Statistical Analysis Plan

Study ID: 205480

Official Title of Study: A Phase 1, observer-blind, randomised, controlled, single-centre study to evaluate the safety, reactogenicity, and immune responses to an adjuvanted and non-adjuvanted conjugate vaccine against Salmonella Typhi and Salmonella Paratyphi A in healthy adults 18 to 50 years of age in Europe

NCT number: NCT05613205

Date of Document: 02-Nov-2022

STATISTICAL ANALYSIS PLAN

205480 (H02_01TP)

A PHASE 1, OBSERVER-BLIND, RANDOMISED, CONTROLLED, SINGLE-CENTRE STUDY TO EVALUATE THE SAFETY, REACTOGENICITY, AND IMMUNE RESPONSES TO AN ADJUVANTED AND NON-ADJUVANTED CONJUGATE VACCINE AGAINST *SALMONELLA* TYPHI AND SALMONELLA PARATYPHI A IN HEALTHY ADULTS 18 TO 50 YEARS OF AGE IN EUROPE

AUTHOR: PPD

VERSION NUMBER AND DATE: V1.0, 25OCT2022

STATISTICAL ANALYSIS PLAN SIGNATURE PAGE - AUTHORS

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STATISTICAL ANALYSIS PLAN SIGNATURE PAGE - APPROVAL

Upon review of this document, the undersigned approves this version of the Statistical Analysis Plan, authorizing that the content is acceptable for the reporting of this study.

	Name	Signature	Date
Approved By:	PPD		November 2, 2022
Position:	Statistician, GVGH	PPD	
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Position:			
Company:			
Approved By:			
Position:			
Company:			

MODIFICATION HISTORY

Listed below are modifications made to the SAP after the signed approval(s).

Unique Identifier for this Version	Date of the Document Version	Author	Significant Changes from Previous Authorized Version
1.0	25OCT2022	PPD	Not Applicable – First Version

TABLE OF CONTENTS

1. INTRODUCTION

This document describes the rules and conventions to be used in the presentation and analysis of safety and immunogenicity data at interim and final analyses for Protocol 205480 (H02_01TP). It describes the data to be summarized and analyzed, including specifics of the statistical analyses to be performed. This statistical analysis plan (SAP) is based on final protocol dated 23 August 2022. In scope of this analysis are all primary and secondary objectives and part of CCI [redacted]. The iSRC/SRT analyses and the remaining CCI [redacted] will be described in separate documents.

2. STUDY OBJECTIVES

2.1. PRIMARY OBJECTIVE

To evaluate the safety profile of the Vi- CRM_{197}+O:2-CRM_{197} vaccine, with and without adjuvant

2.2. SECONDARY OBJECTIVES

- To evaluate the long-term safety profile of the Vi- CRM_{197}+O:2-CRM_{197} vaccine, with and without adjuvant
- To evaluate the immunogenicity profile of the typhoid and paratyphoid A components of the Vi-CRM_{197}+O:2-CRM_{197} vaccine, with and without adjuvant, using enzyme-linked immunoassay (ELISA)
- To evaluate different seroresponse rates to the typhoid and paratyphoid A component of the Vi-CRM_{197}+O:2-CRM_{197} vaccine, with and without adjuvant

CCI [redacted]

3. STUDY DESIGN

3.1. GENERAL DESCRIPTION

This is a Phase 1 observer-blind, controlled, self-contained, randomised, single-centre, dose-escalation study with 3 steps (Step 1a, Step 1b, and Step 2). A total of 96 participants in 7 study groups, including 17 sentinel participants, are planned to be enrolled in the study.

The target will be to enroll approximately 96 eligible participants, 18 to 50 years of age, who will be randomly assigned to the different study groups, according to Step:

Step 1a: 18 adults will be assigned in a 2:1 ratio to the following study groups

- "Step 1a low dose without Alum" (approximately 12 participants)
- "Step 1a control" (approximately 6 participants)

Step 1b: 18 adults will be assigned in a 2:1 ratio to the following study groups

- "Step 1b low dose with Alum" (approximately 12 participants)
- "Step 1b control" (approximately 6 participants)

Step 2: 60 adults will be assigned in a 2:2:1 ratio to the following study groups

- "Step 2 full dose without Alum" (approximately 24 participants)
- "Step 2 full dose with Alum" (approximately 24 participants)
- "Step 2 control" (approximately 12 participants)

The investigational vaccines, Vi-CRM_{197} + O:2-CRM_{197} and ADJ+Vi-CRM_{197} + O:2- CRM_{197}, will be administered in 2 different doses depending on Step. The low dose will be administered by fractional dosing (0.1 mL) retrieved from the same 0.5 mL vial presentation as the full dose. The licensed vaccines (controls), TYPHIM VI and CCI [redacted] will be administered as per their SmPC.

Step 1a:

A "lower dose without Alum" subgroup comprised of 2 study groups (2:1 randomisation [Step 1a low dose without Alum: Step 1a control]) will receive either 2 vaccinations with the candidate low dose Vi-CRM_{197}+O:2-CRM_{197} vaccine without Alum (on Day 1 and Day 169) or 1 vaccination with the TYPHIM VI vaccine on Day 1 (as control for the first vaccination) and 1 vaccination with the CCI [redacted] vaccine on Day 169 (as control for the second vaccination).

First, 6 sentinel participants will receive, on consecutive days, either the low dose of the Vi-CRM197+O:2-CRM_{197} or the TYPHIM VI vaccine (2:1 randomisation). Each sentinel participant will be followed up with a safety phone call approximately 1 day after vaccination. If there are any safety concerns, the sentinel participant will be asked to visit the site to assess any potential SAEs or to assess

if any holding rules have been met. If no holding rules have been met nor SAEs reported by any of the sentinel participants, 12 additional participants will receive sequentially (at least 60 minutes apart) either the low dose of the Vi-CRM_{197}+O:2-CRM_{197} or the TYPHIM VI vaccine, maintaining the 2:1 randomisation.

Step 1b

A "lower dose with Alum" subgroup comprised of 2 study groups (2:1 randomisation [Step 1b low dose with Alum: Step 1b control]) will receive either 2 vaccinations with the low dose Vi-CRM_{197}+O:2-CRM_{197} vaccine with Alum (on Day 1 and Day 169) or 1 vaccination with the TYPHIM VI vaccine (as control for the first vaccination) on Day 1 and 1 vaccination with the CCI vaccine (as control for the second vaccination) on Day 169.

