Application Type	BLA
STN	103738/5162
CBER Received Date	October 27, 2016
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Division / Office	DVRPA/OVRR
Committee Chair	Christina Houck
Clinical Reviewer(s)	Joohee Lee, MD
Project Manager	Taruna Khurana, PhD; Qun Wang, PhD
Priority Review	No
Reviewer Name(s)	Zhong Gao, Ph.D. Mathematical Statistician
Review Completion Date / Stamped Date	
Supervisory Concurrence	Lihan Yan, Ph.D. Team Leader, Bacterial and Allergenic Team
	Amelia Dale Horne, Dr. P.H. Chief, Vaccine Evaluation Branch, DB, OBE
Applicant	SmartPractice Denmark ApS
Established Name	Thin-Layer Rapid Use Epicutaneous Patch Test
(Proposed) Trade Name	T.R.U.E.TEST
Pharmacologic Class	Allergen patch test
Formulation(s), including Adjuvants, etc	Three adhesive panels consisting of 35 allergen and allergen mix patches and a negative control. Panel 1.3 contains 11 allergens and allergen mixes and a negative control. Panel 2.3 contains 12 allergens and allergen mixes. Panel 3.3 contains 12 allergens and allergen mixes.
Dosage Form(s) and Route(s) of Administration	Apply the three adhesive panels of allergens and allergen mixes 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.
Dosing Regimen	N.A.
Indication(s) and Intended Population(s)	For topical use only. 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 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.

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1. Executive Summary

SmartPractice Denmark ApS submitted this BLA efficacy supplement to update the package insert to expand the indication of the Thin-layer Rapid Use Epicutaneous (T.R.U.E.) Patch Test Panel to children and adolescents (6-17 years of age) with suspected allergic contact dermatitis based on symptoms and clinical history.

The applicant provided two clinical studies to support the application. Study Mekos 07 29P1/2/3 401 evaluated the diagnostic performance and safety of the T.R.U.E. Test Panels 1.1, 2.1, and 3.1 in 102 enrolled subjects 6 to 18 years of age; study SP 12 7New 401 (PREA II) evaluated the diagnostic performance and safety of 11 investigational T.R.U.E. TEST allergens, located on Panels 1.3, 2.2, and 3.2, in 116 enrolled subjects 6 to 17 years of age. In both studies, the primary efficacy analysis was based on descriptive analysis of frequencies of positive reactions to the individual allergens. These studies were not designed to obtain information about sensitivity or specificity or agreements on positives and negatives against a reference. Therefore, the traditional measures for diagnostic performance cannot be evaluated. The applicant explained that the true "disease" status (allergic contact dermatitis [ACD] to a specific allergen) is rarely known definitively, and patients may be diagnosed based on clinical findings that may be discordant and change over time. Additionally, this test is indicated for use as an aid in the diagnosis of allergic contact dermatitis. I defer to the medical officer for evaluation of the adequacy of the evidence for efficacy based on regulatory history and the totality of the evidence. In both studies, no unexpected safety trends were observed.

2. Clinical and Regulatory Background

SmartPractice Denmark ApS submitted the BLA efficacy supplement to update the package insert to expand the indication of the Thin-layer Rapid Use Epicutaneous (T.R.U.E) Patch Test Panel to children and adolescents. The initial submission included study SP 12 7New 401 (PREA II) which evaluated the diagnostic performance and safety of 11 investigational T.R.U.E. TEST allergens in children and adolescent subjects of 6-17 years of age with suspected allergic contact dermatitis based on symptoms and clinical history. On January 6, 2017, CBER issued a deficiency letter to the applicant, asking the applicant to submit the final study report and datasets for study Mekos 07 29P1/2/3 401 to the sBLA because the applicant presented the results from this study (referred to as Pediatric Study 1) in the draft package insert.

2.1 Disease or Health-Related Condition(s) Studied

T.R.U.E. TEST is a ready-to-use patch test method designed for use by licensed physicians in the diagnosis of allergic contact dermatitis (ACD).

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

N/A

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

T.R.U.E. TEST was originally granted a Biologics License in the U.S. for 23 allergens and a blank patch (control) in 1994. In 2007, 5 additional clinically relevant allergens were added to a third panel of the T.R.U.E. TEST product. Seven additional allergens were added in 2012. The current U.S.-available T.R.U.E. TEST product includes three panels of 36 allergen polyester patches, one of which is blank.

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

The applicant requested to waive the pediatric assessment requirements for the pediatric age groups defined as neonates (birth to 1 month), infants (1 month to 2 years), and children (2 to 5 years).

2.6 Other Relevant Background Information

N/A

3. Submission Quality and Good Clinical Practices

3.1 Submission Quality and Completeness

The submission is adequately organized for conducting a complete statistical review.

3.2 Compliance with Good Clinical Practices and Data Integrity

The datasets submitted in this submission are generally adequate for statistical review. During the review process, CBER's Bioresearch Monitoring (BIMO) identified issues related to product packaging, labeling, etc. I defer to the BIMO reviewer for further consideration.

4. Significant Efficacy/Safety Issues Related to Other Review Disciplines

N/A

5. Sources of Clinical Data and Other Information Considered in the Review

5.1 Review Strategy

This review is focused on study SP 12 7NEW 401 (PREA II) and study Mekos 07 29P1/2/3 401.

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

- The final Clinical Study Report (CSR) of study SP 12 7NEW 401 (PREA II).
- The final Clinical Study Report (CSR) of study Mekos 07 29P1/2/3 401.

5.3 Table of Studies/Clinical Trials

Two clinical studies (study SP 12 7NEW 401 (PREA II) and study Mekos 07 29P1/2/3 401) were included to support this BLA supplement.

5.4 Consultations

N/A

5.5 Literature Reviewed (if applicable)

N/A

6. DISCUSSION OF INDIVIDUAL STUDIES/CLINICAL TRIALS

6.1 Study PREA II: Clinical Evaluation of T.R.U.E. TEST® Panel 3.2 in Children and Adolescents

6.1.1 Objectives

Primary objectives:
To evaluate the diagnostic performance and safety of 11 T.R.U.E. TEST allergens in children and adolescent subjects (6-17 years of age) with suspected ACD based on symptoms and clinical history.

Secondary objectives:
To evaluate the safety of the 11 investigational T.R.U.E. TEST allergens based on the frequency and characterization of panel adhesion, presence of tape irritation, subject-reported itching and burning, late and persistent reactions, other reactions, and AEs and serious AEs.

6.1.2 Design Overview

This was an open-label, multi-center, non-randomized, Phase III/IV clinical trial designed to evaluate the diagnostic performance and safety of 11 T.R.U.E. TEST investigational allergens in at least 110 consecutive children and adolescents (6 to 17 years old) based on their clinical history and symptoms. This study included no control groups.

