Letter of Amendment # 1 for:

IMPAACT 2021
Randomized Phase I/II Study of the Safety and Immunogenicity of a Single Dose of the Recombinant Live-Attenuated Respiratory Syncytial Virus (RSV) Vaccines RSV ΔNS2/Δ1313/I1314L, RSV 6120/ΔNS2/1030s, RSV 276 or Placebo, Delivered as Nose Drops to RSV-Seronegative Children 6 to 24 Months of Age

Version 3.0, dated 28 April 2022

DAIDS ES # 38530
IND # 018943 Held By DAIDS

Letter of Amendment Date: 25 September 2023

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Information/Instructions to Study Sites from the Division of AIDS

The information contained in this Letter of Amendment (LoA) impacts the IMPAACT 2021 study, including the sample informed consent form (ICF), and will be submitted to the single Institutional Review Board (sIRB), Advarra, centrally by the IMPAACT Operations Center as soon as possible for their review and approval. If applicable, sites must also obtain approval from site IRBs per the policies and procedures of those entities. All IRB and regulatory entity requirements must be followed.

Upon obtaining IRB approval and any other applicable regulatory entity approvals, each site should immediately begin implementing this LoA. After all required approvals are obtained, the updated ICFs should be used for all new participants. In addition, all previously enrolled participants must reconsent to ongoing study participation using the updated site-specific ICF. Re-consenting should take place at each enrolled participant's next study visit after all required approvals are obtained.

Sites are required to submit a LoA registration packet to the DAIDS Protocol Registration Office (DAIDS PRO) at the Regulatory Support Center (RSC). Sites will receive a registration notification for the LoA

after the DAIDS PRO verifies that all required registration documents have been received and are complete. Sites should not await this notification before implementing this LoA.

Please file this LoA, all associated IRB and regulatory entity correspondence, and all correspondence with the DAIDS PRO in your essential documents files for IMPAACT 2021. If the IMPAACT 2021 protocol is amended in the future, the contents of this LoA will be incorporated into the next version of the protocol.

IMPAACT 2021
Randomized Phase I/II Study of the Safety and Immunogenicity of a Single Dose of the Recombinant Live-Attenuated Respiratory Syncytial Virus (RSV) Vaccines RSV ΔNS2/Δ1313/I1314L, RSV 6120/ΔNS2/1030s, RSV 276 or Placebo, Delivered as Nose Drops to RSV-Seronegative Children 6 to 24 Months of Age

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Letter of Amendment Signature Page

I will conduct this study in accordance with the provisions of this protocol and all applicable protocol-related documents. I agree to conduct this study in compliance with United States (US) Health and Human Service regulations (45 CFR 46); applicable US Food and Drug Administration regulations; standards of the International Council for Harmonisation Guideline for Good Clinical Practice (ICH E6); Institutional Review Board/Ethics Committee determinations; all applicable in-country, state, and local laws and regulations; and other applicable requirements (e.g., US National Institutes of Health, Division of AIDS) and institutional policies.

_____ _____

Signature of Investigator of Record Date

_____

Name of Investigator of Record

(printed)

Summary of Modifications and Rationale

The primary purpose of this LoA is to update the licensed RSV product information in the protocol and Informed Consent Form. In August 2023, the Centers for Disease Control and Prevention (CDC) director adopted the recommendation from the CDC Advisory Committee on Immunization Practices to approve nirsevimab, an FDA-licensed extended half-life monoclonal antibody active against RSV. Nirsevimab has been recommended by the CDC for all infants younger than eight months old who are born during or entering their first RSV season. For children between the ages of eight and 19 months who are at increased risk of severe RSV disease, a dose is recommended in their second RSV season. With the CDC director's adoption of the recommendation, nirsevimab is now applicable for official CDC public health guidance and can be added to the childhood immunization schedule. Additionally, in August 2023, the FDA approved an RSV prefusion F vaccine for pregnant people between 32-36 weeks gestation. The vaccine is expected to prevent of lower respiratory tract disease (LRTD) or severe LRTD in infants from birth through six months of age. This LoA also includes updates to the Protocol Team and Study Site Rosters.