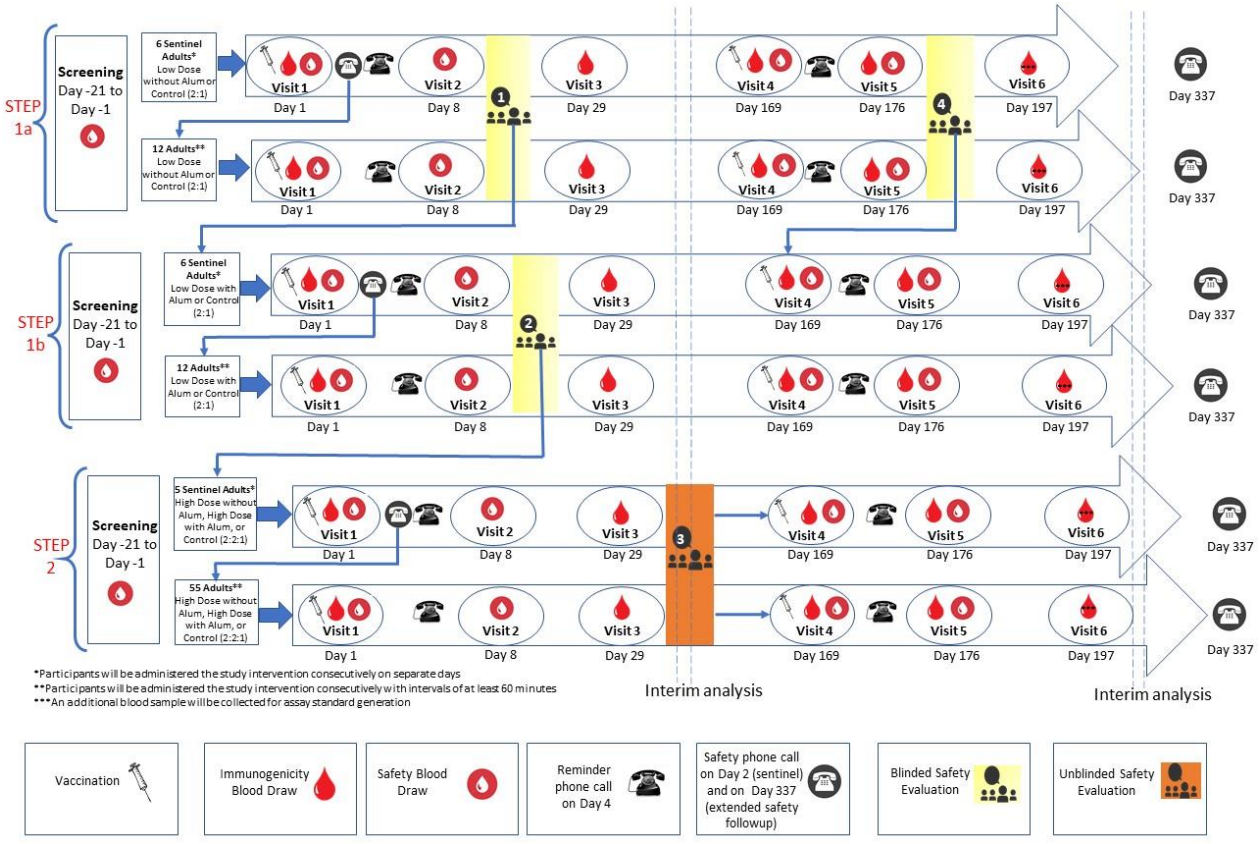
Upon approval from the iSRC/SRT (Safety evaluation #1), 6 sentinel participants will receive on consecutive days the first vaccination with either the low dose Vi- CRM_{197}+O:2-CRM_{197} vaccine with Alum or the TYPHIM VI vaccine (2:1 randomisation). Each sentinel participant will be followed up with a safety phone call approximately 1 day after vaccination. If there are any safety concerns, the sentinel participant will be asked to visit the site to assess any potential SAEs or if any holding rules have been met. If no holding rules have been met nor SAEs reported by any of the sentinel participants, a further 12 participants will receive sequentially (at least 60 minutes apart) either the low dose Vi-CRM_{197}+O:2-CRM_{197} vaccine with Alum or the TYPHIM VI vaccine and CCI vaccine, maintaining the 2:1 randomisation ratio.

Step 2:

A "full dose with and without Alum" subgroup comprised of 3 study groups (2:2:1 randomisation [Step 2 full dose without Alum: Step 2 full dose with Alum: Step 2 control]) will receive either 2 vaccinations with the full dose Vi-CRM_{197}+O:2-CRM_{197} vaccine without Alum (on Day 1 and Day 169) or the full dose Vi-CRM_{197}+O:2-CRM_{197} vaccine with Alum (on Day 1 and Day 169) or 1 vaccination with the TYPHIM VI vaccine on Day 1 (as control for the first vaccination) and 1 vaccination with the CCI vaccine on Day 169 (as control for the second vaccination).

Upon approval from the iSRC/SRT (Safety evaluation #2), 5 sentinel participants will receive on consecutive days the first vaccination with either the full dose Vi- CRM_{197}+O:2-CRM_{197} vaccine without Alum, the full dose Vi-CRM_{197}+O:2-CRM_{197} vaccine with Alum, or the TYPHIM VI vaccine (2:2:1 randomisation). Each sentinel participant will be followed up with a safety phone call approximately 1 day after vaccination. If there are any safety concerns, the sentinel participant will be asked to visit the site to assess any potential SAEs or if any holding rules have been met. If no holding rules have been met nor SAEs reported by any of the sentinel participants, a further 55 participants will receive sequentially (at least 60 minutes apart) either the full dose Vi- CRM_{197}+O:2-CRM_{197} vaccine without Alum, the full dose Vi-CRM_{197}+O:2-CRM_{197} vaccine with Alum, or the TYPHIM VI vaccine, maintaining the 2:2:1 randomisation ratio.

Figure 1 Study Schema



An internal GSK Safety Review Team (SRT) and iSRC will be involved in the safety oversight for this study.

