[redacted] STATISTICAL ANALYSIS PLAN
16 FEBRUARY 2022

SYSTEMIC ALLERGIC REACTIONS TO SARS-COV-2 VACCINATION

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SPONSOR: [redacted]

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DAIT/Rho STATISTICAL ANALYSIS PLAN ACKNOWLEDGMENT AND SIGNATURE SHEET

SYSTEMIC ALLERGIC REACTIONS TO SARS-COV-2 VACCINATION

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Table of Contents

1. PROTOCOL SYNOPSIS

Title	Systemic Allergic Reactions to SARS-CoV-2 Vaccination
Short Title	SARS Vaccination
Clinical Phase	Phase 2
Number of Sites	Approximately 30 clinical sites in the United States
IND Sponsor/Number	National Institute of Allergy and Infectious Diseases (NIAID) / IND# 27215
Study Objectives	The study is designed with two principal aims: First, to estimate the proportions of systemic allergic reactions to the Pfizer-BioNTech COVID-19 Vaccine and the Moderna COVID-19 Vaccine in a High-Allergy/Mast Cell Disorder (HA/MCD) population. Second, if the risk in the HA/MCD is demonstrable, to determine whether the proportions are higher in the HA/MCD versus a comparison population. Primary Objectives: • Assess the proportion of participants with systemic allergic reactions to the Pfizer-BioNTech COVID-19 Vaccine in the HA/MCD and comparison populations • Assess the proportion of participants with systemic allergic reactions to the Moderna COVID-19 Vaccine in the HA/MCD and comparison populations Secondary Objectives: • Assess the proportion of participants with severe (Grade 3 or higher per Consortium for Food Allergy Research (CoFAR) Grading Scale for Systemic Allergic Reactions Version 3.0) systemic allergic reactions to the Pfizer-BioNTech COVID-19 Vaccine in the HA/MCD and comparison populations • Assess the proportion of participants with severe (Grade 3 or higher per CoFAR Grading Scale for Systemic Allergic Reactions Version 3.0) systemic allergic reactions to the Moderna COVID-19 Vaccine in the HA/MCD and comparison populations • Assess the proportion of participants with anaphylactic reactions (Levels 1-3) per Brighton Collaboration Criteria to the Pfizer-BioNTech COVID-19 Vaccine in the HA/MCD and comparison populations • Assess the proportion of participants with anaphylactic reactions (Levels 1-3) per Brighton Collaboration Criteria to the Moderna COVID-19 Vaccine in the HA/MCD and comparison populations • Assess the proportion of participants with systemic allergic reactions to the Pfizer-BioNTech COVID-19 Vaccine in the HA/MCD population by dose

	• Assess the proportion of participants with systemic allergic reactions to the Moderna COVID-19 Vaccine in the HA/MCD population by dose • Assess the proportion of participants with systemic allergic reactions to the Pfizer-BioNTech COVID-19 Vaccine in the HA/MCD after adjusting for placebo • Assess the proportion of participants with systemic allergic reactions to the Moderna COVID-19 Vaccine in the HA/MCD after adjusting for placebo • Assess the difference in proportions of participants with systemic allergic reactions after the second Pfizer-BioNTech COVID-19 Vaccine dose (not placebo arm) versus the first vaccine dose within the placebo arm in the HA/MCD population • Assess the difference in proportion of participants with systemic allergic reactions after the second Moderna COVID-19 Vaccine dose (not placebo arm) versus the first vaccine dose within the placebo arm in the HA/MCD population • Assess the difference in proportion of HA/MCD participants with systemic allergic reactions to the Pfizer-BioNTech COVID-19 Vaccine between the adult and child populations (for this analysis, the HA group will not include children who qualified for the study on the basis of uncontrolled asthma) • Assess the difference in proportion of HA/MCD participants with systemic allergic reactions to the Moderna COVID-19 Vaccine between the adult and child populations (for this analysis, the HA group will not include children who qualified for the study on the basis of uncontrolled asthma) Exploratory Objectives: • Assess the risk of systemic allergic reactions to the Pfizer-BioNTech COVID-19 Vaccine and independently to the Moderna COVID-19 Vaccine in the HA/MCD population by baseline covariates • Examine possible mechanisms of systemic allergic reactions to the Pfizer-BioNTech COVID-19 Vaccine and to the Moderna COVID-19 Vaccine • Identify genotypes associated with increased risk of systemic allergic reactions to the Pfizer-BioNTech COVID-19 Vaccine and to the Moderna COVID-19 Vaccine
Study Design	This is a multi-center, randomized, initially blinded, phase 2 trial to assess SARS-CoV-2 vaccination systemic allergic reactions in two populations: one population including individuals with a history of recent, severe allergic reactions (High-Allergy [HA]), poorly controlled allergic asthma, or mast cell disorders (MCDs) and one comparison population without severe allergies or mast cell disorders. Participants enrolled under protocol versions 1.0 - 4.0, were randomized 2:2:1:1 to receive the Pfizer-BioNTech COVID-19 Vaccine, Moderna COVID-19 Vaccine, placebo + Pfizer-BioNTech COVID-19 Vaccine, or placebo + Moderna COVID-19 Vaccine. Participants enrolled under protocol versions 5.0 – 8.0 will be randomized 2:1 to receive the Pfizer-BioNTech COVID-19 vaccine or placebo + Pfizer-BioNTech COVID-19 vaccine. Active vaccine may be changed from Pfizer-BioNTech to Moderna, if enrollment is robust and sustained, Participants randomized to one of the placebo groups will receive placebo

