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

Summary

EudraCT number	2015-002678-19
Trial protocol	DE IT
Global end of trial date	15 July 2019

Results information

Result version number	v1 (current)
This version publication date	15 August 2021
First version publication date	15 August 2021
Summary attachment (see zip file)	Final Report (Final Report May 19 2020.pdf)

Trial information

Trial identification

Sponsor protocol code	SP148MP201

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02615249
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	SmartPractice
Sponsor organisation address	3400 East McDowell Road, Phoenix, United States, 85008
Public contact	Kathryn Shannon, SmartPractice, 01 602225-05957208, kshannon@smarthealth.com
Scientific contact	Kathryn Shannon, SmartPractice, 01 602225-05957208, kshannon@smarthealth.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	03 February 2020
Is this the analysis of the primary completion data?	Yes
Primary completion date	15 July 2019
Global end of trial reached?	Yes
Global end of trial date	15 July 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the diagnostic performance and safety of metal allergens proposed for inclusion in Metal Panel T.R.U.E. Test. The study will compare the diagnostic performance (primary) and safety (secondary) of ascending patch test doses of aluminum, copper, manganese, molybdenum, tin, titanium, vanadium and zinc allergens.

Protection of trial subjects:

Subjects were patched with 6 investigational patch test panels and 2 petrolatum patch test panels. The 2 petrolatum patch test panels were not used in Germany. Patches were to be worn for approximately 48 hours. Subjects for whom the patch test panels were intolerable were at liberty to remove the patches prior to the 48 hour return visit. None of the study subjects removed the patch tests due to intolerable conditions. Skin test sites were evaluated for allergic contact dermatitis at days 4, 7, 14 and 21 following patch test application.

Background therapy:

Subjects were patch tested with hydrogel experimental metal allergens and the same metal allergens prepared in petrolatum

Evidence for comparator:

Petrolatum allergens were used (in all locations with the exception of Germany) to compare 2 patch test methods. Hydrogel method was used for the investigational product. The same allergens prepared using petrolatum were used as a comparator.

Actual start date of recruitment	03 October 2016
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Netherlands: 20
Country: Number of subjects enrolled	Germany: 30
Country: Number of subjects enrolled	Italy: 9
Country: Number of subjects enrolled	Switzerland: 6
Country: Number of subjects enrolled	Japan: 44
Country: Number of subjects enrolled	United States: 13
Worldwide total number of subjects	122
EEA total number of subjects	59

Notes:

Subjects enrolled per age group	
In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	122
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Subjects were recruited to the study starting 5 December 2016 through 15 July 2019. Each subject's participation was approximately 3 weeks, 21 +/- 2 days

Pre-assignment

Screening details:

Subjects 18 years of age or older, had a past positive patch test result, or suspected to have metal allergy related to a metal implant, were not pregnant or nursing. Immunosuppressives and corticosteroids were not permitted. There were 2 screen fails

Period 1

Period 1 title	Visit 1 Patch Test Application
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor

Blinding implementation details:

The investigators and subjects knew which allergens were being tested, but were blinded to the placement of the allergen doses within each panel.

Arms

Arm title	Single Arm Study

Arm description:

Qualified subjects were patch tested.

Arm type	Experimental
Investigational medicinal product name	Aluminum chloride
Investigational medicinal product code	Panel 1
Other name	
Pharmaceutical forms	Cutaneous patch
Routes of administration	Cutaneous use

Dosage and administration details:

Four doses of aluminum chloride hexahydrate were tested: 0.040 mg/cm², 0.12 mg/cm², 0.36 mg/cm², 0.72 mg/cm²

Investigational medicinal product name	Aluminum lactate
Investigational medicinal product code	Panel 1
Other name	
Pharmaceutical forms	Cutaneous patch
Routes of administration	Cutaneous use

Dosage and administration details:

Four doses of aluminum lactate were tested: 0.047 mg/cm², 0.14 mg/cm², 0.42 mg/cm², 0.84 mg/cm²

Investigational medicinal product name	Copper sulfate
Investigational medicinal product code	Panel 2
Other name	
Pharmaceutical forms	Cutaneous patch
Routes of administration	Cutaneous use

Dosage and administration details:

Four doses of copper sulfate were tested: 0.013, 0.040, 0.080 and 0.12 mg/cm²

Investigational medicinal product name	Manganese chloride
Investigational medicinal product code	Panel 3
Other name	
Pharmaceutical forms	Cutaneous patch
Routes of administration	Cutaneous use

Dosage and administration details:

Four doses of manganese chloride were tested: 0.013, 0.040, 0.080 and 0.24 mg/cm²

Investigational medicinal product name	Ammonium molybdate
Investigational medicinal product code	Panel 3
Other name	
Pharmaceutical forms	Cutaneous patch
Routes of administration	Cutaneous use

Dosage and administration details:

Four doses of ammonium molybdate were tested: 0.0067, 0.020, 0.040 and 0.12 mg/cm² ammonium molybdate

Investigational medicinal product name	Tin chloride
Investigational medicinal product code	Panel 2
Other name	
Pharmaceutical forms	Cutaneous patch
Routes of administration	Cutaneous use

Dosage and administration details:

Four doses of tin chloride were tested: 0.018, 0.037, 0.11 and 0.33 mg/cm²

Investigational medicinal product name	Titanium citrate
Investigational medicinal product code	Panel 4
Other name	
Pharmaceutical forms	Cutaneous patch
Routes of administration	Cutaneous use

Dosage and administration details:

Three doses of titanium citrate were tested: 0.013, 0.040, 0.080 and 0.24 mg/cm²

Investigational medicinal product name	Titanium lactate
Investigational medicinal product code	Panel 4
Other name	
Pharmaceutical forms	Cutaneous patch
Routes of administration	Cutaneous use

Dosage and administration details:

Three doses of titanium lactate were tested: 0.070, 0.14 and 0.28 mg Ti/cm²

Investigational medicinal product name	Ammonium titanium oxide oxalate
Investigational medicinal product code	Panel 4
Other name	
Pharmaceutical forms	Cutaneous patch
Routes of administration	Cutaneous use

Dosage and administration details:

Three doses of ammonium titanium oxide oxalate were tested: 0.055, 0.11 and 0.22 mg Ti/cm²

Investigational medicinal product name	Potassium titanium oxide oxalate
Investigational medicinal product code	Panel 4
Other name	
Pharmaceutical forms	Cutaneous patch
Routes of administration	Cutaneous use

Dosage and administration details:

Three doses of potassium titanium oxide oxalate were tested: 0.060, 0.12 and 0.24 mg Ti/cm²

Investigational medicinal product name	Vanadium chloride
Investigational medicinal product code	Panel 5
Other name	
Pharmaceutical forms	Cutaneous patch
Routes of administration	Cutaneous use

Dosage and administration details:

Four doses of vanadium chloride were tested: 0.0042, 0.0083, 0.025 and 0.050 mg V/cm²

Investigational medicinal product name	Vanadium oxide sulfate
Investigational medicinal product code	Panel 5
Other name	
Pharmaceutical forms	Cutaneous patch
Routes of administration	Cutaneous use

Dosage and administration details:

Four doses of vanadium oxide sulfate were tested: 0.0042, 0.0083, 0.025 and 0.050 mg V/cm²

Investigational medicinal product name	Zinc chloride
Investigational medicinal product code	Panel 2
Other name	
Pharmaceutical forms	Cutaneous patch
Routes of administration	Cutaneous use

Dosage and administration details:

Four doses of zinc chloride were tested: 0.013 mg/cm², 0.040 mg/cm², 0.080 mg/cm², 0.24 mg/cm²

Number of subjects in period 1	Single Arm Study
Started	122
Completed	122

Period 2

Period 2 title	Visits 2-6 Patch Removal and Evaluations
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor

Blinding implementation details:

The investigators and subjects knew which allergens were tested, but were blinded to the placement of the allergen doses within each panel.