The first 62 subjects were tested with T.R.U.E. TEST panels 1.2, 2.2, and 3.2, which are already approved for use in adults. Panel 2.2 included one investigational allergen: methyldibromo glutaronitrile (MDBGN). Panel 3.2 included 6 investigational allergens: gold sodium thiosulfate (GST), hydrocortisone-17-butyrate (H-17-B), bacitracin, parthenolide, disperse blue 106 (DB 106), and 2-bromo-2-nitropropane-1, 3-diol (bronopol). For the last 54 subjects, panel 1.2 was replaced with investigational panel 1.3, which included 4 previously approved but slightly reformulated allergens in terms of

dose or excipient: neomycin sulfate, potassium dichromate, fragrance mix (FM), and ethylenediamine dihydrochloride). These 11 substances comprised the investigational allergens. Only the data from the 11 investigational allergens were considered within the scope of the study.

On Day 0 (Visit 1), subjects answered a questionnaire about their exposure to different allergens at their evaluation before patch placement. The panels were applied to the subjects' backs. The panels were then worn for 48 hours. After the panels were worn for 2 days, they were removed at Visit 2 (Day 2). All test site skin reactions were evaluated along with any irritation related to the panel tape. Additional evaluations of test site skin reactions were conducted on Day 3 (Visit 3 at 72 hours), Day 4 (Visit 4 at 96 hours), Day 7 + 1 (Visit 5), and Day 21 ± 2 (Visit 6) after the initial placement of the patch panels. At each of these evaluations, any adverse events (AEs) were documented. At Visits 5 and 6, late and/or persistent skin reactions were recorded. All subjects exited the study at the completion of Visit 6.

6.1.3 Population

The study population included children and adolescent subjects 6 to 17 years with a clinical history or symptoms of contact dermatitis.

6.1.4 Study Treatments or Agents Mandated by the Protocol

Sixty-two subjects were tested with the following post-marketing T.R.U.E. TEST allergen panels:

- Panel 1.2 (BLA #103738; U.S. License #1623; NDC 67334-0457-*1)
- Panel 2.2 (BLA #103738; U.S. License #1623; NDC 67334-0457-*1)
- Panel 3.2 (BLA #103738-5019/5027; U.S. License #1623; NDC 67334-0457-*1).

The final 54 patients were tested with Panel 1.3 (reformulated allergens), as well as with post-marketing Panels 2.2 and 3.2.

The 11 investigational allergens in the final amended protocol were as follows:

- T.R.U.E. TEST Panel 2.2:
  - Methyldibromoglutaronitrile (0.0053 mg/cm2 in polyvinylpyrrolidone (PVP))
- T.R.U.E. TEST Panel 3.2:
  - Gold sodium thiosulfate (0.075 mg/cm2 in hydroxypropylcellulose (HPC))
  - Hydrocortisone-17-butyrate (0.020 mg/cm2 in PVP)
  - Bacitracin (0.60 mg/cm2 in HPC)
  - Parthenolide (0.0030 mg/cm2 in PVP)
  - Disperse blue 106 (0.050 mg/cm2 in PVP)
  - 2-Bromo-2-nitropropane-1,3-diol (Bronopol) (0.25 mg/cm2 in PVP)
- T.R.U.E. TEST Experimental Panel 1.3 (four reformulated allergens):
  - Neomycin sulfate (0.60 mg/cm2 in PVP)
  - Potassium dichromate (0.054 mg/cm2 in PVP)
  - Fragrance Mix (0.50 mg/cm2 in PVP with β-cyclodextrin)
  - Ethylenediamine dihydrochloride (0.050 mg/cm2 in PVP)

6.1.6 Sites and Centers

This study was conducted at four study centers in the U.S.

6.1.7 Surveillance/Monitoring

N/A

6.1.8 Endpoints

Primary efficacy endpoints
The diagnostic performance of the 11 investigational T.R.U.E. TEST allergens based on the frequency and characterization of scored skin response (positive, negative, irritant, and doubtful reactions).

Safety Endpoints
Safety endpoints included (1) frequency of late and persistent reactions, (2) tape-induced irritation, (3) frequency of subject-reported itching and burning, and (4) number and frequency of AEs and/or SAEs.

6.1.9 Statistical Considerations & Statistical Analysis Plan

(1) Sample size
Initially the applicant planned to include at least 110 subjects in the final data analysis. While data from 116 subjects (111 per-protocol plus 5 discontinued) were included in the analysis for allergens MDBGN, GST, H-17-B, bacitracin, parthenolide, DB 106, and bronopol, data from 54 subjects were included in the analysis for allergens neomycin sulfate, potassium dichromate, FM, and ethylenediamine dihydrochloride.

(2) Definitions of analysis populations
- Per-protocol population (PP): all subjects who received a patch application and who completed the study with no major protocol violations. This population was used to evaluate the primary study endpoints.
- Intent-to-treat (ITT) population: all subjects who received a patch application and had at least one postoperative baseline skin reaction evaluation. The ITT population was used to support the analysis of the primary study endpoints based on the PP population.
- Safety population: all subjects who received a patch application. This population was used to evaluate the safety endpoints.

(3) Statistical Methods
For the primary analysis on diagnostic performance, the frequencies and corresponding confidence intervals of positive reactions based on investigator's determination of positive reactions, and of negative, irritant and doubtful reactions were tabulated for the 11 investigational allergens. Data from the 4 participating centers were pooled. In this clinical trial, a positive disease status ("sensitive") was assigned based on a positive reaction as indicated by the investigator's determination to the T.R.U.E. TEST allergens.

(4) Missing data handling

Subjects with missing data due to lost patch panels or failure to complete the study were not included for the analysis by PP population.

6.1.10 Study Population and Disposition

6.1.10.1 Populations Enrolled/Analyzed

Overall, 116 subjects were enrolled in the study at four investigational sites. Among these subjects, 111 subjects were included in the per-protocol population, and the 113 subjects were included in the intent-to-treat population. The efficacy analyses were based on the 111 subjects in the per-protocol population supported by analyses from the intent-to-treat population. It is noted that data from 54 subjects were included in the analysis for allergens neomycin sulfate, potassium dichromate, FM, and ethylenediamine dihydrochloride analysis.

6.1.10.1.1 Demographics

The mean (standard deviation) of age was 12.6 (3.2) years in the population of enrolled subjects, and were similar for the other populations. Among the enrolled subjects, 12 subjects (10.3%) were 6 to 8 years of age, 40 subjects (34.5%) were 9 to 12 years of age, and 64 subjects (55.2%) were 13 to 17 years of age. The percentage of all enrolled females was 69%. For all enrolled subjects, the percentages of White, African American, Asian, American Indians or Alaska Natives, and Others were 66.4%, 6.0%, 11.2%, 0.9%, and 15.5%, respectively. Hispanics or Latino enrolled was 37.9%. These percentages were similar across all three populations.

6.1.10.1.2 Medical/Behavioral Characterization of the Enrolled Population

N/A

6.1.10.1.3 Subject Disposition

Overall, 116 subjects were enrolled in the study. Five patients were discontinued. One subject did not have all panels applied (Subject 211); one subject failed to return for the day 21 visit and was discontinued based on the investigator's decision; and three subjects were dropped related to panels that fell off or were removed before 48 hours.

