A Study to Evaluate the Safety, Reactogenicity, and Acceptability of a Placebo Microneedle Patch in Healthy Infants and Young Children

Sponsored by:
Micron Biomedical, Inc.

Principal Investigator:
Evan J. Anderson, MD

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Statement of Compliance

The study will be carried out in accordance with Good Clinical Practice (GCP) as required by the following:

- United States Code of Federal Regulations (CFR) applicable to clinical studies (45 CFR Part 46; 21 CFR Part 50, 21 CFR Part 54, 21 CFR Part 56, and 21 CFR Part 312);
- International Conference on Harmonization (ICH) E6; 62 Federal Register 25691 (1997);

Compliance with these standards provides public assurance that the rights, safety and well-being of study subjects are protected, consistent with the principles that have their origin in the Declaration of Helsinki.

All key personnel (all individuals responsible for the design and conduct of this study) have completed Human Subjects Protection Training.

SIGNATURE PAGE

The signature below constitutes the approval of this protocol and the attachments, and provides the necessary assurances that this trial will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality, and according to local legal and regulatory requirements and applicable US federal regulations and ICH guidelines.

Site Investigator: Evan J. Anderson, MD

Signed: _____ Date: _____

Evan J. Anderson, MD

Table of Contents

Table of Contents - *continued*

Table of Contents - *continued*

List of Abbreviations

AE	Adverse Event
CFR	Code of Federal Regulations
CRF	Case Report Form
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GRAS	Generally Recognized as Safe
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IRB	Institutional Review Board
LAR	Legally Authorized Representative
MedDRA	Medical Dictionary for Regulatory Activities
MOP	Manual of Procedures
N	Number (typically refers to subjects)
NOMC	New-Onset Medical Conditions
PI	Principal Investigator
SAE	Serious Adverse Event
SOP	Standard Operating Procedure
USP	United States Pharmacopeia

Title: **A Study to Evaluate the Safety, Reactogenicity and Acceptability of a Placebo Microneedle Patch in Healthy Infants and Young Children**

Population: Healthy infants and children, 6 weeks – 24 months inclusive

Number of Sites: One

Study Duration: Approximately 5 months

Subject Duration: Approximately 4 – 5 weeks

Objectives:

Primary:

- To evaluate the safety and reactogenicity following application of a placebo microneedle patch topically.

Secondary:

- To evaluate unsolicited adverse events following application of a placebo microneedle patch topically.
- To evaluate new-onset medical conditions (NOMC) following application of a placebo microneedle patch topically.
- To evaluate the suitability of application of a placebo microneedle patch to different body locations.
- To evaluate the acceptability to the Legally Authorized Representative (LAR) of applying a placebo microneedle patch topically.

Endpoints

Primary:

Safety:

- Occurrence of placebo microneedle patch-related serious adverse events from Day 1 through the Final Study Visit (Day 27 – 38).
- Occurrence of Grade 3 placebo microneedle patch-related solicited adverse events for the 8 days following application of the patch.

Reactogenicity:

- Occurrence of solicited application site reactogenicity (e.g., erythema, induration, bruising, itching) for the 8 days following application of the patch.

Secondary:

- Occurrence of Grade 3 placebo microneedle patch-related unsolicited adverse events from Day 1 through the Final Study Visit (Day 27 – 38).
- Occurrence of new-onset medical conditions (NOMC) from Day 1 through the Final Study Visit (Day 27 – 38).
- Occurrence of solicited and unsolicited adverse events described at the site at which the placebo microneedle patch was applied.
- Quantitative and qualitative description of LAR responses to survey questions.

Schematic of Study Design:
This is a single-center, unblinded, study in which healthy infants and children (6 weeks – 24 months inclusive) will have placebo microneedle patches applied to the skin. This study is designed to investigate the safety, reactogenicity, and acceptability of a placebo microneedle patch.

Infants and children will be enrolled into one of two possible cohorts that will have placebo microneedle patches administered topically for up to approximately 20 minutes. Cohort 1 will assess one formulation of the microneedle patch (Microneedle Formulation 1). If the Microneedle Formulation 1 is well tolerated in Cohort 1, Cohort 2 may be enrolled using a different formulation of the microneedle patch if available (Microneedle Formulation 2). Infants and children will be enrolled by sequential age groups using an age de-escalation approach (**Table 1**). At least 4 infants or children from each Group must complete Day 8 without halting criteria having been met (as detailed in Section 9.5) before subjects will be enrolled into the next younger age group within a Cohort. For Cohort 1, at least the first 2 children in each Group will have a microneedle patch initially applied to the skin overlying the shoulder blade. If this site is well tolerated without halting criteria having been met (as detailed in Section 9.5), additional microneedle patches may be applied to the same participants and in subsequent participants to the upper arm, forearm, wrist, thigh, shin, and/or foot. For Cohort 2, microneedle patches may be applied to the shoulder blade, upper arm, forearm, wrist, thigh, shin, and/or foot. If the first site is well tolerated in the first two children without halting criteria having been met (as detailed in Section 9.5), additional microneedle patches may be applied to the same participants and in subsequent participants.

Table 1: Cohorts and Groups of Enrolled Infants and Young Children			
Cohort	**Group Age Range***	**Number ****	**Study Product (administered Day 1 and possibly Day 8)**
1	12 – 24 months	Up to 7	Microneedle formulation 1
1	5 – 11 months	Up to 6	Microneedle formulation 1
1	6 weeks – 4 months	Up to 12	Microneedle formulation 1
2	12 – 24 months	Up to 12	Microneedle formulation 2
2	5 – 11 months	Up to 12	Microneedle formulation 2
2	6 weeks – 4 months	Up to 12	Microneedle formulation 2

**All age ranges are inclusive. 4 children from each age group must complete Day 8 without halting criteria having been met (as detailed in Section 9.5) before subjects will be enrolled into the next younger age group.*
*** Total number enrolled into each Cohort will be ≤25.*

Subjects will have an initial microneedle patch placed on Day 1. At Day 8, the LARs of subjects who have no ongoing solicited or unsolicited general AEs or local AEs will have the opportunity to decide to have second and third placebo microneedle patches placed at different body sites from the initial location.

Each subject will receive up to three placebo microneedle patches. Subjects will receive a first placebo microneedle patch on Day 1 and be assessed on Day 2 (+1 day), and Day 8 (+2 days). If the first patch is well tolerated without halting criteria having been met on Day 8 (+2 days), then the LAR will be provided the opportunity to have the subjects receive a second and third placebo microneedle patch on Day 8 and be assessed on Day 9 (+2 days) and Day 15 (+3 days). All subjects will have an end of study telephone call that will occur D27 – Day 38.

Safety will be measured by the occurrence of solicited application site and systemic reactogenicity on the day of microneedle patch administration through Day 8 for the first patch and through Day 15 (+3 days) for those that receive a second and third patch. If symptoms persist, clinic staff will attempt to follow up with the subject daily until two days symptom-free. Maximum severity post Day 8 (Day 15 in those that receive a second and third patch) and stop date of the symptoms will be recorded by clinic staff on the Solicited Events eCRF. Unsolicited AE, and serious adverse events (SAEs) and new-onset medical conditions (NOMC) will be collected through Day 27 and Day 38 after microneedle patch administration.

