Birkner, and Glenn Mannheim were concluded that MPH XR-ODT was statistically significantly superior to placebo at doses of 20 to 60 mg/day in the treatment of ADHD in children ages 6-12 years old measured by SKAMP total score in a laboratory classroom study (NT0102.1004).

SAFETY REVIEW

Dr. Mannheim reviewed the safety data submitted to his submission. There is only one phase 3 clinical study submitted to this NDA application, study NT0102.1004. The study is a laboratory classroom study started with a 5-week open-label treatment (dose optimization and dose stabilization period) with MPH XR-ODT. The double-blind treatment period was only 1 week long and it was after patients had been exposed to MPH XR-ODT for 5 weeks. Therefore, the safety data obtained from the 1 week double blind, placebo-controlled phase did not really present the safety profile of MPH XR-ODT. The safety review of this submission mainly focused on new safety signals and inconsistency of safety findings from our previous knowledge about MPH.

Exposure

There were a total of 185 subjects enrolled across all 4 studies who received at least 1 dose of the study medication. In the Phase 3 study, all 87 subjects received ≥ 20 mg MPH XR-ODT daily for ≥ 7 days. During the double-blind phase, 85 subjects were administered study drug: 6 on 20 mg MPH XR-ODT and 5 on matching placebo; 13 on 30 mg MPH XR-ODT and 8 on matching placebo; 11 on 40 mg MPH XR-ODT and 13 on matching placebo; and 14 on 60 mg MPH XR-ODT and 15 on matching placebo.

Major Safety Results

No deaths or serious adverse events (SAEs) were reported during the course of all studies.

a. Phase I studies

The nature of the adverse events (AEs) reported in the three Phase 1 studies of MPH XR-ODT (NT0102.1001, NT0102.1002, and NT0102.1003) was consistent with the mechanism of action of MPH. The most commonly reported AEs by preferred term (>5%) included nausea, vomiting, anxiety, nervousness, decreased appetite, headache, heart rate increase, and tachycardia. The AEs were mostly mild, some moderate, and none were severe or serious based on the sponsor's report.

b. Phase 3 study

There were 2 discontinuations due to treatment emergent adverse events (TEAEs), 1 due to influenza and 1 due to upper abdominal pain.

The AE profile of MPH XR-ODT appears similar to other MPH extended release-products. The most common TEAEs (i.e., >2% incidence) during the double-blind phase in subjects on MPH XR-ODT that occurred more frequently than in subjects on placebo were upper respiratory tract infection (4 subjects [9.1%]), burns second degree (1 subject [2.3%]), wound (1 subject [2.3%]), dizziness (1 subject [2.3%]), trichotillomania (1 subject [2.3%]), cough (1 subject [2.3%]), and epistaxis (1 subject [2.3%]).

The most common ($\geq 2\%$ in the MPH XR-ODT group and greater than placebo) adverse reactions (causality attributed to study drug by the investigators) reported in the Phase 3 controlled study were dizziness and trichotillomania.

No subjects had clinically significant abnormal laboratory values, vital signs, or end-of-study physical examinations that were assessed by the investigator as clinically significant.

Two subjects had abnormal ECG results. These subjects were referred to a pediatric cardiologist, who assessed the results as not clinically significant.

Per C-SSRS ratings, no subjects were found to exhibit suicidal ideation or suicidal behavior at any study visit.

In summary, no new safety signals from MPH XR-ODT were evident in this NDA submission. No deaths, severe or serious AEs or discontinuations due to TEAEs for MPH XR-ODT were reported in these studies. The MPH XR-ODT formulation was well tolerated. The AEs associated with MPH XR-ODT were consistent with the mechanism of action for MPH. The majority of TEAEs were mild or moderate in severity.

6. The Office of Scientific Investigations Inspection

The Office of Scientific Investigations (OSI) inspected selected data from 2 clinical study sites: Ann Childress, MD (Site 03, 50 subjects enrolled) because of some unusual data patterns observed by the statistical team, and Andrew J. Cutler, MD (Site 01, 19 subjects enrolled) because of large enrollment. The OSI inspection did not find any major deficiencies and a Form FDA 483 was not issued. The OSI reviewer, Jenn W. Sellers,

M.D., PhD. concluded that based on results of the inspections, it appears that the data submitted by the Applicant in support of the requested indication are acceptable and the studies appear to have been conducted adequately.

7. Labeling

Consult Review from the Division of Pediatric and Maternal Health (DPMH)

DPP requests DPMH to review the sponsor proposed labeling update in conformance with Pregnancy and Lactation Labeling Rule (PLLR) and review the available published literatures, with regard to methylphenidate and dexamethylphenidate use in pregnancy and lactation.

On December 4, 2014, the FDA announced the publication of the “Content and Format of Labeling for Human Prescription Drug and Biological Products; Requirements for Pregnancy and Lactation Labeling,” also known as PLLR. The PLLR requirements include a change to the structure and content of labeling for human prescription drug and biologic products with regard to pregnancy and lactation and create a new subsection for information with regard to females and males of reproductive potential. Specifically, the pregnancy categories (A, B, C, D and X) are removed from all prescription drug and biological product labeling and a new format is required for all products that are subject to the 2006 Physicians Labeling Rule format to include information about the risks and benefits of using these products during pregnancy and lactation.

The DPMH reviewer is Miriam Dinatale, D. O., who extensively reviewed 1) literatures, case reports, expert panel reviews from National Toxicology Program Center for Evaluation of Risks to Human Reproduction (2005) and the National Collaborative Perinatal project (1977), regarding methylphenidate and pregnancy; 2) literatures, a report from the American Academy of Pediatrics Committee on Drugs (2013) and books from a breast feeding expert (Dr. Tohomash Hale) related to Methylphenidate and lactation; and 3) literature regarding methylphenidate and human reproductive potential.

Dr. Dinatale had the following comments in her review 1) that there is limited data on the use of methylphenidate in pregnancy. Therefore, it is premature to conclude that methylphenidate is associated with increased risk for spontaneous abortions or adverse fetal outcomes. 2) The characteristics of methylphenidate suggest that methylphenidate is present in breast milk. There are insufficient data to recommend that breastfeeding be contraindicated during maternal use of methylphenidate. Although, there have been reports of infant adverse events with exposure to amphetamines, there have been no reported adverse events seen in infants of mothers who have taken methylphenidate while breastfeeding. 3) The only case report reviewed is not sufficient to conclude a drug associated risk. There are no other reports of any effect of methylphenidate on male or female fertility.

Dr. Dinatale concluded that the Division’s request to conduct deferred pediatric studies in patients 4 to less than 6 years of age has been updated to comply with the PLLR. She

recommended several revisions in section 8 of the product labeling, and these recommendations will be incorporated in the labeling review.

Other Labeling Reviews

Several revisions of physician labeling had been recommended by the review division, clinical pharmacology team, the Office of Prescription Drug Promotion (OPDP), the Division of Medication Error Prevention and Analysis (DMEPA) and Patient Labeling, the Divisions of Medical Policy Programs (DMPP). There recommendations will be incorporated into the product labeling. As it is very likely the Division will take a Complete Response action on this NDA, we will not start labeling negotiation at this time.

8. Pediatric Plan

The Division requested the sponsor to conduct deferred pediatric studies in patients 4 to less than 6 years of age based on the recent evidence that ADHD medications are being used in a substantial number of 4 and 5 year olds. The Division agreed a partial waiver for pediatric patients less than 4 years of age because the product would be ineffective and /or unsafe in this pediatric age group. The Pediatric Review Committee (PeRC) agreed with the Division's granting for a deferral for studies in patients 4 to less than 6 years of age and a partial waiver for pediatric patients less than 4 years of age.