Table 2 Intervals between study visits

Interval	Planned Visit interval	Allowed interval range
Visit 1 → Visit 2	7 days	7 days – 10 days
Visit 1 → Visit 3	28 days	28 days – 33 days
Visit 1 → Visit 4	168 days	158 days – 178 days
Visit 4 → Visit 5	7 days	7 days – 10 days
Visit 4 → Visit 6	28 days	28 days – 33 days
Visit 4 → Follow-up safety phone contact	168 days	154 days – 182 days

Table 2 Intervals between study visits under special circumstances (e.g., COVID-19 pandemic)

Interval	Planned Visit interval	Allowed interval range
Visit 1 → Visit 2	7 days	7 days – 10 days

Visit 1 → Visit 3	28 days	28 days – 38 days
Visit 1 → Visit 4	168 days	154 days – 182 days
Visit 4 → Visit 5	7 days	7 days – 10 days
Visit 4 → Visit 6	28 days	28 days – 38 days
Visit 4 → Follow-up safety phone contact	168 days	154 days – 182 days

3.2. SCHEDULE OF EVENTS

Schedule of activities can be found in Section 1.3, Table 1 of the protocol.

3.3. CHANGES TO ANALYSIS FROM PROTOCOL

There are no changes to analysis from the protocol.

4. PLANNED ANALYSES

4.1. INTERNAL SAFETY REVIEW COMMITTEE (iSRC)

This study will be overseen by an iSRC operating under a charter. Please refer to iSRC charter for details.

4.2. SAFETY REVIEW TEAM (SRT)

Instream blinded monitoring will also be performed by the internal GSK Safety Review Team (SRT). Refer the iSRC charter for details.

4.3. INTERIM ANALYSES

A group-unblinded 1st interim analysis on safety and immunogenicity data collected from all participants until 28 days after the first vaccination in Step 2 (Visit 3, Day 29) will be performed by the unblinded biostatistics team at IQVIA (independent data analysis centre [IDAC]). No individual listings will be generated. Results will not impact the continuation of the study itself but will inform further development of the candidate vaccine in other studies.

After unblinding of the Sponsor personnel (partial observer-blind), a 2nd interim analysis on all data up to and including Day 197 (Visit 6) in Step 2 will be performed and individual listings will be generated. At this point, the entire study team will be unblinded.

All analyses are descriptive and with the aim to characterize the safety and immunogenicity data and therefore no statistical adjustment for interim analyses is required.

Derivations and definitions for the interim analyses will be based on those required for the final analysis contained in this analysis plan, unless deviations are stated within the text.

All tables presenting summary statistics planned for final analysis will be generated at the time of interim analyses, only for the primary cohort (exposed set for safety and per protocol set/full analysis set for immunogenicity analyses). No unblinded individual participant listings and listing tables will be generated at the time of 1st interim analysis. Unblinded individual participant listings and listing tables will be generated for the 2nd interim analysis.

CCI

[redacted]

4.4. FINAL ANALYSIS

Final, planned analysis identified in this SAP will be performed by IQVIA Biostatistics following sponsor authorization of this Statistical Analysis Plan, database lock, and unblinding of treatment.

A final analysis will be performed including all data collected including the extended safety follow-up period up to Day 337 in Step 2.

A final CSR will be produced after Day 337 in Step 2.

5. ANALYSIS SETS

5.1. ENROLLED SET

Participants who provided informed consent and were randomized or received study intervention or underwent a post-screening procedure. The allocation in a group is based on the planned intervention, i.e. 'as randomized'.

Note: participants who never passed screening even if rescreened (screening failures) and participants screened but never enrolled into the study (met eligibility but not needed for the study) are excluded from the Enrolled analysis set.

5.2. EXPOSED SET (ES)

All participants who received at least 1 dose of the study intervention. The allocation in a group is based on the administered intervention.

5.2.1. UNSOLICITED SAFETY SET

All participants who received at least 1 dose of the study intervention (ES) that report unsolicited adverse events (AEs)/report not having unsolicited AEs. The allocation in a group is based on the administered intervention.

Note: Participants will be considered to have reported no unsolicited AEs if they are enrolled in the study up to 28 days after vaccination without providing AEs.

5.2.2. SOLICITED SAFETY SET

All participants who received at least 1 dose of the study intervention (ES) who have solicited safety data for that intervention. The allocation in a group is based on the administered intervention.

5.3. FULL ANALYSIS SET (FAS)

All participants who received at least 1 dose of the study intervention and have post-dose immunogenicity data. The allocation in a group is based on the randomized intervention. The FAS for immunogenicity will be defined by time point.

The Full Analysis Set will be used as second-line analysis for secondary CCI endpoints if the percentage of vaccinated participants (in any study group at any time point) with serological results excluded from the Per-protocol Set for analysis of immunogenicity is 10% or more.

5.4. PER-PROTOCOL SET (PPS)

All eligible participants who received each dose as per-protocol, had immunogenicity results post-dose, complied with dosing/blood draw intervals, without intercurrent conditions that may interfere with immunogenicity, without prohibited concomitant medication/vaccination and without protocol deviation leading to exclusion (Section 11.2). The PPS for immunogenicity will be defined by time point.

The protocol deviations leading to exclusion of the participants are described in Section 11.2. Four Per-protocol Sets for analysis of immunogenicity will be derived:

5.4.1. PER-PROTOCOL SET FOR ANALYSIS OF IMMUNOGENICITY AT DAY 29

The analysis set will contain all participants included in the Per-protocol Set, with no protocol deviations leading to exclusion until Day 29 and with at least 1 valid immunogenicity data available at Day 29.

5.4.2. PER-PROTOCOL SET FOR ANALYSIS OF IMMUNOGENICITY AT DAY 169

The analysis set will contain all participants included in the Per-protocol Set, with at least 1 immunogenicity data available at Day 169 without any protocol deviations that could lead to exclusion.

5.4.3. PER-PROTOCOL SET FOR ANALYSIS OF IMMUNOGENICITY AT DAY 176

The analysis set will contain all participants included in the Per-protocol Set, with at least 1 immunogenicity data available at Day 176 without any protocol deviations that could lead to exclusion.

5.4.4. PER-PROTOCOL SET FOR ANALYSIS OF IMMUNOGENICITY AT DAY 197

The analysis set will contain all participants included in the Per-protocol Set with at least 1 immunogenicity data available at Day 197 without any protocol deviations that could lead to exclusion.