	as a first dose and will receive two doses of their assigned active vaccine at subsequent visits.
Primary Endpoints	1. The proportion of participants who experience a systemic allergic reaction (CoFAR Grade 2 and above regardless of tryptase, or CoFAR Grade 1 with elevated tryptase [1.2 x baseline plus 2 ng/ml]) within the 90-minute post-vaccination observation period to either dose of the Pfizer-BioNTech COVID-19 Vaccine 2. The proportion of participants who experience a systemic allergic reaction (CoFAR Grade 2 and above regardless of tryptase, or CoFAR Grade 1 with elevated tryptase [1.2 x baseline plus 2 ng/ml]) within the 90-minute post-vaccination observation period to either dose of the Moderna COVID-19 Vaccine
Secondary Endpoints	1. The proportion of participants who experience a severe (Grade 3 or higher per CoFAR Grading Scale for Systemic Allergic Reactions Version 3.0) systemic allergic reactions within the 90- minute post-vaccination observation period to either dose of each vaccine 2. The proportion of participants who experience an anaphylactic reaction (Levels 1-3) per Brighton Collaboration Criteria within the 90-minute post-vaccination observation period to either dose of each vaccine 3. The proportion of participants who experience a systemic allergic reaction (CoFAR Grade 2 and above regardless of tryptase, or CoFAR Grade 1 with elevated tryptase [1.2 x baseline plus 2 ng/ml]) within the 90-minute post-vaccination observation period to the first dose 4. The proportion of participants who experience a systemic allergic reaction (CoFAR Grade 2 and above regardless of tryptase, or CoFAR Grade 1 with elevated tryptase [1.2 x baseline plus 2 ng/ml]) within the 90-minute post-vaccination observation period to the second dose conditional on no systemic allergic reaction to the first dose 5. The proportion of participants who experience a systemic allergic reaction (CoFAR Grade 2 and above regardless of tryptase, or CoFAR Grade 1 with elevated tryptase [1.2 x baseline plus 2 ng/ml]) within the 90-minute post-vaccination observation period to the first dose after adjusting for placebo administration 6. The proportion of participants who experience a systemic allergic reaction (CoFAR Grade 2 and above) within 48 hours of either dose of each vaccine
Exploratory Endpoints	1. The proportion of participants who experience a systemic allergic reaction (CoFAR Grade 2 and above regardless of tryptase, or CoFAR Grade 1 with elevated tryptase [1.2 x baseline plus 2 ng/ml]) within the 90-minute post-vaccination observation period to either dose 2. Prevalence of polyethylene glycol (PEG) antibodies in vaccine recipients before each vaccination

	3. Changes in anti-PEG antibody levels 3-4 weeks after the first vaccine dose 4. Changes in biomarkers from pre- to post-vaccination and/or after onset of an allergic reaction (e.g., known mediators of systemic reactions due to mast cell activation, markers of inflammatory response, markers associated with activation of the classical and alternative complement pathways or the kinin system) 5. Changes in blood transcriptomics after vaccination, and plasma and urine proteomics from pre- to post-vaccination and/or after onset of an allergic reaction 6. Genetic variants identified by whole-genome sequencing (applicable only in protocol versions 1.0 - 4.0)
Accrual Objective	This study will enroll up to 3400 participants. Approximately 60% of participants will be in the High-Allergy/Mast Cell Disorder (HA/MCD) group, and 40% will be in the comparison group. Enrollment of participants who qualify only on the basis of reactions to multiple unrelated drugs will be limited to approximately 300. Enrollment of the Mast Cell Disorder group is anticipated to be at least 200, and not more than 300 participants. Approximately two-thirds of participants enrolled in each of the 2 groups will be female. Under protocol versions 1.0 - 4.0, participants were randomized 2:2:1:1 to receive either the Pfizer-BioNTech COVID-19 Vaccine, Moderna COVID-19 Vaccine, placebo+ Pfizer-BioNTech COVID-19 Vaccine, or placebo + Moderna COVID-19 Vaccine. Under protocol versions 5.0 – 8.0, the study will only enroll children ages 5 through 17 years on the date of first study vaccination/placebo administration. Enrollment of participants aged 18 or older will be closed. Children will be randomized 2:1 to receive either the Pfizer-BioNTech COVID-19 Vaccine or placebo + Pfizer-BioNTech COVID-19 Vaccine. Active vaccine may be changed from Pfizer-BioNTech to Moderna if enrollment is robust and sustained. Participants randomized to one of the placebo groups will receive placebo as a first dose and will receive two doses of their assigned active vaccine at subsequent visits.
Study Duration	Participant Vaccination and Follow-up: Participants randomized under protocol versions 1.0 - 4.0: Randomized and vaccinated participants will complete study participation in approximately 29 days if vaccinated with the Pfizer-BioNTech COVID-19 Vaccine, 36 days if vaccinated with the Moderna COVID-19 Vaccine, and 50 or 64 days if administered placebo before receiving two doses of either the Pfizer-BioNTech COVID-19 Vaccine or the Moderna COVID-19 Vaccine, respectively. Participants randomized under protocol versions 5.0 – 8.0: Randomized and vaccinated participants who receive both doses of vaccine will complete study participation in approximately 29 days if vaccinated with the Pfizer-BioNTech COVID-19 Vaccine, 36 days if vaccinated with the Moderna COVID-19 Vaccine, and 36 or 43 days if administered placebo before receiving two doses of either the Pfizer-BioNTech COVID-19 Vaccine or the Moderna COVID-19 Vaccine, respectively.

Treatment Description	Each participant will receive 2 doses of either the Pfizer-BioNTech COVID-19 Vaccine or the Moderna COVID-19 Vaccine. Participants randomized to placebo, will receive a placebo dose before receiving 2 doses of either the Pfizer-BioNTech COVID-19 Vaccine or the Moderna COVID-19 Vaccine.
Inclusion Criteria	Note criteria apply to all cohorts and protocol versions, unless otherwise stated. Individuals who meet all of the following criteria are eligible for enrollment as study participants: <u>Both groups:</u> 1. Participant and/or parent/legal guardian must be able to understand and provide informed consent and/or assent, as applicable 2. Male or non-pregnant female 12 years of age or older on the date of first study vaccination/placebo administration (protocol versions 1.0 - 4.0) **OR** male or non-pregnant female 5 to 17 years of age on the date of first study vaccination/placebo administration (protocol versions 5.0 – 8.0) 3. Females of childbearing potential must have a negative pregnancy test prior to the first vaccination and placebo administration, if applicable. If a participant becomes pregnant after receiving a placebo dose but prior to receiving study vaccination, she will be discontinued from the study. 4. Females of reproductive potential* and sexually active must agree to use Food and Drug Administration (FDA) approved methods of birth control for the duration of the study. These include hormonal contraceptives, intrauterine device, double barrier contraception (i.e., condom plus diaphragm), or male partner with documented vasectomy. *Menopause is defined as at least 12 consecutive months without menses; if in question, a follicle stimulating hormone of ≥25 U/mL must be documented. Hysterectomy, bilateral oophorectomy, or bilateral tubal ligation must be documented, as applicable; if documented, women with these conditions are not required to use additional contraception. <u>High-Allergy and Mast Cell Disorder (HA/MCD) group:</u> Individuals who meet at least one of the following criteria are eligible for enrollment in the HA/MCD group: 1. History of a severe allergic reaction to food(s), allergen immunotherapy, insect venom(s), or latex with use of epinephrine within the last 15 years 2. History of an Emergency Department visit with convincing evidence of a systemic allergic reaction (consistent with CoFAR Grade 3 or higher) to food(s), allergen immunotherapy, insect venom(s) or latex within the last 15 years 3. History of documented, immediate allergic reactions to 2 or more unrelated drugs within the last 15 years