Arms

Arm title	Single Arm Study

Arm description:

All subjects who returned for visit 2

Arm type	Experimental
Investigational medicinal product name	Aluminum chloride
Investigational medicinal product code	Panel 1
Other name	
Pharmaceutical forms	Cutaneous patch
Routes of administration	Cutaneous use

Dosage and administration details:

Four doses of aluminum chloride hexahydrate were evaluated: 0.040 mg/cm², 0.12 mg/cm², 0.36 mg/cm², 0.72 mg/cm²

Investigational medicinal product name	Aluminum lactate
Investigational medicinal product code	Panel 1
Other name	
Pharmaceutical forms	Cutaneous patch
Routes of administration	Cutaneous use

Dosage and administration details:

Four doses of aluminum lactate were evaluated: 0.047 mg/cm², 0.14 mg/cm², 0.42 mg/cm², 0.84 mg/cm²

Investigational medicinal product name	Copper sulfate
Investigational medicinal product code	Panel 2
Other name	
Pharmaceutical forms	Cutaneous patch
Routes of administration	Cutaneous use

Dosage and administration details:

Four doses of copper sulfate were evaluated: 0.013, 0.040, 0.080 and 0.12 mg/cm²

Investigational medicinal product name	Manganese chloride
Investigational medicinal product code	Panel 3
Other name	
Pharmaceutical forms	Cutaneous patch
Routes of administration	Cutaneous use

Dosage and administration details:

Four doses of manganese chloride were evaluated: 0.013, 0.040, 0.080 and 0.24 mg/cm²

Investigational medicinal product name	Ammonium molybdate
Investigational medicinal product code	Panel 3
Other name	
Pharmaceutical forms	Cutaneous patch
Routes of administration	Cutaneous use

Dosage and administration details:

Four doses of ammonium molybdate were evaluated: 0.0067, 0.020, 0.040 and 0.12 mg/cm²

Investigational medicinal product name	Tin chloride
Investigational medicinal product code	Panel 2
Other name	
Pharmaceutical forms	Cutaneous patch
Routes of administration	Cutaneous use

Dosage and administration details:

Four doses of tin chloride were evaluated: 0.018, 0.037, 0.11 and 0.33 mg/cm²

Investigational medicinal product name	Titanium citrate
Investigational medicinal product code	Panel 4
Other name	

Pharmaceutical forms	Cutaneous patch
Routes of administration	Cutaneous use

Dosage and administration details:

Three doses of titanium citrate were evaluated: 0.013, 0.040, 0.080 and 0.24 mg/cm²

Investigational medicinal product name	Titanium lactate
Investigational medicinal product code	Panel 4
Other name	
Pharmaceutical forms	Cutaneous patch
Routes of administration	Cutaneous use

Dosage and administration details:

Three doses of titanium lactate were evaluated: 0.070, 0.14 and 0.28 mg Ti/cm²

Investigational medicinal product name	Ammonium titanium oxide oxalate
Investigational medicinal product code	Panel 4
Other name	
Pharmaceutical forms	Cutaneous patch
Routes of administration	Cutaneous use

Dosage and administration details:

Three doses of ammonium titanium oxide oxalate were evaluated: 0.055, 0.11 and 0.22 mg Ti/cm²

Investigational medicinal product name	Potassium titanium oxide oxalate
Investigational medicinal product code	Panel 4
Other name	
Pharmaceutical forms	Cutaneous patch
Routes of administration	Cutaneous use

Dosage and administration details:

Three doses of potassium titanium oxide oxalate were evaluated: 0.060, 0.12 and 0.24 mg Ti/cm²

Investigational medicinal product name	Vanadium chloride
Investigational medicinal product code	Panel 5
Other name	
Pharmaceutical forms	Cutaneous patch
Routes of administration	Cutaneous use

Dosage and administration details:

Four doses of vanadium chloride were evaluated: 0.0042, 0.0083, 0.025 and 0.050 mg V/cm²

Investigational medicinal product name	Vanadium oxide sulfate
Investigational medicinal product code	Panel 5
Other name	
Pharmaceutical forms	Cutaneous patch
Routes of administration	Cutaneous use

Dosage and administration details:

Four doses of vanadium oxide sulfate were evaluated: 0.0042, 0.0083, 0.025 and 0.050 mg V/cm²

Investigational medicinal product name	Zinc chloride
Investigational medicinal product code	Panel 2
Other name	
Pharmaceutical forms	Cutaneous patch
Routes of administration	Cutaneous use

Dosage and administration details:

Four doses of zinc chloride were evaluated: 0.013 mg/cm², 0.040 mg/cm², 0.080 mg/cm², 0.24 mg/cm²

Number of subjects in period 2	Single Arm Study
Started	122
Completed	122

Baseline characteristics

Reporting groups

Reporting group title	Visit 1 Patch Test Application

Reporting group description: -

Reporting group values	Visit 1 Patch Test Application	Total	
Number of subjects	122	122	
Age categorical Units: Subjects			
In utero		0	
Preterm newborn infants (gestational age < 37 wks)		0	
Newborns (0-27 days)		0	
Infants and toddlers (28 days-23 months)		0	
Children (2-11 years)		0	
Adolescents (12-17 years)		0	
Adults (18-64 years)		0	
From 65-84 years		0	
85 years and over		0	
Age continuous			
122 subjects ages 26 to 84 years old were enrolled			
Units: years			
median	60.0		
full range (min-max)	26 to 84	-	
Gender categorical Units: Subjects			
Female	93	93	
Male	29	29	

Subject analysis sets

Subject analysis set title	Allergens with 15 or more positive responses
Subject analysis set type	Per protocol

Subject analysis set description:

In this single arm study subjects with a past positive patch test were tested with the allergen responsible for the past positive patch test and any other relevant allergen. Those enrolled based on suspicion of metal allergy were tested with all investigational allergens. The primary endpoint was the lowest concentration of each allergen that elicited positive responses in at least 15 subjects. this section will be used to report the number of allergens for which there were at least 15 positive reactions. The attachment will itemize each allergen dose and the corresponding number of positive responses.

Subject analysis set title	Subjects Positive to Investigationall and Reference Allergen
Subject analysis set type	Per protocol

Subject analysis set description:

Subjects were patch tested with the investigational and reference allergens (with the exception of subjects enrolled in Germany who were not tested with the reference allergens).

Subject analysis set title	Subjects Negative to Investigational and Reference Allergen
Subject analysis set type	Per protocol

Subject analysis set description:

Subjects were patch tested with the investigational allergen and corresponding reference allergen.

Percent agreement is measured by the number of subjects with positive or negative reactions to each allergen.

Subject analysis set title	Subjects Positive to Investigational and Negative to Reference
Subject analysis set type	Per protocol

Subject analysis set description:

Subjects were patch tested with the investigational allergen and corresponding reference allergen. Percent agreement is measured by the number of subjects with positive or negative reactions to each allergen.

Subject analysis set title	Subjects Negative to Investigational and Positive to Reference
Subject analysis set type	Per protocol

Subject analysis set description:

Subjects were patch tested with the investigational allergen and corresponding reference allergen. Percent agreement is measured by the number of subjects with positive or negative reactions to each allergen.

Subject analysis set title	Panel 1
Subject analysis set type	Per protocol

Subject analysis set description:

Panel 1 contained aluminum allergens: 0.040, 0.12, 0.36 and 0.72 mg/cm² aluminum chloride hexahydrate and 047, 0.14, 0.42 and 0.84 mg/cm² aluminum lactate

Subject analysis set title	Panel 2
Subject analysis set type	Per protocol

Subject analysis set description:

Panel 2 contained copper, zinc and tin allergens, 0.013, 0.040, 0.080 and 0.12 mg/cm² copper sulfate, 0.013, 0.040, 0.080 and 0.24 mg/cm² zinc chloride and 0.018, 0.037, 0.11 and 0.33 mg/cm² tin chloride

Subject analysis set title	Panel 3
Subject analysis set type	Per protocol

Subject analysis set description:

Panel 3 contained manganese and molybdenum allergens: 0.013, 0.040, 0.080 and 0.24 mg/cm² manganese chloride tetrahydrate and 0.0067, 0.020, 0.040 and 0.12 mg/cm² ammonium molybdate

Subject analysis set title	Panel 4
Subject analysis set type	Per protocol

Subject analysis set description:

Panel 4 contained titanium allergens, Ammonium titanium peroxo citrate: 0.055, 0.11 and 0.22 mg Ti/cm², Ammonium titanium lactate: 0.070, 0.14 and 0.28 mg Ti/cm², Potassium titanium oxide oxalate: 0.060, 0.12 and 0.24 mg Ti/cm² and Ammonium titanium oxide oxalate: 0.055, 0.11 and 0.22 mg Ti/cm²*

Subject analysis set title	Panel 5
Subject analysis set type	Per protocol

Subject analysis set description:

Panel 5 contained vanadium allergens: Vanadium chloride: 0.0042, 0.0083, 0.025 and 0.050 mg V/cm² and Vanadium oxide sulfate: 0.0042, 0.0083, 0.025 and 0.050 mg V/cm²

Subject analysis set title	Panel 6
Subject analysis set type	Per protocol

Subject analysis set description:

Panel 6 contained already approved allergens and negative controls: 0.2 mg/cm2 nickel sulfate, 0.054 mg/cm2 potassium dichromate, 0.02 mg/cm2 cobalt dichloride, 0.075 mg/cm2 gold sodium thiosulfate (GST), Blank patch, Polyvinylpyrrolidone (PVP) and Hydroxypropyl cellulose (HPC)

Subject analysis set title	0.12 mg/cm2 Copper sulfate
Subject analysis set type	Per protocol

Subject analysis set description:

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/cm2 dose which was the only dose that met the minimum criteria of at least 15 subjects with positive responses

Subject analysis set title	0.24 mg/cm2 Manganese chloride
Subject analysis set type	Per protocol

Subject analysis set description:

One hundred four (104) subjects were tested with all doses of the manganese chloride investigational allergen however the 0.040 mg/cm2, 0.080 mg/cm2 and 0.24 mg/cm2 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/cm2 dose which was the only dose that met the minimum criteria of at least 15 subjects with positive responses.