6.1.11 Efficacy Analyses

6.1.11.1 Analyses of Primary Endpoint(s)

The primary efficacy variables included occurrence of positive skin reactions to each of the 11 investigational T.R.U.E. TEST allergens. The patch test sites were evaluated at Visits 3 (after patch removal) through 6. The skin reactions were scored as follows: negative (-), irritant reaction (IR), doubtful reaction (?), weak positive (1+), strong positive (2+), or extreme positive (3+). The definitions of each score, along with representative depictions of the corresponding reactions, are presented in Figure 1. For the purpose of analysis, the applicant defined a positive reaction as a positive response (weak, strong, or extreme), as determined by the investigator, at a minimum of one Visit (Visit 3 through Visit 6).

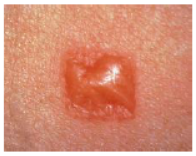
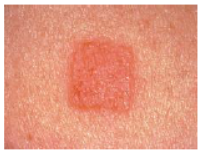
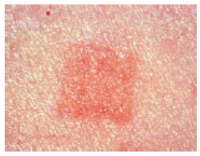
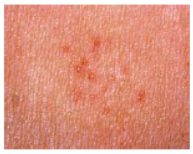
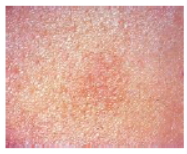
Extreme positive (+++)	Strong positive (++)	Weak positive (+)	Irritant (IR)	Doubtful (?)
				
Coalescing vesicles, bullous reaction	Erythema, papules, infiltration, discrete vesicles	Erythema, infiltration, discrete papules	Discrete, patchy, follicular, or homogenous erythema with no infiltration	Faint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

Figure 1 Skin reaction scoring guidelines
Source: Figure 9.5.1.1-1 in the final study report of study PREA II

Based on the investigator's determination of positive reactions (Table 1), the analysis based on the Per-Protocol population showed that the frequency of positive reactions was 27% for gold sodium thiosulfate (GST), 17.1% for bronopol, 12.6% for bacitracin, and 7.2% for parthenolide. The frequency of positive reactions was 3.8% (2 subjects each) for neomycin, sulfate, potassium dichromate, and FM; 3.6% (4 subjects) for DB 106; 1.8% (2 subjects) for H-17-B; and 0.9% (1 subject) for MDBGN. No positive reactions were associated with ethylenediamine dihydrochloride. The ITT analysis produced similar results.

Table 1: Frequency of Positive Reactions by Investigator Determination (Per Protocol Population)

				Negative			Positive		
Panel	**Position**	**Allergens**	**Total N**	**n (%)**	**95% Lower CL**	**95% Upper CL**	**n (%)**	**95% Lower CL**	**95% Upper CL**
1.3	3	Neomycin sulfate	53	51 (96.23%)	87.02	99.54	2 (3.77%)	0.46	12.98
	4	Potassium dichromate	53	51 (96.23%)	87.02	99.54	2 (3.77%)	0.46	12.98
	6	Fragrance Mix	53	51 (96.23%)	87.02	99.54	2 (3.77%)	0.46	12.98
	11	Ethylenediamine Dihydrochloride	53	53 (100.00%)	93.28	100.00	0 (0.0%)	0	6.72
2.2	19	Methyldibromo Glutaronitrile (MDBGN)	111	110 (99.10%)	95.08	99.98	1 (0.90%)	0.02	4.96
3.2	28	Gold Sodium Thiosulfate (GST)	111	81 (72.97%)	63.72	80.96	30 (27.03%)	19.22	36.59
	31	Hydrocortisone-17-Butyrate (H-17-B)	111	109 (98.20%)	93.64	99.78	2 (1.80%)	0.22	6.41
	33	Bacitracin	111	97 (87.39%)	79.74	92.93	14 (12.61%)	7.14	20.43
	34	Parthenolide	111	103 (92.79%)	86.29	96.84	8 (7.21%)	3.19	13.83

				Negative			Positive		
Panel	**Position**	**Allergens**	**Total N**	**n (%)**	**95% Lower CL**	**95% Upper CL**	**n (%)**	**95% Lower CL**	**95% Upper CL**
	35	Disperse Blue 106 (DB106)	111	107 (96.40%)	91.03	99.01	4 (3.60%)	1.00	9.05
	36	2-Bromo-2-nitropropane-1,3-diol (Bronopol)	111	92 (82.88%)	74.57	89.37	19 (17.12%)	10.73	25.65

Negative: No skin reaction scores (1+, 2+ or 3+) have been assigned to the allergen under review during any of the reaction assessment visits, (Visits 3, 4, 5 or 6)
Positive: The subject has exhibited a skin reaction (score of 1+, 2+ or 3+) during at least one of the reaction assessment visits (Visits 3, 4, 5 or 6)
Source: Table 11.1.1.1-1 in the final study report

Reviewer Comments*: My analysis showed similar results. The primary efficacy analysis evaluated the diagnostic performance of the T.R.U.E. Test by measuring proportions of subjects showing positive or negative reaction to the individual allergens. This study was not designed to evaluate sensitivity or specificity or agreements on positives and negatives against a reference. Therefore, the traditional diagnostic performance parameters, such as sensitivity, specificity, positive predictive value, and negative predictive value, cannot be obtained from this study. The applicant explained that the true "disease" status (ACD to a specific allergen) is rarely known definitively, and patients may be diagnosed based on clinical findings that may be discordant and change over time. In addition, it appears that there is no gold standard in this area. The reviewer defers to the medical officer for consideration of the totality of the evidence.*

6.1.11.2Analyses of Secondary Endpoints

This study has no secondary efficacy endpoints.

6.1.11.3 Subpopulation Analyses

The applicant conducted subgroup analysis on frequency of positive reactions, using the PP population, for subjects by age category (children 6-8, 9-12, and 13-17 years of age), gender, and race (Caucasian and non-Caucasian). The applicant observed some differences in frequency of positives among the demographic subgroups. The results may not be conclusive or interpretable, due to limited and sometimes unbalanced numbers of subjects in the subgroups.

6.1.11.4 Dropouts and/or Discontinuations

Five patients were discontinued. Please refer to section 6.1.10.1.3.

6.1.11.5 Exploratory and Post Hoc Analyses

N/A

6.1.12 Safety Analyses

Of the 116 subjects enrolled in the study who were exposed to the investigational allergens, 48 events occurred in 40 subjects (34.5%). All but one of these events were mild to moderate in severity and non-serious. The one subject with a serious and severe

AE was considered by the investigator as unrelated to the panel application. Among the AEs, eleven events (22.9%) were considered definitely related to panel application, but the symptoms are commonly related to patch testing. All but three AEs had resolved by the end of the study, and no subject was discontinued from the study due to an AE.

