

Summary Basis for Regulatory Action

Date: August 25, 2017

From: Christina Houck, Chair of the Review Committee

BLA/ STN#: 103738/5162

Applicant Name: SmartPractice Denmark ApS

Date of Submission: October 27, 2016

Goal Date: August 25, 2017

Proprietary Name/ Established Name: T.R.U.E. TEST Thin-Layer Rapid Use Epicutaneous Patch Test

Indication: For use as an aid in the diagnosis of allergic contact dermatitis (ACD) in persons 6 years of age and older whose history suggests sensitivity to one or more of the 35 substances included on the T.R.U.E. TEST panels

Recommended Action:

The Review Committee recommends approval.

Review Office(s) Signatory Authority Wellington Sun, M.D., Director, Division of Vaccines and Related Products Applications, Office of Vaccines Research and Review

- I concur with the summary review.
- I concur with the summary review and include a separate review to add further analysis.
- I do not concur with the summary review and include a separate review.

The table below indicates the material reviewed when developing the SBRA.

Document title	Reviewer name, Document date
Clinical Reviews <ul style="list-style-type: none">• <i>Clinical</i>• <i>Postmarketing safety epidemiological review (OBE/DE)</i>• <i>BIMO</i>	Joohee Lee, MD 8/25/2017 Patricia Rohan, MD 6/8/2017 Erin McDowell 6/1/2017
Statistical Review (OBE)	Zhong Gao 7/28/2017
CMC Review/Consult (OVR/DBPAP)	Jennifer Bridgewater 8/6/2017
Labeling Reviews <ul style="list-style-type: none">• Labeling (OCBQ/APLB)	Oluchi Elekwachi 7/6/2017

1. Introduction

T.R.U.E. TEST® (Multiple Products: Allergen Patch Test Allergen Patch Test Kit) is an epicutaneous patch test for use as an aid in the diagnosis of allergic contact dermatitis (ACD) in persons 18 years of age and older whose clinical history suggests sensitivity to one or more of the 35 substances included in patches on the T.R.U.E. TEST panels.

The T.R.U.E. TEST test kit contains three multi-patch panels, numbered as Panels 1.3, 2.3 and 3.3. Panel 1.3 contains 11 allergen patches and a negative control, Panel 2.3 contains 12 allergen patches, and Panel 3.3 contains 12 allergen patches. Each 0.81 cm² patch contains the allergen or allergen mix in a dried, uniform gel coating on polyester sheeting. These allergen gel patches are attached to the panel, which is (b) (4) tape coated with a medical acrylic adhesive.

On October 27, 2016 CBER received an efficacy supplement for T.R.U.E. TEST STN 103738/5162, which included two clinical pediatric studies to evaluate the safety and diagnostic performance in children and adolescents 6 to <18 years of age with suspected ACD. Pediatric Study 1 (Mekos 07 29P1/2/3 401) was an open-label Phase 3 postmarketing study to evaluate the 28 allergens and negative control contained in a previously approved version of T.R.U.E. TEST, in at least 100 subjects 6 to <18 years of age, as specified in the approval letter for STN 103738/5019, dated June 5, 2007. Pediatric Study 2 (SP 12 7NEW 401) was an open-label Phase 3 postmarketing study to evaluate the additional 7 new allergens included in T.R.U.E. TEST, in at least 110 participants 6 to <18 years of age, as specified in the approval letter for STN 103738/5074, dated February 29, 2012. The 7 new allergens added were Gold Sodium Thiosulfate (GST), Hydrocortisone-17-Butyrate (H-17-B), Bacitracin, Parthenolide, Disperse Blue 106 (DB 106), and 2-Bromo-2-Nitropropane-1, 3-Diol (Bronopol) and Methylidibromo Glutaronitrile (MDBGN). After a Type C meeting held on March 10, 2014, CBER requested for Pediatric Study 2 to be amended to include proposed changes in dose and excipient for Neomycin Sulfate, Potassium Dichromate, Fragrance Mix, and Ethylenediamine Dihydrochloride in subjects 6 to <18 years of age.

2. Background

ACD is a common inflammatory skin condition that is estimated to occur in about 20% of adults. The epidemiology of ACD in children and adolescents is less certain due to the fact that this was largely viewed as an adult disorder. The prevailing notion up until the 1990s was that most children had accumulated enough exposure to contact allergens to develop ACD. Retrospective and prospective studies of patch testing in children and adolescents have demonstrated this notion to be false. ACD presents as pruritic eczema with variable distribution. It is typically most intense at areas of exposure to the causative contact allergens. ACD represents a delayed type (IV) hypersensitivity reaction, which is primarily driven by T lymphocytes. This is distinct from the immediate type hypersensitivity reaction underlying anaphylaxis, which is primarily driven by serum

Immunoglobulin E (IgE). In sensitized individuals, ACD reactions normally appear 9 to 96 hours after exposure to the relevant contact allergens.