Analysis	Enrolled Set	Exposed Set	Un-solicited Safety Set	Solicited Safety Set	Full Analysis Set*	Per-protocol (PP) Set			
						PP Set Day 29	PP Set Day 169	PP Set Day 176	PP Set Day 197
Participant Disposition	✓								
Baseline Assessments		✓							
Concomitant Medications		✓							
Exposure		✓							
Immunogenicity Analysis					✓	✓	✓	✓	✓
Protocol Deviations		✓							
Solicited Adverse Events				✓					
Unsolicited Adverse Events			✓						
Solicited and Unsolicited Adverse Events		✓							
Other Safety (lab, vitals)		✓							

* Analysis in this set will be performed if the percentage of vaccinated participants with serological results excluded from the Per-protocol Set for analysis of immunogenicity is 10% or more

6. GENERAL CONSIDERATIONS

The safety summaries, data listings and figures as well as the statistical analysis of the variables will be the responsibility of the study biostatistician at IQVIA.

6.1. SUMMARY STATISTICS

For qualitative variables, the population size (N for sample size and n for available data) and the percentage (of available data) for each class of the variable will be presented. Quantitative variables will be summarized using descriptive statistics, including N (with data available), mean, standard deviation (SD), coefficient of variation (CV%), median, Q1, Q3, minimum, and/or maximum values. Geometric mean will be included for immunogenicity parameters, where applicable. Coefficient of variation will not be presented for change from baseline results.

The exact two-sided 95% CIs for a proportion within a group will be calculated using the Clopper-Pearson exact method.

The geometric mean antibody concentrations (GMCs) and CCI calculations will be performed by taking the anti-log of the mean of the log10 titer transformations. Confidence interval for geometric means will be derived by raising 10 to the confidence interval associated with mean of log10 values i.e., CI of geometric mean = 10^(CI for the mean of log10 values). All participants with valid data will be considered. Participants whose antibody titers are below the cut-off of the assay will be given an arbitrary value of half the cut-off for the purpose of GMC/CCI calculation.

6.2. TREATMENT SUMMARIZATION

In general, data will be presented for each study group:

Step	Study Groups
1a	Low dose without Alum
	Control
1b	Low dose with Alum
	Control
2	Full Dose without Alum
	Full Dose with Alum
	Control

Data for all steps and all study participants combined will also be presented when appropriate (disposition and demographic summaries). Control subjects from Steps 1a, 1b and 2 may be pooled together if needed.

6.3. PRECISION

Safety data (vital signs, laboratory parameters) and immunogenicity data will be reported to the same precision as the source data.

For the reporting of descriptive statistics, the mean, median, Q1, Q3, standard deviation, standard error and confidence intervals will be presented to one digit more precision than the source data. The minimum and maximum will be presented to the same precision as the source data. Coefficient of variation (%) will always be reported to 1 decimal place. P-values, if any, shall be reported to four decimal places or as <0.0001.

The number of decimals used when displaying geometric mean concentrations (GMC)/CCI and their confidence limits is shown in the following table:

GMC/CCI value	Number of decimals to display
<0.1	3
>=0.1 and <10	2
>=10 and <1000	1
>=1000	0

When multiple categories of CCI /GMC values are present in the same table, the number of decimals displayed should match that of the smallest category (i.e., the one with the higher number of decimals). GMR (geometric mean ratios) or CCI /GMC ratios and their confidence limits will be displayed with 2 decimals regardless of the actual values.

6.4. REFERENCE START DATE AND STUDY DAY

Study Day will be calculated from the reference start date and will be used to show start/stop day of assessments and events.

Reference start date is defined as the day of the first dose of study vaccination, (Day 1 is the day of the first dose of study treatment) and will appear in every listing where an assessment date or event date appears.

- If the date of the event is on or after the reference date, then:

Study Day = (date of event – reference date) + 1.

- If the date of the event is prior to the reference date, then:

Study Day = (date of event – reference date).

In the situation where the event date is partial or missing, Study Day, and any corresponding durations will appear partial or missing in the listings. Refer to Section 7.1.1 for rules applicable on partially completed dates when used in calculations.

6.4.1. ATTRIBUTING EVENTS TO VACCINE DOSES

The dose relative to an event is the most recent study dose given to a participant prior to the start of a given event. For example, if the start date of an adverse event is between Dose 1 and Dose 2, the relative dose will be Dose 1.

If an event starts on the same day as a study dose, the relative dose will be derived from the additional information provided in the CRF using the contents of the flag indicating if the event occurred before or after vaccination. If 'after vaccination' is selected or if the selection is missing, the relative dose for the event will be the one administered on the start day of the event. If 'before vaccination' is selected, the relative dose for the event will be the dose prior to this one. Where applicable, the event will be classified as "pre-treatment".

6.5. BASELINE

Baseline is defined as:

- Day 1 pre-dose for seroresponse calculation (4-fold for Anti-O:2 IgG and ≥4.3 µg/mL for Anti-Vi Ag IgG antibody concentrations)
- Day 1 and each vaccination pre-dose for immunogenicity within-participant GMR
- Each vaccination pre-dose for hematology, biochemistry and vital signs assessments.

However, if a participant is missing the planned individual vaccination pre-dose result, change from baseline will not be calculated for within-participant GMR, hematology and biochemistry. For hematology and biochemistry, screening value can be used as Day 1 predose if the value at said timepoint is missing.

6.6. COMMON CALCULATIONS

For quantitative safety measurements (e.g. vital signs, laboratory parameters), change from baseline will be calculated as:

- Observed Value (after baseline) – Baseline Value

For immunogenicity measurements, fold change from baseline will be calculated as:

- Test Value (after baseline)/Baseline Value

6.7. SOFTWARE VERSIONS

All derivations, statistical analyses, summaries, graphs and listings will be generated using SAS version 9.4 or higher (SAS Institute, Inc., Cary, North Carolina).

7. STATISTICAL CONSIDERATIONS

7.1. MISSING DATA

Missing immunogenicity data will be handled as described in Section 15. Following imputation will be used for statistical calculations (and not for participant listings):

7.1.1. DATES

When partially completed birth dates (i.e., with missing day or month) are used in calculations, the following standard rules will be applied:

- A missing day will be replaced by 15
- A missing day and month will be replaced by June 30th

The following exceptions apply:

- Adverse events start dates with missing day:
  - If the event starts in the same month as at least one of the study doses, the contents of AE.AESTRTPT (the flag indicating if the event occurred before or after vaccination) will be used to complete the date. If 'after vaccination' is selected or if the selection is missing, the imputed start date will match the first (or only) study dose given during that month. If 'before vaccination' is selected, the imputed date will be one day before the only study dose given during that month.
- Adverse events start dates with missing day and month:
  - If the event starts in the same year as at least one of the study doses, the contents of AE.AESTRTPT (the flag indicating if the event occurred before or after vaccination) will be used to complete the date. If 'after vaccination' is selected, the imputed start date will match the first (or only) study dose given during that year. If 'before vaccination' is selected, the imputed date will be one day before the first (or only) study dose given during that year.

