BLA Clinical Review Memorandum

Application Type	Supplemental Biologics License Application
STN	103738/5162
CBER Received Date	October 27, 2016
PDUFA Goal Date	Non-PDUFA (Action due date: August 27, 2017)
Division / Office	DVRPA/ OVRR
Priority Review (Yes/No)	No
Reviewer Name(s)	Joohee Lee, MD
Review Completion Date / Stamped Date	August 24, 2017
Supervisory Concurrence	Roshan Ramanathan, MD, MPH Team Leader, Clinical Review Branch 1 Jeff Roberts, MD Branch Chief, Clinical Review Branch 1
Applicant	SmartPractice Denmark ApS
Established Name	Thin-layer Rapid Use Epicutaneous Patch Test
(Proposed) Trade Name	T.R.U.E. TEST
Pharmacologic Class	Contact Dermatitis Patch Test
Formulation(s), including Adjuvants, etc.	Patch
Dosage Form(s) and Route(s) of Administration	Three adhesive panels containing a total of 35 allergens and 1 negative control patches
Dosing Regimen	Apply the adhesive panels of allergens on healthy skin of the back. Remove panels and evaluate the skin 48 hours after application. Re-evaluate the skin 72 to 96 hours after application.
Indication(s) and Intended Population(s)	T.R.U.E. TEST is an epicutaneous patch test indicated 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.
Orphan Designated (Yes/No)	No

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Glossary

ACD	allergic contact dermatitis
AD	atopic dermatitis
AE	adverse event
BLA	Biologics Licensing Application
CBER	Center For Biologics Evaluation and Research
CFR	Code of Federal Regulations
CMC	chemistry, manufacturing, and controls
CRF	Case Report Form
CSR	clinical study report
eCTD	electronic Common Technical Document
ES	Executive Summary
FAERS	Food and Drug Administration Adverse Event Reporting System
FDAAA	Food and Drug Administration Amendments Act of 2007
GRMP	good review management principles
GST	gold sodium thiosulfate
ICD	irritant contact dermatitis
ICDRG	International Contact Dermatitis Research Group
IgE	Immunoglobulin E
IR	information request
ISE	integrated summary of efficacy
MedDRA	Medical Dictionary for Regulatory Activities
MBT	mercaptobenzothiazole
NACDG	North American Contact Dermatitis Group
OCD	occupational contact dermatitis
PeRC	Pediatric Review Committee
PI	package insert
PREA	Pediatric Research Equity Act
PT	patch test
REMS	risk evaluation and mitigation strategy
RPPT	relevant positive patch test
SPD	SmartPractice Denmark
SAE	serious adverse event
sBLA	supplemental biologics licensing application
TCS	topical corticosteroids

1. Executive Summary

T.R.U.E. TEST® is an epicutaneous patch test indicated for use as an aid in the diagnosis of allergic contact dermatitis (ACD) approved for use in adults 18 years of age and older. In this supplemental Biologics License Application (sBLA), SmartPractice Denmark ApS (SPD) proposed to revise the current indication to include children and adolescents 6 through 17 years of age. This sBLA is supported by descriptive clinical data from two open-label Phase 3 studies (Pediatric Study 1 and Pediatric Study 2), which evaluated the diagnostic performance (primary objective) and safety (secondary objective) of T.R.U.E. TEST. Pediatric Study 1 evaluated 24 of the 35 allergens and allergen mixes in the current version of T.R.U.E. TEST licensed in adults. Pediatric Study 2 evaluated 7 new and 4 reformulated allergens and allergen mixes, which were added to the current version of T.R.U.E. TEST through efficacy sBLAs. Both studies enrolled children and adolescents with suspected ACD based on history and physical examination by a clinical investigator. None of the participants had previously confirmed ACD due to specific allergen(s) in T.R.U.E. TEST.

In both studies, investigators applied three T.R.U.E. TEST panels on participants' backs and upper arms (day 0) and instructed participants and guardians to keep the panels in place for 48 hours. Safety monitoring occurred at up to 5 clinic visits scheduled for days 2, 3, 4, 7, and 21 following T.R.U.E. TEST application. Clinical investigators collected spontaneously reported adverse events (AEs) during the 21 days. On day 2, clinical investigators graded the quality of adhesion of the T.R.U.E. TEST panels prior to their removal. After 20 minutes of letting the skin rest, investigators graded tape irritation on participants' backs and upper arms and documented subject-reported burning and itching at each of the three former panel sites. Diagnostic performance was assessed by investigators on days 3 and 4, in accordance with the time frame specified in the T.R.U.E. TEST package insert (PI), as well as on day 7, in accordance with clinical practice guidelines on patch testing. At these clinic visits, investigators graded participants' patch site reactions as positive, negative, irritant, or doubtful on case report forms (CRF). Patch site reactions were also assessed on days 7 and 21 to determine rates of persistent and late positive reactions as safety variables. The final clinic visit at day 21 could be conducted by phone at the investigators' discretion. Since there were no negative control or positive control subjects in either study, the sensitivity and specificity of positive reactions to T.R.U.E. TEST allergens in children and adolescents could not be determined. Instead, diagnostic performance was defined by descriptive rates of positive reactions to the 35 allergens and allergen mixes in T.R.U.E. TEST in a heterogeneous population of children and adolescents suspected to have ACD.

In Pediatric Study 1, thirty-one spontaneously reported adverse reactions (AR) occurred in 25 (25.4%) of the 102 participants. The most common spontaneously reported AR to T.R.U.E. TEST were ectopic flares of pre-existing dermatitis (23.5%), skin infection (2.0%), and rash near panel site(s) (2.0%). Most of the adverse reactions were graded as mild (defined as minimal symptoms that did not interfere with daily functioning) and moderate (defined by need for medication for relief and resulting in some interference with daily functioning). There was one severe case of ectopic flare complicated by superinfection; this participant was managed in the outpatient setting with reinitiation of topical corticosteroids and a course of oral antibiotics. At day 2, poor adhesion (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 was observed in up to 63.4% of the 101 participants who presented to Visit 2. Most of the tape irritation

was 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). Participants most frequently graded their symptoms as minimal/weak (22.8 to 33.7%). Late positive reactions 21 days after T.R.U.E. TEST application were not observed. Persistent reactions present 21 days after T.R.U.E. TEST application were observed in 4 participants (3.9%) to the following allergens: Cl+Me+isothiazolinone (n=1), diazolidinyl urea (n=1), nickel sulfate (n=2), and quaternium-15 (n=1). There were no SAEs or deaths.

In Pediatric Study 2, spontaneously reported ARs occurred in 11 (9.6%) of the 116 participants. The most common were worsening of pre-existing dermatitis (4.5%) and skin infections (1.7%). At day 2, poor adhesion (defined as little to no skin contact with panel or one or more allergen patches not in contact with the skin) of any of the three panels was observed in up to 11.3% of participants, and the panel(s) fell off in up to 3.6% of 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 43.9%). Participants reported itching (43.3 to 63.2%) more commonly than burning (5.6 to 10.5%). Late positive reactions 21 days after T.R.U.E. TEST application occurred in 2 participants (1.7%) to gold sodium thiosulfate. Persistent reactions were observed in 6 participants (5.2%) 21 days after T.R.U.E. TEST application to the following allergens: gold sodium thiosulfate (n=6) and bronopol (n=1). One participant had an unrelated SAE of appendicitis that resolved within the time frame of the study with surgical intervention. The two pediatric studies did not reveal any unexpected safety trends or signals for SAEs. There were no deaths.

Diagnostic performance of T.R.U.E. TEST was assessed in two non-randomized open-label Phase 3 studies in children and adolescents with suspected ACD. None were known positives to specific allergens and allergen mixes in T.R.U.E. TEST. Unlike IgE-mediated allergies, ACD cannot be readily confirmed with a challenge. In addition, the pediatric population has historically been perceived (up until the 1990s) to be unlikely to develop ACD due to insufficient exposure to contact allergens. Therefore, traditional measures of diagnostic performance such as sensitivity and specificity, which rely on recruitment of known positive and known negative control subjects, were difficult to acquire in children and adolescents. As a result, diagnostic performance refers to descriptive rates of positive reactions to the 36 individual patches on T.R.U.E. TEST (Panels 1.3, 2.3, 3.3) in a population representative of the T.R.U.E. TEST user population. Pediatric Study 1 provided diagnostic performance data for 24 of the 35 allergens and allergen mixes and the negative control in T.R.U.E. TEST. No subjects had positive reactions to the negative control or to caine mix. The rates for the other 23 allergens and allergen mixes are provided in descending order: nickel sulfate (30.0%); p-tert-butylphenol formaldehyde resin (17.0%), wool alcohols (16.0%), cobalt dihydrochloride (13.0%), balsam of peru (10.0%), colophony (9.0%), tixocortol -21-pivalate (8.0%), carba mix (7.0%), thiuram mix (7.0%), formaldehyde (7.0%), diazolidinyl urea (5.0%), Cl+Me-isothiazolinone (4.0%), epoxy resin (4.0%), quaternium-15 (4.0%), thimerosal (4.0%), paraben mix (2.0%), black rubber mix (2.0%), imidazolidinyl urea (2.0%), mercaptobenzothiazole (2.0%), mercapto mix (2.0%), p-phenylenediamine (2.0%), budesonide (1.0%), and quinoline mix (1.0%). Although Pediatric Study 2 evaluated all three panels containing the 35 allergens and allergen mixes, the primary analysis of diagnostic performance data was limited to the 4 reformulations and 7 new allergens and allergen mixes. No subjects had positive reactions to the negative control. No subjects had positive reactions to ethylenediamine dihydrochloride. The rates of

positive reactions for the 10 other allergens and allergen mixes are provided in descending order: gold sodium thiosulfate (27.0%), 2-bromo-2-nitropropane-1.3,-diol [bronopol] (17.1%), bacitracin (12.6%), parthenolide (7.2%), fragrance mix (3.8%), neomycin sulfate (3.8%), potassium dichromate (3.8%), disperse blue 106 (3.6%), hydrocortisone-17-butyrate (1.8%), and methyldibromoglutaronitrile (0.9%).

The clinical data from Pediatric Study 1 and Pediatric Study 2 support the approval of T.R.U.E. TEST for use as an aid in the diagnosis of ACD in persons 6 years through 17 years of age. Therefore, we recommend the approval of this sBLA for the proposed indication.

1.1 Demographic Information: Subgroup Demographics and Analysis Summary

In Pediatric Study 1 (Mekos 07 29P1/2/3 401), the mean and median age of the 102 enrolled participants (6 to 17 years old) was 11.6 years and 11 years, respectively. The highest percentage of participants was 13 to 17 years of age (45 participants; 44.1%). The 2 younger age strata were evenly represented, with 29 participants (28.4%) 9 to 12 years of age, and 28 participants (27.5%) 6 to 8 years of age. Females comprised 52% of the trial population. Forty participants were identified as Caucasian (39.2%) and 32 participants as Hispanic (31.4%). The remaining 30 participants were identified as Asian (n=13; 12.7%), Other (n=10; 9.8%), and African-American (n=7; 6.9%). The subpopulations were too small to conduct meaningful subgroup analyses of safety and diagnostic performance by age, race, or sex.

In Pediatric Study 2 (SP 12 7NEW 401), the mean and median age of the 116 enrolled participants (6 to <18 years old) was 12.6 years and 13 years, respectively. As in Pediatric Study 1, most of the participants (55.2%; n=64) were 13 to 17 years of age. This multi-center study aimed to enroll similar numbers of participants from the 2 younger age strata. However, there was greater representation of 9 to 12-year-olds (34.5%; n=40) than 6 to 8-year-olds (10.3%; n=12). Females (n=80) comprised 68.9% of the trial population. Ethnicity was classified as either Hispanic/Latin or not Hispanic or Latino. Forty-four participants (37.9%) were identified as Hispanic/Latino. With respect to race, 77 participants were Caucasian (66.4%), 18 participants were identified as “Other” (15.5%), 13 participants Asian (11.2%), 7 participants African-American (6.0%), and 1 American Indian/Alaska Native (0.9%). The subpopulations were too small to conduct meaningful subgroup analyses of safety and diagnostic performance of specific allergens by age, race, or sex.

2. Clinical and Regulatory Background

2.1 Disease or Health-Related Condition(s) Studied

Allergic contact dermatitis (ACD) is a common inflammatory skin condition with a non-specific presentation of pruritic eczema with variable distribution throughout the body. ACD represents a delayed type (IV) hypersensitivity reaction, and T lymphocytes have been recognized to be central players in ACD pathogenesis (1). Current epidemiological estimates indicate that ACD occurs in adults and children and adolescents at similar rates of 20% and 15% respectively (2). The latter figure is supported by prospective and retrospective patch testing studies in pediatric populations with suspected ACD as well as in those without dermatitis, which demonstrated sensitization to be not uncommon among asymptomatic children. Such data refuted the prevailing notion, up until the

1990s, that children did not have enough exposure to common contact allergens to trigger sensitization (3).

The differential diagnosis for a pruritic and eczematous dermatitis with a distribution consistent with a contact-mediated reaction includes allergic contact dermatitis (ACD), irritant contact dermatitis (ICD), and atopic dermatitis (AD). Although history and physical exam are important, but cannot clearly differentiate ACD from ICD and AD (2, 3). Patch testing serves as a tool for diagnosing ACD. Unlike ICD or AD, eliminating exposure to relevant contact allergen(s) is critical to prevent *recurrence* of ACD. Prevention of ACD recurrence is valuable because it helps individuals avoid unnecessary exposure to topical and oral corticosteroids (4).

> ***Reviewer comment:*** *T.R.U.E.TEST was licensed in adults in 1994 based on descriptive data obtained in open-label studies . Descriptive data were deemed to be adequate for supporting the indication of use as an aid to diagnose ACD. Confirming the clinical relevance of patch testing results requires additional work after patch testing, including identifying sources of exposure in the individuals' environment, eliminating exposure, and monitoring for resolution and absence of recurrences. The time to achieve this will depend on the individual patient. The longer the exposure to the suspected allergens, the longer the time it takes for the resulting ACD to resolve. For these reasons, the wording of the indication for T.R.U.E. TEST indicates that it is meant to be used as an aid to the diagnosis of ACD.*

2.2 Currently Available, Pharmacologically Unrelated Treatment(s)/Intervention(s) for the Proposed Indication(s)

There are no pharmacologically unrelated licensed products for use as an aid in the diagnosis of ACD. However, if a specific allergen is found to be causing dermatitis, such as gold or nickel-plated jewelry, clinicians commonly advise individuals to eliminate exposure and monitor for resolution of the symptoms. This approach would provide adequate support for the diagnosis of ACD . Serum immunoglobulin E (IgE) may be elevated among those with concurrent atopic diseases, like AD, but does not play any role in diagnosing ACD because its pathogenesis is independent of IgE.

2.3 Safety and Efficacy of Pharmacologically Related Products

On March 3, 2017, CBER approved Rubber Panel T.R.U.E. TEST (U.S. License #1888, STN 125579/0), a patch test licensed 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 5 allergens and allergen mixes included on the Rubber Panel T.R.U.E. TEST. Licensure was based on safety and efficacy data from Pediatric Study 1. Review of the data was limited to the patches included in Rubber Panel T.R.U.E. TEST: black rubber mix, carba mix, mercaptobenzothiazole, mercapto mix, thiuram mix, and the negative control.