	4. A convincing clinical history, or a history that is accompanied by a positive skin test, of an immediate reaction to a drug, vaccine, or latex within the last 15 years 5. History of physician-diagnosed idiopathic anaphylaxis requiring epinephrine, or an Emergency Department visit in the last 15 years 6. History of a physician-diagnosed mast cell disorder (e.g., mastocytosis, mast cell activation syndrome (MCAS), or hereditary alpha-tryptasemia). MCAS must meet consensus criteria as defined below: • Criterion A: Typical clinical signs of severe, recurrent (episodic) systemic Mast Cell Activation are present (often in form of anaphylaxis) (definition of systemic: involving at least 2 organ systems) • Criterion B: Involvement of Mast Cell (MC) is documented by biochemical studies: preferred marker: increase in serum tryptase level from the individual's baseline to plus 20% + 2 ng/ml • Criterion C: Response of symptoms to therapy with MC-stabilizing agents, drugs directed against MC mediator production or drugs blocking mediator release or effects of MC-derived mediators All 3 MCAS criteria (A + B + C) must be fulfilled to call a condition MCAS. 7. Poorly controlled allergic asthma as evidenced by one hospitalization or one or more systemic (oral or injectable) steroid burst(s) in the 24 months prior to enrollment and evidence of aeroallergen sensitization by blood work, skin test, or appropriate history. 8. A doctor diagnosis of food allergy with a convincing clinical history and a positive skin test or positive food challenge, with evidence of reactivity within the last 10 years. <u>Comparison group:</u> Individuals who meet all of the following criteria are eligible for enrollment in the comparison group: 1. No history of allergic asthma or atopic dermatitis within the last 10 years 2. No history of chronic spontaneous urticaria, or angioedema 3. No history of allergic reactions to foods or insect venoms 4. No history of allergic reactions to drugs or vaccines 5. No history of anaphylaxis 6. No history of a mast cell disorder (e.g., mastocytosis, MCAS, or hereditary alpha-tryptasemia)
Exclusion Criteria	Individuals who meet any of these criteria are not eligible for enrollment as study participants: 1. Inability or unwillingness of a participant and/or parent/legal guardian to give written informed consent and/or assent, as applicable, or comply with study protocol 2. Weight less than 15 kg 3. Prior receipt of any doses of the Pfizer-BioNTech COVID-19 Vaccine, Moderna COVID-19 Vaccine, or any other COVID-19 vaccine

	4. History of a severe reaction to any component of the Pfizer-BioNTech COVID-19 Vaccine or Moderna COVID-19 Vaccine 5. History of contact dermatitis with confirmed patch test reaction to PEG 6. History of reaction to Doxil 7. Known exposure to SARS-CoV-2 and still within the quarantine window 8. Symptoms consistent with acute COVID-19 infection or known COVID-19 infection (positive PCR or antigen test) and still within the quarantine window 9. Have an acute illness, including body temperature greater than 100.4˚F, within 14 days of the first study vaccination/placebo administration or 3 days prior to each subsequent vaccination 10. History of autoimmune or other disorders requiring systemic immune modulators 11. History of acute urticaria within 28 days of randomization 12. Pregnant 13. Have received any vaccines within 14 days of the first study vaccination/placebo administration or plan to receive other vaccines during the study period 14. Had any allergen immunotherapy administration within 24 hours prior to vaccination/placebo administration or plan to receive within 24 hours after vaccination/placebo administration 15. Have received a biologic therapy within 6 months of randomization 16. Use of systemic steroids for any reason within 28 days of randomization 17. Use of Zileuton within 14 days of randomization 18. Use of any antibody agent for treatment or prevention of COVID-19 within 3 months of randomization 19. Coronary artery disease, peripheral or cerebral vascular disease, unstable angina, or cardiac arrhythmia other than supraventricular tachycardia (SVT) 20. Medically unstable hypertension 21. Current use of beta-blockers, angiotensin-converting-enzyme (ACE) inhibitors, monoamine oxidase (MAO) inhibitors, tricyclic anti-depressants or other agents that could interfere with the treatment of anaphylaxis, in the opinion of the investigator 22. Unstable asthma within 3 months of randomization or symptomatic asthma on the day of vaccination as assessed by the site investigator 23. Have past or current medical problems or findings from physical exam or laboratory testing not listed above, which in the opinion of the investigator, may pose additional risks from participation in the study or which may interfere with the ability to comply with study requirements. This includes individuals with underlying conditions or other medications that, in the opinion of the investigator, may increase risk in the event of an anaphylactic reaction or lead to complications following administration of epinephrine.