All other cases of incomplete AE or concomitant medication/vaccination start date will follow the standard rules as outlined in Section 6.4.

7.1.2. LABORATORY DATA

Missing laboratory results will not be replaced. Safety laboratory tests will be graded using Appendix 9 of the study protocol.

7.1.3. ADVERSE EVENTS

Solicited Adverse Events:

Daily recording of solicited adverse events: for diary cards indicating the presence or absence of solicited adverse events, for studies using paper diaries which have questions in the CRF indicating the presence or absence of solicited events the following rules are applicable:

- Denominators for the summary of administration site (or systemic) solicited adverse events will be calculated using the number of participants who respond “Yes” or “No” to the question concerning the occurrence of administration site (or systemic) adverse events.

- When a specific solicited adverse event is marked as having not occurred following a specific vaccination (i.e., SDTM FA.FAOCCUR=N for the specified post-vaccination period for the adverse event in question), all daily measurements will be imputed as Grade 0.

- When a specific solicited adverse event is marked as having occurred following a specific vaccination (i.e., SDTM FA.FAOCCUR=Y for the specified post-vaccination period for the adverse event in question), any missing daily recordings will be given imputed values to allow them to contribute to the ‘Any’ rows but not to specific grade rows of the solicited adverse event summary tables.

- When the occurrence of a specific solicited adverse event is not present (i.e. SDTM FA.FAOCCUR is neither Y nor N for the specified post-vaccination period for the symptom in question) but the group of solicited adverse events (administration site or systemic) is marked as having occurred (i.e. SDTM FA.FAOCCUR=Y), all missing daily recordings will be given imputed values to allow them to contribute to the ‘Any’ rows but not to specific grade rows of the solicited adverse event summary tables.

The following table shows how participants contribute to each category for a specific solicited adverse event over the Day X to Day Y post-vaccination period:

Solicited adverse event category	Participants included in the calculation of the numerator
Any	All participants with at least one occurrence of the adverse event at grade 1, grade 2, or grade 3 between Day X and Day Y or with the adverse event marked as present and at least one missing daily recording between Day X and Day Y
Grade 1	All participants with at least one occurrence of the adverse event at grade 1, between Day X and Day Y
Grade 2	All participants with at least one occurrence of the adverse event at grade 2 between Day X and Day Y
Grade 3	All participants with at least one occurrence of the adverse event at grade 3 between Day X and Day Y

Unsolicited adverse events

Unsolicited adverse event summaries are including serious adverse events unless specified otherwise. Missing severity, relationship with study vaccine, and outcome of unsolicited adverse events will not be replaced and will appear as 'UNKNOWN' in all statistical listings.

7.2. DATA DERIVATION

7.2.1. BODY MASS INDEX

BMI (kg/m^2) = weight (kg)/height (m^2)

7.2.2. AGE AT VACCINATION IN YEARS

When age at vaccination is to be displayed in years, it will be calculated as the number of complete calendar years between the 15MMMYYYY and the date of vaccination, divided by 365.25. Date of birth is collected only by means of month and year of birth in the database, therefore, by rules defined in Section 7.1.1, 15th day of month is substituted for the day. For example:

DOB = 15SEP1983, Date of vaccination = 14SEP2018 -> Age = 34.998 years

DOB = 15SEP1983, Date of vaccination = 15SEP2018 -> Age = 35.001 years

7.2.3. ONSET DAY

The onset day for an event (e.g., AE, medication, vaccination) is the number of days between the last study vaccination and the start date of the event. This is 1 for an event occurring on the same day as a vaccination (and reported as starting after vaccination).

7.2.4. DURATION OF EVENTS

The duration of an event with a start and end date will be the number of days between the start and end dates plus one day, i.e., an event that starts on 03MAR2018 and ends on 12MAR2018 has a duration of 10 days.

The duration of solicited events will be calculated as the difference between the dates when the first and last symptom reported at grade 1 or higher were observed plus one day (also including days after Day 7 if event is still ongoing).

7.2.5. COUNTING RULES FOR COMBINING SOLICITED AND UNSOLICITED ADVERSE EVENTS

For output combining solicited and unsolicited adverse events, all serious adverse events will be considered systemic events since the administration site flag is not included in the expedited adverse event CRF pages.

Multiple events with the same preferred term which start on the same day are counted as only one occurrence.

7.2.6. COUNTING RULES FOR OCCURRENCES OF SOLICITED ADVERSE EVENTS

When the occurrences of solicited adverse events are summarized, each event recorded as having occurred during a specific period will be counted as only one occurrence regardless of the number of days on which it occurs.

For a given participant and the analysis of solicited symptoms within 7 days post-vaccination, missing or non-evaluable measurements will not be replaced. Therefore, the analysis of the solicited adverse events will include only vaccinated participants for doses with documented safety data (i.e., diary card completed). A diary card is considered complete when it has data recorded for all 7 days post vaccination. More specifically the following rules will be used:

- Participants who documented the absence of a solicited symptom after one dose will be considered not having that symptom after that dose.
- Participants who documented the presence of a solicited symptom and fully or partially recorded daily measurement over the solicited period will be included in the summaries at that dose and classified according to their maximum observed daily recording over the solicited period.
- Participants who documented the presence of a solicited symptom after one dose without having recorded any daily measurement will be assigned the value ‘UNKNOWN’.
- Doses without diary cards documented will be excluded.

7.2.7. GEOMETRIC MEAN CONCENTRATIONS (GMCs)/CCI [redacted]

Geometric Mean Concentration (GMC)/CCI [redacted] calculations are performed by taking the inverse logarithm of the mean of the log CCI [redacted] transformations. CCI [redacted]. The cut-off value will be defined by the laboratory before the analysis.

8. OUTPUT PRESENTATIONS

The templates provided with this SAP describe the presentations for this study and therefore the format and content of the summary tables, figures and listings to be provided by IQVIA Biostatistics.

Some minor modifications may be necessary to the planned design of tables, figures, and listings to accommodate data collected during the actual study conduct.

