1.0 TITLE PAGE

Study Title:	Clinical Evaluation of Metal Panel Allergens: Aluminum, Copper, Manganese, Molybdenum, Tin, Titanium and Zinc Dose Response Study
Name of Investigational Products:	Aluminum chloride Aluminum lactate Copper sulfate Manganese chloride Ammonium molybdate Tin chloride Ammonium titanium peroxo citrate Ammonium titanium lactate Potassium titanium oxide oxalate Ammonium titanium oxide oxalate Vanadium chloride Vanadium sulfate Zinc chloride
Indication Studied:	Diagnosis of allergic contact dermatitis
Study Design:	Multi-center, double-blind, randomized design
Name of Sponsor:	SmartPractice 3400 East McDowell Road Phoenix, Arizona 85008, USA
Protocol Identification Code:	SP14 8MP 201
Development Phase of Study	Phase 2
Study Initiation Date:	December 5, 2016 (first subject enrolled)
Study Completion Date:	July 15, 2019 (final subject completed)
Sponsor's Responsible Medical Officer:	Curt Hamann, M.D.
Sponsor Contact:	Curt Hamann, M.D. Medical Director, SmartPractice Telephone: +1 800.365.6868 Fax: +1 602-225-0597 email: hamann@smartpractice.com
Date of Report:	May 19, 2020

This study was performed in compliance with the ethical principles of the Declaration of Helsinki and Good Clinical Practices (GCP) including the archiving of essential documents.

2.0 SYNOPSIS

Name of Sponsor: SmartPractice **Name of Finished Product:** Metal Panel T.R.U.E. Test **Name of Active Ingredients:** Aluminum chloride Aluminum lactate Copper sulfate Manganese chloride Ammonium molybdate Tin chloride Ammonium titanium citrate Ammonium titanium lactate Potassium titanium oxide oxalate Ammonium titanium oxide oxalate Vanadium chloride Vanadium sulfate Zinc chloride		Individual study table referring to part of Dossier Volume: Page:	*(For National Authority Use only)*

Title of Study:
Clinical Evaluation of Metal Panel Allergens: Aluminum, Copper, Molybdenum, Manganese, Tin, Titanium, Vanadium and Zinc Dose Response Study

Investigators:
1. Patricia L Norris, MD, Portland, Oregon, USA (1 screen fail only. No subjects enrolled at this site)
2. Karin Pacheco, MD, Denver Colorado, USA
3. Prof. Dr. med. Andreas Bircher, Basel Switzerland (Study initiation through June 27, 2018) PD Dr. med. Kathrin Scherer Hofmeier, Basel Switzerland (June 27, 2018 through study completion)
4. Prof. Paolo Pigatto, MD, Milan, Italy
5. Prof. dr. Thomas Rustemeyer, Amsterdam Netherlands
6. Prof. Dr. med. Peter Thomas, Munich, Germany
7. Maki Hosoki, DDS, PhD, Tokushima, Japan
8. Hiromi Kanto MD, PhD, Tokyo, Japan
9. Akiko Yagami, MD, PhD, Nagoya, Japan

Study Centers:
1. Oregon Health & Science University, Portland, Oregon USA
2. National Jewish Health, University of Colorado Denver, Denver, Colorado, USA
3. University Hospital Basel Allergology Unit, Basel, Switzerland
4. Clinical Dermatology, Department of Biomedical, Surgical and Dental Sciences, IRCCS Galeazzi Orthopaedic Institute, University of Milan, Milan, Italy
5. Department of Dermatology, VU University Medical Center, Amsterdam Netherlands
6. Institute of Dermatology and Allergy, Ludwig-Maximilians-Universität München, Munich, Germany
7. Department of Stomatognathic Function and Occlusal Reconstruction Institute of Biomedical Sciences, Tokushima University Graduate School, Tokushima, Japan
8. Department of Dermatology, School of Medicine, Toho University Omori Medical Center, Tokyo, Japan
9. Department of Allergology, Fujita Health University Second Educational Hospital, Nagoya, Japan

Publication (reference):
Not applicable

Study Period:
Date of First Enrollment: December 5, 2016
Date of Last Completed: July 15, 2019

Phase of Development:
Phase 2

Objective:
To determine the optimal test allergen dose of metal allergens proposed for inclusion in a TRUE Test metal panel. The study compared the diagnostic performance (primary endpoint) and safety (secondary endpoint) of ascending patch test doses of aluminum, copper, magnesium, molybdenum, tin, titanium, vanadium and zinc allergens.

Methodology:
This was a prospective, multi-center, randomized, double-blind design. Ascending investigational allergen doses on panels 1-5 were randomized into three different configurations, which were randomly assigned to subjects as they entered the study. Although the Investigators and subjects knew which allergen was being tested, they were blinded to the placement of the allergen doses within each panel. (Panel 6 which included previously approved allergens, excipient controls and a blank patch was not randomized). Investigational allergen panel(s), excipient controls and corresponding reference petrolatum (or aqueous) allergen(s) were applied to the skin for approximately 48-hours to test for potential positive allergic responses. Test sites were evaluated at 3-4, 7-8, 10-14 and 19-23 days after application.

Number of Patients (planned and analyzed):

Planned	Maximum of 400 to ensure 15 positive results per allergen
Enrolled	122
Analyzed for Safety	122
Analyzed for Efficacy	121

Diagnosis and main criteria for inclusion:
Target enrollment consisted of adult subjects with a past positive patch test result (within past 10 years) to one of the investigational allergens or strong suspicion of metal contact allergy. Subjects were recruited from dermatology, allergy or similar medical practice patient populations.

Test product, dose and mode of administration, batch number:
Aluminum allergens:
- 0.040, 0.12, 0.36, 0.72 mg/cm² aluminum chloride, Batch Nos. 16001, 18001
- 0.047, 0.14, 0.42, 0.84 mg/cm² aluminum lactate, Batch Nos. 16001, 18001

Copper allergen:
- 0.013, 0.040, 0.080, 0.12 mg/cm² copper sulfate, Batch Nos. 16002, 18007

Manganese allergen:
- 0.013, 0.040, 0.080, 0.24 mg/cm² manganese chloride, Batch Nos. 16003, 18003

Molybdenum allergen:
- 0.0067, 0.020, 0.040, 0.12 mg/cm² ammonium molybdate, Batch Nos. 16003, 18003

Tin allergen:
- 0.018, 0.037, 0.11 0.33 mg/cm² tin chloride, Batch Nos. 16002, 18007

Titanium allergens:
- 0.055, 0.11, 0.22 mg Ti/cm^2 ammonium titanium peroxo citrate, Batch Nos. 16004, 18004
- 0.070, 0.14, 0.28 mg Ti/cm² ammonium titanium lactate, Batch Nos. 16004, 18004
- 0.060, 0.12, 0.24 mg Ti/cm^2 potassium titanium oxide oxalate, Batch Nos. 16004, 18004
- 0.055, 0.11. 0.22 mg Ti/cm² ammonium titanium oxide oxalate, Batch Nos. 16004, 18004

Vanadium allergens:
- 0.0042, 0.0083, 0.025**,** 0.050 mg V/cm² vanadium chloride; Batch Nos. 16005, 18005
- 0.0042, 0.0083**,** 0.025**,** 0.050 mg V/cm² vanadium sulfate, Batch Nos. 16005, 18005

Zinc allergen:
- 0.013, 0.040, 0.080, 0.24 mg/cm² zinc chloride, Batch Nos. 16002, 18007

Note: The dose per unit area of experimental T.R.U.E. Test allergens is calculated based on the molecular weight of the compound. Exceptions are titanium and vanadium allergens as molecular weights are not known. Hence the dose per unit area for titanium and vanadium allergens is based only on the metal part of the compound.

Previously Approved Allergens (Panel 6):
- 0.20 mg/cm^2 nickel sulfate, Batch Nos. 16006, 18006
- 0.0054 mg/cm^2 potassium dichromate, Batch Nos. 16006, 18006
- 0.075 mg/cm^2 gold sodium thiosulfate, Batch Nos. 16006, 18006
- 0.020 mg/cm^2 cobalt dichloride, Batch Nos. 16006, 18006

Duration of Treatment:
A 48-hour application (approximate) of the investigational and reference allergen panels were applied to the upper backs of study subjects.

Reference therapy, dose and mode of administration, batch number:
- Aluminum chloride hexahydrate, 10 % w/w in petrolatum
- Aluminum lactate, 12 % w/w in petrolatum
- Copper sulfate anhydrous, 2 % w/w in petrolatum
- Manganese chloride tetrahydrate, 2 % w/w in petrolatum
- Ammonium molybdate, 1% aqueous solution.
- Tin chloride dihydrate, 1% w/w in petrolatum
- Ammonium titanium peroxo citrate, 17% w/w in petrolatum
- Ammonium titanium lactate, 34% aqueous solution
- Potassium titanium oxide oxalate, 22% w/w in petrolatum
- Ammonium Titanium oxide oxalate 19% w/w in petrolatum
- Vanadium chloride, 1% w/w in petrolatum
- Vanadium sulfate, 1.5% w/w in petrolatum
- Zinc chloride, 2% w/w in petrolatum

Reference therapy, dose and mode of administration, batch number (continued):
A 48-hour application (approximate) of each petrolatum reference allergen applied to the upper backs of study subjects.

Petrolatum or aqueous reference allergens were prepared and labeled by the Department of Occupational and Environmental Dermatology, Skåne University Hospital, Malmö, Sweden. There was no batch numbering.

Criteria for Evaluation

Efficacy- Primary Endpoints

Determination of optimal test allergen dose as:

- The lowest concentration of each dilution series allergen eliciting positive responses, defined as score of 1+, 2+ or 3+ during at least one reaction assessment visit, in a minimum of 15 subjects. If a significant number of 3+ responses was elicited, the dose was selected based on 1+ and 2+ responses.
- For all sites with the exception of Germany: Concordance was measured using Cohen's kappa where less than 0% indicates no agreement, 0-20% indicates poor agreement, 20-40% indicates fair agreement, 40-60% indicates moderate agreement, 60-80% indicates good agreement and 80% or higher indicates very good agreement. Concordance was measured using all subjects tested with each allergen and corresponding reference allergen.

Safety- Secondary Endpoints

Assessment of allergen safety

- Frequency of tape and polyester chip induced irritation or allergic reactions at visits 2 through 6.
- Frequency of subject reported sensations of itching and/or burning for each allergen panel at patch removal.
- Frequency of positive (1+, 2+, 3+) skin reactions for each investigational and reference allergen dose at each post removal visit and overall.
- Frequency of negative, doubtful, irritant, late and persistent skin reactions for each investigational and reference allergen dose at each post removal visit (late and persistent reactions at visits 4, 5 and 6 only).
- Frequency of all adverse events. Documentation for all local and systemic adverse reactions classified by the Investigator as possibly or definitely related to the study product (e.g., erythema, hyper-pigmentation, hypo-pigmentation, skin thinning or dermatitis flare) including grade (mild, moderate or severe) and time point (clinic visit).

Statistical Methods

Optimal allergen dose based on the lowest concentration of each investigational allergen eliciting positive responses in a minimum of 15 subjects and concordance between the investigational and reference allergen.

Safety evaluations based on frequency of tape and polyester chip induced irritation or allergic reactions at visits 2 through 6, frequency of subject reported itching and burning at patch removal, frequency of skin reactions and frequency of adverse events.

Statistical processing was performed using SAS® software.

SUMMARY – CONCLUSIONS

Efficacy Results:

Aluminum:
The primary endpoint, determination of optimal test allergen dose as the lowest concentration eliciting positive responses in a minimum of 15 subjects, was not met for any dose of aluminum chloride or aluminum lactate. The aluminum allergens will not be further tested nor will they be included on the proposed metal panel.

Copper:
There were 16 subjects with positive responses to the 0.12 mg/cm^2 dose of copper sulfate which was the only dose that met the minimum criteria of at least 15 subjects with positive responses.

- The results of the Kappa statistic indicated fair agreement (28%) between the investigational and reference allergens for the 78 subjects who were tested with both allergens
- All positive responses were graded 1+ or 2+. There were no 3+ reactions.
- All negative responses included 16 subjects with doubtful responses and 10 subjects with irritant responses.
- Among the 16 subjects with positive responses, there were 3 subjects with late responses and 4 subjects with persistent reactions.
- The sensitivity was rated 40.0% and the specificity was 89.7%.

The 0.12 mg/cm^2 dose of copper sulfate has been chosen as the optimal dose.

Manganese:
There were 29 subjects with positive responses to the 0.24 mg/cm^2 dose which was the only dose that met the minimum criteria of at least 15 subjects with positive responses.

- The results of the Kappa statistic indicated moderate agreement (45%) between the investigational and reference allergens for the 69 subjects who were tested with both allergens.
- All positive responses were graded 1+ and 2+. There were no 3+ reactions.
- The negative responses included 17 subjects with doubtful responses and 10 subjects with irritant responses.
- There was 1 subject with a late response and 10 subjects with persistent reactions.
- The sensitivity was rated 90.9% and the specificity was 75.9%.

The 0.24 mg/cm^2 dose of manganese chloride has been chosen as the optimal dose

Molybdenum
The primary endpoint, determination of optimal test allergen dose as the lowest concentration eliciting positive responses in a minimum of 15 subjects, was not met for any dose of ammonium molybdate. The molybdenum allergen will not be further tested nor will it be included on the proposed metal panel.

Tin:
There were 25 subjects with positive responses to the 0.11 mg/cm^2 dose and 65 subjects with positive responses to the 0.33 mg/cm^2 dose. These were the only doses that met the minimum criteria of at least 15 subjects with positive responses. To ensure that all aspects of the response profile of each dose were considered, the following endpoint results were carefully evaluated in order to determine optimal dose.

	0.11 mg/cm²	0.33 mg/cm²
▪ Results of Kappa statistic:	31% fair agreement	23% fair agreement
▪ 1+ and 2+ responses (visits 3-6):	35	**122**
▪ 3+ responses (visits 3-6):	2	3
▪ Negative responses included:	12 doubtful, 6 irritant	12 doubtful, 16 irritant
▪ Late and persistent responses:	5 late, 5 persistent	6 late, **39 persistent**
▪ Sensitivity	45.0%	90%
▪ Specificity	**84.9%**	42.3%

Even though both doses had 12 doubtful reactions, there was a greater difference between the number of doubtful vs. 1+ and 2+ reactions for the 0.33 mg/cm^2 dose which demonstrates better ability to differentiate between the doubtful and positive reactions. In addition, a doubtful response should resolve rather quickly therefore the greater number of persistent reactions for the 0.33 mg/cm^2 dose is favored as true allergic responses take longer to resolve. Although the number of late responses for the two doses is fairly equal, the higher percentage of late responses associated with the 0.11 mg/cm^2 dose is less desirable. Late responses may be missed during the standard 5-day patch test schedule followed in the majority of clinical settings.

The 0.33 mg/cm^2 dose has been chosen as the optimal dose based on the higher number of 1+ and 2+ responses, persistent responses, and a higher rate of sensitivity.

Titanium:
Ammonium titanium oxide oxalate was the only titanium salt that met the minimum criteria of at least 15 subjects with positive responses. There were 21 subjects with positive responses to the 0.11 mg Ti/cm^2 dose and 18 subjects with positive responses to the 0.22 mg Ti/cm^2 dose. Although the number of positive responses for the 0.11 mg Ti/cm^2 dose is higher, there is not a significant difference between the number of positive responses, and both were considered in the selection of optimal dose. To ensure that all aspects of the response profile of each dose were considered, the following endpoint results were carefully evaluated in order to determine optimal dose.

	0.11 mg Ti/cm²	0.22 mg Ti/cm²
▪ Results of Kappa statistic:	33% fair agreement	**40% moderate agreement**
▪ 1+ and 2+ responses (visits 3-6):	23	22
▪ 3+ responses (visits 3-6):	0	0
▪ Negative responses included:	24 doubtful, 9 irritant	27 doubtful, 8 irritant
▪ Late and persistent responses:	1 late, 1 persistent	**0 late, 4 persistent**
▪ Sensitivity	70.0%	70.0%
▪ Specificity	78.8%	83.3%

Because the number of positive reactions, 1+, 2+ and 3+ responses, doubtful responses, irritant responses and sensitivity/specificity for the two doses were nearly equivalent, selection of optimal dose was based on Kappa statistic, and number of late and persistent reactions. The lower percentage of late responses associated with the 0.22 mg Ti/cm^2 dose is preferred. Late responses may be missed during the standard 5-day patch test schedule followed in the majority of clinical settings. In addition, the higher number of persistent reactions associated with the 0.22 mg Ti/cm^2 dose is more favorable because true allergic responses take longer to resolve.

Based on the Kappa statistic, higher number of persistent responses and fewer late responses, the 0.22 mg Ti/cm^2 dose of ammonium titanium oxide oxalate has been chosen as the optimal dose.

Vanadium:
There were 2 doses of vanadium chloride, 0.025 mg V/cm^2 with 25 positive response subjects and 0.050 mg V/cm^2 with 46 positive response subjects, and one dose of vanadium sulfate, 0.050 mg V/cm^2 with 30 positive response subjects, which met the minimum criteria of at least 15 subjects with positive responses. Due to the corrosive nature of the vanadium chloride raw material which complicated its handling during the production and storage of the experimental panel, the vanadium chloride allergens were eliminated from consideration for the final panel. Therefore the 0.050 mg V/cm^2 dose of vanadium sulfate was the only other dose to meet the minimum criteria of at least 15 subjects with positive responses

- The results of the Kappa statistic indicated moderate agreement (52%) between the investigational and reference allergens for the 72 subjects who were tested with both allergens.
- All positive responses were graded 1+ and 2+. There were no 3+ reactions.
- The negative responses included 15 subjects with doubtful responses and 8 subjects with irritant responses.
- There were 7 subjects with late responses and 15 subjects with persistent reactions.
- The sensitivity was rated 100% and the specificity was 80.9%.

The 0.050 mg V/cm^2 dose of vanadium sulfate has been chosen as the optimal dose.

Zinc:
There were 69 subjects with positive responses to the 0.24 mg/cm^2 dose which was the only dose that met the minimum criteria of at least 15 subjects with positive responses.

- The results of the Kappa statistic indicated fair agreement (36%) between the investigational and reference allergens for the 74 subjects who were tested with both allergens.
- All positive responses were graded 1+ and 2+. There were no 3+ reactions.
- The negative responses included 16 subjects with doubtful responses and 9 subjects with irritant responses.
- There were 10 subjects with late responses and 44 subjects with persistent reactions.
- The sensitivity was rated 90.0% and the specificity was 50.0%.

The 0.24 mg/cm^2 dose of zinc chloride has been chosen as the optimal dose.

Secondary Endpoint Results:
Subject reported itching and burning at patch removal and tape and polyester chip induced irritation at visits 2-6 were evaluated.

Eighty-four (84) to 90% of subjects patched with investigational panels 1-6 reported weak or no itching for the duration of the time the panels were worn and 96 to 99% of subjects reported weak or no burning associated with the test panels.

Ninety-eight (98) to 99% of subjects exhibited no tape irritation and 100% of subjects exhibited no chip irritation based on Investigator Determination following evaluations at visits 2-6.

The low prevalence of moderate or strong itching, burning, tape irritation and chip irritation confirm that the test panels are safe to be worn for 48 hours.

Safety Results: Adverse Events
There were 17 adverse events, reported by 10 subjects which were definitely or possibly related to the investigational product.

- The 4 definitely related adverse events which documented patch test site reactions at the day-21 visit were all attributed to one subject.
- The 13 possibly related adverse events were reported by 9 subjects.
  - 5 skin and subcutaneous tissue disorders (itching (2), worsening eczema (2) and worsening palmoplantar pustulosis)
  - 4 nervous system disorders (dizziness, headache (2) and head/neck tension)
  - 2 musculoskeletal and connective tissue disorders (back pain, shoulder pain)
  - 1 general disorder and administration site condition (tiredness)
  - 1 eye disorder (eye dryness)

All of the possibly related adverse events were mild or moderate and had resolved by the end of each subject's participation in the study with the exception of the 3 events associated with worsening of a preexisting condition (worsening atopic eczema, worsening dyshidrotic eczema and worsening palmoplantar pustulosis).

There were 33 not related adverse events reported by 23 subjects. One subject experienced a serious adverse event, ductal carcinoma, right breast, which was not related to the investigational products. Other than the serious adverse event, all of the not related adverse events were common medically related occurrences. The majority of events were mild or moderate. Two events were considered severe, the ductal carcinoma and worsened pain in upper right quadrant.

In conclusion, the low prevalence of definitely or possibly related adverse events (8.2% of FAS population) experienced by the subjects enrolled on this clinical trial indicate no safety signals or trends which would preclude further testing of these investigational allergens.

Conclusion: Primary Endpoints

Ascending doses of aluminum, copper, manganese, molybdenum, tin, titanium, vanadium and zinc investigational allergens were tested in 122 adult subjects, all of whom had a past positive

patch to one of the investigational allergens or a suspicion of contact allergy based on clinical history. The objective of the study was to determine the optimum dose of each investigative allergen. Subjects with a past positive patch test were tested with at least the allergen panels(s) and corresponding reference allergen(s) (with the exception of subjects enrolled in Germany who were not tested with the reference allergens) to which they had the previous response. The Investigator used his or her experience and medical expertise to determine if a subject with a past positive patch result should be tested with all investigational allergen panels or only to the allergen to which the subject had the past response. Subjects with suspicion of metal contact allergy were tested with all investigational and reference allergens (with the exception of subjects enrolled in Germany who were not tested with the reference allergens). All subjects were tested with the excipient controls on panel 6.

One hundred twenty-one (121) of the 122 enrolled subjects completed the study and were compliant with the 2-day patch application period. One subject removed her patched prior to the 2nd visit due to a family emergency. One hundred twenty-two (122) subjects were included in the FAS population and 121 subjects were included in the mFAS population.

The primary endpoints for selection of optimal test allergen dose were the lowest concentration eliciting 1+ or 2+ or 3+ positive reactions in a minimum of 15 of subjects with the fewest number of 3+ reactions and overall concordance and discordance compared to the reference allergen. The frequency of ranked skin responses, positive (1+, 2+, 3+), negative, doubtful, and irritant reactions was calculated for each investigational allergen. Concordance between each dose and the corresponding reference allergens was calculated using Kappa statistic.

Two of the investigational allergens, aluminum and molybdenum, did not meet the minimum criteria of at least 15 subjects with positive responses therefore they will not be included on the final metal panel.

Four allergens, copper, manganese, vanadium sulfate and zinc only had one dose that did meet the minimum criteria of at least 15 subjects with positive responses therefore determination of optimal dose was based solely on this primary endpoint. There were 2 doses of vanadium chloride that also meet the minimum criteria of at least 15 subjects with positive responses, however, the vanadium chloride allergen was eliminated from consideration for the final panel due to the corrosive nature of the vanadium chloride raw material which complicated its handling during the production and storage of the experimental panel.

The tin and titanium allergens each had 2 doses that met the minimum criteria of at least 15 subjects with positive responses therefore both primary and secondary endpoints were considered in the determination of optimal dose.

Tin: There were 25 subjects with positive responses to the 0.11 mg/cm^2 dose of tin chloride and 65 subjects with positive responses to the 0.33 mg/cm^2 dose of tin chloride therefore the secondary endpoint results were considered in the determination of optimal dose.

Only slight differences were observed between the 2 doses for the number of doubtful, 3+ reactions and Kappa statistic. The 0.11 mg/cm^2 dose had fewer irritant responses but, for the

majority of the allergens tested on this study, including tin, the number of irritant responses increased as the dose increased.

Ultimately the decision to select the 0.33 mg/cm^2 dose of tin chloride as optimal dose was based on the greater number of 1+ and 2+ responses, lower percentage of late responses, higher number of persistent reactions and higher sensitivity.

Titanium: Ammonium titanium oxide oxalate was the only titanium salt that met the minimum criteria of at least 15 subjects with positive responses. There were 21 subjects with positive responses to the 0.11 mg Ti/cm^2 dose and 18 subjects with positive responses to the 0.22 mg Ti/cm^2 dose therefore, the secondary endpoint results were considered in the determination of optimal dose.

A nonmonotonic dose response curve was observed for this allergen. There was no statistically significant difference between the 2 doses that met the minimum criteria of at least 15 subjects with positive responses therefore both were considered in the selection of optimal dose. In addition, there were only slight differences between the number of doubtful, irritant, 1+ and 2+ reactions, 3+ reactions, sensitivity and specificity.

The decision to select the 0.22 mg Ti/cm^2 dose as optimal dose was based on favorable Kappa statistic fewer late responses and more persistent reactions.

Date of Report: May 19, 2020

3.0 TABLE OF CONTENTS

Listing of Figures

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4.0 LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

ACD	Allergic Contact Dermatitis
AE	Adverse Event
BL	Biologics License
BLA	Biologics License Application
CI	Confidence Interval
CRF	Case Report Form
CV	Curriculum Vitae
FAS	Full Analysis Set
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act
HPC	Hydroxypropyl cellulose
ICDRG	International Contact Dermatitis Research Group
IEC	Independent Ethics Committee
IR	Irritant Reaction
IRB	Institutional Review Board
Late Reaction	A positive reaction that initially appears at day 7-14
mFAS	Modified Full Analysis Set
N	Total number
n	Number in specified category
Nonmonotonic	A change in the slope of a dose-response relationship over the range of doses tested
Persistent Reaction	A positive reaction that initially appears at day 2- 4 and persists through day 7-21 or beyond.
PVP	Polyvinylpyrrolidone or Povidone
RA	Reference Allergen
SAS	Statistical software from SAS Institute Inc., Cary, NC
Sensitivity	The ability of a test to correctly identify those with the disease (true positive rate),
Specificity	The ability of the test to correctly identify those without the disease (true negative rate).
SOC	System Organ Class
STD	Standard Deviation
T.R.U.E. Test	Thin-layer Rapid Use Epicutaneous Test
USA	United States of America
UV	Ultraviolet

5.0 ETHICS

5.1 Independent Ethics Committee (IEC) or Institutional Review Board (IRB)

Ethics Committee or Review Board	Approval Date
Oregon Health & Science University Institutional Review Board, Portland, Oregon, USA	September 13, 2016
Institutional Review Board National Jewish Health Denver Colorado, USA	January 31, 2017
Prof. A.P. Perruchoud, Präsident EKNZ Ethikkommission Nordwest- und Zentralschweiz Basel, Switzerland	November 9, 2016
Comitato Etico Ospedale San Raffaele Milano, Italy	August 26, 2016
Medisch Ethische Toetsingscommissie VUmc Amsterdam, Netherlands	January 30, 2018
Ethikkommission der Ludwig-Maximilians-Universität München, München, Germany	April 9, 2018
Clinical Trial Center for Developmental Therapeutics Tokushima University Hospital, Tokushima, Japan	October 19, 2016
Toho University Omori Medical Center Institutional Review Board, Omori-Nishi, Ota-ku, Tokyo, Japan	May 1, 2017
Institutional Review Board of Fujita Health University Second Educational Hospital, Nagoya, Japan	June 20, 2017

5.2 Ethical Conduct of the Study

This study was conducted in accordance with Good Clinical Practices (GCP) and the ethical principles that have their origins in the Declaration of Helsinki.