Premature Discontinuation of Investigational Agent	Vaccination will be prematurely discontinued for any participant for any of the following reasons: • Participant has a CoFAR Grade 2 or higher systemic allergic reaction regardless of tryptase, or a CoFAR Grade 1 reaction with elevated tryptase [1.2 x baseline plus 2 ng/ml] that is at least possibly related to the first dose of vaccine. If the systemic allergic reaction took place after the participant has left the vaccination clinic and no tryptase measurements are available, Grade 1 events will not constitute criteria for discontinuation, but counseling by a study physician will be required. • The investigator believes that it is no longer in the best interest of the participant to receive the second vaccination.
Study Stopping Rules	Study enrollment will be suspended and vaccinations will be put on hold pending Data and Safety Monitoring Board (DSMB) expedited review of all pertinent data in the event of any one of the following: 1. One Grade 4 or higher adverse event (AE) that is at least possibly related to the vaccine 2. Five participants in the first 100 HA/MCD participants vaccinated or 5% of HA/MCD participants thereafter experience a Grade 3 systemic allergic reaction at least possibly related to the vaccine

2. INTRODUCTION

This statistical analysis plan includes pre-planned analyses related to the study objectives outlined in the protocol.

3. GENERAL ANALYSIS AND REPORTING CONVENTIONS

The following analyses and reporting conventions will be used:

- Categorical variables will be summarized using counts (n) and percentages (%) and will be presented in the form “n (%).” Percentages will be rounded to one decimal place.
- Numeric variables will be summarized using n, mean, standard deviation (SD), median, minimum (min), maximum (max). The min/max will be reported at the same level of significance as original data. The mean and median will be reported at one more significant digit than the precision of the data, and SD will be reported at two more significant digits than the precision of the data.
- The median will be reported as the average of the two middle numbers if the dataset contains an even number of observations.
- Test statistics including *t* and *z* test statistics will be reported to two decimal places.
- *P*-values will be reported to three decimal places if greater than or equal to 0.001. If less than 0.001, the value will be reported as “<0.001.” A *p*-value can be reported as “1.000”

only if it is exactly 1.000 without rounding. A *p*-value can be reported as "0.000" only if it is exactly 0.000 without rounding.

If departures from these general conventions are present in the specific evaluations section of this SAP, then those conventions will take precedence over these general conventions.

4. ANALYSIS SAMPLES

As-treated sample: All participants who are randomized and receive at least one active vaccination for any active injection analysis or all participants who are randomized and receive a placebo for any placebo injection analysis. Participants will be analyzed according to the vaccine they received.

Per-Protocol sample: All participants who are randomized and receive all assigned vaccination doses. Participants who do not receive a second active vaccination due to experiencing an allergic reaction will be included in the analysis. Participants will be analyzed according to the vaccine they received.

Safety sample: All participants who consent and undergo screening procedures. Participants will be analyzed according to the vaccine they actually received, regardless of the treatment arm to which they were randomized. Non-treatment emergent adverse events (e.g., any adverse event that occurs before the first injection) will be summarized in all participants in the safety sample, while treatment-emergent adverse events (e.g., any adverse event that occurs on or after the first injection) will be summarized in the subset of participants who receive an injection (placebo or active vaccination).

5. STUDY PARTICIPANTS

5.1. Disposition of Participants

The disposition of all enrolled participants will be summarized in tables and listed.

The numbers and percentages of participants randomized, in each treatment group and cohort (HA/MCD or Comparison), and completing each scheduled injection, as well as reasons for early termination from the study will be presented. For participants discontinuing study treatment early, the reasons for discontinuing study treatment early will also be presented.

5.2. Demographic and Other Baseline Characteristics

Summary descriptive statistics for baseline and demographic characteristics will be reported for the as-treated sample. Characteristics to be summarized include site, age, race, ethnicity, sex, body weight, and height, and BMI at enrollment. Additionally, cohort assignment (HA/MCD or Comparison) and associated details will also be presented.

6. STUDY OPERATIONS

6.1. Protocol Deviations

Protocol deviations will be listed by site with information such as type of deviation, severity of the deviation (major or non-major), date of occurrence, and the reason for the deviation. Protocol deviations will be summarized in tabular format by type of deviation.

6.2. Treatment Adherence

Participants in the Pfizer-BioNTech COVID-19 Vaccine and Moderna COVID-19 Vaccine treatment arms will receive two injections, while those in the placebo + Pfizer-BioNTech COVID-19 Vaccine and placebo + Moderna COVID-19 Vaccine treatment arms will receive three injections.

Treatment adherence will be summarized by treatment group within each cohort and overall. Study treatment administration data will be listed by treatment group, cohort (HA/MCD or Comparison) and participant.

7. ENDPOINT EVALUATION

7.1. Overview of Endpoint Analysis Methods

7.1.1. Multicenter Studies

Study participants will be recruited from 29 study sites. For the primary and secondary endpoints, study data will be analyzed as a whole, and no formal accommodation for site-to-site variation will be made.

7.1.2. Assessment Time Windows

Allowable visit windows for all scheduled visits are provided in Appendix 3 of the protocol. In the rare event a vaccination window cannot be met, vaccination may be scheduled beyond the +14-day window. If a participant becomes infected with SARS-CoV-2 or another acute illness following his/her first dose of vaccine, the second vaccination will be delivered, with allowance for a delay up to 90 days following the first dose.

Unscheduled visits may also occur throughout the study.

All data will be included in analyses, regardless of time of assessment. No formal accommodations will be made for out of window visits. Participants who are beyond the 14-day window will be summarized.

7.2. Primary Endpoints

The primary endpoints are as follows:

- The proportion of participants who experience a systemic allergic reaction (CoFAR Grade 2 and above regardless of tryptase, or CoFAR Grade 1 with elevated tryptase [1.2

x baseline plus 2 ng/ml]) within the 90-minute post-vaccination observation period to either dose of the Pfizer-BioNTech COVID-19 Vaccine.

- The proportion of participants who experience a systemic allergic reaction (CoFAR Grade 2 and above regardless of tryptase, or CoFAR Grade 1 with elevated tryptase [1.2 x baseline plus 2 ng/ml]) within the 90-minute post-vaccination observation period to either dose of the Moderna COVID-19 Vaccine.

7.2.1. Computation of the Primary Endpoints

The primary analyses will conducted for participants enrolled under versions 1.0 through 4.0. For each population we will estimate the proportion of participants who experience a systemic allergic reaction (CoFAR Grade 2 and above regardless of tryptase, or CoFAR Grade 1 with elevated tryptase [1.2 x baseline plus 2 ng/ml]) within the 90-minute post-vaccination observation period to either dose of the Pfizer-BioNTech COVID-19 Vaccine and independently the Moderna COVID-19 Vaccine for both the HA/MCD and Comparison populations. These four proportions will be accompanied by their 95% exact (Clopper-Pearson) confidence intervals.