The acceptability of applying a microneedle patch topically will be assessed by LAR survey completed before each microneedle patch application, after microneedle patch removal, Day 2, and at Day 8 (+2 days) (and at Days 9 and 15 (+3 days) in those having an additional application).

1 KEY ROLES

Individuals: **Principal Investigator**: Evan J. Anderson, MD

Institution: Emory University School of Medicine
Emory Children's Center
2015 Uppergate Drive
Atlanta, GA 30322

Contact: Evan J. Anderson, MD
(p) 404-727-1746
(f) 404-727-9223
evanderson@emory.edu

2 BACKGROUND INFORMATION AND SCIENTIFIC RATIONALE

2.1 Background Information

Available vaccine delivery methods include intramuscular or subcutaneous injection using hypodermic needle which is limited by patient needle phobia (Hamilton 1995) and the need for trained medical personnel. Alternative routes of vaccination that avoid hypodermic needles have previously been poorly immunogenic, require live vaccines, utilize bulky devices and/or are unsuitable for self-administration (Mitragotri 2005, Kersten 2007). Novel vaccine delivery methods such as microneedles can render vaccination easier and more acceptable to the public by simplifying vaccine access, and can confer equal or superior immunological responses to that induced by hypodermic needle through conventional intramuscular administration (Kim 2012).

Microneedles are micron-scale needles that administer vaccine directly into the skin using a simple minimally invasive approach without generating sharps waste. The microneedles are solid conical structures made of water-soluble excipients that can encapsulate a vaccine. Excipients used will be on the Food and Drug Administration's (FDA) Generally Recognized as Safe (GRAS) list and/or on FDA's list of inactive ingredients in approved products. The microneedles that are used in the study are painlessly inserted into the skin as a patch with a hypoallergenic adhesive bandage backing. The microneedles are left in place for up to 20 minutes. During this time, the microneedles dissolve in the skin, so that upon removal of the patch, the microneedles have disappeared and the sharps-free patch backing can be discarded as non-sharps medical waste. Therefore, microneedle patch application can be carried out as simply as applying a Band-Aid® adhesive bandage.

Microneedles have been studied for vaccines including influenza, rabies, Bacillus Calmette- Guerin (BCG), West Nile virus, and Human Papilloma Virus (HPV) (Kim 2012). There are a number of approved medical and cosmetic products using microneedles currently sold around the world. Soluvia® is a single hollow microneedle that is 1.5 mm long and is attached to a syringe (http://www.bd.com/pharmaceuticals/products/microinjection.asp). It is marketed worldwide prefilled with influenza vaccine for intradermal vaccination as IDflu®, Intanza® and Fluzone Intradermal®

(http://www.fluzone.com/fluzone-intradermal-quadrivalent-vaccine.cfm). Also MicronJet 600® received FDA clearance as a device (http://www.nanopass.com/product/).

Vaccination by microneedles is designed to increase patient compliance and access to immunization. In focus group studies of the public and healthcare professionals, microneedle patches were generally viewed positively compared to hypodermic needle injections (Birchall 2011). Perceived benefits included reduced pain, tissue damage and risk of infections, as well as possibility for self-administration. Concerns focused on delayed onset, cost, accurate and reliable dosing and the potential for misuse. In separate vaccination surveys associated with hollow microneedle injection of influenza vaccine, most physicians and the general public preferred microneedles over conventional intramuscular injection largely due to the smaller needle size, as well as the increased immunogenicity of intradermal vaccination (Arnou 2011). Physicians and patients alike thought that microneedle-based vaccination could increase vaccination coverage rates.

2.2 Rationale

Vaccines are typically injected using a hypodermic needle, a cost efficient, rapid and direct way for vaccine delivery. However, hypodermic needles cannot be easily used by patients themselves and patient willingness to receive vaccination is limited by pain and by needle-phobia experienced by many patients (Hamilton 1995). Spread of blood borne pathogens by needle re-use is also a major concern, especially in developing countries (Drucker 2001). Microneedles can be prepared as a low-cost patch that is simple for patients to apply for vaccine delivery targeting the many antigen-presenting cells present in the skin. A recent study at Emory University evaluated the safety, reactogenicity, acceptability, and immunogenicity of administration of influenza vaccine by microneedle patch in comparison to hypodermic needle injection. Data from this study demonstrated an excellent profile of the microneedle patch.

Data regarding the safety, reactogenicity, tolerability, and acceptability of a microneedle patch in children are lacking. The goal of this study is to evaluate the safety, reactogenicity, and acceptability of placement of a placebo microneedle patch to the skin of children. Twenty-five to 50 children healthy children between the ages of 6 weeks and 24 months will be enrolled in the study. Subjects will be recruited from the general population of metro Atlanta, GA and enrolled at the Emory Children's Center, located on Emory University campus in Atlanta, GA.

2.3 Potential Risks and Benefits

2.3.1 Potential Risks

Pain

The most significant parameter associated with pain is the microneedle length. However, microneedles shorter than ~1,000 µm are generally considered painless. Microneedles have induced significantly less pain than hypodermic needle controls. Pain from hollow microneedles can be caused by microneedle insertion as well as liquid infusion during injection (Kaushik 2001 and Gill 2008). The patch used in this study has conical solid microneedles with a width of 300 µm at the base without a liquid infusion. In a Phase I study of influenza vaccination, when pain was sometimes reported, it was mild in severity (Rouphael unpublished data). Pain in this study of placebo microneedle patch is thus possible, but is not expected.

Skin irritation

Microneedles can cause mild, transient skin irritation, primarily in the form of highly localized, mild and often punctuate erythema that disappears within hours or, in some cases, days. Erythema varies depending on length of microneedles. Bleeding is not characteristically seen. Itching has also been observed. Influenza vaccination using hollow microneedles has shown more local inflammatory reactions than hypodermic injection in human subjects. This may be due to inflammatory reactions being more easily visible in the skin than those that may occur after intramuscular injection (Arnou 2009).

Skin infection

There have been no reports of skin infection with microneedle insertions in thousands of people and animals (Kim 2012).

Adhesive backing component

The adhesive backing component is made from hypoallergenic material (commercial 3M medical tapes designed to adhere to skin). Local reactions (e.g., erythema, itching) can occur rarely, particularly with removal of the adhesive from the skin.

Placebo Microneedle Patch and Excipients

Excipients (inactive ingredients) used to make the microneedles will be USP-grade and listed on FDA's database of Inactive Ingredients for Approved Drug Products. The final composition of the patch for Cohort 1 and Cohort 2 has not been finalized but all excipients are already in use in FDA-approved drug products (and usually at a much higher dose than will be used in the microneedle patch). Excipients are expected to include trehalose, sorbitol, histidine, maltodextrin, sodium carboxymethylcellulose, polysorbate, xylitol, polyvinyl alcohol, and/or glycerol. The total mass of excipients delivered by placebo microneedle patch will be <1.5 mg.

The microneedle patches used in the placebo study will be manufactured under low bioburden conditions and in compliance with cGMP requirements for Phase 1 clinical trials according to the *FDA's Guidance for Industry 2008: CGMP for Phase 1 Investigational Drugs*. This will be the same process and same controls as those used in the manufacture of microneedle patches investigated in the Phase 1 clinical trial of the microneedle patch for influenza vaccination carried out by Georgia Tech and the Hope Clinic.

