Application Type	Original Application
STN	125579/0
CBER Received Date	August 25, 2015
PDUFA Goal Date	February 26, 2016
Division / Office	DVRPA/OVRR
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Review Completion Date / Stamped Date	
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Applicant	Smart Practice
Established Name	Thin-Layer Rapid Use Epicutaneous Patch Test
(Proposed) Trade Name	Rubber Panel T.R.U.E. TEST
Formulation(s), including Adjuvants, etc	Patch
Dosage Form(s) and Route(s) of Administration	One adhesive panel consisting of 5 allergen and allergen mix patches and a negative control.
Indication(s) and Intended Population(s)	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 5 substances included on the Rubber Panel T.R.U.E. Test.

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GLOSSARY

AE	Adverse Event
CR	Complete Response
CRF	Case Report Form
CSR	Clinical Study Report
GCP	Good Clinical Practice
ICDRG	International Contact Dermatitis Research Group
IEC	Independent Ethics Committee
IR	Irritant Reaction
IRB	Institutional Review Board
STD	Standard Deviation
T.R.U.E.	Thin-layer Rapid Use Epicutaneous
UV	Ultraviolet

1. Executive Summary

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. T.R.U.E. TEST has been evaluated in several large, multi-center clinical studies, and is a combined allergen and patch panel/chamber product currently approved for sale in the United States.

The T.R.U.E. TEST product consists of 3 panels (pieces of surgical tape [5.2 x 13.0 cm]), each containing polyester patches of approximately 0.81 cm^2. Panel 1.1 contains 11 allergen patches and a negative control; Panel 2.1 contains 12 allergen patches; and Panel 3.1 contains 5 allergen patches. Each 0.81 cm^2 patch contains the allergen or allergen mix in a dried, uniform gel coating on polyester sheeting.

The current study was designed to evaluate the diagnostic performance and safety of the T.R.U.E. TEST Panel 1.1, 2.1, and 3.1 in children and adolescents (6-18 years of age) who had suspected allergic contact dermatitis. Across these 3 patch tests, the subjects were exposed to 28 specific allergens that have been shown in previously conducted clinical studies in adults to be safe and effective when used as panels within the T.R.U.E. TEST patch. In this study, while no reference allergens were used, T.R.U.E. TEST Panel 1.1 contains a negative control.

The results of the study indicate that the allergens in T.R.U.E. TEST Panels 1.1, 2.1, and 3.1 are safe and effective when used for the diagnosis of allergic contact dermatitis in children and adolescents 6 to 18 years of age.

2. Clinical and Regulatory Background

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.

Allergic contact dermatitis is reported in both children and adults, with similar frequencies that range from 20% to over 50%. In particular, both adults and children commonly suffer from allergic reactions to nickel, thimerosal, Cl+Me-isothiazolinone, colophony, lanolin, cobalt, fragrance mix, and neomycin. Studies have also reported that female adolescents (like adult women) may be more likely to be diagnosed with contact allergies than their male counterparts, and in particular, are more likely to be diagnosed with contact allergies to nickel and fragrance mix.

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

T.R.U.E. TEST is a ready-to-use patch test designed for use by licensed physicians in the diagnosis of allergic contact dermatitis. This product, approved by the FDA on November 21, 1994, includes the three-panel T.R.U.E. TEST that contains a total of 28 separate allergens (Panel 1.1 with 11 allergen patches and a negative control; Panel 2.1 with 12 allergen patches; and Panel 3.1 with 5 allergen patches).

The current BLA is for a Rubber Panel T.R.U.E. TEST which contains 5 rubber-based allergen patches (black rubber mix, 0.075mg/cm^2; carba mix, 0.25 mg/cm^2; mercapto mix, 0.075 mg/cm^2; mercaptobenzothiazole, 0.075 mg/cm^2; and thiuram mix, 0.025 mg/cm^2), which are all included in the approved T.R.U.E TEST panels . The applicant has reconfigured these 5 rubber allergens into the Rubber Panel T.R.U.E. TEST for use in persons 6-17 years of age. Currently, there are no patch test products licensed by the FDA for persons younger than 18 years of age.

To support this BLA, the applicant submitted data from an open-label single-site Phase III trial of T.R.U.E. TEST that contains a total of 28 separate allergens or allergen mixes, as well as a negative control in three panels 1.1, 2.1, and 3.1. CBER agreed to consider data only relevant to the 5 rubber allergens contained within T.R.U.E TEST, which are the bases for the current BLA and the indication sought.

The BLA was originally submitted on January 5, 2006 under STN 103738/5031, and received Complete Response (CR) letters on June 30, 2006 and on February 12, 2007. It was assigned a new BLA number, STN 125579, when it was re-submitted on August 19, 2014. On January 12, 2015, CBER issued a complete response letter and stopped the review clock for the BLA due to insufficient information provided.

The applicant submitted a complete response to the CR letter, including the required datasets, on August 25, 2015.

3. SUBMISSION QUALITY AND GOOD CLINICAL PRACTICES

3.1 Submission Quality and Completeness

The submission was adequately organized for conducting a complete statistical review without unreasonable difficulty.

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

Data sources including all materials reviewed (applicant's study reports, data sets analyzed, and literature referenced) were provided electronically and are available in the EDR.

5.1 Review Strategy

The BLA is based on protocol Mekos 0729P1/2/3401, clinical evaluation of T.R.U.E. TEST® Panel 1.1, 2.1, and 3.1 in Children and Adolescents. Section 6 of this review discusses all the relevant statistical information from the study that reflects the indication sought by the applicant.

6. DISCUSSION OF INDIVIDUAL STUDIES/CLINICAL TRIALS:

6.1 Study Objectives

To evaluate the diagnostic performance and safety of 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 Overall Study Design and Plan

The study was an open label, prospective, single-center 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 (i.e., consecutive subjects).

On day 0 (Visit 1), all current dermatitis sites were examined and all female subjects 15 to 18 years of age (or with onset of menarche) underwent urine pregnancy tests. Subjects then 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. Subject reports of itching and/or burning at the test site locations were also recorded during the visit.

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. If necessary to verify any of the skin reactions, an additional evaluation (Visit 3b) was conducted 4 days after the initial patch application. 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. Throughout the study, photographs were taken to document the subject's expression of allergic contact dermatitis and specifically patch test reactions. The test sites and any areas of active dermatitis were photographed at Visit 1; all non-negative test site reactions were photographed at Visits 2 and 3; and any late and/or persistent skin reactions were photographed at Visit 5. Finally, all subjects exited the study at the completion of Visit 5, which was either conducted in person or over the telephone.

6.3 Study Population

The study population was planned to include approximately 100 pediatric subjects, 6 to 18 years of age, inclusive, who were in generally good health and had both symptoms and histories that were potentially consistent with allergic contact dermatitis (i.e., consecutive subjects). The enrollment was planned to include approximately 25 subjects aged 6 to 8 years, 25 subjects aged 9 to 12 years, and 50 subjects aged 13 to 18 years. In general, the enrollment also sought to include at least 50% (but not more than 65%) female subjects, as well as approximately 6% to 12% Hispanic, 5% to 10% African American, and 2% to 4% Asian subjects.

6.3.1 Inclusion and Exclusion Criteria

Inclusion Criteria

To be included in the study, all of the following criteria must have been met:

1. Subjects must have reported symptoms and/or a history potentially consistent with allergic contact dermatitis (i.e., subjects were visiting the clinic/physician to diagnose, treat, or resolve this condition).
2. All subjects must have been children or adolescents 6 to 18 years of age who were in general good health.
3. Adolescent females 15 years of age or older (or with menarche) must have consented to a urine pregnancy test; urine test results must have been negative for study inclusion.
4. Informed consent must have been signed and understood by each subject. If the subject was underage, informed consent must have been signed and understood by parent or legal guardian, consistent with all institutional, local, and national regulations.

Exclusion Criteria

To be included in the study, none of the following criteria could have been met:

1. Topical corticosteroid treatment during the 7 days prior to Visit 1 on or near the test area.
2. Systemic treatment with corticosteroids or other immunosuppressants during the 7 days prior to Visit 1.
3. Subjects who were receiving (or had received in the 21 days prior to Visit 1) other investigational drugs, treatments, or devices, and subjects who were participating in another clinical study.
4. Treatment with ultraviolet (UV) light (including tanning) during the 3 weeks prior to Visit 1.
5. Acute dermatitis outbreak or dermatitis on or near the test area on the back.
6. Subjects unable to comply with activity restrictions (e.g., protecting test panels from excess moisture due to showering or vigorous activity).
7. Subjects unable or unwilling to comply with multiple return visits.
8. Female subjects 15 years of age (or with onset of menarche) and older unable to consent to a urine pregnancy test, or those with a positive pregnancy test.

