CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208745Orig1s000

STATISTICAL REVIEW(S)

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 #:	208,745
Supplement #:	Original
Drug Name:	Truelance® (Plecanatide)
Indication(s):	Chronic Idiopathic Constipation (CIC)
Applicant:	Synergy Pharmaceuticals Inc.
Dates:	
Submission date	01/29/2016
Primary review	09/29/2016
PDUFA V	01/29/2017
Review Priority:	Standard
Biometrics Division:	Division of Biometrics 3
Statistical Team:	
Reviewers	Shahla Farr, M.S.
Concurring Reviewer	Yeh-Fong Chen, Ph.D.
Medical Division:	Division of Gastroenterology and Inborn Errors Products
Clinical Team:	
Reviewer	Lesley Hanes, MD
Team Leader	Laurie Muldowney, MD
Project Manager	Maureen Dewey, MPH
EDR Locations:	\\CDSESUB1\evsprod\NDA208745\208745.enx

Keywords: NDA review, clinical study

Table of Contents

1 EXECUTIVE SUMMARY

The sponsor has submitted the results of two identical, Phase 3, multicenter, randomized double-blind, placebo-controlled, parallel-group studies (Study SPD304203-00 and Study SPD304203-03) to support the efficacy of Truelance® (Plecanatide) for the indication of Chronic Idiopathic Constipation (CIC).

The summaries of results for both pivotal studies are as follows:

Study SPD304203-00
Difference between Plecanatide 3 mg and Placebo = 10.6%
95% CI for the difference (6.0%, 15.2%)

Study SPD304203-03)
Difference between Plecanatide 3 mg and Placebo =7.5%
95% CI (2.6%, 12.5%)

After thorough evaluation and clarifications with the sponsor, the statistical review team concluded that results of the submitted two studies are statistically significance and can be used to support Plecanatide's efficacy for the indication of Chronic Idiopathic Constipation (CIC) in adults.

2 INTRODUCTION

(Descriptions in this section are extracted from the sponsor's clinical study report)

Plecanatide (SP-304) is a peptide discovered, synthesized, and patented by Synergy Pharmaceuticals Inc. (hereafter referred to as Synergy) for treating patients with idiopathic or functional constipation.

The sponsor noted in the submission that idiopathic or functional constipation is a common disorder that affects approximately 15% of the population of the United States (US), depending on demographic factors and the definition used. Internationally, similar prevalence rates have been observed in most geographic areas. The sponsor emphasized that although laxatives can be used to relieve constipation, chronic use of laxatives is often inappropriate, and may lead to side effects, such as dependency and progressive tolerance, electrolyte imbalance, and, for the anthraquinones, melanosis coli. In addition, stimulant laxatives may damage the myenteric plexus, resulting in cathartic colon. Laxatives available over the counter are, in general, approved for episodic and not chronic use. [redacted] (b) (4) Therefore, the results are reported, mainly, for the 3 mg plecanatide.

2.1 Overview and Background

The sponsor has submitted two similar Phase 3, multicenter, randomized double-blind, placebo-controlled, parallel-group studies (Study SPD304203-00 and Study SPD304203-03) for duration

of 12 weeks to assess the safety and efficacy of Plecanatide (3 mg and 6 mg) for the indication of Chronic Idiopathic Constipation (CIC). Table 1 lists a brief description of the two studies.

Table 1: Brief Description of the Phase 3 Efficacy Studies

Study #	Design*	Treatment Arm/ Sample Size	Endpoints		Statistical Analyses
			Primary	Secondary	
Study SPD304203-**00**	MC, R, DB, PG, PC	3.0 mg / 471 6.0 mg/ 456 Placebo/ 467	Proportion of durable overall CSBM responders over the 12-week	• Change from baseline in frequency rate of CSBMs and SBMs; • Change from baseline in stool consistency based upon the BSFS; • Change from baseline in Straining Score; • Treatment Satisfaction; • Patient reported symptoms associated with constipation in the Daily Symptom Diary;	Cochran-Mantel-Haenszel (CMH) test stratified by gender
Study SPD304203-**03**	Same as Study 00, above	3.0 mg / 469 6.0 mg/ 471 Placebo/ 469	Same as Study 00, above	Same as Study 00, above	

* MC: multi-center, R: randomized, DB: double-blind, PG: parallel group, PC: placebo controlled

The statistically-relevant changes to the protocol were added in Protocol version 4.0, dated 10 April 2015 as follows:

- Changes to the statistical section of the protocol included use of MRA as the primary method for imputation of missing data and replaced MRA in the list of sensitivity analyses with observed case (originally planned as the primary method).

- Re-organized secondary endpoints into secondary and additional and changed terminology from key secondary to secondary (these changes are described later in the body of this review).

- No difference could be detected when the efficacy of the 3 mg dose was compared to the 6 mg. So, in a mid-cycle communication with the sponsor (dated July 11, 2016), (b) (4)

- There had been some issues regarding the data integrity with (b) (4) (b) (4) (b) (4) as these sites have had previous Agency enforcement action or warning letters. For that reason, we recommended that patients who were enrolled in these study sites be removed from the primary and secondary efficacy analysis for study SP304203-03, as well as the safety analyses. The applicant agreed to remove the (b) (4) patients as requested. On August 5, 2016 Synergy (the applicant) sent summery tables with the (b) (4) patients removed.

During the review cycle, we asked the sponsor to re-analyze the primary endpoint by treating patients who had 4 or more days of missing data in a week as non-responders for that week (i.e.,

DOCKET ALARM

Explore Litigation Insights

Docket Alarm provides insights to develop a more informed litigation strategy and the peace of mind of knowing you're on top of things.

Real-Time Litigation Alerts

Keep your litigation team up-to-date with **real-time alerts** and advanced team management tools built for the enterprise, all while greatly reducing PACER spend.

Our comprehensive service means we can handle Federal, State, and Administrative courts across the country.

Advanced Docket Research

With over 230 million records, Docket Alarm's cloud-native docket research platform finds what other services can't. Coverage includes Federal, State, plus PTAB, TTAB, ITC and NLRB decisions, all in one place.

Identify arguments that have been successful in the past with full text, pinpoint searching. Link to case law cited within any court document via Fastcase.

Analytics At Your Fingertips

Learn what happened the last time a particular judge, opposing counsel or company faced cases similar to yours.

Advanced out-of-the-box PTAB and TTAB analytics are always at your fingertips.

API

Docket Alarm offers a powerful API (application programming interface) to developers that want to integrate case filings into their apps.

LAW FIRMS
Build custom dashboards for your attorneys and clients with live data direct from the court.

Automate many repetitive legal tasks like conflict checks, document management, and marketing.

FINANCIAL INSTITUTIONS
Litigation and bankruptcy checks for companies and debtors.

E-DISCOVERY AND LEGAL VENDORS
Sync your system to PACER to automate legal marketing.