Implementation

The modifications included in this Letter of Amendment are listed below in order of appearance in the protocol and will be incorporated into the next protocol amendment as specified below. Additions to the text are indicated in bold; deletions are indicated by strike-through.

Note: In this LOA, all new references are identified with alphabetic identifiers, with full citations provided on page 8. In the next full amendment of the IMPAACT 2021 protocol, these references will be incorporated into the numeric listing of all references in protocol Section 15.

Protocol Team and Site Study Rosters

1. *Protocol Team*

   To reflect current membership, John Binkowski and Nicole Tobin have been removed from the roster and Grace Malonga, Helty Adisetiyo, and Maggie Albano are added:

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2. *Study Site Roster*

To reflect the current Investigators of Record, Ellen Chadwick has been replaced by Jennifer Jao (site 4001), Sharon Frey has been replaced by Heidi Sallee (site 30344), and Evan Anderson (site 5030) and Jennifer Schuster (site 32017) have been removed from the Study Site Roster:

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Section-Specific

3. *Section 1.2, Background*

   a) Page 22, third paragraph, starting with first sentence: Currently, no licensed vaccine against RSV is available~~, although there is broad consensus that such a vaccine is urgently needed and should be a global health priority~~ **to protect healthy older infants and toddlers**. Although passive immunoprophylaxis with the RSV-neutralizing monoclonal antibody palivizumab (Synagis®;MedImmune) is available for high-risk infants, this approach is not feasible for general use. **In addition, in August 2023, the Centers for Disease Control and Prevention (CDC) director adopted the recommendation from the CDC Advisory Committee on Immunization Practices (ACIP) to approve nirsevimab (1). Nirsevimab is an FDA-licensed monoclonal antibody active against RSV to provide passive immunity to healthy infants up to eight months old during their first RSV season and to high-risk children eight to 19 months during their second RSV season (2). Additionally, on 21 August 2023, licensure of the RSVpreF maternal vaccine was approved for use at 32 through 36 weeks gestational age of pregnancy (3). While both products are expected to provide passive immunity to younger infants, they do not provide active, durable immunity and are not expected to protect healthy older infants and toddlers against RSV disease. Pursuit of vaccines for active immunization against RSV is important because protection from passive antibodies (from either nirsevimab or maternal immunization) is short-lived- lasting no more than 6 months. There is significant burden of RSV disease in children who are older than eight months of age during RSV season who will not be recommended to receive nirsevimab. For example, globally, the incidence in 6-12 months-old children of RSV lower respiratory illness is estimated at 82 per 1000 per year, with an estimated 4.1 to 8 million episodes annually in this age group, resulting in a rate of hospitalization of about 1% annually (estimated numbers: 500,000 – 970,000 hospital admissions) (4), In the United States, for children from 7 to 20 months of age, rates of inpatient RSV infections were ~3 per 1000, emergency room RSV ~30 per 1000, and outpatient visits ~60 per 1000 (5, 6). In contrast to the passive immunity provided by nirsevimab or maternal RSV preF, live-attenuated vaccines studied in this protocol prime the infants' immune system and induce active RSV immunity, which should provide long-lasting immunity with potent memory responses. […]**

4. *Section 4.2, Exclusion Criteria*

   a) 4.2.6, Page 38: Previous enrollment in this trial, previous ~~maternal or~~ pediatric receipt of a licensed or investigational RSV vaccine, or previous maternal or pediatric receipt of or planned administration of any **other** anti-RSV product (such as ribavirin or RSV IG or RSV mAb) **within four months of screening or planned administration of an anti-RSV product between screening and day 56 after enrollment**.