9. Post Marketing Commitments or Requirements

See Section 8 Pediatric Plan. The Division requested the sponsor to conduct deferred pediatric studies in patients 4 to less than 6 years of age to evaluate the efficacy and safety of Methylphenidate XR ODT. The sponsor submitted an initial Pediatric Study Plan. This plan has been reviewed by the Division and PeCR. The comments had been conveyed to the sponsor.

10. Risk Minimization Action Plan

No Risk Minimization Action Plan deemed necessary for this submission.

11. Conclusion and Recommendation

The major deficiencies of this submission is that 1) no adequate link has been established between the clinical trial formulation and the to-be-marketed formulation, and 2) no adequate link has been established between the to-be-marketed formulation (clinical trial formulation), and the RLD (Metadate CD). To address these deficiencies, additional bioequivalence studies would be required. Therefore, I agree with the recommendation from CMC, OCP and clinical team that the Division should take a Complete Response action on this NDA because of these deficiencies.

Study NT0102.1004 have demonstrated that MPH XR-ODT was statistically significantly superior to placebo in reducing the symptoms of ADHD measured by change of SKAMP

total score in pediatric patients 6 to 12 years of age. There is no new safety signals identified in this supplement NDA review.

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/s/

JING ZHANG
10/25/2015

CLINICAL REVIEW

Application Type	NDA, 505(b) (2)
Application Number(s)	NDA 205,489
Priority or Standard	Standard
Submit Date(s)	January 9, 2015
Received Date(s)	January 9, 2015
Filing Meeting	February 26, 2015
PDUFA Goal Date	November 9, 2015
Division / Office	OND I/DPP
Reviewer Name(s)	Glenn Mannheim, M.D.
Review Completion Date	October 02, 2015
Established Name	Methylphenidate Extended Release Orally Disintegrating 10 mg, 20 mg, and 30 mg Tablets
(Proposed) Trade Name	COTEMPLA XR-ODT
Therapeutic Class	Stimulant
Applicant	Neos Therapeutics, Inc.
Formulation(s)	Extended-Release Orally Disintegrating Tablets
Dosing Regimen	20 mg to 60 mg Per Day
Indication(s)	Attention Deficit Disorder
Intended Population(s)	Attention Deficit Disorder (6 Years (b) (4))

Clinical Review

Glenn Mannheim, M.D.

NDA 205489, 505(b) (2)

COTEMPLA XR-ODT: Methylphenidate Extended Release Orally Disintegrating 10 mg, 20 mg, and 30 mg Tablets

I. Recommendation:

Neos Therapeutics, Inc. present 505(b)(2) application for Methylphenidate (MPH) Extended Release Orally Disintegrating Tablets (XR-ODT) for ADHD uses Metadate CD as the reference listed drug (RLD) and requests approval of three strengths of MPH XR-ODT (10 mg, 20 mg, and 30 mg). An OPQ review determined that this formulation is significantly different than the clinical trial formulation, having $\frac{(b) (4)}{(4)}\%$ (w/w) delayed release and $\frac{(b) (4)}{(4)}\%$ (w/w) extended release $\frac{(b) (4)}{(4)}$, and that it lacks a bioequivalence study to bridge the to-be-marketed formulation with the clinical trial formulation. An OCP review has separately determined that the “pediatric pharmacokinetic information obtained with early phase trial formulation (used in the relative bioavailability, food effect, and pediatric pharmacokinetic trials) is insufficient to support extrapolation of efficacy findings from children into adolescents and $\frac{(b) (4)}{(4)}$. Both, OPQ and OCP recommend a Complete Response action which is supported by the DPP Clinical Team.

II. Background:

Metadate CD (methylphenidate hydrochloride) Extended-Release Capsules (NDA 21-259), is an extended release methylphenidate (MPH), which was approved on February 02, 2001, based upon one, 3 week, placebo-controlled clinical study in 321 children, 6-12 years with the combined type of hyperactive-impulsive ADHD at doses of 20-60 mg based on mean changes from baseline in the teacher’s version of the Conners Global Index Scale at week 3.

Under IND 109,108, Neos Therapeutics had a pre-IND meeting with the Division of Psychiatric Products (DPP)/FDA on September 14, 2010; a Type C Meeting with DPP/FDA on May 13, 2013 to review and discuss a proposed laboratory classroom study (NT0102) and a pharmacokinetic study; and Information Advice on January 10, 2014 for a proposed initial Pediatric Study Plan (iPSP) to obtain approval of their extended release (XR) orally disintegrating tablet (ODT) formulation of MPH in children, 6- $\frac{(b) (4)}{(4)}$ years with ADHD using Metadate CD as the Reference Product. Three pharmacokinetic studies [a bioequivalent study in adults showing that MPH XR ODT formulation had a similar release profile to the Reference Product, Metadate CD (Study NT0102.1001); a fed fasted study in adults (Study NT0102.1002); a bioavailability study in children (6-12 years of age) and adolescents (13-17 years of age) with ADHD (Study NT0102.1003)]; and a laboratory classroom study in children, 6-12 years with ADHD (Study NT0102.1004) were determined to be adequate for reliance upon FDA’s previous finding of safety (and efficacy) for Metadate CD .

III. Materials Reviewed

Bioequivalence Study NT0102.1001

Fed Fasted Study NT0102.1002

Bioavailability Study NT0102.1003

Study NT0102.1004: Phase 3, Laboratory classroom study in children, 6-12 years with ADHD

Proposed Labeling

Financial Disclosure Certification

Debarment Certification

Clinical literature included in this submission

IV. Review of Clinical Pharmacology Studies

1. **Study NT0102.1001:** A Single-Dose, Three-Period, Three-Treatment, Three-Way Crossover Bioequivalence Study of Two Extended-Release Oral Disintegrating Tablet Formulations of MPH XR-ODT (Equivalent to 60 mg Methylphenidate HCl) and Metadate CD® under Fasted Conditions.

This was an open-label, randomized, three-period, crossover, active controlled trial to compare the rate of absorption and oral bioavailability of two NT0102 formulations to an equivalent oral dose of Metadate CD. Subjects received the following formulations of the ODT (Formula 1: 2 x 30 mg; NT0102 ODT; Formula 2: 2 x 30 mg; Metadate CD® extended-release capsule 1 x 60 mg; single dose; oral). The study enrolled 42 healthy adult subjects.

Sponsor's Conclusion(s):

Formulation 1:

- *d*-MPH: Bioequivalence criteria were met for AUC0-5, AUC5-24, and AUCinf. The Cmax was approximately 24% higher for Test Formulation 1 relative to the Reference Product. AUC0-3 was approximately 14% lower for Test Formulation 1 relative to the Reference Product. Although bioequivalence criteria were not met for Cmax and AUC0-3, the shapes of the *d*-MPH profiles after Test Formulation 1 and the Reference Product were similar.
- Total MPH (*d* + *l*): Bioequivalence criteria were met for AUC0-3, AUC0-5, AUC5-24, and AUCinf. The Cmax was approximately 25% higher for Test Formulation 1 relative to the Reference Product. Although bioequivalence criteria were not met for Cmax, the shapes of the total MPH profiles after Test Formulation 1 and the Reference Product were similar.