6.3.2 Removal of Subjects from Therapy or Assessment

Subjects who exited from the study before completing all regularly scheduled visits were considered to have discontinued from the study. If a subject discontinued, the investigator completed as much of the case report form (CRF) as possible. Subjects could have discontinued from the study at any time by choice or by investigator option for any reason related to their health or their ability to comply with the study.

In this study, subjects specifically could have been withdrawn if they missed 2 or more clinic visits; subjects would not necessarily have been discontinued solely for missing scheduled visits. Subjects also may have been withdrawn due to an overreaction to an allergen, which was defined as a response to an allergen patch that was greater than +++ (i.e., extreme positive). In this instance, the test panel would have been removed and the reactions would have been treated in accordance with standard medical practice.

Unacceptable AEs, such as the development of severe itching and burning sensations, dermatitis flare-ups, or other AEs could also have resulted in subject discontinuation.

6.4 Study Treatments Dose and Mode of Administration

6.4.1 Treatments Administered

The 3 T.R.U.E. TEST patches (T.R.U.E. TEST Panels 1.1, 2.1, and 3.1) were applied to the back or upper arm of each subject.
T.R.U.E. TEST Panel 1.1 consisted of the following allergens:

- nickel sulfate (0.20 mg/cm^2)
- wool alcohols (1.00 mg/cm^2)
- neomycin sulfate (0.23 mg/cm^2)
- potassium dichromate (0.023 mg/cm^2)
- caine mix (0.63 mg/cm^2)
- fragrance mix (0.43 mg/cm^2)
- colophony (1.20 mg/cm^2)
- paraben mix (1.00 mg/cm^2)
- balsam of Peru (0.80 mg/cm^2)
- ethylenediamine dihydrochloride (0.050 mg/cm^2)
- cobalt dichloride (0.020 mg/cm^2)
- negative control

T.R.U.E. TEST Panel 2.1 consisted of the following allergens:

- *p-tert*-butylphenol formaldehyde resin (0.045 mg/cm^2)
- epoxy resin (0.050 mg/cm^2)
- carba mix (0.25 mg/cm^2)
- black rubber mix (0.075 mg/cm^2)
- Cl+Me-isothiazolinone (0.0040 mg/cm^2)
- quaternium-15 (0.10 mg/cm^2)
- mercaptobenzothiazole (0.0075 mg/cm^2)
- *p*-phenylenediamine (mg/cm^2)
- formaldehyde (0.18 mg/cm^2)
- mercapto mix (0.075 mg/cm^2)
- thimerosal (mg/cm^2)
- thiuram mix (0.025 mg/cm^2)

T.R.U.E. TEST Panel 3.1 consisted of the following allergens:

- diazolidinyl urea (0.55 mg/cm^2)
- imidazolidinyl urea (0.60 mg/cm^2)
- budesonide (0.0010 mg/cm^2)
- tixocortol-21-pivalate (0.0030 mg/cm^2)
- quinoline mix (0.19 mg/cm^2)

The Rubber panel T.R.U.E TEST includes 5 separate substances or mixtures including chemical additives used to preserve, stabilize, and prevent rubber degradation. The panel is based upon knowledge of rubber manufacturing processes together with evaluations in exposed individuals with suspected allergic contact dermatitis (ACD) related to rubber. The 5 allergens and the negative control included in the rubber panel are the following:-

1. Negative control (uncoated (b) (4) polyester patch)
2. Carba mix
3. Black rubber mix
4. Mercaptobenzothiazole
5. Mercapto mix
6. Thiuram mix

All of these 5 allergens are included in panel 2.1 of the T.R.U.E TEST.

6.4.2 Identity of Investigational Product(s)

The T.R.U.E. TEST patches were packaged and labeled by Mekos Laboratories (ApS, Hillerod, Denmark). To protect against light and air, the patches were sealed in opaque, aluminum foil pouches. The products were labeled with allergen batch codes and expiration dates. Given that the 3 T.R.U.E. TEST patches used in this study are already licensed for sale in the US, they were not labeled as investigational.

6.4.3 Method of Assigning Subjects to Treatment Groups

This was an open label study in which all subjects had test allergens applied to their backs or upper arms at Visit 1 with T.R.U.E Test patches. All subjects received the same patch applications.

6.4.4 Selection of Doses in the Study

Allergic contact dermatitis is reported in both children and adults with similar frequencies that range from 20% to over 50%. The majority of patch test studies in children have been conducted almost exclusively in Europe using conventional patch test chambers and petrolatum-based allergens. Although previously there was some debate as to the appropriate concentrations of allergens to be used in children, more recently, there is general consensus that children may be exposed to the same allergen concentrations as adults. The current study, therefore, evaluated the diagnostic performance and safety of the T.R.U.E. TEST Panel 1.1, 2.1, and 3.1 in children and adolescents (6-18 years of age) who had suspected allergic contact dermatitis. These 3 T.R.U.E. TEST patches, which are available commercially within the US, contain 28 specific allergens that have been shown in previously conducted clinical studies to be safe and of diagnostic value in adult subjects.

6.6 Study Centers and Duration of Study

This study was conducted at one investigational center in the United States from December 9, 2008 (first subject enrolled) to October 27, 2009 (last subject exited).

6.8 Endpoints and Assessment Methods

6.8.1 Primary Efficacy Endpoints

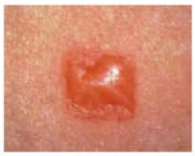
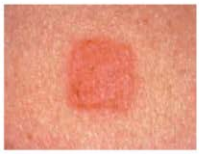
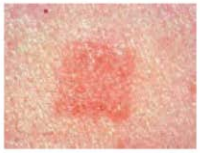
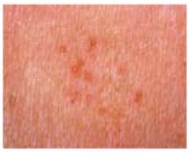
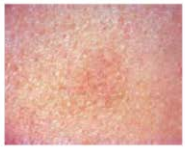
The efficacy primary endpoints collected in this study included skin sensitivity reactions to each of the allergens and the negative control contained in T.R.U.E. TEST Panels 1.1,

2.1, and 3.1. The skin sensitivity evaluations were conducted at Visits 2 (following patch removal) through Visit 5.

All skin reactions were evaluated using standard patch testing guidelines established by the ICDRG. These evaluations took into consideration the presence of erythema, infiltration, papules, discrete vesicles, and bullous reactions. Specifically, the skin reactions were scored as negative (neg), irritant reaction (IR), doubtful reaction (?/+), weak positive (+), strong positive (++), or extreme positive (+++).

Complete definitions of each score, along with representative depictions of the corresponding reactions, are presented in Figure 1.

Fig. 1: Skin reaction scoring Guidelines

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: Adapted from BLA 125579/0; clinical study report for study Mekos 0729P1/2/3 401

Skin reaction scores were used to calculate the frequency of positive reactions to each of the allergens and the frequency of late and persistent reactions, irritation, or other adverse reactions.

6.8.2 Secondary Endpoints (Safety Endpoints)

The safety secondary endpoints include late and/or persistent reactions (i.e., a positive response at Visit 5), tape-induced irritation at the test site upon patch removal, incomplete panel adhesion, and subject-reported sensations of itching or burning following patch removal. Additionally, AEs and serious AEs were assessed and recorded at each post-application study visit.

6.8.3 Measurement methods

The methods employed in this study to evaluate the three T.R.U.E. TEST panels were similar to those used in previous studies conducted with these same panels in adults. Because a negative control was applied to all subjects, the robustness of the evaluations was ensured. Further, the use of both objective (investigator-assessed) and subjective (subject-assessed) evaluations provided an accurate evaluation of the concordance and discordance between the test allergens and their references. Finally, all skin reactions were evaluated using standard patch testing guidelines established by the ICDRG.