The microneedle patch has a history of safe use in human subjects. It has been used in several IRB-approved studies at Georgia Tech in adults and has always exhibited a safe profile that typically consists of itching and/or mild erythema that subsides after a few days. Similarly, the Phase 1 trial of the microneedle patch for influenza vaccination showed that the microneedle patch was safe with no serious adverse events (SAEs) reported. No new chronic medical illnesses or influenza-like illnesses were reported with the patch.

Although the composition of the microneedle patches used in these studies was different from that of the patches for the proposed placebo study in infants and young children, the microneedle patches were made of excipients that had the same safety profile as those that will be used in this placebo study. The controls that will be used to make the infant and young children placebo patches will be at least as strict as those that were used to make the patches used in the Georgia Tech IRB studies and the initial Phase 1 clinical trial of influenza vaccine administration by microneedle patch.

2.3.2 Known Potential Benefits

The knowledge gained from this study will facilitate the design of more effective and acceptable methods for administering vaccines in children by use of a microneedle patch. A future clinical trial of the microneedle patch for inactivated poliovirus (IPV) vaccination in infants is planned to occur in 2018, and the results from this IRB study will inform the design of this future clinical trial and others. There is no direct benefit to study participants.

3 OBJECTIVES

3.1 Study Objectives

3.1.1 Primary Objectives

- To evaluate the safety and reactogenicity following application of a placebo microneedle patch topically.

3.1.2 Secondary Objectives

- To evaluate unsolicited adverse events following application of a placebo microneedle patch topically.
- To evaluate new-onset medical conditions (NOMC) following application of a placebo microneedle patch topically.
- To evaluate the suitability of application of a placebo microneedle patch to different body locations.
- To evaluate the acceptability to the Legally Authorized Representative (LAR) of applying a placebo microneedle patch topically.

3.2 Study Endpoints

3.2.1 Primary Endpoints

Safety:

- Occurrence of placebo microneedle patch-related serious adverse events from Day 1 through the Final Study Visit (Day 27 – 38).
- Occurrence of Grade 3 placebo microneedle patch-related solicited adverse events for the 8 days following application of the patch.

Reactogenicity:

- Occurrence of solicited application site reactogenicity (e.g., erythema, induration, bruising, itching) for the 8 days following application of the patch.

3.2.2 Secondary Endpoints

- Occurrence of Grade 3 placebo microneedle patch-related unsolicited adverse events from Day 1 through the Final Study Visit (Day 27 – 38).

- Occurrence of new-onset medical conditions (NOMC) from Day 1 through the Final Study Visit (Day 27 – 38).
- Occurrence of solicited and unsolicited adverse events described at the site at which the placebo microneedle patch was applied.
- Quantitative and qualitative description of LAR responses to survey questions.

4 STUDY DESIGN

This is a single-center, unblinded, study in which healthy infants and children (6 weeks – 24 months inclusive) will have placebo microneedle patches applied to the skin. This study is designed to investigate the safety, reactogenicity, and acceptability of a placebo microneedle patch.

Infants and children will be recruited from metropolitan Atlanta and will be enrolled at Emory Children's Center. Approximately 25 to 50 infants and young children will be enrolled into one of two possible cohorts that will have placebo microneedle patches administered topically for up to approximately 20 minutes. Cohort 1 will assess one formulation of the microneedle patch (Microneedle Formulation 1). If the Microneedle Formulation 1 is well tolerated in Cohort 1, Cohort 2 may be enrolled using a different formulation of the microneedle patches if available (Microneedle Formulation 2).

After informed consent is obtained, subjects will be screened by history and physical examination at screening. Collected data will include demographic information, medical history, list of current and recent medications, and vaccination history. The placebo microneedle patch will be administered on Day 1 to subjects meeting enrollment criteria. Each subject will have 3 clinic visits: Day 1, Day 2 (+1 day), and Day 8 (+2 days). One telephone call will occur (Day 29 +/- 3 days). In those that receive additional microneedle patches on Day 8 (+2 days), follow-up visits will also occur at Day 9 (+2 days) and Day 15 (+3 days). Refer to the Appendix A for a detailed listing of study days and procedures.

Safety will be measured by the occurrence of solicited application site and systemic reactogenicity on the day of microneedle patch administration through Day 8 (+2 days) for the first patch and through Day 15 (+3 days) for the second and third patch. Unsolicited AE, and serious adverse events (SAEs) and new-onset medical conditions (NOMC) will be collected through Day 29 and Day 38 after microneedle patch administration. The acceptability of applying a microneedle patch topically will be assessed by LAR survey completed before microneedle patch application on Day 1, after microneedle patch removal on Day 1, at Day 2 (+1 day), Day 8 (+2 days), and the Final Study Visit (Day 27 – 38) in everyone. In those that receive additional microneedle patches, it will be also be repeated at Day 9 (+2 days) and Day 15 (+3 days).

Infants and children will be enrolled by sequential age groups using an age de-escalation approach (Table 1). At least 4 infants or children from each Group must complete Day 8 without halting criteria having been met (as detailed in Section 9.5) before subjects will be enrolled into the next younger age group within a Cohort. For Cohort 1, at least the first 2 children in each Group will have the microneedle patch applied to the skin overlying the shoulder blade. If this site is well tolerated without halting criteria having been met (as detailed in Section 9.5), additional microneedle patches may be applied at a different location on the same participant and in subsequent participants to the upper arm, forearm, wrist, thigh, shin, and/or foot. For Cohort 2, microneedle patches may be applied to the

shoulder blade, upper arm, forearm, wrist, thigh, shin, and/or foot. If the first site is well tolerated in the first two children without halting criteria having been met (as detailed in Section 9.5), additional microneedle patches may be applied to the same participants and in subsequent participants.

Table 1: Cohorts and Groups of Enrolled Infants and Young Children

Cohort	Group Age Range*	Number **	Study Product (administered Day 1 and possibly Day 8)
1	12 – 24 months	Up to 7	Microneedle formulation 1
1	5 – 11 months	Up to 6	Microneedle formulation 1
1	6 weeks – 4 months	Up to 12	Microneedle formulation 1
2	12 – 24 months	Up to 12	Microneedle formulation 2
2	5 – 11 months	Up to 12	Microneedle formulation 2
2	6 weeks – 4 months	Up to 12	Microneedle formulation 2

**All age ranges are inclusive. 4 children from each age group must complete Day 8 without halting criteria having been met (as detailed in Section 9.5) before subjects will be enrolled into the next younger age group.*

*** Total number enrolled into each Cohort will be ≤25.*

5 STUDY POPULATION

5.1 Selection of the Study Population

Approximately 25 or 50 healthy male and female infants and young children will be enrolled. The study will be conducted at a single site. Subjects will be recruited from the community at large.

Only infants and young children who meet the inclusion/exclusion criteria will be eligible for enrollment into this study.