2.4 Previous Human Experience with the Product (Including Foreign Experience)

T.R.U.E. TEST (U.S. License #1623) was licensed in the United States in 1994 for use in adults 18 years of age and above based on safety and diagnostic performance data gathered in four open-label studies (N=417 adults, 18 to 82 years of age). Updated

versions of T.R.U.E. TEST were subsequently evaluated in 6 studies that enrolled 751 adults between 18 to 85 years of age. Summaries of these ten clinical studies conducted in North American and Europe are presented in the T.R.U.E. TEST PI, *Clinical Studies (14.1)* (5). The safety profile of T.R.U.E. TEST in adults is based on data from 1168 adults. Adverse reactions occurring in more than 10% of adults were subjective burning (25.4%) and tape irritation (15.8%) documented at the time of panel removal in the clinic. Those that occurred in more than 1% of adults included persistent reactions (6.8%), erythema (5.7%), and hyper/hypopigmentation (4.9%). Late reactions, scarring, and ectopic flare of pre-existing dermatitis occurred in less than 1% of the adult population. The following additional adverse reactions have been identified through post-licensure routine pharmacovigilance: acute allergic reactions, extreme positive reactions, excited skin syndrome ("angry back"), and ICD. All of these are addressed in the PI under Section 5: *Warnings and Precautions*.

When T.R.U.E. TEST was licensed in 1994, all diagnostic data for the allergens and allergen mixes in T.R.U.E. TEST were obtained from adults with suspected ACD, and not from those with previously confirmed ACD ("known positives") or without dermatitis ("known negatives"). Subsequently, CBER requested that the Applicant recruit known positives, known negatives, and include petrolatum-based reference allergens to generate sensitivity, specificity, and concordance data for allergens and allergen mixes added to the legacy product. These data exist for quaternium-15, methyldibromo-glutaronitrile, diazolidinyl urea, tixocortol-21-pivalate, gold sodium thiosulfate, imidazolidinyl urea, budesonide, hydrocortisone-17-butyrate, bacitracin, parthenolide, disperse blue 106, and bronopol, and can be found in the T.R.U.E. TEST PI (see *Clinical Studies (14.1), Table 4*) (5).

> ***Reviewer comment:*** *Recognizing the limitations of data generated from individuals with possible ACD, we have required the Applicant to submit data on sensitivity, specificity, and concordance data for allergens and allergen mixes added to the legacy product through efficacy supplements. Due to the availability of these data from adults, we did not require the Applicant to reproduce these data to fulfill pediatric study requirements for T.R.U.E. TEST.*

2.5 Summary of Pre- and Post-submission Regulatory Activity Related to the Submission

Pre-submission

The number of allergens and allergen mixes contained in T.R.U.E. TEST has increased since it was licensed for use in adults 18 years of age and older in 1994, when the product consisted of two panels containing 23 allergens and allergen mixes and 1 negative control. In 2007, supplement Biologics License Applications (sBLAs; STN 103738/5019 and 103738/5027) were approved to add a third panel (Panel 3.1), which included 5 new allergens and allergen mixes. According to the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new dosage forms, new dosing regimens or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication in pediatric patients, unless this requirement is waived, deferred or inapplicable. A partial waiver was granted for the pediatric study requirements from birth to <6 years of age based on the statutory rationale that necessary studies are impossible or highly impracticable because the number of children younger than 6 years of age with ACD is small (STN 103738/5074, approval letter February 29, 2012). The Applicant received a deferral of pediatric study requirements in children 6 through 17 years of age because T.R.U.E. TEST was ready for approval for use in adults and the pediatric study had not been completed. Pediatric Study 1 was conducted to evaluate the safety and diagnostic performance of the 28 allergens and negative control contained in the 2007 formulation of T.R.U.E. TEST (Panels 1.1, 2.1, and 3.1) in at least 100 participants 6 to <18 years of age.

In 2012, efficacy supplement STN 103738/5074 was approved to include 7 new allergen patches (methyldibromoglutaronitrile, gold sodium thiosulfate, hydrocortisone-17-butyrate, bacitracin, parthenolide, disperse blue 106, and 2-bromo-2-nitropropane-1,3-diol). Methyldibromoglutaronitrile was added to Panel 2.1 (designated thereafter as Panel 2.2) and the other 6 (gold sodium thiosulfate, hydrocortisone-17-butyrate, bacitracin, parthenolide, disperse blue 106, and 2-bromo-2-nitropropane-1,3-diol [bronopol]) 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. T.R.U.E. TEST Panels 1.2, 2.2, and 3.2 contained a total of 35 allergens and allergen mixes and 1 negative control. Following the submission of two additional sBLAs (STN103738/5118 and STN103738/5129), Panel 1.2 was revised to include reformulations of neomycin sulfate, potassium dichromate, and fragrance mix with respect to contact allergen concentration and excipient. Only the excipient was changed for ethylenediamine dihydrochloride. Although unchanged, Panels 2.2 and 3.2 were renumbered as 2.3 and 3.3 to align the numbering scheme with Panel 1.3. Pediatric Study 2 was designed to evaluate the safety and diagnostic performance of the 7 new allergens included in the currently licensed version of T.R.U.E. TEST (Panels 1.3, 2.3, and 3.3) in at least 110 participants 6 to <18 years of age. After a Type C meeting (held on March 10, 2014), CBER requested the revision of the protocol for Pediatric Study 2 to evaluate the updated Panel 1.3 in subjects 6 to <18 years of age. Please refer to Section 4.1 to view the allergens and allergen mixes included in the previously and currently licensed versions of T.R.U.E. TEST evaluated in Pediatric Studies 1 and 2.

> ***Reviewer comment:*** *The open-label study design of Pediatric Study 1 and Pediatric Study 2 conforms to standards for safety and effectiveness defined by CBER at the time of their proposal.*

Post-submission

A total of seven information requests (IRs) were submitted to obtain missing sBLA components, address BIMO inspection-related findings from two of the four clinical study sites for Pediatric Study 2, and resolve data-related discrepancies between the two clinical study reports and the draft PI.

1. The first IR (sent December 6, 2016) was a request for documents missing from the sBLA submission. SmartPractice Denmark provided requested documents at the following time points:
    - Debarment Certificate (December 9, 2016)
    - Clinical Study Report and Datasets for Pediatric Study 1 (December 20, 2016)
    - Financial certifications and disclosures for Pediatric Study 2 and additional documents relating to Pediatric Study 1 (February 20, 2017)
    - Revised package insert reflecting the proposed revision to the indication and Section 8 (February 20, 2017)
    - In response to our request for a current PSUR, the Applicant informed us that based on European regulations, they exempt from routine PSURs. We accepted this response.

2. The second IR (sent March 27, 2017) included 5 specific requests for CMC and BIMO-related issues.
    - The Applicant's response (March 31, 2017) required a follow-up IR (#4) to resolve all issues.

3. The third IR (sent April 5, 2017) asked the Applicant to submit the Pharmacovigilance Plan previously requested in IR #1.
    - The Applicant submitted this on April 10, 2017.

4. The fourth IR (sent May 11, 2017) requested clarification of the Applicant's responses to the second IR.
    - The Applicant's response (May 17, 2017) addressed all questions. We confirmed that the Applicant did not have clinical data regarding the use of T.R.U.E. TEST in pregnant and lactating women. Please refer to the CMC review for a detailed discussion of the CMC issues that required further clarification.

5. In the fifth IR (sent May 25, 2017) and sixth IR (sent June 12, 2017), we requested reconciliation of discrepancies in diagnostic performance data presented in the CSR and in the draft package insert. The Applicant's responses to the two IRs adequately resolved the identified discrepancies.

6. The last IR (sent July 13, 2017) requested additional details regarding the characterization of safety data across the two pediatric studies.
    - In their response, the Applicant adequately addressed lumping and splitting of safety data by providing retabulated safety data and the CRFs for specific participants who had AEs with outlying preferred terms, such as "discomfort," that could possibly be grouped with more commonly reported AEs, like "pruritus". All issues were resolved.

Reviewer comment: *The review of the CRFs confirmed that some of the adverse reactions captured by various terms could be reclassified as ectopic flare of pre-existing dermatitis or pruritus. During this process, transcription errors in causality attribution of adverse events were identified and the corresponding corrections were made in the safety data discussion in this memorandum.*

3. SUBMISSION QUALITY AND GOOD CLINICAL PRACTICES

3.1 Submission Quality and Completeness

The original submission lacked the following components, but were obtained in the responses to Information Request #1 (January 6, 2017):

- Clinical Study Report and Datasets for Pediatric Study 1 (previously submitted to STN 127579/0)
- Financial Disclosure forms
- Debarment Certificate
- Pharmacovigilance Plan

3.2 Compliance With Good Clinical Practices And Submission Integrity

This efficacy supplement included two studies. The single site for Pediatric Study 1 was previously inspected during the BLA review of the Rubber Panel T.R.U.E. TEST (STN 125579). The BIMO reviewer for this supplement conducted inspections of two study sites (Site 1 in Oregon and Site 4 in Colorado), which enrolled 37 (36.3%) of the 102 participants enrolled in Pediatric Study 2. FDA Forms 483 were issued to the 2 investigators. Both sites have responded to the 483, which included acceptable corrective actions to prevent potential issues in the current and future studies. These findings were not assessed to have substantially impacted the data submitted in this efficacy supplement.

3.3 Financial Disclosures

Covered clinical study (name and/or number): Pediatric Study 1 and Pediatric Study 2		
Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from applicant)
Total number of investigators identified: 2 and 6, respectively		
Number of investigators who are sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		

If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: None Significant payments of other sorts: None Proprietary interest in the product tested held by investigator: None Significant equity interest held by investigator in sponsor of covered study: None		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐	No ☐ (Request details from applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☐ (Request information from applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from applicant)

4. SIGNIFICANT EFFICACY/SAFETY ISSUES RELATED TO OTHER REVIEW DISCIPLINES

4.1 Chemistry, Manufacturing, and Controls

Pediatric Study 1 evaluated T.R.U.E. TEST Panels 1.1, 2.1, and 3.1, which comprised the version of the product that was licensed for use in adults when this study began enrollment in 2008. Pediatric Study 2, which began enrollment in 2012, evaluated T.R.U.E. TEST Panels 1.3, 2.3, and 3.3, the most current version licensed for use in adults. This sBLA did not contain CMC data, but a CMC reviewer was consulted regarding issues identified by the BIMO investigator related to labeling and packaging of clinical lots of T.R.U.E. TEST. All issues related to the clinical lots were resolved through the IRs described in Section 2.5. For additional details, please refer to the memorandum completed by Dr. Jennifer Bridgewater, Division of Bacterial Parasitic and Allergenic Products, FDA.

4.4.1 Mechanism of Action

A positive response to the patch test is a classic delayed cell-mediated hypersensitivity reaction (type IV), which normally appears within 9 to 96 hours after exposure. Following primary contact, an allergen penetrates the skin and binds covalently or noncovalently to epidermal Langerhans cells. The processed allergen is presented to helper T-lymphocytes, resulting in inflammation that produces a papular, vesicular, or bullous response with erythema and itching at the site of application (5).

4.5 Statistical

Datasets for Pediatric Study 1 and Pediatric Study 2 were analyzed separately and independently verified by the statistical reviewer. For details, please refer to the statistical memorandum completed by Dr. Zhong Gao (Division of Biostatistics, CBER, FDA).

4.6 Pharmacovigilance

Routine pharmacovigilance is recommended. For additional details on the data mining analyses of spontaneously reported adverse events, please see the review by Dr. Patricia Rohan (Division of Epidemiology, CBER, FDA).

> ***Reviewer comment:*** *A total of 123 cases of suspected adverse reactions were received by the Applicant between 1995 and 2015 and stored in their adverse reaction database (SPD ADR). Of these, five cases initially flagged as serious. The Applicant reviewed these cases and nullified one as being unrelated to T.R.U.E. TEST and identified a case of "insomnia due to itching" as being miscategorized as serious. We recommended continuing routine pharmacovigilance based on an independent assessment of this product's post-marketing safety profile based on the FDA Adverse Events Reporting System (FAERS).*

5. SOURCES OF CLINICAL DATA AND OTHER INFORMATION CONSIDERED IN THE REVIEW

5.1 Review Strategy

Clinical data from two pediatric studies (see Tables 1 and 2) were evaluated for this efficacy supplement, which proposed to extend the indication of T.R.U.E. TEST to children and adolescents 6 through 17 years of age. We reviewed the data for spontaneously reported adverse events and late and persistent reactions 21 days after T.R.U.E. TEST application from both pediatric studies. For day 2 assessment of adhesion, tape irritation, and subjective itching and burning, we emphasized (and labeled) the data from Pediatric Study 2, which defined more stringent criteria for adhesion quality (based on the degree of contact of not just the panel, but also the individual 36 patches to the skin) of the currently licensed T.R.U.E. TEST and analyzed rates of burning and itching as separate symptoms rather than a composite. Diagnostic data from both studies were included in labeling. Pediatric Study 1 provided diagnostic performance data for 24 of the 35 allergens and allergen mixes and the negative control in T.R.U.E. TEST. Although all three panels containing the 35 allergens and allergen mixes were evaluated in Pediatric Study 2, pre-specified primary analysis was limited to the diagnostic performance of the 4 reformulations on Panel 1.3 and the 7 new allergens and allergen mixes on Panels 2.3 and 3.3.

5.2 BLA/IND Documents That Serve as the Basis for the Clinical Review

The following documents submitted to the sBLA served as the basis for this review:

- BLA 103738/5162.0, Clinical Study Reports for Mekos 07 29P1/2/3 401 (Pediatric Study 1) and for SP 12 7NEW 401 (Pediatric Study 2), Financial Disclosures

- BLA 103738 Amendments
    - 103738/5162_5004- Response to BIMO IR
    - 103738/5162_5005- Pharmacovigilance Plan
    - 103738/5162_5006- Response to IR from 28 April 2017
    - 103738/5162_5007- Response to IR from 17 May 2017
    - 103738/5162_5008- Response to IR from 09 June 2017
    - 103738/5162_5009- Certified translation of Batch Product Record
    - 103738/5162_5010- Response to IR from 19 June 2017
    - 103738/5162_5011- Response to IR from 13 July 2017
    - 103738/5162_5012- Revised response to IR from 13 July 2017
    - 103738/5162_5013 through 5015 – Labeling negotiations

5.3 Table of Studies/Clinical Trials

Table 1: Key Features of Pediatric Study 1 (Open-label prospective study)

Study ID	**Mekos 07 29P1/2/3 401**
IND Number	11452
NCT Number	00795951
Study Phase	3
Study Center	Rady Children's Hospital (San Diego, CA)
Start date-End date	December 2008 - October 2009
Participants Planned	100
Participants Enrolled	102
Age Range	6 to < 18 years old
Investigational Product: T.R.U.E. TEST Panels 1.1, 2.1, 3.1 *[see Section 4.1 for details on the the contact allergens included on each panel]*	
Study Duration	21 days
Primary Efficacy Endpoint	Diagnostic performance of 28 allergens and allergen mixes and negative control based on frequencies of positive reactions (four allergens in Panel 1.1 were later replaced with reformulations)

Table 2: Key Features of Pediatric Study 2 (Open-label prospective study)

Study ID	**SP 12 7NEW 401**
IND Number	13546
NCT Number	01797562
Study Phase	3
Study Centers (4)	Patch Test Clinic, Colorado University (Aurora, CO) Dermatology Specialists PSC (Louisville, KY) Rady Children's Hospital (San Diego, CA) Oregon Health & Science University (Portland, OR)
Start date-End date	December 2012 - September 2015
Participants Planned	110
Participants Enrolled	116 (n=62 received Panel 1.2; n=54 received Panel 1.3)
Age Range	6 to <18 years old
Investigational product: T.R.U.E. TEST Panels 1.3, 2.3, and 3.3 *[see Section 4.1 for details on the the contact allergens included on each panel]*	
Study Duration	21 days
Primary Efficacy Endpoint	Diagnostic performance of the 7 new and 4 reformulated contact allergens based on frequencies of positive reactions

5.5 Literature Reviewed

(1) Rietschel, RL. & Fowler Jr., JF. (2008). Pathogenesis of Allergic Contact Hypersensitivity, In: Rietschel, RL. & Fowler Jr., JF., *Fisher's Contact Dermatitis,* 6th ed., BC Decker Inc, Hamilton, pp. 1-10a.