A systemic allergic reaction, categorized as yes or no, is defined as a participant having a reaction to either active dose 1 or active dose 2 (categorized as yes) or to neither active dose (categorized as no). Grade 1 systemic allergic reactions will only be categorized as yes if the tryptase is elevated as determined by the VCU lab. If the tryptase cannot be evaluated for a Grade 1 event (i.e. if missing a pre-treatment and/or post-treatment value), the study management team will determine the subjects categorization based on all available data for the subject.

Participants who do not have a systemic allergic reaction to the 1st active dose and missing data for their 2nd active dose will be removed from this analysis (complete case analysis).

7.2.2. Primary Analysis of the Primary Endpoint

If systemic allergic reactions are observed, we will compare the proportions of participants experiencing a systemic allergic reaction to the Pfizer-BioNTech COVID-19 Vaccine and independently to the Moderna COVID-19 Vaccine between the HA/MCD and comparison populations. The point estimate of the difference in proportions between populations within each vaccine is estimated as p_1-p_0 with p_1= x_1/n_1 and p_0=x_0/n_0 and will be reported, together with the corresponding 95% exact unconditional confidence interval. The proportion difference will be tested using a Barnard's Exact Unconditional Test with a two-sided test using the central method of doubling the one-sided p-value. No multiplicity adjustment will be applied to these two primary endpoints.

```
*** Primary Analysis (Barnard's);
ods output BarnardsTest=BarnardsTestOutput;
proc freq data = d_l order = data;
 title "Primary";
 where dose = 'E' and protocol<5;
 tables group*resp / riskdiff;
 exact riskdiff barnard;
* High computational power, only run on an as needed basis;
run;
```

```
The p-value is equal to (BARNARDSTESTOUTPUT.NVALUE1)*2 where
BARNARDSTESTOUTPUT.NAME1='XPL_RDIF1'.


# R: Primary Analysis (Barnard's) p-value
library(exact2x2)
t <- with(d_l %>% filter(dose == 'E' and protocol<5),
table(group,resp))
uncondExact2x2(t[1,2],sum(t[1,]),
               t[2,2],sum(t[2,]),
               alternative = "less",
               parmtype = "difference",
               method   = "score",
               midp     = TRUE,
               control  = ucControl(nPgrid=5000),
               conf.int = FALSE)
```

Exact unconditional confidence limits for the risk difference are obtained with SAS procedure PROC FREQ and the RISKDIFF option in the EXACT statement. These RISKDIFF options request exact unconditional 95% confidence limits for the risk (proportion) and risk difference for the 2x2 table respectively. PROC FREQ computes the confidence limits by the tail method, which inverts two separate one-sided exact tests of the risk difference, where the tests are based on the score statistic (Chan and Zhang 1999). The size of each one-sided exact test is at most α/2, and the confidence coefficient is at least (1-α/2).

If there is an issue with the calculation of the Barnard's Exact Unconditional Test, we will perform the Risk difference estimates, asymptotic 95% confidence intervals, and p-values using SAS procedure PROC FREQ and the RISKDIFF option without an EXACT statement.

```
*** Primary Analysis (Asymptotic);
proc freq data = d_l order = data;
 title "Primary";
 where dose = 'E' and protocol<5;
 tables group*resp / riskdiff;
run;
```

Additionally, we will compare the proportion of participants experiencing a systemic allergic reaction (as defined in section 7.2.1) between HA/MCD adult (18 years and older at enrollment) and HA/MCD child (less than 18 years of age at enrollment) populations for each vaccine separately. Children who qualified for the study on the basis of uncontrolled allergic asthma will be excluded from this analysis. The point estimate of the difference in proportions between adult and child populations within each vaccine will be estimated along with its corresponding 95% exact unconditional confidence interval. The proportion difference will be tested using a Barnard's Exact Unconditional Test with a two-sided test using the central method of doubling the one-sided p-value. No multiplicity adjustment will be applied.

In the event that there are not enough subjects in a particular population, the reaction rate will be described descriptively.

7.2.3. Sensitivity Analyses of the Primary Endpoint

Missingness (not due to allergic reaction) will be evaluated for each vaccine type separately in each age group. If more than 5% of participants are missing their second active dose for either the Pfizer-BioNTech COVID-19 Vaccine or the Moderna COVID-19 Vaccine, a sensitivity analysis using the tipping-point approach will be conducted to assess the robustness of the primary analysis results. This analysis will only be conducted in the vaccine arm(s) with more than 5% missing. Participants missing both active doses will not be imputed. Tipping point analysis explores the influence of missingness on the overall conclusion from statistical inference by positing a wide spectrum of assumptions regarding the missingness mechanism (from less conservative to more conservative). The analysis finds a (tipping) point in this spectrum of assumptions, at which conclusions of the analysis change. After such a tipping point is determined, clinical judgment can be applied as to the plausibility of the assumptions underlying this tipping point.

7.2.4. Additional Analysis of the Primary Endpoint

The rate of reaction for active dose 1 will be summarized in the following manner:

$$\frac{\#\text{ particpants experiencing a reaction per section 7.2.1 to active dose 1}}{\#\text{ particpants who received active dose 1}}$$

The rate of reaction for active dose 2 will be summarized in the following manner:

$$\frac{\#\text{ particpants experiencing a reaction per section 7.2.1 to active dose 2}}{\#\text{ particpants who received active dose 2}}$$

No imputation will be performed for any reason for any participant who does not receive the second active dose. The rate of reaction for each dose will be summarized separately for the Pfizer- BioNTech and Moderna COVID-19 vaccines.

7.3. Secondary Endpoints

All secondary endpoints will be analyzed for participants enrolled under version 1.0 through 4.0. If sufficient numbers of children are enrolled, then adults 18 years of age and older will be also be analyzed separately from children.