5.2 Subject Inclusion Criteria

A subject must meet all the following criteria to be eligible to participate in this study:

1. LAR provides written informed consent prior to any study procedures being performed.

2. Subject is between the ages of 6 weeks and 24 months, inclusive, on the day of signing informed consent.

3. Subject is in good health as determined by vital signs, medical history, and a targeted physical examination.

4. LAR is able to understand and comply with required study procedures.

5.3 Subject Exclusion Criteria

A subject will not be eligible to participate in this study if any the following criteria apply:

1. Subject has an acute illness with fever (temperature >100.4 °F) within 72 hours prior to enrollment.

2. Subject has a known chronic medical problem.

3. Subject has known immunosuppression due to underlying illness or treatment, including (but not limited to): Human Immunodeficiency Virus (or birth to a HIV-positive mother), hepatitis B or C; organ transplant; active cancer or any history

of hematologic cancer; receipt of chemotherapy or radiation therapy; congenital immunodeficiency, anatomical or functional asplenia.

4. Subject has used long-term* high-dose** oral or parenteral glucocorticoids, or high-dose inhaled steroids.***

   ** Long term is defined as taken for 2 weeks or more in total at any time during the past 2 months.*

   *** High dose defined as prednisone ≥ 20 mg total daily dose, or equivalent dose of other glucocorticoids.*

   **** High dose defined as >800 mcg/day of beclomethasone dipropionate or equivalent.*

5. Subject has a history of an underlying skin condition (e.g., eczema, atopic dermatitis) or an open lesion (e.g., laceration, abrasion), scar, or rash in the areas of the planned microneedle patch administration which will interfere with the assessment of reactogenicity.

6. Subject or family members have a history of keloid formation.

7. Subject has any condition that, in the opinion of the investigator, may put the subject at increased risk of harm, may cause the subject to be unable to meet the requirements or might otherwise interfere with evaluations required by the study.

8. Subject has received any experimental products within 30 days before study entry or plan to receive experimental products at any time during the study.

9. Subject has received a vaccine within 7 days of enrollment or plans to receive a vaccine within 7 days after enrollment.

10. Subject has previously received immunoglobulin or blood products.

5.4 Treatment Assignment Procedures

5.4.1 Subject Identification Procedure

All subjects who are screened for the study (i.e., LAR signing the informed consent) will be assigned a subject identification number and will be included on the Screening and Enrollment Log. Subject identification numbers will be assigned sequentially starting with: ECCMN-001. If a subject does not meet eligibility criteria, that subject is considered a screen failure.

5.4.2 Reasons for Withdrawal

Subjects may by voluntarily withdrawn by their LAR from the study for any reason at any time. A subject may also be withdrawn from the study for one of the following reasons:

- The Investigator deems it is in the subject's best interest, or in the interest of study data integrity, to discontinue the subject from the study for clinical, safety, non-adherence or other reason.
- The subject is lost to follow up.
- New information becomes available that makes further participation unsafe.
- The study is terminated by the Investigator or Sponsor.

5.4.3 Handling of Withdrawals

The LAR(s) of an infant or young child will be informed that they have the right to discontinue their child's study participation at any time without prejudice. Although the LAR(s) are not obligated to state the reason for withdrawal, every attempt should be made to establish if the reason for discontinuation is due to the study product or an AE. LAR(s) who withdraw their child for any reason should be asked to complete an Early Termination Visit.

Ongoing AEs or reactogenicity should be followed to resolution if the LAR is agreeable to continued phone contact by the study staff. Subjects who are withdrawn from the study

for any reason will not be replaced, unless there are fewer than 4 subjects who have reached Day 8 for any given age group.

5.4.4 Termination of Study

The study may be terminated at any time by the Sponsor for clinical, safety or administrative reasons.

6 STUDY INTERVENTION/INVESTIGATIONAL PRODUCT

6.1 Study Product Description

6.1.1 Acquisition

Microneedle patches will be provided by Micron Biomedical.

6.1.2 Formulation, Packaging, and Labeling

Microneedle patches will be manufactured by Micron Biomedical. Microneedle patches will be made of excipients that are expected to include trehalose, sorbitol, histidine, maltodextrin, sodium carboxymethylcellulose, polysorbate, xylitol, polyvinyl alcohol, and/or glycerol. The total mass of excipients delivered by placebo microneedle patch will be <1.5 mg. The microneedle patches used in the placebo study will be manufactured under low bioburden conditions and in compliance with cGMP requirements for Phase 1 clinical trials according to the *FDA's Guidance for Industry 2008: CGMP for Phase 1 Investigational Drugs*. The adhesive backing component is made from hypoallergenic material (commercial 3M medical tapes designed to adhere to skin).

6.1.3 Product Storage and Stability

Microneedle patches will be stored at room temperature (i.e. 20^0C - 25^0C).

6.2 Dosage, Preparation and Administration of Study Intervention/Investigational Product

Microneedle patches will be administered topically by manual application to the skin. The sites of microneedle patch application will be cleaned with an alcohol swab and allowed to dry before the microneedle patch is applied. The microneedle patches will be packaged and provided as single patches.

6.3 Accountability Procedures for the Study Intervention/Investigational Product(s)

The Principal Investigator is responsible for study investigational product accountability, reconciliation, and record maintenance. In accordance with all applicable regulatory requirements, the Principal Investigator or designated study center personnel must maintain accountability records throughout the study.

7 STUDY SCHEDULE

Procedures to be performed at each study visit are detailed below. Refer also to Appendix A: Study Schedule.

7.1 Visit 1: Enrollment/Application of Placebo Microneedle Patch, Day 1

The following assessments will be performed on the day of enrollment prior to administration of the placebo microneedle patch.

- Informed Consent obtained.
- The optional consent for the optional placebo microneedle patches 2/3 may be signed.
- Inclusion/Exclusion criteria review.
- Complete medical history via interview with LAR including vaccination history.
- Record medications administered within the past 30 days and any concomitant medications.
- Vital signs: temperature and pulse.
- Complete physical examination.
- Height and weight.
- Baseline acceptability questionnaire.

The following procedures will be performed after subject eligibility has been verified:

- Subject enrolled.
- A baseline photograph of the area of application may be obtained.
- Application of placebo microneedle patch to the skin by a trained study nurse. The microneedle patch will remain in place for up to 20 minutes. The patch will then be removed and the used patch will be saved.
- The memory aid, thermometer and ruler will be provided to the LAR and instructions will be provided.
- The site of the placebo microneedle patch removal will be assessed at least 15 minutes and 30 minutes post-placebo microneedle patch removal. Per investigator discretion, photographic documentation (refer to MOP) and dermatologic referrals may be obtained.
- Study personnel will assess and record all AE/SAEs that occur after enrollment.
- The acceptability questionnaire will be completed by the LAR.

7.2 Visit 2: Day 2 (+1) Clinic Visit

The following assessments will be performed.

- Obtain interim medical history and note any changes since the last visit.
- Record concomitant medications.
- Symptom-directed physical examination, if needed.
- Vital signs: temperature and pulse.
- Examine placebo microneedle patch application site. Subjects with localized rash, scarring or evidence of infection at placebo microneedle patch application site are to be evaluated by a study investigator. Per investigator discretion, photographic documentation (refer to MOP) and dermatologic referrals may be obtained.
- Study personnel will review the memory aid information with the LAR and record all AE/SAEs.
- The follow-up acceptability questionnaire will be completed by the LAR.

7.3 Visit 3: Day 8 (+2), Clinic Visit

The following assessments will be performed.

