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
Received Date(s)	December 19, 2016
Status Update Meeting	February 22, 2017
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 methylphenidates[1].

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

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: maculopaular 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.

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 NT0102Methylphenidate 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

to remain in the study unit for the duration of the study, and who were not allowed to take any medications or dietary supplements during the study.

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 Cmax, AUC0-3, AUC3-7, AUC7-12, and AUCinf 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 Conclusion[3]: **"**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-marked formulation.

PK Parameters (Mean ±SD) of (*d+l*)-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

end of study) 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. 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 Cmax. 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 studies[2], 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 Zhu[3] 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 Elayan[4] 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 Khairuzzaman[5] 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. Bridges[6] 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. Bradshaw[7] 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 White[8] 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.

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 Nkah[9] 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 Yao[10] 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 old[11]. 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.

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 methyl-phenidate adverse events in this age group and are not substantially different from the 6-15 year age group.

XVII. Appendix

Table 1: Overview of Studies [12]

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

Table 2: List of Investigators: NT0102.1005[13]

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. Hinitt, M.D.	Worldwide Clinical Drug Development Solutions 2455 N.E. Loop, Suite 150 San Antonio, TX 78217	210-635-1500
Steven Hinitt, 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: NT0102.1005[14]

	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)	
System Organ Class\ Preferred Term	**# Reports**	**# Subjects**	**# Reports**	**# Subjects**	**# Reports**	**# Subjects**
Number of Subjects Dosed		47		48		47
Cardiac disorders	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%)
Gastrointestinal disorders	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%)
General disorders and administration site conditions	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%)
Metabolism and nutrition disorders	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%)
Nervous system disorders	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%)
Psychiatric disorders	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) (b) (4)	Lot#	--	2E116E	1E101A	6P081
					(b) (4)

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/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)