5.3 Patient Information and Consent

Prior to enrollment and before any study-specific assessments were conducted, subjects who were willing to participate were given ample opportunity to read the IRB/IEC approved consent form and have all questions answered regarding the purpose, procedures, requirements, restrictions, possible risks, confidentiality of personal protected health information and the right to withdraw . Subjects were also informed about the voluntary nature of participation and whom to contact for questions or concerns. In addition to the original signed version of the consent form maintained by the Investigator, subjects were provided a duplicate copy to retain for his or her records.

6.0 INVESTIGATORS AND STUDY ADMINISTRATIVE STRUCTURE

6.1 Investigators

The study was conducted at 9 investigative sites:

Site 1. Patricia L Norris, M.D. Portland, Oregon, USA (1 screen fail only. No subjects enrolled at this site)
Site 2. Karin Pacheco, MD, Denver Colorado, USA
Site 3. Prof. Dr. med. Andreas Bircher, Basel Switzerland (Study initiation through June 27, 2018) PD Dr. med. Kathrin Scherer Hofmeier, Basel Switzerland (June 27, 2018 through study completion)
Site 4. Prof. Paolo Pigatto, M.D., Milan, Italy
Site 5. Prof. dr. Thomas Rustemeyer, Amsterdam Netherlands
Site 6. Prof. Dr. med. Peter Thomas, Munich, Germany
Site 7. Maki Hosoki, DDS, PhD, Tokushima, Japan
Site 8. Hiromi Kanto MD, PhD, Tokyo, Japan
Site 9. Akiko Yagami, MD, PhD, Nagoya, Japan

6.2 Data Management

The data management was performed by Karmic Lifesciences operating as Cliantha Research, No. 8, Opp. AUDA Garden Bodakdev, Ahmedabad, 380054, India

6.3 Authors of the Report

This report was authored by:

- Kathy Shannon, CRA SmartPractice
- Jeannie Lombardo, Assistant Technical Editor, SmartPractice

7.0 INTRODUCTION

T.R.U.E. Test, (Thin-layer Rapid Use Epicutaneous Patch Test) was originally granted a Biologics License (BL) for 23 allergens and a blank patch (control) in 1994 (BL No. 1888). The allergens were selected from substances widely reported to induce allergic contact dermatitis (ACD). As new allergens become clinically relevant, there is an ever-growing need to expand the number of allergens included in T.R.U.E. Test. The next 5 allergens were added to a third panel of the T.R.U.E. Test product in 2007 (BLA 103738/5019 and BLA 103738/5027). An additional seven allergens were added in 2012. The current U.S.-available T.R.U.E. Test product includes three panels containing 35 allergen patches and a blank patch.

Each 0.81 cm^2 allergen patch is coated with one specific allergen or allergen mix. The allergens/allergen mixes are incorporated in exact dosage in a hydrophilic gel. The allergen-gel preparation is coated on an impermeable backing of polyester and dried to a thin film. The coated sheet is then cut into 9 mm x 9 mm square test patches. These allergen gel test patches are attached to a nonwoven rayon fiber tape coated with a medical acrylic adhesive to form a standard test panel. The 3 panels together form a standard test kit.

Patch test panels are typically applied to the skin of the upper back. The humidity of the skin hydrates the film and transforms to a gel, allowing the allergen to migrate into the skin, thereby reaching the cells of the immune system. The test is removed after 48 hours and read 72-96 hours after the application when the allergic responses are fully developed, and any mild irritant reactions

have faded. Additional readings at 1 week and 21 days after panel placement are also advised in some cases.

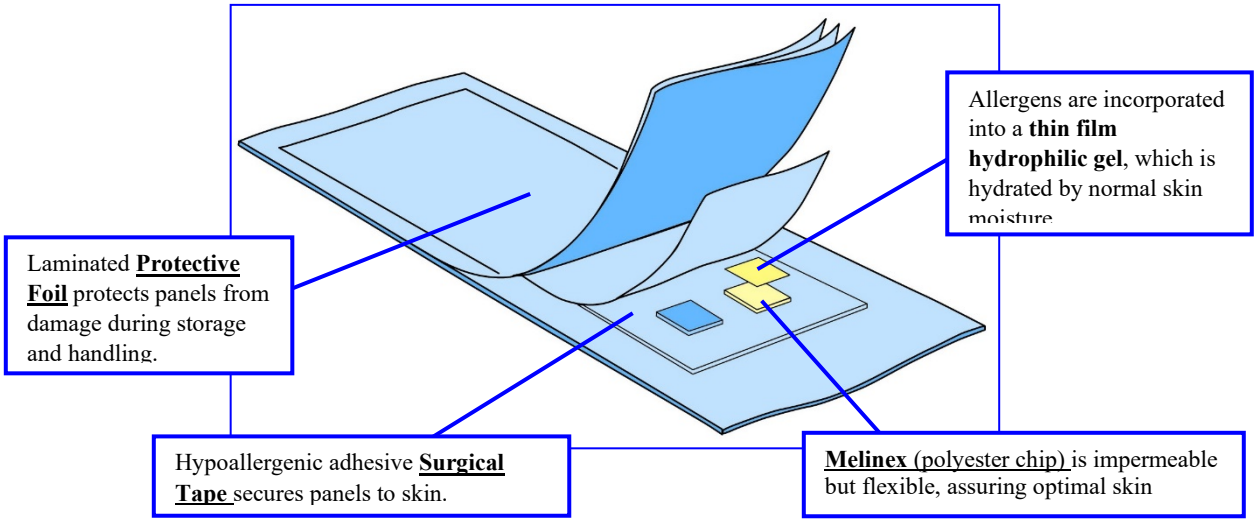
As a ready-to-use patch test method, T.R.U.E. Test is designed for use by licensed physicians in the diagnosis of ACD. T.R.U.E. Test has been evaluated in several large, multi-center clinical studies and is the only CBER approved ACD diagnostic.

Because metal contact allergy is increasing there is a need to develop a series of standardized metal patch test allergens utilizing the same allergen delivery technology as used in the T.R.U.E. Test product. The TRUE Test metal panel will be indicated for patients exposed to cardiac implants (stent, pacemaker, etc.), orthopedic implants (knee, hip or other), gynecological implants or devices, surgical hardware (plates, screws, wires, pins, rods, expanders, staples), dental metal implants, or dental metal appliances, prostheses or fillings whose exposure to has resulted in:

- Inflammation associated with an oral metal implant:
  - Burning mouth syndrome
  - Oral lichen planus
  - Oral lichenoid lesion
  - Palmoplantar pustulosis
  - Stomatitis: gingivitis, cheilitis and/or glossitis
- Itching, papules or nodules at injection site of aluminum containing vaccination
- Dermatitis over site of metal implant
- Systemic contact dermatitis
- Accelerated restenosis of cardiac stent
- Aseptic loosening
- Persistent joint pain
- Persistent and recalcitrant dermatitis
- Dorsal or patchy hand dermatitis
- Leg and foot dermatitis
- Facial dermatitis (excluding seborrheic)
- Discoid dermatitis
- Dermatitis with unusual distribution
- Atypical allergic symptoms

The final configuration of the proposed metal panel will depend on the results of the clinical trials.

Figure 1: Illustration of T.R.U.E. Test Product



8.0 STUDY OBJECTIVE

The objectives of this trial were to evaluate the diagnostic performance and safety of metal allergens proposed for inclusion in a TRUE Test metal panel by comparing the diagnostic performance (primary) and safety (secondary) of ascending patch test doses of aluminum, copper, manganese, molybdenum, tin, titanium, vanadium and zinc allergens and to determine if subjects who have not had previous patch testing are allergic to any of the most common metal allergens, nickel, cobalt chromium and gold.

9.0 INVESTIGATIONAL PLAN

9.1 Overall Study Design and Plan Description

This is a prospective, multi-center, randomized, double-blind design. Investigational allergen doses on panels 1-5 were randomized into three different configurations, which were randomly assigned to subjects as they entered the study. Although the investigators and subjects knew which allergens were being tested, they were blinded to the placement of the investigational allergen doses within each panel. Panel 6 which contained already approved metal allergens, excipient controls and a blank patch was not randomized. A 48-hour application (approximate) of the allergen panel(s) and corresponding reference petrolatum (or aqueous) allergen(s) were applied to the skin of human subjects to test for potential positive allergic responses. Test sites were evaluated at 3-4, 7-8, 10-14 and 19-23 days after application. The chosen evaluation times, consistent with generally accepted international patch test guidelines, are designed to prevent missed late reactions and false negatives. The final clinic visit (day 21) allowed the Investigator to evaluate any late or persistent localized reactions. The Investigator could choose to perform this visit via telephone if there were no residual reactions. If there were persistent escalating reactions noted at visit 6, the Investigator was to determine, and record follow up action.

The study population consisted of subjects with past positive patch test result to at least one of the investigational allergens being tested on this study or strong suspicion of metal contact allergy.

A minimum of 15 subjects per investigational allergen, who exhibit a positive skin response (score of 1+, +2 or 3+ during at least one reaction assessment visit) to the investigational allergen and/or at least one of its corresponding reference allergens, was needed to complete the study.

Subjects with a past positive patch test were tested with the allergen panel and corresponding reference allergens (with the exception of subjects enrolled in Germany who were not tested with the reference allergens) to which they had the previous response. Subjects with suspicion of contact allergy were tested with all investigational and reference allergens (with the exception of subjects enrolled in Germany who were not tested with the reference allergens). All subjects were tested with the excipient controls. The previously approved allergens (nickel, cobalt, chromium and gold) were tested at the discretion of the Investigator.

The study population was to include a reasonable representation of patients who had undergone a metal replacement procedure.

There were no data monitoring, special steering or evaluation committees or interim analysis performed during this trial.

9.2 Discussion of Study Design and Choice of Control Groups

This study was designed to evaluate the diagnostic performance of ascending concentrations of metal allergens in subjects with a historical positive patch test reaction to at least one of the investigational allergens or a suspicion of metal contact allergy.

- Subjects with a past positive patch test result were tested with the allergen to which they had previously reacted and the corresponding reference allergen (with the exception of subjects enrolled in Germany who were not tested with petrolatum reference allergens).
- Subjects who were enrolled based on a suspicion of contact allergy were tested with all investigational and reference allergens (with the exception of subjects enrolled in Germany who were not tested with petrolatum reference allergens).

During the first 2 days of the study, test sites and patch test panels were to remain dry and protected. Activities that involved excess moisture (sweat or water), movement, or sun exposure were to be avoided. After panel removal, through the final visit, subjects had to protect test sites from sun, irritation, medicaments, and foreign or harsh substances.

9.3 Selection of Study Population

A minimum of 15 subjects per investigational allergen, who exhibited a positive skin response (score of 1+, 2+ or 3+ during at least one reaction assessment visit) to each investigational allergen was needed to complete the study.

Subjects were recruited from patients visiting dermatology, allergy or similar medical practices and clinics for patch testing

9.3.1 Inclusion Criteria

a. 18 years of age or older.
b. Past positive patch test result within the past 10 years (to one of the dilution series metals being tested on this study) or strong suspicion of metal contact allergy based on results of the Qualification Questionnaire.
c. Unable to become pregnant or willing to use an acceptable method of contraception to prevent pregnancy if female of childbearing potential.
   - Inability to become pregnant would include all male subjects and female subjects who are postmenopausal for at least 1 year, or surgically sterile- have had a hysterectomy, bilateral ovariectomy, uterine ablation or bilateral tubal ligation.
   - Acceptable methods of contraception include: 1) systemic birth control (i.e., oral contraceptives, skin patch, vaginal ring, implant, injection, or intrauterine device (IUD), which contains either a hormone or copper); 2) double barrier method (i.e., diaphragm, cervical cap, sponge, condom with spermicide); 3) IUD; 4) vasectomized partner; or 5) abstinence from sexual intercourse. Subject must agree to use acceptable contraception for the duration of the entire study.
     (Notes:
     - *Cervical cap and abstinence from sexual intercourse will not be considered as acceptable methods of contraception for subjects enrolled in Japan*
     - *A double-barrier method must be used for all subjects enrolled in Switzerland who are practicing non-systemic methods of birth control.*
     - *Abstinence from sexual intercourse will not be considered an acceptable method of contraception for subjects enrolled in Switzerland)*
d. Understands and signs the approved Informed Consent form which is consistent with all institutional, local and national regulations.

9.3.2 Exclusion Criteria

a. Breastfeeding or pregnant (as determined by urine pregnancy test) or intending to become pregnant during the course of the study. Breastfeeding may be resumed upon completion of the study.
b. Topical treatment with corticosteroids or other immunosuppressive agents on or near the test area 14 days prior to inclusion through the end of the subject's participation in the study.
c. Systemic treatment with corticosteroids (equivalent to > 10 mg prednisone) or other immunosuppressive agents 14 days prior to inclusion through the end of the subject's participation in the study. Inhaled treatments and steroidal nose or eye drops are permitted.
d. Treatment with ultraviolet (UV) light (including tanning) during the 3 weeks prior to inclusion through the end of the subject's participation in the study.
e. Acute dermatitis outbreak or dermatitis on or near the test area on the back.
f. Known or suspected infection of the skin, joints or other site(s) associated with metal exposure
g. Condition such as, fibromyalgia, chronic fatigue, depression, cognitive impairment, flu-like symptoms, diarrhea and/or headache without at least one of the symptoms related to metal exposure listed in Section 10.1 under physical examination.
h. Condition such as, psoriasis, dermatitis herpetiformis, mycosis fungoides or cutaneous T-cell lymphoma that may confound the evaluation of allergic contact dermatitis.

i. Inability to comply with patch test study requirements including multiple return visits and activity restrictions (e.g., protecting test panels from excess moisture due to showering or vigorous activity).
j. Participation in a clinical trial of an investigational drug, treatment or device during this study or 3 weeks prior to inclusion in this study.
k. An opinion of the Investigator that deems the potential subject to be non-compliant, unable to return for study visits or complete the study as detailed in the protocol.

The following exclusion criteria were required in Germany only:

l. Alcohol abuse as well as drug and/or medication abuse.
m. Severe psychiatric, psychological or neurological disorders.
n. Patients in any relationship or dependency with the sponsor and/or Investigator.
o. General inflammatory as well severe acute and chronic inflammatory diseases.
p. Malignancy during the previous 5 years.
q. Completed or ongoing long-term treatment with tranquilizer or psycho active drug.

9.3.3 Removal of Patients from Therapy or Assessment

Subjects were permitted to withdraw from the study at any time. The Investigator was to use his/her discretion to excuse subjects from the study for missing two or more clinic visits, if they could no longer meet study requirements or if medically necessary.

Additional criteria for subject withdrawal include:

- Overreaction to an allergen. Defined as a response greater than Extreme Positive (3+). A severe reaction to the test tape adhesive or allergen patch that either causes the subject to remove the panels prior to the 48-hour return visit or is determined by the Investigator to be significantly greater in severity than expected or as described in the Investigator's Brochure. Test panels would be immediately removed, and reactions treated per standard medical guidelines.
- Unacceptable adverse events. Defined as development of severe itching and burning, a severe dermatitis flare-up or other adverse event that may be considered unacceptable.

Any subject withdrawn from the trial was to continue to receive normal standard of care. Subject withdrawal and reason for withdrawal were to be clearly described and documented in the subject's Case Report Form. Data from withdrawn subjects will be used in safety analysis. Withdrawn subjects were to be replaced.

9.4 Treatments

9.4.1 Treatments Administered

Investigational panels, produced, packed and labeled by the manufacturer SmartPractice Denmark, in Hillerød, Denmark, consisted of a 5.2 x 13.0 cm piece of surgical tape containing as many as 12 gel allergen patches. The allergen panels were applied to the skin of the upper back and worn for approximately 48 hours. While the patches are worn, the humidity of the skin hydrates the gel allowing the allergen to migrate into the skin to reach the cells of the immune system.

Six allergen panels were prepared for use in this clinical trial.

- Panel 1: Ascending doses of aluminum chloride and aluminum lactate
- Panel 2: Ascending doses of copper sulfate, zinc chloride and tin chloride
- Panel 3: Ascending doses of manganese chloride and ammonium molybdate
- Panel 4: Ascending doses of ammonium titanium peroxo citrate, ammonium titanium lactate, potassium titanium oxide oxalate and ammonium titanium oxide oxalate.
- Panel 5 Ascending doses of vanadium chloride and vanadium sulfate
- Panel 6: Nickel sulfate, potassium dichromate, gold sodium thiosulfate, cobalt dichloride, PVP negative control, HPC negative control and blank patch

In addition, subjects were tested with corresponding petrolatum reference allergens.

- The Aluminum Dilution Series were tested concurrently with
  - Aluminum chloride hexahydrate, 10 % w/w in petrolatum
  - Aluminum lactate, 12 % w/w in petrolatum
- The Copper Dilution Series were tested concurrently with copper sulfate anhydrous, 2 % w/w in petrolatum
- The Manganese Dilution Series were tested concurrently with manganese chloride tetrahydrate, 2 % w/w in petrolatum
- The Molybdenum Dilution Series were tested concurrently with ammonium molybdate, 1% aqueous solution.
- The Tin Dilution Series were tested concurrently with tin chloride dihydrate, 1% w/w in petrolatum
- The Titanium Dilution Series were tested concurrently with
  - Ammonium titanium peroxo citrate, 17% w/w in petrolatum
  - Ammonium titanium lactate, 34% aqueous solution
  - Potassium titanium oxide oxalate, 22% w/w in petrolatum
  - Ammonium Titanium oxide oxalate 19% w/w in petrolatum
- The Vanadium Dilution Series were tested concurrently with
  - Vanadium chloride, 1% w/w in petrolatum
  - Vanadium sulfate, 1.5% w/w in petrolatum
- The Zinc Dilution Series were tested concurrently with zinc chloride, 2% w/w in petrolatum

Note: Subjects enrolled in Germany were not tested with the reference allergens.

9.4.2 Identity of Investigational Products

Table 1: Identity of Investigational Panels

Panel 1: Batch Numbers: 16001, 18001

Allergen	Excipients	Doses (mg salt/cm²)	Randomized Among Positions
Aluminum chloride	Water, Ethanol, PVP	0.040, 0.12, 0.36, 0.72	7-10
Aluminum lactate	Water, Ethanol, PVP	0.047, 0.14, 0.42, 0.84	1-4

Panel 2: Batch Numbers: 16002, 18007

Allergen	Excipients	Doses (mg salt/cm²)	Randomized Among Positions
Copper sulfate	HPC, Water	0.013, 0.040, 0.080, 0.12	1, 2, 7, 8
Zinc chloride	HPC, Water	0.013, 0.040, 0.080, 0.24	3, 4, 9, 10
Tin chloride	HPC, Water, Ethanol	0.018, 0.037, 0.11, 0.33	5, 6, 11, 12

Panel 3: Batch Numbers: 16003, 18003

Allergen	Excipients	Doses (mg salt/cm²)	Randomized Among Positions
Manganese chloride	HPC, Water	0.013, 0.040, 0.080, 0.24	1-4
Ammonium molybdate	HPC, Water	0.0067, 0.020, 0.040, 0.12	7-10

Panel 4: Batch Numbers: 16004, 18004

Allergen	Excipients	Doses (mg Ti/cm²)	Randomized Among Positions
Titanium peroxo citrate	PVP, Water	0.055, 0.11, 0.22	1, 2, 3
Titanium lactate	PVP, Ethanol	0.070, 0.14, 0.28	4, 5, 6
Potassium titanium oxide oxalate	PVP, Ethanol	0.060, 0.12, 0.24	7, 8, 9
Ammonium titanium oxide oxalate	PVP, Water	0.055, 0.11, 0.22	10, 11, 12

Panel 5: Batch Numbers: 16005, 18005

Allergen	Excipient	Doses (mg V/cm²)	Randomized Among Positions
Vanadium chloride	HPC, Water	0.0042, 0.0083, 0.025, 0.050	1, 2, 3, 4
Vanadium sulfate	HPC, Water	0.0042, 0.0083, 0.025, 0.050	7, 8, 9,10

Panel 6: Batch Numbers: 16006, 18006

Allergen/Control	Excipient	Dose (mg salt/cm²)	Position
Nickel sulfate	HPC	0.20	1
Potassium dichromate	PVP	0.054	2
Gold sodium thiosulfate	HPC	0.075	3
Blank patch negative control	None	NA	4
Cobalt dichloride	HPC	0.020	7
PVP negative control	PVP	NA	8
HPC negative control	HPC	NA	9

Note: Allergens on panel 6 were not randomized.

The following reference allergens were tested for comparison against the investigational allergens.

Table 2: Identity of Reference Allergens

Allergen	Excipient	Dose
Aluminum chloride hexahydrate	Petrolatum	10 % w/w (20 mg)
Aluminum lactate	Petrolatum	12 % w/w (20 mg)
Copper sulfate anhydrous	Petrolatum	2 % w/w (20 mg)
Manganese chloride tetrahydrate	Petrolatum	2 % w/w (20 mg)
Ammonium molybdate	Water	1 % w/w (20 mg)
Tin chloride dihydrate	Petrolatum	1 % w/w (20 mg)
Ammonium titanium peroxo citrate	Petrolatum	17 % w/w (20 mg)
Ammonium titanium lactate	Water	34 % w/w (20 mg)
Potassium titanium oxide oxalate	Petrolatum	22 % w/w (20 mg)
Ammonium titanium oxide oxalate	Petrolatum	19 % w/w (20 mg)
Vanadium chloride	Petrolatum	1 % w/w (20 mg)
Vanadium sulfate	Petrolatum	1.5 % w/w (20 mg)
Zinc chloride	Petrolatum	2 % w/w (20 mg)

The investigative staff dispensed approximately 20 mg into a patch test chamber in preparation for application of the test chamber onto the subject's back. The Investigator was not blinded to the placement location of the reference allergens.

9.4.3 Method of Assigning Patients to Treatment Groups

The study population consisted of subjects with a past positive patch test result to at least one of the investigational metal allergens being tested on this study or strong suspicion of metal contact allergy. Subjects who reported a past positive patch test result were asked to verify the name of the allergen tested, the test date, test results and past and/or current related symptoms.

Thirty-five (35) subjects with a total 42 past positive responses of were enrolled. Five (5) subjects had past positive responses to 2 allergens and 1 subject had past positive responses to 3 allergens.

Table 3: Number Past Positive Patch Test Responses per Allergen

Allergen (Percentage based on 122 subjects)	Number of Past Positive Patch Test Responses	
	n	%
Aluminum	0	-
Copper	10	8.2
Manganese	7	5.7
Molybdenum	0	-
Tin	3	2.5
Titanium	13	10.7
Vanadium	0	-
Zinc	9	7.4

Source: Table 14.1.4: Summary of Subjects Qualified for Inclusion Based on Past Positive Patch Test Results -FAS Population
See also: Listing 16.2.9.5, Subjects Qualified for Inclusion Based on Past Positive Patch Test

Subjects for whom the Investigator suspected contact allergy associated with metal exposure were asked for the type of implant metal to which they had been exposed (cardiac implant, orthopedic implant, gynecological implant, surgical hardware, dental metal implant, appliance, prosthesis or filling, injection of aluminum containing vaccination or other) in addition to the name and date of the procedure, date symptoms first began, description of symptoms, sites of onset, whether the symptoms are current or sporadic, if there are any additional symptoms and medications taken for the problem.

Ninety-three (93) subjects were enrolled based on suspicion of contact allergy. Twelve (12) of these subjects were enrolled for more than one type of metal exposure. One of the 12 subjects was enrolled for 3 types of metal exposure.

Table 4: Types of Metal Exposure Supporting Suspicion of Contact Allergy

Type of Metal Exposure (Percentage based on 122 subjects)	No. of Subjects per Category	
	n	%
Cardiac implant (stent, pacemaker, etc.)	2	1.6
Orthopedic implant (knee, hip or other)	41	33.6
Gynecological implant or device	1	0.8
Surgical hardware (plates, screws, wires, pins, rods, expanders, staples)	9	7.4
Dental metal implant	15	12.3
Dental metal appliance, prosthesis or filling	35	28.7
Injection of aluminum containing vaccination	0	-
Other	4	3.3

Source: Table 14.1.5: Summary of Subjects Qualified for Inclusion Based on Suspicion of Contact Allergy – FAS Population
See also Listing 16.2.9.6 Subjects Qualified for Inclusion Based on Suspicion of Contact Allergy and Listing 16.2.4.3 for Medications Taken for Metal Allergy.

Investigators were also given the option to enroll subjects based on reason other than past positive patch test or suspicion of contact allergy based on metal exposure. Only 1 subject who was allergic to sunscreen was enrolled exclusively for reason other than past positive patch test or suspicion of contact allergy. The 3 subjects enrolled for past positive lymphocyte proliferation/transformation test were also enrolled for a past positive patch test (1 subject), orthopedic implant (1 subject) and dental implant (1 subject).

Table 5: Other Reasons for Study Inclusion

Other Reason Investigator Believed Subject Qualified for Study Inclusion (Percentage based on 122 subjects)	Number of Subjects per Category	
	n	%
Past Positive lymphocyte proliferation/transformation test	3	2.5
Allergic to sunscreen cream	1	0.8

Source: Listing 16.2.9.4 Subjects Qualified for Inclusion Based on Other Reason

In summary 122 subjects were enrolled.

- 84 subjects were enrolled based on suspicion of contact allergy only

- 28 subjects were enrolled based on past positive patch test only
- 6 subjects were enrolled based on past positive patch test and suspicion of contact allergy
- 1 subject was enrolled based on past positive patch test, suspicion of contact allergy and past lymphocyte proliferation/transformation test (other reason) although results of the lymphocyte proliferation test were negative
- 2 subjects were enrolled based on suspicion of contact allergy and past lymphocyte proliferation/transformation test (other reason)
- 1 subject was enrolled for other reason exclusively (allergic to sunscreen)

Table 6: Summary of Subjects Enrolled

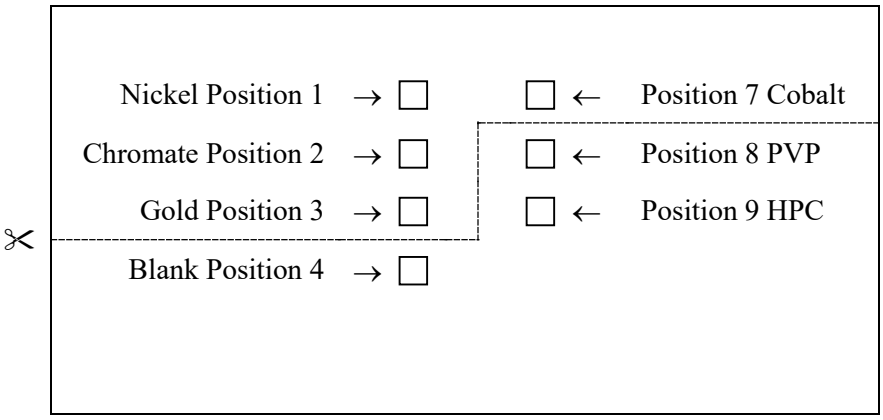
Past Positive Patch Test (28+6+1)		Suspicion of Contact Allergy (84+6+1+2)		Other Reason (1+2+1)	
n	%	n	%	n	%
35	28.7	93	76.2	4	3.3

Source: Table 14.1.6: Summary of Subjects Qualified for Inclusion Based on Past Positive Patch Test, Suspicion of Metal Contact Allergy or Other Reason – FAS Population

The investigational panels were applied to the subject populations per the following:

- Subjects with a past positive patch test were tested with at least the allergen panels(s) and corresponding reference allergen(s) (with the exception of subjects enrolled in Germany who were not tested with the reference allergens) to which they had the previous response.
  - The Investigator used his or her experience and medical expertise to determine if a subject with a past positive patch result should be tested to all investigational allergen panels or only to the allergen to which the subject had the past response.
  - Subjects with a past positive response to copper, zinc, tin, manganese or molybdenum were tested with the panel containing the past positive response allergen plus the other allergen(s) located on the same panel.
- Subjects with suspicion of metal contact allergy were tested with all investigational and reference allergens (with the exception of subjects enrolled in Germany who were not tested with the reference allergens).
- All subjects were tested with the excipient controls on panel 6. The Investigator used his or her experience and medical expertise to determine if a subject with a strong suspicion of metal contact allergy who had not undergone previous patch testing would benefit from being patch tested with the four allergens previously approved in the T.R.U.E. Test BLA103738 (nickel, chromate, cobalt and gold) in order to provide the individual with a complete diagnosis of metal contact allergy. The Investigator was given the option to cut these allergens from panel 6 as illustrated below, before applying the panel.