- Obtain interim medical history and note any changes since the last visit.
- Record concomitant medications.
- Symptom-directed physical examination, if needed.
- Vital signs: temperature and pulse.
- Examine placebo microneedle patch application site. Subjects with localized rash, scarring or evidence of secondary infection at microneedle patch application site are to be evaluated by a study investigator. Per investigator discretion, photographic documentation (refer to MOP) and dermatologic referrals may be initiated for subjects with localized reactions.
- Study personnel will review the memory aid information with the LAR and record all AE/SAEs. If symptoms persist, clinic staff will attempt to follow up with the subject daily until two days symptom-free. Maximum severity post Day 8 and stop date of the symptoms will be recorded by clinic staff on the Solicited Events eCRF.
- The follow-up acceptability questionnaire will be completed by the LAR. The LARs of subjects who have no ongoing solicited or unsolicited general AE or local AEs will have the opportunity to decide to have second and third placebo microneedle patches placed at different body sites from the initial location.
- Subjects with solicited or unsolicited general AE or local AEs or declining the optional microneedle patch 2/3 will then proceed to the Final Study Visit (Days 27 – 38).

Optional Microneedle Patch 2/3 Study Events Day 8 (+2 days)

- The optional consent for the optional placebo microneedle patches 2/3 will be signed before additional study procedures occur on Day 8 (if not already signed).
- Inclusion/Exclusion criteria review.
- A baseline photograph of the area of application may be obtained.

- Application of placebo microneedle patches 2/3 to the skin in a different location than previously by a trained study nurse. The placebo microneedle patches will remain in place for up to 20 minutes. The patches will then be removed and the used patch will be saved.
- The memory aid, thermometer and ruler will be provided to the LAR and instructions will be provided.
- The site of the placebo microneedle patches removal will be assessed at least 15 minutes and 30 minutes post-placebo microneedle patch removal. Per investigator discretion, photographic documentation (refer to MOP) and dermatologic referrals may be obtained.
- Study personnel will assess and record all AE/SAEs that occur after enrollment.
- The acceptability questionnaire will be completed by the LAR.

7.4 Visit 4: Day 9 (+2) Clinic Visit (Only in those with Placebo Microneedle Patches 2/3 placement)

The following assessments will be performed.

- Obtain interim medical history and note any changes since the last visit.
- Record concomitant medications.
- Symptom-directed physical examination, if needed.
- Vital signs: temperature and pulse.
- Examine placebo microneedle patch application sites. Subjects with localized rash, scarring or evidence of infection at placebo microneedle patch application site are to be evaluated by a study investigator. Per investigator discretion, photographic documentation (refer to MOP) and dermatologic referrals may be obtained.
- Study personnel will review the memory aid information with the LAR and record all AE/SAEs.
- The acceptability questionnaire will be completed by the LAR.

7.5 Visit 5: Day 15 (+3), Clinic Visit (Only in those with Placebo Microneedle Patches 2/3 placement)

The following assessments will be performed.

- Obtain interim medical history and note any changes since the last visit.
- Record concomitant medications.
- Symptom-directed physical examination, if needed.
- Vital signs: temperature and pulse.
- Examine placebo microneedle patch application site. Subjects with localized rash, scarring or evidence of secondary infection at placebo microneedle patch application site are to be evaluated by a study investigator. Per investigator discretion, photographic documentation (refer to MOP) and dermatologic referrals may be obtained.

- Study personnel will review the memory aid information with the LAR and record all AE/SAEs. If symptoms persist, clinic staff will attempt to follow up with the LAR daily until the child is symptom-free for 2 days. Maximum severity post Day 15 in those that receive a second and third patch and stop date of the symptoms will be recorded by clinic staff on the Solicited Events eCRF.
- The follow-up acceptability questionnaire will be completed by the LAR.

7.6 Final Visit: Day 27 - 38, Telephone Call

The following assessments will be performed.

- Obtain interim medical history and note any changes since the last visit.
- Record concomitant medications.
- Study personnel will review the memory aid information with the LAR (if ongoing symptoms were noted at Day 8 for placebo microneedle patch 1 and Day 15 for placebo microneedle patch 2/3) and record all AE/SAEs.
- The final acceptability questionnaire will be completed by the LAR.

7.7 Premature Discontinuation Visit (if applicable)

The following activities will be performed (if the LAR agrees) should a premature discontinuation occur:

- Obtain interim medical history and note any changes since the last visit.
- Record concomitant medications.
- Symptom-directed physical examination, if needed.
- Vital signs: temperature and pulse.
- Examine placebo microneedle patch application site. Subjects with localized rash, scarring or evidence of secondary infection at placebo microneedle patch application site are to be evaluated by a study investigator. Per investigator discretion, photographic documentation (refer to MOP) and dermatologic referrals may be obtained.
- Study personnel will review the memory aid information with the LAR and record all AE/SAEs.
- The follow-up acceptability questionnaire will be completed by the LAR.

7.8 Unscheduled Visit (if needed)

The following activities will be performed should an unscheduled visit occur:

- Obtain interim medical history and note any changes since the last visit.
- Record concomitant medications.
- Symptom-directed physical examination, if needed.
- Vital signs: temperature and pulse.

- Examine placebo microneedle patch application site. Subjects with localized rash, scarring or evidence of secondary infection at placebo microneedle patch application site are to be evaluated by a study investigator. Per investigator discretion, photographic documentation (refer to MOP) and dermatologic referrals may be obtained.
- Study personnel will review the memory aid information with the LAR and record all AE/SAEs.
- The follow-up acceptability questionnaire will be completed by the LAR.

8 STUDY PROCEDURES/EVALUATIONS

8.1 Clinical Evaluations

8.1.1 Medical History

A complete medical history will be obtained by direct interview with the LAR. LAR(s) will be asked about any history in their infant or young child of significant medical disorders of the head, eyes, ears, nose, throat, mouth, cardiovascular system, respiratory system, gastrointestinal tract, liver, pancreas, kidney, urologic system, nervous system, blood and lymphatics, endocrine system, musculoskeletal system, skin and genial/reproductive tract. A history of any allergies or hypersensitivities, cancer, immunodeficiency, and autoimmune diseases will be solicited. Interim medical history is also obtained at each clinic visit.

8.1.2 Concomitant Medications

All medications including prescriptions, over-the-counter medications, vitamins and supplements taken by the subject in the 30 days prior to enrollment should be recorded at the screening visit. Assessment of eligibility will also include a review of permitted and prohibited medications per the exclusion criteria. At subsequent visits, LAR(s) will be queried about changes in their infant or young child's medications. Each new concomitant medication or change to existing medication will be recorded through the Final Study Visit (Day 27 – 38).

Medications which may interfere with the evaluation of the investigational product should not be used during the study unless absolutely necessary. Medications or treatments which are prohibited include:

- Vaccines (unless clinically necessary, vaccines should be avoided within 7 days of enrollment. Live vaccines should not be administered during the study).
- Oral, parenteral or high-dose inhaled steroids.
- Immunosuppressive or cytotoxic therapy.
- Blood products or immunoglobulins.
- Experimental products.

8.1.3 Vital Signs

Vital sign assessments including pulse and temperature will be taken at each in-clinic visit through Day 8 (+2 days) (Day 15 +3 days in those having placebo microneedle patches 2/3 placed).