Test Formulation 2

- *d*-MPH: Bioequivalence criteria were met for AUC0-3, AUC0-5, AUC5-24, and AUCinf. The Cmax was approximately 25% higher for Test Formulation 2 relative to the Reference Product. Although bioequivalence criteria were not met for Cmax, the shapes of the *d*-MPH profiles after Test Formulation 2 and the Reference Product were similar.
- Total MPH (*d* + *l*): Bioequivalence criteria were met for AUC0-3, AUC0-5, AUC5-24, and AUCinf. The Cmax was approximately 26% higher for Test Formulation 2 relative to the Reference Product. Although bioequivalence criteria were not met for Cmax, the shapes of the total MPH profiles after Test Formulation 2 and the Reference Product were similar.

Safety:

There were 57 treatment-emergent adverse events (TEAEs) reported by 20 subjects over the course of the study. None were serious and there were no discontinuations due to TEAEs, or deaths during the course of the study. The most commonly reported TEAEs were nausea (*n* = 8; 3 following Treatment A [Test Formulation #1], 2 following Treatment B [Test Formulation #2] and 3 following Treatment C [Metadate CD]) and anxiety (*n* = 6; 2 following Treatment A, 2 following Treatment B and 2 following Treatment C). In total, 17 TEAEs were reported following Treatment A, 20 following Treatment B and 20 following Treatment C.

Three TEAEs reported by 2 subjects had clinically significant out of range vital signs assessments. Subject 134 had tachycardia, judged to be mild and related to the study treatment by the Investigator. Subject 141 was assessed had two TEAEs of tachycardia, which were judged to be mild and related to the study treatment by the Investigator.

Safety Conclusion: These TEAEs were consistent with other methylphenidate products.

2. **Study NT0102.1002:** A Single-Dose, Two-Period, Two-Treatment, Two-Way Crossover Food-Effect Study of a Test Formulation of Methylphenidate Extended-Release Orally Disintegrating Tablet (MPH XR-ODT) (Equivalent to 60 mg Methylphenidate HCl).

This was an open-label, randomized, two-period cross-over study involving 24 healthy subjects to assess the effect of food on the rate and extent of absorption and the oral bioavailability of a single dose (2 x 30 mg ODTs) of MPH XR-ODT, equivalent to 60 mg MPH HCl.

Sponsors Conclusion (s): The study medications were generally well-tolerated and there were no significant safety concerns identified during the study. The presence of food did not significantly alter MPH exposure following the administration of MPH XR-ODT (equivalent to 60 mg MPH HCl) under fed and fasted conditions.

Safety:

There were 34 treatment-emergent adverse events (TEAEs) reported by 14 (58.3%) subjects over the course of the study. Of the 34 AEs reported following dose administration, 19 were mild and 15 were moderate in severity. There were no severe AEs. The most commonly reported AEs were anxiety (n = 8; 4 reports in 4 [16.7%] subjects following Treatment A and 4 reports in 4 [17.4%] subjects following Treatment B) and nausea (n = 7; 5 reports in 5 [20.8%] subjects following Treatment A and 2 reports in 2 [8.7%] subjects following Treatment B). In total, 17 AEs were reported by 10 (41.7%) subjects following Treatment A and 17 AEs were reported by 11 (47.8%) subjects following Treatment B

Three (3) AEs were related to clinically significant out-of-range vital signs. Subject 101 experienced mild, intermittent tachycardia during Period 1 after receiving the study treatment under the fed condition. Subject 114 experienced mild tachycardia during Period 1 after receiving the study treatment under the fed condition. Subject 121 experienced mild tachycardia during Period 1 after receiving the study treatment under the fasted condition.

Safety Conclusion: These TEAEs were consistent with other methylphenidate products.

3. **Study NT0102.1003:** A Single-Dose, Single-Period, One-Treatment, Pharmacokinetic Study of Methylphenidate Extended-Release Oral Disintegrating Tablets under Fasted Conditions in Children (Ages 6-12) and Adolescents (Ages 13-17) with Attention-Deficit Hyperactivity Disorder.

This was a single-dose, open-label, single-period, single-treatment study in which 32 male and female children (ages 6-12) and adolescents (ages 13-17) with a diagnosis of ADHD each received a single oral administration of MPH XR ODT. Study drug was administered to participants after an

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NDA 205489, 505(b) (2)

COTEMPLA XR-ODT: Methylphenidate Extended Release Orally Disintegrating 10 mg, 20 mg, and 30 mg Tablets overnight fast of at least 10 hours, and following a 4-day washout period from their usual prescribed ADHD therapy. In all subjects, PK blood samplings were at 0 (predose), 0.75, 2, 3.5, 5.5, 8, 12, and 24 hours post dose. In addition, measurements of vital signs, clinical laboratory parameters and ECGs were performed.

Sponsors Conclusion (s): The geometric means for weight-normalized CL/F and Vz/F of total methylphenidate ($d + l$) and the respective 95% confidence intervals about means were within the target range of 60% to 140% for each age group of participants from children aged 6-7 years to adolescents aged 13-17 years.

Safety: A total of 32 pediatric subjects were administered a single dose of 2, 30 mg NT0102 ODTs. Of the 32 pediatric subjects, 22 (68.8%) experienced 34 treatment-emergent AEs. There were no deaths, serious adverse events (SAEs), or discontinuations due to an AE. The most commonly reported TEAEs were increased heart rate (12 participants [37.5%]), decreased appetite (11 participants [34.4%]), nausea (2 participants [6.3%]), and vomiting (2 participants [6.3%]). None of the TEAEs occurred as the result of abnormal laboratory evaluations or physical examinations. Clinical laboratory, ECG, and physical examination evaluations were completed with no clinically significant findings.

Safety Conclusion: These TEAEs were consistent with other methylphenidate products.

V. Review of Clinical Efficacy and Safety Data for Single, Phase 3 Study NT0102.1004:

Study NT0102.1004: This was a randomized, multicenter, double-blind, placebo-controlled, parallel group study of NT0102 methylphenidate polistirex extended-release oral disintegrating tablets (equivalent to 20, 30, 40, or 60 mg of methylphenidate hydrochloride) in children (ages 6-12 years) with attention-deficit hyperactivity disorder (ADHD).

Objectives: The primary objective of this study was to determine the efficacy and safety of the NT0102 methylphenidate polistirex (MPP) Extended Release (XR) oral disintegrating tablet (ODT) in children with ADHD in a laboratory classroom setting.

Primary efficacy was the average of all Swanson, Kotkin, Agler, M-Flynn, and Pelham (SKAMP) Combined score (total score for all 13 items of the SKAMP-Combined score) assessed at baseline (pre-dose), and 1, 3, 5, 7, 10, 12, and 13 hours post-dose on the testing day (Visit 8).

Key secondary efficacy endpoints consisted of the onset of effect consisted of: 1) onset of effect (defined as the first time point at which NT0102 separates from placebo on SKAMP-Combined scores) and 2) duration of effect (defined as the last time point at which NT0102 separates from placebo on SKAMP-Combined scores) .

Methodology: Eighty-seven children, 6 to 12 years, diagnosed with any subtype of ADHD (inattentive, hyperactive-impulsive, or primarily combined subtypes) based upon the Diagnostic and Statistical Manual of Mental Disorders, 4th edition, text revision (DSM-IV-TR) criteria; with a history of positive response to treatment of the ADHD and taking a stable dose of 20-60 mg

COTEMPLA XR-ODT: Methylphenidate Extended Release Orally Disintegrating 10 mg, 20 mg, and 30 mg Tablets
Metadate CD or comparable dose of another MPH IR or XR medication were enrolled in 4 centers across the US. Subjects primarily had a combined or hyperactive impulsive ADHD subtype; a CGI-Severity score of > 3; and were > 90 % on the ADHD Rating Scale either total score, hyperactive impulsive subscale, or inattentive subscale; and were judged by the investigator to be of average intelligence.