Figure 2: Illustration of Panel



9.4.4 Selection of Doses in the Study

Investigational panels were produced with ascending doses of allergen and an excipient control. The dose of each investigational allergen salt was selected based on the dose of the marketed petrolatum allergen. Incremental increases and decreases from the marketed dose were used to calculate higher and lower doses to produce each ascending dose series.

9.4.5 Selection and Timing of Dose for Each Patient

Investigational allergen panels and corresponding reference allergens (with the exception of subjects enrolled in Germany) were applied to the paraspinal region of the upper back at visit 1 (day 0) after the informed consent was signed and all inclusion/exclusion criteria were satisfied.

Patches, worn for approximately 48 hours, were removed at visit 2 (day 2) of the study.

9.4.6 Blinding

Investigational allergen patch doses were randomized within each allergen panel on panels 1-5 into three different configurations, per standard protocol. These different allergen configurations were randomly assigned to subjects as they entered the study. Although the investigators and subjects knew the allergen to which they were being tested, they were blinded to the placement of the allergen doses within each panel.

Because the Investigator was aware of the allergens and doses to which their subjects were being tested, a treatment code was not provided to the Investigator during the study.

The Investigator was not blinded to the placement location of panel 6 allergens and controls and the reference allergens.

9.4.7 Prior and Concomitant Therapy

Subjects were excluded from the study if they had undergone topical treatment with corticosteroids or other immunosuppressive agents on or near the test area during the 14 days prior to screening. Subjects also were excluded if, during this same time period, they had undergone systemic treatment with corticosteroids (equivalent to >10 mg prednisone) or other immunosuppressive

agents. Finally, subjects must not have used ultraviolet light treatments (including tanning) during the 3 weeks before screening.

All subjects were qualified for enrollment based on their previous medical history, use of non-exclusionary concomitant medications, results of urine pregnancy testing and satisfaction of inclusion/exclusion criteria. In addition, the Investigator performed a physical examination to record current symptoms of dermatitis related to metal exposure and additional sites of dermatitis prior to patch placement.

See also:
- Listing 16.2.2 Inclusion-Exclusion Criteria,
- Listing 16.2.4.2 Other Medical History Concomitant Medications
- Listing 16.2.8.1 Urine Pregnancy Test Results
- Listing 16.2.9.1.1 Current Symptoms Associated with Metal Exposure
- Listing 16.2.9.1.2 Additional Sites of Dermatitis

9.4.8 Treatment Compliance

Subjects were considered to have followed all aspects of the trial if they:

- Wore the patch test panels for approximately 48 hours
  All subjects wore test panels for approximately 48 hours (2 days) with the exception of:
  - Subject 4-00001: Subject removed her patches prior to 48 hours to attend to a family emergency. Subject was dropped from the study.
  - Subject 7-00016: All reference allergen patch test panels were detached when subject returned for visit 2. (Investigational allergen panels were in place).
  - Subject 7-00021: Only the perimeters of panels 1-4, 6 and both reference panels were in contact with the skin when subject returned for visit 2. Individual patches had lifted, were not in contact with the skin. (Panel 5 remained in place).

- Adhered to the study schedule (returned for all visits)
  All subjects returned for all study visits with the exception of:
  - Subject 4-00001: Subject completed visit 2 then dropped from the study to attend to a family emergency.

  Although the following subjects returned for all visits, they deviated from the study schedule as follows
  - Subject 2-00012: Visit 4 was 1 day late
  - Subject 3-00001: Visit 6 was 2 days late
  - Subject 4-00002: Visit 6 was 7 days late
  - Subject 4-00003: Visit 5 was 1 day early
  - Subject 4-00005: Visit 3 was 1 day late
  - Subject 4-00009: Visit 3 was 1 day late
  - Subject 5-00010: Visit 6 was 1 day late
  - Subject 6-00004: Visit 6 was 1 day late
  - Subject 6-00005: Visit 6 was 5 days late
  - Subject 6-00010: Visit 6 was 2 days late

- Subject 6-00011: Visit 6 was 2 days late
- Subject 6-00013: Visit 6 was 1 day late
- Subject 7-00022: Visit 6 was 1 day early

- Avoided use of exclusionary medications
- Restricted activities that involved excess moisture (sweat or water), movement, or sun exposure while the patches were being worn.
- Protected the test sites from sun, irritation, medicaments, and foreign or harsh substances until their final study visit was completed.

There were no reports of exclusionary medications used during the study, activities that could have compromised panel adhesion during the application period or sun, irritation, medicaments or foreign harsh substances used by study subjects which could have compromised patch test site evaluations.

9.5 Efficacy and Safety Variables

9.5.1 Efficacy and Safety Measurements Assessed and Flow Chart

In order to satisfy the primary endpoint (efficacy measurements) patch test site skin reactions were graded 4 times during the 21-day evaluation period (i.e., 21 days after initial patch application). Investigational allergens, negative controls, and corresponding reference allergen skin sites were evaluated at 3-4, 7-8, 10-14 and 19-23 days after application. Test sites were evaluated for the presence of erythema, infiltration, papules, discrete vesicles and bullous reactions (primary endpoints) in addition to late and persistent reactions and tape irritation (secondary endpoints).

Documentation of potential adverse events (safety measurements) occurred at every post application study visit.

Table 7: Study Flow Chart

Day	0	2	3-4	7-8	10-14	19-23
Visit	1	2	3	4	5	6
Read and Sign Consent	X					
Study Eligibility Questions	X					
Urine Pregnancy Test	X					
Skin Examination	X					
Patch Application	X					
Adhesion Evaluation		X				
15-minute wait		X				
Tape Irritation Evaluation		X				
Itching and Burning		X				
Skin Reaction Evaluation			X	X	X	X
Possible Photographs of Patch Sites			X	X	X	X
Changes to Medications or Illness Questions		X	X	X	X	X

Note visit 6 may have been conducted over the telephone at the discretion of the Investigator. Subjects with no remaining residual reactions only.

9.5.2 Appropriateness of Measurements

The methods used in this study to evaluate patch test skin site reactions are similar to those used in the development of the T.R.U.E. TEST product. Skin reactions were evaluated using standard patch testing guidelines established by the International Contact Dermatitis Research Group (ICDRG). In addition, the excipient controls, blank patch and reference allergen comparators added to the robustness of the evaluations.

Evaluation of panel adhesion, tape irritation and chip irritation in addition to subject reported itching and burning associated with the test panels, contributed to the assessment of product safety.

9.5.3 Primary Efficacy Variables

The primary endpoint, determination of optimal test allergen dose as the lowest concentration eliciting either 1+ or 2+ or 3+ positive reaction in a minimum of 15 subjects with the fewest number of 3+ reactions, was measured by Investigator evaluation of patch test skin response scores at visits 3-6.

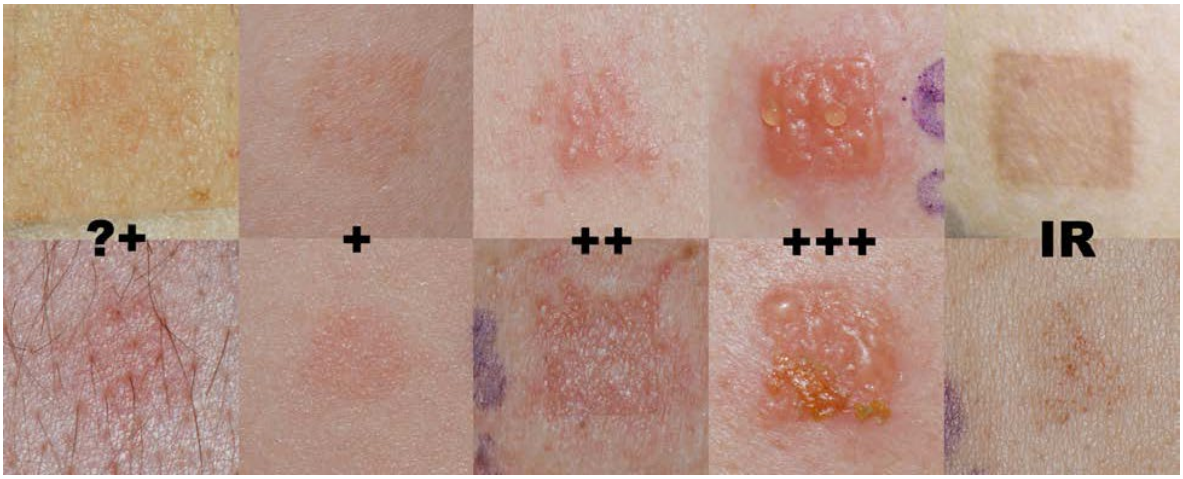
Investigational and reference allergen patch test site skin reactions were evaluated using standard patch testing guidelines established by the ICDRG.

Table 8: Patch Test Scoring Scale

Negative	No skin changes in the tested area
Doubtful (+?)	Faint, nonpalpable erythema, possibly few papules
1+ (+)	Palpable erythema, moderate edema or infiltrate, possibly few papules, no vesicles. Weak reaction.
2+ (++)	Strong infiltrate, numerous papules, possibly few vesicles present. Strong reaction.
3+ (+++)	Coalescing vesicles, bullae or ulceration. Extreme reaction.
Irritant (IR)	Inflammation sharply limited to the exposed area, lack of infiltrate, small petechiae, pustules, and efflorescences other than papules and vesicles.

Additionally, the following illustration of patch test reactions was presented to all Investigators to ensure consistent interpretation of evaluations across all study sites.

Figure 3: Skin Reaction Scoring Guidelines



Upon completion of visit 6, the Investigator categorized each patch test site skin reaction as either negative or positive. No positive skin reaction scores (1+, 2+ or 3+) assigned to during any of the reaction assessment visits (visits 3-6) constituted a negative reaction. A positive skin reaction was defined as an assigned score of 1+, +2 or 3+ during at least one reaction assessment visit (visits 3-6).

Positive reactions that initially appeared at day 7 or later were categorized as late. Positive reactions that initially appeared at day 3-4 and persisted through day 7-21 or beyond were categorized as persistent.

Collection of the parameters below contributed to the assessment of the primary and secondary endpoints.

- Frequency of positive, negative, doubtful, irritant, late and persistent skin reactions for each investigational and reference allergen dose in order to determine optimal dose
- Measurement of concordance between the investigational and reference allergens

9.5.4 Drug Concentration Measurements

This section does not apply to this clinical trial. No drug biological samples were collected to measure drug concentrations in relation to timing of administration or other physiological factors.

9.6 Data Quality Assurance

The study was performed according to ICH Harmonized Tripartite Guidelines for Good Clinical Practice, national legislation and SmartPractice internal SOPs for Clinical Studies. Study sites were visited at least once prior to initiation of the study, at approximately 4 to 8-week intervals or as needed during the study, and at the conclusion of the study. The monitoring visits were made to assess compliance with current GCP guidelines, to evaluate clinical trial progress, to assess the continued acceptance of the clinical trial site facilities, and to verify the data recorded on the CRFs. The final monitoring visits took place after the last subject exited the study (monitoring close-out visit). The sponsor performed all monitoring.

Subject source data were recorded on paper data collection forms. These data were entered into electronic case report forms by members of the study staff at each location and were proofread for entry errors. Statistical analysis was performed according to Good Clinical Practice and ICH guidelines using SAS software per the respective analytical parameters.

Medical monitoring processes and procedures were instituted to ensure that all medical data were valid and reliable. The procedures were designed to provide early recognition, identification, and reporting of issues that could have affected the health and well-being of the subjects. The designated medical monitor's responsibilities included providing requested clarification to sites regarding protocol procedures, querying protocol violations/deviations and asking for clarification or further information related to reported safety events and other clinical data. Subject safety was ensured by noting that appropriate consent documents existed, that appropriate study procedures were followed, and that AEs were reported and followed as appropriate. The Investigators maintained detailed records on all study subjects; study-specific data were recorded onto source document/case report forms (CRFs) for each subject. A 100% verification of the data was performed.

To enable evaluations and/or audits from health authorities and/or SmartPractice, the investigators agreed to keep appropriate records, including original Informed Consent/Assent forms, the identification of all participating subjects (sufficient information to link records, e.g., CRFs and hospital records) and supporting study documentation. Records are to be stored at the investigative sites, as written in the ICH guideline section 4.9.5 until "2 years after the last approval of a marketing application in ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product." Storage of all original CRFs and detailed records of the investigational product will be maintained by SmartPractice or their designated agent according to the current international clinical research regulations. CRFs are not to be made available in any form to third parties without written permission from SmartPractice, except to authorized representatives from regulatory authorities, Data Protection Agency and IRB/IEC.

9.7 Statistical Methods and Determination of Sample Size

9.7.1 Statistical and Analytical Plans

The frequency of ranked skin responses, positive (1+, 2+, 3+), negative, doubtful and irritant reactions was calculated for each allergen dose tested. The optimal allergen dose based on reaction scores was based on lowest dose eliciting positive reactions in a minimum of 15 subjects. If a significant number of 3+ reactions were elicited, the optimal allergen dose based on 1+ and 2+ positive reactions would have been selected.

Statistical processing was performed using SAS® software. Statistical significance was based on two-sided hypothesis testing resulting in p-values of 0.05 or less. Responses from each allergen dose were compared and the agreement was assessed by kappa statistic. P-value from testing against the null hypothesis that agreement was from chance alone was also presented.

The frequencies of adverse events were tabulated. Serious adverse events were described in detailed case reports.

9.7.2 Determination of Sample Size

The study population consisted of subjects with a past positive patch test result to at least one of the dilution series metals being tested on this study or strong suspicion of metal contact allergy. A minimum of 15 subjects per dilution series allergen, who exhibited a positive skin response (score of 1+, 2+ or 3+ during at least one reaction assessment visit) to the dilution series allergen and/or at least the corresponding reference allergen, was needed to complete the study. The study population was to include a reasonable representation of patients who had undergone a metal replacement procedure. Previous studies have indicated that this number of sensitive patients is sufficient for determining an effective allergen dose.

9.8 Changes in the Conduct of the Study or Planned Analyses

There were no changes to the conduct of the study or planned analysis which involved dropping a treatment group, investigational product dosage or adjusting the sample size.

The protocol was amended five times.

Amendment I:

- Address change for Dr. Pigatto in Milan, Italy
- Primary endpoint wording changed from approximately 50% of positive responses to at least 50% of positive responses
- Adverse event wording was enhanced
- Use of systemic and topical corticosteroids and immunosuppressive agents was changed from 14 days prior to inclusion to 14 days prior to inclusion through the end of the subject's participation.
- Treatment with UV light was changed from 3 weeks prior to inclusion to 3 weeks prior to inclusion through the end of the subject's participation.
- Exclusion criteria f was added: Known or suspected infection of the skin, joints or other site(s) associated with metal exposure
- Inclusion criteria h was added: A condition such as, psoriasis, dermatitis herpetiformis, mycosis fungoides or cutaneous T-cell lymphoma that may confound the evaluation of allergic contact dermatitis.
- Age of diagnosis, distribution, severity and current medication use (including those being withheld for the duration of the study) will be captured for subjects who exhibit concurrent atopic dermatitis and irritant dermatitis was added.
- Two paragraphs: Patches that do not remain in place (completely detached) for the intended wear period (approximately 48 hours or two days) will not be replaced. The subject will be asked to return for follow-up visits until all patch sites reactions have resolved but data from this subject will not be included in the analysis of positive responses necessary to determine optimal dose.
  Subjects whose patches are not worn for the intended wear period may return to be retested after 3 weeks at the discretion of the Investigator providing the skin site remains free of conditions that may affect test results were added.
- The section on randomization of dosages was enhanced.

Amendment II:

- Prof. Thomas Rustemeyer's credentials were updated
- Dr. Pigatto's phone number was updated
- The sentence 'The common allergens will be tested at the discretion of the Investigator' was added
- Wording in the following sentence was updated ' Metal Panel T.R.U.E. TEST will be indicated for patients exposed to cardiac implants (stent, pacemaker, etc.), orthopedic implants (knee, hip or other), gynecological implants or devices, surgical hardware (plates, screws, wires, pins, rods, expanders, staples), dental metal implants, or dental metal appliances, prostheses or fillings whose exposure to has resulted in: (remainder of list unchanged)
- Methods of systemic birth control were listed.
- Note regarding cervical cap and abstinence from sexual intercourse not be considered as acceptable methods of contraception for subjects enrolled in Japan was added
- Breastfeeding may be resumed upon completion of the study was added.
- A table with the visit schedule was added
- Note regarding legal representative in addition to subject must sign consent form for subjects aged 18-19, enrolled in Japan was added
- Description of dipstick pregnancy test was added.
- Numeric descriptors for positive skin reactions were added 1+, 2+, 3+ (not +, ++, +++)
- Definitions for late, persistent hyperpigmentation, hypopigmentation and pruritus were added.
- The sentence 'Panels are to be stored under refrigeration at 2-8ºC (36-46ºF)' was added.
- The sentence 'The allergens on panel 6 will not be randomized into different configurations. Should the Investigator elect to omit the common allergens from an individual's patch testing, the panel should be cut below positions 2 and 8 as shown in Figure 5', and Figure 5 were added
- The sentence 'Unused portion of the panel is not to be discarded' was added.
- The words 'number and identification of specific panels applied, application (or not) of common allergens' were added to the sentence 'The use of investigational product for the individual subject, including number and identification of specific panels applied, application (or not) of common allergens and date and time of application and removal will be documented'.
- The column headings in the dilution series tables were changed from 'Dose' to 'Ascending Dosages' and 'Randomized Among Positions'
- The column heading Position was added to the Common Allergens Excipient Control Table
- Insurance information was updated.

Amendment III:

- The contact information for Kayoko Matsunaga, M.D., Ph.D was updated.
- The address for Akiko Yagami, MD, PhD was updated.
- Information including contact information, site location and IRB for a new investigative site was added, Hiromi Kanto MD, PhD
- Information including contact information, site location and IRB for Investigator Risa Tamagawa-Mineoka MD was deleted.
- Professor Yoshiaki Kubo from Tokushima University Hospital was added as Sub-I.
- The order of the words in the sentence 'This is a prospective, multi-center, randomized, double-blind design was changed from double blind, randomized to randomized, double blind.

- The sentences 'That is, the allergen doses on each panel will be randomized into three different configurations, which will be randomly assigned to subjects as they enter the study. Although the Investigators and subjects will know which allergen is being tested, they will be blinded to the placement of the allergen doses within each panel were added.
- Determination of optimal test allergen dose wording was updated for clarification.
- The sentence 'The study population should include a reasonable representation of patients who have undergone a metal replacement procedure' was added.
- Justification of sample size was updated for clarification.
- Subjects enrolled in Germany will not be tested with the reference allergens was added to all sections where the use of reference allergens was mentioned.
- The sentence 'De-identified photographs of site reactions may be taken at the discretion of the Investigator and will not be reviewed or collected by the study sponsor,' was changed from Photographs of site reactions may be taken at the discretion of the Investigator.
- Characterizations of hyper/hypo pigmentation and/or pruritus or other described symptoms were removed from descriptions of late and persistent reactions.
- The sentence 'When this maximum number of subjects has been reached the sponsor of the study will inform the Investigator that the study has been concluded at that site' was added.
- Wording 'and to the FDA, European Commission and PMDA within 1 year of study completion was added to the end of the sentence 'The final report will be submitted to the Principal Investigator within 120 days of data base lock'.
- The sentence 'Independent IRB/Ethics committee approval of study protocol, any amendments and the informed consent form will be obtained prior to study initiation or prior to implementation of protocol changes' was changed to 'The study protocol, any amendments and the informed consent will receive favorable approvals from all regulatory authorities (US-FDA, Switzerland-Health Authority Swissmedic, Italy-Italian Medicines Agency, Netherlands-Medicines Evaluation Board, Germany-Paul Ehrlich Institut, Japan- PMDA) and from independent IRB/Ethics committees for each study site prior to study initiation or prior to implementation of protocol changes'.
- The following changes were made to methods of birth control:
  - A double-barrier method must be used for all subjects enrolled in Switzerland who are practicing non-systemic methods of birth control.
  - Abstinence from sexual intercourse will not be considered an acceptable method of contraception for subjects enrolled in Switzerland.
- Exclusion criteria l through q were added for subjects enrolled in Germany.
- The words 'and will remain anonymous' were added to the sentence 'Data from withdrawn subjects may be used in safety analysis'.
- The definition of overreaction to an allergen was enhanced for clarification
- The sentence 'The Investigator may withdraw a subject if the subject does not meet the study requirements' was added.
- The sentence 'The use of PatchMap will be required in Germany' was added.
- The sentence 'In summary, within these parameters, investigators will use their medical expertise to determine panel placement based on the features of each subject's back as they would normally do in clinical practice' was added.

- The Investigator will use his or her experience and medical expertise to determine if a subject with a past positive patch result should be tested to all dilution series allergens or only to the allergen to which the subject has had the past response.
- Subjects with a past positive response to copper, zinc, tin, manganese or molybdenum will be tested with the panel containing the past positive response allergen plus the other allergen(s) located on the same panel. Specifically, panel 2 contains copper, zinc and tin, and panel 3 contains manganese and molybdenum. Hence, subjects with a past positive response to one of the allergens on the panel will also be tested with the other allergen(s) located on the same panel. It will not be necessary to test the additional reference allergens were added.
- More complete direction and a figure regarding patch testing with nickel, chromium, cobalt and gold was added regarding cutting the panels to eliminate these allergens.
- The words 'panel 1-6' were removed from the sentence 'Following the 15-minute wait, tape sites (entire panel minus the chip sites) then the polyester chip sites will be evaluated for skin irritation'.
- More complete instruction regarding evaluation of tape vs, gel chip irritation was provided.
- Late and persistent reactions were redefined.
- A figure and wording to illustrate position numbering was added.
- Instructions regarding placement of panel 6 without the nickel, cobalt, chromium and gold allergens was added.
- Definitions and reporting procedures for adverse drug reactions and suspected unexpected serious adverse reactions were updated.
- Definition of active sensitization was updated.
- Anaphylactic reaction was changed to acute anaphylactic reaction and Investigator reference to the Guideline for Acute Therapy and Management of Anaphylaxis was added.
- The definition of tape reaction was updated.
- The sentence 'In the event that the study is prematurely terminated or interrupted all regulatory agencies will be notified within 15 days' was added.

Amendment IV

- Assistant Medical Director, Dathan Hamann, MD. was added to the study.
- The phone number for Kayoko Matsunaga, MD., PhD. was changed.
- Investigator, Patricia Norris, MD, left OHSU therefore would no longer be participating in the study. The investigative site and IRB were also removed from the protocol.
- The title for Maki Hosoki, DDS, PhD was updated.
- The reference for the Declaration of Helsinki was updated.
- The direction and illustration for cutting the nickel, chromium, cobalt and gold patches from panel 6 was updated.
- The location of PVP and gold on panel 6 was clarified

Amendment V

- Investigator, Prof Dr. med. Andreas Bircher who retired from the University Hospital, Basel was replaced by PD Dr. med. Kathrin Scherer Hofmeier
- The title for Maki Hosoki, DDS, PhD was updated.

- Investigator Akiko Yagami, M.D., Ph.D completed all her study obligations therefore was removed from the protocol.

10.0 STUDY PATIENTS (SUBJECTS)

10.1 Disposition of Subjects

One hundred twenty-two (122) subjects were enrolled:

- 13 at the site in Denver, Colorado, USA,
- 6 at the site in Basel, Switzerland,
- 9 at the site in Milan, Italy,
- 20 at the site in Amsterdam, Netherlands,
- 30 at the site in Munich, Germany,
- 24 at the site in Tokushima Japan,
- 15 at the site in Tokyo, Japan
- 5 at the site in Nagoya, Japan.

The first subject entered the study on December 5, 2016 and the last subject exited the study on July 15, 2019. One subject dropped from the study due to a family emergency. One hundred twenty-one subjects completed the study without major protocol violations (mFAS population).

Table 9: Summary of Subject Disposition

Subject Status	n	%
Number of subjects screened	124	
Number of screen failure subjects	2	
Number of subjects randomized in the study	122	100
Number of subjects completed the study	121	99.2
Number of subjects analyzed in FAS population	122	100
Number of subjects analyzed in mFAS population	121	99.2
Number of subjects who discontinued from the study	1	0.8
Reason for Discontinuation		
Adverse Event	0	-
Investigator's decision	0	-
Lost to follow-up	0	-
Subject withdrew consent	0	-
Other	1	0.8

Source: Table 14.1.1: Summary of Subject Disposition
See also: Listing 16.1.8: All Enrolled Subjects, Visit Dates and Final Status, Listing: 16.1.9: All Subjects by Population, Listing 16.2.1: Subject Disposition

10.2 Protocol Deviations

The following table summarizes the protocol deviations.

Table 10: Protocol Deviations

Protocol Deviation	n	%
Number of subjects with at least one protocol deviation	29	23.8
Type of Deviation		
Major	0	-
Inclusion/Exclusion Criteria	0	-
Source data	0	-
Study procedure	0	-
Visit Schedule	0	-
Minor	29	23.8
Inclusion/Exclusion Criteria	3	2.5
Source data	9[1]	7.4
Study procedure	4	3.3
Visit Schedule	14	11.5

[1]Total number of subjects with source data deviations is 9. Total number of source data deviations is 10. One subject had 2 source data protocol deviations
Source: Table 14.1.2: Summary of Protocol Deviations – FAS Population

Each deviation refers to a single incident unless otherwise indicated.