8.1.4 Physical Examination

A complete physical examination (PE) will be performed at the Day 1 visit. A symptom-directed PE will be performed at all other in-clinic study visits. All PEs will be performed by a clinician licensed to make medical diagnoses and listed on the Form 1572 as the site principal investigator or sub-investigator.

8.1.5 Reactogenicity

The LAR will be provided with a memory aid, thermometer and ruler and will be instructed to record the presence of solicited symptoms and oral temperature through the Day 8 (+2 days) (Day 15 +3 days in those having microneedle patches 2/3 placed).. If a symptom is still present at that time, the LAR will continue to follow that symptom until two days symptom-free. Memory aids will be reviewed and collected by study staff at follow-up visits.

Solicited local microneedle patch application site symptoms include:

- Pain
- Erythema
- Ecchymosis (bruising)
- Induration/swelling
- Pruritus (itching)
- Tenderness

Solicited systemic reactions include:

- Fever
- Irritability (fussiness) above baseline
- Lethargy (drowsiness)
- Decreased appetite
- Vomiting

The LAR will use the following grading scale for describing symptoms:

Grade 0: Not present
Grade 1: Mild (present but easily tolerated)
Grade 2: Moderate (able to tolerate routine activity with effort)
Grade 3: Severe (unable to continue routine activity)

8.1.6 Acceptability Assessments:

To gauge LAR acceptability of vaccination using a microneedle patch, the LAR will complete a survey at Days 1, 2 (+1 day), 8 (+2 days), and Day 27 - 38 (Day 9 (+2 days) and Day 15 (+3 days) in those having placebo microneedle patches 2/3) including items that assess vaccination acceptability items (outcomes) via continuous scales (0-10 likelihood) and vaccination knowledge, attitudes, perceptions, and beliefs using Likert-type measurement (1-5 agreement levels) for multiple time point ANOVA and correlational analyses. The LAR will report on absolute and relative scores of ease of use, pain, product apprehension, comparative product utility, and overall preference comparing placebo microneedle patch application to previous experience with needle and syringe injection (Day 1); preference comparing the post-patch period to prior experience with vaccination (Day 8 (+2 days), and 27 – 38; also Day 9 (+2 days) and Day 15 (+3 days) in those having placebo microneedle patches 2/3); and perception of ease with which they might administer a microneedle patch in the future. The same LAR will complete the survey at all follow-up time points whenever possible. Basic sociodemographic characteristics will also be included, such as race/ethnicity, healthcare utilization/access, parental educational attainment, healthcare experience including previous immunization history, and socioeconomic indicators (household income, education).

9 SAFETY ASSESSMENT AND REPORTING

9.1 Definitions

9.1.1 Definition of an Adverse Event (AE)

An AE is any untoward or unfavorable medical occurrence in a human subject, including any abnormal sign (e.g., abnormal physical exam or laboratory finding), symptom, or disease temporally associated with the use of study treatment, whether or not considered related to the study treatment.

9.1.2 Definition of a Serious Adverse Event (SAE)

A "Serious Adverse Event" (SAE) is defined in 21 CFR 312.32. An SAE is any adverse event that meets at least one of the following criteria

- Death;
- Life-threatening;

  Life-threatening: an adverse event is considered "life-threatening" if, in the view of either the investigator or sponsor, its occurrence places the subject at immediate risk of death. It does not include an adverse event that, had it occurred in a more severe form, might have caused death.

- Hospitalization (initial or prolonged);
- Disability or permanent damage;
- Other important medical event.

  Important Medical Event: Events which do not fit the other outcomes, but may jeopardize the subject and may require medical or surgical intervention (treatment) to prevent one of the other outcomes. Examples include allergic bronchospasm (a serious problem with breathing) requiring treatment in an emergency room, serious blood dyscrasias (blood disorders) or seizures/convulsions that do not result in hospitalization.

9.2 Methods and Timing for Assessing, Recording, and Analyzing Safety Parameters

All safety parameters will be graded using the scales listed in the Appendices B and C.

9.2.1 Adverse Events

All AEs occurring while on study during the AE reporting period must be documented appropriately regardless of seriousness, severity, or causal relationship to study produce administration. AEs will be recorded on the AE page of the CRF. Solicited AEs will be collected from Day 1 (after placebo microneedle placement) through Day 8 following placebo microneedle administration (Day 15 in those receiving placebo microneedle patches 2/3). Unsolicited AEs and SAEs will be collected from Day 1 (after placebo microneedle placement) through the Day 27 – 38 end of study visit. AE details will be collected via interview with the subject LAR. Information to be collected includes event description, date of onset, severity and date of resolution/stabilization of the event. Severity and relationship to study product (either “related” or “unrelated”) must be assessed by the Investigator or sub-investigator. Signs and symptoms due to a single diagnosis will be reported as the diagnosis. For example, cough, pharyngitis, rhinitis would be reported as “upper respiratory infection”. If multiple signs/symptoms presenting simultaneously cannot be attributed to the same etiology, then each symptom should be reported separately.

Any medical condition present at the time the subject is screened, or occurring prior to placebo microneedle placement will not be considered an AE, but will be captured in the medical history form. If a preexisting condition worsens (changes in severity or quality, not consistent with the subject’s reported past history of the condition) at any time during the study, this change should be captured as an AE.

9.2.2 Reactogenicity

Reactogenicity events are reactions that are common and known to or expected to occur following the administration of the study product. Subjects LAR will be provided with a memory aid, thermometer and ruler and will be instructed to record the presence of solicited symptoms and oral temperature through Day 8 after placebo microneedle

placement (Day 15 in those receiving placebo microneedle patches 2/3). If a symptom is still present at Day 8 (Day 15 in those receiving placebo microneedle patches 2/3), the subject LAR will continue to follow that symptom until two days symptom-free. Memory aids will be reviewed and collected by study staff at follow up visits. Reactogenicity event details will be collected via review of the subject's memory aid and by interview with the subject LAR. Memory aid will not be considered source. The subject memory aid will be reviewed with the subject LAR at subsequent visits. Reactogenicity will be analyzed using Appendices B + C.

9.2.3 Serious Adverse Events

SAEs will be collected from Day 1 (after placebo microneedle administration) through the end of study participation. Any suspected SAE that occurs outside of the protocol-specified follow-up period and considered to be caused by the study placebo microneedle must be reported.

9.2.4 Procedures to be followed in the Event of Abnormal Laboratory Test Values or Abnormal Clinical Findings

AEs/SAEs will be followed until resolved or stable even if this extends beyond the study-reporting period. Resolution of an AE/SAE is defined as the return to pretreatment status or stabilization of the condition with the expectation that it will remain chronic.

9.3 Reporting Procedures

Related AE grade 3 and above will be reported to the Sponsor within 5 business days.

9.3.1 Serious Adverse Event Detection and Reporting

The following procedures will apply to all events meeting the definition of SAE as described in Section 9.1.2 SAEs:

The site Investigator must submit an initial SAE report immediately (within 24 hours of site awareness) to the Sponsor.