There were 5 periods in this study: a screening period (approximately 4 weeks), a washout period (3-7 days), an open-label stepwise dose optimization period (4 weeks), a dose stabilization period (1 week), and a double-blind parallel group treatment period, culminating in a full-day laboratory classroom assessment (1 week). The overall study schedule is shown in the sponsor's table, copied below.

Study Schedule

Study Periods									
	Screening	Washout ^a	Dose Optimization	Dose Stabilization	Practice Session	Double-Blind Treatment	Classroom Session	Final Visit	Follow-up Call
Period Duration	Up to 4 weeks	1 week	4 weeks	1 week	1 day	6 days	1 day	1 day	1 day
Study Days	-34 to -7	-6 to -0	1-28	29-34	35	36-41	42	43* *	75
Visit(s)*	1		2-5	6	7 ^b		8 ^c	9	Follow-up

*Note: Visits 3 through 6 include a window of ± 2 days

**Note: Final visit is Day 43 (+2 days)

^aWashout of at least 3 days (up to 1 week)

^bVisit 7 is the "practice" classroom testing day.

^cVisit 8 is the "actual" classroom testing day.

Study Subjects: There were 54 males (65.9 %) enrolled in the study with a slightly higher percentage in the NT0102 (69.8%) compared to the placebo (61.5%) group. Age, race, ethnicity, height, weight, and body mass index (BMI) were similar in both groups. The mean (standard deviation [SD]) age in years was 9.2 (1.75) across both groups. The majority of the subjects were White (79.3%) followed by Black or African American (12.2%), Other (4.9%), Asian (2.4%), and Native Hawaiian or Other Pacific Islander (1.2%). There were 34.1% of subjects who were Hispanic or Latino. The average (SD) height was 138 (13.1) cm, range 108 to 169 cm. The average (SD) weight was 36.3 (12.73) kg, range 15.4 to 82.6 kg. The most common (≥10%) medical and psychiatric conditions ongoing at the screening visit were ADHD (100%), rhinitis allergic (29.3%), asthma (18.3%), myopia (18.3%), and headache (14.6%). Overall ADHD subtypes consisted of: inattentive [21 (24.1 %)], hyperactive/impulsive [1 (1.1 %)], and combined type [65 (74.7 %)].

Efficacy Data for Study NT0102.1004:

Sponsor's Results:

The primary efficacy endpoint was the SKAMP-Combined score calculated as the total score of all 13 items of the SKAMP-Combined score. SKAMP ratings were performed at pre-dose (baseline) and at 1, 3, 5, 7, 10, 12, and 13 hours post-dose during the classroom testing day on

COTEMPLA XR-ODT: Methylphenidate Extended Release Orally Disintegrating 10 mg, 20 mg, and 30 mg Tablets
Visit 8. The primary efficacy endpoint was the average of all SKAMP-Combined scores during the 13-hour post-dose period on the classroom testing day (Visit 8) versus placebo. The primary analysis utilized an Analysis of Covariance (ANCOVA) model, which estimated the average post-dose SKAMP-Combined score averaged over the classroom testing day, while adjusting for baseline SKAMP-Combined treatment- and site-level effects in the FAS data set.

A lower SKAMP-Combined score indicates less symptomatology (i.e., is better). The model showed a treatment effect of -11.0 (95% CI: -13.9, -8.2) at a significance level of $p < 0.0001$ in the FAS (primary endpoint).

Sponsor's table, copied and pasted below, and summarizes the differences in least squares means (LS means) between MPH XR-ODT and placebo treatment groups for SKAMP-Combined scores.

Table: Primary Analysis Results for the SKAMP-Combined Averaged Over the Classroom Testing Day (N=82)

	SKAMP-Combined (Full Analysis Set) N=82 (Primary Endpoint Analysis)	SKAMP-Combined (Per Protocol Set) N=80 (Primary Endpoint Sensitivity Analysis)	SKAMP-Attention (Full Analysis Set) N=82	SKAMP- Depotment (Full Analysis Set) N=82
LS Mean (95% CI)				
NT0102	14.3 (12.2, 16.4)	14.6 (12.4, 16.7)	7.7 (6.7, 8.7)	6.7 (5.2, 8.1)
Placebo	25.3 (23.0, 27.6)	25.9 (23.5, 28.3)	12.2 (11.1, 13.4)	12.8 (11.3, 14.3)
Difference	-11.04 (-13.9, -8.20)	-11.29 (-14.2, -8.42)	-4.49 (-5.91, -3.08)	-6.13 (-7.97, -4.28)
P-value	<0.0001	<0.0001	<0.0001	<0.0001
Baseline Pre-dose				
P-value	<0.0001	<0.0001	<0.0001	<0.0001
Site Main Effect				
P-value	0.1216	0.1338	0.0098	0.6299

Abbreviations: CI= confidence interval, LS Mean=least squares mean, SKAMP=Swanson, Kotkin, Agler, M-Flynn, and Pelham
Source: [Table 14.2.1.1](#), [Table 14.2.1.2](#), [Table 14.2.2.1](#), [Table 14.2.4.1](#), and [Listing 16.2.6.1.1](#)

Key Secondary Efficacy Endpoint Analyses: Onset and Duration of Effect

Key secondary endpoints included the onset of effect and duration of NT0102 (defined as the first and last points, respectively, at which active drug separates from placebo on SKAMP-Combined scores). A mixed model repeated measures (MMRM) model was used to assess whether the effect of treatment on the SKAMP-Combined Score post-dose was dependent on the time of assessment post-dose. Onset of efficacy was met at the first post-dose assessment of 1 hour, and duration of efficacy was consecutively observed through Hour 12, but not at Hour 13. Sponsor's figure, copied and pasted below summarizes the SKAMP-Combined score during the classroom testing day for the Full Analysis Set (FAS).

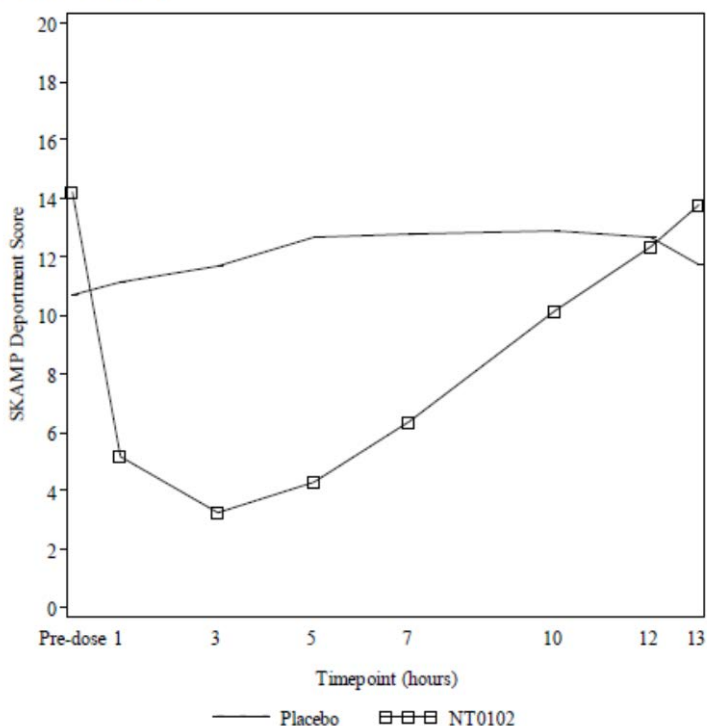
Table: Lease Squares Mean SKAMP-Combined Scores at All Time Points