Inclusion/Exclusion Criteria Deviations (3):
- Subject, enrolled in Germany, was taking a maintenance anti-depression medication
- Subjects were enrolled into the study with a past positive patch test greater than 10 years ago. (2 subjects)

Source Data Deviations (10):
- AE questions were asked at visit 5, but answers were not recorded
- DCF did not include categorization of hypopigmentation, hyperpigmentation or pruritus at visits 4, 5 and 6 (8 subjects)
- Late entries for visit 2 evaluations after confirmation with medical record

Study Procedure Deviations (4):
- Subjects were enrolled due to suspicion of contact allergy but were not tested with all investigational panels
  - Panel 3 was not applied
  - Panels 1, 3, 4 and 5 were not applied
- Subject was enrolled due to suspicion of contact allergy but was not tested with all reference allergens
  - Only copper and zinc were applied
- Panel 6 was not applied

Visit Schedule Deviations (14):

- Visit 3 was out of window. Visit was 1 day late (2 subjects)
- Visit 4 was out of window. Visit was 1 day late
- Visit 5 was out of window. Visit was 1 day early
- Visit 6 was out of window.
  - Visit was 1 day early
  - Visit was 2 days early (3 subjects)
  - Visit was 1 day late (3 subjects)
  - Visit was 2 days late (2 subjects)
  - Visit was 5 days late

Source: Listing 16.2.3: Protocol Deviations

11.0 EFFICACY EVALUATION

11.1 Data Sets Analyzed

For inclusion in this study, subjects had to have a past positive patch test to one of the investigational allergens or a suspicion of contact allergy. Subjects with a past positive patch test were tested with the allergen panels(s) and corresponding reference allergen(s) (with the exception of subjects enrolled in Germany who were not tested with the reference allergens) to which they had the previous response unless the Investigator determined that the subject should be tested with additional investigational allergen panels.

Subjects with suspicion of metal contact allergy were tested with all investigational and reference allergens (with the exception of subjects enrolled in Germany who were not tested with the reference allergens).

All subjects were tested with the excipient controls on panel 6 with the exception of one subject for whom it was inadvertently not applied.

Due to differences between requirements for subjects with past positive patch tests versus those enrolled due to suspicion of contact allergy, a different number of subjects tested each panel and reference allergen.

Number of subjects testing each investigational panel:

- Panel 1: 105 subjects patched; all subjects completed the study
- Panel 2: 111 subjects patched; all subjects completed the study
- Panel 3: 105 subjects patched; 104 subjects completed the study
- Panel 4: 110 subjects patched; 109 subjects completed the study
- Panel 5: 107 subjects patched; 106 subjects completed the study
- Panel 6: 121 subjects patched; 120 subjects completed the study

Source: Listing 16.2.5.1: Investigational Panels Applied

Number of subjects testing each reference allergen:

- Aluminum chloride: 81 subjects patched; all subjects completed the study

- Aluminum lactate: 81 subjects patched; all subjects completed the study
- Copper sulfate: 83 subjects patched; all subjects completed the study
- Manganese chloride: 79 subjects patched; all subjects completed the study
- Ammonium molybdate: 80 subjects patched; 79 subjects completed the study
- Tin chloride: 79 subjects patched; 78 subjects completed the study
- Titanium citrate: 84 subjects patched; 83 subjects completed the study
- Titanium lactate: 84 subjects patched; 83 subjects completed the study
- Potassium titanium oxide oxalate: 84 subjects patched; 83 subjects completed the study
- Ammonium titanium oxide oxalate: 84 subjects patched; 83 subjects completed the study
- Vanadium chloride: 82 subjects patched; 81 subjects completed the study
- Vanadium sulfate: 82 subjects patched; 81 subjects completed the study
- Zinc chloride: 79 subjects patched; all subjects completed the study

Source: Listing 16.2.5.2: Reference Allergens Applied

In order to calculate concordance, sensitivity and specificity the number of paired comparisons was needed: that is, only subjects who tested and had results for both the investigational and corresponding reference allergen could be included in each calculation. The following lists the number of paired comparisons used for each allergen-corresponding reference allergen calculation.

Panel 1:
- 71 paired comparisons for all aluminum doses

Panel 2:
- 78 paired comparisons for all copper doses
- 73 paired comparisons for 0.018, 0.037 and 0.11 mg/cm^2 tin
- 72 paired comparisons for 0.33 mg/cm^2 tin
- 74 paired comparisons for all zinc doses

Panel 3:
- 70 paired comparisons for 0.013 mg/cm^2 manganese
- 69 paired comparisons for 0.040, 0.080 and 0.24, mg/cm^2 manganese
- 70 paired comparisons for 0.0067, 0.02 mg/cm^2 molybdenum
- 69 paired comparisons for 0.040 and 0.12 mg/cm^2 molybdenum

Panel 4:
- 76 paired comparisons for all allergens 0.11 and 0.055 mg/cm^2 titanium citrate, all titanium lactate, all potassium titanium oxide oxalate and all ammonium titanium oxide oxalate doses.
- 75 paired comparisons for 0.22 mg/cm^2 titanium citrate

Panel 5:
- 72 paired comparisons for all vanadium doses

Source: Table 14.1.7: Summary of Subjects Patched with Investigational and Corresponding Reference Allergen

Efficacy computations and tabulations were conducted using the number of enrolled subjects who tested each allergen and completed the study (mFAS population).

11.2 Demographic and Other Baseline Characteristics

Table 11: Summary of Subject Demographics – Safety Population

Demographic Characteristic	Statistic	Number of Subjects	
Age (Years)	n	122	
	Mean ± SD	59.2 ± 13.79	
	Median	60.0	
	Min, Max	26, 84	
		n	%
Age (Groups)	18 – 30	3	2.5
	31 – 40	13	10.7
	41 – 50	14	11.5
	>50	92	75.4
Gender	Male	29	23.8
	Female	93	76.2
Ethnicity (Origin)	African	0	-
	Asian	44	36.1
	European	64	52.5
	Latin/South American/Caribbean	1	0.8
	Oceanic	0	-
	North American	13	10.7
For North American only		n	%
Ethnicity	Hispanic or Latino	1	7.7
	Not Hispanic or Latino	12	92.3
Race	American Indian or Alaska Native	0	-
	Asian	1	7.7
	Black or African American	0	-
	White	12	92.3
	Other	0	-

Source: Table 14.1.3: Summary of Demographic Characteristics – FAS Population
See also Listing 16.2.4.1: Demographic Data

11.3 Measurements of Treatment Compliance

Allergen panels were applied at visit 1 and were to be worn for approximately 48 hours. Subjects returned two days later (visit 2) at which time the patches were removed. All patches were worn for the required amount of time with the exceptions of 3 subjects:

- Subject 4-00001 removed her patch test panels (subject was patched with investigational panels 3-6 and reference allergens 5-10 on panel 1) prior to 48 hours to attend to a family emergency. Subject was consequently dropped from the study.
- Subject 7-00016: Both reference panels were detached when subject returned for visit 2. (Investigational panels were in place).

- Subject 7-00021: Only the perimeters of panels 1-4, 6 and both reference panels were in contact with the skin when subject returned for visit 2. Individual patches had lifted, were not in contact with the skin. Panel 5 remained adhered.

Patch wear times for the all other subjects ranged from a minimum of 41 hours, 30 minutes to a maximum of 53 hours, 13 minutes. Average wear time was 47 hours, 36 minutes.

Source: Listing 16.2.5.1: Investigational Panels Applied and Listing 16.2.9.2 Panel Removal Dates and Times- All Subjects

In addition to patch wear time, adhesion of the panels was evaluated at visit 2 prior to panel removal according to the following scale.

Table 12: Adhesion Score Scale

Excellent	Skin contact good; all tape edges adherent; all allergens in contact with the skin
Good	Skin contact acceptable; some tape edges lifting; all allergens in contact with the skin
Poor	Little to no skin contact with panel; one or more allergens not in contact with the skin
Detached	Panel completely off the skin; none of the allergens in contact with the skin

The purpose of evaluating panel adhesion was to document allergen-to-skin contact during the 48-hour panel application period. Investigators were permitted to further secure panels with medical tape to ensure treatment compliance. The positions that were not in contact for each poor or detached score are detailed in Table 14

Table 13: Summary of Adhesion Scores

Panel	N	Excellent		Good		Poor		Detached		Missing[1]	
		n	%	n	%	n	%	n	%	n	%
Panel 1	105	102	97.1	1	1.0	2	1.9	0	-	0	-
Panel 2	111	103	92.8	3	2.7	5	4.5	0	-	0	-
Panel 3	105	98	93.3	3	2.9	3	2.9	0	-	1	1.0
Panel 4	110	105	95.5	1	0.9	3	2.7	0	-	1	0.9
Panel 5	107	100	93.5	6	5.6	0	-	0	-	1	0.9
Panel 6	121	113	93.4	5	4.1	2	1.6	0	-	1	0.8
Reference Panel 1	92	83	90.2	4	4.4	3	3.3	1	1.1	1	1.1
Reference Panel 2	86	77	89.5	6	7.0	1	1.2	1	1.2	1	1.2

[1]Subject 4-00001 removed patches prior to visit 2 due to a family emergency. Subject is included in FAS population although there is no adhesion score.
Source Table 14.1.8: Summary of Panel Adhesion at Visit 2 (Day 2) Prior to Removal – FAS Population

Table 14: Positions Not in Contact for Each Poor or Detached Adhesion Score

	Poor: Positions not in contact	Detached: Positions not in contact
Panel 1:	▪ Position 1 ▪ Positions 1-4, 7-10[1]	

	Poor: Positions not in contact	Detached: Positions not in contact
Panel 2:	▪ Position 1 ▪ Positions 1-12[1] ▪ Positions 5-6, 11-12 ▪ Position 6[2] ▪ Positions 6, 12	
Panel 3:	▪ Positions 1, 7 ▪ Positions 1-3, 7-8[2] ▪ Positions 1-4, 7-10[1]	
Panel 4:	▪ Position 1[2] ▪ Positions 1-12[1] ▪ Positions 6 and 12	
Panel 6:	▪ Position 1 ▪ Positions 1-4, 7-9[1]	
Reference Panel 1:	▪ Positions 1-10[1] ▪ Positions 3-5 ▪ Positions 7-10	▪ Positions 1-10[3]
Reference Panel 2:	▪ Positions 1-3[1]	▪ Positions 1-3[3]

[1] When Subject 7-00021 returned for patch removal only the perimeters of the indicated panels were in contact with the skin therefore, adhesion was evaluated as poor rather than detached although none of the individual patch positions were in contact with the skin. Patch test sites were not scored. Data from this subject is not included in paired comparison evaluations.
[2] Positions were not scored due to the fact that the patch test sites were not in contact with the skin when Subject 7-00010 returned for patch removal. Data for the individual positions is not included in the paired comparison evaluations
[3] Patch test sites were not scored. Data from Subject 7-00016 is not included in paired comparison evaluations.
Source: Listing 16.2.6.1 Investigational and Reference Panel Adhesion Evaluation at Visit 2 (Day 2) Prior to Removal.

Skin Condition and factors that may have affected panel adhesion were recorded following panel removal.

Table 15: Summary of Skin Condition at Panel Removal

Skin Condition	N	Normal		Dry		Oily	
		n	%	n	%	n	%
	121	110	90.9	8	6.6	3	2.5

Source: Listing 16.2.9.3: Factors that may have Affected Panel Adhesion

Table 16: Summary of Factors that May Have Affected Adhesion at Panel Removal

Factors	N	None		Oily Skin		Excess Hair		Wet Panel		Sweat Skin Moisture		Activity Associated	
		n	%	n	%	n	%	n	%	n	%	n	%
	121	113	93.4	0	-	0	-	1	0.8	5	4.1	2	1.7

Source: Listing 16.2.9.3: Factors that may have Affected Panel Adhesion

11.4 Efficacy Results and Tabulations of Individual Patient Data

11.4.1 Analysis of Efficacy

The primary endpoints were used to determine the optimal test dose. In cases where more than one dose met the primary endpoint, the secondary endpoints were included in the selection criteria in order to choose the dose that was most able to elicit the majority of positive patch test responses within the first week, had better concordance with the reference allergen, more 1+ and 2+ responses than 3+ responses, a greater number of persistent (sustained) reactions or produced fewer doubtful and irritant reactions

Primary Endpoints:

- The lowest concentration of each dilution series allergen eliciting positive responses in a minimum of 15 subjects. Positive responses are defined as score of 1+, 2+ or 3+ during at least one reaction assessment visit. If a significant number of 3+ responses are elicited, the dose will be selected based on 1+ and 2+ responses.
- For all sites with the exception of Germany: Concordance will be measured using Cohen's kappa where less than 0% indicates no agreement, 0-20% indicates poor agreement, 20-40% indicates fair agreement, 40-60% indicates moderate agreement, 60-80% indicates good agreement and 80% or higher indicates very good agreement. Concordance will be measured using all subjects who are tested with each allergen and corresponding reference allergen.

Secondary Endpoints used in dose selection when more than 1 dose met the primary endpoint:

- Frequency of positive (1+, 2+, 3+) skin reactions for each investigational and reference allergen dose at each post removal visit and overall.
- Frequency of negative, doubtful, irritant, late and persistent skin reactions for each investigational and reference allergen dose at each post removal visit (late and persistent reactions at visits 4, 5 and 6 only).

Although not included in the primary or secondary endpoints, sensitivity and specificity were calculated for additional comparison between each investigational and corresponding reference allergen. Because the efficacy of the reference allergens has not been validated, measurement of true positive or true negative cannot be confirmed. The sensitivity and specificity results were only used to justify selection of optimal dose when all other options had been exhausted.

11.4.1.1 Aluminum

One hundred five (105) subjects were tested with all doses of the aluminum investigational allergens, however the primary endpoint, determination of optimal test allergen dose as the lowest

concentration eliciting positive responses in a minimum of 15 subjects, was not met for these allergens.

Table 17 summarizes the number and percentage of subjects with positive and negative responses to the aluminum investigational allergen doses based on the Investigator's Determination of Positive Reactions.

Table 17: Number and Frequency of Positive Responses: Aluminum Allergens

Aluminum Allergens		Positive			Negative		
		n	%	95% CI	n	%	95% CI
Aluminum chloride							
0.040 mg/cm²	N=105	0	-	(0.00, 3.45)	105	100	(96.55, 100.00)
0.12 mg/cm²	N=105	0	-	(0.00, 3.45)	105	100	(96.55, 100.00)
0.36 mg/cm²	N=105	1	0.9	(0.02, 5.19)	104	99.1	(94.81, 99.98)
0.72 mg/cm²	N=105	4	3.8	(1.05, 9.47)	101	96.2	(90.53, 98.95)
Aluminum lactate							
0.047 mg/cm²	N=105	0	-	(0.00, 3.45)	105	100	(96.55, 100.00)
0.14 mg/cm²	N=105	0	-	(0.00, 3.45)	105	100	(96.55, 100.00)
0.42 mg/cm²	N=105	0	-	(0.00, 3.45)	105	100	(96.55, 100.00)
0.84 mg/cm²	N=105	0	-	(0.00, 3.45)	105	100	(96.55, 100.00)

Source: Table 14.2.7: Summary of Investigator Determination of Positive Reactions – mFAS population See also: Listing 16.2.5.3: Investigator Determination of Positive Reactions at Post Visit 6

The insufficient number of subjects with positive test reactions to any dose of either aluminum allergen precluded meeting the primary endpoint of optimal dose. The aluminum allergen will not be further tested nor will be considered for inclusion on the proposed metal panel.

The remaining endpoints, fewest number of 3+ reactions, concordance between the investigational and reference allergens, frequency of 1+ and 2+ reactions, frequencies of late, persistent, irritant and doubtful reactions will not be discussed in the body of this report. Refer to the following tables and listings for complete results.

- Table 14.2.1: Summary of Skin Reactions Scores of Investigational and Reference Allergen Panels (Aluminum Panel) - mFAS population
- Table 14.2.8: Summary of Number of Subjects with Positive Responses to each Investigational Allergen - mFAS population.
- Table 14.2.9: Summary of Concordance on Investigator Determination of Aluminum Dilution Series of Positive Reaction - mFAS population.
- Table 14.2.17: Comparison of Skin Reactions for Aluminum Dilution Series vs. Reference Panel - mFAS population
- Table 14.2.25: Analysis of Sensitivity and Specificity for Aluminum Dilution Series vs Reference Panel - mFAS population.

- Table 14.2.33: Late Reactions at Visit 4 (Day 7-8), Visit 5 (Day 10-14) and Visit 6 (Day 19-23) - mFAS population
- Table 14.2.34: Persistent Reactions Visit 4 (Day 7-8), Visit 5 (Day 10-14) and Visit 6 (Day 19-23) - mFAS population
- Listing 16.2.6.4: Evaluation of Skin Reactions and Determination of Late and/or Persistent Reactions

11.4.1.2 Copper

One hundred eleven (111) subjects were tested with all doses of the copper sulfate investigational allergen. There were 16 subjects with positive responses to the 0.12 mg/cm^2 dose which was the only dose that met the minimum criteria of at least 15 subjects with positive responses. All other responses were negative which included 16 subjects with doubtful responses and 10 subjects with irritant responses. All positive responses were graded 1+ and 2+. There were no 3+ reactions.

Among the 16 subjects with positive responses, there were 3 subjects with late responses and 4 subjects with persistent reactions. All 3 late reactions occurred at visit 4. Two (2) of the persistent reactions persisted through visit 4, the other 2 persisted through visit 5. There were no persistent escalating reactions at or beyond visit 6 (day 21).

The following tables summarize the number and percentage of subject responses to the copper sulfate investigational allergen doses based on the Investigator's Determination of Positive Reactions.

Table 18: Number and Frequency of Positive Responses: Copper

Copper sulfate		Positive			Negative		
		n	%	95% CI	n	%	95% CI
0.013 mg/cm²	N=111	2	1.8	(0.22, 6.36)	109	98.2	(93.64, 99.78)
0.040 mg/cm²	N=111	9	8.1	(3.77, 14.83)	102	91.9	(85.17, 96.23)
0.080 mg/cm²	N=111	10	9.0	(4.41, 15.94)	101	91.0	(84.06, 95.59)
0.12 mg/cm²	N=111	16	14.4	(8.47, 22.35)	95	85.6	(77.65, 91.53)

Source: Table 14.2.7: Summary of Investigator Determination of Positive Reactions – mFAS population
See also: Listing 16.2.5.3: Investigator Determination of Positive Reactions at Post Visit 6

Table 19: Doubtful, Irritant, Positive, Late and Persistent Reactions: Copper

Copper sulfate 0.12 mg/cm^2											
Number of subjects tested =111								Number of subjects positive = 16			
Doubtful		Irritant		1+ and 2+		3+		Late		Persistent	
n	%	n	%	n	%	n	%	n	%	n	%
16	14.4	10	9.0	21	4.7	0	-	3	18.8	4	25.0

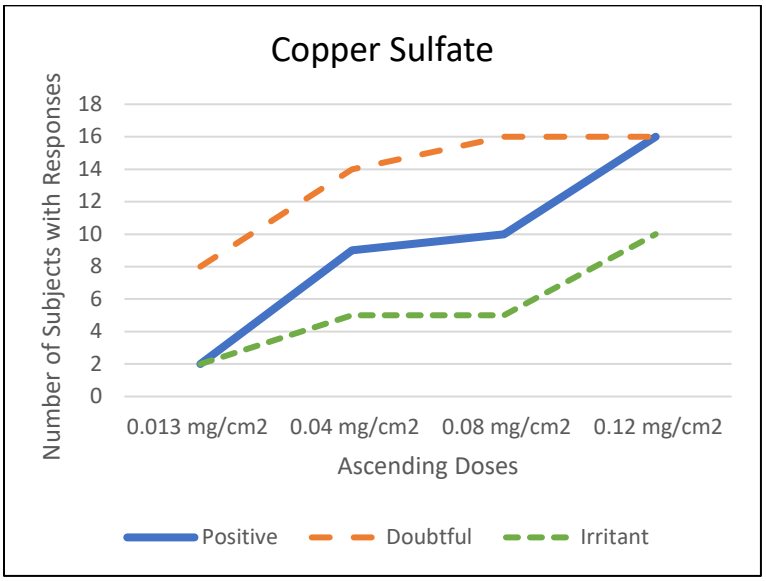
Source: Table 14.2.2: Summary of Skin Reaction Scores of Investigational and Reference Allergen Panels (Copper, Zinc, Tin Panel) – mFAS population.
Table 14.2.33: Late Reactions at Visit 4 (Day 7-8), Visit 5 (Day 10-14) and Visit 6 (Day 19-23) -mFAS population

Table 14.2.34: Persistent Reactions at Visit 4 (Day 7-8), Visit 5 (Day 10-14) and Visit 6 (Day 19-23) -mFAS population.

Percentages presented in the above table were calculated as follows:
- Doubtful and irritant: Total divided by number of subjects tested (scored once, at visit 3 only)
- 1+ and 2+, 3+: Total divided by number of subjects tested x 4 (scored 4 times, at visits 3-6)
- Late and persistent: Total divided by number of subjects positive

The following figure illustrates the dose response curve for the ascending doses of the copper sulfate allergen compared to the number of doubtful and irritant responses. Positive trendlines were observed for all parameters. Although the number of doubtful responses is equal to the number of positive responses for the 0.12 mg/cm^2 dose, (16 doubtful responses, 16 positive responses), the number of positive responses increased from 10 to 16 between the 0.080 mg/cm^2 dose and the 0.12 mg/cm^2 dose whereas, the number of doubtful responses remained constant.

Figure 4: Dose Response Curve: Copper Sulfate



Agreement between 0.12 mg/cm^2 dose of copper sulfate investigational allergen and 2% copper sulfate in petrolatum reference allergen was calculated for the 78 subjects who were tested with both the allergens. Table 20 presents concordance, sensitivity and specificity results for each subject paired comparison. Table 21 presents results for the number of subjects with positive and negative reactions who were tested with both allergens.

Table 20: Concordance and Sensitivity-Specificity: Copper

Investigational Allergen		Reference Allergen: Copper sulfate 2% pet	
		Positive	**Negative**
Copper sulfate 0.12 mg/cm^2	**Positive**	4	7
	Negative	6	61
	Percent agreement	5.13	78.21
	Kappa Statistics	0.28 (fair agreement)	
	95% CI	(-0.01, 0.58)	
	p-value	0.0117	
	Sensitivity	40.0%	
	Specificity	89.7%	
	Nº of paired comparisons	78	

Source: Table 14.2.10: Summary of Concordance on Investigator Determination of Copper Dilution Series of Positive Reactions – mFAS population
Source: Table 14.2.26: Analysis of Sensitivity and Specificity for Copper Dilution Series vs. Reference Panel -mFAS population

Table 21: Comparison of Skin Reactions to Reference Allergen: Copper

Copper sulfate		Positive		Negative	
		n	%	n	%
Copper sulfate 0.12 mg/cm^2	Nº tested both = 78	11	14.1	67	85.9
Copper sulfate 2% pet		10	12.8	68	87.2
95% CI		(-0.09, 0.12)			
p-value		0.8145			

Source: Table 14.2.18: Comparison of Skin Reaction for Copper Dilution Series vs. Reference Panel – mFAS population

11.4.1.3 Manganese

One hundred four (104) subjects were tested with all doses of the manganese chloride investigational allergen however the 0.040 mg/cm^2, 0.080 mg/cm^2 and 0.24 mg/cm^2 doses (positions 3, 2 and 1 respectively) for a single subject were not scored due to poor adhesion at patch removal. Of the 103 subjects with study results, there were 29 subjects with positive responses to the 0.24 mg/cm^2 dose which was the only dose that met the minimum criteria of at least 15 subjects with positive responses. All other responses were negative which included 17 subjects with doubtful responses and 10 subjects with irritant responses. All positive responses were graded 1+ and 2+. There were no 3+ reactions.

Among the 29 subjects with positive responses, there was 1 subject with a late response and 10 subjects with persistent reactions. The late response occurred at visit 4. Six (6) of the persistent

reactions persisted through visit 4, the other 4 persisted through visit 5. There were no persistent escalating reactions at or beyond visit 6 (day 21).

The following tables summarize the number and percentage of subject responses to the manganese chloride investigational allergen doses based on the Investigator's Determination of Positive Reactions.

Table 22: Number and Frequency of Positive Responses: Manganese

Manganese chloride		Positive			Negative		
		n	%	95% CI	n	%	95% CI
0.013 mg/cm²	N=104	1	1.0	(0.02, 5.24)	103	99.0	(94.76, 99.98)
0.040 mg/cm²	N=103[1]	0	-	(0.00, 3.52)	103	100[2]	(96.48, 100.00)
0.080 mg/cm²	N=103[1]	4	3.9[2]	(1.07, 9.65)	99	96.1[2]	(90.35, 98.93)
0.24 mg/cm²	N=103[1]	29	28.2[2]	(19.73, 37.87)	74	71.8[2]	(62.13, 80.27)

[1]Subject 7-00010, positions 1, 2 and 3, 0.24 mg/cm², 0.080 mg/cm² and 0.040 mg/cm² were not scored due to poor adhesion at patch removal.
[2]Percent positive and percent negative have been recalculated using number of results (vs number tested) for purposes of presentation in this report. 95% CI has not been recalculated
Source: Table 14.2.7: Summary of Investigator Determination of Positive Reactions – mFAS population
See also: Listing 16.2.5.3: Investigator Determination of Positive Reactions at Post Visit 6

Table 23: Doubtful, Irritant, Positive, Late and Persistent Reactions: Manganese

Manganese chloride 0.24 mg/cm²											
Number of subjects with results = 103								Number of subjects positive = 29			
Doubtful		Irritant		1+ and 2+		3+		Late		Persistent	
n	%	n	%	n	%	n	%	n	%	n	%
17	16.5[1]	10	9.7[1]	42	10.2[1]	0	-	1	3.4	10	34.5

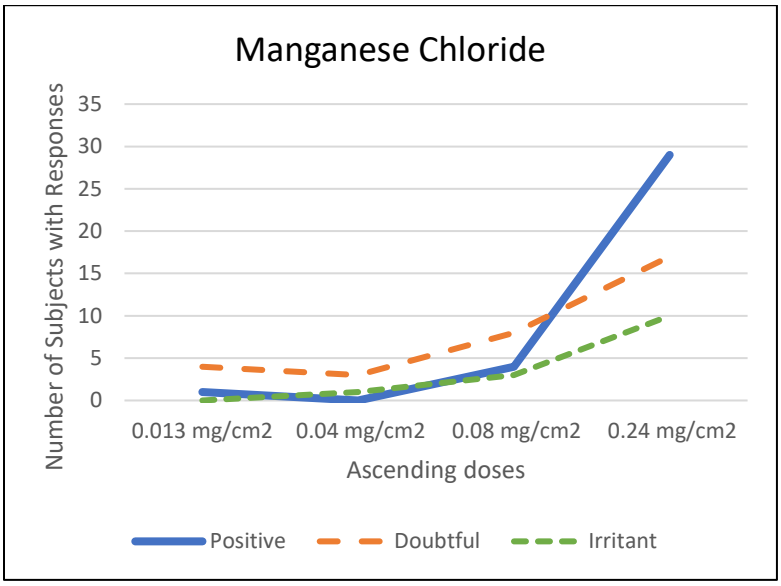
[1]Percentages have been recalculated using number of subjects with results (vs number tested) for purposes of presentation in this report.
Source: Table 14.2.3: Summary of Skin Reaction Scores of Investigational and Reference Allergen Panels (Manganese, Molybdenum Panel) – mFAS population.
Table 14.2.33: Late Reactions at Visit 4 (Day 7-8), Visit 5 (Day 10-14) and Visit 6 (Day 19-23) -mFAS population
Table 14.2.34: Persistent Reactions at Visit 4 (Day 7-8), Visit 5 (Day 10-14) and Visit 6 (Day 19-23) -mFAS population.