- Complete an initial SAE report form, reviewed and signed by PI or physician sub-investigator
- Initial report submitted by the PI on an expedited basis to the Sponsor
- SAEs must be reviewed and followed to resolution by a study physician
- Follow up reports submitted to document additional pertinent information and resolution of the event

9.3.2 Reporting to IRB

The PI is responsible for reporting AEs to the site IRB in accordance with the IRB's requirements for expedited reporting and continuing review reporting.

9.3.3 Type and Duration of the Follow-up of Subjects After Adverse Events

AEs and SAEs will be followed until resolution or stability even if this extends beyond the study reporting period. Resolution is defined as when the condition resolves (either with or without residual effects), returns to baseline for a pre-existing condition or has stabilized and is expected to remain chronic.

9.4 Individual Halting Rules

Enrolled subjects will not be eligible to receive placebo microneedle patches 2/3 placement at Day 8 (+2 days) if any of the following occur:

- An ongoing ≥Grade 1 local site reaction (see Appendix B).
- An ongoing ≥Grade 1 solicited general AE (see Appendix C) or unsolicited AE.

Subjects unable to receive placebo microneedle patches 2/3 due to meeting an individual halting rule will continue to follow up according to the protocol through Day 27 – 38.

9.5 Study Halting Rules

Further enrollment and placebo microneedle patch application (e.g., placebo microneedle patch 2/3 placement) to subjects will be halted if any of the following occur:

- Any death following placebo microneedle patch application.
- Any subject develops erosion, ulceration, or abscess at the administration site related to study product administration.
- Any subject develops laryngospasm, bronchospasm or anaphylaxis within 24 hours of placebo microneedle patch administration.
- Any subject experiences a placebo microneedle patch-related SAE.
- Any Grade 3 AEs or an SAE that cannot be clearly attributed to another cause.

If the study is halted, the site will immediately notify the Sponsor and the Emory IRB. Prior to recommencing enrollment, all available safety data will be reviewed by the site Investigator and the Sponsor.

10 CLINICAL MONITORING STRUCTURE

10.1 Study Documentation

The Principal Investigator will maintain appropriate medical and research records for this trial, in compliance with ICH-GCP, regulatory and institutional requirements for the protection of confidentiality of subjects. Source documents are the original data source used by the Investigator that allow verification of the study data collected, captured on CRFs and entered into the study database. Source documents may include but are not limited to: clinical charts and progress notes, memoranda, pharmacy dispensing records and other research records maintained for the clinical trial. Study CRFs may serve as the original source document.

The Investigator will permit authorized representatives of the Sponsor and regulatory agencies to examine (and when required by applicable law, to copy) clinical records for the purposes of quality assurance reviews, audits and evaluation of the study safety and progress.

10.2 Data Collection and Data Management

The Investigator and designated study staff will keep accurate records to ensure that the conduct of the study is fully documented. The investigator will ensure that all CRFs and subject study files are legible and complete for every subject. A detailed description of each of the forms and the procedures required for forms completion and submission can be found in the MOP. The Investigator or designee must record all required subject data, and an explanation must be documented for any missing data.

Clinical research data will be collected and recorded in a timely fashion in a secure electronic web-based database (e.g., REDCap). Extracted data will be sent to the statisticians for statistical analysis as needed. The final study database and statistical evaluations will be transferred to the Sponsor at the study completion.

10.3 Data Quality Control/Quality Assurance

The Principal Investigator, through the use of an internal Quality Management Plan and appropriate internal site monitoring staff, will be responsible for the regular review of the conduct of the trial, for verifying adherence to the protocol, and for confirming the completeness,

consistency, and accuracy of all documented data and accuracy of source documentation verification.

10.4 Site Monitoring Plan

The study data integrity and compliance with the protocol will be assured by the monitoring of the study documentation and study conduct by an internal monitor. Routine data monitoring and protocol compliance will be performed by the site investigators, study coordinator and quality assurance staff on an ongoing basis. The study clinical monitoring plan and the data quality monitoring plan will be developed and followed by the study site.

10.5 Timing/Reports

A cumulative report of related AE grade 3, major deviations and subject terminations is sent to sponsor on a monthly basis. SAEs are reported within 24 hours to the IRB and the sponsor.

10.6 Study Records Retention

Study records including source documentation, CRFs, informed consent documents, laboratory report forms, study product accountability records and regulatory files will be retained for a period of 18 years after the submission of the final report and closeout procedures on the research project for which the clinical trials records were prepared or termination of the study, unless a longer retention period is specified by Emory policy, the sponsor, or regulation. In addition, records must be maintained for at least 2 years after a marketing application is approved for the study product (i.e. microneedle patch). The Investigator must notify the study Sponsor prior to destroying any study records. Consent forms for future use samples must be maintained as long as the sample exists.

10.7 Protocol Deviations

A protocol deviation is any change, deviation or departure from the study design or procedures of the research protocol that is not approved by the Sponsor and/or IRB prior to its initiation or implementation, or deviation from standard operating procedures, Good Clinical Practices (GCPs), federal state or local regulations. These protocol violations may be major or

minor violations. The Investigator and study staff will have ongoing monitoring to identify any protocol deviations during the conduct of the study and to report any deviations to the Sponsor or Emory IRB as appropriate.

Minor protocol deviations are deviations from the research protocol that do not (a) adversely affect the rights, welfare or safety of subjects; (b) adversely affect the integrity of research data; (c) adversely affect the subjects' willingness to continue participation in the research; or (d) were not undertaken to prevent immediate hazard to a human subject. A minor protocol deviation or protocol non-compliance will be reported to the Sponsor on an ongoing basis. Minor deviations do not require reporting to the Emory IRB for review unless subject safety is a concern. A major protocol deviation must be reported to the Sponsor and Emory IRB (per IRB reporting guidelines) immediately upon discovery of the deviation and no later than 10 days after site awareness.

11 STATISTICAL CONSIDERATIONS

11.1 Study Outcome Endpoints

Primary:

Safety:

- Occurrence of placebo microneedle patch-related serious adverse events from Day 1 through the Final Study Visit (Day 27 – 38).
- Occurrence of Grade 3 placebo microneedle patch-related solicited adverse events for the 8 days following application of the patch.

Reactogenicity:

- Occurrence of solicited application site reactogenicity (e.g., erythema, induration, bruising, itching) for the 8 days following application of the patch.

Secondary:

- Occurrence of Grade 3 placebo microneedle patch-related unsolicited adverse events from Day 1 through the Final Study Visit (Day 27 – 38).
- Occurrence of new-onset medical conditions (NOMC) from Day 1 through the Final Study Visit (Day 27 – 38).
- Occurrence of solicited and unsolicited adverse events described at the site at which the placebo microneedle patch was applied.
- Quantitative and qualitative description of LAR responses to survey questions.

11.2 Sample Size Considerations

For sample size calculation and statistical analysis plan the primary and secondary endpoints will mainly be addressed. The small numbers in this study allow only rough estimates of safety. With 25 subjects per cohort, if the true event rate is 5%, we will have 34% chance to observe one AE and 12% chance to observe more. If the true event rate is 10%, the chance to observe one AE is 38%, and the chance to observe more than one AEs is 34%.

11.3 Analysis Plan

The safety population includes all subjects who receive the placebo microneedle patch. The safety population will be the primary analysis population for safety analyses. AEs will be analyzed using the safety population. Subjects will be analyzed as treated.