7.3.1. Secondary Endpoint 1

Endpoint: The proportion of participants who experience a severe (Grade 3 or higher per CoFAR Grading Scale for Systemic Allergic Reactions Version 3.0) systemic allergic reactions within the 90-minute post-vaccination observation period to either dose of each vaccine.

Computation: A Grade 3 or higher systemic allergic reaction, categorized as yes or no, is defined as a participant having a Grade 3 or higher (per CoFAR Grading Scale V3.0) systemic allergic reaction to either active dose 1 or active dose 2 (categorized as yes) or to neither active dose (categorized as no).

Participants who do not have a systemic allergic reaction to the 1st active dose but missing data for their 2nd active dose will be removed from this analysis (complete case analysis).

Analysis: This analysis will be carried out as outlined in Section 7.2.2. A sensitivity analysis will be carried out as outlined in Section 7.2.3.

7.3.2. Secondary Endpoint 2

Endpoint: The proportion of participants who experience an anaphylactic reaction (Levels 1-3) per Brighton Collaboration Criteria within the 90-minute post-vaccination observation period to either dose of each vaccine.

Computation: An anaphylactic reaction (Levels 1-3) per Brighton Collaboration Criteria, categorized as yes or no, is defined as a participant having an anaphylactic reaction (Levels 1-3) per Brighton Collaboration Criteria to either active dose 1 or active dose 2 (categorized as yes) or to neither active dose (categorized as no).

Participants who do not have a systemic allergic reaction to the 1st active dose but missing data for their 2nd active dose will be removed from this analysis (complete case analysis).

Analysis: This analysis will be carried out as outlined in Section 7.2.2. A sensitivity analysis will be carried out as outlined in Section 7.2.3.

7.3.3. Secondary Endpoints 3/4

Objective (**paired**)
Assess the proportion of participants with systemic allergic reactions to the Pfizer-BioNTech COVID-19 Vaccine in the HA/MCD population by dose
Endpoint
The proportion of participants who experience a systemic allergic reaction (CoFAR Grade 2 and above regardless of tryptase, or CoFAR Grade 1 with elevated tryptase [1.2 x baseline plus 2 ng/ml]) within the 90-minute post-vaccination observation period to the first dose and to the second dose conditional on no systemic allergic reaction to the first dose.
Statistical Test
Endpoint will be analyzed using an exact McNemar's test.
Checks & Diagnostics
This analysis will not be carried out if there are no systemic allergic reactions.
Model Results Presentation
Proportions and 95% exact confidence intervals will be presented for the 1st and 2nd dose. The mid p-value will be reported using an exact McNemar's test. Placebo & Pfizer -BioNTech COVID-19 Vaccine (1st)

Placebo & Pfizer -BioNTech COVID-19 Vaccine (2nd)

Placebo + Pfizer	placebo	1st	2nd
Pfizer	1st	2nd	

SAS Code

```
*** Paired doses;
proc freq data = d_w order=data;
 title "Paired";
 where group = 'HA/MCD';
 tables D1*D2 / riskdiff;
 exact mcnem riskdiff / midp;
run;
```

R Code

```
library(exact2x2)
t <- with(d_w %>% filter(group == 'HA/MCD'), table(D1, D2))
mcnemar.exact(t, conf.level=.95)
mcnemarExactDP(n=sum(t),
               m=t[1,2]+t[2,1],
               x=t[2,1])
```

Supportive Statistical Analyses

A sensitivity analysis will be performed using a GEE logistic regression model & NLMeans macro to obtain the proportion difference and 95% confidence interval. There will be no adjustment for covariates.

```
*** Paired doses (Sensitivity);
proc genmod data = d_l;
 title "Paired (Sensitivity)";
 where dose in ('D1','D2') & group = 'HA/MCD';
 class id dose;
 model resp(event = '1') = dose / dist=binomial link = logit;
 repeated subject=id / type = ind;
 lsmeans dose / e ilink diff exp;
 store out=genmod;
 ods output coef = coeffs;
run;
%NLMeans(instore=genmod, coef=coeffs, link=logit, title= Paired Prop
Diff);
```

Handling of Missing Data

Participants with missing data for their 2nd active dose for reasons other than systemic allergic reactions in their 1st active dose will be removed from this analysis (complete case analysis).

Participants with missing data for their 2nd active dose because of a systemic allergic reaction to their 1st active dose (inherent missingness given the current design) will be examined using an extreme case scenario (replacement of all 2nd active dose missing by either yes or no). If the results from this extreme case scenario differs and if there is at least 10 systemic allergic reactions in the 1st active dose a tipping point analysis will be conducted.

Notes

The same analysis will be repeated for the Moderna COVID-19 Vaccine.

Objective (**priming**)

Assess the difference in proportions of participants with systemic allergic reactions after the second Pfizer-BioNTech COVID-19 Vaccine dose (not placebo arm) versus the first vaccine dose within the placebo arm in the HA/MCD population.

Endpoint

The proportion of participants who experience a systemic allergic reaction (CoFAR Grade 2 and above regardless of tryptase, or CoFAR Grade 1 with elevated tryptase [1.2 x baseline plus 2 ng/ml]) within the 90-minute post-vaccination observation period to the second dose conditional on no systemic allergic reaction to the first dose in the Pfizer-BioNTech COVID-19 Vaccine arm and the first active dose in the Placebo- Pfizer-BioNTech COVID-19 Vaccine arm.

Model Specification

- Endpoint is as defined above.
- Endpoint will be analyzed using Barnard's unconditional exact test.

Model Checking & Diagnostics

This analysis will not be carried out if there are no systemic allergic reactions in the 1st dose among the placebo arm and/or 2nd dose among the Pfizer arm.

Model Results Presentation

Proportions, 95% exact unconditional confidence intervals and p-value will be presented for the 1st dose among Placebo & Pfizer and 2nd dose among the Pfizer arm.