9. DISPOSITION AND WITHDRAWALS

All participants who provide informed consent and were randomized or received study intervention or underwent a post-screening procedure will be accounted for in this study. Participant disposition will be tabulated for each step, each study treatment, and for all participants combined per step and overall (using the Enrolled Set) with the number of participants who did not meet eligibility criteria, randomly assigned to treatment, completed Day 29, complete Day 169, completed Day 197, complete Day 337, complete the study, prematurely discontinue, and the reason for early discontinuation. A listing will present dates of completion or early withdrawal and the reason for early discontinuation, if applicable, for each participant.

Listings of treatment discontinuation, participant visits, inclusion/exclusion criteria responses, study protocol deviations, treatment randomization and study treatment administration will be provided.

A listing of participants whose trial participation was impacted by COVID-19 will be presented along with the description of the impact.

Number of participants who discontinued study drug or study due to COVID-19 infection or issues related to the COVID-19 pandemic will be summarized for each study treatment, each step and for all participants combined.

10. DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

Individual participant demographics and baseline characteristics (medical history and results from viral serology, and urine pregnancy tests) will be presented in listings.

Demographic characteristics such as age, sex, race, height, weight, and body mass index (BMI) will be

summarized and tabulated for each treatment, each step and for all participants overall. Descriptive statistics (mean, median and standard deviation) will be presented for age, height, weight, and BMI. Frequency counts and percentages will be presented for sex, race, and step.

No statistical testing will be carried out for demographic or other baseline characteristics.

11. PROTOCOL DEVIATIONS

11.1. DEVIATIONS RELATED TO STUDY CONDUCT

A deviation from a protocol occurs when Investigator site staff or a study participant does not adhere to the Protocol's stipulated requirements, whether inadvertently or planned. Protocol deviations will be listed and will include a classification of minor or major, as determined by clinical staff.

Important protocol deviations will be reviewed by the study team to identify deviations which have the potential to affect the immunogenicity results.

11.2. DEVIATIONS RELATED TO IMMUNOGENICITY ANALYSIS

Changes to the procedures or events, which may impact the quality of the immunogenicity data, will be considered important protocol deviations and will be described within the clinical study report. These changes or events will include any circumstances that will alter the evaluation of the immunogenicity results. Examples include, but may not be limited to, sample processing errors that lead to inaccurate immunogenicity results, and/or inaccurate dosing.

Participants may be eliminated from the per-protocol set for analysis of immunogenicity if, during the study, they incur a condition that has the capability of altering their immune response or are confirmed to have an alteration of their initial immune status. Participants may also be eliminated from the per-protocol set as described in Section 7.2 and Section 9.3 of the protocol. Such scenarios will be discussed by the study team and decision to exclude a participant and/or data from the Per-protocol analysis set (Day 29, Day 169, Day 176 and Day 197) will be taken on a case-by-case basis.

Other deviations (not a comprehensive list) leading to elimination from the per-protocol set are:

- Invalid informed consent
- Fraudulent data
- randomization code broken
- dose volume insufficient
- vaccination not according to protocol
- vaccine dose storage conditions (temperature deviation)

- vaccine administered out of expiry date
- violation of inclusion/exclusion criteria

interval between doses

- two doses not in the same treatment group
- concomitant infection related to study vaccine or not related to study vaccine that may alter the immune response
- serology result at post vaccination not available for all assays (blood sample not available or result not available)

Protocol Deviation Management Plan (PDMP) describes the complete list of elimination codes that could lead to exclusion from the per-protocol set.

12. MEDICAL HISTORY

Medical History coded using MedDRA Version 25.0 will be listed for the exposed set.

13. MEDICATIONS

Medication usage coded using the WHO Drug Dictionary Version GlobalC3Mar22 will be listed for the exposed set.

'Prior' medications are medications which started and stopped prior to the first dose of study treatment.

'Concomitant' medications are medications which were taken during the treatment period, or specifically:

- started after the first dose of study treatment or
- started prior to the first dose of study medication and were continued after the first dose of study treatment

The percentage of participants using concomitant medications (any medication, any antipyretic and any antipyretic taken prophylactically, respectively) during the 7-day follow-up period and during the 28-day follow-up period will be summarized by group after each vaccination and overall.

14. STUDY MEDICATION EXPOSURE

Exposure to study treatment as the number of doses administered will be presented for each treatment, each step and all participants overall.

15. IMMUNOGENICITY ANALYSIS

The immunogenicity analysis will be based on the Per-protocol Set for analysis of immunogenicity. If, in any study group at any time point, the percentage of vaccinated participants with serological results excluded from the Per-protocol Set for analysis of immunogenicity is 10% or more, a second-line analysis based on the Full Analysis Set will be performed.

Numerical serology results will be derived from the content of IS.ISORRES in the SDTM dataset. For assays with a specific cut-off, the following derivation rules apply:

IS.ISORRES	Derived value
"NEG", "-", or "(-)"	cut-off/2
"POS", "+", or "(+)"	cut-off
"< value" and value is <= assay cut-off	cut-off/2
"< value" and value is > assay cut-off	value
"> value" and value is < assay cut-off	cut-off/2
"> value" and value is >= assay cut-off	value
"value" and value is < cut-off	cut-off/2
"value" and value is >= cut-off	value
All other cases	missing

The following derivation rules will apply in the context of LLOQ values:

- If baseline value is below LLOQ
  - 4-fold is defined as 4 times the LLOQ cut-off value
  - GMR is defined as within-participant GMR against LLOQ/2
- If baseline value is above or equal to LLOQ
  - 4-fold is defined as 4 times the baseline value
  - within-participant GMR is defined as within-participant GMR against the baseline value.

The following immunogenicity variables will be assessed:

Blood sampling timepoint		No. participants	Component
Type of contact and	Sampling timepoint		
Visit 1 (Day 1)	Pre-1st vaccination	96	Anti-Vi antigen IgG (ELISA) Anti-O:2 IgG (ELISA) CCI [redacted]
Visit 3 (Day 29)	Post-1st vaccination	96	Anti-Vi antigen IgG (ELISA) Anti-O:2 IgG(ELISA) CCI [redacted]
Visit 4 (Day 169)	Pre-2nd vaccination	96	Anti-Vi antigen IgG (ELISA) Anti-O:2 IgG (ELISA) CCI [redacted]
Visit 5 (Day 176)	Post-2nd vaccination 1	96	Anti-Vi antigen IgG (ELISA) Anti-O:2 IgG (ELISA) CCI [redacted]
Visit 6 (Day 197)	Post-2nd vaccination 2	96	Anti-Vi antigen IgG (ELISA) Anti-O:2 IgG (ELISA) CCI [redacted]

A listing of collection dates and times for the immunogenicity variables will be presented for participants within each treatment group. For each component, the concentration/CCI [redacted] will be listed and summarized by treatment groups across all scheduled timepoints during entire study for each step.