(2) Fonacier L, Bernstein DI, Pacheco K, Holness DL, Blessing-Moore J, Khan D, Lang D, Nicklas R, Oppenheimer J, Portnoy J, Randolph C, Schuller D, Spector S, Tilles S, Wallace D. Contact dermatitis: a practice parameter-Update 2015. J Allergy Clin Immunol Pract. 2015; 3(3 Suppl): S1-39.

(3) Goldenberg A, Silverberg N, Silverberg J, Treat J, Jacob S. Pediatric Allergic Contact Dermatitis: Lessons for Better Care. J Allergy Clin Immunol 2015; 661-667.

(4) Zug KA, Pham AK, Belsito DV, DeKoven JG, et al. Patch Testing in Children From 2005 to 2012: Results from the North American Contact Dermatitis Group. Dermatitis 2014; 345-55.

(5) T.R.U.E. TEST [package insert]. SmartPractice Denmark ApS, Hillerod, Denmark. http://www.fda.gov/downloads/BiologicsBloodVaccines/Allergenics/UCM294327.pdf. Accessed May 31, 2017.

6. DISCUSSION OF INDIVIDUAL STUDIES/CLINICAL TRIALS

6.1 Trial #1

Pediatric Study 1 (NCT: 00795951)
Protocol title: Mekos 07 29P1/2/3 401
Trial enrollment began in December 2008 and the last participant exited in October 2009. The final study report was completed on March 11, 2011.

6.1.1 Objectives
The primary objective of the study was to characterize 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. Diagnostic performance was evaluated in terms of the skin reaction frequencies by the 4 pre-specified categories (positive, negative, irritant, indeterminate) for the 28 allergen patches and the negative control.

The secondary objective was to describe safety. Safety endpoints included panel adhesion, tape irritation, and subject-reported burning and itching at day 2, spontaneously reported adverse events occurring during the 21 days of participation in the study, and late and persistent reactions.

6.1.2 Design Overview
The study was an open-label, non-randomized, phase 3 clinical 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) with suspected ACD.

Table 3: Study Schedule for the 6 Clinic Visits in Pediatric Study 1

Procedure	Day 0 [a] *Visit 1*	Day 2 *Visit 2*	Day 3 *Visit 3a*	Day 4 *Visit 3b*	Day 7 *Visit 4*	Day 21 [c] *Visit 5*
Informed Consent/HIPAA	X					
Inclusion/Exclusion	X					
Demographics	X					
Prior patch test result	X					
Pregnancy test[d]	X					
Current evidence of contact dermatitis	X					
Apply patches	X					
Remove patches[e]		X				
Record tape irritation and itching/burning		X				
Record skin reactions		X	X	X	X	X
Photograph test sites		X	X	X	X	X
Record AEs		X	X	X	X	X

Source: Adapted from STN 103728/5162 Pediatric Study 1 CSR, Table 9-1

AE=adverse event; HIPAA=Health Insurance Portability and Accountability Act; Screen=screening visit

[a] May have occurred prior to or at the same time as Visit 1

[b] In Pediatric Study 1, an additional visit (Visit 3b) 4 days after Visit 1 (+1 day) was included if reassessment of specific sites was desired by the investigator.

[c] May have been conducted via telephone at the investigator's discretion if no late or persistent skin reactions were present.

[d] To be performed for female participants 15-18 years of age, inclusive (or with onset of menarche)

[e] Prior to removing the patches, investigators inspected the integrity of the patches and recorded any apparent loss of skin contact to grade according to a pre-specified scale. Pediatric Study 1 used a 5 point scale and Pediatric Study 2 used a 4 point scale.

[f] Before investigators evaluated skin reactions after patch removal, the skin was allowed to rest for 20 minutes.

[g] Not done if the participant had no late or persistent skin reactions and participated via telephone.

6.1.3 Population

Inclusion criteria sought healthy children and adolescents between the ages of 6 years and less than 18 years old with suspected ACD, as determined by study investigators based on a history and exam consistent with ACD.

Exclusion criteria included topical or systemic corticosteroids and immunosuppressants within 1 week on or near the patch test area, exposure to ultraviolet light, tanning, and investigational drugs or devices, participation in another clinical trial within the 3 preceding weeks, dermatitis affecting the sites for patch placement (back and/or upper arms), unwillingness to comply with activity restrictions (e.g., no swimming, no bathing, no vigorous exercise) required for patch testing, and unable or unwilling to comply with the multiple clinic visits.

6.1.4 Study Treatments or Agents Mandated by the Protocol

Pediatric Study 1 evaluated a version of T.R.U.E. TEST (Panels 1.1, 2.1, and 3.1) that was US licensed in adults at the time this study was conducted in 2008. Although 4 of the allergens on Panel 1.1 have been reformulated in Panel 1.3, the remaining 24

allergens and negative control are still included in Panels 2.3 and 3.3. Please refer to Section 2.5 for the pre-licensure regulatory history for this study.

Each of the three panels listed below include 12 patches. Each 0.81 cm^2 patch contains the allergen or allergen mix or negative control in a dried, uniform gel coating on polyester sheeting. These allergen gel patches are attached to the panel, which is made of non-woven rayon fiber tape coated with a medical acrylic adhesive.

T.R.U.E. TEST Panel 1.1

1. Nickel Sulfate
2. Wool Alcohols
3. Neomycin Sulfate
4. Potassium Dichromate
5. Caine Mix
6. Fragrance Mix
7. Colophony
8. Paraben Mix
9. Balsam of Peru
10. Ethylenediamine Dihydrochloride
11. Cobalt Dichloride
12. Negative Control

T.R.U.E. TEST Panel 2.1:

13. *p-tert*-butylphenol Formaldehyde Resin
14. Epoxy Resin
15. Carba Mix
16. Black Rubber Mix
17. Cl+Me-isothiazolinone
18. Quaternium-15
19. Mercaptobenzothiazole
20. *p*-phenylenediamine
21. Formaldehyde
22. Mercapto Mix
23. Thimerosal
24. Thiuram Mix

T.R.U.E. TEST Panel 3.1

25. Diazolidinyl urea
26. Imidazolidinyl urea
27. Budesonide
28. Tixocortol-21-pivalate
29. Quinoline mix

6.1.5 Directions for Use

The adhesive panels of T.R.U.E. TEST were placed on healthy skin of the back and upper arm of study participants by clinical investigators. Participants and guardians were instructed to not touch the panels and to keep the skin dry, which meant avoiding physical exertion and showering. The panels were removed in the clinic by investigators.

6.1.6 Sites and Centers

This study was conducted at the Rady Children's Hospital (San Diego, CA) and had 2 site investigators (Sharon Jacob, MD and Lawrence Eichenfield, MD).

> ***Reviewer comment:*** *The eligibility criteria in Pediatric Study 1 allowed for enrollment of a heterogeneous population of children and adolescents with suspected ACD. Generalizability of data from this study is limited because they do not include sensitivity or specificity. However, the overall order of positive reactions by contact allergens should reflect the prevalence of common contact allergens. The North American Contact Dermatitis Group (NACDG) regularly publishes a list of the most common contact allergens in adults and in children because this changes over time.*

6.1.7 Surveillance/Monitoring

The total duration of the study was 21 days and included up to 6 clinic visits (see Table 3). Children and adolescents with suspected ACD had a previously approved version of T.R.U.E. TEST (Panels 1.1, 2.1 and 3.1) applied to their backs and upper arms by investigators. Participants and guardians were instructed to limit physical activity and bathing to ensure that the adhesive panels remained in place for 48 hours. The safety monitoring plan included investigator's assessment of panel adhesion, tape irritation, and participant reporting of burning and itching (as a combined symptom) when panels were removed 2 days after placement. Panel adhesion was evaluated and characterized using a 5-point scale based on degree of skin-to-panel contact and tape edge adherence. Panels with good skin contact and all edges adherent were graded as excellent. Panels with "acceptable" skin contact and "loosening" of the panel observed in some areas were graded as good. Fair adhesion was defined by variable skin-to-panel contact with lifting observed at tape edges. Poor adhesion indicated little to no skin contact with the panel. The lowest grade was given if the panel fell off. After 20 minutes of letting participants' panel sites rest, investigators graded the sites for tape irritation and solicited a combined symptom of burning and itching from participants. Safety surveillance included persistent and late positive reactions detected at clinic visits on days 7 and 21, as well as adverse events, serious adverse events, and deaths reported during the 21 days of the trial.

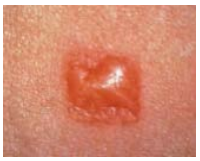
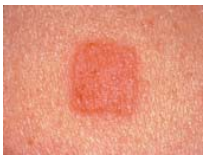
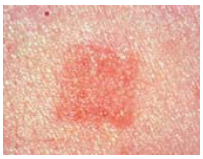
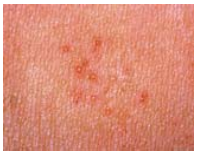
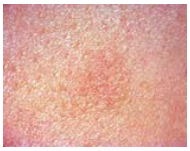
> ***Reviewer comment:*** *This safety monitoring plan is the same as what was performed for the adult trials for T.R.U.E. TEST and is consistent with current patch testing guidelines. The grading system of adhesion was more generous than the criteria used in Pediatric Study 2. Burning and itching was solicited as a combined symptom instead of separately, as done in Pediatric Study 2. For these reasons, day 2 safety data from Pediatric Study 1 were not included in the T.R.U.E. TEST PI.*

Spontaneously reported AEs were graded using the following 3-point scale:

- Mild: minimal symptoms / annoying / minimal discomfort; did not interfere with the participant's usual function
- Moderate: definite discomfort / required medication for relief; interfered to some extent with participant's usual function
- Severe: symptoms interfered significantly with the participant's usual function (daily activity/sleep)

With respect to diagnostic performance, investigators evaluated and graded patch site skin reactions at day 3 (Visit 3a) using the skin reaction scoring system established by the International Contact Dermatitis Research Group (ICDRG) guidelines (Figure 1). Participants could return on day 4 to verify doubtful reactions (Visit 3b). Patch site readings conducted on days 7 (Visit 4) and 21 (Visit 5) were intended to characterize safety endpoints of late positive reactions (occurring ≥7 days after T.R.U.E. TEST application) and persistent positive reactions.

Figure 1: Skin Reaction Scoring Guidelines for Patch Testing

Extreme positive (+++)	Strong positive (++)	Weak positive (+)	Irritant (IR)	Doubtful (?/+)
				
Coalescing vesicles, bullous reaction	Erythema, papules, infiltration, discrete vesicles	Erythema, infiltration, discrete papules	Discrete, patchy, follicular, or homogenous erythema with no infiltration	Faint macular or homogenous erythema with no infiltration

Source: Pediatric Study 1 CSR, Figure 9-1

> ***Reviewer comment:*** *The skin reaction monitoring plan over 21 days after T.R.U.E. TEST application for this pediatric population is the same one used in the adult studies. It goes beyond the current patch testing guidelines, which recommends removal and an initial reading of patch test sites at 48 hours after application, and a second reading between 3 and 7 days after application (2).*

6.1.8 Endpoints and Criteria for Study Success

The primary endpoint of diagnostic performance was the frequency of reactions that were positive (subgraded as +, ++, and +++), negative, irritant, and doubtful.

> ***Reviewer Comment:*** *This study was not designed to determine sensitivity, specificity, or concordance for any of the contact allergens.*

Secondary endpoints of safety included frequencies of spontaneously reported AEs, serious AEs, and anticipated AEs including incomplete panel adhesion, tape-induced irritation at each test site upon patch removal, participant-reported pruritus or burning after panel removal, and late and/or persistent reactions to any of allergens in Panels 1.1, 2.1, and 3.1. Based on the CSR, there were no modifications of study endpoints during or after completion of the study.

6.1.9 Statistical Considerations & Statistical Analysis Plan

The sample size of 100 was justified to detect an increase in adverse events from 7.6% (based on data from the licensed T.R.U.E. TEST in adults) to 15.6% (in the present study with T.R.U.E. TEST in children and adolescents) with a power of 80% and a significance level of 0.05 using a one-sided test of the null hypothesis, which is that Pe (new allergen) = Pc (historical control).

6.1.10 Study Population and Disposition

One hundred and two participants (6 to <18 years old) were enrolled at one investigational site. Two participants dropped out; one withdrew consent 1 day after patch application and the other participant was lost to follow-up after presenting to the day 3 clinic visit. No participants had reapplication of panels after Day 0 (Visit 1).

Reviewer comment: *The overall drop-out rate is lower than the typical 10% assumed rate used in study size calculations. Notably, none of the drop-outs were due to known AEs.*

6.1.10.1 Populations Enrolled/Analyzed

The three analysis populations used to evaluate diagnostic performance and safety were as follows:

- Per-protocol population (PP) - all subjects who received T.R.U.E. TEST and completed the study without major protocol violations. This was the primary analysis population for diagnostic performance, which was described in terms of frequencies of positive reactions at days 3, 4, and 7 after T.R.U.E. TEST application.
- Intent-to-treat (ITT) population - all subjects who received T.R.U.E. TEST 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 – all subjects who received T.R.U.E. TEST were considered for safety data.

6.1.10.1.1 Demographics

All 102 participants enrolled were analyzed for demographics. The mean and median ages were11.6 years and 11 years, 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. Participants were classified by race. Forty participants were identified as Caucasian (39.2%) and 32 participants as Hispanic (31.4%). The remaining 30 participants were identified as Asian (n=13; 12.7%), Other (n=10; 9.8%), and African-American (n=7; 6.9%).