Placebo & Pfizer-BioNTech COVID-19 Vaccine (1st)

Pfizer-BioNTech COVID-19 Vaccine (2nd)

Placebo + Pfizer	placebo	1st	2nd
Pfizer	1st	2nd	

SAS Code

```
*** Priming;
proc freq data = d_l;
 title "Priming";
 where group = 'HA/MCD' &
  ((dose = 'D1' & Placebo = 'Yes') | (dose = 'D2' & Placebo = 'No'));
 tables dose*resp / riskdiff;
```

```
 exact riskdiff barnard;
run;
```

Supportive Statistical Analyses

If there is an issue with the calculation of the Barnard's Exact Unconditional Test, we will perform a univariate logistic regression.

```
*** Priming (Sensitivity);
proc genmod data = d_1;
 title "Priming (Sensitivity)";
 where group = 'HA/MCD' &
  ((dose = 'D1' & Placebo = 'Yes') | (dose = 'D2' & Placebo = 'No'));
 class dose;
 model resp(event = '1') = dose / dist=binomial link = logit;
 lsmeans dose / e ilink diff exp;
 store out=genmod;
 ods output coef = coeffs;
run;
%NLMeans(instore=genmod, coef=coeffs, link=logit, title= Priming Prop
Diff);
```

Handling of Missing Data

Participants with missing data for their 2nd active dose for reasons other than systemic allergic reactions in their 1st active dose will be removed from this analysis (complete case analysis).

Participants with missing data for their 2nd active dose because of a systemic allergic reaction to their 1st active dose (inherent missingness given the current design) will be examined using an extreme case scenario (replacement of all 2nd active dose missing by either yes or no). If the result from this extreme case scenario differs and if there is at least 10 systemic allergic reactions in the 1st active dose a tipping point analysis will be conducted.

Notes

The same analysis will be repeated for the Moderna COVID-19 Vaccine.

7.3.4. Secondary Endpoint 5

Objective (First dose comparison to Placebo)

Assess the proportion of participants with systemic allergic reactions to the Pfizer-BioNTech COVID-19 Vaccine in the HA/MCD after adjusting for placebo

Endpoint

The proportion of participants who experience a systemic allergic reaction (CoFAR Grade 2 and above regardless of tryptase, or CoFAR Grade 1 with elevated tryptase [1.2 x baseline plus 2 ng/ml]) within the 90-minute post-vaccination observation period to the first dose of the Pfizer-BioNTech COVID-19 Vaccine after adjusting for placebo administration

Model Specification

- Endpoint is as defined above.
- Endpoint will be analyzed using Barnard's unconditional exact test.

Model Checking & Diagnostics

This analysis will not be carried out if there are no systemic allergic reactions for the placebo dose.

Model Results Presentation

Proportion difference, 95% exact unconditional confidence interval and p-value will be presented for the comparison between 1st dose (active arm) and placebo dose (placebo arm)

Placebo + Pfizer-BioNTech/Placebo + Moderna COVID-19 Vaccine (placebo) vs Pfizer-BioNTech COVID-19 Vaccine (1st)

Placebo + Pfizer/Placebo + Moderna	placebo	1st	2nd
Pfizer	1st	2nd	

SAS Code

```
*** 1st dose comparison to Placebo;
proc freq data = d_l;
 title "1st dose comparison to Placebo";
 where group = 'HA/MCD' &
       ((dose = 'P1' & Placebo = 'Yes') |
        (dose = 'D1' & Placebo = 'No' ));
 tables dose*resp / riskdiff;
 exact riskdiff barnard;
run;
```

Supportive Statistical Analyses

If there is an issue with the calculation of the Barnard's Exact Unconditional Test, we will perform a univariate logistic regression. NLMeans macro will be used to obtain the proportion difference and 95% confidence interval. There will be no adjustment for covariates*** 1st 1st dose comparison to Placebo (Sensitivity);

```
proc genmod data = d_l;
 title "1st dose comparison to Placebo (Sensitivity)";
 where group = 'HA/MCD' &
       ((dose = 'P1' & Placebo = 'Yes') |
        (dose = 'D1' & Placebo = 'No' ));
 class id dose;
 model resp(event = '1') = dose / dist=binomial link = logit;
 lsmeans dose / e ilink diff exp;
 store out=genmod;
 ods output coef = coeffs;
run;
%NLMeans(instore=genmod, coef=coeffs, link=logit, title= 1st dose comparison to Placebo Prop Diff);
```

Handling of Missing Data

Participants with missing data for their placebo or 1st active dose will be removed from this analysis (complete case analysis).

Notes
The same analysis will be repeated for the Moderna COVID-19 Vaccine.

7.3.5. Secondary Endpoint 6

Endpoint: The proportion of participants who experience a systemic allergic reaction (CoFAR Grade 2 and above) within 48 hours of either dose of each vaccine.

Computation: A Grade 2 or higher systemic allergic reaction, categorized as yes or no, is defined as a participant having a Grade 2 or higher (per CoFAR Grading Scale V3.0) systemic allergic reaction within 48 hours to either active dose 1 or active dose 2 (categorized as yes) or to either active dose within 48 hours (categorized as no). Due to the nature of patient reported events, any systemic allergic reaction reported within 2 days after the date of injection will be counted as occurring within 48 hours.

Participants who do not have a systemic allergic reaction to the 1st active dose but missing data for their 2nd active dose will be removed from this analysis (complete case analysis).

Analysis: This analysis will be carried out as outlined in Section 7.2.2. A sensitivity analysis will be carried out as outlined in Section 7.2.3.

8. SAFETY EVALUATION

8.1. Overview of Safety Analysis Methods

All safety analyses will be carried out using the safety sample defined in Section 4 unless otherwise noted. Missing safety information will not be imputed. These analyses will not be stratified by site.

Listings will be prepared for all safety measurements. All listings will be sorted in order of treatment, cohort assignment (HA/MCD or Comparison), participant identifier (ID), and time of assessment (e.g., visit, time, and/or event). All displays will be presented separately for adult and child populations.

8.2. Adverse Events

All AEs will be classified by system organ class (SOC) and preferred term, according to a standardized thesaurus (Medical Dictionary for Regulatory Activities [MedDRA] version 24.0). The severity of non-allergic AEs will be classified using the FDA Guidance for Industry Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials (September 2007), and the severity of systemic allergic reactions will be graded using CoFAR Grading Scale for Systemic Allergic Reactions Version 3.0. Each AE is entered on the electronic case report form (eCRF) once at the highest severity. As such, no additional data manipulation is needed to identify events.