Time Point (Hour)	Placebo LS Mean (SE)	NT0102 LS Mean (SE)	Difference LS Mean (SE)	95% CI	P Value
1	21.2 (1.19)	10.5 (0.993)	-10.7 (1.44)	(-13.6, -7.86)	<0.0001
3	23.4 (1.43)	7.28 (0.831)	-16.1 (1.55)	(-19.2, -13.0)	<0.0001
5	25.5 (1.52)	9.86 (1.16)	-15.7 (1.82)	(-19.3, -12.1)	<0.0001
7	24.8 (1.51)	12.1 (1.42)	-12.7 (1.99)	(-16.7, -8.77)	<0.0001
10	25.6 (1.80)	18.5 (1.48)	-7.11 (2.25)	(-11.6, -2.61)	0.0024
12	27.1 (1.48)	22.7 (1.42)	-4.46 (1.97)	(-8.37, -0.542)	0.0262
13	25.2 (1.60)	26.0 (1.52)	0.817 (2.13)	(-3.42, 5.06)	0.7022

Abbreviations: CI= confidence interval, LS Mean=least squares mean, SKAMP=Swanson, Kotkin, Agler, M-Flynn, and Pelham
Source: [Table 14.2.1.3](#) and [Listing 16.2.6.1.1](#)

Sponsor's figure copied and pasted below shows the mean profile for the SKAMP-Combined Score during the classroom testing day comparing NT0102 subjects to placebo at pre-dose and at 13 hours. Similar findings were present for the SKAMP Attention and Department scores.

Mean Profiles



Division of Biometrics Review:

The sponsor's results for both the primary (Average of SKAMP-Combined Scores over duration of the classroom day) and key secondary endpoints (defined as the first and last points, respectively, at which active drug separates from placebo on SKAMP-Combined scores) were confirmed by Biometrics. They thought that collective evidence showed that subjects

COTEMPLA XR-ODT: Methylphenidate Extended Release Orally Disintegrating 10 mg, 20 mg, and 30 mg Tablets “randomized to MPH XT-ODT in the laboratory classroom study (NT0102.1004), achieved on average better results on the SKAMP compared to the placebo patients. The primary analysis estimates a difference of -11 points (95% CI: -13.9, -8.2) when averaging the results over the 13 hour classroom session (primary endpoint). This difference is highly statistically significant.” They identified no statistical issues impacting the overall conclusions and concluded that the statistical results provide adequate evidence to support the claims proposed in the NDA.

Safety Data for Study NT0102.1004:

No deaths or serious AEs were reported during the course of the study.

There were 2 discontinuations due to TEAEs, 1 due to influenza and 1 due to upper abdominal pain. Subject 1011 was a 10-year-old who developed severe influenza while on placebo during the double blind phase, requiring his withdrawal and his being started on Tamiflu. Subject 1012 was an 11-year-old who developed a distorted sense of taste (dysgeusia) while receiving 20 mg NT0102, then moderate abdominal pain, decreased appetite, and mild headache while receiving 40 mg NT0102 during the dose optimization/stabilization phase. The subject was withdrawn with symptom resolution at follow-up 2 weeks later.

During the dose optimization/stabilization phase, 70 of 87 enrolled subjects (80.5%) experienced 170 TEAEs. During the double-blind phase, 10 of 41 subjects who received placebo (24.4%) experienced 13 TEAEs, and 11 of 44 subjects who received NT0102 (25.0%) experienced 11 TEAEs. The most common TEAE's during the *dose optimization/stabilization phase* were decreased appetite [23 subjects (26.4 %)]; upper abdominal pain [21 subjects (24.1 %)]; headache [19 subjects (21.8 %)]; infections [13 subjects (14.9 %)] with 10 subjects (11.5 %) having upper respiratory infections; insomnia [11 subjects (12.6 %)]; labile affect [9 subjects (10.3 %)]; irritability [7 subjects (8 %)]; vomiting [5 subjects (5.7 %)]; skin/subcutaneous disorders [4 subjects (4.6 %)] with 2 subjects having rash [1: maculopapular; 1: rash], 1 subject alopecia [1], and pruritus [1]; constipation [3 subjects (3.4 %)]; fatigue [2 subjects (2.3 %)] and tics [2 subjects (2.3 %)]. The most common TEAEs (i.e., >2% incidence) occurring more frequently in subjects on NT0102 than on placebo during the *double-blind phase* were upper respiratory tract infection (4 subjects [9.1%]); second degree burn (1 subject [2.3%]), wound (1 subject [2.3%]); dizziness (1 subject [2.3%]); trichotillomania (1 subject [2.3%]); cough (1 subject [2.3%]); and epistaxis (1 subject [2.3%]).

Clinical laboratory tests (chemistry, hematology, and urinalysis) were performed at screening and at the end of the study. Three (3) subjects had clinically significant laboratory abnormalities. Subject 1002 had an elevated creatine kinase at screening (373 U/L; normal range = 2 to 177 U/L), which increased to 537 U/L after receiving 20 mg NT0102 daily during the double-blind phase. Subject 3034 had a high AST result at Visit 1 (70 U/L; normal range = 0 to 40 U/L), received 60 mg NT0102 daily during the double-blind phase, and had a value of 64 U/L at study end. Subject 3042 with a combined type ADHD had a previous history of viral gastroenteritis; ongoing medical history of eczema, asthma, allergic rhinitis, and insomnia received 60 mg placebo daily during the double-blind phase, had an elevated ALT at screening (57 U/L; normal range = 5 to 25 U/L) which increased to 147 U/L at the final visit.

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No subjects had clinically significant abnormal laboratory values, vital signs, or end-of-study physical examinations that were assessed by the investigator as clinically significant. Two subjects had abnormal ECG results that were flagged as clinically significant. These subjects were referred to a pediatric cardiologist, who assessed the results as not clinically significant.

Per C-SSRS ratings, no subjects were found to exhibit suicidal ideation or suicidal behavior at any study visit.

Safety Conclusion for Study NT0102.1004:

In general NT0102 was generally well tolerated in this study. The most common TEAE's during the open-label, dose optimization/stabilization phase were decreased appetite, upper abdominal pain, headache, infections and insomnia. No comparator was available. On face, these findings are similar to those known to occur with other methylphenidate products (e.g. insomnia, anorexia, abdominal pain, and headache). The most common TEAEs (i.e., >2% incidence) during the double-blind phase in subjects on NT0102 that occurred more frequently than in subjects on placebo were upper respiratory tract infection, burn-wound related, dizziness, trichotillomania, and epistaxis. There were no SAE's. There were only 2 discontinuations due to TEAEs, 1 due to influenza and 1 due to upper abdominal pain. The safety data from this study suggest that NT0102 is well tolerated and has a safety profile similar to that of other extended release MPH pharmacotherapies.

Overall Safety

Adverse events reported in the 3 Phase 1 studies of MPH XR-ODT (NT0102.1001, NT0102.1002, and NT0102.1003) were consistent with other methylphenidate products. The most commonly reported adverse events by PT (>5%) were: nausea, vomiting, anxiety, nervousness, decreased appetite, headache, increased heart rate, and tachycardia. The most commonly reported adverse events were gastrointestinal disorders. The adverse events were mostly mild, some moderate, and none were severe or serious. The nature of TEAEs reported in these Phase 1 studies is provided in sponsors table of Adverse Events by System Organ Class, copied and pasted in the Appendix of this review.

