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)

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 (b) (4)% (b) (4) (w/w) delayed release and (b) (4)% (w/w) (b) (4) extended release (b) (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 (b) (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-(b) (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

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

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 show 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)
[a] Washout of at least 3 days (up to 1 week)
[b] Visit 7 is the "practice" classroom testing day.
[c] Visit 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

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-Deportment (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).

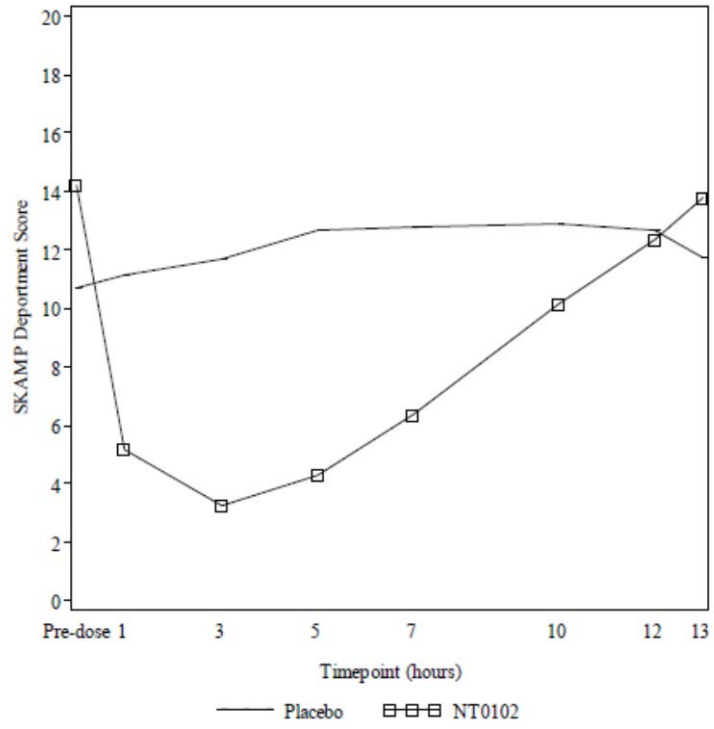
Table: Lease Squares Mean SKAMP-Combined Scores at All Time Points

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 Deportment 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

"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.

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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: maculopaular; 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 that 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 (s) 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.

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 know 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 (b) (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)

reviewed the Patient Labeling: Medication Guide and provided various comments and thought that the Medication Guide would be acceptable with their recommended changes..

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 hydrochloride) 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 (b) (4) 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 dexmethylphenidate 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.

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.

XVI. Appendix

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. Riesenberg, 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

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%)
Gastrooesophageal 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%)
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%)
Myclonus	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%)

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%)**
Hyperhydrosis	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

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%)

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
10/09/2015

JING ZHANG
10/11/2015