6.1.10.1.2 Medical/Behavioral Characterization of the Enrolled Population

Among the 102 enrolled participants, 101 had active dermatitis, with variable distribution. Seventy-four participants had dermatitis affecting the legs and/or feet (73.3%), 69 participants had dermatitis affecting the arms and/or hands (68.3%), 48 (47.5) had dermatitis of the face and/or scalp and/or neck, and 42 (41.6%) had truncal involvement. Most of the participants had a history of ACD (97.1%). In addition, over half of the participants concurrently had a history of AD (53.9%), and about a quarter had a history of ICD (25.5%). As expected in a pediatric population, none had occupational dermatitis.

6.1.10.1.3 Subject Disposition

All 102 participants underwent patch testing with T.R.U.E. TEST and thus, were included in the safety analysis set. However, one participant removed the panels and withdrew assent prior to day 2 and did not present on day 2 for investigator assessment of tape irritation and subject reporting of burning and itching. One hundred and one participants presented for test site reading at Visit 3 and 96 presented for test site reading at Visit 4. Two participants withdrew from the study. No significant protocol deviations, specifically missing 2 or more clinic visits, were reported for the 100 participants in the PP population (see Table 4).

Table 4: Children and Adolescents 6 to <18 Years of Age Presenting for the 5 Clinic Visits in Pediatric Study 1

Day	Visit	N
0	1	102
2	2	101[a]
3/4	3a/3b	101
7	4	96[b]
21	5	100[c]

Source: Adapted from sBLA 103738/5162; Pediatric Study 1 CSR
[a] Population used to describe Day 2 safety data (adhesion, tape irritation, burning and itching)
[b] Among the 5 participants who did not present for Visit 4 (Participant 009, 054, 055, 058, and 083), four had positive reactions to at least one of the 28 allergens at Visit 3 while one participant had no positive reactions.
[c] Per-protocol population

6.1.11 Efficacy Analyses
The efficacy data are descriptive.

6.1.11.1 Analyses of Primary Endpoint(s)
Table 5 summarizes the frequencies of positive, negative, irritant, and doubtful reactions to the 24 allergens and allergen mixes in T.R.U.E. TEST. Positive patch test reactions were characterized by investigators as weak (+), strong (++), and extreme positive (+++) based on the presence and degree of erythema, infiltration, papules, vesicles, and bullae. Positive reaction rates were inclusive of all three grades. Of the 101 participants who presented on day 3, none reacted to the negative control and caine mix. The positive reaction rates for the 23 other allergens and allergen mixes are provided in descending order: nickel sulfate (30.0%); p-tert-butylphenol formaldehyde resin (17.0%), wool alcohols (16.0%), cobalt dihydrochloride (13.0%), balsam of peru (10.0%), colophony (9.0%), tixocortol -21-pivalate (8.0%), carba mix (7.0%), thiuram mix (7.0%), formaldehyde (7.0%), diazolidinyl urea (5.0%), Cl+Me-isothiazolinone (4.0%), epoxy resin (4.0%), quaternium-15 (4.0%), thimerosal (4.0%), paraben mix (2.0%), black rubber mix (2.0%), imidazolidinyl urea (2.0%), mercaptobenzothiazole (2.0%), mercapto mix (2.0%), p-phenylenediamine (2.0%), budesonide (1.0%), and quinoline mix (1.0%). Table 5 provides the rates of positive, negative, irritant, and doubtful reactions to the 24 contact allergens relevant to T.R.U.E. TEST Panels 1.3, 2.3, and 3.3. .

Table 5: Frequencies of Reactions at Day 3 and Day 7 to the 24 Allergens and Allergen Mixes and 1 Negative Control in T.R.U.E. TEST Pediatric Study 1 (All Subjects)

Panel and Allergen	Day	N	Positive n (%)	Negative n (%)	Irritant n (%)	Doubtful n (%)
Panel 1.1						
Nickel Sulfate	3	101	29 (28.7)	66 (65.3)	1 (1.0)	5 (5.0)
	7	96	17 (17.7)	75 (78.1)	0 (0.0)	4 (4.2)
Wool Alcohols	3	101	16 (15.8)	84 (83.2)	0 (0.0)	1 (1.0)
	7	96	6 (6.3)	85 (88.5)	0 (0.0)	5 (5.2)
Caine Mix	3	101	0 (0.0)	101 (100.0)	0 (0.0)	0 (0.0)
	7	96	0 (0.0)	96 (100.0)	0 (0.0)	0 (0.0)
Colophony	3	101	9 (8.9)	91 (90.1)	0 (0.0)	1 (1.0)
	7	96	4 (4.2)	90 (93.8)	0 (0.0)	1 (1.0)
Paraben Mix	3	101	2 (2.0)	99 (98.0)	0 (0.0)	0 (0.0)
	7	96	1 (1.0)	94 (97.9)	0 (0.0)	1 (1.0)
Negative control	3	101	0 (0.0)	101 (100.0)	0 (0.0)	0 (0.0)
	7	96	0 (0.0)	96 (100.0)	0 (0.0)	0 (0.0)
Balsam of Peru	3	101	10 (9.9)	88 (87.1)	1 (1.0)	2 (2.0)
	7	96	2 (2.1)	92 (95.8)	0 (0.0)	2 (2.1)
Cobalt Dihydrochloride	3	101	12 (11.9)	88 (87.1)	1 (1.0)	0 (0.0)
	7	96	6 (6.3)	88 (91.7)	0 (0.0)	2 (2.1)
Panel 2.1	Day	N	Positive n (%)	Negative n (%)	Irritant n (%)	Doubtful n (%)
p-tert-Butylphenol Formaldehyde Resin	3	101	16 (15.8)	84 (83.2)	0 (0.0)	1 (1.0)
	7	96	7 (7.3)	87 (90.6)	0 (0.0)	2 (2.1)
Epoxy Resin	3	101	3 (3.0)	96 (95.0)	0 (0.0)	2 (2.0)
	7	96	2 (2.1)	94 (97.9)	0 (0.0)	0 (0.0)
Carba Mix	3	101	7 (6.9)	93 (92.1)	0 (0.0)	1 (1.0)
	7	96	1 (1.0)	95 (99.0)	0 (0.0)	0 (0.0)
Black Rubber Mix	3	101	2 (2.0)	97 (96.0)	0 (0.0)	2 (2.0)
	7	96	0 (0.0)	95 (99.0)	0 (0.0)	1 (1.0)
Cl+Me-Isothiazolinone	3	101	4 (4.0)	96 (95.0)	0 (0.0)	1 (1.0)
	7	96	3 (3.1)	91 (94.8)	0 (0.0)	2 (2.1)
Quaternium-15	3	101	3 (3.0)	96 (95.0)	0 (0.0)	2 (2.0)
	7	96	3 (3.1)	91 (94.8)	0 (0.0)	2 (2.1)
Mercaptobenzothiazole	3	101	2 (2.0)	99 (98.0)	0 (0.0)	0 (0.0)
	7	96	1 (1.0)	95 (99.0)	0 (0.0)	0 (0.0)
p-Phenylenediamine	3	101	2 (2.0)	99 (98.0)	0 (0.0)	0 (0.0)
	7	96	0 (0.0)	96 (100.0)	0 (0.0)	0 (0.0)
Formaldehyde	3	101	5 (5.0)	91 (90.1)	0 (0.0)	5 (5.0)
	7	96	3 (3.1)	91 (94.8)	0 (0.0)	2 (2.1)
Mercapto Mix	3	101	2 (2.0)	99 (98.0)	0 (0.0)	0 (0.0)
	7	96	1 (1.0)	94 (97.9)	0 (0.0)	1 (1.0)
Thimerosal	3	101	4 (4.0)	96 (95.0)	1 (1.0)	0 (0.0)
	7	96	2 (2.1)	94 (97.9)	0 (0.0)	0 (0.0)

Panel and Allergen	Day	N	Positive n (%)	Negative n (%)	Irritant n (%)	Doubtful n (%)
Thiuram Mix	3	101	6 (5.9)	92 (91.1)	1 (1.0)	2 (2.0)
	7	96	1 (1.0)	91 (94.8)	0 (0.0)	4 (4.2)
Panel 3.1	Day	N	Positive n (%)	Negative n (%)	Irritant n (%)	Doubtful n (%)
Diazolidinyl urea	3	101	4 (4.0)	95 (94.1)	0 (0.0)	2 (2.0)
	7	96	2 (2.1)	92 (95.8)	0 (0.0)	2 (2.1)
Imidazolidinyl urea	3	101	1 (1.0)	97 (96.0)	1 (1.0)	2 (2.0)
	7	96	1 (1.0)	94 (97.9)	0 (0.0)	1 (1.0)
Budesonide	3	101	1 (1.0)	100 (99.0)	0 (0.0)	0 (0.0)
	7	96	1 (1.0)	95 (99.0)	0 (0.0)	0 (0.0)
Tixocortol -21-pivalate	3	101	8 (7.9)	93 (92.1)	0 (0.0)	0 (0.0)
	7	96	3 (3.1)	91 (94.8)	0 (0.0)	2 (2.1)
Quinoline Mix	3	100	1 (1.0)	100 (99.0)	0 (0.0)	0 (0.0)
	7	96	0 (0.0)	96 (100.0)	0 (0.0)	0 (0.0)

Source: STN 103738/5162, Pediatric Study 1 CSR

Reviewer comment: *Nickel sulfate, p-tert-butylphenol formaldehyde resin, wool alcohols, balsam of peru, and cobalt dihydrochloride were among the most common allergens eliciting positive reactions. Irritant reactions occurred infrequently. Doubtful reactions, which resolve or can evolve into positive reactions at later time points, were most frequently with nickel sulfate and thiuram mix (4 participants each). Although frequencies do not provide insight on traditional parameters of diagnostic performance like sensitivity and specificity, it is reassuring to see that there is overlap with epidemiologic trends published in the NACDG surveys. Confirmation of the clinical relevance of positive reactions is outside the scope of study.*

6.1.11.2 Analyses of Secondary Endpoints

This study had no secondary efficacy endpoints .

6.1.11.3 Subpopulation Analyses

The Applicant evaluated diagnostic performance by age strata (children 6 through 12 years of age and adolescents 13 through 17 years of age), sex, and race (Caucasian and non-Caucasian). Given the overall low frequencies of positive reactions to T.R.U.E. TEST allergens, the study was too small to draw any conclusions from the subpopulation analyses of diagnostic performance.

6.1.11.4 Dropouts and/or Discontinuations

Two participants dropped out of the study. One withdrew consent after placement of the panels, which he removed after 24 hours. The second participant was lost to follow-up.

6.1.12 Safety Analyses

6.1.12.1 Methods

Safety data analysis included the 102 subjects who received T.R.U.E. TEST.

6.1.12.2 Overview of Adverse Events

Data on adhesion, tape irritation, and subjective itching and burning collected from the subjects who presented 2 days after T.R.U.E. TEST application are summarized in Table 6.

Table 6: Safety Endpoints Assessed on Day 2 in Pediatric Study 1 (All Subjects)

Safety Endpoint Assessed	**Panel 1.1** n (% of participants)	**Panel 2.1** n (% of participants)	**Panel 3.1** n(% of participants)
Adhesion Number of subjects	100*	100*	100*
Adhesion Excellent Skin contact good, all tape edges adherent	71 (71.0)	72 (72.0)	82 (82.0)
Adhesion Good Skin contact acceptable, some tape edges loose	19 (19.0)	19 (19.0)	14 (14.0)
Adhesion Fair Skin-to-panel contact variable, tape edges lifting	8 (8.0)	9 (9.0)	3 (3.0)
Adhesion Poor Little to no skin contact with panel	2 (2.0)	0 (0.0)	1 (1.0)
Adhesion Test Panel Fell Off Detached	0 (0.0)	0 (0.0)	0 (0.0)
Burning and Itching Number of Subjects	101	101	101
Burning and Itching None	34 (33.7)	45 (44.6)	61 (60.4)
Burning and Itching Weak	34 (33.7)	32 (31.7)	23 (22.8)
Burning and Itching Moderate	12 (11.9)	15 (14.9)	5 (5.0)
Burning and Itching Strong	21 (20.8)	9 (8.9)	12 (11.9)
Tape Irritation Number of subjects	101	101	101
Tape Irritation None	38 (37.6)	37 (36.6)	40 (39.6)
Tape Irritation Weak	44 (43.6)	44 (43.6)	41 (40.6)
Tape Irritation Moderate	16 (15.8)	16 (15.8)	5 (5.0)
Tape Irritation Strong	3 (3.0)	4 (4.0)	12 (11.9)

Source: STN 103738/5162, Pediatric Study 1 CSR, Table 10.1.5

*Adhesion was not documented for one of the 101 subjects presenting at the day 2 clinic visit.

> ***Reviewer comment:*** *The day 2 safety data from Pediatric Study 1 were not included in the PI for 2 main reasons. The adhesion grading scale used in this study did not account for adhesion of the individual patches on each panel (as done for Pediatric Study 2). In addition, subject-reported burning and itching were documented as a composite symptom. Separate reporting would have been more useful.*

With respect to spontaneously reported AEs, 35 participants reported a total of 52 AEs, with 31 (59.6%) AEs assessed to be related to T.R.U.E. TEST by study investigators (see Table 7). Twenty-five participants (25.4%) in Pediatric Study 1 had 31 ARs. The majority of ARs were ectopic flares/worsening of pre-existing dermatitis (n=25). Two of the 25 participants who were observed to have worsening of pre-existing dermatitis had

severe cases with superimposed infection, and were managed with topicals (corticosteroid, calcineurin inhibitor), wet wraps, and oral cephalexin.

Table 7: Summary of Spontaneously Reported Adverse Events Following T.R.U.E. TEST Application in Children and Adolescents 6 to <18 Years of Age (Pediatric Study 1)

AE	Event (n)	Participant n (%) Total N=101
Overall	52	35 (34.3)
Mild	28 (53.8)	
Moderate	22 (42.3)	
Severe	2 (3.9)	
Possibly or definitely related AEs	31	25 (25.4)
Ectopic flare/worsening of underlying dermatitis	29	24 (23.5)
Reaction at panel site(s)	2	2 (2.0)
Superinfection	2	2 (2.0)

Sources: STN 103738/5162, Pediatric Study 1 CSR, Listing 16.2.7.1, and the Applicant's response to IR from July 13, 2017.

> ***Reviewer comment:*** *Most of the AEs following T.R.U.E. TEST application were cutaneous and included tape irritation, itching, and burning (summarized in Table 6), which are common occurrences with patch testing. The most common spontaneously reported AE was ectopic flare/worsening of pre-existing dermatitis. Two of these individuals also had "superinfection" of pre-existing dermatitis. Additionally, three participants had nonspecific cutaneous reactions near panel sites, one had a "boil" on the forehead, and another had "edema, vesiculation" of the hands, which was a site of pre-existing dermatitis in that participant. Subgroup analyses did not reveal skewed distribution of the numbers of adverse events by age, sex, or race.*

No late positive reactions were observed at day 21. On day 21, five persistent reactions remained in 4 participants to the following allergens: Cl+Me+isothiazolinone (n=1), diazolidinyl urea (n=1), nickel sulfate (n=2), and wuaternium-15 (n=1)

6.1.12.3 Deaths
There were no deaths.

6.1.12.4 Nonfatal Serious Adverse Events
There were no nonfatal SAEs.

6.1.12.5 Adverse Events of Special Interest (AESI)
There were no cases of anaphylaxis or sensitization or excited skin ("angry back") syndrome (defined as a regional state of skin hyper-reactivity caused by the presence of a strong positive reaction which may result in other patch test sites to become reactive). 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. It was noted to have decreased in severity by day 7 and resolved by day 21.