The most common adverse events reported in the single phase 3 study, NT0102.100, consisted of decreased appetite, upper abdominal pain, headache, infections and insomnia during the open-label, dose optimization/ stabilization phase. The most common TEAEs (i.e., >2% incidence) during the double-blind phase in subjects on NT0102 that occurred more frequently than in subjects on placebo were upper respiratory tract infection, burn-wound related, dizziness, trichotillomania, and epistaxis. There were no SAE's. There were only 2 discontinuations due to TEAEs, 1 due to influenza and 1 due to upper abdominal pain. The nature of TEAEs reported in this study is provided in sponsors table of Adverse Events by System Organ Class, copied and pasted in the Appendix of this review.

Overall Safety Conclusion:

The safety data from the three phase 1 studies and single phase 3 study suggest that NT0102 was well tolerated with a safety profile similar to that of other extended release methylphenidates.

VI. OCP Review

Praveen Balimane, Hao Zhu and Mehul of the Office of Clinical Pharmacology (OCP)/Division of Clinical Pharmacology I has determined that no adequate link has been established between the clinical trial formulation and the to-be-marketed formulation, and recommends a Complete Response action. This recommendation is based upon OPQ's determination the to-be-marketed formulation is significantly different from the clinical trial formulation. The to-be-marketed drug product will have (b) (4) % (b) (4) (weight/weight) delayed release and (b) (4) % (weight/weight) (b) (4) extended release (b) (4) than the clinical trial formulation (used in the efficacy and safety trial). A bioequivalence study is recommended to bridge the to-be-marketed formulation with the clinical trial formulation.

VII. Pharmacology/Toxicology Review

A review by Drs. Mathew and Fossom concluded that based upon the absence of impurities, degradants, or novel excipients in the Methylphenidate Extended Release Orally Disintegrating Tablets, no additional toxicological characterization was required and there were no Pharmacology/Toxicology issues preventing approval of this NDA.

VIII. Quality Assessment Review

A combined Office of Pharmaceutical Quality Review by David Claffey, Dahlia Woody, Gene Holbert, Andrei Ponta, Akm Khairuzzaman, Linda Ng, Ge Bai and Jose Martinez concluded that the Methylphenidate Extended Release Orally Disintegrating Tablets will have (b) (4) % (b) (4) (w/w) delayed release and (b) (4) % (w/w) (b) (4) extended release (b) (4) than the clinical drug product. These differences were supported by in vitro data. The review team determined that changes of this extent, especially to the extended release (b) (4), would require bioequivalence studies. The proposed product would contain (u) (4) the amount of extended release (b) (4) than the product studied in clinical studies. The risk to the patients of faster release, higher Cmax with possible shorter duration of effect were unknown. Critical deficiencies identified consist of: 1) the need for a bioequivalence study to bridge the clinical and commercial drug product formulations; and 2) the need to establish, validate and fully justify an unequivocal commercial (b) (4) operation and control.

IX. Proprietary Name Review

Danielle Harris, Irene Chan and Kellie Taylor of the Division of Medication Error Prevention and Analysis (DMEPA) reviewed the proposed proprietary name, Cotempla XR-ODT, and concluded that this name was acceptable.

X. Patient Labeling Review

LaShawn Griffiths, Marcia Williams, Sharon Williams and Susannah O'Donnell of the Divisions of Medical Policy Programs (DMPP) and Office of Prescription Drug Promotion (OPDP)

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XI. Label, Labeling and Packaging Review

Susannah O'Donnell of the Office of Prescription Drug Promotion (OPDP) reviewed the draft product labeling, Medication Guide, and carton/container labeling for COTEMPLA XR-ODT (methylphenidate (b) (4) extended-release orally disintegrating tablets and provided various comments.

Deborah Meyers, Danielle Harris, Irene Chan and Todd Bridges of Division of Medication Error Prevention and Analysis (DMEPA) reviewed the proposed Cotempla XR-ODT container label, carton, package insert labeling, and medication guide for vulnerabilities to medication errors and provided comments. They concluded that a revised Unit-Dose Blister Label was unacceptable from a medication error perspective.

XII. Inspection

The Office of Scientific Investigations (OSI)\ Division of Clinical Compliance Evaluation\Good Clinical Practice Assessment Branch conducted inspections of two sites (Site 03, Dr. Childress, Las Vegas, NV; and Site 01, Dr. Cutler, Bradenton, FL) comprising about 69 study subjects for Study NT0102.1004, and identified no significant regulatory violations, and found the data to be acceptable.

XIII. Pregnancy and Lactation Labeling Review

Miriam Dinatale, Tamara Johnson, and Lynne Yao of the Division of Pediatric and Maternal Health (DPMH) reviewed “the firm’s proposed labeling update in conformance with PLLR and review a summary of the available published literature, with regard to methylphenidate and dextmethylphenidate use in pregnancy and lactation.” They concluded that COTEMPLA XR-ODT had been updated to comply with the PLLR. A review of the literature revealed no new data with methylphenidate use in pregnant or lactating women. DPMH revised sections 8.1 and 8.2 of Cotempla XR-ODT labeling for compliance with the PLLR.

XIV. Pediatric Plan

Sponsor has requested (b) (4). The Division has informed them that we would grant a Partial Waiver only for children age 0-4 years of age with ADHD and a Deferral for ADHD studies in children (4-6 years old)..

Pediatric Review Committee (PeRC) Waivers and Deferral templates have been submitted to PERC and will likely be modified once DPP has received and reviewed sponsor’s proposals for the above studies.

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XV. Conclusions and Recommendations

The efficacy and safety data from the primary efficacy and safety study (Study NT0102.1004) suggest that NT0102 was effective and well tolerated with a safety profile similar to that of other extended release MPH pharmacotherapies. However, based upon OPQ and OCP's determinations of differences between the, to be marketed formulation, and the clinical trial formulation, and that bridging and pediatric pharmacokinetic studies are required, a Complete Response is also recommended.

Table 1: List of Investigators

Name	Address	Phone Number
NT0102.1001		
Cynthia A. Zimora, M.D.	Worldwide Clinical Trials Early Phase Services, LLP 2455 N.E. Loop, Suite 150 San Antonio, TX 78217	210-635-1500
NT0102.1002		
Mark T. Leibowitz, M.D.	Worldwide Clinical Trials Early Phase Services, LLP 2455 N.E. Loop, Suite 150 San Antonio, TX 78217	210-635-1500
NT0102.1003		
Robert A. Riesenber, M.D.	Atlanta Center for Medical Research, Inc. 501 Fairburn Road SW Atlanta, GA 30331	404-881-5800
NT0102.1004		
Ann C. Childress, MD	Center for Psychiatry and Behavioral Medicine, Inc. 7351 Prairie Falcon Rd, Ste 150 & 160 Las Vegas, NV 89128	702-838-0742
Andrew J. Cutler, MD	Florida Clinical Research Center LLC 8043 Cooper Creek Blvd, Ste 107 Bradenton, FL 34201	941-747-7900
Scott H. Kollins, Ph.D.	Duke Child & Family Study Center Duke University Medical Center 2608 Erwin Road Pavilion East, Ste 300 Durham, NC 27705	919-681-0014
Andrea Marraffino, M.D.	Lakeside Behavioral Healthcare 434 West Kennedy Blvd. Orlando, FL 32810	407-875-3700

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Table: Adverse Events by System Organ Class and Preferred Term- Phase 1 Studies