Percentages presented in the above table were calculated as follows
- Doubtful and irritant: Total divided by number of subjects with results x 1 (scored once, at visit 3 only).
- 1+ and 2+, 3+: Total divided by number of subjects with results x 4 (scored 4 times, at visits 3-6)
- Late and persistent: Total divided by number of subjects positive

The following figure illustrates the dose response curve for the ascending doses of the manganese chloride allergen compared to the number of doubtful and irritant responses. Although the number of irritant and doubtful reactions generally increased as the dose increased, there was a greater

difference between the number of doubtful and irritant reactions compared to the number of positive reactions at the 0.24 mg/cm^2 dose compared to the lower doses which is preferred.

Figure 5: Dose Response Curve: Manganese Sulfate



Agreement between the 0.24 mg/cm^2 dose of manganese chloride investigational allergen and 2% manganese chloride in petrolatum reference allergen was calculated for the 69 subjects who were tested with both allergens. Table 24 presents concordance, sensitivity and specificity results for each subject paired comparison. Table 25 presents results for the number of subjects with positive and negative reactions who were tested with both allergens.

Table 24: Concordance and Sensitivity-Specificity: Manganese

		Reference Allergens	
Investigational Allergen		Manganese chloride 2% pet	
		Positive	**Negative**
Manganese chloride 0.24 mg/cm^2	**Positive**	10	14
	Negative	1	44
	Percent agreement	14.5	63.8
	Kappa Statistics	0.45 (moderate agreement)	
	95% CI	(0.24, 0.66)	
	p-value	<.0001	
	Sensitivity	90.9%	
	Specificity	75.9%	
	Nº of paired comparisons	69	

Source: Table 14.2.11: Summary of Concordance on Investigator Determination of Manganese Dilution Series of Positive Reactions – mFAS population.

Source: Table 14.2.27: Analysis of Sensitivity and Specificity for Manganese Dilution Series vs. Reference Panel -mFAS population

Table 25: Comparison of Skin Reactions to Reference Allergen: Manganese

Manganese chloride		Positive		Negative	
		n	%	n	%
Manganese chloride 0.24 mg/cm^2	N^o tested both = 69	24	34.8	45	65.2
Manganese chloride 2% pet		11	15.9	58	84.1
95% CI		(0.05, 0.33)			
p-value		0.0110			

Source: Table 14.2.19: Comparison of Skin Reactions for Manganese Dilution Series vs. Reference Panel – mFAS population

11.4.1.4 Molybdenum

One hundred four (104) subjects were tested with all doses of the ammonium molybdate investigational allergen, however the primary endpoint, determination of optimal test allergen dose as the lowest concentration eliciting positive responses in a minimum of 15 subjects, was not met for this allergen.

Table 26 summarizes the number and percentage of subjects with positive and negative responses to the ammonium molybdate investigational allergen doses based on the Investigator's Determination of Positive Reactions.

Table 26: Number and Frequency of Positive Responses: Molybdenum

Ammonium molybdate		Positive			Negative		
		n	%	95% CI	n	%	95% CI
0.0067 mg/cm^2	N=104	1	1.0	(0.02, 5.24)	103	99.0	(94.76, 99.98)
0.02 mg/cm^2	N=104	0	-	(0.00, 3.48)	104	100	(96.52, 100.00)
0.040 mg/cm^2	N=103[1]	0	-	(0.00, 3.52)	103	100[2]	(96.48, 100.00)
0.12 mg/cm^2	N=103[1]	0	-	(0.00, 3.52)	103	100[2]	(96.48, 100.00)

[1]Subject 7-00010, positions 8 and 8, 0.12 mg/cm^2 and 0.040 mg/cm^2 were not scored due to poor adhesion at patch removal.
[2]Percent positive and percent negative have been recalculated using number of results (vs number tested) for purposes of presentation in this report. 95% CI has not been recalculated
Source: Table 14.2.7: Summary of Investigator Determination of Positive Reactions – mFAS population
See also: Listing 16.2.5.3: Investigator Determination of Positive Reactions at Post Visit 6

The insufficient number of subjects with positive test reactions to ammonium molybdate precluded meeting the primary endpoint of optimal concentration. The molybdenum allergen will not be further tested nor will it be considered for inclusion on the proposed metal panel.

The remaining endpoints, fewest number of 3+ reactions, concordance between the investigational and reference allergens, frequency of 1+ and 2+ reactions, frequencies of late, persistent, irritant and

doubtful reactions will not be discussed in the body of this report. Refer to the following tables and listings for complete results.

- Table 14.2.3 Summary of Skin Reactions Scores of Investigational and Reference Allergen Panels (Manganese, Molybdenum Panel) - mFAS population
- Table 14.2.8: Summary of Number of Subjects with Positive Responses to each Investigational Allergen - mFAS population.
- Table 14.2.12 Summary of Concordance on Investigator Determination of Molybdenum Dilution Series of Positive Reaction - mFAS population.
- Table 14.2.20: Comparison of Skin Reactions for Molybdenum Dilution Series vs. Reference Panel - mFAS population
- Table 14.2.28: Analysis of Sensitivity and Specificity for Molybdenum Dilution Series vs Reference Panel - mFAS population.
- Table 14.2.33: Late Reactions at Visit 4 (Day 7-8), Visit 5 (Day 10-14) and Visit 6 (Day 19-23) - mFAS population
- Table 14.2.34: Persistent Reactions Visit 4 (Day 7-8), Visit 5 (Day 10-14) and Visit 6 (Day 19-23) - mFAS population
- Listing 16.2.6.4: Evaluation of Skin Reactions and Determination of Late and/or Persistent Reactions

11.4.1.5 Tin

One hundred eleven (111) subjects were tested with all doses of the tin chloride investigational allergen however the 0.33 mg/cm^2 dose (position 6) for a single subject was not scored due to poor adhesion at patch removal. Of the subjects with study results there were 25 subjects with positive responses to the 0.11 mg/cm^2 dose and 65 subjects with positive responses to the 0.33 mg/cm^2 dose. All other responses to the 0.11 mg/cm^2 and 0.33 mg/cm^2 doses were negative which included 12 subjects with doubtful responses to each dose, 6 subjects with irritant responses to the 0.11 mg/cm^2 dose and 16 subjects with irritant responses to the 0.22 mg/cm^2 dose. The majority of positive responses were graded 1+ and 2+.

0.11 mg/cm^2 dose: Among the 25 subjects with positive responses, there were 5 subjects with late responses and 5 subjects with persistent reactions. Two (2) late responses occurred at visit 4, 2 occurred at visit 5 and 1 occurred at visit 6. The late response that occurred at visit 6 was captured as an adverse event. One (1) persistent reaction persisted through visit 4, 1 persisted through visit 5, and 3 persisted through visit 6. All visit 6 persistent reactions were scored 1+, persistent healing. There were no persistent escalating responses at visit 6 (day 21).

0.33 mg/cm^2 dose: Among the 65 subjects with positive responses, there were 6 subjects with late responses and 39 subjects with persistent reactions. All late responses occurred at visit 4. Twenty (20) persistent reactions persisted through visit 4, 13 persisted through visit 5, and 6 persisted through visit 6. Four of the visit 6 persistent reactions were scored 1+, persistent healing, one was graded 2+, persistent healing (was 3+ at visit 5) and 1 increased from a 1+ at visit 5 to 2+ at visit 6. This single, persistent escalating response was captured as an adverse event.

The following tables summarize the number and percentage of subject responses to the tin chloride investigational allergen doses based on the Investigator's Determination of Positive Reactions.

Table 27: Number and Frequency of Positive Responses: Tin

Tin chloride		Positive			Negative		
		n	%	95% CI	n	%	95% CI
0.0018 mg/cm²	N=111	1	0.9	(0.02, 4.92)	110	99.1	(95.08, 99.98)
0.037 mg/cm²	N=111	4	3.6	(0.99, 8.97)	107	96.4	(91.03, 99.01)
0.11 mg/cm²	N=111	25	22.5	(15.14, 31.43)	86	77.5	(68.57, 84.86)
0.33 mg/cm²	N=110[1]	65	59.1[2]	(49.31, 68.37)	45	40.9[2]	(31.63, 50.69)

[1]Subject 7-00010, position 6, 0.33 mg/cm² was not scored due to poor adhesion at patch removal.
[2]Percent positive and percent negative have been recalculated using number of results (vs number tested) for purposes of presentation in this report. 95% CI has not been recalculated
Source: Table 14.2.7: Summary of Investigator Determination of Positive Reactions – mFAS population
See also: Listing 16.2.5.3: Investigator Determination of Positive Reactions at Post Visit 6

Table 28: Doubtful, Irritant, Positive, Late and Persistent Reactions: Tin

Tin chloride 0.11 mg/cm²											
Number of subjects tested = 111								Number of subjects positive = 25			
Doubtful		Irritant		1+ and 2+		3+		Late		Persistent	
n	%	n	%	n	%	n	%	n	%	n	%
12	10.8	6	5.4	35	7.9	2	0.5	5	20.0	5	20.0
Tin chloride 0.33 mg/cm²: N=111											
Number of subjects with results = 110								Number of subjects positive = 65			
Doubtful		Irritant		1+ and 2+		3+		Late		Persistent	
n	%	n	%	n	%	n	%	n	%	n	%
12	10.9[1]	16	14.5[1]	122[1]	27.7[1]	3	0.7[1]	6	9.2	39	60.0

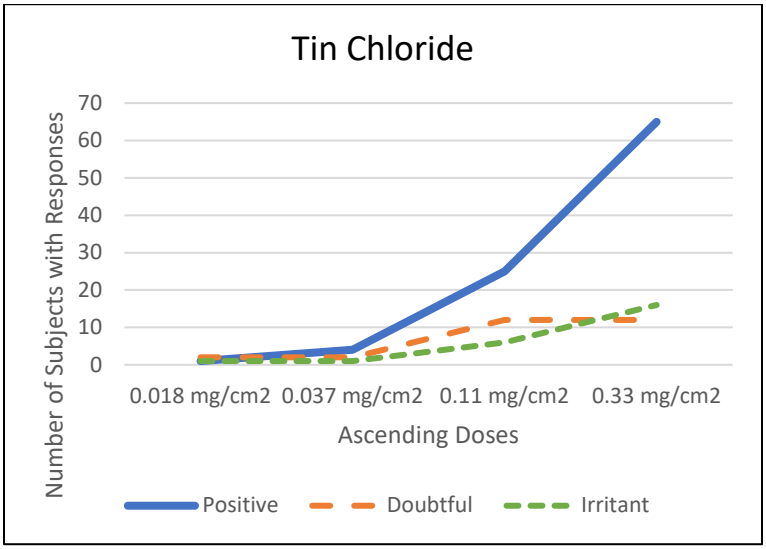
[1]Percentages have been recalculated using number of subjects with results (vs number tested) for purposes of presentation in this report.
Source: Table 14.2.2: Summary of Skin Reaction Scores of Investigational and Reference Allergen Panels (Copper, Zinc, Tin Panel) – mFAS population.
Table 14.2.33: Late Reactions at Visit 4 (Day 7-8), Visit 5 (Day 10-14) and Visit 6 (Day 19-23) -mFAS population
Table 14.2.34: Persistent Reactions at Visit 4 (Day 7-8), Visit 5 (Day 10-14) and Visit 6 (Day 19-23) -mFAS population.

Percentages presented in the above table were calculated as follows
- Doubtful and irritant: Total divided by number of subjects tested/number of subjects with results (scored once, at visit 3 only).
- 1+ and 2+, 3+: Total divided by number of subjects tested/number of subjects with results x 4 (scored 4 times, at visits 3-6)
- Late and persistent: Total divided by number of subjects positive

The following figure illustrates the dose response curve for the ascending doses of the tin chloride allergen compared to the number of doubtful and irritant responses. Although both the 0.11 mg/cm² and 0.33 mg/cm² doses had the same number of doubtful reactions, there was a greater difference

between the number of doubtful and irritant reactions compared to the number of positive responses for the 0.33 mg/cm^2 dose which is preferred.

Figure 6: Dose Response Curve: Tin Chloride



Agreement between the 0.11 mg/cm^2 dose of tin chloride investigational allergen and 1% tin chloride in petrolatum reference allergen and between the 0.33 mg/cm^2 dose of tin chloride investigational allergen and 1% tin chloride in petrolatum reference allergen was calculated for the subjects who were tested with both allergens. There are 73 paired comparisons for the 0.11 mg/cm^2 dose and 72 paired comparisons for the 0.33 mg/cm^2 dose. Table 29 presents concordance, sensitivity and specificity results for each subject paired comparison. Table 30 presents results for the number of subjects with positive and negative reactions who were tested with both allergens.

Table 29: Concordance and Sensitivity-Specificity: Tin

		Reference Allergens	
Investigational Allergen		Tin chloride 1% pet	
		Positive	**Negative**
Tin chloride 0.11 mg/cm^2	**Positive**	9	8
	Negative	11	45
	Percent agreement	12.3	61.6
	Kappa Statistics	0.31 (fair agreement)	
	95% CI	(0.07, 0.56)	
	p-value	0.0070	
	Sensitivity	45.0%	
	Specificity	84.9%	
	Nº of paired comparisons	73	

Investigational Allergen		Reference Allergens: Tin chloride 1% pet	
		Positive	**Negative**
Tin chloride 0.33 mg/cm^2	**Positive**	18	30
	Negative	2	22
	Percent agreement	25.0	30.6
	Kappa Statistics	0.23 (fair agreement)	
	95% CI	(0.07, 0.38)	
	p-value	0.0092	
	Sensitivity	90.0%	
	Specificity	42.3%	
	Nº of paired comparisons	72[1]	

[1]Data from subject 7-00010, position 6, 0.33 mg/cm^2 was not included in paired comparison due to poor adhesion when subject returned for patch removal. Site was not scored.
Source: Table 14.2.13: Summary of Concordance on Investigator Determination of Tin Dilution Series of Positive Reactions -mFAS population.
Source: Table 14.2.29: Analysis of Sensitivity and Specificity for Tin Dilution Series vs. Reference Panel - mFAS population

Table 30: Comparison of Skin Reactions to Reference Allergen: Tin

Tin chloride		Positive		Negative	
		n	%	n	%
Tin chloride 0.11 mg/cm^2	Nº tested both = 73	17	23.3	56	76.7
Tin chloride 1% pet		20	27.4	53	72.6
95% CI		(-0.18, 0.10)			
p-value		0.5681			
Tin chloride 0.33 mg/cm^2	Nº tested both = 72[1]	48	66.7	24	33.3
Tin chloride 1% pet		20	27.8	52	72.2
95% CI		(0.24, 0.54)			
p-value		<.0001			

[1]Data from subject 7-00010, position 6, 0.33 mg/cm^2 was not included in paired comparison due to poor adhesion when subject returned for patch removal. Site was not scored.
Source: Table 14.2.21: Comparison of Skin Reactions for Tin Dilution Series vs. Reference Panel -mFAS population

11.4.1.6 Titanium

One hundred nine (109) subjects were tested with all doses of the titanium investigational allergens however the 0.22 mg Ti/cm^2 dose of titanium citrate (position 1) for a single subject was not scored due to poor adhesion at patch removal.

Ammonium titanium oxide oxalate was the only titanium salt that met the minimum criteria of at least 15 subjects with positive responses. There were 21 subjects with positive responses to the 0.11 mg Ti/cm^2 dose and 18 subjects with positive responses to the 0.22 mg Ti/cm^2 dose. All other responses were negative which included 24 subjects with doubtful responses to the 0.11 mg Ti/cm^2 dose, 27 subjects with doubtful responses to the 0.22 mg Ti/cm^2 dose, 9 subjects with irritant responses to the 0.11 mg Ti/cm^2 dose and 8 subjects with irritant responses to the 0.22 mg Ti/cm^2 dose. All positive responses were graded 1+ and 2+. There were no 3+ reactions.

0.11 mg Ti/cm^2 dose: Among the 21 subjects with positive responses, there was 1 subject with a late response and 1 subject with a persistent reaction. The late response occurred at visit 5. The persistent reaction persisted through visit 5. There were no persistent escalating reactions at or beyond visit 6 (day 21).

0.22 mg Ti/cm^2 dose: Among the 18 subjects with positive responses, there were no late responses and 4 subjects with persistent reactions. All persistent reactions persisted through visit 4. There were no persistent escalating reactions at or beyond visit 6 (day 21).

The following tables summarize the number and percentage of subject responses to the titanium investigational allergen doses based on the Investigator's Determination of Positive Reactions.

Table 31: Number and Frequency of Positive Responses: Titanium

Titanium Allergen Doses		Positive			Negative		
		n	%	95% CI	n	%	95% CI
Titanium citrate							
0.0055 mg Ti/cm²	N=109	1	0.9	(0.02, 5.01)	108	99.1	(94.99, 99.98)
0.11 mg Ti/cm²	N=109	2	1.8	(0.22, 6.47)	107	98.2	(93.53, 99.78)
0.22 mg Ti/cm²	N=108[1]	2	1.9[2]	(0.23, 6.53)	106	98.1[2]	(93.47, 99.77)
Titanium lactate							
0.07 mg Ti/cm²	N=109	2	1.8	(0.22, 6.47)	107	98.2	(93.53, 99.78)
0.14 mg Ti/cm²	N=109	2	1.8	(0.22, 6.47)	107	98.2	(93.53, 99.78)
0.28 mg Ti/cm²	N=109	4	6.7	(1.01, 9.13)	105	96.3	(90.87, 98.99)
Potassium Titanium oxide oxalate							
0.060 mg Ti/cm²	N=109	1	1.0	(0.02, 5.01)	108	99.0	(94.99, 99.98)
0.12 mg Ti/cm²	N=109	5	4.6	(1.51, 10.38)	104	95.4	(89.62, 98.49)
0.24 mg Ti/cm²	N=109	2	1.8	(0.22, 6.47)	107	98.2	(93.53, 99.78)
Ammonium Titanium oxide oxalate							
0.055 mg Ti/cm²	N=109	13	11.9	(6.51, 19.53)	96	88.1	(80.47, 93.49)
0.11 mg Ti/cm²	N=109	21	19.3	(12.34, 27.93)	88	80.7	(72.07, 87.7)
0.22 mg Ti/cm²	N=109	18	16.5	(10.09, 24.84)	91	83.5	(75.16, 89.9)

[1]Subject 7-00010, position 1, 0.22 mg/cm^2 titanium citrate, was not scored due to poor adhesion when subject returned for patch removal.
[2]Percent positive and percent negative have been recalculated using number of results (vs number tested) for purposes of presentation in this report. 95% CI has not been recalculated.
Source: Table 14.2.7: Summary of Investigator Determination of Positive Reactions – mFAS population
See also: Listing 16.2.5.3: Investigator Determination of Positive Reactions at Post Visit 6

Table 32: Doubtful, Irritant, Positive, Late and Persistent Reactions: Titanium

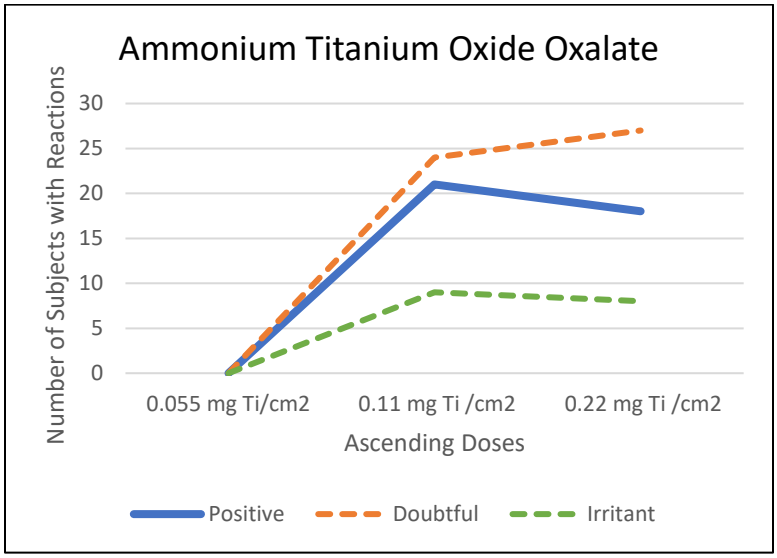
Ammonium titanium oxide oxalate 0.11 mg Ti/cm^2											
Number of subjects tested =109								Number of subjects positive = 21			
Doubtful		Irritant		1+ and 2+		3+		Late		Persistent	
n	%	n	%	n	%	n	%	n	%	n	%
24	22.0	9	8.3	23	5.3	0	-	1	4.8	1	4.8
Ammonium titanium oxide oxalate 0.22 mg Ti/cm^2 N=109											
Number of subjects tested =109								Number of subjects positive = 18			
Doubtful		Irritant		1+ and 2+		3+		Late		Persistent	
n	%	n	%	n	%	n	%	n	%	n	%
27	24.8	8	7.3	22	5.0	0	-	0	-	4	22.2

Source: Table 14.2.4: Summary of Skin Reaction Scores of Investigational and Reference Allergen Panels (Titanium Panel) – mFAS population.
Table 14.2.33: Late Reactions at Visit 4 (Day 7-8), Visit 5 (Day 10-14) and Visit 6 (Day 19-23) -mFAS population
Table 14.2.34: Persistent Reactions at Visit 4 (Day 7-8), Visit 5 (Day 10-14) and Visit 6 (Day 19-23) -mFAS population.

Percentages presented in the above table were calculated as follows
- Doubtful and irritant: Total divided by number of subjects tested (scored once, at visit 3 only).
- 1+ and 2+, 3+: Total divided by number of subjects tested x 4 (scored 4 times, at visits 3-6)
- Late and persistent: Total divided by number of subjects positive

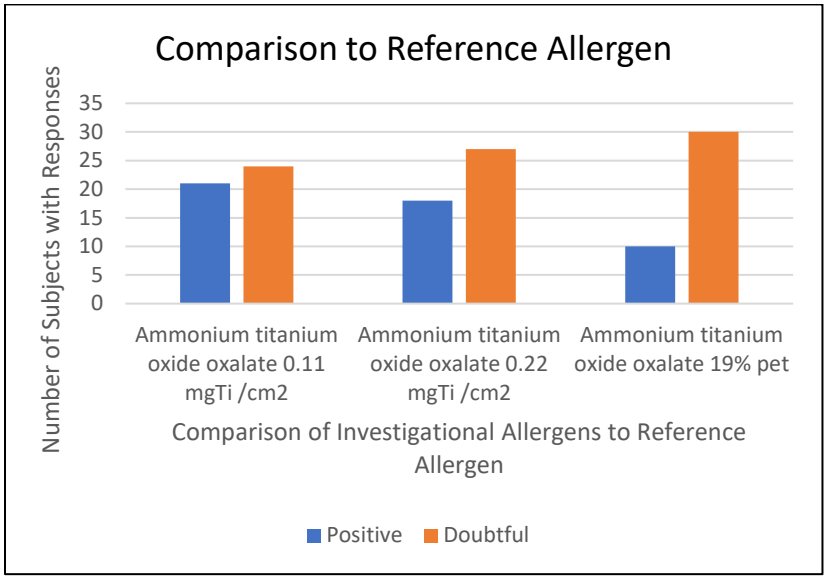
The following figure illustrates the dose response curve for the ascending doses of the ammonium titanium oxide oxalate allergen compared to the number of doubtful and irritant responses. Unlike the other allergens tested for which a classic dose response curve (positive trend) is observed, all 3 parameters (positive, doubtful and irritant responses) have nonmonotonic curves. Because there are non-significant differences in the number of positive responses between the 0.11 mg Ti/cm^2 dose and the 0.22 mg Ti/cm^2 dose this nonmonotonic curve still supported consideration of the 0.22 mg Ti/cm^2 dose. This is the only allergen tested for which there was a greater number of doubtful responses at the doses which met the minimum criteria.

Figure 7: Dose Response Curve: Ammonium Titanium Oxide Oxalate



To determine if the greater number of doubtful responses vs. positive responses was specific to the hydrogel technology the same comparison, number of doubtful responses vs number of positive responses, was made for the corresponding reference allergen, 19% ammonium titanium oxide oxalate in petrolatum. The results, shown in Figure 8 below, indicate a greater disparity between the number of positive responses (10) and the number of doubtful responses (30) for the reference allergen.

Figure 8: Comparison to Reference Allergen: Ammonium Titanium Oxide Oxalate



Agreement between the 0.11 mg Ti/cm^2 dose of ammonium titanium oxide oxalate investigational allergen and 19% ammonium titanium oxide oxalate in petrolatum reference allergen and between 0.22 mg Ti/cm^2 dose of ammonium titanium oxide oxalate investigational allergen and 19% ammonium titanium oxide oxalate in petrolatum reference allergen was calculated for the 76 subjects who were tested with both allergens. Table 33 presents concordance, sensitivity and specificity results for each subject paired comparison. Table 34 presents results for the number of subjects with positive and negative reactions who were tested with both allergens.

Table 33: Concordance and Sensitivity-Specificity: Titanium

Investigational Allergen		Reference Allergens: Ammonium titanium oxide oxalate 19% pet	
		Positive	**Negative**
Ammonium titanium oxide oxalate 0.11 mg Ti/cm^2	**Positive**	7	14
	Negative	3	52
	Percent agreement	9.2	68.4
	Kappa Statistics	0.33 (fair agreement)	
	95% CI	(0.10, 0.57)	
	p-value	0.0013	
	Sensitivity	70.0%	
	Specificity	78.8%	
	Nº of paired comparisons	76	

Investigational Allergen		Reference Allergens: Ammonium titanium oxide oxalate 19% pet	
		Positive	**Negative**
Ammonium titanium oxide oxalate 0.22 mg Ti/cm^2	**Positive**	7	11
	Negative	3	55
	Percent agreement	9.2	72.4
	Kappa Statistics	0.40 (moderate agreement)	
	95% CI	(0.15, 0.65)	
	p-value	0.0002	
	Sensitivity	70.0%	
	Specificity	83.3%	
	Nº of paired comparisons	76	

Source: Table 14.2.14: Summary of Concordance on Investigator Determination of Titanium Dilution Series of Positive Reaction -mFAS population
Source: Table 14.2.30: Analysis of Sensitivity and Specificity for Titanium Dilution Series vs. Reference Panel -mFAS population

Table 34: Comparison of Skin Reactions to Reference Allergen: Titanium

Titanium Allergens		Positive		Negative	
		n	%	n	%
Ammonium titanium oxide oxalate 0.11 mg Ti/cm^2	N^o tested both = 76	21	27.6	55	72.4
Ammonium titanium oxide oxalate 19% pet		10	13.2	66	86.8
95% CI		(0.02, 0.27)			
p-value		0.0268			
Ammonium titanium oxide oxalate 0.22 mg Ti/cm^2	N^o tested both = 76	18	23.7	58	76.3
Ammonium titanium oxide oxalate 19% pet		10	13.2	66	86.8
95% CI		(-0.02, 0.23)			
p-value		0.0942			

Source: Table 14.2.22: Comparison of Skin Reaction for Titanium Dilution Series vs. Reference Panel mFAS population

11.4.1.7 Vanadium

One hundred six (106) were tested with all doses of the vanadium investigational allergens. There were 2 doses of vanadium chloride and one of vanadium sulfate which met the minimum criteria of at least 15 subjects with positive responses.