> ***Reviewer comment:*** *The abovementioned AESIs were identified during post-approval use of T.R.U.E. TEST in adults. Extreme positive reactions may present in extremely sensitive patients Because AESI are continuously reported voluntarily without a clear denominator, it is difficult to establish reliable rates of occurrence in practice.*

6.1.12.7 Dropouts and/or Discontinuations

Two of the 102 enrolled participants dropped out of Pediatric Study 1. The first was an 11-year-old Hispanic male (Subject ID 075) who removed the panels on his own after Visit 1 and his mother withdrew consent before Visit 2 by telephone. He did not present for any subsequent study visits (Pediatric Study 1 CSR, Line Listing 16.2.9.1). The second participant was a 15-year-old Hispanic female (Subject ID 035) who did not return after the panels were removed at Day 2, and did not respond to 3 phone calls).

> ***Reviewer Comment:*** *Based on the available documentation on the 2 participants who dropped out of Pediatric Study 1, it is uncertain whether or not the subject removed the panels and did not respond to phone calls due to adverse events. It is possible that the 11 year old boy removed the panels because they caused itching or discomfort. However, study records did not include any direct indicators of adverse reactions in participants, such as phone calls for an unscheduled visit or prescription requests. In general, the 2 observed cases of dropouts and discontinuations do not raise concerns regarding the conduct of the study or safety of the product.*

6.1.13 Study Summary and Conclusions

No subjects had positive reactions to the negative control and to caine mix. The rates for the 23 other allergens and allergen mixes are provided in descending order: nickel sulfate (30.0%); p-tert-butylphenol formaldehyde resin (17.0%), wool alcohols (16.0%), cobalt dihydrochloride (13.0%), balsam of peru (10.0%), colophony (9.0%), tixocortol - 21-pivalate (8.0%), carba mix (7.0%), thiuram mix (7.0%), formaldehyde (7.0%), diazolidinyl urea (5.0%), Cl+Me-isothiazolinone (4.0%), epoxy resin (4.0%), quaternium-15 (4.0%), thimerosal (4.0%), paraben mix (2.0%), black rubber mix (2.0%), imidazolidinyl urea (2.0%), mercaptobenzothiazole (2.0%), mercapto mix (2.0%), p-phenylenediamine (2.0%), budesonide (1.0%), and quinoline mix (1.0%). Irritant and doubtful reactions were observed, but did not tend to occur with specific allergens. The data support the use of T.R.U.E. TEST as an aid to diagnosis of ACD due to one or more of the allergens contained in the product. Confirming clinical relevance of positive reactions requires medical follow-up, and was outside of the scope of the design of this study. The safety profile was favorable. None of the panels on the 101 subjects who presented to the day 2 clinic visit fell off prior to scheduled removal. Rates of suboptimal adhesion, namely fair and poor, ranged between 3 to 9% and 1 to 2%, respectively, across the three panels. Most participants had none to weak local symptoms of burning and itching at the panel sites (67 to 83%) and none to weak tape irritation (93%). No late reactions were observed 21 days after T.R.U.E. TEST application. Persistent reactions were observed in 4 participants (3.9%) 21 days after T.R.U.E. TEST application. About 34% of study participants experienced an AE during the 21 days of monitoring, but only 25% of participants had AEs assessed to be related to T.R.U.E. TEST. The majority of AEs were mild (53.8%) to moderate (42.3%). Two of the AEs (one assessed to be related and another unrelated) graded as severe were superinfection of an ectopic flare, and both resolved with outpatient management.

6.2 Trial #2

Pediatric Study 2 (NCT: 01797562)
Protocol title: SP 12 7NEW 401
Trial enrollment began in December 2012 and ended in September 2015.

6.2.1 Objectives

The primary objective of the study was to characterize the diagnostic performance of the 7 new contact allergens (methyldibromoglutaronitrile, gold sodium thiosulfate, hydrocortisone-17-butyrate, bacitracin, parthenolide, disperse blue 106, and bronopol) added to T.R.U.E. TEST Panels 2.3 and 3.3, and the 4 reformulated allergens (neomycin sulfate, potassium dichromate, fragrance mix, and ethylenediamine dihydrochloride) on Panel 1.3. Diagnostic performance was evaluated in terms of the skin reaction frequencies by the 4 pre-specified categories (positive, negative, irritant, doubtful). The secondary objective was to describe safety.

6.2.2 Design Overview

Pediatric Study 2 was an open-label, non-randomized, multi-center Phase 3 trial of the safety and diagnostic performance of the 11 investigational allergens on T.R.U.E. TEST Panels 1.3, 2.3, and 3.3 in children and adolescents with suspected ACD based on history and physical examination. Section 6.2.4 provides a listing of these in the context of the total of 36 patches included on Panels 1.3, 2.3, and 3.3. Each participant was followed for at least 21 days, with up to 6 clinical visits. As with Pediatric Study 1, the final visit could be conducted over the phone at the investigator's discretion. The study schedule is provided below in Table 8. See 6.2.7 for discussion of differences in the surveillance and monitoring across the 2 pediatric studies.

Table 8: Study Schedule for the 6 Clinic Visits in Pediatric Study 2

Procedure	**Day 0** [a] *Visit 1*	**Day 2** *Visit 2*	**Day 3** *Visit 3a*	**Day 4** *Visit 4*	**Day 7** *Visit 5*	**Day 21** [b] *Visit 6*
Informed Consent/HIPAA	X					
Inclusion/Exclusion	X					
Demographics	X					
Prior patch test result	X					
Pregnancy test[c]	X					
Current evidence of contact dermatitis	X					
Apply patches	X					
Remove patches[d]		X				
Record tape irritation and itching/burning		X				
Record skin reactions		X	X	X	X	X
Photograph test sites		X	X	X	X	X
Record AEs		X	X	X	X	X

Source: Adapted from STN 103728/5162 Pediatric Study 2 CSR, Table 9-5.1-1

AE=adverse event; HIPAA=Health Insurance Portability and Accountability Act;

[a] May have occurred prior to or at the same time as Visit 1

[b] May have been conducted via telephone at the investigator's discretion if no late or persistent skin reactions were present.

[c] To be performed for female participants 15-18 years of age, inclusive (or with onset of menarche)

[d] Prior to removing the patches, investigators inspected the integrity of the patches and recorded any apparent loss of skin contact to grade according to a pre-specified scale.

6.2.3 Population
Inclusion criteria included healthy children and adolescents between the ages of 6 years and less than 18 years old with suspected ACD, which was subjectively determined by investigators based on history and physical exam.

Exclusion criteria included topical or systemic corticosteroids and immunosuppressants within 1 week on or near the test area, exposure to ultraviolet light, tanning, exposure to investigational drugs or devices or participation in another clinical trial within the 3 preceding weeks, dermatitis affecting the sites for patch placement (back and/or upper arms), unwillingness to comply with activity restrictions (e.g. no swimming, no bathing, no vigorous exercise) required for patch testing, and unable or unwilling to comply with the multiple clinic visits. At screening, eligible children and adolescents completed an exposure questionnaire consisting of 22 questions pertaining to history of or current exposure to items known to contain common contact allergens.

> ***Reviewer Comment:*** *The eligibility criteria for Pediatric Study 2 are identical to that of Pediatric Study 1. However, since this study was conducted at 4 clinical sites, ranging from academic to private practice, the safety data may be more generalizable than those from Pediatric Study 1. As stated in earlier comments, the generalizability of diagnostic performanc from individuals with suspected ACD is limited.*

6.2.4 Study Treatments or Agents Mandated by the Protocol
Pediatric Study 2 evaluated the version of T.R.U.E. TEST currently approved for use in adults (Panel 1.3, 2.3, and 3.3). At the time of this study, the last two panels were designated as 2.2 and 3.2. Panel 2.2 included a new contact allergen (methyldibromo glutaronitrile) in place of mercaptobenzothiazole (which was moved to Panel 3.2), and Panel 3.2 contained 6 new contact allergens (gold sodium thiosulfate, hydrocortisone-17-butyrate, bacitracin, parthenolide, disperse blue 106, and 2-bromo-2-nitropropane-1,3-diol).

> ***Reviewer comment:*** *When the protocol began, subjects received Panels 1.2, 2.2, and 3.2. As a result of negotiations after a Type C meeting, we requested that the protocol be revised to evaluate the 4 reformulated contact allergens on Panel 1.3. This revision occurred after over 60 participants received T.R.U.E. TEST Panels 1.2, 2.2, and 3.2. As a result, 54 participants were tested with Panel 1.3, while all 116 participants received the same version of Panels 2 and 3, since 2.2 and 3.2 were identical to 2.3 and 3.3.*

The 36 patches included in Panels 1.3, 2.3, and 3.3 are as follows:
Panel Panel 1.3 (* reformulation)

1. Nickel Sulfate
2. Wool Alcohols
3. Neomycin Sulfate *
4. Potassium Dichromate*
5. Caine Mix
6. Fragrance Mix *
7. Colophony
8. Paraben Mix
9. Negative Control
10. Balsam of Peru
11. Ethylenediamine Dihydrochloride *
12. Cobalt Dichloride

Panel 2.3 (same as 2.2; **new allergen**)

13. p- tert-Butylphenol Formaldehyde Resin
14. Epoxy Resin
15. Carba Mix
16. Black Rubber Mix
17. Cl+ Me-Isothiazolinone (MCI/MI)
18. Quaternium-15 (Q-15)
19. **Methyldibromoglutaronitrile (MDBGN)**
20. p- Phenylenediamine
21. Formaldehyde
22. Mercapto Mix
23. Thimerosal
24. Thiuram Mix

Panel 3.3 (same as 3.2; **new allergen**)

25. Diazolidinyl Urea (DU) (Germall® II)
26. Quinoline Mix
27. Tixocortol-21- Pivalate (TIX)
28. **Gold Sodium Thiosulfate (GST)**
29. Imidazolidinyl Urea (IMID) (Germall® 115)
30. Budesonide (BUD)
31. **Hydrocortisone-17-Butyrate (H-17-B)**
32. Mercaptobenzothiazole
33. **Bacitracin**
34. **Parthenolide**
35. **Disperse Blue 106 (DB106)**
36. **2-Bromo-2-nitropropane-1,3-diol**

6.2.5 Directions for Use

The adhesive panels of T.R.U.E. TEST were placed on healthy skin of the back and upper arm of study participants by clinical investigators. Participants and guardians were instructed to not touch the panels and to keep the skin dry, which meant avoiding physical exertion and showering. The panels were removed in the clinic by investigators.

6.2.6 Sites and Centers

This multi-center study was conducted at the following four sites by 6 investigators:

1. Colorado University Patch Test Clinic (Aurora, CO; Cory Dunnick, MD)
2. Dermatology Specialists PSC (Louisville, KY; J. Fowler, MD and J. Kasteler, MD)
3. Rady Children's Hospital (San Diego, CA; Sharon Jacob, MD and Lawrence Eichenfield, MD)
4. Oregon Health & Science University (Portland, OR; Patricia Norris, MD)

6.2.7 Surveillance/Monitoring

1. As in Pediatric Study 1, participants in Pediatric Study 2 were followed for 21 days after enrollment. See Section 6.2.7 (Table 8). There were three differences in surveillance in Pediatric Study 2 compared to Pediatric Study 1. At Day 2, panel adhesion was graded using a 4-point scale that eliminated the category of "fair" included in the five-point scale used in Pediatric Study 1. In addition, a grading of "good" required all allergen patches to be in contact with skin. If any allergens from a given panel were not in contact with the skin, adhesion of that panel was automatically assessed by the study investigator to be "poor."
2. At Day 2, burning and itching were solicited as separate symptoms, rather than as a composite.
3. Evaluation and grading of test site skin reactions at Day 4 was a mandatory timepoint rather than an optional visit (as it was in Pediatric Study 1, intended for verification of questionable sites assessed at Day 3).

Spontaneously reported AEs collected for 21 days after T.R.U.E. TEST application were graded with the following 3-point scale:

- Mild: minimal symptoms / annoying / minimal discomfort; did not interfere with the participant's usual function
- Moderate: definite discomfort / required medication for relief; interfered to some extent with participant's usual function

- Severe: symptoms interfered significantly with the participant's usual function (daily activity/sleep)

Reviewer comment: *Day 2 safety data (i.e., investigator-graded adhesion, tape irritation, participant-reported itching and burning) from Pediatric Study 2 were considered more relevant than those from Pediatric Study 1 for the following reasons: (1) The revised classification of adhesion used in Pediatric Study 2 was more stringent than the 5-point classification system used in Pediatric Study 1 because it required an assessment of contact of individual patches in addition to the whole panel. Adhesion previously graded as "fair" in Pediatric Study 1 would be graded as "poor" in Pediatric Study 2. In addition, burning and itching were documented separately since these are distinct symptoms and it is uncertain if they necessarily occur together. For these reasons, we only labeled day 2 safety data from Pediatric Study 2. However, spontaneously reported adverse reactions were considered from both pediatric studies.*

With respect to diagnostic performance, investigators evaluated and graded allergen patch site skin reactions at day 3 (Visit 3) and day 4 (Visit 4) using the skin reaction scoring system established by the ICDRG guidelines (see Figure 1 in Section 6.1.7). Patch site readings were also conducted on days 7 (Visit 4) and 21 (Visit 5) characterize late positive reactions and persistent positive reactions.

6.2.8 Endpoints and Criteria for Study Success

The primary endpoint of diagnostic performance was the frequency of reactions that were positive (subgraded as +, ++, and +++), negative, irritant, and doubtful. This study was not designed to determine sensitivity, specificity, or concordance for any of the contact allergens.

Secondary endpoints of safety included reporting of frequencies of AEs and serious AEs and product-specific parameters of incomplete panel adhesion, tape-induced irritation at each test site upon patch removal, participant-reported pruritus or burning after panel removal, and of late and/or persistent reactions to any of allergens in Panels 1.1, 2.1, and 3.1. Based on the CSR, there were no modifications of endpoints during the study.

Reviewer Comment: *Endpoints were identical to those from Pediatric Study 1 (see Section 6.1.8), except that these endpoints were analyzed for 11 allergens (the 7 investigational allergens in Panels 2.2 and 3.2 and the 4 reformulated allergens in Panel 1.3).*

6.2.9 Statistical Considerations & Statistical Analysis Plan

The proposed sample size of 110 was justified to detect an increase in adverse events from 7.6% (based on data from the licensed T.R.U.E. TEST in adults) to 15.6% (in the present study with T.R.U.E. TEST in children and adolescents) with a power of 80% and a significance level of 0.05 using a one-sided test of the null hypothesis, which is that Pe (new allergen) = Pc (historical control).

6.2.10 Study Population and Disposition

A total of 116 participants (6 to <18 years old) were enrolled at 4 investigational sites. None of the participants discontinued from the study due to an AE. Five participants

were excluded from the PP population (n=111). Of these 5 participants, 3 (Subject IDs 308, 344, 416) were excluded because the patch panels fell off or were removed prior to Day 2.Two participants (Subjects IDs 207, 210) were excluded because they missed patch site assessments on Visit 3 and Visit 4, respectively. These 2 participants were included in the ITT population (n=113).