SOC/ Preferred Term	Number of Subjects Reporting (%)					
	NT0102.1001			NT0102.1002		NT0102.1003
	MPH XR-ODT Formulation 1 2 x 30 mg	MPH XR-ODT Formulation 2 2 x 30 mg	METADATE CD 1 x 60 mg	MPH XR-ODT Fasted 2 x 30 mg	MPH XR-ODT Fed 2 x 30 mg	MPH XR-ODT Fasted 2 x 30 mg
Number of subjects	41	39	40	24	23	32
Total with AEs	11 (26.8%)	12 (30.8%)	12 (30.0%)	10 (41.7%)	11 (47.8%)	22 (68.8%)
Gastrointestinal disorders	3 (7.3%)	4 (10.3%)	4 (10.0%)	6 (25.0%)	3 (13.0%)	3 (9.4%)
Nausea	3 (7.3%)	2 (5.1%)	3 (7.5%)	5 (20.8%)	2 (8.7%)	2 (6.3%)
Vomiting	1 (2.4%)	1 (2.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (6.3%)
Dry mouth	0 (0.0%)	0 (0.0%)	1 (2.5%)	1 (4.2%)	0 (0.0%)	0 (0.0%)
Abdominal pain	0 (0.0%)	1 (2.6%)	1 (2.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Dyspepsia	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (4.3%)	0 (0.0%)
Gastroesophageal reflux disease	0 (0.0%)	0 (0.0%)	1 (2.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Psychiatric disorders	3 (7.3%)	7 (17.9%)	3 (7.5%)	4 (16.7%)	4 (17.4%)	0 (0.0%)
Anxiety	2 (4.9%)	2 (5.1%)	2 (5.0%)	4 (16.7%)	4 (17.4%)	0 (0.0%)
Nervousness	0 (0.0%)	4 (10.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Affect lability	0 (0.0%)	1 (2.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Insomnia	1 (2.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Bruxism	0 (0.0%)	1 (2.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

SOC/ Preferred Term	Number of Subjects Reporting (%)					
	NT0102.1001			NT0102.1002		NT0102.1003
	MPH XR-ODT Formulation 1 2 x 30 mg	MPH XR-ODT Formulation 2 2 x 30 mg	METADATE CD 1 x 60 mg	MPH XR-ODT Fasted 2 x 30 mg	MPH XR-ODT Fed 2 x 30 mg	MPH XR-ODT Fasted 2 x 30 mg
Euphoric mood	0 (0.0%)	0 (0.0%)	1 (2.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Nightmare	0 (0.0%)	0 (0.0%)	1 (2.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Metabolism and nutrition disorders	1 (2.4%)	2 (5.1%)	0 (0.0%)	2 (8.3%)	2 (8.7%)	11 (34.4%)
Decreased appetite	1 (2.4%)	2 (5.1%)	0 (0.0%)	2 (8.3%)	2 (8.7%)	11 (34.4%)
Nervous system disorders	2 (4.9%)	1 (2.6%)	3 (7.5%)	3 (12.5%)	2 (8.7%)	1 (3.1%)
Headache	0 (0.0%)	0 (0.0%)	2 (5.0%)	1 (4.2%)	2 (8.7%)	0 (0.0%)
Dizziness	1 (2.4%)	0 (0.0%)	1 (2.5%)	1 (4.2%)	0 (0.0%)	1 (3.1%)
Hypoaesthesia	0 (0.0%)	1 (2.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Presyncope	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (4.2%)	0 (0.0%)	0 (0.0%)
Tremor	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (4.2%)	0 (0.0%)	0 (0.0%)
Myoclonus	1 (2.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Investigations	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	12 (37.5%)
Heart rate increased	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	12 (37.5%)
Cardiac disorders	2 (4.9%)	0 (0.0%)	1 (2.5%)	1 (4.2%)	2 (8.7%)	2 (6.3%)
Tachycardia	2 (4.9%)	0 (0.0%)	1 (2.5%)	1 (4.2%)	2 (8.7%)	1 (3.1%)
Palpitations	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (4.3%)	0 (0.0%)
Sinus tachycardia	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (3.1%)

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SOC/ Preferred Term	Number of Subjects Reporting (%)					
	NT0102.1001			NT0102.1002		NT0102.1003
	MPH XR-ODT Formulation 1 2 x 30 mg	MPH XR-ODT Formulation 2 2 x 30 mg	METADATE CD 1 x 60 mg	MPH XR-ODT Fasted 2 x 30 mg	MPH XR-ODT Fed 2 x 30 mg	MPH XR-ODT Fasted 2 x 30 mg
General disorders and administration site conditions	1 (2.4%)	0 (0.0%)	2 (5.0%)	0 (0.0%)	2 (8.7%)	1 (3.1%)
Vessel puncture site haemorrhage	1 (2.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Vessel puncture site haematoma	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (4.3%)	0 (0.0%)
Fatigue	1 (2.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Injection site haemorrhage	0 (0.0%)	0 (0.0%)	1 (2.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Early satiety	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (4.3%)	0 (0.0%)
Vessel puncture site pain	0 (0.0%)	0 (0.0%)	1 (2.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Pyrexia	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (3.1%)
Musculoskeletal & connective tissue disorders	2 (4.9%)	3 (7.7%)	1 (2.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Muscle tightness	2 (4.9%)	1 (2.6%)	1 (2.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Back pain	0 (0.0%)	1 (2.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Muscle spasms	0 (0.0%)	0 (0.0%)	1 (2.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Sensation of heaviness	0 (0.0%)	1 (2.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

SOC/ Preferred Term	Number of Subjects Reporting (%)					
	NT0102.1001			NT0102.1002		NT0102.1003
	MPH XR-ODT Formulation 1 2 x 30 mg	MPH XR-ODT Formulation 2 2 x 30 mg	METADATE CD 1 x 60 mg	MPH XR-ODT Fasted 2 x 30 mg	MPH XR-ODT Fed 2 x 30 mg	MPH XR-ODT Fasted 2 x 30 mg
Injury, poisoning & procedural complications	0 (0.0%)	0 (0.0%)	1 (2.5%)	0 (0.0%)	1 (4.3%)	0 (0.0%)
Skin lacerations	0 (0.0%)	0 (0.0%)	1 (2.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Arthropod bite	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (4.3%)	0 (0.0%)
Skin and subcutaneous tissue disorders	1 (2.4%)	1 (2.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Hyperhidrosis	1 (2.4%)	1 (2.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Infections and infestations	0 (0.0%)	1 (2.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Viral upper respiratory tract infection	0 (0.0%)	1 (2.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Vascular disorders	0 (0.0%)	0 (0.0%)	1 (2.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Flushing	0 (0.0%)	0 (0.0%)	1 (2.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

Abbreviations: ODT = oral disintegrating tablet; SOC = system organ class; XR = extended release.

