U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA #:	205,489 [SN27 Resubmission]
Drug Name:	Cotempla XR-ODT (Methylphenidate extended release ODT) 10, 20, and 30 mg tablets
Indication(s):	Attention-Deficit Hyperactivity Disorder (ADHD)
Applicant:	NEOS Therapeutics
Dates:	Submitted: 12/19/2016 PDUFA: 06/19/2017
Review Priority:	Standard
Biometrics Division:	**Division of Biometrics I**
Statistical Reviewer:	Thomas Birkner, Ph.D.
Concurring Reviewers:	Peiling Yang, Ph.D. (Team leader) H.M. James Hung, Ph.D. (Division director)
Medical Division:	**Division of Psychiatry Products**
Clinical Team:	Glenn Mannheim, M.D. Jasmine Gatti, M.D.
Project Manager:	William Bender, Pharm.D.

Keywords: Analysis of covariance, baseline imbalance, randomization

Resubmission

This memo refers to Neos Therapeutics resubmission received December 19, 2016 of their 505(b)(2) application for Methylphenidate Extended-Release Orally Disintegrating Tablets (XR-ODT) - 10 mg, 20 mg, and 30 mg for ADHD. The proposed tradename is Cotempla XR-ODT.

EDR Location: \\CDSESUB1\evsprod\NDA205489\0027

Reference is made to the New Drug Application (NDA) dated January 9, 2015 and the Complete Response (CR) Letter dated November 6, 2015. In the CR letter FDA requested a study to bridge between the clinical trial formulation and the to-be-marketed formulation and from the to-be marketed product to the reference product (i.e., Metadate CD). The other major issue was a CMC problem (i.e., (b) (4) operation and control).

Further reference is made to the statistical review of the original submission filed to DARRTS on 10/14/2015 [Reference ID: 3829245]. The conclusion of the original statistical review was that the results of the clinical study provide adequate statistical evidence that Methylphenidate XR-ODT is superior to placebo in the treatment of ADHD in the pediatric population (6-12 years) on the endpoints studied:

> "Patients randomized to MPH XT-ODT in the laboratory classroom study (NT0102.1004), the only efficacy study under this 505(b)(2) application, 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." (Statistical review p. 30)

Labeling was not negotiated with the sponsor during the review of the original submission. The sponsor submitted an updated version of the label with the resubmission. The statistical contribution to the review of this resubmission was the review of section 14 of the proposed label. An efficacy table describing the results for the primary efficacy endpoint was added to section 14.

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

/s/

THOMAS BIRKNER
05/18/2017

PEILING YANG
05/19/2017