6.9 Statistical Considerations & Statistical Analysis Plan

6.9.1 Primary (Efficacy) Analysis

The frequencies and 95% confidence intervals (CIs) for positive, negative, irritant, and doubtful reactions were tabulated for all subjects, as well as for subjects by age category (children [6-12 years of age] and adolescents [13-18 years of age]), sex, and race (Caucasian and non-Caucasian).

The frequency of positive responses among the 100 consecutive subjects enrolled in the study was expected to vary by allergen. In particular, the reaction frequencies for corticosteroids were expected to be very low, if present at all, while the reaction frequencies for nickel, fragrance mix, and rubber were expected to fall approximately within the range of 4% to 10%.

6.9.2 Safety Analyses

Frequency tabulations were presented for subjects who reported none, weak, moderate, and strong tape irritation, incomplete panel adhesion, and itching and burning upon patch test removal. The frequencies of late and persistent skin reactions were also tabulated. Finally, the overall frequencies of subjects who reported AEs, who reported severe AEs, and who reported serious AEs were tabulated; a listing of AEs by subject was also produced. Each of the secondary endpoint analyses was conducted using the population of all enrolled subjects, as well as the population of all enrolled subjects by age category, sex, and race.

6.9.3 Sample size determination

The prevalence of allergic contact dermatitis varies greatly (≤1%-10%) in consecutive subjects. Therefore, estimates of sample size and study power are based on overall AE rates, which are generally similar across populations and test allergens for which there are relevant historical data.

In the previous 8 clinical trials conducted with T.R.U.E. TEST Panels 1.1, 2.1, and 3.1, 155 AEs were reported in 858 subjects, yielding an overall AE rate of 18%. Further, approximately 25% to 31% of the subjects reported itching and burning at patch removal. The reported events were generally mild in severity, and usually included erythema, hyperpigmentation, and pruritus (each ~5%) after patch removal. Reports of urticaria, scarring, late reactions, and other severe AEs occurred infrequently (<1%).
For the evaluation of allergens in this study, it was expected that AE rates should not exceed those observed previously. Therefore, the presumed frequencies of AEs associated with T.R.U.E. TEST Panels 1.1, 2.1, and 3.1 allergens were compared to historical data. Specifically, given the null hypothesis that the rate of AEs in this study would be equal to that observed previously and the alternate hypothesis that the rate of AEs in this study would be greater than what was observed previously (H_o: $P_e = P_c$; H_a: $P_e > P_c$), a type I error (alpha) rate of 0.05, and power of 0.80, a sample size of 100 subjects would be sufficient to detect an increase in AEs from 7.6% to 15.6%.

6.9.4 Data Sets Analyzed

All computations and tabulations were conducted using the entire study population (i.e., all enrolled subjects).

6.9.5 Handling of Dropouts or Missing Data

No imputations were made for missing data

6.9.6 Multiple Comparisons (Multiplicity)

Not applicable.

6.10 Study Population and Disposition

6. 10.1 Disposition of Subjects

Overall, 102 subjects were enrolled at a single investigational center in the US. The first patch was applied to the first subject on December 9, 2008, and the last subject completed the study on October 27, 2009. Two subjects discontinued early from the study; one subject was lost to follow-up; and the other subject withdrew consent. No other subjects discontinued for any reason.

A complete tabulation of subject disposition is presented in Table 1.

Table 1: Summary of Subject Disposition

Number of subjects enrolled	102
Number of subjects who completed the study [a]	100 (98%)
Number of subjects who withdrew from the study [a]	2 (2%)
Primary reason for withdrawal: [b] Adverse event	0
Investigator's decision	0
Lost to follow-up	1 (50%)
Subject's wish	1 (50%)
Other	0

[a] Proportion based on number of subjects.
[b] Proportion based on number of withdrawn subjects
Source: Adapted from BLA 125579/0; clinical study report for study Mekos 0729P1/2/3 401.

6.10.2 Protocol Deviations

There were no protocol deviations reported in the study.

6.10.3 Demographic and Baseline Characteristics

Table 2 below presents a summary of subject demographic characteristics.

Table 2: Summary of Subject Demographic Characteristics

Age (Years)	
N	102
Mean	11.6
STD	3.61
Median	11.0
Min. to Max.	6 to 17
6 to 8 Years of Age	28 (27.5%)
9 to 12 Years of Age	29 (28.4%)
13 to 18 Years of Age	45 (44.1%)
Gender	
N	102
Male	49 (48%)
Female	53 (52%)
Race	
N	102
Caucasian	40 (39.2%)
Hispanic	32 (31.4%)
Asian	13 (12.7%)
African American	7 (6.9%)
Other*	10 (9.8%)

*Other includes one subject from each of the following: Caucasian Asian, Caucasian Hispanic, Indian American, Afghan, Hispanic and African American, South Asian (Indian), Middle Eastern – Kurdish, Iranian/Asian/Hispanic, Colombian/German/ Hispanic/ Caucasian, Hispanic/German/ Caucasian/Coloumbian.
Source: Adapted from BLA 125579/0; clinical study report for study Mekos 0729P1/2/3 401

The study succeeded in recruiting female subjects (52.0% of the population) and African American subjects (6.9% of the population) within the planned ranges. However, the proportions of subjects who were 6 to 8 years of age (27.5% of the population) and 9 to 12 years of age (28.4% of the population), were just above the planned ranges of 25% each, while the proportion of subjects who were 13 to 18 years of age (44.1% of the population) fell just below the planned range (50%). The proportions of Hispanic (31.4% of the population) and Asian (12.7% of the population) subjects were considerably higher than anticipated (6% to 12% for Hispanic and 2% to 4% for Asian).

The baseline characteristics of the subjects in each of the age, sex, and race categories were similar to one another and to the population of all enrolled subjects with respect to the type of dermatitis and the proportion of subjects who presented with dermatitis symptoms at screening (i.e., at least 95% of the subjects within each of the subgroups had allergic dermatitis and 97.5%-100.0% presented with dermatitis symptoms). However, greater proportions of subjects who were 6 to 12 years of age had dermatitis symptoms involving the trunk relative to subjects 13 to 18 years of age (50.9% versus 29.5%, respectively); more female subjects had dermatitis symptoms involving the face and/or scalp and/or neck than male subjects (57.7% versus 36.7%, respectively); and more male subjects had dermatitis symptoms involving the legs and/or feet than female subjects (81.6% versus 65.4%, respectively).

6.11 Efficacy Evaluation

6.11.1 Primary Efficacy Analysis Results

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 was tabulated at each visit. In order to identify general trends in the reaction frequencies, the outcomes for all enrolled subjects were reviewed separately at Visit 3 and Visit 4. (See table A.1- A.6 in the appendix).

Table 3 presents the number and frequency of subjects with positive, negative, irritant, and doubtful reactions at visit 3 specific for rubber panel T.R.U.E TEST

Table 3: Frequency and 95% CI of Positive, Negative, Irritant, and Doubtful Reactions at Visit 3 for Rubber panel T.R.U.E TEST

Allergen Type	N	Positive Reaction* (+,++,+++)	Negative Reaction (Neg)	Irritant Reaction (IR)	Doubtful Reaction (?/+)
Carba mix, 0.25 mg/cm^2 95% CI	101	7 (6.9%) (2.8%, 13.8%)	93 (92.1%) (85.0%, 96.5%)	0 (0.0%, 3.6%)	1(1.0%) (0.0%, 5.4%)
Black rubber mix, 0.075 mg/cm^2 95% CI	101	2 (2.0%) (0.2%, 7.0%)	97 (96.0%) (90.2%, 98.9%)	0 (0.0%, 3.6%)	2 (2.0%) (0.2%, 7.0%)
Mercaptobenzothiazole, 0.0075 mg/cm^2 95% CI	101	2 (2.0%) (0.2%, 7.0%)	99 (98.0%) (93.0%, 99.8%)	0 (0.0%, 3.6%)	0 (0.0%, 3.6%)
Mercapto mix, 0.075 mg/cm^2 95% CI	101	2 (2.0%) (0.2%, 7.0%)	99 (98.0%) (93.0%, 99.8%)	0 (0.0%, 3.6%)	0 (0.0%, 3.6%)
Thiuram mix, 0.025 mg/cm^2 95% CI	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%)

*Some subjects reacted to more than one allergen.

Source: Summarized from Table A.2 in the appendix of this review memo page 28

Positive reactions associated with the 5 allergens present in the rubber T.R.U.E TEST panel occurred in less than 7% of the subjects.