Subject analysis set title	0.11 mg/cm2 Tin chloride
Subject analysis set type	Per protocol

Subject analysis set description:

One hundred eleven (111) subjects were tested with all doses of the tin chloride investigational allergen. There were 25 subjects with positive responses to the 0.11 mg/cm2 dose

Subject analysis set title	0.33 mg/cm2 Tin chloride
Subject analysis set type	Per protocol

Subject analysis set description:

One hundred eleven (111) subjects were tested with all doses of the tin chloride investigational allergen however the 0.33 mg/cm2 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 65 subjects with positive responses to the 0.33 mg/cm2 dose.

Subject analysis set title	0.11 mg Ti/cm2 Ammonium titanium oxide oxalate
Subject analysis set type	Per protocol

Subject analysis set description:

One hundred nine (109) subjects were tested with all doses of the titanium investigational allergens. 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/cm2 dose /

Subject analysis set title	0.22 mg Ti/cm2 Ammonium titanium oxide oxalate
Subject analysis set type	Per protocol

Subject analysis set description:

One hundred nine (109) subjects were tested with all doses of the titanium investigational allergens. Ammonium titanium oxide oxalate was the only titanium salt that met the minimum criteria of at least 15 subjects with positive responses. There were 18 subjects with positive responses to the 0.22 mg Ti/cm2 dose.

Subject analysis set title	0.025 mg V/cm2 Vanadium chloride
Subject analysis set type	Per protocol

Subject analysis set description:

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/cm2 dose.

Subject analysis set title	0.050 mg V/cm2 Vanadium chloride
Subject analysis set type	Per protocol

Subject analysis set description:

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 46 subjects with positive responses to the 0.050 mg V/cm2 dose.

Subject analysis set title	0.050 mg V/cm2 Vanadium sulfate
Subject analysis set type	Per protocol

Subject analysis set description:

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 sulfate: There were 30 subjects with positive responses to the 0.050 mg V/cm2 dose of vanadium sulfate

Subject analysis set title	0.24 mg/cm2 Zinc chloride
Subject analysis set type	Per protocol

Subject analysis set description:

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/cm2 dose which was the only dose that met the minimum criteria of at least 15 subjects with positive responses

Reporting group values	Allergens with 15 or more positive responses	Subjects Positive to Investigationall and Reference Allergen	Subjects Negative to Investigational and Reference Allergen
Number of subjects	121	91	91
Age categorical			
Units: Subjects			
In utero			
Preterm newborn infants (gestational age < 37 wks)			
Newborns (0-27 days)			
Infants and toddlers (28 days-23 months)			
Children (2-11 years)			
Adolescents (12-17 years)			
Adults (18-64 years)			
From 65-84 years			
85 years and over			
Age continuous			
122 subjects ages 26 to 84 years old were enrolled			
Units: years			
median	60.0		
full range (min-max)	26 to 84		
Gender categorical			
Units: Subjects			
Female	92		
Male	29		

Reporting group values	Subjects Positive to Investigational and Negative to Reference	Subjects Negative to Investigational and Positive to Reference	Panel 1
Number of subjects	91	91	105
Age categorical			
Units: Subjects			
In utero			
Preterm newborn infants (gestational age < 37 wks)			
Newborns (0-27 days)			
Infants and toddlers (28 days-23 months)			
Children (2-11 years)			
Adolescents (12-17 years)			
Adults (18-64 years)			
From 65-84 years			
85 years and over			
Age continuous			
122 subjects ages 26 to 84 years old were enrolled			
Units: years			
median			
full range (min-max)			

Gender categorical Units: Subjects			
Female Male			

Reporting group values	Panel 2	Panel 3	Panel 4
Number of subjects	111	104	109
Age categorical Units: Subjects			
In utero Preterm newborn infants (gestational age < 37 wks) Newborns (0-27 days) Infants and toddlers (28 days-23 months) Children (2-11 years) Adolescents (12-17 years) Adults (18-64 years) From 65-84 years 85 years and over			
Age continuous			
122 subjects ages 26 to 84 years old were enrolled			
Units: years median full range (min-max)			
Gender categorical Units: Subjects			
Female Male			

Reporting group values	Panel 5	Panel 6	0.12 mg/cm2 Copper sulfate
Number of subjects	106	120	111
Age categorical Units: Subjects			
In utero Preterm newborn infants (gestational age < 37 wks) Newborns (0-27 days) Infants and toddlers (28 days-23 months) Children (2-11 years) Adolescents (12-17 years) Adults (18-64 years) From 65-84 years 85 years and over			
Age continuous			
122 subjects ages 26 to 84 years old were enrolled			
Units: years median full range (min-max)			

Gender categorical Units: Subjects			
Female Male			

Reporting group values	0.24 mg/cm2 Manganese chloride	0.11 mg/cm2 Tin chloride	0.33 mg/cm2 Tin chloride
Number of subjects	104	111	110
Age categorical Units: Subjects			
In utero Preterm newborn infants (gestational age < 37 wks) Newborns (0-27 days) Infants and toddlers (28 days-23 months) Children (2-11 years) Adolescents (12-17 years) Adults (18-64 years) From 65-84 years 85 years and over			
Age continuous			
122 subjects ages 26 to 84 years old were enrolled			
Units: years median full range (min-max)			
Gender categorical Units: Subjects			
Female Male			

Reporting group values	0.11 mg Ti/cm2 Ammonium titanium oxide oxalate	0.22 mg Ti/cm2 Ammonium titanium oxide oxalate	0.025 mg V/cm2 Vanadium chloride
Number of subjects	109	109	106
Age categorical Units: Subjects			
In utero Preterm newborn infants (gestational age < 37 wks) Newborns (0-27 days) Infants and toddlers (28 days-23 months) Children (2-11 years) Adolescents (12-17 years) Adults (18-64 years) From 65-84 years 85 years and over			
Age continuous			
122 subjects ages 26 to 84 years old were enrolled			
Units: years median full range (min-max)			

Gender categorical Units: Subjects			
Female Male			

Reporting group values	0.050 mg V/cm2 Vanadium chloride	0.050 mg V/cm2 Vanadium sulfate	0.24 mg/cm2 Zinc chloride
Number of subjects	106	106	111
Age categorical Units: Subjects			
In utero Preterm newborn infants (gestational age < 37 wks) Newborns (0-27 days) Infants and toddlers (28 days-23 months) Children (2-11 years) Adolescents (12-17 years) Adults (18-64 years) From 65-84 years 85 years and over			
Age continuous			
122 subjects ages 26 to 84 years old were enrolled			
Units: years median full range (min-max)			
Gender categorical Units: Subjects			
Female Male			