T.R.U.E. TEST was licensed in the United States in 1994 for use in adults 18 years of age and above and consisted of two panels containing 23 allergens and allergen mixes and one negative control. In 2007, supplement Biologics License Applications (sBLA) STN 103738/5019 and 103738/5027 were approved to include a third panel (Panel 3.1), which included 5 new allergens and allergen mixes. Pediatric Study 1 was conducted as a postmarketing commitment to evaluate the safety and diagnostic performance of the 28 allergens and negative control contained in a previously approved formulation of T.R.U.E. TEST in at least 100 participants 6 to <18 years of age (STN 103738/5019).

In supplement STN 103738/5074, T.R.U.E. TEST was expanded with the addition of 7 new allergens and allergen mixes (Methyldibromoglutaronitrile, Gold Sodium Thiosulfate, Hydrocortisone-17-Butyrate, Bacitracin, Parthenolide, Disperse Blue 106, and 2-Bromo-2-Nitropropane-1,3-Diol) for persons 18 years and older. Methyldibromoglutaronitrile was included on Panel 2.1 (designated thereafter as Panel 2.2) and the other six were added to Panel 3.1 (designated thereafter as Panel 3.2). No changes were made to Panel 1.1, but it was renumbered as 1.2 for internal consistency. A total of 35 allergens and allergen mixes and one negative control was included in T.R.U.E. TEST Panels 1.2, 2.2, and 3.2. Pediatric Study 2 was a postmarketing requirement to evaluate the 7 new allergens included in the version of T.R.U.E. TEST currently licensed in adults in at least 110 participants 6 to <18 years of age. Under STN 103738/5074 a partial waiver was granted for the requirement to conduct studies in individuals 0 to <6 years of age because necessary studies are impossible or highly impracticable because the number of children younger than 6 years of age with allergic contact dermatitis is small. Under STN 103738/5118, Panel 1.2 was revised with reformulations of Neomycin Sulfate, Potassium Dichromate, and Fragrance Mix with respect to contact allergen concentration and excipient and of Ethylenediamine Dihydrochloride with respect to excipient, which was replaced under STN 103738/5129. Although unchanged, Panels 2.2 and 3.2 were renumbered as 2.3 and 3.3 to align them with Panel 1.3.

3. Chemistry Manufacturing and Controls (CMC)

a) Product Quality

The sBLA did not contain CMC information for review, but a CMC reviewer was consulted regarding issues discovered by the BIMO investigators related to labeling and packaging of clinical lots. Through multiple Information Requests (IR) all issues related to the clinical lots were resolved.

b) CBER Lot Release

A review of Product Release Branch records indicate that there are no pending lots or issues that would affect approval of the submission.

4. Nonclinical Pharmacology/Toxicology

No new pharmacology/toxicology data were submitted as part of this supplement.

5. Clinical Pharmacology

No new clinical pharmacology data were submitted as part of this supplement.

6. Clinical/Statistical/Pharmacovigilance

a) Clinical Program

The clinical data provided for T.R.U.E. TEST was evaluated in children and adolescents 6 through 17 years of age in two pediatric studies, Pediatric Study 1 (Mekos 07 29P1/2/3 401) and Pediatric Study 2 (SP 12 7NEW 401).

Pediatric Study 1 - Mekos 07 29P1/2/3 401

Pediatric Study 1 was an open-label, non-randomized, single-site Phase 3 trial of T.R.U.E. TEST Panels 1.1, 2.1, and 3.1 in children and adolescents (n=102; 6 to <18 years of age). The study was designed to evaluate the diagnostic performance of the 28 allergen patches and 1 negative control on T.R.U.E. TEST Panels 1.1, 2.1, and 3.1 in children and adolescents with suspected ACD. Positive control and negative control subjects were not enrolled. Diagnostic performance was evaluated in terms of the skin reaction frequencies by the four pre-specified categories (positive, negative, irritant, indeterminate) for the 28 allergen patches and the negative control. The adhesive panel of allergens was placed on the healthy skin of the back. Panels were removed and the skin was evaluated 48 and 72-96 hours after application