5. *Section 5.11, Concomitant Medications*

   a) 5.11.2, Precautionary Concomitant Medications, Page 46, new bullet point:

   Due to their potentially confounding effect on immunogenicity results, the following treatments should be avoided after study product administration unless clinically indicated:

   - Systemic corticosteroids for more than 14 days at a dosage equivalent to prednisone at >2 mg/kg or 20 mg daily or other immune-modifying drugs
   - Immunoglobulins and/or any blood products
   - **Anti-RSV products (such as ribavirin or RSV IG or RSV mAb)**

6. *Section 7.2, Safety-Related Data Collection*
   a) Laboratory Test Results, Page 62, Table 5: AE eCRF Entry Requirements, Row Throughout Study, Column Concomitant Medications to enter into eCRFs:

Study Phase at the time of event onset	Calendar Date	AEs to enter into eCRFs	Concomitant Medications to enter into eCRFs
Throughout study	ANY	• Updated data on unresolved AEs or serious AEs with onset date during the timeframe from study product administration (Day 0) to midnight on the 28th day after Day 0 • Updated data on unresolved serious AEs with onset date prior to midnight on the 56th day following Day 0 • Updated data on unresolved serious AEs with onset date during RSV Surveillance Period or related to the Post-RSV Season Study Visit Note: unresolved events should be followed to resolution or until no further change is expected.	• All concomitant medications administered to treat the entered event • **All prohibited and precautionary medications (see Section 5.11)**

Informed Consent Forms

7. *Appendix VI, Informed Consent Form for Study Participation*

   a) Key Information, Page 96, last bullet: You may choose to not allow your child to take part in this study. **Two products have been developed to protect young infants against RSV disease.**

However, ~~T~~there ~~are~~ **is** currently no licensed ~~vaccines to protect against RSV illness~~ **product available to provide long-lasting protection against RSV disease to healthy older infants and children**.

b) Why Is This Study Being Done?, Page 96, third paragraph: RSV can cause serious lung infections such as pneumonia and wheezing. **Two products have been developed to protect young infants against RSV disease.** ~~At this time~~ **However**, there is **currently** no ~~approved vaccine to prevent RSV illness~~ licensed **product available to provide long-lasting protection against RSV disease to healthy older infants and children**.

c) What Other Choices Does My Child Have Besides This Study?, Page 102: **Two products have been developed to protect young infants against RSV disease.** If your child is younger than eight months of age at the start of their first RSV season, your child may be eligible to receive an FDA-licensed product for short-term protection against RSV during your child's first RSV season. **However, ~~T~~t**here ~~are~~ **is currently** no licensed ~~vaccines to protect against RSV illness at this time~~ **product available to provide long-lasting protection against RSV disease to healthy older infants and children**. ~~There is no other similar study or approved vaccine that we can offer your child.~~ You may choose to not allow your child to take part in this study.

References

1. Centers for Disease Control and Prevention. CDC Recommends a Powerful New Tool to Protect Infants from the Leading Cause of Hospitalization 2023. [cited 2023 9 Aug]. Available from: https://www.cdc.gov/media/releases/2023/p-0803-new-tool-prevent-infant-hospitalization-.html.
2. US Food and Drug Administration. FDA Approves New Drug to Prevent RSV in Babies and Toddlers 2023. [cited 2023 9 Aug]. Available from: https://www.fda.gov/news-events/press-announcements/fda-approves-new-drug-prevent-rsv-babies-and-toddlers#:~:text=Today%2C%20the%20U.S.%20Food%20and,remain%20vulnerable%20to%20severe%20RSV.
3. Food and Drug Administration. FDA Approves First Vaccine for Pregnant Individuals to Prevent RSV in Infants 2023. [cited 2023 22 Aug]. Available from: https://www.fda.gov/news-events/press-announcements/fda-approves-first-vaccine-pregnant-individuals-prevent-rsv-infants#:~:text=Abrysvo%20is%20approved%20for%20use,years%20of%20age%20and%20older.
4. Network RVGE, Li Y, Wang X, Blau DM, Caballero MT, Feikin DR, et al. Global, regional, and national disease burden estimates of acute lower respiratory infections due to respiratory syncytial virus in children younger than 5 years in 2019: a systematic analysis. The Lancet. 2022;399(10340):2047-64.
5. Rha B, Curns AT, Lively JY, Campbell AP, Englund JA, Boom JA, et al. Respiratory syncytial virus–associated hospitalizations among young children: 2015–2016. Pediatrics. 2020;146(1).
6. Hall CB, Weinberg GA, Iwane MK, Blumkin AK, Edwards KM, Staat MA, et al. The burden of respiratory syncytial virus infection in young children. N Engl J Med. 2009;360(6):588-98.