End points

End points reporting groups

Reporting group title	Single Arm Study
Reporting group description:	
Qualified subjects were patch tested.	
Reporting group title	Single Arm Study
Reporting group description:	
All subjects who returned for visit 2	
Subject analysis set title	Allergens with 15 or more positive responses
Subject analysis set type	Per protocol
Subject analysis set description:	
In this single arm study subjects with a past positive patch test were tested with the allergen responsible for the past positive patch test and any other relevant allergen. Those enrolled based on suspicion of metal allergy were tested with all investigational allergens. The primary endpoint was the lowest concentration of each allergen that elicited positive responses in at least 15 subjects. this section will be used to report the number of allergens for which there were at least 15 positive reactions. The attachment will itemize each allergen dose and the corresponding number of positive responses.	
Subject analysis set title	Subjects Positive to Investigationall and Reference Allergen
Subject analysis set type	Per protocol
Subject analysis set description:	
Subjects were patch tested with the investigational and reference allergens (with the exception of subjects enrolled in Germany who were not tested with the reference allergens).	
Subject analysis set title	Subjects Negative to Investigational and Reference Allergen
Subject analysis set type	Per protocol
Subject analysis set description:	
Subjects were patch tested with the investigational allergen and corresponding reference allergen. Percent agreement is measured by the number of subjects with positive or negative reactions to each allergen.	
Subject analysis set title	Subjects Positive to Investigational and Negative to Reference
Subject analysis set type	Per protocol
Subject analysis set description:	
Subjects were patch tested with the investigational allergen and corresponding reference allergen. Percent agreement is measured by the number of subjects with positive or negative reactions to each allergen.	
Subject analysis set title	Subjects Negative to Investigational and Positive to Reference
Subject analysis set type	Per protocol
Subject analysis set description:	
Subjects were patch tested with the investigational allergen and corresponding reference allergen. Percent agreement is measured by the number of subjects with positive or negative reactions to each allergen.	
Subject analysis set title	Panel 1
Subject analysis set type	Per protocol
Subject analysis set description:	
Panel 1 contained aluminum allergens: 0.040, 0.12, 0.36 and 0.72 mg/cm² aluminum chloride hexahydrate and 047, 0.14, 0.42 and 0.84 mg/cm² aluminum lactate	
Subject analysis set title	Panel 2
Subject analysis set type	Per protocol
Subject analysis set description:	
Panel 2 contained copper, zinc and tin allergens, 0.013, 0.040, 0.080 and 0.12 mg/cm² copper sulfate, 0.013, 0.040, 0.080 and 0.24 mg/cm² zinc chloride and 0.018, 0.037, 0.11 and 0.33 mg/cm² tin chloride	
Subject analysis set title	Panel 3
Subject analysis set type	Per protocol

Subject analysis set description:

Panel 3 contained manganese and molybdenum allergens: 0.013, 0.040, 0.080 and 0.24 mg/cm² manganese chloride tetrahydrate and 0.0067, 0.020, 0.040 and 0.12 mg/cm² ammonium molybdate

Subject analysis set title	Panel 4
Subject analysis set type	Per protocol

Subject analysis set description:

Panel 4 contained titanium allergens, Ammonium titanium peroxo citrate: 0.055, 0.11 and 0.22 mg Ti/cm², Ammonium titanium lactate: 0.070, 0.14 and 0.28 mg Ti/cm², Potassium titanium oxide oxalate: 0.060, 0.12 and 0.24 mg Ti/cm² and Ammonium titanium oxide oxalate: 0.055, 0.11 and 0.22 mg Ti/cm²*

Subject analysis set title	Panel 5
Subject analysis set type	Per protocol

Subject analysis set description:

Panel 5 contained vanadium allergens: Vanadium chloride: 0.0042, 0.0083, 0.025 and 0.050 mg V/cm² and Vanadium oxide sulfate: 0.0042, 0.0083, 0.025 and 0.050 mg V/cm²

Subject analysis set title	Panel 6
Subject analysis set type	Per protocol

Subject analysis set description:

Panel 6 contained already approved allergens and negative controls: 0.2 mg/cm2 nickel sulfate, 0.054 mg/cm2 potassium dichromate, 0.02 mg/cm2 cobalt dichloride, 0.075 mg/cm2 gold sodium thiosulfate (GST), Blank patch, Polyvinylpyrrolidone (PVP) and Hydroxypropyl cellulose (HPC)

Subject analysis set title	0.12 mg/cm2 Copper sulfate
Subject analysis set type	Per protocol

Subject analysis set description:

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/cm2 dose which was the only dose that met the minimum criteria of at least 15 subjects with positive responses

Subject analysis set title	0.24 mg/cm2 Manganese chloride
Subject analysis set type	Per protocol

Subject analysis set description:

One hundred four (104) subjects were tested with all doses of the manganese chloride investigational allergen however the 0.040 mg/cm2, 0.080 mg/cm2 and 0.24 mg/cm2 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/cm2 dose which was the only dose that met the minimum criteria of at least 15 subjects with positive responses.

Subject analysis set title	0.11 mg/cm2 Tin chloride
Subject analysis set type	Per protocol

Subject analysis set description:

One hundred eleven (111) subjects were tested with all doses of the tin chloride investigational allergen. There were 25 subjects with positive responses to the 0.11 mg/cm2 dose

Subject analysis set title	0.33 mg/cm2 Tin chloride
Subject analysis set type	Per protocol

Subject analysis set description:

One hundred eleven (111) subjects were tested with all doses of the tin chloride investigational allergen however the 0.33 mg/cm2 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 65 subjects with positive responses to the 0.33 mg/cm2 dose.

Subject analysis set title	0.11 mg Ti/cm2 Ammonium titanium oxide oxalate
Subject analysis set type	Per protocol

Subject analysis set description:

One hundred nine (109) subjects were tested with all doses of the titanium investigational allergens. 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/cm2 dose /

Subject analysis set title	0.22 mg Ti/cm2 Ammonium titanium oxide oxalate

Subject analysis set type	Per protocol

Subject analysis set description:

One hundred nine (109) subjects were tested with all doses of the titanium investigational allergens. Ammonium titanium oxide oxalate was the only titanium salt that met the minimum criteria of at least 15 subjects with positive responses. There were 18 subjects with positive responses to the 0.22 mg Ti/cm2 dose.

Subject analysis set title	0.025 mg V/cm2 Vanadium chloride
Subject analysis set type	Per protocol

Subject analysis set description:

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/cm2 dose.

Subject analysis set title	0.050 mg V/cm2 Vanadium chloride
Subject analysis set type	Per protocol

Subject analysis set description:

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 46 subjects with positive responses to the 0.050 mg V/cm2 dose.

Subject analysis set title	0.050 mg V/cm2 Vanadium sulfate
Subject analysis set type	Per protocol

Subject analysis set description:

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 sulfate: There were 30 subjects with positive responses to the 0.050 mg V/cm2 dose of vanadium sulfate

Subject analysis set title	0.24 mg/cm2 Zinc chloride
Subject analysis set type	Per protocol

Subject analysis set description:

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/cm2 dose which was the only dose that met the minimum criteria of at least 15 subjects with positive responses

Primary: Allergens with at least 15 positive Responses

End point title	Allergens with at least 15 positive Responses[1]

End point description:

Patch test sites were evaluated at days 3(+1), 7(+1), 10(+/-2) and 21(+/-2). Following all evaluations the Investigator categorized each patch test site as either negative (no 1+, 2+ or 3+ reactions) or positive (1+, 2+ or 3+ during at least one evaluation visit). A minimum of 15 positive (+) reactions were needed to be considered for the final metal panel. Results are posted for the number subjects with + responses. The posted results are only for the allergens/allergen doses for which there were a minimum of 15 positive responses. None of the other allergen doses met the criteria of at least 15 positive responses. The allergens/allergen doses chosen for the final panel are: 0.12mg/cm2 copper sulfate, 0.24 mg/cm2 manganese chloride, 0.33 mg/cm2 tin chloride, 0.22 mg Ti/cm2 ammonium titanium oxide oxalate, 0.050 mg V/cm2 vanadium sulfate and 0.24 mg/cm2 tin chloride

End point type	Primary

End point timeframe:

Post Visit 6 (at study completion).

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Statistical analysis not performed. Endpoint is defined as a minimum threshold

End point values	0.12 mg/cm2 Copper sulfate	0.24 mg/cm2 Manganese chloride	0.11 mg/cm2 Tin chloride	0.33 mg/cm2 Tin chloride
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	111	104	111	110
Units: Positive Responses				
Positive Reaction	16	29	25	65
Negative Reaction	69	48	68	17
Doubtful Reaction	16	17	12	12
Irritant Reaction	10	10	6	16

End point values	0.11 mg Ti/cm2 Ammonium titanium oxide oxalate	0.22 mg Ti/cm2 Ammonium titanium oxide oxalate	0.025 mg V/cm2 Vanadium chloride	0.050 mg V/cm2 Vanadium chloride
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	109	109	106	106
Units: Positive Responses				
Positive Reaction	21	18	25	46
Negative Reaction	55	56	57	28
Doubtful Reaction	24	27	18	14
Irritant Reaction	9	8	6	18

End point values	0.050 mg V/cm2 Vanadium sulfate	0.24 mg/cm2 Zinc chloride		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	106	111		
Units: Positive Responses				
Positive Reaction	30	69		
Negative Reaction	53	17		
Doubtful Reaction	15	16		
Irritant Reaction	8	9		

Attachments (see zip file)	Table 14.2.8 Summary of No of Positive Responses to Each

Statistical analyses

No statistical analyses for this end point

Primary: Concordance Copper Sulfate 0.12mg/cm2 and 2% pet

End point title	Concordance Copper Sulfate 0.12mg/cm2 and 2% pet

End point description:

Percent agreement= [observed agreement /N1] x 100, based on total number of subjects having

responses for investigational and reference allergen.