Source: NT0102.1001, NT0102.1002 and NT0102.1003, [Table 14.3.4](#)

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Table: Adverse Events by System Organ Class and Preferred Term-NT0102.1004

SOC/ Preferred Term	Number of Subjects Reporting (%)			
	MPH XR-ODT During the dose optimization/ stabilization phase	Double-blind phase		On MPH XR-ODT
		Placebo	MPH-XR ODT	
Number of subjects	87	41	44	87
Total with AEs	70 (80.5%)	10 (24.4%)	11 (25.0%)	74 (85.1%)
Gastrointestinal disorders	27 (31.0)	0 (0.0%)	0 (0.0%)	27 (31.0)
Abdominal pain upper	19 (21.8%)	0 (0.0%)	0 (0.0%)	19 (21.8%)
Constipation	3 (3.4%)	0 (0.0%)	0 (0.0%)	3 (3.4%)
Diarrhea	1 (1.1%)	0 (0.0%)	0 (0.0%)	1 (1.1%)
Dyspepsia	1 (1.1%)	0 (0.0%)	0 (0.0%)	1 (1.1%)
Oral pain	1 (1.1%)	0 (0.0%)	0 (0.0%)	1 (1.1%)
Retching		0 (0.0%)	0 (0.0%)	1 (1.1%)
Vomiting	5 (5.7%)	0 (0.0%)	0 (0.0%)	5 (5.7%)
Metabolism and nutrition disorders	24 (27.6%)	0 (0.0%)	0 (0.0%)	24 (27.6%)
Decreased appetite	23 (26.4%)	0 (0.0%)	0 (0.0%)	23 (26.4%)
Polydipsia	1 (1.1%)	0 (0.0%)	0 (0.0%)	1 (1.1%)
Nervous system disorders	21 (24.1%)	1 (2.4%)	2 (4.5%)	22 (25.3%)
Dizziness	1 (1.1%)	0 (0.0%)	1 (2.3%)	2 (2.3%)
Dysgeusia	4 (4.6%)	0 (0.0%)	0 (0.0%)	4 (4.6%)
Headache	17 (19.5%)	1 (2.4%)	1 (2.3%)	17 (19.5%)
Migraine	1 (1.1%)	0 (0.0%)	0 (0.0%)	1 (1.1%)
Somnolence	3 (3.4%)	0 (0.0%)	0 (0.0%)	3 (3.4%)
Tremor	1 (1.1%)	0 (0.0%)	0 (0.0%)	1 (1.1%)
Psychiatric disorders	20 (23.0%)	0 (0.0%)	1 (2.3%)	20 (23.0%)
Affect lability	8 (9.2%)	0 (0.0%)	0 (0.0%)	8 (9.2%)
Emotional disorder	1 (1.1%)	0 (0.0%)	0 (0.0%)	1 (1.1%)
Initial insomnia	2 (2.3%)	0 (0.0%)	0 (0.0%)	2 (2.3%)
Insomnia	11 (12.6%)	0 (0.0%)	0 (0.0%)	11 (12.6%)
Middle insomnia	1 (1.1%)	0 (0.0%)	0 (0.0%)	1 (1.1%)
Negativism	1 (1.1%)	0 (0.0%)	0 (0.0%)	1 (1.1%)
Tic	2 (2.3%)	0 (0.0%)	0 (0.0%)	2 (2.3%)
Trichotillomania	0 (0.0%)	0 (0.0%)	1 (2.3%)	1 (1.1%)
Infections and infestations	13 (14.9%)	5 (12.2%)	4 (9.1%)	17 (19.5%)
Bronchitis	0 (0.0%)	1 (2.4%)	0 (0.0%)	0 (0.0%)
Gastroenteritis viral	1 (1.1%)	0 (0.0%)	0 (0.0%)	1 (1.1%)
Influenza	1 (1.1%)	1 (2.4%)	0 (0.0%)	1 (1.1%)
Nasopharyngitis	0 (0.0%)	1 (2.4%)	0 (0.0%)	0 (0.0%)
Otitis media	1 (1.1%)	0 (0.0%)	0 (0.0%)	1 (1.1%)
Pharyngitis streptococcal	1 (1.1%)	0 (0.0%)	0 (0.0%)	1 (1.1%)
Upper respiratory tract infection	10 (11.5%)	3 (7.3%)	4 (9.1%)	14 (16.1%)

SOC/ Preferred Term	Number of Subjects Reporting (%)			
	MPH XR-ODT During the dose optimization/ stabilization phase	Double-blind phase		On MPH XR-ODT
		Placebo	MPH-XR ODT	
General disorders and administration site conditions	9 (10.3%)	0 (0.0%)	0 (0.0%)	9 (10.3%)
Fatigue	2 (2.3%)	0 (0.0%)	0 (0.0%)	2 (2.3%)
Irritability	6 (6.9%)	0 (0.0%)	0 (0.0%)	6 (6.9%)
Pyrexia	1 (1.1%)	0 (0.0%)	0 (0.0%)	1 (1.1%)
Injury, poisoning and procedural complications	6 (6.9%)	3 (7.3%)	2 (4.5%)	8 (9.2%)
Arthropod bite	2 (2.3%)	0 (0.0%)	0 (0.0%)	2 (2.3%)
Burns second degree	0 (0.0%)	0 (0.0%)	1 (2.3%)	1 (1.1%)
Excoriation	1 (1.1%)	2 (4.9%)	0 (0.0%)	1 (1.1%)
Laceration	1 (1.1%)	0 (0.0%)	0 (0.0%)	1 (1.1%)
Ligament sprain	0 (0.0%)	1 (2.4%)	0 (0.0%)	0 (0.0%)
Muscle strain	1 (1.1%)	0 (0.0%)	0 (0.0%)	1 (1.1%)
Periorbital haematoma	1 (1.1%)	0 (0.0%)	0 (0.0%)	1 (1.1%)
Wound	0 (0.0%)	0 (0.0%)	1 (2.3%)	1 (1.1%)
Investigations	2 (2.3%)	1 (2.4%)	0 (0.0%)	2 (2.3%)
Blood pressure increased	1 (1.1%)	0 (0.0%)	0 (0.0%)	1 (1.1%)
Liver function test abnormal	0 (0.0%)	1 (2.4%)	0 (0.0%)	0 (0.0%)
Weight decreased	1 (1.1%)	0 (0.0%)	0 (0.0%)	1 (1.1%)
Weight increased	1 (1.1%)	0 (0.0%)	0 (0.0%)	1 (1.1%)
Respiratory, thoracic and mediastinal disorders	6 (6.9%)	0 (0.0%)	2 (4.5%)	8 (9.2%)
Cough	5 (5.7%)	0 (0.0%)	1 (2.3%)	6 (6.9%)
Dyspnea	1 (1.1%)	0 (0.0%)	0 (0.0%)	1 (1.1%)
Epistaxis	0 (0.0%)	0 (0.0%)	1 (2.3%)	1 (1.1%)
Skin and subcutaneous tissue disorders	4 (4.6%)	0 (0.0%)	0 (0.0%)	4 (4.6%)
Alopecia	1 (1.1%)	0 (0.0%)	0 (0.0%)	1 (1.1%)
Pruritus	1 (1.1%)	0 (0.0%)	0 (0.0%)	1 (1.1%)
Rash	1 (1.1%)	0 (0.0%)	0 (0.0%)	1 (1.1%)
Rash maculo-papular	1 (1.1%)	0 (0.0%)	0 (0.0%)	1 (1.1%)
Musculoskeletal and connective tissue disorders	2 (2.3%)	1 (2.4%)	0 (0.0%)	2 (2.3%)
Arthralgia	1 (1.1%)	0 (0.0%)	0 (0.0%)	1 (1.1%)
Back pain	1 (1.1%)	0 (0.0%)	0 (0.0%)	1 (1.1%)
Myalgia	0 (0.0%)	1 (2.4%)	0 (0.0%)	0 (0.0%)
Cardiac disorders	1 (1.1%)	0 (0.0%)	0 (0.0%)	1 (1.1%)
Ventricular arrhythmia	1 (1.1%)	0 (0.0%)	0 (0.0%)	1 (1.1%)

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/s/

GLENN B MANNHEIM
10/09/2015

JING ZHANG
10/11/2015