At Visit 4, the proportions of subjects with positive reactions to each of the 5 allergens present in the rubber T.R.U.E TEST were lower than those observed at Visit 3 (Table 4).

Table 4: Frequency and 95% CI of Positive, Negative, Irritant, and Doubtful Reactions at Visit 4 for Rubber panel T.R.U.E TEST

	N	Positive Reaction* (+,++,+++)	Negative Reaction (Neg)	Irritant Reaction (IR)	Doubtful Reaction (?/+)
Carba mix, 0.25 mg/cm^2 95% CI	96	1 (1%) (0.0%, 5.7%)	95 (99%) (94.3%, 100%)	0 (0.0%, 3.8%)	0 (0.0%, 3.8%)
Black rubber mix, 0.075 mg/cm^2 95% CI	96	0 (0.0%, 3.8%)	95 (99.0%) (94.3%, 100%)	0 (0.0%, 3.8%)	1 (1.0%) (0.0%, 5.7%)
Mercaptobenzothiazole, 0.0075 mg/cm^2 95% CI	96	1 (1.0%) (0.0%, 5.7%)	95 (99.0%) (94.3%, 100%)	0 (0.0%, 3.8%)	0 (0.0%, 3.8%)
Mercapto mix, 0.075 mg/cm^2 95% CI	96	1 (1.0%) (0.0%, 5.7%)	94 (97.9%) (92.7%, 99.7%)	0 (0.0%, 3.8%)	1 (1.0%) (0.0%, 5.7%)
Thiuram mix, 0.025 mg/cm^2 95% CI	96	1 (1.0%) (0.0%, 5.7%)	91 (94.8%) (88.3%, 98.3%)	0 (0.0%, 3.8%)	4 (4.2%) (1.1%, 10.3%)

*Some subjects reacted to more than one allergen

Source: Summarized from Table A.5 in the appendix of this review memo page 31

No subject at Visit 3 or Visit 4 experienced a positive reaction to the negative control. Additionally, at Visit 4, no subject experienced a positive reaction to black rubber mix. Across both Visits 3 and 4, doubtful reactions associated with any single allergen were observed in no more than 5 subjects.

Looking at all the 28 allergens at visit 3 (Table A.2 in the appendix), 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%]). Reactions observed in 5% to 10% of the subjects included those associated with balsam of Peru (10 subjects [9.9%]), potassium dichromate and colophony (9 subjects [8.9%] for each allergen), tixocortol-21-pivalate (8 subjects [7.9%]), neomycin sulfate and carba mix (7 subjects [6.9%] for each allergen), ethylenediamine dihydrochloride and thiuram mix (6 subjects [5.9%] for each allergen), and formaldehyde (5 subjects [5.0%]).

Positive reactions that occurred in more than 5% of the subjects were associated to allergens not included in the rubber panel T.R.U.E TEST. More than 10% of the subjects included only those associated with nickel sulfate (17 subjects [17.7%]), reactions observed in 5% to 10% of the subjects included those associated with *p-tert*-butylphenol formaldehyde resin (7 subjects [7.3%]), wool alcohols, neomycin sulfate, and cobalt dichloride (6 subjects [6.3%] for each allergen), and fragrance mix (5 subjects [5.2%]). Positive reactions associated with the remaining allergens occurred in less than 5% of the subjects.

Overall, no more than 2 subjects had irritant reactions associated with any single allergen at Visit 3, and no subject had irritant reactions to any of the allergens at Visit 4. In total, 8 irritant reactions associated with 7 allergens were observed in 7 subjects. This included reactions to nickel sulfate (observed in 1 subject), potassium dichromate (observed in 2

subjects), balsam of Peru (observed in 1 subject), cobalt dichloride (observed in 1 subject), thimerosal (observed in 1 subject), thiuram mix (observed in 1 subject), and imidazolidinyl urea (observed in 1 subject). The subject who reacted to cobalt dichloride was 1 of the 2 subjects who had an irritant reaction to potassium dichromate.

It should be noted that, while both the total number of reactions and the specific number of subjects who experienced reactions were low, of the 7 subjects who had irritant reactions, 5 were children (6-12 years of age) and 5 were female. All but 1 of the subjects was Caucasian.

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

6.11.8 Efficacy Subgroup Analysis

The frequencies of positive, negative, irritant, and doubtful reactions were tabulated for subjects by age category (children [6-12 years of age] and adolescents [13-18 years of age]), sex, and race (Caucasian and non-Caucasian).

Table 5 presents the distribution of the positive reactions to each of the rubber allergens by age categories (children (6-12 year old), and adolescents (13-18 year old), sex, and race (Caucasian and non-Caucasian) at visit 3.

Table 5: Frequency of Positive Reactions to the Rubber Panel T.R.U.E. TEST Allergens by Age, Sex, and Race in Children and Adolescents

Rubber Panel T.R.U.E. TEST Allergen	Total subjects (N=101)	Age		Sex		Race	
		6-12 years (N=56)	13-18 years (N=45)	Male (N=49)	Female (N=52)	Caucasian N=40)	Non-Caucasian (N=61)
Carba Mix	7	4	3	3	4	1	6
Thiuram Mix	6	1	5	4	2	4	2
Black Rubber mix	2	2	0	2	0	1	1
Mercaptobenzothiazole	2	1	1	1	1	1	1
Mercapto Mix	2	0	2	1	1	1	1

Source: Adapted from BLA 125579/0; clinical study report for study Mekos 0729P1/2/3 401

6.11.8.1 Frequency of Positive Reactions by Age

At Visit 3, a greater proportion of adolescents (subjects 13-18 years of age) compared to children (subjects 6-12 years of age) had positive reactions to thiuram mix (5 subjects [11.1%] versus 1 subject [1.8%], respectively). By contrast, positive reactions to black rubber mix were observed only among children and positive reactions to mercapto mix only among adolescents but at low frequencies (2 subjects for each allergen).

Although minor variations were noted, the frequencies of positive reactions to each of the remaining allergens were similar in children and adolescents at Visits 3 and 4.

The trends observed for the frequencies of cumulative positive reactions (i.e., positive reactions observed either at Visit 3 or Visit 4) were similar to those observed for the frequencies of positive reactions at Visit 3 among children and adolescents.

6.11.8.2 Frequency of Positive Reactions by Sex

At Visit 3, all the positive reactions to black rubber mix were observed only in male subjects (2 subjects [4.2%]).

At Visit 4, positive reactions to carba mix, mercaptobenzothiazole, mercapto mix, were observed only among female subjects (1-2 subjects [2.0%-4.0%] for each allergen). Positive reactions to thiuram mix were observed only in 1 male subject (2.2%).

The frequencies of positive reactions to the remaining allergens were similar in female and male subjects at Visits 3 and 4.

The trends observed for the frequencies of cumulative positive reactions (i.e., positive reactions observed either at Visit 3 or Visit 4) were similar to those observed for the frequencies of positive reactions at Visit 3 among female and male subjects.

6.11.8.3 Frequency of Positive Reactions by Race

Greater proportion of non-Caucasian subjects than Caucasian subjects had positive reactions to carba mix at Visit 3 (6 subjects versus 1 subject, respectively).

At Visit 4, positive reactions to carba mix and thiuram mix were observed only among non-Caucasian subjects (1-2 subjects [1.8%-3.5%] for each allergen). By contrast, positive reactions to mercaptobenzothiazole, mercapto mix, were observed only among Caucasian subjects (1-3 subjects [2.6%-7.7%] for each allergen).

Although minor variations were noted, the frequencies of positive reactions to each of the remaining allergens were similar in Caucasian and non-Caucasian subjects at both visits 3 and 4.

The trends observed in the frequencies of cumulative positive reactions (i.e., positive reactions observed either at Visit 3 or Visit 4) were similar to those observed in the frequencies of positive reactions at Visit 3 among Caucasian and non-Caucasian subjects.

6.11.9 Efficacy Conclusion

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. No other subjects discontinued for any reason.

The efficacy evaluations in this study showed:

- At Visit 3, 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%]). But none of these allergens are components of the rubber panel T.R.U.E TEST

- 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.
- No subject experienced a positive reaction to the negative control at either Visit 3 or Visit 4.
- No subject experienced a positive reaction to black rubber mix at Visit 4.
- No more than 2 subjects had irritant reactions associated with any single allergen at Visit 3, while no subject had irritant reactions to any of the allergens at Visit 4.
- Doubtful reactions associated with any single allergen were observed in no more than 5 subjects at either Visit 3 or Visit 4.