End point type	Primary

End point timeframe:

Day 21

End point values	Subjects Positive to Investigationall and Reference Allergen	Subjects Negative to Investigational and Reference Allergen	Subjects Positive to Investigational and Negative to Reference	Subjects Negative to Investigational and Positive to Reference
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	4	61	6	7
Units: Agreement				
Agreement	4	61	6	7

Attachments (see zip file)	Concordance Copper Sulfate/Table 14.2.10 Summary of

Statistical analyses

Statistical analysis title	Kappa Statistic

Statistical analysis description:

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 will be measured using all subjects who are tested with each allergen and corresponding reference allergen pair.

Comparison groups	Subjects Positive to Investigationall and Reference Allergen v Subjects Negative to Investigational and Reference Allergen v Subjects Positive to Investigational and Negative to Reference v Subjects Negative to Investigational and Positive to Reference
Number of subjects included in analysis	78
Analysis specification	Post-hoc
Analysis type	equivalence
Method	Fisher exact
Parameter estimate	Cohen's Kappa Coefficient
Point estimate	0.28
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.01
upper limit	0.58

Statistical analysis title	Kappa Statistic

Statistical analysis description:

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 will be measured using all subjects who are tested with each allergen and corresponding reference allergen pair.

Comparison groups	Subjects Positive to Investigationall and Reference Allergen v Subjects Negative to Investigational and Reference Allergen v Subjects Positive to Investigational and Negative to Reference v Subjects Negative to Investigational and Positive to Reference
Number of subjects included in analysis	78
Analysis specification	Pre-specified
Analysis type	equivalence[2]
P-value	= 0.0117
Method	Fisher exact
Parameter estimate	Cohen's Kappa Coefficient
Point estimate	0.28
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.01
upper limit	0.58

Notes:

[2] - Subjects were patch tested with the investigational and reference allergens (with the exception of subjects enrolled in Germany who were not tested with the reference allergens). Patch test sites were evaluated at days 4(-1), 7(+1), 12(+/-2), and 21(+/-2). Following the completion of all visits (day 21), the investigator categorized the skin reactions as either negative (no 1+, 2+ or 3+ scores) or positive (at least one 1+, +2 or 3+ score). Concordance was measured using Cohen’s kappa.

Statistical analysis title	Kappa Statistic

Statistical analysis description:

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 will be measured using all subjects who are tested with each allergen and corresponding reference allergen pair.

Comparison groups	Subjects Positive to Investigationall and Reference Allergen v Subjects Negative to Investigational and Reference Allergen v Subjects Positive to Investigational and Negative to Reference v Subjects Negative to Investigational and Positive to Reference
Number of subjects included in analysis	78
Analysis specification	Pre-specified
Analysis type	equivalence[3]
P-value	= 0.0117
Method	Fisher exact
Parameter estimate	Kappa Statistic
Point estimate	0.28
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.01
upper limit	0.58

Notes:

[3] - Subjects were patch tested with the investigational and reference allergens (with the exception of subjects enrolled in Germany who were not tested with the reference allergens). Patch test sites were evaluated at days 4(-1), 7(+1), 12(+/-2), and 21(+/-2). Following the completion of all visits (day 21), the investigator categorized the skin reactions as either negative (no 1+, 2+ or 3+ scores) or positive (at least one 1+, +2 or 3+ score). Concordance was measured using Cohen’s kappa

Primary: Concordance Manganese 0.24mg/cm2 vs 2% pet	
End point title	Concordance Manganese 0.24mg/cm2 vs 2% pet
End point description:	
Percent agreement= [observed agreement /N1] x 100, based on total number of subjects having responses for investigational and reference allergen.	
End point type	Primary
End point timeframe:	
Day 21	

End point values	Subjects Positive to Investigationall and Reference Allergen	Subjects Negative to Investigational and Reference Allergen	Subjects Positive to Investigational and Negative to Reference	Subjects Negative to Investigational and Positive to Reference
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	10	44	14	1
Units: Agreement				
Agreement	10	44	14	1

Attachments (see zip file)	Concordance Manganese chloride/Table 14.2.11 Summary of

Statistical analyses

Statistical analysis title	Kappa Statistic
Statistical analysis description:	
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 will be measured using all subjects who are tested with each allergen and corresponding reference allergen pair.	
Comparison groups	Subjects Positive to Investigationall and Reference Allergen v Subjects Negative to Investigational and Reference Allergen v Subjects Positive to Investigational and Negative to Reference v Subjects Negative to Investigational and Positive to Reference
Number of subjects included in analysis	69
Analysis specification	Pre-specified
Analysis type	equivalence[4]
P-value	< 0.0001
Method	Fisher exact
Parameter estimate	Kappa Statistic
Point estimate	0.45
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.24
upper limit	0.66

Notes:

[4] - Subjects were patch tested with the investigational and reference allergens (with the exception of subjects enrolled in Germany who were not tested with the reference allergens). Patch test sites were evaluated at days 4(-1), 7(+1), 12(+/-2), and 21(+/-2). Following the completion of all visits (day 21), the investigator categorized the skin reactions as either negative (no 1+, 2+ or 3+ scores) or positive (at least one 1+, +2 or 3+ score). Concordance was measured using Cohen's kappa

Primary: Concordance Tin Chloride 0.11 mg/cm2 vs 1% pet

End point title	Concordance Tin Chloride 0.11 mg/cm2 vs 1% pet

End point description:

Percent agreement= [observed agreement /N1] x 100, based on total number of subjects having responses for investigational and reference allergen.

End point type	Primary

End point timeframe:

Day 21

End point values	Subjects Positive to Investigationall and Reference Allergen	Subjects Negative to Investigational and Reference Allergen	Subjects Positive to Investigational and Negative to Reference	Subjects Negative to Investigational and Positive to Reference
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	9	45	8	11
Units: Agreement				
Agreement	9	45	8	11

Attachments (see zip file)	Concordance Tin chloride/Table 14.2.13 Summary of

Statistical analyses

Statistical analysis title	Kappa Statistic

Statistical analysis description:

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 will be measured using all subjects who are tested with each allergen and corresponding reference allergen pair.

Comparison groups	Subjects Positive to Investigationall and Reference Allergen v Subjects Negative to Investigational and Reference Allergen v Subjects Positive to Investigational and Negative to Reference v Subjects Negative to Investigational and Positive to Reference
Number of subjects included in analysis	73
Analysis specification	Pre-specified
Analysis type	equivalence[5]
P-value	= 0.007
Method	Fisher exact
Parameter estimate	Kappa Statistic
Point estimate	0.31

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.07
upper limit	0.56

Notes:

[5] - Subjects were patch tested with the investigational and reference allergens (with the exception of subjects enrolled in Germany who were not tested with the reference allergens). Patch test sites were evaluated at days 4(-1), 7(+1), 12(+/-2), and 21(+/-2). Following the completion of all visits (day 21), the investigator categorized the skin reactions as either negative (no 1+, 2+ or 3+ scores) or positive (at least one 1+, +2 or 3+ score). Concordance was measured using Cohen's kappa

Primary: Concordance Tin Chloride 0.33 mg/cm2 vs 1% pet

End point title	Concordance Tin Chloride 0.33 mg/cm2 vs 1% pet

End point description:

Percent agreement= [observed agreement /N1] x 100, based on total number of subjects having responses for investigational and reference allergen.

End point type	Primary

End point timeframe:

Day 21

End point values	Subjects Positive to Investigationall and Reference Allergen	Subjects Negative to Investigational and Reference Allergen	Subjects Positive to Investigational and Negative to Reference	Subjects Negative to Investigational and Positive to Reference
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	18	22	30	2
Units: Agreement				
Agreement	18	22	30	2

Attachments (see zip file)	Concordance Tin chloride/Table 14.2.13 Summary of

Statistical analyses

Statistical analysis title	Kappa Statistic

Statistical analysis description:

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 will be measured using all subjects who are tested with each allergen and corresponding reference allergen pair.