> ***Reviewer comment:*** *In general, patch testing can be more challenging to perform in children and adolescents than in adults due to smaller body surface areas and less control over behavioral responses to itch and discomfort associated with the activity restrictions (e.g. exercise and bathing) required by patch testing. The exclusion of subjects who missed Visits 3 and 4 from the per-protocol assessment is reasonable because these are the time points specified in the PI for reading the patch test sites. The fact that no one discontinued due to an AE indicates that T.R.U.E. TEST is likely to be well tolerated in children and adolescents.*

6.2.10.1 Populations Enrolled/Analyzed

6.2.10.1.1 Demographics

Table 9: Demographics of the Participants Enrolled in Pediatric Study 2 by Analyses Populations

Demographic	Safety Population N=116	Per Protocol Population N=111	Intent to Treat Population N=113
Male; n (%)	36 (31.0)	35 (31.5)	35 (31.5)
Female; n (%)	80 (69.0)	76 (68.5)	78 (69.0)
Hispanic/Latino n(%)	44 (37.9)	44 (39.6)	44 (39.6)
Not Hispanic/Latino n(%)	72 (62.1)	67 (60.4)	69 (61.1)
White n(%)	77 (66.4)	75 (67.6)	77 (68.1)
Other n(%)	18 (15.5)	18 (16.2)	18 (15.9)
Asian n(%)	13 (11.2)	13 (11.7)	13 (11.5)
Black or African American n(%)	7 (6.0)	5 (4.5)	5 (4.4)
American Indian or Alaska Native n(%)	1 (0.9)	0 (0.0)	0 (0.0)
Mean (yrs)	12.6	12.8	12.7
Median (yrs)	13.0	13.0	13.0

Source: Adapted from STN 103738/5162 Pediatric Study 2 CSR (p.131)

> ***Reviewer comment:*** *White female adolescents had the greatest representation in this study. ACD is more common in females, but is not known to vary by race. Regardless of these demographic differences in Pediatric Study 2 compared to Pediatric Study 1, generalizability of the diagnostic performance data from both studies are limited because they enrolled individuals with suspected ACD rather than known ACD.*

6.2.10.1.2 Medical/Behavioral Characterization of the Enrolled Population
Among the 116 participants who enrolled in Pediatric Study 2, 103 participants had ongoing dermatitis symptoms (88.8%) at the time of enrollment and presumably throughout the study. Among these 103 participants, many had more than one area of involvement (i.e. face/scalp/neck; trunk; arms/hands; and legs/feet. The most common affected sites were the arms and hands (57.8%; n=67) and the least common was the face/scalp/neck region (43.1%; n=50). The majority reported a history of allergic contact dermatitis (80.2%; n=93), almost half had atopic dermatitis (45.7%; n=53), and irritant dermatitis (13.8%; n=16). As expected in a pediatric population, none had occupational dermatitis.

> ***Reviewer comment:*** *Neither Pediatric Study 1 nor Pediatric Study 2 collected information on exposure to specific allergens and allergen mixes included on T.R.U.E. TEST. The exposure questionnaire used in Pediatric Study 2 did not allow for capturing a temporal link between exposure to a variety of items commonly containing any of the T.R.U.E. TEST allergens, which included items (e.g., shampoo and hand sanitizer and disposable wipes) that most people, regardless of whether they have dermatitis or not, use. It was important to characterize the dermatologic histories of participants because the baseline condition of the participants' skin will influence the safety profile of T.R.U.E. TEST.*

6.2.11 Efficacy Analyses

6.2.11.1 Analyses of Primary Endpoint(s)

The primary efficacy analysis was conducted on rates of positive reactions to 11 of the 35 allergens and allergen mixes contained on T.R.U.E. TEST (see Tables 10 and 11). The number of subjects who received panels containing these allergens differed because the panel version for Panel 1 was changed during the study.

> ***Reviewer comment:*** *Doubtful reactions were observed at higher frequencies on Day 3 compared to Days 4 and 7. All but one doubtful reaction (to GST) resolved by Day 4. Irritant reactions were not frequently observed. Three irritant reactions (due to GST (n=2) and Bronopol (n=1)) were observed after day 3 (data not shown in the table). The diagnostic performance data for the 11 allergens suggest that interpretation at day 4 or outside the labeled reading time frame at day 7 may be more optimal, especially to allow for a doubtful reaction to resolve or declare itself as a positive reaction, especially for Gold Sodium Thiosulfate.*

Table 10: Numbers and Frequencies of Patch Site Reactions for Days 2, 3, and 7+/-1, and 21 +/-2 After T.R.U.E. TEST Application in Pediatric Study 2 (All Subjects)

Panel and Reaction	Day	Total N	***Negative*** *n(%)*	***Doubtful*** *n(%)*	***Irritant*** *n(%)*	***Positive*** *n(%)*
Panel 1.3 Neomycin Sulfate	3	54	51 (94.4)	1 (1.9)	0 (0.0)	2 (3.7)
	4	54	50 (92.6)	1 (1.9)	0 (0.0)	3 (5.6)
	7	52	50 (96.2)	0 (0.0)	0 (0.0)	2 (3.7)
	21	53	53 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)
Panel 1.3 Potassium Dichromate	3	54	51 (94.4)	2 (3.7)	0 (0.0)	1 (1.9)
	4	54	52 (96.3)	2 (3.7)	0 (0.0)	0 (0.0)
	7	52	51 (98.1)	0 (0.0)	0 (0.0)	1 (1.9)
	21	53	53 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)
Panel 1.3 Fragrance Mix	3	54	49 (90.7)	3 (5.6)	0 (0.0)	2 (3.7)
	4	54	52 (96.3)	0 (0.0)	0 (0.0)	2 (3.7)
	7	52	50 (96.2)	0 (0.0)	0 (0.0)	2 (3.8)
	21	53	53 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)
Panel 1.3 Ethylenediamine Dihydrochloride	3	54	54 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)
	4	54	54 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)
	7	52	52 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)
	21	53	53 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)
Panel 2.3 Methyldibromoglutaronitrile	3	110	107 (97.3)	3 (2.7)	0 (0.0)	0 (0.0)
	4	110	107 (97.3)	2 (1.8)	0 (0.0)	1 (0.9)
	7	110	110 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)
	21	111	111 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)
Panel 3.3 Gold Sodium Thiosulfate	3	110	72 (65.5)	22 (20.0)	0 (0.0)	16 (14.5)
	4	110	78 (70.9)	6 (5.5)	2 (1.8)	24 (21.8)
	7	110	86 (78.2)	0 (0.0)	0 (0.0)	24 (21.8)
	21	111	103 (92.8)	0 (0.0)	0 (0.0)	8 (7.2)
Panel 3.3 Hydrocortisone-17-Butyrate	3	110	108 (98.2)	2 (1.8)	0 (0.0)	0 (0.0)
	4	110	107 (97.3)	1 (0.9)	0 (0.0)	2 (1.8)
	7	110	109 (99.1)	0 (0.0)	0 (0.0)	1 (0.9)
	21	111	111 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)
Panel 3.3 Bacitracin	3	110	90 (81.8)	11 (10.0)	0 (0.0)	9 (8.2)
	4	110	93 (84.6)	3 (2.7)	0 (0.0)	14 (12.7)
	7	110	96 (87.3)	0 (0.0)	0 (0.0)	14 (12.7)
	21	111	111 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)
Panel 3.3 Parthenolide	3	110	103 (93.6)	6 (5.5)	0 (0.0)	1 (0.9)
	4	110	102 (92.7)	3 (2.7)	0 (0.0)	5 (4.6)
	7	110	106 (96.4)	0 (0.0)	0 (0.0)	4 (3.6)
	21	111	111 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)
Panel 3.3 Disperse Blue 106	3	110	101 (91.8)	7 (6.4)	0 (0.0)	2 (1.8)
	4	110	106 (96.4)	0 (0.0)	0 (0.0)	4 (3.6)
	7	110	106 (96.4)	0 (0.0)	0 (0.0)	4 (3.6)
	21	111	111 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)
Panel 3.3 2-Bromo-2-nitropropane-1.3,-diol	3	110	94 (85.5)	10 (9.1)	0 (0.0)	6 (5.5)
	4	110	90 (81.8)	4 (3.6)	1 (0.9)	15 (13.6)
	7	110	92 (83.6)	0 (0.0)	0 (0.0)	18 (16.4)
	21	111	110 (99.1)	0 (0.0)	0 (0.0)	1 (0.9)

Source: Adapted from Pediatric Study 2 CSR, Table 11.1.1.1-2

Table 11: Rates of Positive Reactions to the 11 Investigational Allergens and Allergen Mixes in T.R.U.E. TEST in Per Protocol and Intent-to-Treat Populations

Panel	Reaction	Per Protocol (N=53)	Intent to Treat N=53)
Panel 1.3	Neomycin Sulfate	2 (3.8%)	2 (3.8%)
Panel 1.3	Potassium Dichromate	2 (3.8%)	2 (3.8%)
Panel 1.3	Fragrance Mix	2 (3.8%)	2 (3.8%)
Panel 1.3	Ethylenediamine Dihydrochloride	0 (0.0%)	0 (0.0%)
Panel		Per Protocol (N=111)	Intent to Treat (N=113)
Panel 2.3	Methyldibromoglutaronitrile	1 (0.9%)	1 (0.9%)
Panel 3.3	Gold Sodium Thiosulfate	30 (27.0%)	31 (27.4%)
Panel 3.3	Hydrocortisone-17-Butyrate	2 (1.8%)	2 (1.8%)
Panel 3.3	Bacitracin	14 (12.6%)	14 (12.6%)
Panel 3.3	Parthenolide	8 (7.2%)	8 (7.2%)
Panel 3.3	Disperse Blue 106	4 (3.6%)	5 (4.4%)
Panel 3.3	2-Bromo-2-nitropropane-1.3,-diol (Bronopol)	19 (17.1%)	19 (16.8%)

Source: Adapted from STN 103738/5162 Pediatric Study 2 CSR, Table 11.1.11-1

Reviewer comment: *Although the descriptive diagnostic performance data are limited, it is reassuring that the contact allergens eliciting positive reaction rates most frequently are ones that have been cited in epidemiological and similarly designed open-label studies data as being the most prevalent and clinically relevant, namely the metals, formaldehyde-releasing preservatives, textile-associated dyes and preservatives, topical antibiotics, and rubber-related chemicals. The 0% positive reaction rate to ethylenediamine may be attributed to the small sample size (n=53) and to the fact that this contact allergen has been taken out as an ingredient in topical products. Determination of the clinical relevance of positive reactions is outside the scope of study.*

6.2.11.3 Subpopulation Analyses of Diagnostic Performance of T.R.U.E. TEST

The Applicant performed subgroup analyses of diagnostic performance. Positive reactions to T.R.U.E. TEST based on the per-protocol population were presented separately for the 3 age strata (6 through 8 years old, 9 through 12 years old, and 13 through 17 years old), gender, and race (Caucasian and non-Caucasian). Some numerical differences were observed based on these subgroups, but the general trends did not indicate that positive reactions were concentrated in specific subgroups (data not shown).

6.2.11.4 Dropouts and/or Discontinuations

Five patients were excluded from the PP population. One subject did not have all panels applied due to parent request (Subject 211), one subject failed to return for the day 21 visit and was discontinued based on the investigator's decision, and three subjects had panels that fell off or were removed before 48 hours. No participants dropped out or discontinued due to adverse events.

6.2.12 Safety Analyses

6.2.12.1 Methods

Day 2 assessments of panel adhesion, tape irritation, and subjective itching and burning were limited to the subjects who presented to the Day 2 visit (see Table 12).

6.2.12.2 Overview of Adverse Events

Table 12: Safety Endpoints Assessed on Day 2 in Pediatric Study 2 (All Subjects)

Safety Endpoint	**Panel 1.3** n(%)	**Panel 2.3** n(%)	**Panel 3.3** n(%)
Adhesion Number of subjects	55[a]	115[b]	115[b]
Adhesion Excellent Skin contact good; all tape edges adherent; all allergens in contact with the skin	43 (78.2)	88 (76.5)	95 (82.6)
Adhesion Good Skin contact acceptable; some tape edges lifting; all allergens in contact with the skin	5 (9.1)	11 (9.6)	7 (6.1)
Adhesion Poor Little to no skin contact with panel; one or more allergens not in contact with the skin	5 (9.1)	13 (11.3)	9 (8.0)
Adhesion Detached Panel completely off the skin; none of the allergens in contact with the skin	2 (3.6)	3 (2.6)	3 (2.6)
Burning/ Itching Number of Subjects	54[c]	114[d]	114[d]
Burning Any	3 (5.6)	7 (6.1)	12 (10.5)
Burning Severe	0 (0.0)	0 (0.0)	1 (0.9)
Itching Any	31 (57.4)	62 (54.4)	72 (63.2)
Itching Severe	1 (1.9)	7 (6.1)	11 (9.7)
Tape Irritation Number of subjects	54	114	114
Tape Irritation Any	27 (50.0)	56 (49.1)	53 (46.5)
Tape Irritation Severe	0 (0.0)	1 (0.9)	0 (0.0)

Source: STN 103738/5162 Pediatric Study 2 CSR, Table 10.5.2

[a] Fifty-five of the 116 subjects received Panel 1.3. The others received Panel 1.2. Fifty-four participants were present at the Day 2 visit.

[b] Of the 116 subjects who received T.R.U.E. TEST, 115 presented to visit 2.
and had itching, burning, and tape irritation data documented.

[c] Fifty-four of the 55 participants who received Panel 1.3 had burning/itching and tape irritation documented.

[d] Tape irritation and subjective burning and itching were recorded for 114 subjects.

The safety analysis population included all 116 participants who received T.R.U.E. TEST. In Pediatric Study 2, forty (34.8%) participants had at least 1 AE during the 21 days of enrollment. However, only 11 (9.6%) had AEs attributed to T.R.U.E. TEST. Table 13 summarizes these spontaneously reported adverse events as well as the numbers of participants who had any late reactions and persistent reactions to T.R.U.E. TEST.

Table 13: Summary of Spontaneously Reported Adverse Events, Late Reactions, and Persistent Reactions Among Children and Adolescents 6 through 17 Years of Age in Pediatric Study 2 (Safety Analysis Population)

Study Day	Adverse Event	N=116
	Total number of participants with ≥1 AE (%)	40 (34.8)
Day 0 to 21	Total number of participants with ≥1 AR (%)	11 (9.6)
	Ectopic flare/Worsening of pre-existing dermatitis *n* participants (%)	5 (4.3)
	Pruritus at panel site(s) *n* participants (%	1 (0.9)
	Skin reaction at panel site(s) *n* participants (%	1 (0.9)
	Skin infection *n* participants (%)	2 (1.7)
At Day 21	Late positive reaction	2 (1.7%)
At Day 21	Persistent positive reaction	6 (5.2)

Sources: Adapted from STN 103738/5162, Pediatric Study 2 CSR, Table 14.3.1-5 and Applicant's IR Response dated July 19, 2017

Reviewer comment: *The notably lower rate of ectopic flare observed in Pediatric Study 2 (compared to over 20% in Pediatric Study 1) is likely due to confounding factors. There were less participants who had active dermatitis in Pediatric Study 2 (86.9%) than in Pediatric Study 1 (99.0%) at the time of patch testing. Although about 50% of participants in both pediatric studies had pre-existing AD, it is unknown if the two subpopulations had similar distributions of AD severity (i.e., mild, moderate, severe, prone to superinfections) and management status (i.e., well-controlled, poorly-controlled). Those with less severe and better controlled AD at baseline are less likely to have a flare in the setting of discontinuing topical corticosteroids for 1 week and being subjected to cutaneous provocation by patch testing.*

6.2.12.3 Deaths

No deaths occurred in Pediatric Study 2.