The majority of subjects experienced no or weak tape-induced irritation to the 3 investigational panels (Panel 1.3, 92.6%; Panel 2.2, 93%; Panel 3.2, 88.6%). Twelve late reactions were observed at Visit 5. All but one late reaction had resolved by the end of the study. Also, 59 persistent reactions occurred in association with 8 allergens.

The overall proportions of subjects with an AE were similar across age groups. Numerically higher proportions of subjects in the two older age groups (20.0% for 9-12 years and 23.4% for 13-17 years) had moderate AEs compared to the youngest group (8.3% for 6-8 years). The overall proportions of subjects with AEs were similar between genders as well (females, 35%; males, 33.3%), while a lower proportion of females tended to have mild AEs (10 subjects, 12.5%) and higher proportion had moderate AEs (20 subjects, 25%) compared to males (mild AEs: 8 subjects, 22.3%; moderate AEs: 4 subjects, 11.1%). The applicant also observed differences in the proportions of subjects with AEs across race groups. Note that these subgroup results may not be conclusive or interpretable due to limited and sometimes unbalanced numbers of subjects in the demographic subgroups.

6.1.12.1 Methods

Evaluation of the safety endpoints was descriptive in nature.

6.1.12.3 Deaths

No deaths were reported in the study.

6.1.12.4 Nonfatal Serious Adverse Events

One subject with a serious and severe AE developed appendicitis, which was considered to be unrelated to panel application.

6.1.12.5 Adverse Events of Special Interest (AESI)

N/A

6.1.12.6 Clinical Test Results

N/A

6.1.12.7 Dropouts and/or Discontinuations

No subject was discontinued from the study due to an AE.

6.2 Protocol Mekos 07 29P1/2/3 401: Clinical Evaluation of T.R.U.E. TEST® Panel 1.1, 2.1, and 3.1 in Children and Adolescents

6.2.1 Objectives

To evaluate the diagnostic performance and safety of Thin-layer Rapid Use Epicutaneous (T.R.U.E.) Test Panels 1.1, 2.1, and 3.1 in children and adolescent subjects (6-18 years of age) with suspected allergic contact dermatitis, based on symptoms and clinical history.

6.2.2 Design Overview

This was an open label study designed to evaluate the diagnostic performance and safety of 28 allergens in T.R.U.E. TEST Panels 1.1, 2.1, and 3.1 in pediatric subjects (6-18 years of age, inclusive) with suspected allergic contact dermatitis.

On day 0 (Visit 1), subjects had each of the 3 T.R.U.E. TEST patches applied to their back or upper arm. The T.R.U.E Test patches were removed 2 days later at Visit 2. During this visit, the integrity of the test panels was assessed and, after allowing the skin to rest for 20 minutes, all test site skin reactions and any instances of tape irritation were evaluated. Evaluations of test site skin reactions were conducted 3 days (Visit 3), 7 days (Visit 4), and 3 weeks (Visit 5) after the initial patch applications. Adverse events (AEs) and serious AEs were documented at Visits 2 through 5 and, at Visit 5, late and/or persistent skin reactions were recorded.

6.2.3 Population

The study population included pediatric subjects (6-18 years of age, inclusive) with suspected allergic contact dermatitis.

6.2.4 Study Treatments or Agents Mandated by the Protocol

- T.R.U.E. TEST Panel 1.1 (BLA #103738, IND# 2466; U.S. License # 1623; NDC 67334-0457-*1)
- T.R.U.E. TEST Panel 2.1 (BLA #103738, IND# 2466; U.S. License # 1623; NDC 67334-0457-*1)
- T.R.U.E. TEST Panel 3.1 (BLA# 103738-5019/5027)

6.2.6 Sites and Centers

This study was conducted at one investigational center in the U.S.

6.2.7 Surveillance/Monitoring

N/A

6.2.8 Endpoints

Primary endpoints
The diagnostic performance of each of the T.R.U.E. TEST Panel 1.1, 2.1, and 3.1 allergens based on frequency and characterization of the reactions to each allergen.

Secondary Endpoints

The safety of the T.R.U.E. TEST Panel 1.1, 2.1, and 3.1 allergens, including:

- The frequency and characterization of late and/or persistent reactions, tape-induced irritation at each test site upon patch removal, incomplete panel adhesion, and subject-reported sensations of itching or burning during the test period
- The frequency of AEs and serious AEs

6.2.9 Statistical Considerations & Statistical Analysis Plan

(1) Sample size

The applicant proposed a sample size of 100 based on consideration of safety assessment.

(2) Definitions of analysis populations

The efficacy and safety analyses were conducted using the entire study population (i.e., all enrolled subjects).

(3) Statistical Methods

The frequency and 95% confidence intervals (CIs) for positive, negative, irritant, and doubtful reactions were calculated.

(4) Missing data handling

No imputations for missing data were performed.

6.2.10 Study Population and Disposition

6.2.10.1 Populations Enrolled/Analyzed

All analyses were conducted using the entire study population.

6.2.10.1.1 Demographics

The mean (standard deviation) age of the enrolled subjects was 11.6 (3.61) years. The proportion of subjects who were 6 to 8 years of age, 9 to 12 years of age, and 13 to 18 years of age was 27.5%, 28.4%, and 44.1%, respectively. The percentage of enrolled female subjects was 52.0%. The percentages of racial groups in the study population were as follows: Caucasian 39.2%, Hispanic 31.4%, Asian 12.7%, African American 6.9%, and Other 9.8%.

6.2.10.1.2 Medical/Behavioral Characterization of the Enrolled Population

N/A

6.2.10.1.3 Subject Disposition

Overall, 102 subjects were enrolled at a single investigational center in the US. Two subjects discontinued early from the study; 1 subject was lost to follow-up, and the other subject withdrew consent.

6.2.11 Efficacy Analyses

6.2.11.1 Analyses of Primary Endpoint(s)

The efficacy variable was the frequency of test site skin reactions associated with each of the allergens/controls contained in T.R.U.E. TEST Panels 1.1, 2.1, and 3.1. For each allergen, the number and frequency of subjects with positive, negative, irritant, and doubtful reactions were reported separately at Visit 3 and Visit 4 (Table 2 and Table 3).

At Visit 3, the most frequent positive reactions (i.e., positive reactions observed in more than 10% of the subjects) were associated with nickel sulfate (29 subjects [28.7%]), followed by wool alcohols and *p-tert*-butylphenol formaldehyde resin (16 subjects [15.8%] for each allergen), fragrance mix (13 subjects [12.9%]), and cobalt dichloride (12 subjects [11.9%]). At Visit 4, the proportions of subjects with positive reactions to each of the allergens were similar to or lower than those observed at Visit 3. Positive reactions that occurred in more than 10% of the subjects included only those associated with nickel sulfate (17 subjects [17.7%]). No subject at Visit 3 or Visit 4 experienced a positive reaction to caine mix or the negative control. Additionally, at Visit 4, no subject experienced a positive reaction to black rubber mix, *p*-phenylenediamine, or quinoline mix.