The population used to evaluate safety (secondary objective) for this study was comprised of 102 participants who received T.R.U.E. TEST at visit 1. The mean (standard deviation) age of the enrolled subjects was 11.6 (3.61) years. The proportion of subjects who were 6 to 8 years of age, 9 to 12 years of age, and 13 to 18 years of age was 27.5%, 28.4%, and 44.1%, respectively. The greatest age representation was intended to be among adolescent participants 13 to <18 years of age (45 participants; 44.1%) and evenly distributed between the 2 younger age strata, with 29 participants (28.4%) who were 9 to 12 years old, and 28 participants (27.5%) 6 to 8 years old. Females comprised 52% of the trial population. Caucasian and Hispanic participants were somewhat overrepresented while Asian and African-American participants were underrepresented relative to the U.S. population.

The primary objective was to evaluate the diagnostic performance of T.R.U.E. TEST based on frequencies of positive, negative, irritant, and doubtful reactions to each of the 24 allergens and allergen mixes included in T.R.U.E. TEST Panels 1.3, 2.3, and 3.3. This study was not designed to determine sensitivity, specificity, or concordance for any of the contact allergens. The frequency and 95% confidence intervals (CIs) for positive, negative, irritant, and doubtful reactions were reported for all subjects separately at Visit 3 and Visit 4. At Visit

3, the most frequent positive reactions, observed in more than 10% of the subjects, were associated with nickel sulfate (28.7%, n=29), followed by wool alcohols and *p-tert*-butylphenol formaldehyde resin (15.8%, n=16), fragrance mix (12.9%, n=13), and cobalt dichloride (11.9%, n=12). At Visit 4, the proportions of subjects with positive reactions to each of the allergens were similar to or lower than those observed at Visit 3. Of the 101 participants who presented on Day 3, none experienced a positive reaction to caine mix or the negative control. Additionally, at Visit 4, no subject experienced a positive reaction to black rubber mix, *p*-phenylenediamine, or quinoline mix.

Finally, in regard to the frequencies of cumulative positive reactions (i.e., positive reactions that were observed either at Visit 3 or Visit 4) to each allergen, trends were similar to those observed in the frequencies of positive reactions at Visit 3 for all subjects.

A Bioresearch Monitoring (BIMO) inspection was previously completed for this site during the review of BLA 125579/0 for Rubber Panel T.R.U.E. TEST. A review of the inspection results did not reveal any sponsor or monitoring issues or problems that impact the data submitted in this supplement.

Pediatric Study 2 - SP 12 7NEW 401

Pediatric Study 2 was an open-label, non-randomized, multi-center Phase 3 trial of T.R.U.E. TEST Panels 1.3, 2.3, and 3.3. The study was designed to evaluate the diagnostic performance of the 7 new contact allergens added to T.R.U.E. TEST Panels 2.2 and 3.2 and the four reformulated allergens included in Panel 1.3 in children and adolescents with suspected ACD. The adhesive panels of T.R.U.E. TEST were placed on the healthy skin of the back and upper arm of study participants. The panels were evaluated by clinical investigators for grading of adhesion. Twenty minutes after removal, objective signs of tape irritation and subject-reported symptoms of burning and or itching were documented. The participants returned at days 3, 4, 7, and 21 for investigators to assess the 36 patch sites. Each participant was followed for at least 21 days, with up to 6 clinical visits. As in Pediatric Study 1, no negative or positive control subjects were enrolled. This study was not designed to determine sensitivity, specificity, or concordance for any of the contact allergens.

The mean (standard deviation) of age was 12.6 (3.2) years in the population of enrolled subjects. The proportion of subjects who were 6 to 8 years of age, 9 to 12 years of age, and 13 to 18 years of age was 10.3%, 34.5%, and 55.2%, respectively. The three analysis populations represented in the study were as follows:

- Per-protocol population (PP) (n=111) - all subjects who received a patch application and who completed the study with no major protocol violations. This population was the primary population for diagnostic performance, which was described in terms of frequencies of positive,

negative, irritant, and doubtful reactions to T.R.U.E. TEST allergens at days 3, 4, and 7 after panel placement.

- Intent-to-treat (ITT) population (n=113) - all subjects who received a patch application and had at least one postoperative baseline skin reaction evaluation. The ITT population was used to support the analysis of diagnostic performance based on the PP population.
- Safety population (n=116) - all subjects who received T.R.U.E. TEST were considered for safety data.