6.2.12.4 Nonfatal Serious Adverse Events

One participant (Subject 418) was diagnosed with appendicitis, which was judged to be unrelated to patch testing due to lack of biological plausibility. This resolved with surgical intervention.

6.2.12.5 Adverse Events of Special Interest (AESI)

No cases of anaphylaxis, neosensitization, or excited skin (angry back) syndrome (defined as a regional state of skin hyper-reactivity caused by the presence of a strong

positive reaction which may result in other patch test sites to become reactive)occurred in Pediatric Study 2. There was one positive extreme reaction to gold sodium thiosulfate on day 3 and it resolved by day 21.

> ***Reviewer comment:*** *The safety data from Pediatric Study 2 supports continuing routine pharmacovigilance.*

6.2.12.7 Dropouts and/or Discontinuations

Of the 116 participants enrolled, 1 dropped out prior to T.R.U.E. TEST application. No participants discontinued the study due to AEs.

6.2.13 Study Summary and Conclusions

The combined rates of positive reactions detected at days 3, 4,and 7 varied by allergen. No subjects had positive reactions to the negative control. No subjects had positive reactions to ethylenediamine dihydrochloride. The rates for the remaining 10 other allergens and allergen mixes are provided in descending order: gold sodium thiosulfate (27.0%), 2-bromo-2-nitropropane-1.3,-diol [bronopol] (17.1%), bacitracin (12.6%), parthenolide (7.2%), fragrance mix (3.8%), neomycin sulfate (3.8%), potassium dichromate (3.8%), disperse blue 106 (3.6%), hydrocortisone-17-butyrate (1.8%), and methyldibromoglutaronitrile (0.9%). Confirming clinical relevance of positive reactions requires medical follow-up, and was not within the scope of this study.

Suboptimal panel adhesion was defined more strictly in Pediatric Study 2 than in Pediatric Study 1, which accounted for the higher rate of poor adhesion reported in the former study. After removal of T.R.U.E. TEST panels, itching (up to 61.2%) was more common than burning (up to 10.5%). About half of all participants had tape irritation at each of the panel sites. Eleven (9.6%) participants had spontaneously reported ARs following T.R.U.E. TEST application. The most commonly reported AR was ectopic flare of pre-existing dermatitis (4.5%). Late positive reactions 21 days after T.R.U.E. TEST application occurred in 2 participants (1.7%) to gold sodium thiosulfate. Persistent reactions were observed in 6 participants (5.2%) 21 days after T.R.U.E. TEST application to the following allergens: gold sodium thiosulfate (n=6) and bronopol (n=1). One participant had an unrelated SAE of appendicitis that resolved within the time frame of the study with surgical intervention. There were no deaths. The pediatric safety data did not reveal any unexpected safety trends or signals for SAEs.

7. INTEGRATED OVERVIEW OF EFFICACY

7.1 Indication #1

T.R.U.E. TEST is an epicutaneous patch test indicated 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 on the T.R.U.E. TEST panels.

7.1.1 Methods of Integration

Two studies were conducted in the US to evaluate the diagnostic performance of T.R.U.E. TEST in children and adolescents 6 through 17 years of age. Pediatric Study 1 provided the diagnostic data for 24 allergens and allergen mixes and Pediatric Study 2 provided the diagnostic data for 11 allergens and allergen mixes, totaling the 35 allergens and allergen mixes included on the currently approved version of T.R.U.E. TEST. See Section 6.1.4 for details on the investigational and reformulated contact allergens evaluated in both studies.

7.1.2 Demographics and Baseline Characteristics

In general, there were no significant differences in the demographics and baseline characteristics among the children and adolescents evaluated in Pediatric Study 1 and Pediatric Study 2. For details, see Section 1.1.

7.1.3 Subject Disposition

See Sections 6.1.10 and 6.2.10 for discussion of subject disposition of the populations for these two pediatric studies.

7.1.4 Analysis of Primary Endpoint(s)

The primary endpoint analysis was based on the per-protocol (PP) population, which included all participants who received T.R.U.E. TEST application and who completed the study without major protocol violations. Analysis of the diagnostic performance among the intent-to-treat (ITT) population, which included all participants with T.R.U.E. TEST application and at least one post-baseline skin reaction evaluation, was used to support primary analysis. Diagnostic performance for the 35 allergens and allergen mixes and negative control in T.R.U.E. TEST in children and adolescents and adults are presented in Table 12.

> ***Reviewer comment:*** *Common contact allergens (including metals and chemicals used in hygiene products and clothing) affect both pediatric and adult populations. As such, we do not expect substantially different rates of positive reactions with respect to these highly prevalent allergens in children and adolescents compared to adults. In addition, since we have the more generalizable sensitivity and specificity data for 12 of the 35 allergens in adults, in the opinion of this reviewer, it is of clinical interest to provide these data in an integrated table (see Table 14).*

Table 14: Summary of Positive Reactions for T.R.U.E. TEST Panels 1.3, 2.3, and 3.3 in Pediatric and Adult Studies (Per Protocol Populations)

Panel	Position	Allergen	Pediatric Study 1 n (%)	Pediatric Study 2 n (%)	Adult Studies[a] n (%)
1.3			**N=100**	**N=53**[b]	***variable***
1.3	1	Nickel Sulfate	30 (30.0)	NA	90/345 (26.1)
1.3	2	Wool Alcohols	16 (16.0)	NA	4/290 (1.4)
1.3	3	Neomycin Sulfate	NA	2 (3.8)	16/345 (4.6)
1.3	4	Potassium Dichromate	NA	2 (3.8)	5/345 (1.4)
1.3	5	Caine Mix	0 (0.0)	NA	7/345 (2.0)
1.3	6	Fragrance Mix	NA	2 (3.8)	23/345 (6.7)
1.3	7	Colophony	9 (9.0)	NA	11/345 (3.2)
1.3	8	Paraben Mix	2 (2.0)	NA	5/290 (1.7)
1.3	9	Negative Control (uncoated polyester patch)	0 (0.0)	0 (0.0)	0 (0.0)
1.3	10	Balsam of Peru	10 (10.0)	NA	17/345 (4.9)
1.3	11	Ethylenediamine Dihydrochloride	NA	0 (0.0)	7/345 (2.0)
1.3	12	Cobalt Dihydrochloride	13 (13.0)	NA	29/345 (8.4)
2.3			**N=100**	**N=111**	
2.3	13	p-tert-Butylphenol Formaldehyde Resin	17 (17.0)	NA	9/290 (3.0)
2.3	14	Epoxy Resin	4 (4.0)	NA	5/345 (1.4)
2.3	15	Carba Mix	7 (7.0)	NA	6/290 (2.1)
2.3	16	Black Rubber Mix	2 (2.0)	NA	5/290 (1.7)
2.3	17	Cl+Me-Isothiazolinone (MCI/MI)	4 (4.0)	NA	8/290 (2.8)
2.3	18	Quaternium-15 (Q-15)	4 (4.0)	NA	21/290 (7.2)[c]
2.3	19	Methyldibromoglutaronitrile (MDBGN)	NA	1 (0.9)	1/110 (0.9)[c]
2.3	20	p-Phenylenediamine	2 (2.0)	NA	13/345 (3.8)
2.3	21	Formaldehyde	7 (7.0)	NA	10/169 (5.9)
2.3	22	Mercapto Mix	2 (2.0)	NA	9/290 (3.1)
2.3	23	Thimerosal	4 (4.0)	NA	31/290 (10.7)
2.3	24	Thiuram Mix	7 (7.0)	NA	14/345 (4.1)
3.3			**N=100**	**N=111**	
3.3	25	Diazolidinyl Urea (DU)	5 (5.0)	NA	4/98 (4.1)[c]
3.3	26	Quinoline Mix	1 (1.0)	NA	2/290 (0.7)

Panel	Position	Allergen	Pediatric Study 1 n (%)	Pediatric Study 2 n (%)	Adult Studies[a] n (%)
3.3	27	Tixocortol-21-Pivalate (TIX)	8 (8.0)	NA	9/292 (3.1)[c]
3.3	28	Gold Sodium Thiosulfate (GST)	NA	30 (27.0)	28/110 (25.5)[c]
3.3	29	Imidazolidinyl Urea (IMID)	2 (2.0)	NA	3/98 (3.1)
3.3	30	Budesonide (BUD)	1 (1.0)	NA	3/292 (1.0)[c]
3.3	31	Hydrocortisone-17-Butyrate	NA	2 (1.8)	0/205 (0.0)[c]
3.3	32	Mercaptobenzothiazole	2 (2.0)	NA	8/290 (2.8)[c]
3.3	33	Bacitracin	NA	14 (12.6)	5/110 (4.5)[c]
3.3	34	Parthenolide	NA	8 (7.2)	1/110 (0.9)[c]
3.3	35	Disperse Blue 106	NA	4 (3.6)	1/110 (0.9)[c]
3.3	36	2-Bromo-2-nitropropane-1,3-diol (Bronopol)	NA	19 (17.1)	3/110 (2.7)[c]

Source: STN 103738/5162, Pediatric Study 2 CSR, Table 11.1.1-3
[a] Adult data taken from the T.R.U.E. TEST PI (*Clinical Studies* (14.1), Table 4)
[b] Only 53 subjects in Pediatric Study 2 in the per-protocol analysis set received Panel 1.3
[c] Sensitivity,specificity, concordance data available in the T.R.U.E. TEST PI (*Clinical Studies* (14.1), Table 4)
NA= Not Applicable/Not Available.The results are not applicable because the allergens and allergen mixes were either from previously approved formulations, not evaluated or not pre-specified as the primary endpoint of the study.

Reviewer comment: *Pediatric Study 1 provided data for 24 of the allergens and allergen mixes in the currently licensed version of T.R.U.E. TEST. Although Pediatric Study 2 evaluated Panels 1.3, 2.3, and 3.3, the pre-specified primary objective was limited to analyzing the diagnostic performance of the 4 reformulated and 7 new allergens and allergen mixes. Generalizability of the diagnostic data from studies of individuals with suspected as opposed to confirmed ACD is limited. However, the general ordering of contact allergens based on epidemiologic prevalence should be preserved. As expected, nickel sulfate and gold sodium thiosulfate were the most common contact allergens in pediatric and adult populations with suspected ACD.*

7.1.11 Efficacy Conclusions

Positive reaction rates for the 35 allergens and allergen mixes in T.R.U.E. TEST in children and adolescents were derived from two pediatric studies. No subjects had positive reactions to the negative control. No subjects had positive reactions to ethylenediamine dihydrochloride or caine mix. The positive reactions rates varied by allergen and were consistent with published data on common contact allergens. The following positive reactions rates were reported cumulatively for assessments conducted from days 3, 4, and 7: nickel sulfate (30.0%), gold sodium thiosulfate (27.0%), 2-bromo-2-nitropropane-1.3,-diol [bronopol] (17.1%), p-tert-butylphenol formaldehyde resin (17.0%), wool alcohols (16.0%), cobalt dihydrochloride (13.0%), bacitracin (12.6%), balsam of peru (10.0%), colophony (9.0%), tixocortol-21-pivalate (8.0%), parthenolide (7.2%), carba mix (7.0%), formaldehyde (7.0%), thiuram mix (7.0%), diazolidinyl urea

(5.0%), Cl+Me-isothiazolinone (4.0%), epoxy resin (4.0%), quaternium-15 (4.0%), thimerosal (4.0%), fragrance mix (3.8%), neomycin sulfate (3.8%), potassium dichromate (3.8%), disperse blue 106 (3.6%), black rubber mix (2.0%), imidazolidinyl urea (2.0%), mercaptobenzothiazole (2.0%), mercapto mix (2.0%), paraben mix (2.0%), p-phenylenediamine (2.0%), hydrocortisone-17-butyrate (1.8%), budesonide (1.0%), quinoline mix (1.0%), and methyldibromoglutaronitrile (0.9%).

8. INTEGRATED OVERVIEW OF SAFETY

8.1 Safety Assessment Methods

Safety analysis sets included participants who received the investigational product. Day 2 safety data assessments were limited to the participants who presented to the clinic.

8.2 Safety Database

8.2.1 Studies/Clinical Trials Used to Evaluate Safety

Table 15: Safety Database by Investigational Panel

Study Panels Applied	Pediatric Study 1	Pediatric Study 2
Panel 1.1	102	Not applicable
Panel 2.1	102	Not applicable
Panel 3.1	102	Not applicable
Panel 1.3	NA	54
Panel 2.2 (renumbered 2.3)	NA	116[a]
Panel 3.2 (renumbered 3.3)	NA	116[a]

[a] One participant did not have all three panels of T.R.U.E. TEST applied due to refusal by parent.

> ***Reviewer comment:*** *CBER agreed to the proposed study size of 100 children and adolescents for Pediatric Study 1 and of 110 for Pediatric Study 2. We accepted the statistical basis (i.e., two-fold increase in rates of expected adverse events) for these study size calculations.*

8.2.2 Overall Exposure, Demographics of Pooled Safety Populations

The pediatric safety database is comprised of 218 children and adolescents (n=102 and up to 116 from Pediatric Study 1 and 2, respectively) who were exposed to T.R.U.E. TEST panels for 48 hours and followed for 21 days.