The applicant also evaluated the frequencies of cumulative positive reactions (i.e., positive reactions that were observed either at Visit 3 or Visit 4) to each allergen. Trends were similar to those observed in the frequencies of positive reactions at Visit 3 for all subjects (Table 4). The applicant included the cumulative positive reaction results in the package insert as the efficacy results from study 1.

Table 2 Frequency and 95% CI of Positive, Negative, Irritant, and Doubtful Reactions at Visit 3 (All Subjects)

	N	Positive Reaction (+, ++, +++)	Negative Reaction (Neg)	Irritant Reaction (IR)	Doubtful Reaction (?/+)
Panel 1.1 Allergens					
Nickel sulfate, 0.20 mg/cm^2	101	29 (28.7%) (20.1%, 38.6%)	66 (65.3%) (55.2%, 74.5%)	1 (1.0%) (0.0%, 5.4%)	5 (5.0%) (1.6%, 11.2%)
Wool alcohols, 1.00 mg/cm^2	101	16 (15.8%) (9.3%, 24.4%)	84 (83.2%) (74.4%, 89.9%)	0 (0.0%) (0.0%, 3.6%)	1 (1.0%) (0.0%, 5.4%)
Neomycin sulfate, 0.23 mg/cm^2	101	7 (6.9%) (2.8%, 13.8%)	94 (93.1%) (86.2%, 97.2%)	0 (0.0%) (0.0%, 3.6%)	0 (0.0%) (0.0%, 3.6%)
Potassium dichromate, 0.023 mg/cm^2	101	9 (8.9%) (4.2%, 16.2%)	90 (89.1%) (81.3%, 94.4%)	2 (2.0%) (0.2%, 7.0%)	0 (0.0%) (0.0%, 3.6%)
Caine mix, 0.63 mg/cm^2	101	0 (0.0%) (0.0%, 3.6%)	101 (100.0%) (96.4%, 100.0%)	0 (0.0%) (0.0%, 3.6%)	0 (0.0%) (0.0%, 3.6%)
Fragrance mix, 0.43 mg/cm^2	101	13 (12.9%) (7.0%, 21.0%)	88 (87.1%) (79.0%, 93.0%)	0 (0.0%) (0.0%, 3.6%)	0 (0.0%) (0.0%, 3.6%)
Colophony, 1.20 mg/cm^2	101	9 (8.9%) (4.2%, 16.2%)	91 (90.1%) (82.5%, 95.1%)	0 (0.0%) (0.0%, 3.6%)	1 (1.0%) (0.0%, 5.4%)

	N	Positive Reaction (+, ++, +++)	Negative Reaction (Neg)	Irritant Reaction (IR)	Doubtful Reaction (?/+)
Paraben mix, 1.00 mg/cm^2	101	2 (2.0%) (0.2%, 7.0%)	99 (98.0%) (93.0%, 99.8%)	0 (0.0%) (0.0%, 3.6%)	0 (0.0%) (0.0%, 3.6%)
Balsam of Peru, 0.80 mg/cm^2	101	10 (9.9%) (4.9%, 17.5%)	88 (87.1%) (79.0%, 93.0%)	1 (1.0%) (0.0%, 5.4%)	2 (2.0%) (0.2%, 7.0%)
Ethylenediamine dihydrochloride, 0.050 mg/cm^2	101	6 (5.9%) (2.2%, 12.5%)	95 (94.1%) (87.5%, 97.8%)	0 (0.0%) (0.0%, 3.6%)	0 (0.0%) (0.0%, 3.6%)
Cobalt dichloride, 0.020 mg/cm^2	101	12 (11.9%) (6.3%, 19.8%)	88 (87.1%) (79.0%, 93.0%)	1 (1.0%) (0.0%, 5.4%)	0 (0.0%) (0.0%, 3.6%)
Negative control	101	0 (0.0%) (0.0%, 3.6%)	101 (100.0%) (96.4%, 100.0%)	0 (0.0%) (0.0%, 3.6%)	0 (0.0%) (0.0%, 3.6%)
Panel 2.1 Allergens					
p-tert-Butylphenol formaldehyde resin, 0.045 mg/cm^2	101	16 (15.8%) (9.3%, 24.4%)	84 (83.2%) (74.4%, 89.9%)	0 (0.0%) (0.0%, 3.6%)	1 (1.0%) (0.0%, 5.4%)
Epoxy resin, 0.050 mg/cm^2	101	3 (3.0%) (0.6%, 8.4%)	96 (95.0%) (88.8%, 98.4%)	0 (0.0%) (0.0%, 3.6%)	2 (2.0%) (0.2%, 7.0%)
Carba mix, 0.25 mg/cm^2	101	7 (6.9%) (2.8%, 13.8%)	93 (92.1%) (85.0%, 96.5%)	0 (0.0%) (0.0%, 3.6%)	1 (1.0%) (0.0%, 5.4%)
Black rubber mix, 0.075 mg/cm^2	101	2 (2.0%) (0.2%, 7.0%)	97 (96.0%) (90.2%, 98.9%)	0 (0.0%) (0.0%, 3.6%)	2 (2.0%) (0.2%, 7.0%)
Cl+Me-Isothiazolinone, 0.0040 mg/cm^2	101	4 (4.0%) (1.1%, 9.8%)	96 (95.0%) (88.8%, 98.4%)	0 (0.0%) (0.0%, 3.6%)	1 (1.0%) (0.0%, 5.4%)
Quaternium-15, 0.10 mg/cm^2	101	3 (3.0%) (0.6%, 8.4%)	96 (95.0%) (88.8%, 98.4%)	0 (0.0%) (0.0%, 3.6%)	2 (2.0%) (0.2%, 7.0%)
Mercaptobenzothiazole, 0.0075 mg/cm^2	101	2 (2.0%) (0.2%, 7.0%)	99 (98.0%) (93.0%, 99.8%)	0 (0.0%) (0.0%, 3.6%)	0 (0.0%) (0.0%, 3.6%)
p-Phenylenediamine, 0.090 mg/cm^2	101	2 (2.0%) (0.2%, 7.0%)	99 (98.0%) (93.0%, 99.8%)	0 (0.0%) (0.0%, 3.6%)	0 (0.0%) (0.0%, 3.6%)
Formaldehyde, 0.18 mg/cm^2	101	5 (5.0%) (1.6%, 11.2%)	91 (90.1%) (82.5%, 95.1%)	0 (0.0%) (0.0%, 3.6%)	5 (5.0%) (1.6%, 11.2%)
Mercapto mix, 0.075 mg/cm^2	101	2 (2.0%) (0.2%, 7.0%)	99 (98.0%) (93.0%, 99.8%)	0 (0.0%) (0.0%, 3.6%)	0 (0.0%) (0.0%, 3.6%)
Thimerosal, 0.0080 mg/cm^2	101	4 (4.0%) (1.1%, 9.8%)	96 (95.0%) (88.8%, 98.4%)	1 (1.0%) (0.0%, 5.4%)	0 (0.0%) (0.0%, 3.6%)
Thiuram mix, 0.025 mg/cm^2	101	6 (5.9%) (2.2%, 12.5%)	92 (91.1%) (83.8%, 95.8%)	1 (1.0%) (0.0%, 5.4%)	2 (2.0%) (0.2%, 7.0%)
Panel 3.1 Allergens					
Diazolidinyl urea, 0.55 mg/cm^2	101	4 (4.0%) (1.1%, 9.8%)	95 (94.1%) (87.5%, 97.8%)	0 (0.0%) (0.0%, 3.6%)	2 (2.0%) (0.2%, 7.0%)
Imidazolidinyl urea, 0.60 mg/cm^2	101	1 (1.0%) (0.0%, 5.4%)	97 (96.0%) (90.2%, 98.9%)	1 (1.0%) (0.0%, 5.4%)	2 (2.0%) (0.2%, 7.0%)
Budesonide, 0.0010 mg/cm^2	101	1 (1.0%) (0.0%, 5.4%)	100 (99.0%) (94.6%, 100.0%)	0 (0.0%) (0.0%, 3.6%)	0 (0.0%) (0.0%, 3.6%)