6.12 Safety Results and Evaluation

6.12.1 Extent of Exposure

All enrolled subjects had the same T.R.U.E. TEST panels containing the same allergens applied to their backs or upper arms at Visit 1. All T.R.U.E. TEST patches were removed after 2 days of occluded exposure. Thus, the extent of exposure was approximately the same for all enrolled subjects.

6.12.2 Adverse events

In this study, an AE was defined as any untoward medical occurrence in a study subject who was administered a drug or biologic (medicinal product), or used a medical device. The event did not necessarily have to have had a causal relationship with the patch or its usage. Reporting of all AEs began following patch application at Visit 1 and ended at the last study visit (Visit 5). Any known AEs that were considered possibly related to the study that occurred following Visit 5 were also reported.

6.12.3 Analysis of Adverse Events (AEs)

Of the 102 subjects enrolled in the study, 35 (34.3%) subjects reported AEs, all of which were non-serious. The majority (96.1%) of these reported events were mild to moderate in severity, while 2 AEs (both reported as “worsening rash”) 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. No subject discontinued from the study due to an AE. A summary of AE characteristics inclusive of all the 28 allergens on the 3 T.R.U.E TEST panels is provided in Table 6 and Table 7 presents total AE associated with 5 allergens that are components of the rubber panel T.R.U.E TEST.

Table 6: Summary of Adverse Event Characteristics (All Subjects)

Number of subjects	102
Number of events reported	52
Number of subjects who reported 1 or more events[1]	35 (34.3%)
Severity	
Mild	28 (53.8%)
Moderate	22 (42.3%)
Severe	2 (2%)
Number of subjects who reported 1 or more serious AE[2]	0
Event possibly related to panel application[2]:	
Yes	31 (59.6%)
No	21 (40.4%)
Subject received medication for event[2]:	
Yes	28 (53.8%)
No	24 (46.2%)

[1] Proportion based on number of subjects.
[2] Proportion based on number of events.
Source: Reviewer analysis based on submitted data

Reviewer's Comment: *The 34.3% AE rate is significantly higher than the historical AE rate (18%) reported in the 8 previous studies that has been used as the basis for the sample size and power calculation of this study. In planning the current study, the applicant stated: "In evaluating the product in this new study, adverse event rates should not be substantially higher (greater than 8%) from those previously observed. Therefore, the frequency of adverse events associated with T.R.U.E. TEST allergens in this study will be compared to historical data."*
The clinical assessment/implication of this finding is deferred to the clinical reviewer.

Table 7: Total Adverse Events Associated with Rubber Panel T.R.U.E. TEST Allergens

	Black Rubber Mix	Carba mix	MB*	Mercapto mix	Thiuram mix	Neg Control
	N=102	N=102	N=102	N=102	N=102	N=102
Adverse Events n (%)	1 (0.98%)	6 (5.88%)	0	0	1 (0.98%)	0
Erythema	0	0	0	0	0	0
Dermatitis Flare	1 (0.98%)	5 (4.90%)	0	0	1(0.98%)	0
Mild	1 (0.98%)	4 (3.92%)			1 (0.98%)	0
Moderate	0	1 (0.98%)			0	0
Rash	0	1 (0.98%)	0	0	0	0
Mild	0	1 (0.98%)	0	0	0	0

*MB= Mercaptobenzothiazole
Source: Adapted from applicant's IR response submission; BLA 125579/0;

6.12.5 Serious adverse events (SAE)

A serious AE was defined as any AE that resulted in death, a life-threatening event, required hospitalization or prolonged an existing hospitalization, caused a persistent or significant disability/incapacity, or resulted in a congenital anomaly or birth defect. Other significant events were defined as any AE that led to an intervention, including

discontinuation from the study, or the need for treatment with significant additional concomitant medication.

6.12.5.1 Deaths

There were no deaths reported in the study.

6.12.5.2 Serious Adverse Events

There were no serious AEs reported in the study.

6.12.5.3 Other Significant Adverse Events

There were no other significant AEs reported in the study.

6.12.6 Evaluation of Tape-induced Irritation, Panel Adhesion, and Itching and Burning

Results for the number and frequency of all subjects who reported none, weak, moderate, and strong tape irritation, the quality of panel adhesion, and the number and frequency of subjects who reported itching and burning upon patch test removal are presented in Table 8 for all enrolled subjects.

Table 8: Frequency of Itching, Burning, Panel Adhesion, and Tape Irritation at Patch Test Removal (All Subjects)

	T.RU.E TEST Panel 1.1	T.RU.E TEST Panel 2.1	T.RU.E TEST Panel 3.1
Number of Subjects	102	102	102
Panel Adhesion			
N	100	100	100
Excellent	71 (71%)	72 (72%)	82 (82%)
Good	19 (19%)	19 (19%)	14 (14%)
Fair	8 (8%)	9 (9%)	3 (3%)
Poor	2 (2%)	0	1 (1%)
Test panel fell off	0	0	0
Panel Irritation:			
N	101	100	101
None	38 (37.6%)	37	40
Weak	44 (43.6%)	44	41
Moderate	16 (15.8%)	16	18
Strong	3 (3.0%)	4	2
Itching and Burning:			
N	101	101	101
None	34 (33.7%)	45 (44.6%)	61 (60.4%)
Weak	34 (33.7%)	32 (31.7%)	23 (22.8%)
Moderate	12 (11.9%)	15 (14.9%)	5 (5.0%)
Strong	21 (20.8%)	9 (8.9%)	12 (11.9%)

Source: Adapted from BLA 125579/0; clinical study report for study Mekos 0729P1/2/3 401.

Of the 102 enrolled subjects, the largest proportions had excellent adhesion of T.R.U.E. TEST panels 1.1 (containing the negative control), 2.1 (containing the 5 rubber allergens), and 3.1 (containing none of the rubber allergens) (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. There was,

however, 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. Specifically, a greater proportion of subjects reported no itching or burning upon removal of T.R.U.E. TEST panel 3.1 than upon removal of T.R.U.E. TEST panels 1.1 and 2.1 (60.4%, 33.7%, and 44.6%, respectively). Further, 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).

6.12.7 Evaluations of Late Skin Reactions

The number and frequency of late skin reactions observed at Visit 5 was tabulated for all subjects in Table 9 below. According to the database, 2 of the 101 enrolled subjects (~2.0%) who attended Visit 5 had late skin reactions; the mean (STD) time to exhibiting a reaction was 3.0 (1.41) days. It should be noted, however, that the skin reactions observed at Visit 5 for these 2 subjects were pre-existing (#001 [mild infiltration, hyperpigmentation, and pruritus associated with nickel sulfate] and #096 [mild hyperpigmentation associated with quaternium-15]). Thus, while the CRFs indicate that the reactions were both persistent and late, they were, in fact, only persistent.

Table 9: Summary of Late Reactions (All Subjects)

Number of subjects	102
Subjects with late reaction:	
N	101
Yes	2 (2%)
No	99 (98%)
Time to distinct reaction symptoms (days):	
N	2
Mean	3.0
STD	1.41
Median	3.0
Min. to Max.	2 to 4
Subject received medication for event[2]:	
Yes	28 (53.8%)
No	24 (46.2%)

Source: Adapted from BLA 125579/0; clinical study report for study Mekos 0729P1/2/3 401

6.12.9 Safety Subgroup Analysis

The occurrence of AEs was also evaluated by age category (Table 10), sex (Table 11), and race (Table 12). Overall, similar numbers of AEs occurred among subjects within each of the age category, sex, and race subgroups.