Females comprised 69% of the trial population. Caucasian and Hispanic participants were somewhat overrepresented while Asian and African-American participants were underrepresented relative to the U.S. population. The demographic percentages and data were similar across all three populations.

The primary objective was to evaluate the diagnostic performance of the 11 investigational T.R.U.E. TEST allergens based on the frequency of patch site reactions (i.e., positive, negative, irritant, and doubtful reactions) at days 3 through 7 after T.R.U.E. TEST application.

The primary endpoints for diagnostic performance were the frequencies of positive skin reactions to each of the 11 investigational T.R.U.E. TEST allergens. The patch test sites were evaluated at days 3 (Visit 3), 4 (Visit 4), 7 (Visit 5), and 21 (Visit 6) after T.R.U.E. TEST application. The skin reactions were scored as follows: negative (-), irritant reaction, doubtful reaction (?), weak positive (1+), strong positive (2+), or extreme positive (3+). Positive reactions at days 3, 4, and 7 corresponded to diagnostic performance, whereas those detected at day 21 corresponded to late and persistent reactions, which were safety endpoints.

Based on data analyzed for the determination of positive reactions for the seven new allergens, the PP population showed that the frequency of positive reactions for the 7 new allergens was 27% (n=30) for GST, 17.1% (n=19) for Bronopol, 12.6% (n=14) for Bacitracin, and 7.2% (n=8) for Parthenolide, 3.6% (n=4) for DB 106, 1.8% (n=2) for H-17-B, and 0.9% (n=1) for MDBGN. No positive reactions to the negative control were observed. The frequency of positive reactions for the 4 reformulations was 3.8% (2 subjects each) for Neomycin, Sulfate, Potassium Dichromate, and Fragrance Mix. No positive reactions were associated with Ethylenediamine Dihydrochloride. The ITT analysis showed similar results.

Bioresearch Monitoring Inspections

During the review of this sBLA, two domestic clinical study sites were inspected under the Agency's Bioresearch Monitoring program. Discrepancies were identified during inspection at both sites and both sites were issued a Form FDA 483 (483). Both sites responded to the 483 with acceptable corrective actions to prevent potential issues in current and future studies.

b) Pediatrics

In this supplement, the two pediatric studies submitted were conducted to comply with PREA. The pediatric assessment was presented to the FDA Pediatric Review Committee and was deemed acceptable. Under STN 103738/5074 a partial waiver was granted in children 6 years of age under. Consequently, safety and effectiveness of T.R.U.E. TEST have not been established in persons younger than 6 years of age.

7. Safety

The safety populations from the two pediatric studies was comprised of 218 children and adolescents 6 to >18 years of age. There were 102 subjects in Pediatric Study 1 and 116 subjects in Pediatric Study 2 who received the T.R.U.E. TEST product. In both pediatric studies, subjects were followed for 21 days after T.R.U.E. TEST application for spontaneously reported adverse events. Subjects and guardians were instructed to keep the T.R.U.E. TEST panels on their backs and upper arms in place and to return to the clinic in 2 days for evaluation of panel adhesion prior to removal and tape irritation and subjective burning and itching after panel removal. Due to differences in grading panel adhesion and soliciting symptoms of burning and itching (as a combined symptom in Pediatric Study 1 and as separate symptoms in Pediatric Study 2), greater emphasis was placed on Pediatric Study 2 data. Safety endpoints also included late positive reactions and persistent positive reactions, which were captured during patch site readings conducted on days 7 and 21 after T.R.U.E. TEST placement.

AEs

For Pediatric Study 1, 52 spontaneously reported AEs occurred in 35 subjects over the 21 days of protocol enrollment. The majority of AEs were mild (53.8%, n=28) to moderate (42.3%, n=22). Twenty-five participants (25.4%) had 31 adverse reactions. The majority of adverse reactions were worsening of pre-existing dermatitis (23.5%), presumed infections affecting sites of worsening dermatitis (2.0%), and reactions at panel adhesion sites (2.0%). Two of the 25 participants who had severe worsening of pre-existing dermatitis, complicated by superinfection, were managed with topical therapy and oral antibiotics. At day 2, poor adhesion, which was defined as little to no skin contact with panel, was observed in up to 2% of the participants. None of the panels fell off. After removal of T.R.U.E. TEST, tape irritation at the three panel sites was observed in 60.4 to 63.4% of the 101 participants who presented to Visit 2. Most cases were characterized by faint to definite pink erythema and graded as weak (40.6 to 43.6% across the three panels). Subject-reported burning and itching ranged from 39.6% (Panel 3.1) to 66.3% (Panel 1.1). Seven participants had 10 positive reactions first observed on day 7. No late reactions were observed at day 21. On day 7, seven persistent reactions were observed in 4 participants. All were graded as mild to moderate. Four of the reactions were due to Nickel Sulfate, and the remaining three were due to Cl⁺ Me-Isothiazolinone, Quaternium-15, and Diazolidinyl urea. No serious adverse events or deaths occurred in the study. No subject discontinued from the study due to an AE. Two subjects dropped out of the study. No serious adverse events or deaths occurred in the study.