Vanadium chloride: There were 25 subjects with positive responses to the 0.025 mg V/cm^2 dose and 46 subjects with positive responses to the 0.050 mg V/cm^2 dose. All other responses were negative which included 18 subjects with doubtful responses to the 0.025 mg V/cm^2 dose and 14 subjects with doubtful responses to the 0.050 mg V/cm^2 dose. Six (6) subjects had irritant responses to the 0.025 mg V/cm^2 dose and 18 subjects had irritant responses to the 0.050 mg V/cm^2 dose. All responses were graded 1+ and 2+. There were no 3+ reactions.

Among the 25 subjects with positive responses to the 0.025 mg V/cm^2 dose, there were 4 subjects with late responses and 11 subjects with persistent reactions. All 4 late reactions occurred at visit 4. Five (5) persistent reactions persisted through 4, 5 persisted through visit 5 and 1 persisted through visit 6. The visit 6 persistent reaction was graded 1+, persistent healing. There were no persistent escalating reactions at or beyond visit 6 (day 21).

Among the 46 subjects with positive responses to the 0.050 mg V/cm^2 dose, there were 9 subjects with late responses and 24 subjects with persistent reactions. All late responses occurred at visit 4. Ten (10) persistent reactions persisted through visit 4, 10 persisted through visit 5 and 2 persisted through visit 6. The two visit 6 persistent reactions were graded 1+, healing. There were no persistent escalating reactions at or beyond visit 6 (day 21).

Vanadium sulfate: There were 30 subjects with positive responses to the 0.050 mg V/cm^2 dose of vanadium sulfate. All other responses were negative which included 15 subjects with doubtful responses and 8 subjects with irritant responses. All responses were graded 1+ and 2+. There were no 3+ reactions.

Among the 30 subjects with positive responses, there were 7 subjects with late responses and 15 subjects with persistent reactions. Six late responses occurred at visit 4, the other occurred at visit 6. Five (5) persistent reactions persisted through visit 4, 9 persisted through visit 5, and 1 persisted through visit 6. The visit 6 persistent reaction was graded 1+, healing. There were no persistent escalating reactions at or beyond visit 6 (day 21).

The following tables summarize the number and percentage of subject responses to the vanadium investigational allergen doses based on the Investigator's Determination of Positive Reactions.

Table 35: Number and Frequency of Positive Responses: Vanadium

Vanadium Allergen Doses		Positive			Negative		
		n	%	95% CI	n	%	95% CI
Vanadium chloride							
0.0042 mg V/cm²	N=106	0	-	(0.00, 3.42)	106	100	(96.58, 100.00)
0.0083 mg V/cm²	N=106	4	3.8	(1.04, 9.38)	102	96.2	(90.62, 98.96)
0.025 mg V/cm²	N=106	25	23.6	(15.88, 32.82)	81	76.4	(67.18, 84.12)
0.050 mg V/cm²	N=106	46	43.4	(33.80, 53.37)	60	56.6	(46.63, 66.20)
Vanadium sulfate							
0.0042 mg V/cm²	N=106	6	5.7	(2.11, 11.91)	100	94.3	(88.09, 97.89)
0.0083 mg V/cm²	N=106	7	6.6	(2.70, 13.13)	99	93.4	(86.87, 97.30)
0.025 mg V/cm²	N=106	10	9.4	(4.62, 16.67)	96	90.6	(83.33, 95.38)
0.050 mg V/cm²	N=106	30	28.3	(19.98, 37.88)	76	71.7	(62.12, 80.02)

Source: Table 14.2.7: Summary of Investigator Determination of Positive Reactions – mFAS population
See also: Listing 16.2.5.3: Investigator Determination of Positive Reactions at Post Visit 6

Table 36: Doubtful, Irritant, Positive, Late and Persistent Reactions: Vanadium

Vanadium chloride 0.025 mg V/cm^2											
Number of subjects tested =106								Number of subjects positive = 25			
Doubtful		Irritant		1+ and 2+		3+		Late		Persistent	
n	%	n	%	n	%	n	%	n	%	n	%
18	17.0	6	5.7	42	9.9	0	-	4	16.0	11	44.0
Vanadium chloride 0.050 mg V/cm^2											
Number of subjects tested =106								Number of subjects positive = 46			
Doubtful		Irritant		1+ and 2+		3+		Late		Persistent	
n	%	n	%	n	%	n	%	n	%	n	%
14	13.2	18	17.0	84	19.8	0	-	9	19.6	24	52.2

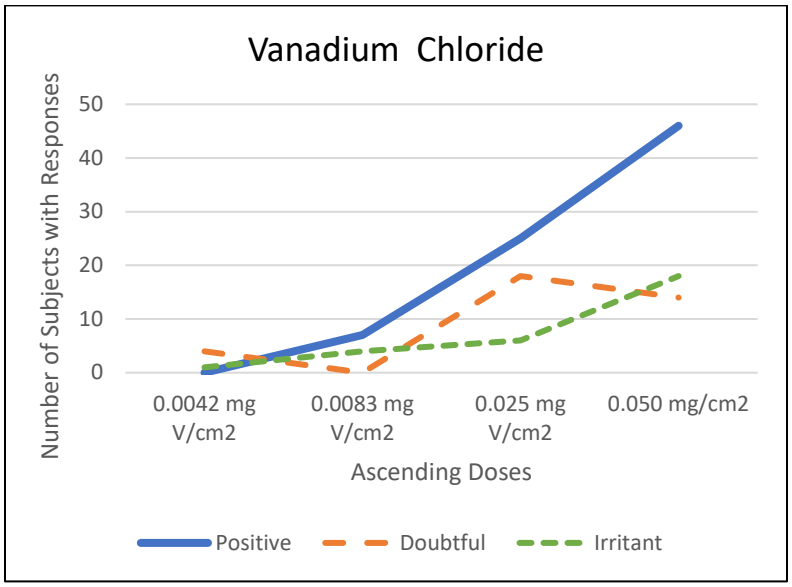
Vanadium sulfate 0.050 mg V/cm^2											
Number of subjects tested =106								Number of subjects positive = 30			
Doubtful		Irritant		1+ and 2+		3+		Late		Persistent	
n	%	n	%	n	%	n	%	n	%	n	%
15	14.2	8	7.5	52	12.3	0	-	7	23.3	15	50.0

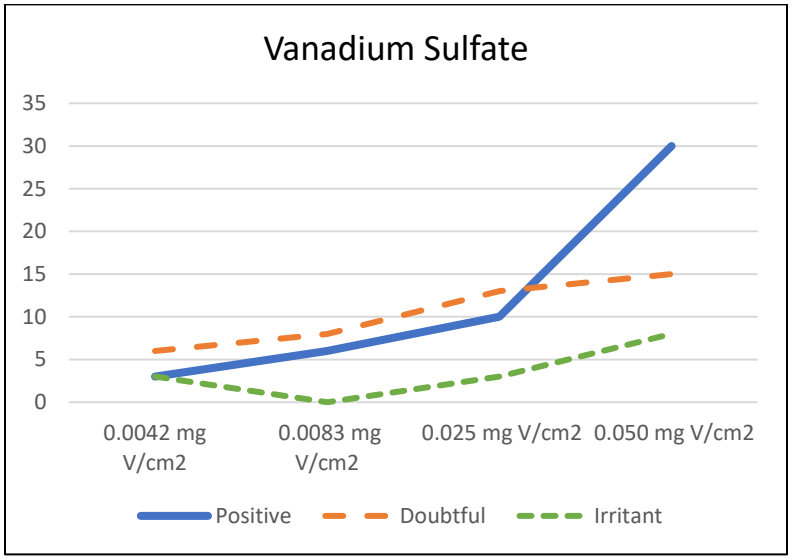
Source: Table 14.2.5: Summary of Skin Reaction Scores of Investigational and Reference Allergen Panels (Vanadium Panel) – mFAS population.
Source: Table 14.2.33: Late Reactions at Visit 4 (Day 7-8), Visit 5 (Day 10-14) and Visit 6 (Day 19-23) - mFAS population
Source: Table 14.2.34: Persistent Reactions at Visit 4 (Day 7-8), Visit 5 (Day 10-14) and Visit 6 (Day 19-23) -mFAS population.

Percentages presented in the above table were calculated as follows
- Doubtful and irritant: Total divided by number of subjects tested (scored once, at visit 3 only).
- 1+ and 2+, 3+: Total divided by number of subjects tested x 4 (scored 4 times, at visits 3-6)
- Late and persistent: Total divided by number of subjects positive

The following figures illustrate the dose response curve for the ascending doses of the vanadium allergens compared to the number of doubtful and irritant responses. Both allergens had similar trends, the number of positive responses exceeded the number of doubtful and irritant responses at all doses that met the minimum criteria of at least 15 subjects with positive responses. For both allergens the number of doubtful reactions were similar at the highest doses whereas the number of irritant responses increased from 1 at the lowest dose to 18 at the highest dose for vanadium chloride but only increased from 3 at the lowest dose to 8 at the highest dose for vanadium sulfate.

Figure 9: Dose Response Curve: Vanadium Allergens





Agreement between the 0.025 mg V/cm^2 dose of vanadium chloride investigational allergen and 1% vanadium chloride in petrolatum reference allergen, between the 0.050 mg V/cm^2 dose of vanadium chloride investigational allergen and 1% vanadium chloride in petrolatum reference allergen and between the 0.050 mg V/cm^2 dose of vanadium sulfate investigational allergen and 1.5% vanadium sulfate in petrolatum reference allergen was calculated for the 72 subjects who were tested with both allergens. Table 37 presents concordance, sensitivity and specificity results for each subject paired comparison. Table 38 presents results for the number of subjects with positive and negative reactions who were tested with both allergens.

Table 37: Concordance and Sensitivity-Specificity: Vanadium

Investigational Allergen		Reference Allergens	
		Vanadium chloride 1 % pet	
		Positive	**Negative**
Vanadium chloride 0.025 mg V/cm^2	**Positive**	2	13
	Negative	1	56
	Percent agreement	2.78	77.78
	Kappa Statistics	0.16 (poor agreement)	
	95% CI	(-0.07, 0.40)	
	p-value	0.0458	
	Sensitivity	66.67%	
	Specificity	81.16%	
	Nº of paired comparisons	72	

Investigational Allergen		Reference Allergens: Vanadium chloride 1 % pet	
		Positive	**Negative**
Vanadium chloride 0.050 mg V/cm^2	**Positive**	3	25
	Negative	0	44
	Percent agreement	4.17	61.11
	Kappa Statistics	0.13 (poor agreement)	
	95% CI	(-0.01, 0.26)	
	p-value	0.0266	
	Sensitivity	100%	
	Specificity	63.77%	
	Nº of paired comparisons	72	

Investigational Allergen		Reference Allergens: Vanadium sulfate 1.5 % pet	
		Positive	**Negative**
Vanadium sulfate 0.050 mg V/cm^2	**Positive**	9	12
	Negative	0	51
	Percent agreement	12.5	70.8
	Kappa Statistics	0.52 (moderate agreement)	
	95% CI	(0.30, 0.73)	
	p-value	<.0001	
	Sensitivity	100%	
	Specificity	80.9%	
	Nº of paired comparisons	72	

Source: Table 14.2.15: Summary of Concordance on Investigator Determination of Vanadium Dilution Series of Positive Reactions -mFAS population
Source: Table 14.2.31: Analysis of Sensitivity and Specificity for Vanadium Dilution Series vs. Reference Panel -mFAS population

Table 38: Comparison of Skin Reactions to Reference Allergen: Vanadium

Vanadium chloride		Positive		Negative	
		n	%	n	%
Vanadium chloride 0.025 mg V/cm^2	Nº tested both = 72	15	20.8	57	79.2
Vanadium chloride 1% pet		3	4.2	69	95.8
95% CI		(0.06, 0.27)			
p-value		0.0025			

Vanadium chloride		Positive		Negative	
		n	%	n	%
Vanadium chloride 0.050 mg V/cm^2	N^o tested both = 72	28	38.9	44	61.1
Vanadium chloride 1% pet		3	4.2	69	95.8
95% CI		(0.23, 0.47)			
p-value		<.0001			
Vanadium sulfate		Positive		Negative	
		n	%	n	%
Vanadium sulfate 0.050 mg V/cm^2	N^o tested both = 72	21	29.2	51	70.8
Vanadium sulfate 1.5% pet		9	12.5	63	87.5
95% CI		(0.04, 0.30)			
p-value		0.0138			

Source: Table 14.2.23: Comparison of Skin Reaction for Vanadium Dilution Series vs. Reference Panel – mFAS population

11.4.1.8 Zinc

One hundred eleven (111) subjects were tested with all doses of the zinc chloride investigational allergen. There were 69 subjects with positive responses to the 0.24 mg/cm^2 dose which was the only dose that met the minimum criteria of at least 15 subjects with positive responses. All other responses were negative which included 16 subjects with doubtful responses and 9 subjects with irritant responses. All responses were graded 1+ and 2+. There were no 3+ reactions.

Among the 69 subjects with positive responses there were 10 subjects with late responses and 44 subjects with persistent reactions. Eight (8) late reactions occurred at visit 4, 1 occurred at visit 5 and 1 occurred at visit 6. Twenty-one (21) persistent reactions persisted through visit 4, 22 persisted through visit 5, and 1 persisted through visit 6. The visit 6 persistent reaction was graded 1+, healing. There were no persistent escalating reactions at or beyond visit 6 (day 21).

The following tables summarize the number and percentage of subject responses to the zinc investigational allergen doses based on the Investigator's Determination of Positive Reactions.

Table 39: Number and Frequency of Positive Responses: Zinc

Zinc Chloride		Positive			Negative		
		n	%	95% CI	n	%	95% CI
0.013 mg/cm²	N=111	2	1.8	(0.22, 6.36)	109	98.2	(93.64, 99.78)
0.040 mg/cm²	N=111	7	6.3	(2.57, 12.56)	104	93.7	(87.44, 97.43)
0.080 mg/cm²	N=111	13	11.7	(6.39, 19.19)	98	88.3	(80.81, 93.61)
0.24 mg/cm²	N=111	69	62.2	(52.46, 71.20)	42	37.8	(28.80, 47.54)

Source: Table 14.2.7: Summary of Investigator Determination of Positive Reactions – mFAS population
See also: Listing 16.2.5.3: Investigator Determination of Positive Reactions at Post Visit 6

Table 40: Doubtful, Irritant, Positive, Late and Persistent Reactions: Zinc

Zinc chloride 0.24 mg/cm^2											
Number of subjects tested =111								Number of subjects positive = 69			
Doubtful		Irritant		1+ and 2+		3+		Late		Persistent	
n	%	n	%	n	%	n	%	n	%	n	%
16	14.4	9	8.1	132	29.7	0	-	10	14.5	44	63.8

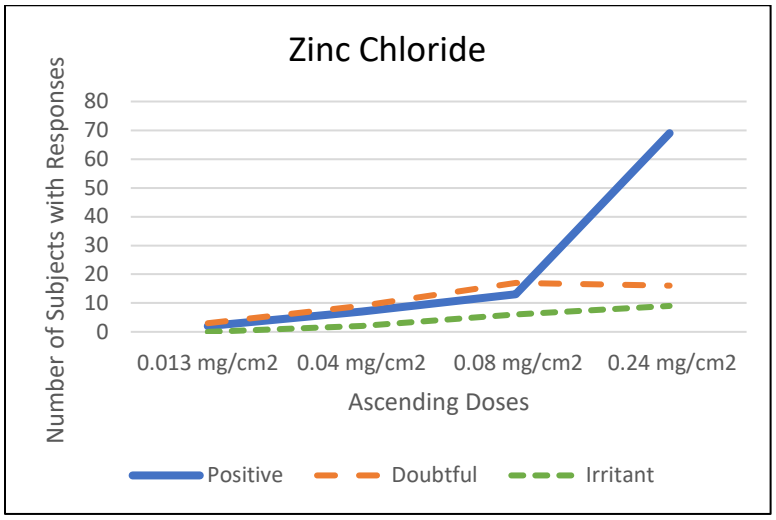
Source: Table 14.2.2: Summary of Skin Reaction Scores of Investigational and Reference Allergen Panels (Copper, Zinc, Tin Panel) – mFAS population.
Table 14.2.33: Late Reactions at Visit 4 (Day 7-8), Visit 5 (Day 10-14) and Visit 6 (Day 19-23) -mFAS population.
Table 14.2.34: Persistent Reactions at Visit 4 (Day 7-8), Visit 5 (Day 10-14) and Visit 6 (Day 19-23) -mFAS population.

Percentages presented in the above table were calculated as follows

- Doubtful and irritant: Total divided by number of subjects tested (scored once, at visit 3 only).
- 1+ and 2+, 3+: Total divided by number of subjects tested x 4 (scored 4 times, at visits 3-6)
- Late and persistent: Total divided by number of subjects positive

The following figure illustrates the dose response curve for the ascending doses of the zinc chloride allergen compared to the number of doubtful and irritant responses. Although the number of doubtful and irritant responses was fairly equal to the number of positive responses at the lower doses, there was a clear distinction between positive vs. doubtful and irritant responses at the highest dose.

Figure 10: Dose Response Curve: Zinc Chloride



Agreement between the 0.24 mg/cm^2 zinc chloride investigational allergen and 2% zinc chloride in petrolatum reference allergen was calculated for the 74 subjects who were tested with both allergens. Table 41 presents concordance, sensitivity and specificity results for each subject paired

comparison. Table 42 presents results for the number of subjects with positive and negative reactions who were tested with both allergens.

Table 41: Concordance and Sensitivity-Specificity: Zinc

Investigational Allergen		Reference Allergens	
		Zinc chloride 2% pet	
		Positive	**Negative**
Zinc chloride 0.24 mg/cm^2	**Positive**	27	22
	Negative	3	22
	Percent agreement	36.5	29.7
	Kappa Statistics	0.36 (fair agreement)	
	95% CI	(0.18, 0.54)	
	p-value	0.0004	
	Sensitivity	90.0%	
	Specificity	50.0%	
	Nº of paired comparisons	74	

Source: Table 14.2.16: Summary of Concordance on Investigator Determination of Zinc Dilution Series of Positive Reaction -mFAS population
Source: Table 14.2.32: Analysis of Sensitivity and Specificity for Zinc Dilution Series vs. Reference Panel -mFAS population

Table 42: Comparison of Skin Reactions to Reference Allergen: Zinc

Zinc chloride		Positive		Negative	
		n	%	n	%
Zinc chloride 0.24 mg/cm^2	Nº tested both = 74	49	66.2	25	33.8
Zinc chloride 2% pet		30	40.5	44	59.5
95% CI		(0.10, 0.41)			
p-value		0.0017			

Source: Table 14.2.24: Comparison of Skin Reaction for Zinc Dilution Series vs. Reference Panel -mFAS population

11.4.2 Statistical/Analytical Issues

11.4.2.1 Adjustments for Covariates

No adjustments were made for covariates

11.4.2.2 Handling of Dropouts or Missing Data

No imputations for missing data were performed.

11.4.2.3 Interim Analyses and Data Monitoring

There were no interim analyses. No data monitoring was performed by the Data Safety Monitoring Board; however, the study sites were routinely monitored by the Clinical Research Associate.

11.4.2.4 Multicenter Studies

The clinical study was conducted under a common protocol at each investigational site with the intention of pooling the data for analysis. Because all investigators and study personnel received identical training, used the same scales, and followed the same procedures, no statistical analyses were conducted to evaluate the appropriateness of combining data across the investigational sites.

11.4.2.5 Multiple Comparisons/Multiplicity

No adjustments were made for multiple comparisons.

11.2.4.6 Use of an Efficacy Subset of Patients

A total of 122 subjects were enrolled. One subject dropped from the study prior to the second visit due to a family emergency. The mFAS population included all subjects who received a patch application and completed the study with no major protocol violations (N = 121). This population was used to evaluate the study endpoints for each of the investigational metal panel allergens.

All enrolled subjects who received a patch application are included in the safety population (N= 122) This population was used to analyze safety and to support the study endpoints.

11.4.2.7 Active-Control Studies Intended to Show Equivalence

This was not an active-controlled study intended to show equivalence. Rather, the objective of this study was to evaluate the diagnostic performance and safety of different doses and formulations of metal allergens intended for inclusion on an all metal patch test panel.

11.4.2.8 Examination of Subgroups

The frequency of positive, negative, irritant, and doubtful reactions reported at visits 3, 4, 5 and 6 were tabulated for all subjects for each dose of each investigational metal allergen and corresponding reference allergen in the mFAS population. The Investigator's determination of positive reactions was used to calculate the number of subjects with positive responses to each allergen dose.

The study was conducted at 9 investigative sites, 2 in the US, 4 in Europe and 3 in Japan. One of the US sites had 1 screen fail only. No subjects were enrolled.

11.4.3 Tabulation of Individual Response Data

Individual efficacy response data are appended in Listing 16.2.6.4

11.4.4 Drug Dose, Drug Concentration and Relationship to Response

This was a dose-response study in which ascending concentrations of aluminum copper, manganese, molybdenum, tin, titanium, vanadium and zinc were evaluated for their diagnostic performance. The expected response to increasing concentration of allergens would be linear, meaning the number and intensity of positive responses would increase as the dose increased.

11.4.5 Drug-Drug and Drug-Disease Interactions

The investigational allergens tested in this study are indicated for use as an aid in the diagnosis of ACD therefore no drug-drug or drug-disease interactions were evaluated.

11.4.6 By-Patient Displays

The individual subject data is displayed in tabular listings which are appended to this report. There are no individual patient profiles in other formats.

11.4.7 Efficacy Conclusions

Two allergens, aluminum and molybdenum, did not meet the minimum criteria of at least 15 subjects with positive responses therefore will not be included on the final metal panel.

Four allergens, copper, manganese, vanadium sulfate and zinc only had one dose that did meet the minimum criteria of at least 15 subjects with positive responses therefore determination of optimal dose was based solely on this primary endpoint. Although there were 2 doses of vanadium chloride that met the minimum criteria of at least 15 subjects with positive responses, the vanadium chloride allergen was eliminated from consideration for the final panel due to the corrosive nature of the vanadium chloride raw material which complicated its handling during the production and storage of the experimental panel.

The remaining allergens, tin and titanium had more than one dose that met the minimum criteria of at least 15 subjects with positive responses therefore the entire profile of each allergen was considered, which included both primary and secondary endpoints, in the determination of optimal dose.

The current study inclusion criteria included subjects with a suspicion of contact allergy, in addition to those with a past positive patch test, because the metals being tested on this study did not have a large database of patients with past positive patch test results. The original intention was to conclude the study when a total of 400 subjects were tested whether or not the 15 positive responses per allergen quota was met as little information was available on the expected prevalence of positive responses and it was initially anticipated that the majority of subjects would test negative. Subjects with a suspicion of contact allergy were tested with all investigational allergens, at the discretion of the Investigator, which exposed a greater number of subjects to each allergen. The number of positive reactions overall was higher than expected which may have been attributed to the higher number of subjects exposed to each allergen. Determination of optimal dose for tin and titanium presented a challenge with the multiple doses that met the primary endpoint. If the sole consideration of optimal dose was based only on the number of positive reactions, some aspects of an ideal allergen dose would be overlooked. For example, late responses associated with the lower dose may be missed during the standard 5-day patch test schedule followed in the majority of clinical settings. Or a dose that produces 3+ reactions should not be automatically dismissed if the number of 3+ reactions is not significant or the rate of resolution for the 3+ responses surpasses the rates of resolution for 1+ and 2+ responses. Other considerations include the number and type of persistent reactions and comparisons between the number of positive vs. irritant and doubtful responses.

The following primary endpoints were considered during optimal allergen dose selection

- The lowest concentration of each dilution series allergen eliciting positive responses in a minimum of 15 subjects. Positive responses are defined as score of 1+, 2+ or 3+ during at least one reaction assessment visit. If a significant number of 3+ responses are elicited, the dose will be selected based on 1+ and 2+ responses.
- For all sites with the exception of Germany: Concordance will be measured using Cohen's kappa where less than 0% indicates no agreement, 0-20% indicates poor agreement, 20-40% indicates fair agreement, 40-60% indicates moderate agreement, 60-80% indicates good agreement and 80% or higher indicates very good agreement. Concordance will be measured using all subjects who are tested with each allergen and corresponding reference allergen.

Because all aspects of the response profile were considered during the selection of optimal dose, the following secondary endpoints were included in the selection process for the allergens that had more than one dose meet the minimum criteria.

- Frequency of positive (1+, 2+, 3+) skin reactions for each investigational and reference allergen dose at each post removal visit and overall.
- Frequency of negative, doubtful, irritant, late and persistent skin reactions for each investigational and reference allergen dose at each post removal visit (late and persistent reactions at visits 4, 5 and 6 only).

11.4.7.1 Aluminum

The primary endpoint, determination of optimal test allergen dose as the lowest concentration eliciting positive responses in a minimum of 15 subjects, was not met for any dose of aluminum chloride or aluminum lactate. The aluminum allergens will not be further tested nor will they be included on the proposed metal panel.

11.4.7.2 Copper

One hundred eleven (111) subjects were tested with all doses of the copper sulfate investigational allergen. Of these, there were 16 subjects with positive responses to the 0.12 mg/cm^2 dose. This was the only dose that met the minimum criteria of at least 15 subjects with positive responses. All other responses for this dose were negative including 16 subjects with doubtful responses and 10 subjects with irritant responses. All positive responses were graded 1+ or 2+. There were no 3+ reactions. Among the 16 subjects with positive responses, there were 3 subjects with late responses and 4 subjects with persistent responses.

Agreement between the 0.12 mg/cm^2 dose of copper sulfate investigational allergen and 2% copper sulfate in petrolatum reference allergen was calculated for the 78 subjects who were tested with both allergens. Concordance, sensitivity and specificity were calculated for each subject paired comparison. The results of the Kappa statistic indicated fair agreement (28%) between the investigational and reference allergen. The sensitivity was rated 40.0% and the rate of specificity was 89.7%.