Table 10: Summary of Adverse Event Frequency by Age Category

	6 -12 Years of Age	13-18 Years of Age
Number of subjects	57	45
Number of events reported	27	25
Number of subjects who reported 1 or more events[1]	18 (31.6%)	17 (37.8%)
Severity		
Mild	13 (48.1%)	15 (60%)
Moderate	13 (48.1%)	9 (36%)
Severe	1 (3.7%)	1 (4%)
Number of subjects who reported 1 or more serious AE[2]	0	0
Event possibly related to panel application[2]:		
Yes	19 (70.4%)	12 (48%)
No	8 (29.6%)	13 (52%)
Subject received medication for event[2]:		
Yes	16 (59.3%)	12 (48%)
No	11 (40.7%)	13 (52%)
Adverse event outcome[2]:		
Resolved	3 (11.1%)	5 (20%)
Ongoing	24 (88.9%)	20 (80%)

[1] Proportion based on number of subjects; [2] Proportion based on number of events.
Source: Adapted from BLA 125579/0; clinical study report for study Mekos 0729P1/2/3 401

Table 11: Summary of Adverse Event Frequency by Sex

	Female	Male
Number of subjects	53	49
Number of events reported	29	23
Number of subjects who reported 1 or more events[1]	18 (34%)	17 (34.7%)
Severity		
Mild	17 (58.6%)	11 (47.8%)
Moderate	10 (34.5%)	12 (52.2%)
Severe	2 (6.9%)	0
Number of subjects who reported 1 or more serious AE[2]	0	0
Event possibly related to panel application[2]:		
Yes	18 (62.1%)	13 (56.5%)
No	11 (37.9%)	10 (43.5%)
Subject received medication for event[2]:		
Yes	18 (62.1%)	10 (43.5%)
No	11 (37.9%)	13 (43.5%)
Adverse event outcome[2]:		
Resolved	6 (20.7%)	2 (8.7%)
Ongoing	23 (79.3%)	21 (91.3%)

[1] Proportion based on number of subjects; [2] Proportion based on number of events.
Source: Adapted from BLA 125579/0; clinical study report for study Mekos 0729P1/2/3 401

Table 12: Summary of Adverse Event Frequency by Race

	Caucasian	Non-Caucasian
Number of subjects	40	62
Number of events reported	24	28
Number of subjects who reported 1 or more events[1]	16 (40%)	19 (30.6%)
Severity		
Mild	14 (58.3%)	14 (50.0%)
Moderate	10 (41.7%)	12 (42.9%)
Severe	0	2 (7.1%)
Number of subjects who reported 1 or more serious AE[2]	0	0
Event possibly related to panel application[2]:		
Yes	12 (50%)	19 (67.9%)
No	12 (50%)	9 (32.1%)
Subject received medication for event[2]:		
Yes	10 (41.7%)	18 (64.3%)
No	14 (58.3%)	10 (35.7%)
Adverse event outcome[2]:		
Resolved	3 (12.5%)	5 (17.9%)
Ongoing	21 (87.5%)	23 (82.1%)

[1] Proportion based on number of subjects; [2] Proportion based on number of events.
Source: Adapted from BLA 125579/0; clinical study report for study Mekos 0729P1/2/3 401

6.12.10 Safety Conclusion

The study evaluated the safety of 28 allergens within T.R.U.E. TEST Panels 1.1, 2.1, and 3.1 among pediatric subjects (6-18 years of age, inclusive). Overall, the results of the study indicate that the allergens in the 3 T.R.U.E. TEST panels were safe and well tolerated.

- Overall, 35 (34.3%) subjects reported 52 AEs, all of which were non-serious, and the majority (96.1%) of which were mild to moderate in severity; 2 AEs were severe and neither were associated with the rubber panel T.R.U.E TEST.
- There were no deaths, no other serious AEs, no significant AEs, and no events that led to subject discontinuation.
- A majority of the AEs (59.6%) were considered possibly related to panel application.
- Adhesion of T.R.U.E. TEST panels 1.1, 2.1, and 3.1 was considered excellent for the majority of subjects (71.0%, 72.0%, and 82.0%, respectively).
- The largest proportion of enrolled subjects (approximately 80%) experienced no or weak tape-induced irritation associated with any of the T.R.U.E. TEST panels.
- A greater proportion of subjects reported no itching or burning upon removal of T.R.U.E. TEST panel 3.1 than upon removal of T.R.U.E. TEST panels 1.1 and 2.1 (60.4%, 33.7%, and 44.6%, respectively).
- Greater proportions of subjects experienced weak to strong itching and burning after removal of T.R.U.E. TEST panels 1.1 and 2.1 than after removal of T.R.U.E. TEST panel 3.1 (66.3%, 55.4%, and 39.6%, respectively).
- Reports of erythema, infiltration, hyperpigmentation, hypopigmentation, pruritus, and other reactions were few in number. Additionally, all reported reactions were mild to moderate in severity and no subject experienced a severe skin reaction of any type to any of the allergens.

- Overall, 4 subjects experienced 7 persistent reactions, including 4 reactions associated with nickel sulfate (1 instance each of mild infiltration and mild pruritus, and 2 instances of mild hyperpigmentation), and 1 reaction each associated with Cl+Me-isothiazolinone (moderate hypopigmentation), quaternium-15 (mild hyperpigmentation), and diazolidinyl urea (mild hyperpigmentation).
- There were no meaningful differences observed in the frequency or severity of AEs; the quality of panel adhesion; the instances of tape irritation; the reports of burning and stinging following patch removal; the frequency of late skin reactions; or the frequency, intensity, or symptoms of persistent reactions when evaluated by age category, sex, or race.

10. CONCLUSIONS

10.1 Statistical Issues and Collective Evidence

Overall, 102 pediatric 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. No other subjects discontinued for any reason.

Among all subjects, the most commonly reported form of dermatitis was allergic (97.1%). The majority of subjects (99.0%) presented with dermatitis symptoms at the time of entry into the study (generally on the arms and/or hands and the legs and/or feet).

For the rubber panel T.R.U.E TEST positive reactions observed in more than 5% of the subjects were associated with carba mix (6.9%) followed by Thiuram mx (5.9%). The proportion of subjects with positive reactions at each of the remaining allergens of the rubber panel T.R.U.E TEST was less than 2% at either visit 3 or 4.

Overall for the 28 allergens in the T.R.U.E TEST positive reactions observed in more than 10% of the subjects were associated with nickel sulfate (not more than 29% of the subjects at either visit), followed by wool alcohols and *p-tert*-butylphenol formaldehyde resin (not more than 16% of the subjects at either visit), fragrance mix (not more than 13% of the subjects at either visit), and cobalt dichloride (not more than 12% of the subjects at either visit). The proportions of subjects with positive reactions to each of the allergens at Visit 4 were similar to or lower than those observed at Visit 3. Positive reactions that occurred in more than 10% of the subjects at Visit 4 included only those associated with nickel sulfate (17 subjects [17.7%]).

At Visit 5, 4 subjects experienced 7 persistent reactions, including 4 reactions to nickel sulfate (1 instance each of mild infiltration and mild pruritus, and 2 instances of mild hyperpigmentation), and 1 reaction each to Cl+Me-isothiazolinone (moderate hypopigmentation), quaternium-15 (mild hyperpigmentation), and diazolidinyl urea (mild hyperpigmentation). None of these reactions appeared to involve the 5 allergens in the rubber test.

Overall, 35 (34.3%) subjects reported 52 AEs, all of which were non-serious and the majority (96.1%) of which were mild to moderate in severity. There were no deaths, no other serious AEs, and no significant AEs.
Adhesion of T.R.U.E. TEST panels 1.1, 2.1, and 3.1 was considered excellent for the majority of all subjects (71.0%, 72.0%, and 82.0%, respectively). Further, the largest proportions of enrolled subjects (approximately 80%) experienced no or weak tape-induced irritation regardless of which panel was evaluated. A greater proportion of subjects, however, reported no itching or burning upon removal of T.R.U.E. TEST panel 3.1 than upon removal of T.R.U.E. TEST panels 1.1 and 2.1 (60.4%, 33.7%, and 44.6%, respectively).

There were no meaningful differences observed when evaluated by age category, sex, or race in the frequency or severity of AEs; the quality of panel adhesion; the instances of tape irritation; the reports of burning and stinging following patch removal; or the frequency, intensity, or symptoms of persistent reactions.

10.2 Conclusions and Recommendations

The study was an open-label one and had no pre-specified criteria for efficacy; thus, it may not be appropriate to regard it as providing conclusive evidence of efficacy. The results of the safety analyses suggest that the allergens in rubber panel T.R.U.E. TEST were safe when used for the diagnosis of allergic contact dermatitis in the children and adolescents 6 to 18 years of age (inclusive) enrolled in the study.