Comparison groups	Subjects Positive to Investigationall and Reference Allergen v Subjects Negative to Investigational and Reference Allergen v Subjects Positive to Investigational and Negative to Reference v Subjects Negative to Investigational and Positive to Reference

Number of subjects included in analysis	72
Analysis specification	Pre-specified
Analysis type	equivalence[6]
P-value	= 0.0092
Method	Fisher exact
Parameter estimate	Kappa Statistic
Point estimate	0.23
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.07
upper limit	0.38

Notes:

[6] - Subjects were patch tested with the investigational and reference allergens (with the exception of subjects enrolled in Germany who were not tested with the reference allergens). Patch test sites were evaluated at days 4(-1), 7(+1), 12(+/-2), and 21(+/-2). Following the completion of all visits (day 21), the investigator categorized the skin reactions as either negative (no 1+, 2+ or 3+ scores) or positive (at least one 1+, +2 or 3+ score). Concordance was measured using Cohen's kappa.

Primary: Concordance Ammonium titanium oxide oxalate 0.11mgTi/cm2 vs 19% pet

End point title	Concordance Ammonium titanium oxide oxalate 0.11mgTi/cm2 vs 19% pet

End point description:

Percent agreement= [observed agreement /N1] x 100, based on total number of subjects having responses for investigational and reference allergen.

End point type	Primary

End point timeframe:

Day 21

End point values	Subjects Positive to Investigationall and Reference Allergen	Subjects Negative to Investigational and Reference Allergen	Subjects Positive to Investigational and Negative to Reference	Subjects Negative to Investigational and Positive to Reference
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	7	52	14	3
Units: Agreement				
Agreement	7	52	14	3

Attachments (see zip file)	Concordance Titanium Allergens/Table 14.2.14 Summary of

Statistical analyses

Statistical analysis title	Kappa Statistic

Statistical analysis description:

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 will be measured using all subjects who are tested with each allergen and corresponding reference allergen pair.

Comparison groups	Subjects Positive to Investigationall and Reference Allergen v Subjects Negative to Investigational and Reference Allergen v Subjects Positive to Investigational and Negative to Reference v Subjects Negative to Investigational and Positive to Reference
Number of subjects included in analysis	76
Analysis specification	Pre-specified
Analysis type	equivalence[7]
P-value	= 0.0013
Method	Fisher exact
Parameter estimate	Kappa Statistic
Point estimate	0.33
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.1
upper limit	0.57

Notes:

[7] - Subjects were patch tested with the investigational and reference allergens (with the exception of subjects enrolled in Germany who were not tested with the reference allergens). Patch test sites were evaluated at days 4(-1), 7(+1), 12(+/-2), and 21(+/-2). Following the completion of all visits (day 21), the investigator categorized the skin reactions as either negative (no 1+, 2+ or 3+ scores) or positive (at least one 1+, +2 or 3+ score). Concordance was measured using Cohen's kappa

Primary: Concordance Ammonium titanium oxide oxalate 0.22mgTi/cm2 vs 19% pet

End point title	Concordance Ammonium titanium oxide oxalate 0.22mgTi/cm2 vs 19% pet

End point description:

Percent agreement= [observed agreement /N1] x 100, based on total number of subjects having responses for investigational and reference allergen.

End point type	Primary

End point timeframe:

Day 21

End point values	Subjects Positive to Investigationall and Reference Allergen	Subjects Negative to Investigational and Reference Allergen	Subjects Positive to Investigational and Negative to Reference	Subjects Negative to Investigational and Positive to Reference
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	7	55	11	3
Units: Agreement				
Agreement	7	55	11	3

Attachments (see zip file)	Concordance Titanium Allergens/Table 14.2.14 Summary of

Statistical analyses

Statistical analysis title	Kappa Statistic

Statistical analysis description:

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 will be measured using all subjects who are tested with each allergen and corresponding reference allergen pair.

Comparison groups	Subjects Positive to Investigationall and Reference Allergen v Subjects Negative to Investigational and Positive to Reference v Subjects Positive to Investigational and Negative to Reference v Subjects Negative to Investigational and Reference Allergen
Number of subjects included in analysis	76
Analysis specification	Pre-specified
Analysis type	equivalence[8]
P-value	= 0.0002
Method	Fisher exact
Parameter estimate	Kappa Statistic
Point estimate	0.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.15
upper limit	0.65

Notes:

[8] - Subjects were patch tested with the investigational and reference allergens (with the exception of subjects enrolled in Germany who were not tested with the reference allergens). Patch test sites were evaluated at days 4(-1), 7(+1), 12(+/-2), and 21(+/-2). Following the completion of all visits (day 21), the investigator categorized the skin reactions as either negative (no 1+, 2+ or 3+ scores) or positive (at least one 1+, +2 or 3+ score). Concordance was measured using Cohen’s kappa

Primary: Concordance Vanadium chloride 0.050 mgV/cm2 vs 1% pet

End point title	Concordance Vanadium chloride 0.050 mgV/cm2 vs 1% pet

End point description:

Percent agreement= [observed agreement /N1] x 100, based on total number of subjects having responses for investigational and reference allergen.

End point type	Primary

End point timeframe:

Day 21

End point values	Subjects Positive to Investigationall and Reference Allergen	Subjects Negative to Investigational and Reference Allergen	Subjects Positive to Investigational and Negative to Reference	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	3	44	25	
Units: Agreement				
Agreement	3	44	25	

Attachments (see zip file)	Concordance Vanadium Allergens/Table 14.2.15 Summary of

Statistical analyses

Statistical analysis title	Kappa Statistic

Statistical analysis description:

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 will be measured using all subjects who are tested with each allergen and corresponding reference allergen pair.

Comparison groups	Subjects Negative to Investigational and Reference Allergen v Subjects Positive to Investigational and Negative to Reference v Subjects Positive to Investigationall and Reference Allergen
Number of subjects included in analysis	72
Analysis specification	Pre-specified
Analysis type	equivalence[9]
P-value	= 0.0266
Method	Fisher exact
Parameter estimate	Kappa Statistic
Point estimate	0.13
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.01
upper limit	0.26

Notes:

[9] - Subjects were patch tested with the investigational and reference allergens (with the exception of subjects enrolled in Germany who were not tested with the reference allergens). Patch test sites were evaluated at days 4(-1), 7(+1), 12(+/-2), and 21(+/-2). Following the completion of all visits (day 21), the investigator categorized the skin reactions as either negative (no 1+, 2+ or 3+ scores) or positive (at least one 1+, +2 or 3+ score). Concordance was measured using Cohen’s kappa

Primary: Concordance Vanadium chloride 0.025 mgV/cm2 vs 1% pet

End point title	Concordance Vanadium chloride 0.025 mgV/cm2 vs 1% pet

End point description:

Percent agreement= [observed agreement /N1] x 100, based on total number of subjects having responses for investigational and reference allergen.

End point type	Primary

End point timeframe:

Day 21

End point values	Subjects Positive to Investigationall and Reference Allergen	Subjects Negative to Investigational and Reference Allergen	Subjects Positive to Investigational and Negative to Reference	Subjects Negative to Investigational and Positive to Reference
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	2	56	13	1
Units: Agreement				
Agreement	2	56	13	1

Attachments (see zip file)	Concordance Vanadium Allergens/Table 14.2.15 Summary of

Statistical analyses

Statistical analysis title	Kappa Statistic

Statistical analysis description:

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 will be measured using all subjects who are tested with each allergen and corresponding reference allergen pair

Comparison groups	Subjects Negative to Investigational and Reference Allergen v Subjects Positive to Investigationall and Reference Allergen v Subjects Positive to Investigational and Negative to Reference v Subjects Negative to Investigational and Positive to Reference
Number of subjects included in analysis	72
Analysis specification	Pre-specified
Analysis type	equivalence[10]
P-value	= 0.0458
Method	Fisher exact
Parameter estimate	Kappa Statistic
Point estimate	0.16
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.07
upper limit	0.4

Notes:

[10] - Subjects were patch tested with the investigational and reference allergens (with the exception of subjects enrolled in Germany who were not tested with the reference allergens). Patch test sites were evaluated at days 4(-1), 7(+1), 12(+/-2), and 21(+/-2). Following the completion of all visits (day 21), the investigator categorized the skin reactions as either negative (no 1+, 2+ or 3+ scores) or positive (at least one 1+, +2 or 3+ score). Concordance was measured using Cohen's kappa

Primary: Concordance Vanadium sulfate 0.050 mgV/cm2 vs 1.5% pet

End point title	Concordance Vanadium sulfate 0.050 mgV/cm2 vs 1.5% pet

End point description:

Percent agreement= [observed agreement /N1] x 100, based on total number of subjects having responses for investigational and reference allergen.