The 0.12 mg/cm^2 dose of copper sulfate has been chosen as the optimal dose

11.4.7.3 Manganese

One hundred four (104) subjects were tested with all doses of the manganese chloride investigational allergen however, the 0.040 mg/cm^2, 0.080 mg/cm^2 and 0.24 mg/cm^2 doses (positions 3, 2 and 1 respectively) for a single subject were not scored due to poor adhesion at patch removal. Of the 103 subjects with study results, there were 29 subjects with positive responses to the 0.24 mg/cm^2 dose. This was the only dose that met the minimum criteria of at least 15 subjects with positive responses. All other responses for this dose were negative which included 17 subjects with doubtful responses and 10 subjects with irritant responses. All positive responses were graded 1+ and 2+. There were no 3+ reactions. Among the 29 subjects with positive responses there was 1 subject with a late response and 10 subjects with persistent responses.

Agreement between the 0.24 mg/cm^2 dose of manganese chloride investigational allergen and 2% manganese chloride in petrolatum reference allergen was calculated for the 69 subjects who were tested with both allergens. Concordance, sensitivity and specificity were calculated for each subject paired comparison. The results of the Kappa statistic indicated moderate agreement (45%) between the investigational and reference allergen. The sensitivity was rated 90.9% and the rate of specificity was 75.9%.

The 0.24 mg/cm^2 dose of manganese chloride has been chosen as the optimal dose

11.4.7.4 Molybdenum

The primary endpoint, determination of optimal test allergen dose as the lowest concentration eliciting positive responses in a minimum of 15 subjects, was not met for any dose of ammonium molybdate. The molybdenum allergen will not be further tested nor will it be included on the proposed metal panel.

11.4.7.5 Tin

One hundred eleven (111) subjects were tested with all doses of the tin chloride investigational allergen however the 0.33 mg/cm^2 dose (position 6) for a single subject was not scored due to poor adhesion at patch removal. Of the subjects with study results, there were 25 subjects with positive responses to the 0.11 mg/cm^2 dose and 65 subjects with positive responses to the 0.33 mg/cm^2 dose therefore, the entire profile of each allergen dose was considered in the selection of optimal dose.

Agreement between the 0.11 mg/cm^2 dose of tin chloride investigational allergen and 1% tin chloride in petrolatum reference allergen was calculated for 73 subjects who were tested with both allergens and between the 0.33 mg/cm^2 dose of tin chloride investigational allergen and 1% tin chloride in petrolatum for the 72 subjects who were tested with both allergens. Concordance, sensitivity and specificity were calculated for each subject paired comparison. The results of the Kappa statistic indicate fair agreement between both doses and the reference allergen.

Tin chloride	N^o of Subjects Positive[1]	Kappa statistic	Sensitivity	Specificity
0.11 mg/cm^2 N=73	25 (22.5%)	31% (fair agreement)	45.0%	84.9%
0.33 mg/cm^2 N= 72[2]	65 (59.1%)	23% (fair agreement)	90.0%	42.3%

[1]Percentage based on number of subjects tested N=111
[2]Subject 7-00010, position 6, 0.33 mg/cm^2 was not scored due to poor adhesion at patch removal.

The following secondary endpoint results were assessed to ensure that all aspects of the response profile of each considered dose were carefully evaluated in order to determine optimal dose.

Comparison of 0.11 mg/cm^2 tin chloride to 0.33 mg/cm^2 tin chloride

Tin chloride	Doubtful	Irritant	1+ and 2+	3+	Late	Persistent
0.11 mg/cm² N=111	12 (10.8%)	6 (5.4%)	35 (7.9%)	2 (0.5%)	5 (20.0%)	5 (20.0%)
0.33 mg/cm² N=110[1]	12 (10.9%)	16 (14.5%)	122 (27.7%)	3 (0.7%)	6 (9.2%)	39 (60.0%)

[1]Subject 7-00010, position 6, 0.33 mg/cm^2 was not scored due to poor adhesion at patch removal.

A major factor in the evaluation of patch test reactions is the ability of the allergen to produce a robust positive response. Because there is only a slight distinction on the evaluation scale between a doubtful response (non-palpable erythema) and 1+ (palpable erythema), even experienced patch test evaluators may misinterpret a patch test reaction at the 72 or 96-hour evaluation. Because doubtful reactions were only scored once, at visit 3 (72 or 96-hour evaluation), the following comparison was made.

Tin chloride Visit 3 scores only	Doubtful	1+
0.11 mg/cm² N=111	12 (10.8%)	18 (16.2%)
0.33 mg/cm² N=110	12 (10.9%)	53 (48.2%)

Even though both doses had 12 doubtful reactions, there was greater contrast between the number of doubtful vs 1+ reactions for the 0.33 mg/cm^2 dose. This clearly shows that evaluators were better able to differentiate between doubtful and positive reactions which is preferred. In addition, a doubtful response should resolve rather quickly therefore the greater number of persistent reactions for the 0.33 mg/cm^2 dose is also favored as true allergic responses take longer to resolve. Although the number of late responses for the two doses is fairly equal, the higher percentage of late responses associated with the 0.11 mg/cm^2 dose is less desirable. Late responses may be missed during the standard 5-day patch test schedule followed in the majority of clinical settings.

In this study, all of the allergens that met the primary endpoint also induced irritant reactions. Generally, the number of irritant reactions increased as the dose increased. The proportion of irritant vs. positive reactions is more favorable for the 0.33 mg/cm^2 dose. (0.11 mg/cm^2 = 5.4% irritant vs 22.5% positive. 0.33 mg/cm^2 = 14.5% irritant vs. 59.1% positive).

The results of the Kappa statistic indicate fair agreement between both doses and the reference allergen. The rate of sensitivity was higher for the 0.33 mg/cm^2 dose which also supports selection of this dose.

Based on its superior ability to elicit positive responses in a greater number of subjects with a higher numbers of 1+, 2+ and persistent responses, fewer late responses and a higher rate of sensitivity, the 0.33 mg/cm^2 dose of tin chloride has been chosen as the optimal dose.

11.4.7.6 Titanium

One hundred nine (109) subjects were tested with all doses of ammonium titanium oxide oxalate which is the only titanium salt that met the minimum criteria of at least 15 subjects with positive responses. There were 21 subjects with positive responses to the 0.11 mg Ti/cm^2 dose and 18 subjects with positive responses to the 0.22 mg Ti/cm^2 dose therefore, the entire profile of each allergen dose was considered in the selection of optimal dose. Although the number of positive responses generally increases as the dose is increased this nonmonotonic curve has been known to occur, although infrequently, in past dose response studies. In this case there is not a significant difference between the number of positive responses for the two doses that met the minimum criteria, and both were considered in the selection of optimal dose.

Agreement between the 0.11 mg Ti/cm^2 dose of ammonium titanium oxide oxalate investigational allergen and 19% ammonium titanium oxide oxalate in petrolatum reference allergen and between the 0.22 mg Ti/cm^2 dose of ammonium titanium oxide oxalate investigational allergen and 19% ammonium titanium oxide oxalate in petrolatum was calculated for the 76 subjects who were tested with both allergens. Concordance, sensitivity and specificity were calculated for each subject paired comparison. The results of the Kappa statistic indicate moderate agreement between the 0.22 mg Ti/cm^2 dose and the reference allergen but only fair agreement between the 0.11 mg Ti/cm^2 dose and the reference allergen. The rate of sensitivity is equal for both doses although the rate of specificity was a little higher for the 0.22 mg Ti/cm^2 dose.

N=76	N^o subjects positive[1]	Kappa statistic	Sensitivity	Specificity
0.11 mg Ti/cm² N=76	21 (19.3%)	33% (fair agreement)	70.0%	78.8%
0.22 mg Ti/cm² N=76	18 (16.5%)	40% (moderate agreement)	70.0%	83.3%

[1]Percentage calculated based on total number tested N=109

The following secondary endpoint results were assessed to ensure that all aspects of the response profile of each considered dose were carefully evaluated in order to determine optimal dose.

Comparison of 0.11 mg Ti/cm^2 and 0.22 mg Ti/cm^2 ammonium titanium oxide oxalate

N=109	Doubtful	Irritant	1+ and 2+	3+	Late	Persistent
0.11 mg Ti/cm²	24 (22.0%)	9 (8.3%)	23 (5.3%)	0	1 (4.8%)	1 (4.8%)
0.22 mg Ti/cm²	27 (24.8%)	8 (7.3%)	22 (5.0%)	0	0	4 (22.2%)

Overall, there were 25 subjects with 52 positive reactions to ammonium titanium oxide oxalate
- 9 subjects were positive to all 3 doses
- 9 subjects were positive to 2 doses
- 7 subjects were positive to one dose

The overall number of positive responses and increasing need for a standardized titanium patch test allergen, warranted inclusion of the ammonium titanium oxide oxalate allergen on the final panel. However, selection of the optimal dose for the titanium allergen was problematic due to only slight differences between the two doses that met the minimum criteria.

Because the number and percentage of positive reactions, sensitivity and specificity, doubtful, irritant, 1+, 2+ and 3+ responses for each dose were nearly equivalent, selection of optimal dose was based on late and persistent reactions and Kappa statistic. The lower percentage of late responses associated with the 0.22 mg Ti/cm^2 dose is preferred. Late responses may be missed during the standard 5-day patch test schedule followed in the majority of clinical settings. In addition, the higher number of persistent reactions associated with the 0.22 mg Ti/cm^2 dose is more favorable because true allergic responses take longer to resolve.

For all of the allergens with a dose that met the minimum criteria, number of irritant and doubtful reactions generally increased as the dose increased. However, the same type of nonmonotonic curve was observed for the doubtful and irritant responses to the ammonium titanium oxide oxalate allergen. In addition, this allergen was the only allergen that had a greater number of doubtful responses at the highest dose. This unusual pattern of reactivity was also seen with the corresponding reference allergen.

Based on the Kappa statistic, higher number of persistent responses and fewer late responses, the 0.22 mg Ti/cm^2 dose of ammonium titanium oxide oxalate has been chosen as the optimal dose.

11.4.7.7 Vanadium

One hundred six (106) subjects were tested with all doses of the vanadium chloride and vanadium sulfate investigational allergens. The 2 doses of vanadium chloride which met the minimum criteria of at least 15 subjects with positive responses (0.025 mg V/cm^2, 25 subjects and 0.050 mg V/cm^2, 46 subjects) were eliminated from consideration for the final panel due to the corrosive nature of the vanadium chloride raw material which complicated its handling during the production and storage of the experimental panel. The only other dose to meet the minimum criteria of at least 15 subjects with positive responses was 0.050 mg V/cm^2 of vanadium sulfate with 30 positive response subjects.

Other responses to vanadium sulfate included 73 subjects with negative responses, 15 of which were doubtful and 8 were irritant. All positive responses were graded 1+ or 2+. There were no 3+ reactions. Among the 30 subjects with positive responses, there were 7 late responses and 15 persistent responses.

Agreement between the 0.050 mg V/cm^2 dose of vanadium sulfate investigational allergen and 1.5% vanadium sulfate in petrolatum reference allergen was calculated for the 72 subjects who were tested with both allergens. Concordance, sensitivity and specificity were calculated for each subject paired comparison. The results of the Kappa statistic indicated moderate agreement (52%) between the investigational and reference allergen. The sensitivity was rated 100%, and the rate of specificity was 80.9%.

The 0.050 mg V/cm^2 dose of vanadium sulfate has been chosen as the optimal dose.

11.4.7.8 Zinc

One hundred eleven (111) subjects were tested with all doses of the zinc chloride investigational allergen. Of these, there were 69 subjects with positive responses to the 0.24 mg/cm^2 dose. This was

the only dose that met the minimum criteria of at least 15 subjects with positive responses. All other responses were negative which included 16 doubtful and 9 irritant responses. All positive responses were graded 1+ and 2+. There were no 3+ reactions. Among the 69 subjects with positive responses there were 10 late and 44 persistent reactions.

Agreement between the 0.24 mg/cm^2 dose of zinc chloride investigational and 2% zinc chloride in petrolatum reference allergen was calculated for the 74 subjects who were tested with both allergens. Concordance, sensitivity and specificity were calculated for each subject paired comparison. Overall rates of positive and negative reactions were calculated for all subjects who tested both allergens. The results of the Kappa statistic indicated fair agreement (36%) between the investigational and reference allergen. The sensitivity was rated 90.0%, and the rate of specificity was 50.0%.

The 0.24 mg/cm^2 dose of zinc chloride has been chosen as the optimal dose.

12.0 SAFETY EVALUATION

12.1 Extent of Exposure

Five investigational allergen panels containing ascending dose concentrations of aluminum, copper, manganese, molybdenum, tin, titanium, vanadium and zinc, 1 panel containing previously approved metal allergens and negative controls and 2 panels containing reference petrolatum or aqueous allergens corresponding to each investigational allergen (with exception of subjects enrolled in Germany who were not patched with the reference allergens) were applied to the upper backs of study subjects and were worn for approximately 48 hours (2 days).

Test site skin reactions were evaluated 4 times, at 3-4, 7-8, 10-14 and 19-23 days after application.

12.2 Adverse Events

The adverse event-reporting period for each study subject began at panel application and ended at the day 21 visit. In addition, any adverse event reported after day 21 that the Investigator determined as definitely or possibly related to the investigational product was to have been reported.

Subjects were asked at visits 2-6 if they had experienced any changes to their health or use of concomitant medications. Any yes answer warranted documentation of an adverse event.

Reference: Listing 16.2.5: Per Visit Adverse Event Responses

12.2.1 Brief Summary of Adverse Events

A total of 50 adverse events was reported by 30 subjects. Table 43 lists the number of subjects with adverse events in each category.

Table 43: Summary of Adverse Events – FAS Population

Summary of Adverse Events N=122 (FAS population)	n	%
Total number of adverse events	50	
Number of subjects experiencing at least one adverse event	30	24.6

Summary of Adverse Events N=122 (FAS population)	n	%
Action Taken (number of subjects, not number of events)		
None	18	14.7
Medication	16	13.1
Discontinued Study	0	-
Severity (number of subjects, not number of events)		
Mild	17	13.9
Moderate	13	10.7
Severe	2	1.6
Relationship to study panel (number of subjects, not number of events)		
Not Related	23	18.8
Possibly related	9	7.4
Definitely related	1	0.8
Expected (number of subjects, not number of events)		
No	25	20.5
Yes	7	5.7
Follow-up of Related Events (number of subjects, not number of events)		
NA (Event Resolved or Not related)	28	22.9
Chronic	3	2.5
Stable	0	-

Source: Table 14.3.1.1 Summary of Adverse Events FAS Population

12.2.2 Display of Adverse Events

Table 44: Display of Adverse Events

Definitely Related Adverse Events

There were 4 definitely related adverse events, all reported by one subject.

Subject	Severity	Definitely Related Adverse Event	Preferred Term
7-00018	Mild	Erythema at Patch Test Sites: Panel 2 position 6	Application site erythema
	Mild	Erythema at Patch Test Sites: Panel 2 position 12	Application site erythema
	Mild	Erythema at Patch Test Sites: Reference Panel 1 position 6[1]	Application site erythema
	Mild	Erythema at Patch Test Sites: Panel 2 position 5	Application site erythema

[1]Adverse Event was erroneously reported as Panel 1 in CRF but verification with source document confirmed it should have been recorded as Reference Panel 1.

Possibly Related Adverse Events

There were 13 possibly related adverse events reported by 9 subjects

Subject	Severity	Possibly Related Adverse Event	Preferred Term
7-00010	Mild	Atopic eczema-worsening	Dermatitis atopic
6-00012	Moderate	Dizziness	Dizziness
7-00008	Moderate	Dyshidrotic eczema- worsening	Dyshidrotic eczema
6-00014	Moderate	Eye dryness	Dry eye

Subject	Severity	Possibly Related Adverse Event	Preferred Term
6-00012	Moderate	Headache	Headache
6-00024	Mild	Headache	Headache
5-00016	Mild	Itchiness- back	Pruritus
6-00001	Mild	Itching- upper body for 2 days	Pruritus
5-00016	Mild	Pain and discomfort, mild- entire back	Back pain
7-00009	Moderate	Palmoplantar pustulosis - worsening	Pustular psoriasis
6-00014	Moderate	Shoulder pain- left shoulder	Musculoskeletal pain
3-00003	Moderate	Tension in head through shoulder- right side	Tension headache
5-00016	Mild	Tiredness- extreme	Fatigue

Not Related Adverse Events

There were 33 not related adverse events reported by 23 subjects.

Subject	Severity	Not Related Adverse Event	Preferred Term
2-00008	Mild	Cervical block-ablation of C2 nerve, right side	Therapeutic nerve ablation
6-00020	Mild	Cold-like symptoms	Viral upper respiratory tract infection
7-00003	Mild	Common cold	Viral upper respiratory tract infection
7-00018	Mild	Common cold	Viral upper respiratory tract infection
7-00018	Mild	Cystitis	Cystitis
6-00008	Mild	Dizziness	Dizziness
8-00011	Moderate	Dry skin	Dry skin
8-00013	Moderate	Dry skin	Dry skin
8-00010	Severe	Ductal carcinoma right breast[1]	Intraductal proliferative breast lesion
6-00018	Moderate	Dyspnea by effort	Dyspnoea exertional
3-00001	Mild	Feels exhausted	Fatigue
5-00001	Moderate	Fever	Pyrexia
7-00009	Mild	Fever	Pyrexia
5-00019	Mild	Flu-like symptoms	Influenza-like illness
6-00005	Mild	Flu-like symptoms	Influenza-like illness
8-00009	Moderate	Follicle inflammation	Inflammation
8-00013	Moderate	Glossitis	Glossitis
3-00001	Mild	Headache	Headache
2-00009	Mild	Hive on outer upper right thigh	Urticaria
6-00005	Moderate	Itching dermatitis upper right arm	Dermatitis
3-00001	Mild	Malaise	Malaise
6-00008	Mild	Nausea	Nausea
6-00009	Mild	Nausea	Nausea
5-00016	Moderate	Pain in amalgam fillings	Toothache
2-00002	Severe	Pain in upper right quadrant- worsened	Abdominal pain upper
3-00002	Moderate	Pain in right arm	Pain in extremity
3-00002	Moderate	Pain in right groin	Groin pain
7-00005	Mild	Pericoronitis	Periodontal inflammation
8-00009	Moderate	Stye	Hordeolum
5-00019	Mild	Tiredness	Fatigue
2-00009	Mild	Tooth damage requiring root canal	Endodontic procedure
6-00004	Moderate	Vertigo	Vertigo

Subject	Severity	Not Related Adverse Event	Preferred Term
7-00004	Mild	Vomiting	Vomiting

[1] Serious Adverse Event.
Source: Table 14.3.1.2: Summary of Adverse Events by System Organ Class with Preferred Term- FAS Population
Source: Table 14.3.1.3: Summary of Adverse Events by System Organ Class, Preferred Term and Relationship- FAS Population
See also Listing 16.2.4.4: Medications Taken for Adverse Events

12.2.3 Analysis of Adverse Events

Three (3) of the 4 definitely related adverse events for erythema at patch test sites, were reported by the Investigator to document patch test reactions at the final visit for subject 7-00018 on November 5, 2018.

- Panel 2, position 6 (0.33 mg/cm^2 tin chloride) was negative at visit 5 and 2+ at visit 6 (persistent escalating reaction)
- Panel 2 position 12 (0.11 mg/cm^2 tin chloride) was negative at visit 5 and 1+ at visit 6 (late reaction)
- Reference Allergen Panel 1, position 6, (1% tin chloride in petrolatum) was negative at visit 5 and 2+ at visit 6. (late reaction). Note: Adverse Event was erroneously reported as Panel 1 in CRF but verification with source document confirmed it should have been recorded as Reference Panel 1.

The 4th event was reported 1 week later when subject 7-00018 sent a photograph of his back and the Investigator noted an erythematic response at panel 2 position 5 (0.037 mg/cm^2 tin chloride). All scores for this position were negative at visits 3-6. The adverse event of erythema does not necessarily indicate a late positive response just erythema at the patch test site which was not earlier observed.

All 4 events were mild and resolved by December 11, 2018.

Three of the metal allergens tested in this study, tin chloride, vanadium sulfate and zinc chloride had at least 1 late reaction that initially appeared at visit 6 and 1 reaction that persisted through visit 6. The only persistent escalating response was to the 0.33 mg/cm^2 dose of tin chloride. This low number of mild, late and persistent responses among the 121 subjects in the mFAS population does not present a safety signal which would preclude further testing of these allergens.

There were 13 possibly related adverse events reported by 9 subjects.

- 5 skin and subcutaneous tissue disorders (itching (2), worsening eczema (2) and worsening palmoplantar pustulosis)
- 4 nervous system disorders (dizziness, headache (2) and head/neck tension)
- 2 musculoskeletal and connective tissue disorders (back pain, shoulder pain)
- 1 general disorder and administration site condition (tiredness)
- 1 eye disorder (eye dryness)

The 5 skin and subcutaneous tissue disorder events have clear association with symptoms that night be experienced by a patient with a history of contact dermatitis. It is more difficult to explain the

association between nervous system disorders, musculoskeletal/connective tissue disorders, general disorders or an eye disorder and the application of metal patch test allergens. Three (3) of the possibly related adverse events itching, backpain and fatigue were attributed to a single subject. One (1) subject experienced dizziness and headache, another reported dry eye and shoulder pain. Because these subjects experienced multiple symptoms which could not be attributed to a specific disease or disorder, the Investigators determined they may have a slight relationship to the study panels.

All of the possibly related adverse events were mild or moderate and had resolved by the end of each subject's participation in the study with the exception of the 3 events associated with worsening of a preexisting chronic, condition (worsening atopic eczema, worsening dyshidrotic eczema and worsening palmoplantar pustulosis).

Other than the 1 serious adverse event, all of the not related adverse events were common medically related occurrences. The majority of events were mild or moderate. Two events were considered severe, ductal carcinoma, right breast (SAE) and worsened pain in upper right quadrant.

12.2.4 Listing of Adverse Events by Subject (Patient)

The compilation of all adverse events can be found in Listing 16.2.7.1, Adverse Events.

For additional information on adverse events Listing 16.2.7.3: Narrative for Adverse Events

12.3 Deaths, Other Serious Adverse Events and Other Significant Adverse Events

12.3.1 Listing of Deaths, Other Serious AEs and Other Significant AEs

Subject 8-00010 discovered a lump in her right breast which she reported to the Investigator at her 5th study visit on December 11, 2018. Subject was advised to seek medical treatment and was diagnosed with ductal carcinoma, right breast on December 27, 2018. The site was made aware of the diagnosis on January 17, 2019.

There were no other serious adverse events or other significant adverse events.

12.3.1.1 Deaths

There were no deaths during the course of the clinical trial

12.3.1.2 Other Serious Adverse Events

There were no other serious adverse events during the course of the clinical trial.

12.3.1.3 Other Significant Adverse Events

12.3.2 Narratives of Deaths, Other Serious AEs and Certain Other Significant AEs

Subject 8-00001: Ductal carcinoma, right breast: Following an MRI and biopsy, a total mastectomy was performed on March 6, 2019. On March 14, 2019 the subject was released from the hospital. The subject was considered recovered on March 19, 2019.

12.3.3 Analysis and Discussion of Deaths, Other Serious AEs and Other Significant AEs

Subject 8-00001: Ductal carcinoma, right breast: This adverse event was not related to the investigational product.

12.4 Clinical Laboratory Evaluation

12.4.1 Listing of Individual Laboratory Measurements

In order to qualify for study inclusion female subjects had to be unable to become pregnant or willing to use an acceptable method of contraception to prevent pregnancy if they were of childbearing potential. All females of childbearing potential were administered a urine pregnancy test prior to enrollment. Only those with a negative test result were eligible to continue with the study procedures.

12.4.2 Evaluation of Each Laboratory Parameter

Ninety-three (93) female subjects were enrolled

- 22 female subjects were issued the pregnancy test. All results were negative
  The following methods of birth control were used by the 22 female subjects who were of childbearing potential.
  - Abstinence: 4
  - Double barrier: 14
  - IUD: 1
  - Systemic: 3
- 61 female subjects were postmenopausal
- 10 female subjects were surgically sterile

Source: Listing 16.2.8.1: Urine Pregnancy Test

12.4.2.1 Laboratory Values Over Time

The only clinical laboratory evaluation was administration of a urine pregnancy test at enrollment. There were no further measurements.

12.4.2.2 Individual Patient Changes

There were no measurements of individual patient changes based on laboratory evaluations.

12.4.2.3 Individual Clinically Significant Abnormalities

There were no measurements of individual clinically significant abnormalities based on laboratory evaluations.

12.5 Vital Signs, Physical Findings and Other Observations Related to Safety

Other observations related to safety included itching, burning, tape irritation and chip irritation associated with the patch test panels.

Itching and burning were evaluated at visit 2, at least 15 minutes following panel removal. Tape and chip irritation were evaluated at visit 2, at least 15 minutes following panel removal and at visits 3-6.

The amount of time between panel removal and the itching/burning/irritation evaluation at visit 2 ranged from 15 minutes to 1 hour and 15 minutes for all subjects. The average between time removal and evaluation was 25 minutes.

12.5.1 Other Observations Related to Safety: Itching and Burning

Subjects were asked to evaluate the intensity of itching or burning associated with the patch test panels during the 48-hour patch test panel wear time. The following scale was used to evaluate the responses.

None	No discomfort
Weak	Minimal discomfort
Moderate	Definite discomfort
Strong	Significantly bothersome; possible interference with sleep or daily activity

Table 45 summarizes the itching and burning responses reported by subjects at visit 2.

Table 45: Summary of Itching and Burning at Visit 2

Itching	None		Weak		Moderate		Strong	
	n	%	n	%	n	%	n	%
Panel 1 N=105	77	73.3	16	15.2	9	8.6	3	2.9
Panel 2 N=111	62	55.9	32	28.8	12	10.8	5	4.5
Panel 3 N=104[1]	77	74.0	17	16.4	7	6.7	3	2.9
Panel 4 N=109[1]	73	67.0	20	18.3	12	11.0	4	3.7
Panel 5 N=106[1]	71	67.0	20	18.9	13	12.3	2	1.9
Panel 6 N=120[1]	82	68.3	21	17.5	11	9.2	6	5.0
Burning	**None**		**Weak**		**Moderate**		**Strong**	
	n	%	n	%	n	%	n	%
Panel 1 N=105	96	91.4	5	4.8	4	3.8	0	-
Panel 2 N=111	99	89.2	8	7.2	4	3.6	0	-
Panel 3 N=104[1]	93	89.4	10	9.6	1	1.0	0	-
Panel 4 N=109[1]	94	86.2	11	10.1	3	2.7	1	1.0
Panel 5 N=106[1]	98	92.4	4	3.8	4	3.8	0	-
Panel 6 N=120[1]	108	90.0	9	7.5	3	2.5	0	-

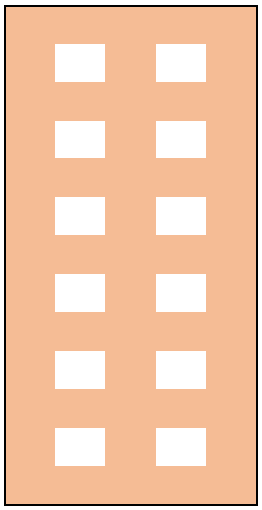
[1]Subject 4-00001 was patched with Investigational Panels 3-6 but did not return for visit 2. Although included in FAS population there is no adhesion score for this subject.
Source: Listing 16.2.6.2: Irritation, Itching and Burning at Visit 2. Table 14.2.36: Summary of Itching and Burning

12.5.2 Other Observations Related to Safety: Tape Irritation

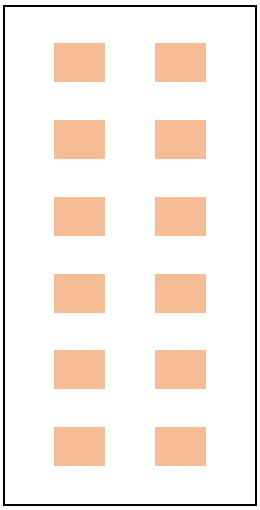
Irritation attributed to the adhesive used to adhere the panels to the skin (tape irritation) and irritation attributed to the polyester chips (chip irritation) were evaluated at visit 2, at least 15 minutes following removal of test panels and at visits 3-6. To ensure that irritation resulting from skin contact with the polyester chip was not confused with an allergic response to a specific allergen, all of the polyester chip sites must have presented with the same or nearly the same degree of irritation.