Primary Outcome Endpoints

AEs, reactogenicity events and SAEs will be recorded throughout the study. AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) dictionary. AE summary tables will be based on treatment-emergent AEs for the safety population. Descriptive statistics (e.g., number and percentage of subjects) will be used for each treatment group. AEs will be summarized by severity, relationship to treatment, and AEs leading to discontinuation. SAEs will also be tabulated by overall and treatment related events.

Secondary Outcome Endpoints

Unsolicited AEs and new-onset medical conditions (NOMC) will be recorded. AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) dictionary. AE summary tables will be based on treatment-emergent AEs for the safety population. Descriptive statistics (e.g., number and percentage of subjects) will be used for each treatment group. AEs will be summarized by severity, relationship to treatment, and AEs leading to discontinuation. NOMC will also be tabulated by overall and treatment related events.

12 ETHICS/PROTECTION OF HUMAN SUBJECTS

12.1 Ethical Standard

This study will be conducted in accordance with the protocol, the Declaration of Helsinki, ICH E6 GCP and local regulations.

12.2 Institutional Review Board

Prior to initiating any study procedures, the Investigator will submit the following documents to the Emory IRB for review and approval: protocol and any amendments, informed consent, any documents to be given to the subject (e.g., memory aid), recruitment materials, and any other documents as requested by the IRB. A copy of the IRB approval will be submitted to the Sponsor.

Any amendments to the protocol or changes to the consent form must be submitted and approved by the IRB prior to implementation at the site. The Investigator will also ensure the timely dissemination of SAE and study safety reporting to the IRB in accordance with local IRB regulations and guidance.

12.3 Informed Consent Process

Voluntary written informed consent must be obtained before any study-related procedures are performed in accordance with International Conference on Harmonization (ICH) guidelines and the requirements of informed consent (Title 21 Code of Federal Regulations (CFR) Parts 50.20 and 50.25). Consent must be documented by the use of a written consent form approved by the site's institutional review board (IRB) in accordance with Title 21 CFR Part 50.27.

Subject's LAR will be given an adequate amount of time to read the consent and ask any questions prior to signing the document. A copy of the signed informed consent will be provided to the subject LAR signing the form and the original retained in the source documents of the study subject.

12.4 Subject Confidentiality

The investigational site participating in this study will maintain the highest degree of confidentiality for the clinical and research information obtained from the subjects in this clinical trial. Medical and research records will be maintained at each site in the strictest confidence. However, as a part of the quality assurance and legal responsibilities of an investigation, the investigational site will permit authorized representatives of FDA and health authorities to examine (and when required by applicable law, to copy) clinical records for the purpose of quality assurance reviews, audits, and evaluations of the study safety and progress. Unless required by the laws that permit copying of records, only the coded identity associated with documents or with other subject data may be copied (and all personally identifying information will be removed). Authorized representatives as noted above are bound to maintain the strict confidentiality of medical and research information that is linked to identify individuals.

A subject's privacy and confidentiality will be respected throughout the study. Each subject will be assigned a sequential identification number, and these numbers, rather than names, will be used during collection, storage, and reporting of subject information.

12.5 Study Discontinuation

If the study is discontinued, enrolled subjects will continue to be followed for safety assessments as specified in the protocol.

13 LITERATURE REFERENCES

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14 SUPPLEMENTS/APPENDICES

14.1 Appendix A: Study Schedule

Visit #		1	2	3	4[&]	5[&]	Final*		
Procedures		D1	D2 +1	D8 +2	D9 +2	D15 +3	D27 - D38	Unscheduled Visit (If needed)	Premature Discontinuation
Signed Consent Form		X							
Inclusion/Exclusion Review		X							
Complete Medical History		X							
Concomitant Medications		X	X	X	X[&]	X[&]	X	X	X
Interim Medical History			X	X	X[&]	X[&]	X	X	X
Sign Optional Consent For Microneedle Patch 2/3		(X)		(X)					
Application of microneedle patch		X		X[&]					
Distribute memory aid, ruler & thermometer		X		X[&]					
Review memory aid			X	X	X[&]	X[&]	(X)	(X)	(X)
Physical Exam	Complete Physical Exam	X							
	Assessment of microneedle patch application site	X**	X	X**[&]	X[&]	X[&]		X	X
	Symptom-Directed Physical Exam		(X)	(X)	(X)[&]	(X)[&]		(X)	(X)
	Height and weight	X							
	Vital Signs^	X	X	X	(X)[&]	(X)[&]		X	X
Photograph site of placebo microneedle patch		(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)
Assessment of Adverse Events and SAEs		X**	X	X	(X)[&]	(X)[&]	X	X	X
Acceptability Questionnaire		X	X	X	(X)[&]	(X)[&]	X	X	X

** The final study visit will be a telephone call at D27 – D38*

*** Occurring 15 minutes and 30 minutes after microneedle patch removal.*

& At Day 8 the LARs of subjects who no ongoing solicited or unsolicited general AE or local AEs will have the opportunity to decide to have second and third placebo microneedle patches placed at different body sites from the initial location. In those that elect to have a second/third placebo microneedle patch placed, they will return for clinic visits on Day 9 and Day 15.

^ Vital signs will include temperature and pulse.

(X) – As indicated/appropriate.

14.2 Appendix B: Adverse Event & Reactogenicity Grading - LOCAL SITE REACTIONS

	LOCAL SITE REACTIONS			
	Grade			
	0	1	2	3
Induration/ Swelling *	None to less than 2.5 cm	2.5 – 5 cm and does not interfere with activity	5.1 – 10 cm or interferes with activity	> 10 cm or prevents daily activity, erosion, or ulceration
Erythema**	None to less than 2.5 cm	2.5 – 5 cm	5.1 – 10 cm	> 10 cm, erythroderma, or a diffuse rash >15% of the body surface area
Ecchymosis	None	2.5 – 5 cm	5.1 – 10 cm	> 10 cm
Tenderness	None	Mild discomfort to touch	Discomfort with movement	Significant discomfort at rest
Pain	None	Does not interfere with activity	Repeated use of non-narcotic pain reliever > 24 hours or interferes with activity	Any use of narcotic pain reliever or prevents daily activity
Pruritus (Itching)	None	Mild	Moderate itching; limiting instrumental activities of daily living	Severe itching; limiting self-care activities of daily living

*Induration/swelling should be evaluated and graded using the functional scale as well as the actual measurement

**In addition to grading the measured local reaction at the greatest single diameter, the measurement should be recorded as a continuous variable.

14.3 Appendix C: Adverse Event & Reactogenicity Grading - GENERAL ADVERSE REACTIONS

	GENERAL ADVERSE REACTIONS			
	Grade			
	0	**1**	**2**	**3**
Irritability (fussiness)	None	No interference with activity	Some interference with activity	Significant; prevents daily activity
Lethargy (drowsiness)	None	No interference with activity	Some interference with activity	Significant; prevents daily activity
Decreased appetite	None	No interference with activity	Some interference with activity	Significant; prevents daily activity
Vomiting	None	No interference with activity	Some interference with activity	Prevents daily activity, requires outpatient IV hydration
Fever	None	100.4 – 101.1 F	101.2 – 102.1 F	>102.1 F