Based on a review of the specified safety outcomes (late and/or persistent reactions, i.e., a positive response at visit 5; tape-induced irritation at the test site upon patch removal; incomplete panel adhesion; and subject-reported sensations of itching or burning following path removal), no unexpected safety signals or trends were observed.

11. APPENDIX (ADDITIONAL TABLES)

Table A.1: Frequency of Positive, Negative, Irritant, and Doubtful Reactions at Visit 3 for T.R.U.E TEST panel 1.1

	N	Positive Reaction (+,++,+++)	Negative Reaction (Neg)	Irritant Reaction (IR)	Doubtful Reaction (?/+)
Nickel sulfate, 0.20 mg/cm^2	101	29 (28.7%)	66 (65.3%)	1 (1.0%)	5 (5.0%)
95% CI		(20.1%, 38.6%)	(55.2%, 74.5%)	(0.0%, 5.4%)	(1.6%, 11.2%)
Wool alcohols, 1.00 mg/cm^2	101	16 (15.8%)	84 (83.2%)	0 (0.0%)	1 (1.0%)
95% CI		(9.3%, 24.4%)	(74.4%, 89.9%)	(0.0%, 3.6%)	(0.0%, 5.4%)
Neomycin sulfate, 0.23 mg/cm^2	101	7 (6.9%)	94 (93.1%)	0 (0.0%)	0 (0.0%)
95% CI		(2.8%, 13.8%)	(86.2%, 97.2%)	(0.0%, 3.6%)	(0.0%, 3.6%)
Potassium dichromate, 0.023 mg/cm^2	101	9 (8.9%)	90 (89.1%)	2 (2.0%)	0 (0.0%)
95% CI		(4.2%, 16.2%)	(81.3%, 94.4%)	(0.2%, 7.0%)	(0.0%, 3.6%)
Caine mix, 0.63 mg/cm^2	101	0 (0.0%)	101 (100.0%)	0 (0.0%)	0 (0.0%)
95% CI		(0.0%, 3.6%)	(96.4%, 100.0%)	(0.0%, 3.6%)	(0.0%, 3.6%)
Fragrance mix, 0.43 mg/cm^2	101	13 (12.9%)	88 (87.1%)	0 (0.0%)	0 (0.0%)
95% CI		(7.0%, 21.0%)	(79.0%, 93.0%)	(0.0%, 3.6%)	(0.0%, 3.6%)
Colophony, 1.20 mg/cm^2	101	9 (8.9%)	91 (90.1%)	0 (0.0%)	1 (1.0%)
95% CI		(4.2%, 16.2%)	(82.5%, 95.1%)	(0.0%, 3.6%)	(0.0%, 5.4%)
Paraben mix, 1.00 mg/cm^2	101	2 (2.0%)	99 (98.0%)	0 (0.0%)	0 (0.0%)
95% CI		(0.2%, 7.0%)	(93.0%, 99.8%)	(0.0%, 3.6%)	(0.0%, 3.6%)
Balsam of Peru, 0.80 mg/cm^2	101	10 (9.9%)	88 (87.1%)	1 (1.0%)	2 (2.0%)
95% CI		(4.9%, 17.5%)	(79.0%, 93.0%)	(0.0%, 5.4%)	(0.2%, 7.0%)
Ethylenediamine dihydrochloride, 0.050 mg/cm^2	101	6 (5.9%)	95 (94.1%)	0 (0.0%)	0 (0.0%)
95% CI		(2.2%, 12.5%)	(87.5%, 97.8%)	(0.0%, 3.6%)	(0.0%, 3.6%)
Cobalt dichloride, 0.020 mg/cm^2	101	12 (11.9%)	88 (87.1%)	1 (1.0%)	0 (0.0%)
95% CI		(6.3%, 19.8%)	(79.0%, 93.0%)	(0.0%, 5.4%)	(0.0%, 3.6%)
Negative control	101	0 (0.0%)	101 (100.0%)	0 (0.0%)	0 (0.0%)
95% CI		(0.0%, 3.6%)	(96.4%, 100.0%)	(0.0%, 3.6%)	(0.0%, 3.6%)

Source: Adapted from BLA 125579/0; clinical study report for study Mekos 0729P1/2/3 401

Table A.2: Frequency of Positive, Negative, Irritant, and Doubtful Reactions at Visit 3 for T.R.U.E TEST panel 2.1 Allergens

	N	Positive Reaction (+,++,+++)	Negative Reaction (Neg)	Irritant Reaction (IR)	Doubtful Reaction (?/+)
p-tert-Butylphenol formaldehyde resin, 0.045 mg/cm^2	101	16 (15.8%)	84 (83.2%)	0 (0.0%)	1 (1.0%)
95% CI		(9.3%, 24.4%)	(74.4%, 89.9%)	(0.0%, 3.6%)	(0.0%, 5.4%)
Epoxy resin, 0.050 mg/cm^2	101	3 (3.0%)	96 (95.0%)	0 (0.0%)	2 (2.0%)
95% CI		(0.6%, 8.4%)	(88.8%, 98.4%)	(0.0%, 3.6%)	(0.2%, 7.0%)
Carba mix, 0.25 mg/cm^2	**101**	**7 (6.9%)**	**93 (92.1%)**	**0 (0.0%)**	**1 (1.0%)**
95% CI		**(2.8%, 13.8%)**	**(85.0%, 96.5%)**	**(0.0%, 3.6%)**	**(0.0%, 5.4%)**
Black rubber mix, 0.075 mg/cm^2	**101**	**2 (2.0%)**	**97 (96.0%)**	**0 (0.0%)**	**2 (2.0%)**
95% CI [a]		**(0.2%, 7.0%)**	**(90.2%, 98.9%)**	**(0.0%, 3.6%)**	**(0.2%, 7.0%)**
Cl+Me-Isothiazolinone, 0.0040 mg/cm^2	101	4 (4.0%)	96 (95.0%)	0 (0.0%)	1 (1.0%)
95% CI		(1.1%, 9.8%)	(88.8%, 98.4%)	(0.0%, 3.6%)	(0.0%, 5.4%)
Quaternium-15, 0.10 mg/cm^2	101	3 (3.0%)	96 (95.0%)	0 (0.0%)	2 (2.0%)
95% CI		(0.6%, 8.4%)	(88.8%, 98.4%)	(0.0%, 3.6%)	(0.2%, 7.0%)
Mercaptobenzothiazole, 0.0075 mg/cm^2	**101**	**2 (2.0%)**	**99 (98.0%)**	**0 (0.0%)**	**0 (0.0%)**
95% CI		**(0.2%, 7.0%)**	**(93.0%, 99.8%)**	**(0.0%, 3.6%)**	**(0.0%, 3.6%)**
p-Phenylenediamine, (b) (4) mg/cm^2	101	2 (2.0%)	99 (98.0%)	0 (0.0%)	0 (0.0%)
95% CI		(0.2%, 7.0%)	(93.0%, 99.8%)	(0.0%, 3.6%)	(0.0%, 3.6%)
Formaldehyde, 0.18 mg/cm^2	101	5 (5.0%)	91 (90.1%)	0 (0.0%)	5 (5.0%)
95% CI		(1.6%, 11.2%)	(82.5%, 95.1%)	(0.0%, 3.6%)	(1.6%, 11.2%)
Mercapto mix, 0.075 mg/cm^2	**101**	**2 (2.0%)**	**99 (98.0%)**	**0 (0.0%)**	**0 (0.0%)**
95% CI		**(0.2%, 7.0%)**	**(93.0%, 99.8%)**	**(0.0%, 3.6%)**	**(0.0%, 3.6%)**
Thimerosal, (b) (4) mg/cm^2	101	4 (4.0%)	96 (95.0%)	1 (1.0%)	0 (0.0%)
95% CI		(1.1%, 9.8%)	(88.8%, 98.4%)	(0.0%, 5.4%)	(0.0%, 3.6%)
Thiuram mix, 0.025 mg/cm^2	**101**	**6 (5.9%)**	**92 (91.1%)**	**1 (1.0%)**	**2 (2.0%)**
95% CI		**(2.2%, 12.5%)**	**(83.8%, 95.8%)**	**(0.0%, 5.4%)**	**(0.2%, 7.0%)**

Bold indicates allergens that are components of the rubber panel .