An overall summary table will be developed to report the number of events and the number and percentage of participants having at least one event in the following categories:

- AEs
- AEs indicated as systemic allergic reactions

- AEs that lead to study treatment discontinuation
- AEs indicated as serious
- AEs with an outcome of death
- AEs that were reported as being related to vaccine/placebo
- AEs reported by severity

In addition, AEs classified by MedDRA SOC and preferred term will be summarized for each treatment group and overall.

Summary tables will present the total number of events as well as the number and percentage of participants experiencing the events. If a participant experiences the same AE on multiple occasions, the event will be counted once for each occurrence when reporting the number of AEs. When reporting the number of participants experiencing the events, a participant will only be counted once if they experience an event within the particular SOC or preferred term. Percentages will be based on the number of participants in the safety population.

In addition, treatment-emergent AEs classified by MedDRA SOC and preferred term will be summarized for each treatment group, cohort assignment (HA/MCD or Comparison), and overall. The proportion of participants in each study arm experiencing each type of AE will be compared using a Fisher's Exact test. The frequency of treatment-emergent AEs will also be summarized by SOC and preferred term for severity (grade) and relationship to study treatment.

8.3. Deaths and Serious Adverse Events

Serious adverse events (SAEs) will be listed and summarized in the same manner described in Section 8.2. Separate displays listing and summarizing death, including time to death and cause of death, will also be created.

8.4. Clinical Laboratory Evaluation

Clinical laboratory measurements include hematology. Results will be converted to standardized units where possible. Descriptive statistics of laboratory values and the change from baseline of laboratory values will be presented for each treatment group and overall.

Laboratory data will be plotted to show patterns over time. Data will be plotted as a spaghetti plot where each participant's values will be plotted and connected by line segments, forming one line per participant. Quantile plots with treatment group means (or medians) as well as 25th and 75th percentiles plotted over time will be created.

All data mentioned above will also be summarized by those with and without allergic reactions.

8.5. Vital Signs, Physical Findings, and Other Observations Related to Safety

8.5.1. Vital Signs

Descriptive statistics of vital signs results and change from baseline of vital signs will be summarized for each treatment group and overall. Data listings sorted by treatment group, participant, vital sign parameter, and time of assessment will be provided for vital signs measurements.

8.5.2. Physical Examinations

Physical examination results of normal, abnormal, and not done will be summarized as frequencies and percentages by body system and visit. Data listings will be provided for

physical examination results and sorted by treatment group, participant, body system, and time of assessment.

9. OTHER ANALYSES

9.1. Use of Medications

Medications will be coded according to the World Health Organization (WHO) Drug Dictionary (version 2021-MAR). Medications reported on the CRF will be categorized for analysis as prior, concomitant, or after study treatment by comparing the medication start and stop dates with the first and last dose of study treatment dates. Prior medications will have both the medication start and stop dates prior to the first dose of study treatment date. After medications will have both the medication start and stop dates after the last dose of study treatment date. All other medications will be classified as concomitant, indicating that use of the medication overlapped with use of the study treatment by at least one day.

The number and percentage of participants receiving prior, concomitant, and after medications will be presented overall and by medication class. When reporting the number of participants receiving the medication, a participant will only be counted once if they ever received the medication within the medication class. Percentages will be based on the number of participants in the safety sample.

10. INTERIM ANALYSES AND DATA MONITORING

The progress of the study will be monitored by the Data and Safety Monitoring Board (DSMB). The DSMB will be chartered to review safety data and to make recommendations regarding continuation, termination, or modification of the study. The DSMB will formally review the safety data when planned milestones for randomization/first vaccination are reached (approximately every 500 participants complete their vaccination schedule). Unblinded data for the planned safety reviews will include, at a minimum, a listing of all reported AEs and SAEs by vaccine arm/placebo and population. Outcome data will show the counts, proportions (with corresponding 95% CI), and difference in proportions between the HA/MCD and comparison group within each vaccine (with corresponding 95% CI) of the primary and key secondary endpoints. Interim p-values will be available upon request. Data may be reviewed and discussed via email or by teleconference. The DSMB may recommend continuing the study, modifying the study, stopping the study, and/or announcing information while the study is still ongoing.

In addition, safety data will be reviewed by the DSMB when an event occurs that is of sufficient concern to the National Institute of Allergy and Infectious Diseases (NIAID) medical monitor or protocol chair to warrant review, or when an event occurs that could contribute to a predefined stopping rule specified in the protocol.

Findings will be reported to Institutional Review Boards (IRBs) and health authorities.

10.1. Interim Analysis of the Primary Endpoint

After fifty percent of participants have completed their vaccination schedule (approximately 1700 participants), a test of the primary analysis (see Section 7.2.2) will be conducted using a two-sided alpha level of 0.001, without adjustment of the final analysis (i.e. using a Haybittle–Peto boundary). Interim analysis results will be reviewed by the DSMB. The DSMB may recommend continuing the study, modifying the study, or stopping the study.

11. CHANGES TO THE ANALYSES PLANNED IN THE PROTOCOL

As treated sample definition was updated to reflect placebo analyses.

12. REFERENCES

1. Chan, I. S. F., and Zhang, Z. (1999). “Test-Based Exact Confidence Intervals for the Difference of Two Binomial Proportions.” Biometrics 55:1202–1209.
2. Liublinska, Victoria, and Donald B. Rubin. "Sensitivity analysis for a partially missing binary outcome in a two-arm randomized clinical trial." Statistics in Medicine 33.24 (2014): 4170-4185. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4297215/#FD7
3. SAS/STAT User's Guide. Cary, NC SAS Institute Inc. https://documentation.sas.com/?docsetId=statug&docsetTarget=titlepage.htm&docsetVersion=15.2&locale=en
4. Usage Note 46997: Estimating the risk (proportion) difference for matched pairs data with binary response https://support.sas.com/kb/46/997.html

13. APPENDICES

13.1. Study Flow Chart

See protocol Figure 1: Study Trial Design.

13.2. Schedule of Events

See protocol Appendix 3.