	N	Positive Reaction (+, ++, +++)	Negative Reaction (Neg)	Irritant Reaction (IR)	Doubtful Reaction (?/+)
Tixocortol-21-pivalate, 0.0030 mg/cm^2	101	8 (7.9%) (3.5%, 15.0%)	93 (92.1%) (85.0%, 96.5%)	0 (0.0%) (0.0%, 3.6%)	0 (0.0%) (0.0%, 3.6%)
Quinoline mix, 0.19 mg/cm^2	101	1 (1.0%) (0.0%, 5.4%)	100 (99.0%) (94.6%, 100.0%)	0 (0.0%) (0.0%, 3.6%)	0 (0.0%) (0.0%, 3.6%)

Source: Table 11-3 from the study 1 CSR

Table 3 Frequency and 95% CI of Positive, Negative, Irritant, and Doubtful Reactions at Visit 4 (All Subjects)

	N	Positive Reaction (+,++,+++)	Negative Reaction (Neg)	Irritant Reaction (IR)	Doubtful Reaction (?/+)
Panel 1.1 Allergens					
Nickel sulfate, 0.20 mg/cm^2	96	17 (17.7%) (10.7%, 26.8%)	75 (78.1%) (68.5%, 85.9%)	0 (0.0%) (0.0%, 3.8%)	4 (4.2%) (1.1%, 10.3%)
Wool alcohols, 1.00 mg/cm^2	96	6 (6.3%) (2.3%, 13.1%)	85 (88.5%) (80.4%, 94.1%)	0 (0.0%) (0.0%, 3.8%)	5 (5.2%) (1.7%, 11.7%)
Neomycin sulfate, 0.23 mg/cm^2	96	6 (6.3%) (2.3%, 13.1%)	88 (91.7%) (84.2%, 96.3%)	0 (0.0%) (0.0%, 3.8%)	2 (2.1%) (0.3%, 7.3%)
Potassium dichromate, 0.023 mg/cm^2	96	3 (3.1%) (0.6%, 8.9%)	91 (94.8%) (88.3%, 98.3%)	0 (0.0%) (0.0%, 3.8%)	2 (2.1%) (0.3%, 7.3%)
Caine mix, 0.63 mg/cm^2	96	0 (0.0%) (0.0%, 3.8%)	96 (100.0%) (96.2%, 100.0%)	0 (0.0%) (0.0%, 3.8%)	0 (0.0%) (0.0%, 3.8%)
Fragrance mix, 0.43 mg/cm^2	96	5 (5.2%) (1.7%, 11.7%)	90 (93.8%) (86.9%, 97.7%)	0 (0.0%) (0.0%, 3.8%)	1 (1.0%) (0.0%, 5.7%)
Colophony, 1.20 mg/cm^2	96	4 (4.2%) (1.1%, 10.3%)	90 (93.8%) (86.9%, 97.7%)	0 (0.0%) (0.0%, 3.8%)	2 (2.1%) (0.3%, 7.3%)
Paraben mix, 1.00 mg/cm^2	96	1 (1.0%) (0.0%, 5.7%)	94 (97.9%) (92.7%, 99.7%)	0 (0.0%) (0.0%, 3.8%)	1 (1.0%) (0.0%, 5.7%)
Balsam of Peru, 0.80 mg/cm^2	96	2 (2.1%) (0.3%, 7.3%)	92 (95.8%) (89.7%, 98.9%)	0 (0.0%) (0.0%, 3.8%)	2 (2.1%) (0.3%, 7.3%)
Ethylenediamine dihydrochloride, 0.050 mg/cm^2	96	3 (3.1%) (0.6%, 8.9%)	93 (96.9%) (91.1%, 99.4%)	0 (0.0%) (0.0%, 3.8%)	0 (0.0%) (0.0%, 3.8%)
Cobalt dichloride, 0.020 mg/cm^2	96	6 (6.3%) (2.3%, 13.1%)	88 (91.7%) (84.2%, 96.3%)	0 (0.0%) (0.0%, 3.8%)	2 (2.1%) (0.3%, 7.3%)
Negative control	96	0 (0.0%) (0.0%, 3.8%)	96 (100.0%) (96.2%, 100.0%)	0 (0.0%) (0.0%, 3.8%)	0 (0.0%) (0.0%, 3.8%)
Panel 2.1 Allergens					
p-tert-Butylphenol formaldehyde resin, 0.045 mg/cm^2	96	7 (7.3%) (3.0%, 14.4%)	87 (90.6%) (82.9%, 95.6%)	0 (0.0%) (0.0%, 3.8%)	2 (2.1%) (0.3%, 7.3%)
Epoxy resin, 0.050 mg/cm^2	96	2 (2.1%) (0.3%, 7.3%)	94 (97.9%) (92.7%, 99.7%)	0 (0.0%) (0.0%, 3.8%)	0 (0.0%) (0.0%, 3.8%)
Carba mix, 0.25 mg/cm^2	96	1 (1.0%) (0.0%, 5.7%)	95 (99.0%) (94.3%, 100.0%)	0 (0.0%) (0.0%, 3.8%)	0 (0.0%) (0.0%, 3.8%)