> ***Reviewer comment:*** *Twenty-one days allows for data collection on persistent and late reactions and most of the other items identified under warnings and precautions. The exception is repeat testing, which can be pursued weeks to months after the first round of testing when sensitization is suspected. However, the safety and efficacy of repetitive testing with T.R.U.E. TEST is unknown and not part of the the product indication.*

8.2.3 Categorization of Adverse Events

Table 16: Combined Summary of Adverse Reactions (AR) from Pediatric Study 1 and Pediatric Study 2 Compared to Adult Data (Safety Analysis Populations)

Timepoint of Assessment	Adverse Reaction	Pediatric Study 1 N=102	Pediatric Study 2 N=116	Adult Studies *Variable*
Through Day 21	Total number of participants with ≥1 AR (%)	25 (24.5)	11 (9.6)	Not Available
	Ectopic flare/Worsening of pre-existing dermatitis *n* participants (%)	23 (22.5)	5 (4.3)	2/458 (0.4)
	Skin reaction at panel site(s)	2 (2.0)	1 (0.9)	Not Available
	Pruritus at panel site(s) after day 2	1 (1.0)	1 (0.9)	Not Available
	Skin infection *n* participants (%)	2 (2.0)	2 (1.7)	Not Available
Day 21	Late positive reaction	0 (0.0)	2 (1.7)	8/1168 (0.7)
Day 21	Persistent positive reaction	4 (3.9)	6 (5.2)	79/1168 (6.8)

Sources: STN 103738/5162, Pediatric Study 1 CSR, Table ; Pediatric Study 2 CSR, Table 14.3.1-5; T.R.U.E. TEST PI [*Adverse Reactions (6.1), Table 2]*

Reviewer comment: *Approximately half of the subjects in Pediatric Study 1 (53.9%) and Pediatric Study 2 (45.7%) had pre-existing AD. AD is not as common among adults, but when present, the distribution of the AD is typically more localized to the hands with a more chronic "burned out" phenotype of inflammation on histopathology. In children and adolescents, the cutaneous inflammation of AD tends to be subacute and its distribution includes the face, trunk and proximal limbs, which are closer to the sites of patch testing. This could explain the higher rates of children and adolescents with ectopic flare (22.5% in Pediatric Study 1, 4.3% in Pediatric Study 2) than in adults (0.4%, from T.R.U.E. TEST package insert [see Adverse Reactions (6.1), Table 2]) are not unexpected.*

The 5-fold higher rate of worsening of pre-existing dermatitis observed in Pediatric Study 1 (22.5%) than in Pediatric Study 2 (4.3%) may be attributed to the single site of enrollment being an academic center. This population had a slightly greater percentage of individuals with pre-existing AD and had greater representation in the youngest age strata of 6 to 8 year olds than Pediatric Study 2. Baseline AD severity and clinical control status was not well characterized in either of the pediatric studies. However, the difference in rates of worsening of pre-existing AD strongly suggests that participants with AD in Pediatric Study 1 had more severe and less controlled AD at baseline.

8.3 Caveats Introduced by Pooling of Data Across Studies/Clinical Trials

Data on poor panel adhesion, burning and itching, and tape irritation were not pooled due to differences in the grading scales and soliciting participant-reported burning and itching as a composite symptom in Pediatric Study 1 and as separate symptoms in Pediatric Study 2. For the remaining clinical data, pooling did not pose significant problems given the descriptive nature of safety and diagnostic performance endpoints and similar monitoring schedules in the 2 studies. Pooling was needed to capture late and persistent reactions associated with all 35 allergens and allergen mixes.

Diagnostic data for all 35 allergens and allergen mixes were obtained from two studies. Pediatric Study 1 evaluated 24 of the 35 allergens and allergen mixes included on the licensed T.R.U.E. TEST. The pre-specified primary analysis in Pediatric Study 2 was limited to the 4 reformulated allergens on Panel 1.3 and the 7 new allergens on Panel 2.3 and Panel 3.3.

8.4 Safety Results

8.4.1 Deaths

No deaths occurred in either of the two studies.

8.4.2 Nonfatal Serious Adverse Events (SAEs)

Nonfatal SAEs did not occur in Pediatric Study 1. One participant in Pediatric Study 2 was diagnosed with appendicitis during the 21 days of study participation.

8.4.3 Study Dropouts/Discontinuations

See Sections 6.1.10 and 6.2.10.

8.4.4 Common Adverse Events

Table 16 summarizes the common adverse reactions observed with T.R.U.E. TEST across the pediatric studies and from adults.

8.4.8 Adverse Events of Special Interest

Adverse events of special interest specific to T.R.U.E TEST include systemic allergic reactions/anaphylaxis, neosensitization, and extreme reactions at the panel application sites. Noneof the first two were reported to have occurred in either of the two pediatric studies included in this efficacy supplement. One extreme positive reaction was observed in 1 participants from each of the 2 pediatric studies. In both instances, they resolved by study completion 21 days after T.R.U.E. TEST placement.

8.6 Safety Conclusions

Adverse reactions occurred in 36 (16.6%) of the 218 children and adolescents who received T.R.U.E. TEST in Pediatric Study 1 and Pediatric Study 2. Poor (and fair, in Pediatric Study 1) adhesion of at least one of the three T.R.U.E. TEST panels was observed in about 10% of subjects in Pediatric Study 1 (9.8%) and Pediatric Study 2 (11.3%). No panels fells off in Pediatric Study 1, while panel(s) fell off in up to 3.6% of participants in Pediatric Study 2. Tape irritation, mostly mild to moderate, was observed

in over half of the participants in Pediatric Study 1 (62.7%) and Pediatric Study 2 (50.4%). Symptoms of itching and burning were reported by 65.7% of participants in Pediatric Study 1. Separate recording of these 2 symptoms in Pediatric Study 2 revealed that itching (62.6%) was more commonly reported than burning (10.4%) after removal of T.R.U.E. TEST. Late positive reactions occurred in 2 subjects (0.9%) 21 days after T.R.U.E. TEST application to gold sodium thiosulfate. Persistent reactions occurred in 10 subjects (4.6%) 21 days after T.R.U.E. TEST application to the following allergens: bronopol (n=1), Cl+Me+isothiazolinone (n=1), diazolidinyl urea (n=1), gold sodium thiosulfate (n=6), nickel sulfate (n=2), and quaternium-15 (n=1). The most common spontaneously reported ARs were ectopic flare/worsening of pre-existing dermatitis (12.8%), skin infection (1.8%), and skin reactions at panel site(s) (1.4%). Most of the ARs were graded as mild (defined by minimal symptoms that did not interfere with daily functioning) and moderate (defined by need for medication for relief and resulting in some interference with daily functioning). The two pediatric studies did not provide any signals for serious adverse events.

9. ADDITIONAL CLINICAL ISSUES

9.1 Special Populations

9.1.1 Human Reproduction and Pregnancy Data

TheApplicant indicated that they are not aware of clinical data on the use of T.R.U.E. TEST during pregnancy.

9.1.2 Use During Lactation

The Applicant indicated that there are no data on the use of T.R.U.E. TEST in lactating women.

9.1.3 Pediatric Use and PREA Considerations

This efficacy supplement fulfills the PREA requirement to perform a pediatric assessment in children and adolescents 6 to <18 years of age. A partial waiver was granted in children under 6 years of age under STN 103738/5074 (approval letter February 29, 2012 and correction issued June 15, 2012). Consequently, safety and effectiveness of T.R.U.E. TEST have not been established in persons younger than 6 years of age.

9.1.4 Immunocompromised Patients

There are no data on immunocompromised participants in this efficacy supplement. (Participants were required to withhold specific medications (e.g., topical and systemic corticosteroids, topical and systemic immunomodulators) for 7 days prior to scheduled placement of T.R.U.E. TEST panels.

9.1.5 Geriatric Use

The ten adult trials of T.R.U.E. TEST enrolled individuals with an upper age range of 68 to 86 years of age (5). These data are already included in the PI.

10. CONCLUSIONS

The diagnostic performance and safety data from Pediatric Studies 1 and 2 support the use of T.R.U.E. TEST as an aid to diagnosis of ACD in children and adolescents 6 to <18 years of age whose history suggests sensitivity to one or more of the 35 allergens and allergen mixes included on the T.R.U.E. TEST panels.

11. RISK-BENEFIT CONSIDERATIONS AND RECOMMENDATIONS

11.1 Risk-Benefit Considerations

Evaluation of the risk-benefit profile for the approval of T.R.U.E. TEST for use in children and adolescents 6 through 17 years of age is presented in Table 17 and discussed in Section 11.2. The risk-benefit profile for the use of T.R.U.E. TEST is favorable. No safety signals for serious adverse events were identified.

Table 17: Risk-Benefit Considerations for Licensure of T.R.U.E. TEST in Children and Adolescents 6 to <18 Years of Age

Decision Factor	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• ACD is a common and chronic condition that affects about 15% of the pediatric population. • Patch testing is necessary to support the diagnosis of ACD, which has a clinical presentation shared by a number of other dermatoses. History and physical exam alone does not reliably distinguish ACD from the phenotypically similar conditions of ICD or AD. • Patch testing enables clinicians to identify potential allergens triggering ACD. Patch testing results can guide targeted elimination strategies that can prevent future recurrences of ACD.	• Management of acute ACD relies on topical corticosteroids and immunosuppressants. However, recurrences are likely due to continued exposure to triggering allergens. Accurate diagnosis will enable the prevention of recurrences of ACD.
Unmet Medical Need	• The only patch test product approved for individuals under 18 years old is the Rubber Panel T.R.U.E. TEST, which contains only 5 of the contact allergens included in T.R.U.E. TEST. Rubber Panel T.R.U.E. TEST does not include the most prevalent contact allergens in children, such as metals and preservatives in textiles and topical medications and toiletries.	• T.R.U.E. TEST contains 35 common contact allergens (i.e., metals and preservatives in textiles and toiletry products) that are <u>not</u> included in the 5 rubber allergens contained in the Rubber Panel T.R.U.E. TEST, which is currently the only licensed patch test product for children and adolescents.
Clinical Benefit	• No participants had positive reactions to the negative control in T.R.U.E. TEST. Rates of positive reactions to the allergens and allergen mixes in T.R.U.E. TEST ranged from 1% to 30%. The most common allergens and allergen mixes eliciting positive reactions in this at-risk population were consistent with published data on the most prevalent contact allergens in the pediatric population. These included nickel sulfate [30%], gold sodium thiosulfate [27.0%], p-tert-butylphenol formaldehyde resin [17.0%], 2-bromo-2-nitropropane-1,3-diol (bronopol) [13.6%], cobalt dihydrochloride [13.0%], and bacitracin [12.7%].	• The data support the use of T.R.U.E. TEST 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 included in T.R.U.E. TEST.
Risk	• The majority of participants from the 2 studies had weak to no tape irritation at the sites of the three T.R.U.E. TEST panels (Panel 1.3 = 92.6% Panel 2.3 = 93% Panel 3.2 = 88.6%). Local burning and itching was mostly weak or absent in most participants (67 to 83%) in Pediatric Study 1. Pediatric Study 2 evaluated the 2 symptoms separately and found that weak to moderate itching (50%) was more common than weak to moderate burning (5 to 10%) • Most ARs were mild to moderate. The most common spontaneously reported AR was ectopic flare of pre-existing dermatitis (4.3 to 22.5%). No AEs resulted in study discontinuation. • There were no case of anaphylaxis. No related SAEs or deaths were observed. • Irritant reactions were observed at low rates (1 to 2%). • No late reactions at day 21 were observed among participants of Pediatric Study 1. Late positive reactions at Day 21 were observed in 2 participants (1.7%) to gold sodium thiosulfate in Pediatric Study 2. No late reactions at Day 21 were observed to the other 10 investigational allergens. • In Pediatric Study 1, persistent reactions at Day 21 were observed in 4 participants (3.9%) to the following allergens: Cl+Me+isothiazolinone (n=1), diazolidinyl urea (n=1), nickel sulfate (n=2), and quaternium-15 (n=1). In Pediatric Study 2, persistent reactions were observed in 6 participants (5.2%) 21 days after T.R.U.E. TEST application to the following allergens: gold sodium thiosulfate (n=6) and bronopol (n=1).	• The evidence indicates that the risk of patch testing with the T.R.U.E. TEST is minimal. • Worsening of pre-existing dermatitis is not unexpected given that topical immunosuppressants had to be withheld for at least one week. About half of the participants in both studies had co-existing AD and >86% of participants had active dermatitis at enrollment.
Risk Management	• In children and adolescents, the most common spontaneously reported ARs across both pediatric studies were worsening of pre-existing dermatitis (12.8%), infection of lesional skin (1.8%), reactions at former panel sites (1.4%). Ectopic flares of pre-existing dermatitis can be attributed to the withholding topical corticosteroids and immunomodulators for at least 1 week. This is common practice for patch testing and therefore, transient and treatable worsening of pre-existing dermatitis is an expected risk.	• Routine measures, such as the package insert and the current pharmacovigilance plan, would be adequate to manage the risks.

11.2 Risk-Benefit Summary and Assessment

The clinical data from Pediatric Study 1 and Pediatric Study 2 present a favorable risk-benefit profile. No safety signals for SAEs were identified. In general, the observed reactions were mild and moderate, which was defined by the need for prescription medications. The majority of participant who presented to patch testing had active dermatoses. About half of the participants in both studies had co-existing AD. In the setting of withholding chronic topical medication use for at least 7 days, as required by the study protocol, ectopic flares and worsening of pre-existing dermatitis were not unexpected. None of the exacerbations required hospitalization. Outpatient management was sufficient. The trends in the diagnostic performance data for the 35 T.R.U.E. TEST allergens mirror published data regarding common contact allergens in the pediatric population, and therefore, support the proposed indication as an aid to diagnosis of ACD.

11.4 Recommendations on Regulatory Actions

The safety and diagnostic performance data included in this sBLA support the approval 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.

11.5 Labeling Review and Recommendations

With this efficacy supplement, the PI was revised to justify the inclusion of children and adolescents 6 years of age and older for the product indication, which was previously limited to adults 18 years of age and older. Specific changes in content and organization are presented below by their respective section:

- **1 Indications and Usage**
  - *T.R.U.E. TEST is an epicutaneous patch test indicated for use as an aid in the diagnosis of allergic contact dermatitis in persons* ***6*** *~~18~~ years of age and older whose history suggests sensitivity to one or more of the 35 ~~substances~~* ***allergens and allergen mixe****s included on the T.R.U.E. TEST panels.*
  - We recommended substituting the term “substances” with “allergens and allergen mixes” for consistency as well as for accuracy. The Applicant concurred.

- **2 Dosage and Administration**
  - This section was renumbered due to designating *Dose* as 2.1, and moving the following three subsections down by one.
  - The temporal definition of late reactions was revised from 7 to 10 days to 7 to 21 days to be consistent with the conduct of the study. There was no Day 10 in the study protocol.
  - A redundant statement pertaining to patient instructions was deleted.

- **5 Warnings and Precautions**
  - 5.8 Late Reactions: The temporal definition of late reactions was revised to reflect the scheduled assessment of late reactions at Day 21.

- **6 Safety**
  - CBER added an introductory summary of adverse reactions in adults and in children and adolescents.
  - 6.1 Clinical Trials Experience: This section was organized with subheadings of “Adult Participants 18 Years of Age and Older” and “Children and Adolescents 6 through 17 Years of Age.”
  - The Applicant accepted all revisions to text and condensed approach to tabulating data from the two pediatric studies.

- **8 Use in Specific Populations**
  - 8.1 Pregnancy: The risk summary indicates that there are no human or animal data to establish the presence or absence of T.R.U.E. TEST-associated risks during pregnancy.
  - 8.2 Lactation: The risk summary indicates that there are no available data to assess the effects of T.R.U.E. TEST on the breastfed child or on milk production/excretion.
  - 8.4 Pediatric Use: The statement regarding safety and effectiveness in children was revised to reflect the updated indication to include children and adolescents 6 through 17 years of age,

- **14 Clinical Studies**
  - 14.2 Children and Adolescents 6 through 17 Years of Age: The Applicant accepted all revisions to the text and approach to the tabulation of diagnostic performance data from the per-protocol populations and to the 35 allergens included on the licensed T.R.U.E. TEST.

11.6 Recommendations on Postmarketing Actions

Routine pharmacovigilance is recommended.