Figure 11: Illustration of Tape and Polyester Chip Irritation

Tape Irritation: Skin site of entire panel *with exception of chip sites* shows signs of skin irritation



Chip Irritation: Only chip sites show signs of irritation. *All sites* must have the same or nearly the same degree of irritation



The following score scale was used to evaluate tape and polyester chip irritation

None	No irritation
Weak	Faint to definite pink erythema
Moderate	Moderate erythema, definite redness
Strong	Severe erythema, very intense redness

Table 46: Summary of Tape and Chip Irritation Visits 2-6

Panel 1 N=105											
Visit	Evaluation	None		Weak		Moderate		Strong		Yes	
		n	%	n	%	n	%	n	%	n	%
2	Tape Irritation	93	88.6	10	9.5	2	1.9	0	-		
	Chip Irritation	103	98.1	2	1.9	0	-	0	-		
3	Tape Irritation	100	95.2	4	3.8	1	1.0	0	-		
	Chip Irritation	105	100	0	-	0	-	0	-		
	Persist or Increase									1	1.0
4	Tape Irritation	104	99.1	1	0.9	0	-	0	-		
	Chip Irritation	105	100	0	-	0	-	0	-		
	Persist or Increase									0	-
5	Tape Irritation	105	100	0	-	0	-	0	-		
	Chip Irritation	105	100	0	-	0	-	0	-		
	Persist or Increase									0	-
6	Tape Irritation	105	100	0	-	0	-	0	-		
	Chip Irritation	105	100	0	-	0	-	0	-		
	Persist or Increase									0	-

Panel 2 N=111											
Visit	Evaluation	None		Weak		Moderate		Strong		Yes	
		n	%	n	%	n	%	n	%	n	%
2	Tape Irritation	98	88.2	11	9.9	2	1.8	0	-		
	Chip Irritation	109	98.2	2	1.8	0	-	0	-		
3	Tape Irritation	107	96.4	3	2.7	1	0.9	0	-		
	Chip Irritation	111	100	0	-	0	-	0	-		
	Persist or Increase									3	2.7
4	Tape Irritation	110	99.1	1	0.9	0	-	0	-		
	Chip Irritation	111	100	0	-	0	-	0	-		
	Persist or Increase									0	-
5	Tape Irritation	111	100	0	-	0	-	0	-		
	Chip Irritation	111	100	0	-	0	-	0	-		
	Persist or Increase									0	-
6	Tape Irritation	111	100	0	-	0	-	0	-		
	Chip Irritation	111	100	0	-	0	-	0	-		
	Persist or Increase									0	-

Panel 3 N=104											
Visit	Evaluation	None		Weak		Moderate		Strong		Yes	
		n	%	n	%	n	%	n	%	n	%
2	Tape Irritation	94	90.4	7	6.7	3	2.9	0	-		
	Chip Irritation	102	98.1	2	1.9	0	-	0	-		
3	Tape Irritation	101	97.1	0	-	3	2.9	0	-		
	Chip Irritation	104	100	0	-	0	-	0	-		
	Persist or Increase									2	1.9
4	Tape Irritation	104	100	0	-	0	-	0	-		
	Chip Irritation	104	100	0	-	0	-	0	-		
	Persist or Increase									0	-
5	Tape Irritation	104	100	0	-	0	-	0	-		
	Chip Irritation	104	100	0	-	0	-	0	-		
	Persist or Increase									0	-
6	Tape Irritation	104	100	0	-	0	-	0	-		
	Chip Irritation	104	100	0	-	0	-	0	-		
	Persist or Increase									0	-

Panel 4 N=109											
Visit	Evaluation	None		Weak		Moderate		Strong		Yes	
		n	%	n	%	n	%	n	%	n	%
2	Tape Irritation	99	90.8	7	6.4	3	2.8	0	-		
	Chip Irritation	107	98.2	2	1.8	0	-	0	-		
3	Tape Irritation	105	96.3	2	1.8	2	1.8	0	-		
	Chip Irritation	109	100	0	-	0	-	0	-		
	Persist or Increase									1	0.9

Panel 4 N=109											
Visit	Evaluation	None		Weak		Moderate		Strong		Yes	
		n	%	n	%	n	%	n	%	n	%
4	Tape Irritation	109	100	0	-	0	-	0	-		
	Chip Irritation	109	100	0	-	0	-	0	-		
	Persist or Increase									0	0
5	Tape Irritation	109	100	0	-	0	-	0	-		
	Chip Irritation	109	100	0	-	0	-	0	-		
	Persist or Increase									0	-
6	Tape Irritation	109	100	0	-	0	-	0	-		
	Chip Irritation	109	100	0	-	0	-	0	-		
	Persist or Increase									0	-

Panel 5 N=106											
Visit	Evaluation	None		Weak		Moderate		Strong		Yes	
		n	%	n	%	n	%	n	%	n	%
2	Tape Irritation	96	90.6	9	8.5	1	0.9	0	-		
	Chip Irritation	103	97.2	3	2.8	0	-	0	-		
3	Tape Irritation	104	98.1	1	0.9	1	0.9	0	-		
	Chip Irritation	106	100	0	-	0	-	0	-		
	Persist or Increase									1	0.9
4	Tape Irritation	105	99.1	1	0.9	0	-	0	-		
	Chip Irritation	106	100	0	-	0	-	0	-		
	Persist or Increase									0	-
5	Tape Irritation	106	100	0	-	0	-	0	-		
	Chip Irritation	106	100	0	-	0	-	0	-		
	Persist or Increase									0	-
6	Tape Irritation	106	100	0	-	0	-	0	-		
	Chip Irritation	106	100	0	-	0	-	0	-		
	Persist or Increase									0	-

Panel 6 N=120											
Visit	Evaluation	None		Weak		Moderate		Strong		Yes	
		n	%	n	%	n	%	n	%	n	%
2	Tape Irritation	108	90.0	10	8.3	2	1.7	0	-		
	Chip Irritation	117	97.5	3	2.5	0	-	0	-		
3	Tape Irritation	116	96.7	3	2.5	1	0.8	0	-		
	Chip Irritation	120	100	0	-	0	-	0	-		
	Persist or Increase									2	1.7
4	Tape Irritation	120	100	0	-	0	-	0	-		
	Chip Irritation	119	99.2	1	0.8	0	-	0	-		
	Persist or Increase									0	-
5	Tape Irritation	120	100	0	-	0	-	0	-		
	Chip Irritation	120	100	0	-	0	-	0	-		
	Persist or Increase									0	-

Panel 6 N=120											
Visit	Evaluation	None		Weak		Moderate		Strong		Yes	
		n	%	n	%	n	%	n	%	n	%
6	Tape Irritation	120	100	0	-	0	-	0	-		
	Chip Irritation	120	100	0	-	0	-	0	-		
	Persist or Increase									0	-

Source: Table 14.2.36: Summary of Irritation, Itching and Burning at Visit 2, Table 14.2.37 Summary of Tape and Chip Irritation Visits 3-6

Following visit 6, the Investigators were asked to rate panel tape and polyester chip irritation for each subject, based on the overall trend observed at visits 2-6. Subjects who exhibited irritation at visit 2 that resolved by visit 3 were considered to have no irritation (none) resulting from the tape or chip overall. Skin under occlusion from an adhesive material would be expected to have minimal irritation shortly after the panel is removed. Irritation that persisted or increased in severity beyond visit 3 but resolved by the following visit would have been rated as irritant. An allergic response was considered if irritation persisted beyond visit 3, increased in severity and had symptoms consistent with criteria used to score positive skin reactions according to standard patch testing guidelines established by the International Contact Dermatitis Research Group.

Table 47: Summary of Investigator Determination of Tape and Chip Irritation

Tape Irritation	None		Irritant		Allergic	
	n	%	n	%	n	%
Panel 1 N=105	103	98.1	2	1.9	0	-
Panel 2 N=111	109	98.2	2	1.8	0	-
Panel 3 N=104	103	99.0	1	1.0	0	-
Panel 4 N=109	108	99.1	1	0.9	0	-
Panel 5 N=106	105	99.1	1	0.9	0	-
Panel 6 N=120	119	99.2	1	0.8	0	-

Chip Irritation	None		Irritant		Allergic	
	n	%	n	%	n	%
Panel 1 N=105	105	100	0	-	0	-
Panel 2 N=111	111	100	0	-	0	-
Panel 3 N=104	104	100	0	-	0	-
Panel 4 N=109	109	100	0	-	0	-
Panel 5 N=106	106	100	0	-	0	-
Panel 6 N=120	120	100	0	-	0	-

Source: Table 14.2.35: Summary of Investigator Determination Tape and Chip Irritation, Listing 16.2.5.4 Investigator Determination of Tape Chip Irritation at Post Visit 6, Listing 16.2.6.2 Irritation, Itching and Burning at Visit 2, Listing 16.2.6.3 Tape Irritation at Visits 3-6

12.6 Safety Conclusions

12.6.1 Adverse Events

There were 4 definitely related adverse events, erythema at patch test sites, attributed to a single subject. The events were mild, and all had resolved when the patient was re-contacted 36 days later. All 4 events were associated with the tin chloride allergen.

- Erythema at panel 2, position 6 (0.33 mg/cm^2 tin chloride), persistent escalating reaction at visit 6
- Erythema at panel 2 position 12 (0.11 mg/cm^2 tin chloride), late reaction at visit 6
- Erythema at reference allergen panel 1, position 6, (1% tin chloride in petrolatum), late reaction at visit 6. Note: Adverse Event was erroneously reported as Panel 1 in CRF but verification with source document confirmed it should have been recorded as Reference Panel 1.
- Erythema at panel 2 position 5 (0.037 mg/cm^2 tin chloride). Event was reported 1 week later based on photograph subject sent of his back. The event does not necessarily indicate a late positive response just erythema at a patch test site that was not earlier observed.

Overall, there were 95 positive reactions to the investigational tin chloride allergen. (1 subject positive to the 0.018 mg/cm^2 dose, 4 subjects positive to the 0.037 mg/cm^2 dose, 25 subjects positive to the 0.11 mg/cm^2 dose and 65 positive to the 0.33 mg/cm^2 dose). Only 2 of these positive reactions were either late or persistent escalating at visit 6. This low number of late and persistent responses among the 111 subjects tested does not present a safety signal which would preclude further testing of this allergen.

The 13 possibly related adverse events were reported by 9 subjects. All events were mild or moderate. All possibly related adverse events had resolved by the time the subjects completed the study with exception of 3 events involving worsening of preexisting chronic, conditions.

There were 33 not related adverse events reported by 23 subjects. One subject experienced a serious adverse event, ductal carcinoma, right breast, which was not related to the investigational products. Other than the serious adverse event, all of the not related adverse events were common medically related occurrences. The majority of events were mild or moderate. Two events were considered severe, the ductal carcinoma (SAE) and worsened pain in upper right quadrant.

Overall, 10 subjects (8.2% of the FAS population) experienced definitely or possibly related adverse events. In conclusion, based on the number and type of definitely or possibly related adverse events reported on this clinical trial there were no safety signals or trends which would preclude further testing of these investigational allergens.

12.6.2 Other Observations Related to Safety: Itching, Burning, Tape and Chip Irritation

Among panels 1-6, 84 to 90% of subjects reported weak or no itching and 96 to 99% of subjects reported weak or no burning sensations associated with test panel application. Ninety-eight (98)-99% of subjects exhibited no tape irritation and 100% of subjects exhibited no chip irritation based on Investigator Determination following evaluations at visits 2-6.

The low prevalence of moderate or strong itching, burning, tape irritation and chip irritation indicate that the test panels are safe to be worn for 48 hours.

13.0 DISCUSSION AND OVERALL CONCLUSIONS

13.1 Efficacy Conclusions

Allergens in petrolatum are used in standard diagnostic patch testing for ACD. However, allergen composition, test conditions, patient sensitivity, and physician experience among other factors introduce considerable variability which can influence the intensity and interpretation of skin reactions. In contrast, T. R.U.E. Test, a ready-to-use patch test method designed for use by licensed physicians in the diagnosis of ACD, has been evaluated in several large, multicenter clinical studies and is the only combined allergen and patch panel product currently approved by the FDA in the United States. As new allergens become clinically relevant, there is an ever-growing need to expand the number of allergens included in T.R.U.E. TEST product. To that end, the current study was designed to evaluate the diagnostic performance of eight metal allergens under consideration for inclusion in a new TRUE Test product that would only include metal allergens.

Ascending doses of aluminum, copper, manganese, molybdenum, tin, titanium, vanadium and zinc investigational allergens were tested in 122 adult subjects, all of whom had a past positive patch to one of the investigational allergens or a suspicion of contact allergy based on clinical history. The objective of the study was to determine the optimal dose of each investigational allergen. Subjects with a past positive patch test were tested with at least the allergen panels(s) and corresponding reference allergen(s) (with the exception of subjects enrolled in Germany who were not tested with the reference allergens) to which they had the previous response. The Investigator used his or her experience and medical expertise to determine if a subject with a past positive patch result should be tested with all investigational allergen panels or only to the allergen to which the subject had the past response. Subjects with suspicion of metal contact allergy were tested with all investigational and reference allergens (with the exception of subjects enrolled in Germany who were not tested with the reference allergens). All subjects were tested with the excipient controls and a blank patch on panel 6.

One hundred twenty-one (121) of the 122 enrolled subjects completed the study and were compliant with the 2-day patch application period. One subject removed her patches prior to the 2nd visit due to a family emergency. One hundred twenty-two (122) subjects were included in the FAS population and 121 subjects were included in the mFAS population.

The primary endpoints for selection of optimal test allergen dose were the lowest concentration eliciting 1+ or 2+ or 3+ positive reactions in a minimum of 15 of subjects with the fewest number of 3+ reactions and overall concordance and discordance compared to the reference allergen. The frequency of ranked skin responses, positive (1+, 2+, 3+), negative, doubtful, and irritant reactions was calculated for each investigational allergen. Concordance between each dose and the corresponding reference allergens was calculated using Kappa statistic.

Two of the investigational allergens, aluminum and molybdenum, did not meet the minimum criteria of at least 15 subjects with positive responses therefore will not be further tested nor included on the final metal panel.

Four allergens, copper, manganese, vanadium sulfate and zinc only had one dose that did meet the minimum criteria of at least 15 subjects with positive responses therefore determination of optimal dose was based solely on this primary endpoint. Two (2) doses of vanadium chloride also met the minimum criteria of at least 15 subjects with positive responses however, the vanadium chloride allergen was eliminated from consideration for the final panel due to the corrosive nature of the vanadium chloride raw material which complicated its handling during the production and storage of the experimental panel.

The tin and titanium allergens each had 2 doses that met the minimum criteria of at least 15 subjects with positive responses therefore both primary and secondary endpoints were considered in the determination of optimal dose.

Tin chloride: There were 25 subjects with positive responses to the 0.11 mg/cm^2 dose and 65 subjects with positive responses to the 0.33 mg/cm^2 dose.

Only slight differences were observed between the 2 doses for the number of doubtful, 3+ reactions and Kappa statistic.

Tin chloride	Doubtful	3+ Reactions	Kappa Statistic
0.11 mg/cm²	12 (10.8%)	2 (0.5%)	31% Fair
0.33 mg/cm²	12 (10.9%)	3 (0.7%)	22% Fair

The 0.11 mg/cm^2 dose did have fewer irritant responses but, for the majority of the allergens tested on this study, including tin, the number of irritant responses increased as the dose increased.

Ultimately the decision to select the 0.33 mg/cm^2 dose of tin chloride as optimal dose was based on the greater number of 1+ and 2+ responses, lower percentage of late responses, higher number of persistent reactions and higher rate of sensitivity.

Tin chloride	1+ and 2+	Late	Persistent	Sensitivity
0.11 mg/cm²	35 (7.9%)	5 (20.0%)	5 (20.0%)	45.0%
0.33 mg/cm²	122 (27.7%)	6 (9.2%)	39 (60.0%)	90%

Titanium: Ammonium titanium oxide oxalate was only titanium salt that met the minimum criteria of at least 15 subjects with positive responses.

There were 21 subjects with positive responses to the 0.11 mg Ti/cm^2 dose and 18 subjects with positive responses to the 0.22 mg Ti/cm^2 dose. There was no statistically significant difference between the 2 doses that met the minimum criteria of at least 15 subjects with positive responses and both were considered in the selection of optimal dose.

Although the number of positive responses generally increases as the dose is increased a nonmonotonic curve was observed for this allergen. In addition, there were only slight differences

between the number of doubtful, irritant, 1+ and 2+ reactions, 3+ reactions, sensitivity and specificity.

Ammonium titanium oxide oxalate	Doubtful	Irritant	1+ and 2+	3+	Sensitivity	Specificity
0.11 mg/cm²	24 (22.0%)	9 (8.3%)	23 (5.3%)	0	70.0%	78.8%
0.33 mg/cm²	27 (24.8%)	8 (7.3%)	22 (5.0%)	0	70.0%	83.3%

Ultimately, the decision to select the 0.22 mg Ti/cm^2 dose as optimal dose was based on a more favorable Kappa statistic, fewer late responses and the higher number of persistent reactions.

Ammonium titanium oxide oxalate	Kappa statistic	Late	Persistent
0.11 mg Ti/cm²	33% (fair agreement)	1 (4.8%)	1 (4.8%)
0.22 mg Ti/cm²	40% (moderate agreement)	0	4 (22.2%)

13.2 Safety Conclusions: Adverse Events

Three (3) of the 4 definitely related adverse events for erythema at patch test sites, were reported by the Investigator to document patch test reactions to tin chloride at the final visit. The 4th definitely related event which noted an erythematic response at the tin chloride patch test site was reported 1 week later based on photograph of the subject's back. All events were mild and had resolved by the time the subject was re-contacted.

- Panel 2, position 6 (0.33 mg/cm^2 tin chloride), persistent escalating reaction at visit 6
- Panel 2 position 12 (0.11 mg/cm^2 tin chloride), late reaction at visit 6
- Reference allergen panel 1, position 6, (1% tin chloride in petrolatum), late reaction at visit 6. Note: Adverse Event was erroneously reported as Panel 1 in CRF but verification with source document confirmed it should have been recorded as Reference Panel 1.

Reported 1 week later:

- Panel 2 position 5 (0.037 mg/cm^2 tin chloride). Erythema is not necessarily a late positive response.

Of the 95 positive reactions to investigational tin chloride allergen, only 2 were either late or persistent escalating at visit 6. This low number of late and persistent responses among the 111 subjects tested does not present a safety signal which would preclude further testing of this allergen.

There were 13 possibly related adverse events reported by 9 subjects.

- 5 skin and subcutaneous tissue disorders (itching (2), worsening eczema (2) and worsening palmoplantar pustulosis)
- 4 nervous system disorders (dizziness, headache (2) and head/neck tension)
- 2 musculoskeletal and connective tissue disorders (back pain, shoulder pain)
- 1 general disorder and administration site condition (tiredness)
- 1 eye disorder (eye dryness)

All of the possibly related adverse events were mild or moderate and had resolved by the end of

each subject's participation in the study with the exception of the 3 events associated with worsening of a preexisting condition.

There were 33 not related adverse events reported by 23 subjects. One subject experienced a serious adverse event, ductal carcinoma, right breast, which was not related to the investigational products. Other than the serious adverse event, all of the not related adverse events were common medically related occurrences. The majority of events were mild or moderate. Two events were considered severe, the ductal carcinoma and worsened pain in upper right quadrant.

In conclusion, the low prevalence of definitely or possibly related adverse events (8.2% of FAS population) experienced by the subjects enrolled on this clinical trial indicate no safety signals or trends which would preclude further testing of these investigational allergens.

13.3 Safety Conclusions: Itching, Burning, Tape Irritation and Chip Irritation

Eighty-four (84) to 90% of subjects patched with investigational panels 1-6 reported weak or no itching during the time the panels were applied, and 96 to 99% of subjects reported weak or no burning associated with the test panels. Ninety-eight (98) to 99% of subjects exhibited no tape irritation, and 100% of subjects exhibited no chip irritation based on Investigator Determination following evaluations at visits 2-6. The low prevalence of moderate or strong itching, burning, tape irritation and chip irritation confirm that the test panels are safe to be worn for 48 hours.

14.0 TABLES, FIGURES, GRAPHS REFERRED TO BUT NOT INCLUED IN TEXT

15.0 REFERENCE LIST

16.0 APPENDICES

16.1 Study Information

16.1.1 Protocol and Protocol Amendments

Final Protocol, October 19, 2015
Amendment I, March 3, 2016
Amendment II, August 18, 2016
Amendment III, March 29, 2017
Amendment IV, February 6, 2018
Amendment V, June 27, 2018

16.1.2 Sample Case Report Forms

Sample Case Report Form

16.1.3 List of IRB and IECs

Site 1. Oregon Health & Science University Institutional Review Board, Portland, Oregon, USA
Site 2. Institutional Review Board National Jewish Health, Denver Colorado, USA
Site 3. Prof. A.P. Perruchoud, Präsident EKNZ, Ethikkommission Nordwest- und Zentralschweiz Basel, Switzerland
Site 4. Comitato Etico Ospedale San Raffaele, Milano, Italy
Site 5. Medisch Ethische Toetsingscommissie VUmc, Amsterdam, Netherlands

Site 6. Ethikkommission der Ludwig-Maximilians-Universität München, München, Germany
Site 7. Clinical Trial Center for Developmental Therapeutics, Tokushima University Hospital, Tokushima, Japan
Site 8. Toho University Omori Medical Center Institutional Review Board, Omori-Nishi, Ota-ku, Tokyo, Japan
Site 9. Institutional Review Board of Fujita Health University Second Educational Hospital, Nagoya, Japan

IRB/IEC Approvals and Consent Forms

16.1.4 List and Description of Investigators

Site 1. Patricia L Norris, MD, Oregon Health & Science University, Portland, Oregon, USA (1 screen fail only. No subjects enrolled at this site)
Site 2. Karin Pacheco, MD, National Jewish Health, University of Colorado Denver, Denver, Colorado, USA
Site 3. Prof. Dr. med. Andreas Bircher, University Hospital Basel Allergology Unit, Basel, Switzerland (Study initiation through 27 June 2018) / PD Dr. med. Kathrin Scherer Hofmeier, University Hospital Basel Allergology Unit, Basel, Switzerland (27 June 2018 through study completion)
Site 4. Prof. Paolo Pigatto, MD, University of Milano-Dipartimento di Scienze Biomediche, Milan, Italy
Site 5. Prof. dr. Thomas Rustemeyer, Department of Dermatology, VU University Medical Center, Amsterdam Netherlands
Site 6. Prof. Dr. med. Peter Thomas, Institute of Dermatology and Allergy, Ludwig-Maximilians-Universität München, Munich, Germany
Site 7. Maki Hosoki, DDS, PhD, Department of Stomatognathic Function and Occlusal Reconstruction Institute of Biomedical Sciences, Tokushima University Graduate School, Tokushima, Japan
Site 8. Hiromi Kanto MD, PhD, Department of Dermatology, School of Medicine, Toho University Omori Medical Center, Tokyo, Japan
Site 9. Akiko Yagami, MD, PhD, Department of Allergology, Fujita Health University Second Educational Hospital, Nagoya, Japan

Investigator CVs

16.1.5 Signature of SmartPractice Responsible Medical Director

SMARTPRACTICE MEDICAL DIRECTOR SIGNATURE

Study Title:	Clinical Evaluation of Metal Panel Allergens: Aluminum, Copper, Manganese, Molybdenum, Tin, Titanium, Vanadium and Zinc Dose Response Study
Study Authors:	Kathy Shannon, CRA SmartPractice Jeannie Lombardo, Assistant Technical Editor, SmartPractice
Medical Director:	Curt Hamann, MD

Medical Director Signature and Date:

Signature: _____

Curt Hamann, MD

Date: May 19. 2020

16.1.7 Listing of Subjects Receiving Investigational Product

See Listing 16.2.1: Subject Disposition

16.1.7 Randomization Scheme and Codes

See Listing 16.1.7: Randomization Details

16.1.8 Audit Certificates

Section does not apply. Study was not audited.

16.1.9 Documentation of Statistical Methods

16.1.10 Documentation of Inter-Laboratory Methods and Quality Assurance

Section does not apply. No contract laboratories were used for this study.

16.1.11 Publications based on the Study

Section does not apply. There have been no publications based on this study.

16.1.12 Important Publications Referenced in the Report

Section does not apply. There were no important publications reference in the report

16.2 Patient Data Listings

16.2.1 Discontinued Subjects

See Listing 16.2.1 Subject Disposition

16.2.2 Protocol Deviations

See Listing 16.2.3 Protocol Deviations

16.2.3 Patients Excluded from Efficacy Analysis

See Listing 16.1.9 All Subjects by Population

16.2.4 Demographic Data

See Listing 16.2.4.1 Demographic Data

16.2.5 Compliance and/or Drug Concentration Data

See Listing 16.2.5.1 Investigational Panels Applied, Listing 16.2.5.2 Reference Allergens Applied, Listing 16.2.6.1 Adhesion Evaluations at Day 2 and Listing 16.2.6.2 Irritation, Itching and Burning at Visit 2 (contains panel removal times)

16.2.6 Individual Efficacy Response Data

See Listing 16.2.6.4 Evaluation of Skin Reactions and Late/Persistent Reactions

16.2.7 Adverse Event Listings

See Listing 16.2.7.1 Adverse Events, Listing 16.2.7.3 Narrative for Adverse Events,

Listing 16.2.4.4 Medications Taken for Adverse Events, Listing 16.2.7.2 Serious Adverse Events, Listing 16.2.7.4 Narrative for Serious Adverse Events and Listing 16.2.4.5 Medications Taken for Serious Adverse Events

16.2.8 Listing of Individual Laboratory Measurements by Subject

See Listing 16.2.8.1 Urine Pregnancy Test Results

16.3 Case Report Forms

16.3.1 CRFs for Deaths, Other Serious AEs and Withdrawals for AEs

SAE Report for Subject 8-00010

CRF for Subject 8-00010

16.3.2 Other CRFs Submitted

No case report forms are included in the body of this report but are available upon request.

I6.4 Individual Patient Data Listings

This section does not apply. No subject profiles were produced.