End point type	Primary

End point timeframe:

Day 21

End point values	Subjects Positive to Investigationall and Reference Allergen	Subjects Negative to Investigational and Reference Allergen	Subjects Positive to Investigational and Negative to Reference	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	9	51	12	
Units: Agreement				
Agreement	9	51	12	

Attachments (see zip file)	Concordance Vanadium Allergens/Table 14.2.15 Summary of

Statistical analyses

Statistical analysis title	Kappa Statistic

Statistical analysis description:

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 will be measured using all subjects who are tested with each allergen and corresponding reference allergen pair.

Comparison groups	Subjects Positive to Investigationall and Reference Allergen v Subjects Negative to Investigational and Reference Allergen v Subjects Positive to Investigational and Negative to Reference
Number of subjects included in analysis	72
Analysis specification	Pre-specified
Analysis type	equivalence[11]
P-value	< 0.0001
Method	Fisher exact
Parameter estimate	Kappa Statistic
Point estimate	0.52
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.3
upper limit	0.73

Notes:

[11] - Subjects were patch tested with the investigational and reference allergens (with the exception of subjects enrolled in Germany who were not tested with the reference allergens). Patch test sites were evaluated at days 4(-1), 7(+1), 12(+/-2), and 21(+/-2). Following the completion of all visits (day 21), the investigator categorized the skin reactions as either negative (no 1+, 2+ or 3+ scores) or positive (at least one 1+, +2 or 3+ score). Concordance was measured using Cohen's kappa

Primary: Concordance Zinc 0.24 mg/cm2 vs 2% pet

End point title	Concordance Zinc 0.24 mg/cm2 vs 2% pet

End point description:

Percent agreement= [observed agreement /N1] x 100, based on total number of subjects having responses for investigational and reference allergen.

End point type	Primary

End point timeframe:

Day 21

End point values	Subjects Positive to Investigationall and Reference Allergen	Subjects Negative to Investigational and Reference Allergen	Subjects Positive to Investigational and Negative to Reference	Subjects Negative to Investigational and Positive to Reference
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	27	22	22	3
Units: Agreement				
Agreement	27	22	22	3

Attachments (see zip file)	Concordance Tin chloride/Table 14.2.16 Summary of

Statistical analyses

Statistical analysis title	Kappa Statistic

Statistical analysis description:

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 will be measured using all subjects who are tested with each allergen and corresponding reference allergen pair.

Comparison groups	Subjects Positive to Investigationall and Reference Allergen v Subjects Negative to Investigational and Reference Allergen v Subjects Positive to Investigational and Negative to Reference v Subjects Negative to Investigational and Positive to Reference
Number of subjects included in analysis	74
Analysis specification	Pre-specified
Analysis type	equivalence[12]
P-value	= 0.0004
Method	Fisher exact
Parameter estimate	Kappa Statistic
Point estimate	0.36
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.18
upper limit	0.54

Notes:

[12] - Subjects were patch tested with the investigational and reference allergens (with the exception of subjects enrolled in Germany who were not tested with the reference allergens). Patch test sites were evaluated at days 4(-1), 7(+1), 12(+/-2), and 21(+/-2). Following the completion of all visits (day 21), the investigator categorized the skin reactions as either negative (no 1+, 2+ or 3+ scores) or positive (at least one 1+, +2 or 3+ score). Concordance was measured using Cohen's kappa

Secondary: Tape Irritation

End point title	Tape Irritation

End point description:

Tape irritation was evaluated at visits 2-6 Following visit 6, the Investigator summarized the rape irritation as none, irritant response or allergic response.

End point type	Secondary

End point timeframe:

Days 2, 3 (+1), 7 (+1), 12 (+/-2) and 21 (+/- 2)

End point values	Panel 1	Panel 2	Panel 3	Panel 4
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	105	111	104	109
Units: Subjects				
No Irritation	103	109	103	108
Irritant Response	2	2	1	1

End point values	Panel 5	Panel 6		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	106	120		
Units: Subjects				
No Irritation	105	120		
Irritant Response	1	0		

Attachments (see zip file)	Tape Irritation/Table 14.2.35 Summary of Investigator

Statistical analyses

No statistical analyses for this end point

Secondary: Chip Irritation

End point title	Chip Irritation

End point description:

Chip irritation was evaluated at visits 2-6 Following visit 6, the Investigator summarized the rape irritation as none, irritant response or allergic response.

End point type	Secondary

End point timeframe:

Days 2, 3(+1), 7(+1), 10 (+/-2), 21(+/-2)

End point values	Panel 1	Panel 2	Panel 3	Panel 4
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	105	111	104	109
Units: Subjects				
No Chip Irritation	105	111	104	109

End point values	Panel 5	Panel 6		

Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	106	120		
Units: Subjects				
No Chip Irritation	106	120		

Attachments (see zip file)	Chip Irritation/Table 14.2.35 Summary of Investigator

Statistical analyses

No statistical analyses for this end point

Secondary: Itching and Burning

End point title	Itching and Burning

End point description:

Subjects were asked to report any itching or burning sensations they experienced while wearing the patch test panels.

End point type	Secondary

End point timeframe:

Day 2, following panel removal

End point values	Panel 1	Panel 2	Panel 3	Panel 4
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	105	111	104	109
Units: Subjects				
Itching-None	77	62	77	73
Itching-Weak	16	32	17	20
Itching-Moderate	9	12	7	12
Itching-Strong	3	5	3	4
Burning-None	96	99	93	94
Burning-Weak	5	8	10	11
Burning-Moderate	4	4	1	3
Burning-Severe	0	0	0	1

End point values	Panel 5	Panel 6		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	106	120		
Units: Subjects				
Itching-None	71	82		
Itching-Weak	20	21		
Itching-Moderate	13	11		
Itching-Strong	2	6		
Burning-None	98	108		
Burning-Weak	4	9		

Burning-Moderate	4	3		
Burning-Severe	0	0		

Attachments (see zip file)	Itching and Burning/Table 14.2.36 Summary of Itching and

Statistical analyses

No statistical analyses for this end point

Secondary: Late and Persistent Reactions

End point title	Late and Persistent Reactions

End point description:

A late reaction is defined as a reaction that initially appears at visit 4 or later. A persistent reaction is defined as a reaction that initially appears at one visit then persists through to the next visit.

End point type	Secondary

End point timeframe:

Late and persistent reactions are evaluated at visits 4 (day 7(+1), 5 (day 10+/- 2) and 6 (day 21+/-2)

End point values	0.12 mg/cm2 Copper sulfate	0.24 mg/cm2 Manganese chloride	0.11 mg/cm2 Tin chloride	0.33 mg/cm2 Tin chloride
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	111	103	111	110
Units: Subjects				
Late Reactions	3	1	5	6
Persistent Reactions	4	10	5	39

End point values	0.11 mg Ti/cm2 Ammonium titanium oxide oxalate	0.22 mg Ti/cm2 Ammonium titanium oxide oxalate	0.025 mg V/cm2 Vanadium chloride	0.050 mg V/cm2 Vanadium chloride
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	109	109	106	106
Units: Subjects				
Late Reactions	1	0	4	9
Persistent Reactions	1	4	11	24

End point values	0.050 mg V/cm2 Vanadium sulfate	0.24 mg/cm2 Zinc chloride		

Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	106	111		
Units: Subjects				
Late Reactions	7	10		
Persistent Reactions	15	44		

Attachments (see zip file)	Late Reactions/Table 14.2.33 Late Reactions.rtf Persistent Reactions/Table 14.2.34 Persistent Reactions.rtf

Statistical analyses

No statistical analyses for this end point

Secondary: Adhesion

End point title	Adhesion

End point description:

Adhesion of the panels was evaluated at visit 2 prior to panel removal according to the following 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.