Source: Adapted from BLA 125579/0; clinical study report for study Mekos 0729P1/2/3 401

Table A.3: Frequency of Positive, Negative, Irritant, and Doubtful Reactions at Visit 3 for T.R.U.E TEST panel 3.1 Allergens

	N	Positive Reaction (+,++,+++)	Negative Reaction (Neg)	Irritant Reaction (IR)	Doubtful Reaction (?/+)
Diazolidinyl urea, 0.55 mg/cm^2	101	4 (4.0%)	95 (94.1%)	0 (0.0%)	2 (2.0%)
95% CI		(1.1%, 9.8%)	(87.5%, 97.8%)	(0.0%, 3.6%)	(0.2%, 7.0%)
Imidazolidinyl urea, 0.60 mg/cm^2	101	1 (1.0%)	97 (96.0%)	1 (1.0%)	2 (2.0%)
95% CI		(0.0%, 5.4%)	(90.2%, 98.9%)	(0.0%, 5.4%)	(0.2%, 7.0%)
Budesonide, 0.0010 mg/cm^2	101	1 (1.0%)	100 (99.0%)	0 (0.0%)	0 (0.0%)
95% CI		(0.0%, 5.4%)	(94.6%, 100.0%)	(0.0%, 3.6%)	(0.0%, 3.6%)
Tixocortol-21-pivalate, 0.0030 mg/cm^2	101	8 (7.9%)	93 (92.1%)	0 (0.0%)	0 (0.0%)
95% CI		(3.5%, 15.0%)	(85.0%, 96.5%)	(0.0%, 3.6%)	(0.0%, 3.6%)
Quinoline mix, 0.19 mg/cm^2	101	1 (1.0%)	100 (99.0%)	0 (0.0%)	0 (0.0%)
95% CI		(0.0%, 5.4%)	(94.6%, 100.0%)	(0.0%, 3.6%)	(0.0%, 3.6%)

Source: Adapted from BLA 125579/0; clinical study report for study Mekos 0729P1/2/3 401

Table A.4: Frequency of Positive, Negative, Irritant, and Doubtful Reactions at Visit 4 for T.R.U.E TEST panel 1.1 Allergens

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

Source: Adapted from BLA 125579/0; clinical study report for study Mekos 0729P1/2/3 401

Table A.5: Frequency of Positive, Negative, Irritant, and Doubtful Reactions at Visit 4 for T.R.U.E TEST panel 2.1 Allergens

	N	Positive Reaction (+,++,+++)	Negative Reaction (Neg)	Irritant Reaction (IR)	Doubtful Reaction (?/+)
p-tert-Butylphenol formaldehyde resin, 0.045 mg/cm^2	96	7 (7.3%)	87 (90.6%)	0 (0.0%)	2 (2.1%)
95% CI [a]		(3.0%, 14.4%)	(82.9%, 95.6%)	(0.0%, 3.8%)	(0.3%, 7.3%)
Epoxy resin, 0.050 mg/cm^2	96	2 (2.1%)	94 (97.9%)	0 (0.0%)	0 (0.0%)
95% CI [a]		(0.3%, 7.3%)	(92.7%, 99.7%)	(0.0%, 3.8%)	(0.0%, 3.8%)
Carba mix, 0.25 mg/cm^2	**96**	**1 (1.0%)**	**95 (99.0%)**	**0 (0.0%)**	**0 (0.0%)**
95% CI [a]		**(0.0%, 5.7%)**	**(94.3%, 100.0%)**	**(0.0%, 3.8%)**	**(0.0%, 3.8%)**
Black rubber mix, 0.075 mg/cm^2	**96**	**0 (0.0%)**	**95 (99.0%)**	**0 (0.0%)**	**1 (1.0%)**
95% CI [a]		**(0.0%, 3.8%)**	**(94.3%, 100.0%)**	**(0.0%, 3.8%)**	**(0.0%, 5.7%)**
Cl+Me-Isothiazolinone, 0.0040 mg/cm^2	96	3 (3.1%)	91 (94.8%)	0 (0.0%)	2 (2.1%)
95% CI [a]		(0.6%, 8.9%)	(88.3%, 98.3%)	(0.0%, 3.8%)	(0.3%, 7.3%)
Quaternium-15, 0.10 mg/cm^2	96	3 (3.1%)	93 (96.9%)	0 (0.0%)	0 (0.0%)
95% CI [a]		(0.6%, 8.9%)	(91.1%, 99.4%)	(0.0%, 3.8%)	(0.0%, 3.8%)
Mercaptobenzothiazole, 0.0075 mg/cm^2	**96**	**1 (1.0%)**	**95 (99.0%)**	**0 (0.0%)**	**0 (0.0%)**
95% CI [a]		**(0.0%, 5.7%)**	**(94.3%, 100.0%)**	**(0.0%, 3.8%)**	**(0.0%, 3.8%)**
p-Phenylenediamine, (b) (4) mg/cm^2	96	0 (0.0%)	96 (100.0%)	0 (0.0%)	0 (0.0%)
95% CI [a]		(0.0%, 3.8%)	(96.2%, 100.0%)	(0.0%, 3.8%)	(0.0%, 3.8%)
Formaldehyde, 0.18 mg/cm^2	96	3 (3.1%)	91 (94.8%)	0 (0.0%)	2 (2.1%)
95% CI [a]		(0.6%, 8.9%)	(88.3%, 98.3%)	(0.0%, 3.8%)	(0.3%, 7.3%)
Mercapto mix, 0.075 mg/cm^2	**96**	**1 (1.0%)**	**94 (97.9%)**	**0 (0.0%)**	**1 (1.0%)**
95% CI [a]		**(0.0%, 5.7%)**	**(92.7%, 99.7%)**	**(0.0%, 3.8%)**	**(0.0%, 5.7%)**
Thimerosal, (b) (4) mg/cm^2	96	2 (2.1%)	94 (97.9%)	0 (0.0%)	0 (0.0%)
95% CI [a]		(0.3%, 7.3%)	(92.7%, 99.7%)	(0.0%, 3.8%)	(0.0%, 3.8%)
Thiuram mix, 0.025 mg/cm^2	**96**	**1 (1.0%)**	**91 (94.8%)**	**0 (0.0%)**	**4 (4.2%)**
95% CI [a]		**(0.0%, 5.7%)**	**(88.3%, 98.3%)**	**(0.0%, 3.8%)**	**(1.1%, 10.3%)**

Bold indicates allergens that are components of the rubber panel .

Source: Adapted from BLA 125579/0; clinical study report for study Mekos 0729P1/2/3 401

Table A.6: Frequency of Positive, Negative, Irritant, and Doubtful Reactions at Visit 4 for T.R.U.E TEST panel 3.1 Allergens

	N	Positive Reaction (+,++,+++)	Negative Reaction (Neg)	Irritant Reaction (IR)	Doubtful Reaction (?/+)
Diazolidinyl urea, 0.55 mg/cm^2	96	2 (2.1%)	92 (95.8%)	0 (0.0%)	2 (2.1%)
95% CI [a]		(0.3%, 7.3%)	(89.7%, 98.9%)	(0.0%, 3.8%)	(0.3%, 7.3%)
Imidazolidinyl urea, 0.60 mg/cm^2	96	1 (1.0%)	94 (97.9%)	0 (0.0%)	1 (1.0%)
95% CI [a]		(0.0%, 5.7%)	(92.7%, 99.7%)	(0.0%, 3.8%)	(0.0%, 5.7%)
Budesonide, 0.0010 mg/cm^2	96	1 (1.0%)	95 (99.0%)	0 (0.0%)	0 (0.0%)
95% CI [a]		(0.0%, 5.7%)	(94.3%, 100.0%)	(0.0%, 3.8%)	(0.0%, 3.8%)
Tixocortol-21-pivalate, 0.0030 mg/cm^2	96	3 (3.1%)	91 (94.8%)	0 (0.0%)	2 (2.1%)
95% CI [a]		(0.6%, 8.9%)	(88.3%, 98.3%)	(0.0%, 3.8%)	(0.3%, 7.3%)
Quinoline mix, 0.19 mg/cm^2	96	0 (0.0%)	96 (100.0%)	0 (0.0%)	0 (0.0%)
95% CI [a]		(0.0%, 3.8%)	(96.2%, 100.0%)	(0.0%, 3.8%)	(0.0%, 3.8%)

Source: Adapted from BLA 125579/0; clinical study report for study Mekos 0729P1/2/3 401