	N	Positive Reaction (+,++,+++)	Negative Reaction (Neg)	Irritant Reaction (IR)	Doubtful Reaction (?/+)
Black rubber mix, 0.075 mg/cm^2	96	0 (0.0%) (0.0%, 3.8%)	95 (99.0%) (94.3%, 100.0%)	0 (0.0%) (0.0%, 3.8%)	1 (1.0%) (0.0%, 5.7%)
Cl+Me-Isothiazolinone, 0.0040 mg/cm^2	96	3 (3.1%) (0.6%, 8.9%)	91 (94.8%) (88.3%, 98.3%)	0 (0.0%) (0.0%, 3.8%)	2 (2.1%) (0.3%, 7.3%)
Quaternium-15, 0.10 mg/cm^2	96	3 (3.1%) (0.6%, 8.9%)	93 (96.9%) (91.1%, 99.4%)	0 (0.0%) (0.0%, 3.8%)	0 (0.0%) (0.0%, 3.8%)
Mercaptobenzothiazole, 0.0075 mg/cm^2	96	1 (1.0%) (0.0%, 5.7%)	95 (99.0%) (94.3%, 100.0%)	0 (0.0%) (0.0%, 3.8%)	0 (0.0%) (0.0%, 3.8%)
p-Phenylenediamine, 0.090 mg/cm^2	96	0 (0.0%) (0.0%, 3.8%)	96 (100.0%) (96.2%, 100.0%)	0 (0.0%) (0.0%, 3.8%)	0 (0.0%) (0.0%, 3.8%)
Formaldehyde, 0.18 mg/cm^2	96	3 (3.1%) (0.6%, 8.9%)	91 (94.8%) (88.3%, 98.3%)	0 (0.0%) (0.0%, 3.8%)	2 (2.1%) (0.3%, 7.3%)
Mercapto mix, 0.075 mg/cm^2	96	1 (1.0%) (0.0%, 5.7%)	94 (97.9%) (92.7%, 99.7%)	0 (0.0%) (0.0%, 3.8%)	1 (1.0%) (0.0%, 5.7%)
Thimerosal, 0.0080 mg/cm^2	96	2 (2.1%) (0.3%, 7.3%)	94 (97.9%) (92.7%, 99.7%)	0 (0.0%) (0.0%, 3.8%)	0 (0.0%) (0.0%, 3.8%)
Thiuram mix, 0.025 mg/cm^2	96	1 (1.0%) (0.0%, 5.7%)	91 (94.8%) (88.3%, 98.3%)	0 (0.0%) (0.0%, 3.8%)	4 (4.2%) (1.1%, 10.3%)
Panel 3.1 Allergens					
Diazolidinyl urea, 0.55 mg/cm^2	96	2 (2.1%) (0.3%, 7.3%)	92 (95.8%) (89.7%, 98.9%)	0 (0.0%) (0.0%, 3.8%)	2 (2.1%) (0.3%, 7.3%)
Imidazolidinyl urea, 0.60 mg/cm^2	96	1 (1.0%) (0.0%, 5.7%)	94 (97.9%) (92.7%, 99.7%)	0 (0.0%) (0.0%, 3.8%)	1 (1.0%) (0.0%, 5.7%)
Budesonide, 0.0010 mg/cm^2	96	1 (1.0%) (0.0%, 5.7%)	95 (99.0%) (94.3%, 100.0%)	0 (0.0%) (0.0%, 3.8%)	0 (0.0%) (0.0%, 3.8%)
Tixocortol-21-pivalate, 0.0030 mg/cm^2	96	3 (3.1%) (0.6%, 8.9%)	91 (94.8%) (88.3%, 98.3%)	0 (0.0%) (0.0%, 3.8%)	2 (2.1%) (0.3%, 7.3%)
Quinoline mix, 0.19 mg/cm^2	96	0 (0.0%) (0.0%, 3.8%)	96 (100.0%) (96.2%, 100.0%)	0 (0.0%) (0.0%, 3.8%)	0 (0.0%) (0.0%, 3.8%)

Source: Table 11-4 from the study 1 CSR

Table 4 Frequency of Cumulative Positive Reactions (+, ++, or +++) at Visit 3 or Visit 4 (All Subjects with Reactions Recorded at Visit 3 or Visit 4)

Allergen	Frequency (95% CI)	Allergen	Frequency (95% CI)
T.R.U.E. Test Panel 1.1 Nickel sulfate	30 (29.7%) (21.0%, 39.6%)	Black rubber mix	2 (2.0%) (0.2%, 7.0%)
Wool alcohols	16 (15.8%) (9.3%, 24.4%)	Cl+Me-Isothiazolinone	4 (4.0%) (1.1%, 9.8%)
Neomycin sulfate	8 (7.9%) (3.5%, 15.0%)	Quaternium-15	4 (4.0%) (1.1%, 9.8%)
Potassium dichromate	9 (8.9%) (4.2%, 16.2%)	Mercaptobenzothiazole	2 (2.0%) (0.2%, 7.0%)
Caine mix	0 (0.0%) (0.0%, 3.6%)	*p*-Phenylenediamine	2 (2.0%) (0.2%, 7.0%)
Fragrance mix	13 (12.9%) (7.0%, 21.0%)	Formaldehyde	7 (6.9%) (2.8%, 13.8%)
Colophony	9 (8.9%) (4.2%, 16.2%)	Mercapto mix	2 (2.0%) (0.2%, 7.0%)
Paraben mix	2 (2.0%) (0.2%, 7.0%)	Thimerosal	4 (4.0%) (1.1%, 9.8%)
Negative control	0 (0.0%) (0.0%, 3.6%)	Thiuram mix	7 (6.9%) (2.8%, 13.8%)
Balsam of Peru	10 (9.9%) (4.9%, 17.5%)	**T.R.U.E. Test Panel 3.1** Diazolidinyl urea	5 (5.0%) (1.6%, 11.2%)
Ethylenediamine dihydrochloride	6 (5.9%) (2.2%, 12.5%)	Imidazolidinyl urea	2 (2.0%) (0.2%, 7.0%)
Cobalt dichloride	13 (12.9%) (7.0%, 21.0%)	Budesonide	1 (1.0%) (0.0%, 5.4%)
T.R.U.E. Test Panel 2.1 *p-tert*-Butylphenol formaldehyde resin	17 (16.8%) (10.1%, 25.6%)	Tixocortol-21-pivalate	8 (7.9%) (3.5%, 15.0%)
Epoxy resin	4 (4.0%) (1.1%, 9.8%)	Quinoline mix	1 (1.0%) (0.0%, 5.4%)
Carba mix	7 (6.9%) (2.8%, 13.8%)		

Source: Adapted from Table 14.2.5.1 in study 1 CSR

Reviewer Comments*: My calculations showed similar results. Similar to study PREA II, the primary efficacy analysis was mainly based on evaluation of frequency of positive reactions to the allergens. This study was not designed to obtain the traditional measures for diagnostic performance.*

6.2.11.2 Analyses of Secondary Endpoints

This study had no secondary efficacy endpoints.

6.2.11.3 Subpopulation Analyses

The applicant examined the efficacy results by age category (children [6-12 years of age] and adolescents [13-18 years of age]), sex, and race (Caucasian and non-Caucasian). The applicant observed some numerical differences in frequencies of positive reactions across the demographic subgroups. Additionally, positive reactions to some allergens were only observed, at low frequencies (0%-11.3%), in certain subgroups. Due to small sample

sizes, the frequencies may be more variable. Since the subgroup results would unlikely provide useful information, details are not described in this review.

6.2.11.4 Dropouts and/or Discontinuations

Please refer to section 6.2.10.1.3.