For each study group, each step, at each timepoint that blood samples are collected for humoral immune response and for each component as measured by ELISA CCI [redacted]:

- Geometric mean concentrations/CCI [redacted] and their 95% CI at each timepoint will be calculated
- Within-subject Geometric mean ratio for Day 29 versus Day 1, Day 169 versus Day 1, Day 176 versus Day 1, Day 197 versus Day 1, Day 176 versus Day 169 and Day 197 versus Day 169 with their 95% CI will be tabulated
- Percentage of participants with >=4 fold-increase in Anti-O:2 IgG antibody concentrations at, Day 29, Day 169, Day 176, and Day 197 compared to Day 1 baseline with their exact 95% CI will be calculated

For each study group, at each step, at each timepoint that blood samples are collected for humoral immune response and for each component as measured by ELISA

- The number and percentage of participants with Anti-Vi Ag IgG antibody concentrations ≥4.3 µg/mL* and their 95% exact CI at each timepoint will be calculated

- The number and percentage of participants with Anti-Vi Ag IgG antibody concentrations ≥2.0 µg/mL* and their 95% exact CI at each timepoint will be calculated

For step 2, at each timepoint that blood samples are collected for humoral immune response and for each component as measured by ELISA CCI as applicable:

- Unadjusted between-group ratio of GMC with 95% CI between full dose with Alum vs full dose without Alum will be computed for each component specific IgG, visit, and administration
- Adjusted between-group ratio of GMC with 95% CI between full dose with Alum vs full dose without alum will be computed for each specific IgG, visit, and administration

The above tabulations may be performed by LLOQ status at baseline (above or equal to cut-off versus below the cut-off) for all 2 components, data permitting [if at least 6 participants are available in these sub-group and in at least one active arm].

Only for Anti-Vi antigen IgG antibody component the above tabulations may be performed by Anti-Vi antigen IgG antibody concentrations status at baseline as measured by ELISA (>=4.3 µg/mL* and <4.3 µg/mL*, >=2.0 µg/mL* and <2.0 µg/mL*), data permitting [if at least 6 participants are available in these sub-group and in at least one active arm].

Linear mixed model with repeated measures (MMRM) will be used to perform pairwise comparison between full dose with Alum and full dose without Alum at Day 29, Day 169, Day 176 and Day 197. The model will use fixed effects for treatment, time point, treatment*time point and baseline immunogenicity value as covariate, and a repeated time point effect within a participant under an unstructured covariance matrix. Variance between the groups will not be considered equal unless the assumption leads to convergence issues. Additional covariance structures and suitable transformation (e.g., log) may be explored to attain convergence and meet model assumptions, respectively.

```
proc mixed data=indsn;
by parameter;
class subjid trta avisit;
model aval= trta avisit trta*avisit baseline/ddfm=satterth;
repeated avisit/subject=subjid type=un group=trta;
lsmeans trta*avisitn/pdiff cl alpha=0.05;
run;
```

* The IgG against Vi antigen will be determined using ELISA and the results will be presented in EU/mL unit, which may be further converted to µg/mL, based on correlation with concentration of the standard calibrated against the international standard/another standard already calibrated.

CCI

16. SAFETY OUTCOMES

There will be no statistical comparisons between the treatment groups for safety data, unless otherwise specified with the relevant section.

16.1. ADVERSE EVENTS

The analysis of solicited adverse event will be performed in the Solicited Safety Set. The percentage of participants with at least 1 administration site AE (solicited and unsolicited), with at least 1 systemic AE (solicited and unsolicited) and with any AE during the 7-day or the 28-day follow-up period, for each step, will be tabulated with exact 95% CI after each vaccination and overall. The same calculations will be performed for symptoms rated as grade 3 (severe). This combined analysis of solicited and unsolicited AEs will be performed on the Exposed Set as requested for public disclosure. Solicited events and unsolicited AEs will be coded by MedDRA.

The percentage of doses followed by at least 1 administration site AE and by at least 1 systemic AE will be tabulated, overall vaccination course, with exact 95% CI. The same computations will be done for Grade 3 AEs, any AEs considered related to vaccination, any Grade 3 AEs considered related to vaccination and any AEs resulting in a medically attended visit.

The percentage of participants/doses reporting each individual solicited administration site and systemic AE during the 7-day follow-up period will be tabulated with exact 95% CI as follows:

- Over the 2 doses, the percentage of participants with the symptom and its exact 95% CI.
- Over the 2 doses, the percentage of doses with the symptom and its exact 95% CI.
- At each study dose (visit), the percentage of participants with the symptom and its exact 95% CI.

Percentage of participants with at least one fever event will be reported per grade (as per protocol scale) and per 0.5°C cumulative increments as from ≥38°C to >=40°C

Solicited events ongoing after the observation period reported by maximum intensity will be left out of summary tables and only reported in solicited AE listings. Any solicited event with onset day greater than solicited period (i.e., 7 days) will be reported as unsolicited AE and will be included in unsolicited summary tables and listings.

The analysis of unsolicited adverse event will be performed in the Unsolicited Safety Set. The verbatim reports of unsolicited symptoms will be reviewed by a physician and the signs and symptoms will be coded per the Medical Dictionary for Regulatory Activities (MedDRA), Version 25.0. Every verbatim term will be matched with the appropriate preferred term (PT). The percentage of participants with unsolicited AEs within 28 days after any doses with its exact 95% CI will be tabulated by group, step and by MedDRA preferred term. Similar tabulation will be done for Grade 3 unsolicited AEs, for unsolicited AEs that resulted in a medically attended visit, for Grade 3 and causally related unsolicited

AEs and for unsolicited AEs causally related to vaccination. These tabulations will include System Organ Class (SOC) and SOC/PT analyses.

The number of participants who experienced at least 1 SAE after any dose, from dose 1 until 28 days post second dose (Day 197) and from Day 198 until Day 337 will be reported by treatment.