In Pediatric Study 2, 48 spontaneously reported AEs occurred in 40 (34.8%) subjects during the 21 days of follow-up. The majority of AEs were mild (15.5%, n=18) to moderate (20.7%, n=24). Spontaneously reported adverse reactions occurred in 11 (9.6%) of the 116 participants in Pediatric Study 2. The most common was worsening of pre-existing dermatitis (4.3%) and skin infections (1.7%). Adverse reactions in the remaining 4 subjects were “discomfort” at patch test sites, cough, ear pain, vasovagal reaction due to pain induced by panel removal. Poor adhesion was observed in up to 11.3% of the participants. After removal of T.R.U.E. TEST, tape irritation at the three panel sites was observed in 47.5 to 50% of participants, but cases were predominantly graded as weak (36.0 to 42.6%). Half of the participants reported itching (62.6%) more commonly than burning (10.5%) at the former panel sites. Late positive reactions occurred in 1.7% of subjects and persistent positive reactions in 5.2% of subjects. No participants dropped out or discontinued due to adverse events. No deaths occurred in the study.

Nonfatal Serious Adverse Event

In Pediatric Study 2 (SP 12 7NEW 401), one participant was diagnosed with appendicitis, which was judged to be unrelated to patch testing due to lack of biological plausibility. The appendicitis resolved with surgical intervention.

Adverse Events of Special Interest (AESI)

In Pediatric Study 1 (Mekos 07 29P1/2/3 401), one participant had an extreme positive reaction (+++, indicating a bullous or ulcerative reaction with pronounced erythema, infiltration, and coalescing vesicles) to Nickel Sulfate at Day 3. By day 7, it decreased to a strong positive (++) and was resolved by day 21.

In Pediatric Study 2 (SP 12 7NEW 401), one participant experienced one positive extreme reaction to Gold Sodium Thiosulfate on day 3, which resolved by day 21.

8. Advisory Committee Meeting

A Vaccines and Related Biological Products Advisory Committee (VRBPAC) meeting was not held for this supplement, as there were no issues or concerns that presented during the course of review of the supplement that required consult from the advisory committee.

9. Other Relevant Regulatory Issues

There are no additional relevant regulatory issues in addition to the discussions in this summary.

10. Labeling

The T.R.U.E. TEST package insert (PI) included safety and efficacy data from Pediatric Study 1 (Mekos 07 29P1/2/3 401) and Pediatric Study 2 (SP 12 7NEW 401). To comply with the 2014 Final Rule, *Content and Format of Labeling for Human Prescription Drug*

and Biological Products; Requirements for Pregnancy and Lactation Labeling, also known as the Pregnancy and Lactation Labeling Rule (PLLR), a request was made to the Applicant to submit a Package Insert (PI) to include language to comply with the PLLR. The proposed PI was primarily reviewed by the Clinical, Statistical and Advertising and Promotional Labeling Branch reviewers and revisions were made to Section 6 Adverse Reactions, Section 8 Use in Specific Populations, and Section 14 Clinical Studies. All labeling issues were satisfactorily resolved through communication with SmartPractice.

11. Recommendations and Risk/ Benefit Assessment

a) Recommended Regulatory Action

The safety and diagnostic performance data provided in this supplement support the use of T.R.U.E. TEST for use as an aid in the diagnosis of ACD in persons 6 years of age and older whose history suggests sensitivity to one or more of the 35 allergens and allergen mixes included in T.R.U.E. TEST.

b) Risk/ Benefit Assessment

The risk-benefit profile for the use of T.R.U.E. TEST is favorable. No safety signals for serious adverse events were identified. Most of the adverse reactions were cutaneous, graded as mild to moderate, and were most commonly related to worsening of pre-existing dermatoses, including AD and ACD.

c) Recommendation for Postmarketing Activities

There is no recommendation for postmarketing activities. Based on a review of the submitted clinical data, the review committee concurs with continued routine safety surveillance.