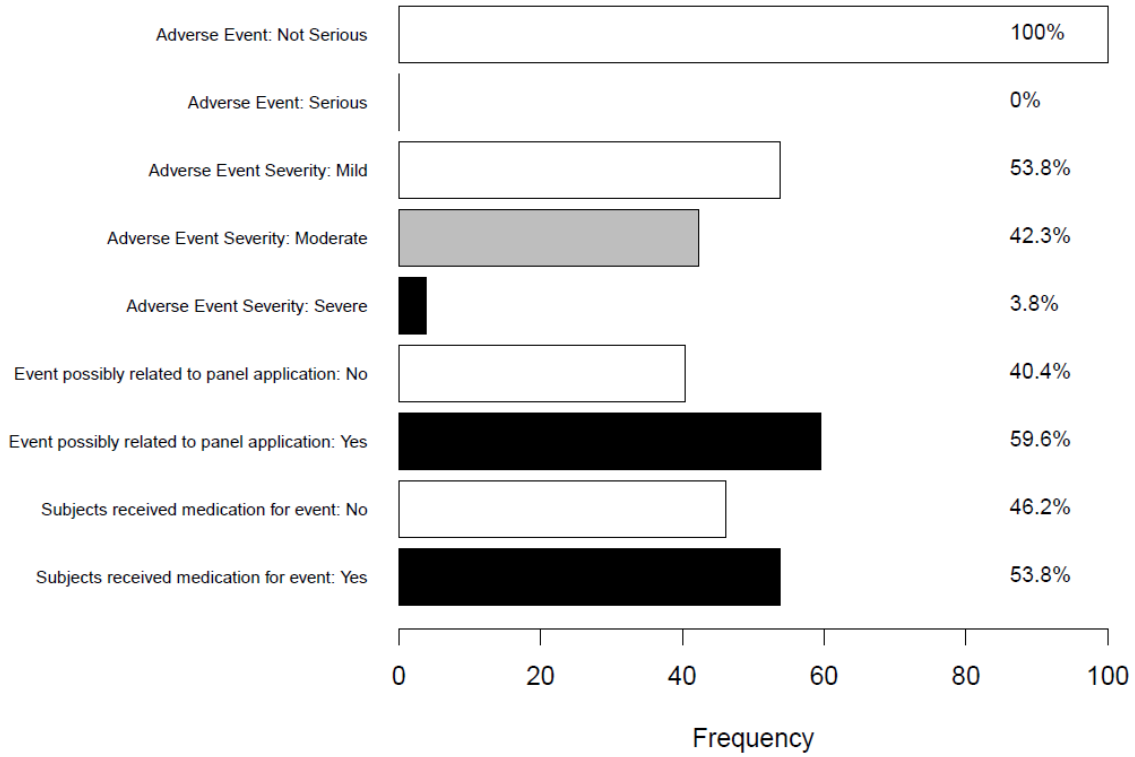
6.2.11.5 Exploratory and Post Hoc Analyses

N/A

6.2.12 Safety Analyses

Of the 102 subjects enrolled in the study, 35 (34.3%) subjects reported 52 AEs, all of which were non-serious. The majority (96.1%) of these reported events were mild to moderate in severity, while 2 AEs were severe. Overall, 59.6% of the events were considered possibly related to the panel application and 53.8% of the AEs necessitated the use of a concomitant medication (Figure 1).

Figure 1: Summary of Adverse Event Characteristics (All Subjects)



(Source: Generated by the reviewer based on data from Table 12-1 in study 1 CSR)

Of the 102 enrolled subjects, the proportions of subjects who had excellent adhesion of T.R.U.E. TEST panels 1.1, 2.1, and 3.1 were 71.0%, 72.0%, and 82.0%, respectively. Additionally, regardless of the T.R.U.E. TEST panel, approximately 80% of the subjects experienced either no or weak tape-induced irritation. However, there was some variability in the proportions of subjects who experienced itching and burning upon the removal of each of the T.R.U.E. TEST panels. For instance, greater proportions of

subjects experienced weak to strong itching and burning upon removal of T.R.U.E. TEST panels 1.1 and 2.1 than upon removal of T.R.U.E. TEST panel 3.1 (66.3%, 55.4%, and 39.6%, respectively).

The number and frequency of late skin reactions were evaluated at Visit 5 for all subjects. Two of the 101 enrolled subjects (2.0%) who attended Visit 5 had late skin reactions. It should be noted, however, that the skin reactions observed at Visit 5 for these 2 subjects were pre-existing. Evaluations of persistent skin reactions were conducted by evaluating the frequencies (by severity) of erythema, infiltration, hyperpigmentation, hypopigmentation, pruritus, and other reactions at Visit 5. Overall, among all subjects, reports of erythema, infiltration, hyperpigmentation, hypopigmentation, pruritus, and other reactions were few in number; specifically, 7 reactions were observed in 4 subjects. Additionally, all reported reactions were mild to moderate in severity and no subject experienced a severe persistent skin reaction of any type to any of the allergens.

6.2.12.1 Methods

Evaluation of the safety endpoints was descriptive in nature.

6.2.12.3 Deaths

No deaths were reported in the study.

6.2.12.4 Nonfatal Serious Adverse Events

No serious events occurred during the study.

6.2.12.5 Adverse Events of Special Interest (AESI)

N/A

6.2.12.6 Clinical Test Results

N/A

6.2.12.7 Dropouts and/or Discontinuations

No subject discontinued from the study due to an AE.

7. INTEGRATED OVERVIEW OF EFFICACY

N/A

8. INTEGRATED OVERVIEW OF SAFETY

N/A

9. ADDITIONAL STATISTICAL ISSUES

N/A

10. CONCLUSIONS

10.1 Statistical Issues and Collective Evidence

In both studies, the primary efficacy analyses evaluated diagnostic performance of the T.R.U.E. Test by measuring the proportion of subjects showing positive or negative reaction in response to the individual allergens. This study was not designed to obtain information about sensitivity or specificity or agreements on positives and negatives against a reference. Therefore, the traditional diagnostic performance measures such as sensitivity, specificity, positive predictive value, and negative predictive value, cannot be measured in these studies. The applicant explained that the true "disease" status (ACD to a specific allergen) is rarely known definitively, and patients may be diagnosed based on clinical findings that may be discordant and change over time. Additionally, this test is indicated for use as only an aid in the diagnosis of allergic contact dermatitis. I defer to the medical officer for consideration of the diagnostic performance of this test based on the totality of the evidence.

10.2 Conclusions and Recommendations

The studies included in this submission were open-label studies without pre-defined criteria for efficacy. Also, these studies were not designed to allow assessment of the traditional measures for diagnostic performance. Hence, the evidence of efficacy (diagnostic performance) provided by the two studies might not be conclusive from the statistical perspective. In the safety analyses, no unexpected safety trends were observed. I defer to the medical officer for consideration of adequacy of the evidence for efficacy based on the regulatory history of the product and the totality of the evidence.