The following summaries for COVID-19 infections will be presented:

- Number of participants with an AE of suspected, probable or confirmed assessment of COVID-19 infection
- Number of participants who had a COVID-19 diagnosis test performed and the number of participants with positive, negative or indeterminate results
- Incidence of COVID-19 as AEs and SAEs

16.1.1. Adverse Events Leading to Discontinuation from Study or from Treatment

Adverse events leading to permanent discontinuation from study and leading to discontinuation of study vaccine but continued further study procedures (safety or immunogenicity) will be identified by using the variable pertaining to outcome the Adverse Events page of the (e)CRF, and listed, separately. AEs leading to discontinuation from treatment will be listed.

16.1.2. Serious Adverse Events

Serious adverse events (SAEs) are those events recorded as “Serious” on the Adverse Events page of the (e)CRF, and will be listed.

16.1.3. Derivation

Adverse Event	Intensity grade	Parameter
Redness/swelling at administration site (greatest surface diameter in mm)	0	<25 mm.
	1 (Mild)	≥25 to ≤50 mm.
	2 (Moderate)	>50 to ≤100 mm.
	3 (Severe)	>100 mm.
Temperature[a]	0	<38.0°C.
	1 (Mild)	≥38.0°C to <38.5°C.
	2 (Moderate)	≥38.5°C to <39.0°C.

	3 (Severe)	≥39.0°C.

[a]Fever is defined as temperature ≥38.0°C/100.4°F

Grading of other solicited events not requiring derivation can be found in Table 20, Appendix 3 of the protocol.

16.2. SAFETY LABORATORY EVALUATIONS

Laboratory results will be included in the reporting of this study for Hematology and Biochemistry. A list of laboratory assessments to be included in the outputs is included in Appendix 9 of the protocol.

For each group and for each haematology and biochemistry parameter:

- The percentage of participants having hematology and biochemistry results below or above the local laboratory reference ranges versus baseline will be tabulated by treatment, timepoint and step.
- The percentage of participants with hematology and biochemistry results by grade versus baseline (visit 1 for first vaccination, Visit 4 for second vaccination) will be tabulated by treatment, timepoint and step.

16.2.1. GRADING FOR LABORATORY DATA

Grades will be based on local laboratory reference ranges and derived from Food and Drug Administration [FDA] Guidance to Industry "Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials", according to appendix 9 of the study protocol. Laboratory parameters not included in the FDA grading scale will not be graded and their assessment will be based on laboratory normal ranges and medical judgement.

16.3. VITAL SIGNS

The following Vital Signs measurements will be reported for this study:

- Resting systolic and diastolic blood Pressure (mmHg)
- Pulse rate (bpm)
- Respiratory rate (breaths per minute)
- Temperature (°C)

The following summary will be provided for vital signs data:

- Descriptive stats for observed values

17. DATA NOT SUMMARIZED OR PRESENTED

The other variables not summarized or presented are:

- Comments

These variables will not be summarized or presented, but will be available in the clinical study database, SDTM and/or ADaM datasets.

18. REFERENCES

Clopper CJ, Pearson ES. The use of confidence or fiducial limits illustrated in the case of binomial. Biometrika. 1934;26:404-413

U.S. Department of Health and Human Services. Guidance for Industry-Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials 2007. Accessed 1 August 2022. https://www.fda.gov/media/73679/download

DocuSign

Certificate Of Completion

Envelope Id: PPD
Status: Completed
Subject: Complete with DocuSign: GSK205480_H02_01TP_SAP_FS_Ver 1.0.docx
Project Code (Enter 0 for non-billable projects): HAB61752
IQVIA ID (Login ID): PPD
Business Unit:
DSSR
Source Envelope:
Document Pages: 33
Signatures: 2
Envelope Originator:
Certificate Pages: 5
Initials: 0
PPD
AutoNav: Enabled
EnvelopeId Stamping: Disabled
Time Zone: (UTC-05:00) Eastern Time (US & Canada)
IP Address: PPD

Record Tracking

Status: Original
01-Nov-2022 | 18:50
Holder: PPD
PPD
Location: DocuSign

Signer Events	Signature	Timestamp
PPD Sr Biostatistician IQVIA Security Level: Email, Account Authentication (Required)	PPD Signature Adoption: Pre-selected Style Signature ID: PPD Using IP Address: PPD With Signing Authentication via DocuSign password With Signing Reasons (on each tab): I am the author of this document	Sent: 01-Nov-2022 | 18:56 Viewed: 02-Nov-2022 | 08:35 Signed: 02-Nov-2022 | 08:36
Electronic Record and Signature Disclosure: Not Offered via DocuSign		
PPD Security Level: Email, Account Authentication (Required)	PPD Signature Adoption: Pre-selected Style Signature ID: PPD Using IP Address: PPD With Signing Authentication via DocuSign password With Signing Reasons (on each tab): I approve this document	Sent: 01-Nov-2022 | 18:56 Viewed: 02-Nov-2022 | 05:22 Signed: 02-Nov-2022 | 05:26
Electronic Record and Signature Disclosure: Accepted: 25-Oct-2022 | 08:40 ID: PPD		

In Person Signer Events	Signature	Timestamp

Editor Delivery Events	Status	Timestamp

Agent Delivery Events	Status	Timestamp

Intermediary Delivery Events	Status	Timestamp

Certified Delivery Events	Status	Timestamp

Carbon Copy Events	Status	Timestamp

Witness Events	Signature	Timestamp

Notary Events	Signature	Timestamp

Envelope Summary Events	Status	Timestamps
Envelope Sent	Hashed/Encrypted	01-Nov-2022 | 18:56
Certified Delivered	Security Checked	02-Nov-2022 | 05:22
Signing Complete	Security Checked	02-Nov-2022 | 05:26
Completed	Security Checked	02-Nov-2022 | 08:36

Payment Events	Status	Timestamps

Electronic Record and Signature Disclosure

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Required hardware and software

Operating Systems:	Windows® 2000, Windows® XP, Windows Vista®; Mac OS® X
Browsers:	• Internet Explorer (Windows Only) 8.0 or above – compatibility mode is supported only for 9.0 and above. • Windows Edge Current Version • Mozilla Firefox Current Version • Safari (Mac OS only) 6.2 or above • Google Chrome Current Version
PDF Reader:	Acrobat® or similar software may be required to view and print PDF files
Screen Resolution:	1024 x 768 Recommended
Enabled Security Settings:	Allow per session cookies
Mobile Signing:	• Apple iOS 7.0 or above • Android 4.0 or above

** These minimum requirements are subject to change. If these requirements change, we will provide you with an e-mail message at the e-mail address we have on file for you at the time the hardware and software requirements are revised.

Pre-release (e.g. beta) versions of operating systems and browsers are not supported.

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