End point type	Secondary

End point timeframe:

Adhesion was measured at Visit 2 prior to removal of patch test panels

End point values	Panel 1	Panel 2	Panel 3	Panel 4
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	105	111	105	110
Units: Number of Subjects				
Adhesion: Excellennt	102	103	98	105
Adhesion: Good	1	3	3	1
Adhesion Poor	2	5	3	3
Adhesion: Detached	0	0	0	0
Adhesion: Missing Score	0	0	1	1

End point values	Panel 5	Panel 6		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	107	121		
Units: Number of Subjects				
Adhesion: Excellennt	100	113		
Adhesion: Good	6	5		
Adhesion Poor	0	2		
Adhesion: Detached	0	0		

Adhesion: Missing Score	1	1		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events: Day 1-21	
Assessment type	Systematic
Dictionary used	
Dictionary name	MedDRA
Dictionary version	20.0
Reporting groups	
Reporting group title	Adverse Events
Reporting group description: Subjects were asked at visits 2-6 if they had any changes to their health or medications	

Serious adverse events	Adverse Events		
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 122 (0.82%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Intraductal proliferative breast lesion			
subjects affected / exposed	1 / 122 (0.82%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 0.2 %

Non-serious adverse events	Adverse Events		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	30 / 122 (24.59%)		
Surgical and medical procedures			
Endodontic procedure			
subjects affected / exposed	1 / 122 (0.82%)		
occurrences (all)	1		
Therapeutic nerve ablation			
subjects affected / exposed	1 / 122 (0.82%)		
occurrences (all)	1		
Nervous system disorders			

Dizziness			
subjects affected / exposed	2 / 122 (1.64%)		
occurrences (all)	2		
Headache			
subjects affected / exposed	3 / 122 (2.46%)		
occurrences (all)	3		
Tension headache			
subjects affected / exposed	1 / 122 (0.82%)		
occurrences (all)	1		
General disorders and administration site conditions			
Abdominal pain upper			
subjects affected / exposed	1 / 122 (0.82%)		
occurrences (all)	1		
Application site erythema			
subjects affected / exposed	1 / 122 (0.82%)		
occurrences (all)	1		
Fatigue			
subjects affected / exposed	3 / 122 (2.46%)		
occurrences (all)	3		
Inflammation			
subjects affected / exposed	1 / 122 (0.82%)		
occurrences (all)	1		
Influenza type illness			
subjects affected / exposed	2 / 122 (1.64%)		
occurrences (all)	2		
Malaise			
subjects affected / exposed	1 / 122 (0.82%)		
occurrences (all)	1		
Pyrexia			
subjects affected / exposed	2 / 122 (1.64%)		
occurrences (all)	2		
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	1 / 122 (0.82%)		
occurrences (all)	1		
Eye disorders			

Dry eye subjects affected / exposed occurrences (all) Hordeolum subjects affected / exposed occurrences (all)	 1 / 122 (0.82%) 1 1 / 122 (0.82%) 1		
Gastrointestinal disorders Glossitis subjects affected / exposed occurrences (all) Nausea subjects affected / exposed occurrences (all) Periodontal inflammation subjects affected / exposed occurrences (all) Toothache subjects affected / exposed occurrences (all) Vomiting subjects affected / exposed occurrences (all)	 1 / 122 (0.82%) 1 2 / 122 (1.64%) 2 1 / 122 (0.82%) 1 1 / 122 (0.82%) 1 1 / 122 (0.82%) 1		
Respiratory, thoracic and mediastinal disorders Dyspnoea exertional subjects affected / exposed occurrences (all)	 1 / 122 (0.82%) 1		
Skin and subcutaneous tissue disorders Dermatitis subjects affected / exposed occurrences (all) Dermatitis atopic subjects affected / exposed occurrences (all) Dry skin subjects affected / exposed occurrences (all)	 1 / 122 (0.82%) 1 1 / 122 (0.82%) 1 2 / 122 (1.64%) 2		

Dyshidrotic eczema			
subjects affected / exposed	1 / 122 (0.82%)		
occurrences (all)	1		
Pruritus			
subjects affected / exposed	2 / 122 (1.64%)		
occurrences (all)	2		
Pustular psoriasis			
subjects affected / exposed	1 / 122 (0.82%)		
occurrences (all)	1		
Urticaria			
subjects affected / exposed	1 / 122 (0.82%)		
occurrences (all)	1		
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	1 / 122 (0.82%)		
occurrences (all)	1		
Groin pain			
subjects affected / exposed	1 / 122 (0.82%)		
occurrences (all)	1		
Musculoskeletal pain			
subjects affected / exposed	1 / 122 (0.82%)		
occurrences (all)	1		
Pain in extremity			
subjects affected / exposed	1 / 122 (0.82%)		
occurrences (all)	1		
Infections and infestations			
Cystitis			
subjects affected / exposed	1 / 122 (0.82%)		
occurrences (all)	1		
Viral upper respiratory tract infection			
subjects affected / exposed	3 / 122 (2.46%)		
occurrences (all)	3		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
03 March 2016	1. Address change for Dr. Pigatto in Milan, Italy 2. Primary endpoint wording changed from approximately 50% of positive responses to at least 50% of positive responses 3. Adverse event wording was enhanced 4. 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. 5. 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. 6. Exclusion criteria f was added: Known or suspected infection of the skin, joints or other site(s) associated with metal exposure 7. 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. 8. 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. 9. 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. 10.The section on randomization of dosages was enhanced.
18 August 2016	1. Prof. Rustemeyer's credentials updated 2. Dr. Pigatto's phone numbers updated 3. The common allergens will be tested at the discretion of the Investigator' added 4. Wording 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) 5. Systemic birth control were listed 6. Cervical cap and abstinence from sexual intercourse not acceptable in Japan 7. Breastfeeding may be resumed upon completion of the study 8. Visit schedule added 9. Legal representative must sign consent for subjects aged 18-19 in Japan added 10. Description of dipstick pregnancy test added 11. Numeric descriptors for positive skin reactions were added 12. Definitions for late, persistent hyperpigmentation, hypopigmentation and pruritus added. 13. Panels to be stored under refrigeration at 2-8oC added. 14. The allergens on panel 6 will not be randomized into different configurations. 15. Unused portion of the panel is not to be discarded added. 16. Number and identification of specific panels applied, application (or not) of common allergens added 17 The column headings in the dilution series tables were changed from 'Dose' to 'Ascending Dosages' and 'Randomized Among Positions' 18. The column heading Position was added to the Common Allergens Excipient Control Table 19. Insurance information was updated.

29 March 2017	1. Contact info for Kayoko Matsunaga updated 2. Address for Akiko Yagami updated 3. Info for Hiromi Kanto MD, PhD added 4. Info for Risa Tamagawa-Mineoka deleted 5. Yoshiaki Kubo added as Sub-I 6. Study population include patients with metal replacement procedure added 7. Justification of sample size updated 8. Subjects enrolled in Germany not be tested with the reference allergens 9. Symptoms removed from late and persistent reactions 10. Double-barrier method to be used for subjects enrolled in Switzerland who are practicing non-systemic methods of birth control. 11. Abstinence from sexual intercourse not be considered an acceptable method of contraception for subjects enrolled in Switzerland 12. Exclusion criteria l through q were added for subjects enrolled in Germany 13. The definition of overreaction to an allergen added 14. Investigator may withdraw a subject if the subject does not meet the study requirements added 15. Use of PatchMap will required in Germany added 16. Investigators will use medical expertise to determine panel placement added 17. Investigator will use experience and medical expertise to determine if a subject with a past positive patch result should be tested to all allergens or only to the allergen to which the subject has had the past response 18. Subjects with 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 19. Direction for cutting panels to avoid testing nickel, chromium, cobalt and gold added 20. Late and persistent reactions redefined 21. Definitions and reporting procedures for adverse drug reactions and SUSAR updated 22. Definition of active sensitization updated 23. Anaphylactic reaction changed to acute anaphylactic reaction 24. Definition of tape reaction updated 25. Regulatory agencies notified within 15 days if study is prematurely discontinued
06 February 2018	1. Assistant Medical Director, Dathan Hamann, MD. was added to the study. 2. The phone number for Kayoko Matsunaga, MD., PhD. was changed. 3. 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. 4. The title for Maki Hosoki, DDS, PhD was updated. 5. The reference for the Declaration of Helsinki was updated. 6. The direction and illustration for cutting the nickel, chromium, cobalt and gold patches from panel 6 was updated. 7. The location of PVP and gold on panel 6 was clarified
17 June 2018	1. Investigator, Prof Dr. med. Andreas Bircher who retired from the University Hospital, Basel was replaced by PD Dr. med. Kathrin Scherer Hofmeier 2. The title for Maki Hosoki, DDS, PhD was updated. 3. Investigator Akiko Yagami, M.D., Ph.D completed all her study obligations therefore was removed from the protocol.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

The number of positive responses per allergen could not be included within body of online form. Reference needs to be made to the attachment.

Notes: