Statistical Analysis Plan

Study ID: 213514

Official Title of Study: A Multicentre, Open-label, Non-comparative Phase IV Clinical Study to Evaluate the Safety andClinical Efficacy of Augmentin Extra Strength (ES)-600 (amoxicillin/potassium clavulanate 14:1 combination) in Children with Acute Respiratory Tract Infections (ARTIs) in India

NCT Number-NCT04600752

Approval Date of Document: 18 Jul 2022

STATISTICAL ANALYSIS PLAN

213514

A Multicentre, Open-label, Non-comparative Phase IV Clinical Study to Evaluate the Safety and Clinical Efficacy of Augmentin Extra Strength (ES)-600 (amoxicillin/potassium clavulanate 14:1 combination) in Children with Acute Respiratory Tract Infections (ARTIs) in India

AUTHOR: PPD

VERSION NUMBER AND DATE: V1.0, 18JUL2022

STATISTICAL ANALYSIS PLAN SIGNATURE PAGE

Statistical Analysis Plan v1.0 (Dated 18Jul2022) for Protocol 213514/Amendment 01.

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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.

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MODIFICATION HISTORY

Unique Identifier for this Version	Date of the Document Version	Author	Significant Changes from Previous Authorized Version
1.0	18JUL2022	PPD	Not Applicable – First Version

ABBREVIATIONS

AE	Adverse Event
ABRS	Acute bacterial rhinosinusitis
ALT	Alanine aminotransferase
AMC	Amoxicillin
AOM	Acute otitis media
ARTI	Acute Respiratory Tract Infections
AST	Aspartate aminotransferase
ATC	Anatomical Therapeutic Class
CABP	Community-Acquired Bacterial Pneumonia
CI	Confidence Interval
CTMS	Clinical Trial Management System
CVA	Clavulanic acid
DMC	Data Monitoring Committee
ECG	Electrocardiogram
EOT	End of Treatment
ENR	Enrolled Population
FU	Follow Up
ES	Extra Strength
ITT	Intent-To-Treat
MEdDRA	Medical Dictionary for Regulatory Activities

OT	On Therapy
PT	Preferred term
PDD	Protocol Defined Diarrhea
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SOC	System Organ Class
TEAE	Treatment Emergent Adverse Event
WHO	World Health Organization
WHO-DD	WHO Drug Dictionary

TABLE OF CONTENTS

1. INTRODUCTION

This document describes the rules and conventions to be used in the presentation and analysis of safety and clinical efficacy data for Protocol 213514. 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 protocol version 1.0 amendment 01 dated 19May2021.

2. STUDY OBJECTIVES, ENDPOINTS AND ESTIMANDS

2.1. PRIMARYAND SECONDARY OBJECTIVE

Table 1

Objectives	Endpoints
Primary	Primary
• The primary objective of the study is to assess treatment-emergent adverse events (TEAEs) in children receiving Augmentin (ES)-600 (AMC/CVA 14:1) at 90/6.4 mg/kg/day in two divided doses, administered for 10 days in ARTIs(AOM, ABRS or CABP).	• Safety will be evaluated by assessing the incidences of treatment emergent adverse events (TEAE).
Secondary	Secondary
• The secondary objective of the study is to assess clinical efficacy and incidence of protocol defined diarrhoea (PDD) in children receiving Augmentin (ES)-600 AMC/CVA 14:1 at 90/6.4 mg/kg/day in two divided doses administered for 10 days in ARTIs (AOM, ABRS or CABP).	• Efficacy assessment will be based on: 1. Early clinical response at the on-therapy visit (Day 3 to 5), defined in terms of 'success' or 'failure' to study intervention. 2. Primary clinical response at the end-of-therapy visit (Day 12 to 14), defined in terms of 'success' or

	'failure' to study intervention 3. Secondary clinical response at follow-up (day 22 to 28) i.e., 'success' or 'failure'. • Incidence of protocol-defined diarrhea (PDD) in children receiving Augmentin (ES)-600 (AMC/CVA 14:1) at 90/6.4 mg/kg/day in two divided doses administered for 10 days in ARTIs (AOM, ABRS or CABP).

2.2. ESTIMANDS

The primary, and secondary estimands to support regulatory decisions are described in following table:

Primary Estimand: -

The primary clinical question of interest is:

To assess treatment-emergent adverse events (TEAEs) in children receiving Augmentin (ES)-600 (AMC/CVA 14:1) at 90/6.4 mg/kg/day in two divided doses, administered for 10 days in ARTIs (AOM, ABRS or CABP).

The primary estimand is described by the following attributes:

- Population:
  Children with acute respiratory tract infections (ARTIs) in India between 6 months to 12 years of either gender
- Treatment conditions:
  Augmentin (ES)-600 with dose level 90/6.4 mg/kg/day twice daily (12 hourly) for 10 days.
- Variables/Endpoints:
  Treatment emergent adverse events (TEAEs), Serious treatment emergent adverse events (TESAEs).
- Summary measure:

Counts and percentages for incidence of TEAEs and TESAEs, 95% CI for subjects who have at least one or Any TEAE.

- Intercurrent events (ICEs):

  Discontinuation of study treatment due to any reason – While-on-treatment strategy for TEAEs and TESAEs.

Rationale for Estimand:

The rationale of the while-on-treatment strategy is to estimate the occurrence of TEAEs and TESAEs when subjects have taken the dose/treatment condition.

Treatment Policy will be used for post-treatment AEs, Pre- and Post- treatment SAEs.

The reasoning of treatment policy (as collected) is to estimate the occurrence of post-treatment AEs, and pre- and post-treatment SAEs until subjects are on study will be collected and reported.

No intercurrent event is defined for other safety endpoints. The data will be analyzed as collected.

Secondary Estimands :-

The secondary clinical questions of interest are:

To assess Early and Primary responses in children receiving Augmentin (ES)-600 (AMC/CVA 14:1) at 90/6.4 mg/kg/day in two divided doses administered for 10 days in ARTIs (AOM, ABRS or CABP).

The secondary estimands are described by the following attributes:

1. Early clinical response at on-therapy [(OT) (Day 3 to 5)]

- Population:

  Children with acute respiratory tract infections (ARTIs) in India between 6 months to 12 years of either gender.

- Treatment conditions:

  Augmentin (ES)-600 with dose level 90/6.4 mg/kg/day twice daily (12 hourly) for 10 days.

- Variable/Endpoint:

  Proportion of successful early clinical response at on-therapy (OT) visit.

- Summary measure:

  Counts and percentages for early clinical response at on-therapy (OT) visit with corresponding 95%CI.

- Intercurrent events (ICEs):

- Discontinuation of study treatment due to AE, discontinuation of study treatment due to lack of efficacy and use of rescue medication - Composite strategy

If subject discontinue due to above mentioned ICEs, then early response for that subject will be imputed as a failure.

- Discontinuation of study treatment due to any other reason – Treatment Policy

Rationale for estimand:

Discontinuation of study treatment due to AE, discontinuation of study treatment due to lack of efficacy and use of rescue medication will affect the early clinical response thus the early clinical response will be counted as failure under composite strategy.
The reasoning of treatment policy is to estimate the early clinical response until subjects are on study will be collected and reported (regardless of the intercurrent event occurring).

2. Primary clinical response at end of therapy [EOT (Day 12 to 14)]

- Population:
  Children with acute respiratory tract infections (ARTIs) in India between 6 months to 12 years of either gender.
- Treatment conditions:
  Augmentin (ES)-600 with dose level 90/6.4 mg/kg/day twice daily (12 hourly) for 10 days.
- Variable/Endpoint:
  Proportion of successful primary clinical response at end of therapy (EOT) visit.
- Summary measure:
  Counts and percentages for primary clinical response at end of therapy (EOT) visit with corresponding 95%CI.
- Intercurrent events (ICEs):

- Lack of compliance (<80%) - Principal stratum

Only those subjects who have **at least (≥) 80% compliance** would be considered in the calculation for proportion of primary clinical response

- Discontinuation of study treatment due to AE, discontinuation of study treatment due to lack of efficacy and use of rescue medication - Composite strategy

If subject discontinue due to above mentioned three ICEs, then primary clinical response for that subject will be **imputed as a failure.**

- Discontinuation of study treatment due to any other reason – Treatment Policy

Rationale for estimand:

Lack of compliance (<80%) will impact on primary clinical response therefore subjects who have at least (≥) 80% would be considered for primary clinical response under principal stratum strategy.

Discontinuation of study treatment due to AE, discontinuation of study treatment due to lack of efficacy and use of rescue medication will affect the primary clinical response thus the primary clinical response will be counted as failure under composite strategy.

The reasoning of treatment policy is to estimate the primary clinical response until subjects are on study will be collected and reported (regardless of the intercurrent event occurring).

No intercurrent event is defined for secondary clinical response endpoint as no events are expected to occur during the follow-up period. The data will be analyzed as collected.
No intercurrent event is defined for Protocol-defined diarrhoea (PDD) endpoint. The data will be analyzed as collected.

3. STUDY DESIGN

3.1. GENERAL DESCRIPTION

This study is an open label, multi-centre, non-comparative study. Subjects will be children aged between 6 months to 12 years, presenting with ARTIs including AOM, ABRS and CABP.

At Preliminary Visit (Day 0) after signing the inform consent form by the parent/guardian and assent form by children between 7 to 12 years of age, a series of screening evaluations will be performed in order to determine whether prospective study participant meets the inclusion criteria. Enrolled and screen passed subjects will receive Augmentin (ES)-600 at 90/6.4 mg/kg/day administered in two divided doses, every 12 hours with food for 10 days.
The incidence of protocol-defined diarrhoea will be determined from information collected from the Patient Diary cards, which will be appropriately translated for all languages required based on sites participating in the trial.

After a minimum of two treatment days (four doses) of study intervention has been taken, an 'on-therapy' (OT) visit will be scheduled between Day 3 and 5. During this visit, the investigator/study coordinator shall assess safety (primary endpoint) and 'early clinical response' (secondary endpoint). Safety parameter includes treatment emergent adverse events (TEAEs) for primary study objective. Additionally, clinical status, study intervention compliance, completion of Patient Diary cards, and concomitant medications use will also be assessed. The Investigator will assess safety parameters and clinical status whereas study coordinator will check other parameters with coordinated effort.

Subjects with clinical 'failure' or having PDD or severe AE or SAE at OT visit (Day 3 to 5), will be withdrawn from the study intervention (as per Investigator discretion) and treated appropriately. In such case, the OT visit will be considered as End of Therapy (EOT), and all evaluations that are planned at scheduled EOT (Day 12 to 14) will be completed in this visit. However, these Subjects will return at FU visit (Day 22 to 28) for safety assessment.

Subjects with clinical 'failure' or having PDD or severe AE or SAE after OT visit (Day 3 to 5) but prior to EOT, will be scheduled to return to the site for an interim evaluation, within 24 hours of notification to the Investigator. Subjects will then be withdrawn from the study intervention (as per Investigator discretion) and treated appropriately. In such case, the interim visit will be considered as EOT visit, and all evaluations that are planned at scheduled EOT (Day 12 to 14) will be completed in this visit. However, these Subjects will return at FU visit (Day 22 to 28) for safety assessment.
The Subjects continuing in the study will return for the scheduled 'end of therapy' (EOT) evaluation between Day 12 and 14. The Investigator will enquire the participant or parent/legal guardian about development of AEs and use of concomitant medication(s).

The Investigator will perform safety (primary endpoint) and primary clinical response (secondary endpoint) evaluation. Patient Diary cards and unused medication will be returned at this visit.

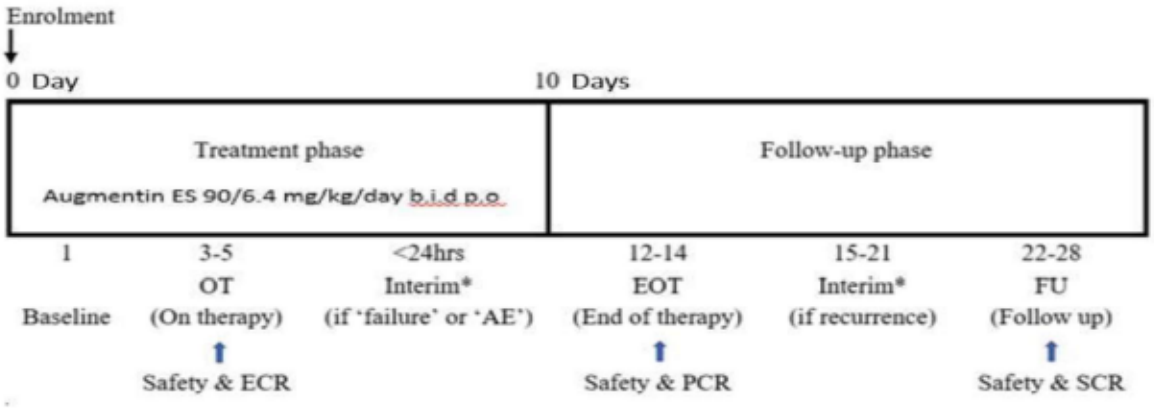
Subjects who experience recurrence of signs/symptoms *after* EOT visit (Day 12 to 14), but prior to scheduled FU visit (Day 22 to 28) will be required to visit the study site twice post EOT - once for the interim visit at the time of any recurrence (Day 15 to 21) and for the scheduled FU visit (Day 22 to 28). At the interim visit, all the evaluations
which are to be performed at scheduled FU visit will be conducted. However, in such cases, all evaluations except secondary clinical response will be repeated at scheduled FU visit (Day 22 to 28). All Subjects experiencing recurrence post EOT will be treated according to the Investigator's discretion.

All Subjects, including withdrawals or clinical 'failures' at EOT or had disease recurrence after EOT, will return for scheduled FU visit on Day 22 to 28. This visit is required for safety assessment and administration of additional medication, if warranted.

The Subjects continuing in the study will return for the scheduled 'follow-up' (FU) visit between Day 22 and 28. The visit be considered as 'end of study' visit, where the Investigator will perform final safety (primary endpoint) and secondary clinical response (secondary endpoint) evaluation (except for recurrence) during the visit.

In general, FU visit at Day 22 to 28 includes both safety and efficacy assessment for Subjects who were clinical 'success' at EOT, but only safety assessment for the Subjects who were clinical 'failures' at EOT or had disease recurrence after EOT. These Subjects are, by definition, clinical failures at follow-up visit.

Table 2: Study Flow Chart



3.2. SCHEDULE OF EVENTS

Schedule of events can be found in Section 1.3 of the protocol.

3.3. CHANGES TO ANALYSIS FROM PROTOCOL

There is no change in analysis from protocol.

4. PLANNED ANALYSES

4.1. DATA MONITORING COMMITTEE (DMC)

There will be no DMC for this study.

4.2. INTERIM ANALYSIS

There will be no Interim analysis for this study.

4.3. FINAL ANALYSIS

All analyses identified in this SAP will be performed by IQVIA Biostatistics following Sponsor Authorization of this Statistical Analysis Plan and Database Lock.

5. ANALYSIS POPULATIONS

The following analysis population will be defined for this study:

5.1. ENROLLED POPULATION [ENR]

The all subjects enrolled (ENR) population will contain all subjects who provide informed consent for this study.
This analysis population will be used to summarize subject disposition (screen failures and reason for screen failure).

5.2. INTENT TO TREAT POPULATION (ITT)

All Subjects who are enrolled and receive at least 1 administration of the investigational product (Augmentin [ES]-600) will be included in the intent-to treat population. The ITT population will be used for all safety and efficacy analyses.

6. GENERAL CONSIDERATIONS

6.1. 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 medication, (Day 1 is the day of the first dose of study medication) 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.

6.2. BASELINE

The baseline values (non-missing) for each parameter will be the last available assessment result prior to the first dose of study administration. In case first dose can be given on Day 0 (after laboratory test result availability), the same will be considered as Day 1.

- Change from Baseline = Post-Dose Visit Value – Baseline
- Percentage Change from Baseline = 100 x [(Post-Dose Visit Value – Baseline) / Baseline

6.3. COMPUTATION OF AGE

Each subject's age will be calculated based on their date of birth relative to the date of the preliminary visit. Where only a subject's year of birth is collected, their date of birth will be imputed with 30th June (30 Jun YYYY).

6.4. ANALYSIS PERIOD

The following analysis periods are defined for this study:

- Pre-treatment period = Date of Preliminary Visit (Day 0) to Date of first dose - 1
- On-treatment period = Date of first dose to Date of last dose inclusive +1
- Post-treatment period = End of last dose +1 days to End of study date

Treatment Period for Adverse Events:

Pre-Treatment AE's:

An AE will be said to be pre-treatment AE if
AE Start Date < Study Treatment Start Date

Treatment Emergent Adverse Event:
An AE will be defined as Treatment emergent adverse event (TEAE) if the AE start date is on or after treatment start date & on or before treatment stop date +1

Study Treatment Start Date ≤ AE Start Date ≤ Study Treatment Stop Date +1

If the last dose of study drug is missing and the AE start date is on or after the first dose of study drug, then the AE will be considered as TEAE

If the AE start date is missing or partial then the AE will be considered TEAE unless there is evidence to the contrary (e.g. month/year of onset date is present and is earlier than the month/year of first dose of study medication).

Post Treatment AE's:
An AE will be defined as post treatment AE if the AE start date is after the treatment stop date

AE Start Date > Study Treatment Stop Date +1

Duration of adverse event:

(AE resolution date – AE onset or start date) +1

Treatment Emergent Adverse Event (TEAE):

During treatment Period + lag time of 1day.

Onset Time Since 1st Dose (Days):
If Treatment Start Date > AE Start Date:
Onset Time = AE Onset Date - Treatment Start Date
If Treatment Start Date ≤ AE Onset Date:
Onset Time = AE Onset Date - Treatment Start Date +1

Study/Treatment Period for Concomitant medication
Pre-Treatment Period:
If con-med start date < date of Visit 1 (or con-med date is missing)

On-Treatment Period:
If Con-med start date < study treatment start date (or Con-med start date is missing) and con-med stop date ≥ study treatment start date (or Con-med start date is missing), or

If study treatment start date ≤ Con-med start date ≤ study treatment stop date+1.

If the study treatment stop date is missing and the con-med start date is on or after the study treatment start date, then the con-med will be on-treatment.

If the con-med start or stop date is missing or partial, then the con-med will be considered on-treatment unless there is evidence to the contrary (e.g. month/year of con-med stop date is present and is before the month/year of study treatment start date).

Post -Treatment Period:
If con-med stop date is after the treatment stop date+1

Con-med Stop Date > Study Treatment Stop Date+1

Definition of on-set for an Event:
Con-med duration (Days):

Con-med Stop Date – Con-med Start Date + 1

Time Since 1st Dose (Days):

If Treatment Start Date > Con-med Start Date:
Time = Con-med Start Date - Treatment Start Date

If Treatment Start Date ≤ Con-med Start Date:
Time = Con-med Start Date - Treatment Start Date +1

If Treatment Start Date or start date of Con-med is missing
Time = missing.

6.5. RETESTS, UNSCHEDULED VISITS AND EARLY TERMINATION DATA

For by-visit summaries, refer Section 6.6 (visit windows).

Listings will include scheduled, unscheduled, retest and early discontinuation data.

6.6. WINDOWING CONVENTIONS

The following visit window will be used for efficacy as well as safety assessment.

Visit	Target Days	Visit Window
Baseline	0	Prior to first dose of study medication
Visit 1	1	#1
On-therapy visit or OT visit	3	2-5
End of therapy visit or EOT visit	12	6-14
Interim visit recurrence	18	15-21
Follow-up visit	25	≥22

Visit 1 will be considered as baseline for patient diary card assessments if subject does not have patient diary data prior to Visit 1.

* **Interim visit** (< 24 hrs of notification) is required only if subject having clinical failure or PDD or server AE of SAE after OT visit prior to EOT visit. In this case all assessment of interim visit will be mapped to EOT visit as scheduled.

If there is more than one record for a given parameter within a specific visit window, then the non-missing record closest to the target day will be summarized. If there are multiple records on the same day for a parameter, then the average value will be considered for continuous parameters, and the worst value will be considered for the categorical parameters.

Study treatment discontinuation and unscheduled visit will also be considered for deriving the visit window for parameters.

6.7. STATISTICAL TESTS

The default significant level will be 5%. All confidence intervals will be computed at 95% and all tests will be two-sided, unless otherwise specified in the description of the analyses.

6.8. SAMPLE SIZE ESTIMATION

A total of 310 subjects will be enrolled and dosed. These 310 participants will be enrolled for each indication based on the respective prevalence as mentioned in the table below.
These prevalence values are based on all ARTIs in India.

Study	Indication	Prevalence %
Kumari et al (2016)	AOM	17.6
Acharya et al (2003)	CAP	8.6 (0.5% severe)
Shahid et al (2012)	ABRS	14

The approximate ratio of samples in each indication will be 18:9:14 (AOM: CABP:ABRS). Based on this ratio, at least 136 subjects with AOM, 68 with CABP and 106 with ABRS will be enrolled for the study.
If the proportion of participants reporting at least one TEAE is 37.9% (as observed in Young et al, 2003), and assuming a sample size of 310 participants, it is estimated that the width of the 95% confidence interval would be within +/- 5.43% of the sample proportion (ie, [32.5%, 43.3%]), which equates to the lower and upper bounds of the 95% confidence interval lying within approximately 14% of the estimated proportion.

The sensitivity of the precision is calculated with respect to 5 different proportions estimated as presented below:

Proportion estimate	**Sample size**	**Precision**	**95% CI**
30%	310	5.10%	(24.9%, 35.1%)
35%	310	5.31%	(29.7%, 40.3%)
37.9%	**310**	**5.43%**	**(32.5%, 43.3%)**

40%	310	5.45%	(34.5%, 45.5%)
45%	310	5.54%	(39.5%, 50.5%)
50%	310	5.57%	(44.4%, 55.6%)

6.9. SOFTWARE VERSION

All analyses will be conducted using SAS version 9.4 or higher.

7. STATISTICAL CONSIDERATIONS

Continuous data will be summarized using the number of subjects (n), arithmetic mean (mean), standard deviation (SD), median, minimum value (min), and maximum value (max) values unless otherwise specified. Categorical variables will be summarized using the frequency counts (n) and percentages (%) for each possible value. Data from unscheduled visits will be included in the by-subject listings.

7.1. ADJUSTMENTS FOR COVARIATES AND FACTORS TO BE INCLUDED IN ANALYSES

This section is not applicable for this study.

7.2. MULTICENTER STUDIES

This study will be conducted by multiple investigators at multiple centers.

7.3. MISSING DATA

Missing data will not be imputed in this study.

7.4. MULTIPLE COMPARISONS/ MULTIPLICITY

There is no multiplicity adjustment planned for this study.

8. OUTPUT PRESENTATIONS

APPENDIX 1 shows conventions for presentation of data in outputs.
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.

9. DISPOSITION AND WITHDRAWALS

All subjects who provide informed consent will be accounted for in this study.

9.1. DISPOSITION

Subject disposition will be summarized based on the ITT population by overall and indication. The following summaries will be included in the disposition table:

- Total number of subjects enrolled in the ITT population
- Number of subjects who completed the study treatment
- Number of subjects who completed the study
- Number and percentage of subjects who discontinued from the study
- Number and percentage of subjects who pre-maturely discontinued the study treatment as well as from the study along with reason for discontinuation.

Percentages will be based on the number of subjects in the ITT population.

A summary of reasons for screen failure and the number of subjects included in ITT population by overall and indication will be presented separately based on the enrolled population. The percentages will be based on the number of subjects in the All Enrolled analysis population.

In addition, summary of visits impacted by COVID-19 pandemic will be generated based on the ITT population by overall and indication.

Subject listings of reasons for study withdrawal, treatment discontinuation and reasons for screen failures for each indication will be provided using ITT and enrolled population respectively.

9.2. PROTOCOL DEVIATIONS

Protocol deviations are the deviations from the procedure outlined in the protocol. All the important protocol deviations (PDs) will be summarized using ITT population as obtained from Clinical Trial Management System (CTMS) logs. PDs will be identified and discussed with the Investigator/Sponsor in PD review discussion and to finalize analysis set assignment.

Summary of important protocol deviations related to COVID-19 pandemic will also be provided by overall and indication using ITT population.

A subject listing of important protocol deviations identified by the study team will be presented each indication.

10. DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

The following demographic data and other baseline characteristics will be presented for the ITT population by overall and indication:

- Derived Age (years)
- Age in categories (≤ 6 months, > 6 months and < 2 years, ≥ 2 years and < 5 years, ≥5 years and < 8 years, ≥8 years)
- Sex
- Race
- Ethnicity
- Weight (kg)
- Weight in categories (≤12kg, > 12 kg and ≤ 23 kg, > 23 kg and ≤ 40 kg, >40kg)
- Height (cm)

Baseline characteristics will include vital signs parameters, bowel movements, and radiological assessments (X-Ray of chest and nasal/paranasal sinus), as performed at the time of preliminary visit.

Continuous demographic and baseline characteristics data will be summarized using descriptive statistics. For categorical data, counts and percentage of subjects in each category will be provided.

Subjects listing of demographic characteristics by indication will be provided for ITT population.

Baseline Signs and Symptoms:

The following summaries will be generated for baseline signs and symptoms with counts and percentages -

- Baseline signs and symptoms by indication using ITT population
- Baseline signs and symptoms by severity and indication using ITT population

By-subjects listing of baseline sign and symptoms by indication will be generated.

Baseline Bowel Habits:

The following summaries will be generated for baseline bowel habits-

- Descriptive statistics (n, mean, standard deviation, median, minimum, and maximum) on frequency of bowel movements at baseline by indication overall and indication using ITT population
- Summary (counts and percentages) and Descriptive statistics (n, mean, standard deviation, median, minimum, and maximum) on consistency of bowel movements at baseline by indication overall and indication using ITT population

Subject listing of radiographic evaluation by indication will be produced.

11. SURGICAL AND MEDICAL HISTORY

Medical History conditions are defined as those conditions which stop prior to or at preliminary visit. Medical history will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 24.1 and will be summarized by system organ class (SOC) and Preferred Term (PT) with counts and percentages based on the intent to treat analysis population. A subject having more than one medical condition/disease within the same SOC/PT will be counted only once for that SOC or PT.

Medical history will be sorted by descending order of system organ class (SOC) and total frequency of preferred term (PT) within each system organ class (SOC).

Past and current medical conditions will also be summarized with counts and percentages using ITT population by overall and indication.

12. CONCOMITANT MEDICATIONS

Pre-treatment medication is defined as any medication that started and stopped prior to the first dose of study drug.
Concomitant medication is defined as any medication which started before the first dose of study drug AND was ongoing at the time of the first dose of study drug, or started on or after the date of first dose of study drug.
Medications with partially or completely missing start and/or stop dates will be handled as described in Section 6.4.
All medications will be coded using the World Health Organization (WHO) Drug Global dictionary version B3 September 2021.
Concomitant medications will be summarized using anatomical therapeutic class (ATC) level1 and ingredient by overall and indication for pre-,on and post- treatment based on the ITT analysis population. A subject having more than one medication within the same ATC Level 1 or ingredient will be counted only once for that ATC Level 1 or ingredient .Subjects listings will be provided for concomitant medications.

Concomitant medications will be sorted in descending order of total incidence across Augmentin ES treatment group for the ATC level 1 and in descending order of total incidence for the ingredient within each ATC level 1 class.

13. STUDY MEDICATION EXPOSURE

Exposure to study medication in days will be presented for the ITT population.

The total exposure to Augmentin Extra Strength (ES)-600 (amoxicillin/potassium clavulanate 14:1 combination) is calculated based on derivation as mentioned in section 13.1. Subjects who entered treatment period but did not report any treatment dates will be categorized as having zero days of exposure.

Descriptive statistics summary on extent-of-exposure by overall and indication will be presented for study medication exposure using ITT population.

Subject listing of exposure for study medication by indication will also be generated.

13.1. DERIVATIONS

Duration of exposure days = (date of last study drug administration – date of first study drug administration) + 1.

14. STUDY MEDICATION COMPLIANCE

Subject compliance will be assessed by measuring the number of doses per number of days on drug (refer section 14.1). A minimum of 80% and a maximum of 120% compliance with the study medication regimen will be required for the patient to considered evaluable per protocol.
Subject compliance will be checked through patient diary card and it will be returned to the site at the end of treatment (EOT).
Summary statistics for study medication compliance will be presented by overall and indication using <80%, 80% - 120% and >120% categories with ITT population.
Subject listings of study medication compliance and non-compliance by indication will be presented using ITT population. Each subject will be checked for possible overdosing using the information on maximum recommended dose by body weight provided in APPENDIX 4.
Instances of overdosing, if any, will be listed.

14.1. DERIVATIONS

Overall percentage of the study intervention compliance will be calculated as follows:
Compliance = number of doses taken/ (number of days on therapy x 2) x 100%

15. EFFICACY ENDPOINTS

15.1. SECONDARY EFFICACY ENDPOINTS

There are no primary efficacy endpoints defined for this study. The efficacy analysis is defined in terms of secondary and patient diary endpoints.

Secondary Endpoints -

- *Early clinical response* at the on-therapy visit (Day 3 to 5), defined in terms of 'success'

or 'failure' to study intervention.

- *Primary clinical response* at the end-of-therapy visit (Day 12 to 14), defined in terms of 'success' or 'failure' to study intervention.
- *Secondary clinical response* at follow-up (Day 22 to 28), defined in terms of 'success' or 'failure' to study intervention.
- Incidence of protocol-defined diarrhea (PDD) in children receiving Augmentin (ES)-600 (AMC/CVA 14:1) at 90/6.4 mg/kg/day in two divided doses administered for 10 days in ARTIs (AOM, ABRS or CABP).

Definition of clinical responses

Early or Primary Clinical Response will be defined using following criteria:

Table 3:

Success	Clinical cure	Sufficient resolution or improvement of the signs and symptoms such that no additional antibiotic therapy is indicated.
	Improvement	Improvement in at least 1 presenting sign/symptoms. No additional antibiotic indicated.
Failure	Clinical failure	Non-improvement or deterioration in any sign/symptoms after 2 or more days of therapy. Additional antibiotic therapy is indicated.
	Unable to determine	A valid assessment of clinical outcome could not be made (eg, participant did not attend or consent to clinical examination or lost to follow-up).

The proportion of early and primary response will be calculated as follows-

- Proportion of early response = The number of subject who is categorized as success (clinical cure or improvement) at on therapy (OT) visit / the number of subjects in ITT population
- Proportion of primary response = The number of subject who is categorized as success (clinical cure or improvement) at end of therapy (EOT) visit/ the number of subjects in ITT population

Secondary Clinical response will be described using following criteria:

Table 4:

Success	Persistent clinical cure*	Sufficient resolution of signs/symptoms for those Subjects who were clinically cured or improved at the end of therapy. No additional antibiotic indicated.
Failure	Clinical recurrence	Reappearance of signs/symptoms for those Subjects who were clinically cured or improved at the end of therapy. Additional antibiotic therapy is indicated.
	Unable to determine	A valid assessment of clinical outcome could not be made (eg, participant did not attend end of therapy visit, or extenuating circumstances or lost to follow-up).

* Subjects who showed 'improvement' at EOT (i.e., clinical 'success') and remained same at FU without requiring additional intervention, will be categorized as 'persistent clinical cure'.

The proportion of secondary response will be calculated as follows-

- Proportion of secondary response = The number of subject who is categorized as success (persistent clinical cure) at follow-up (FU) visit / the number of subjects in ITT population

Definition of Protocol-defined diarrhoea (PDD)-

The incidence of Protocol-defined diarrhoea (PDD) will be determined based on following rules:

- 3 or more watery stools in one day OR
- 4 or more loose/watery stools in one day OR
- 2 watery stools per day for two consecutive days OR
- 3 loose/watery stools per day for two consecutive days

Patient diary endpoints:

Bowel habits

- Mean movement frequency per day
- Maximum movement frequency per day
- Maximum single consistency score

Description of Bowel Habits:

Bowel habit ((frequency and consistency of patient's stools) data will be collected using patient diary cards as per schedule of protocol. Bowel movement consistency will be recorded for each patient in five categories –

[redacted] = 1, [redacted] = 2, [redacted] = 3, [redacted] = 4, [redacted] = 5.

Summary measures of bowel habit movement frequency and consistency are defined as –

- Mean movement frequency per day: this measures the mean number of bowel movements experienced by each patient during the study
- Maximum movement frequency per day: this measures the maximum number of bowel movements experienced in a day for each patient
- Maximum single consistency score: this measures the maximum consistency score for each patient at any time during the study

Clinical Recurrence of Disease - Reappearance of signs/symptoms for those participants who were clinically cured or improved at the end of therapy.

15.1.1. Analysis of Secondary Endpoint

15.1.1.1. Clinical Response

Frequency and proportion of early, primary, and secondary clinical response will be presented along with 95% CI using exact binomial method

Secondary clinical response statistical analysis will be performed based on as collected data. The following summaries will be generated for early, primary, and secondary clinical response by overall and indication.

- Early clinical response at on-therapy (OT) visit
- Primary clinical response at end of therapy (EOT) visit
- Secondary clinical response at follow-up (FU) visit

Clinical recurrence of disease at follow-up will be summarized with frequency and percentage by overall and indication.

15.1.1.2. Incidence of protocol- defined diarrhoea (PDD).

No intercurrent event is defined for this endpoint. The data will be analyzed as collected.

Frequency and percentage of subjects with incidence of protocol- defined diarrhoea (PDD) will be presented along with 95% CI using exact method (refer SAS code APPENDIX 3)
The following summaries will be generated for incidence of protocol- defined diarrhoea (PDD) by overall and indication.

- Incidence of protocol-defined diarrhoea (PDD)
- Incidence of protocol defined diarrhoea (PDD) over time

Figure for incidence of protocol defined diarrhoea (PDD) over time will also be displayed by overall and indication.

The statistical analysis for incidence of protocol- defined diarrhoea (PDD) will be based on as collected data.

15.1.1.3. Patient diary endpoints

Bowel habits-
The following summaries will be generated for patient summary measures of bowel habit movement by overall and indication.

- Summary and descriptive statistics for patient bowel habit summary measure - mean movement frequency per day
- Summary and descriptive statistics for patient bowel habit summary measure - maximum movement frequency per day
- Summary and descriptive statistics for patient bowel habit summary measure - maximum consistency score

Subject listing of bowel movement by indication will be presented using ITT population.

16. SAFETY ENDPOINTS

All analysis for safety endpoints will be based on the Intent to treat Analysis Set.

16.1. ADVERSE EVENTS

The primary safety endpoint is the number of subjects reporting at least one treatment emergent

adverse event (TEAE).
A TEAE duration is defined as an AE which has its onset date during the treatment period + lag time of 1 day.
Adverse Events (AEs) will be coded using MedDRA version 24.1. TEAE's and SAE's will be summarized. All AE's will be listed.

16.1.1. TEAEs: Primary Safety Endpoint

AEs occurring from when a subject sign informed consent to when a subject exits the study will be accounted for in the reporting. AEs occurring pre-treatment, treatment emergent adverse event (on-treatment) and post-treatment periods will be summarized and listed for the ITT population.
A treatment -emergent adverse event is defined as any adverse event that develops after initiation of the study treatments or any adverse event already present that worsens following exposure to study treatment.
The primary safety endpoint will be summarized with counts and percentage of subjects reporting any TEAEs and subjects with at least one or any TEAE with corresponding 95% CI using exact binomial method
The following summaries will be generated for adverse events:

- Adverse event overview by period
- Adverse event overview by period for acute otitis media (AOM)
- Adverse event overview by period for acute bacterial rhinosinusitis (ABRS)
- Adverse event overview by period for community acquired bacterial pneumonia (CABP)
- Treatment emergent adverse events by system organ class, preferred term, overall and indication
- Adverse events by system organ class, preferred term, overall and indication - post-treatment
- Common (>=1%) treatment emergent adverse events by preferred term, overall and indication
- Common (>=1%) adverse events by preferred term, overall and indication - post-treatment

AEs and TEAEs will be sorted by descending order of system organ class (SOC) and total frequency of preferred term (PT) within each system organ class (SOC).

AEs and TEAEs related to study drug will presented in decreasing order of preferred term (PT).

Subjects listing of adverse events by indication (TEAE and post-treatment period) will be produced.

16.1.1.1. Severity

Severity is classified as mild, moderate, and severe. An AE with missing severity will be classified as 'Unknown'.
Subjects who experience the same event several times, with different intensities, will only be counted with the maximum intensity.
The following tables will be generated to summarize the severity of adverse event

- Treatment emergent adverse events by system organ class, preferred term, maximum severity, overall and indication
- Adverse events by system organ class, preferred term, maximum severity, overall and indication -post treatment

Sorting order will be presented same as section 16.1.1.

16.1.1.2. Relationship to Study Medication

Summary for drug-related treatment emergent adverse events by preferred term, overall and indication will be presented.

16.1.2. TEAEs Leading to PermanentDiscontinuation of Study Medication or Withdrawal Study

Treatment emergent adverse events leading to permanent discontinuation of study medication or withdrawal from study by system organ class, preferred term, overall and indication will be displayed.
Adverse events leading to withdrawal from study will also be presented by system organ class, preferred term, overall and indication.

Sorting order will be presented same as section 16.1.1.
Subject listing of treatment emergent adverse events leading to permanent discontinuation of study medication or withdrawal from study will also be generated.

16.1.3. Serious Adverse Events

The following summaries will be presented for serious adverse events:

- Treatment emergent serious adverse events by system organ class, preferred term, overall and indication
- Serious adverse events by system organ class, preferred term, overall and indication - post-treatment
- Treatment emergent serious adverse events by system organ class and preferred term, maximum severity, overall and indication
- Serious adverse events by system organ class, preferred term, maximum severity, overall and indication -post treatment
- Drug-related treatment emergent serious adverse events by preferred term, overall and indication

Sorting order will be presented same as section 16.1.1.

The following serious adverse event listings will be produced:

- Listing of reasons for considering as a serious adverse event by indication- pre-treatment
- Listing of fatal and non-fatal serious adverse events (TEAE and post-treatment period)
- Listing of reasons for considering as a serious adverse event by indication (TEAE and post-treatment period)

16.1.4. Adverse Events Leading to Death

Subject listing will be generated for adverse event leading to death.

16.1.5. . Cardiovascular Events

The following AE's/SAE's will be classified as Cardiovascular events:

- Myocardial infarction/unstable angina
- Congestive heart failure
- Arrhythmias
- Valvulopathy
- Pulmonary hypertension

- Cerebrovascular events/stroke and transient ischemic attack
- Peripheral arterial thromboembolism
- Deep venous thrombosis/pulmonary embolism
- Revascularization

Subject listing will be generated for all cardiovascular events recorded in the study.

16.2. DEATHS

Subject listing will be generated for any death that happens during the study.

16.3. LABORATORY EVALUATIONS

Laboratory parameters assessed for the study are listed below:

Table 5:

Assessments	Parameters		
Hematology	Platelet Count RBC Count Hemoglobin Hematocrit	RBC Indices: MCV MCH %Reticulocytes	WBC count with Differential: Neutrophils Lymphocytes Monocytes Eosinophils Basophils
Clinical Chemistry	Plasma creatinine	Aspartate Aminotransferase (AST) Alanine Aminotransferase (ALT)	Total and direct bilirubin
Radiography	Chest X ray to be performed for patients presumed to a diagnosis of CABP. X ray of nasal/paranasal sinus to be performed for patients presumed to have ABRS (both only for reference, as per investigators discretion)		

- Clinical laboratory evaluations include hematology, clinical chemistry, A list of laboratory assessments is mentioned in Table 5which will be used for statistical analysis.
- Descriptive statistics (n, mean, standard deviation (SD), median, minimum value

(min), and maximum value (max)) will be presented for quantitative measurements of laboratory parameters by overall and indication, Frequency and percentage will be displayed for qualitative measurements of laboratory parameters by overall and indication.

- Subjects listing of baseline laboratory parameters by indication will also be generated.

16.4. ECG EVALUATIONS

ECG assessment will not be performed for this study.

16.5. VITAL SIGNS

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

- Respiratory Rate (breaths/min)
- Temperature (^{0} C)
- Pulse rate
- Weight (kg)
- Height

Actual vital signs results, change from baseline values and percentage change from baseline will be summarized for each analysis visit.

Subjects listing of vital signs parameters by indication will also be generated.

16.6. OTHER SAFETY ASSESSMENTS

Summary for visits impacted by COVID-19 pandemic will be presented by overall and indication.

Subject listing of Covid-19 pandemic study impact (TEAE and post-treatment period) will be displayed.

Subject listing of local examination by indication will be generated.

Subject listing will be generated for pregnancy.

17. DATA NOT SUMMARIZED OR PRESENTED

Not applicable

18. REFERENCES

Protocol number 213514 | Protocol Amendment 01 19 May 2021.

APPENDIX 1. PROGRAMMING CONVENTIONS FOR OUTPUTS

IQVIA OUTPUT CONVENTIONS

Outputs will be presented according to IQVIA Global Biostatistics Standard Output Conventions

DATES & TIMES

Depending on data available, dates and times will take the format DDMMMYYYY; times will take the format HH:MM; combined dates and times will take the format DDMMMYYYY/HH:MM. Time will be based on a 24 hour clock.

SPELLING FORMAT

English UK, including for MedDRA where British English is used.

LISTINGS

All listings will be ordered by the following (unless otherwise indicated in the template):

- Subject ID
- Date and time (where applicable)

PRESENTATION OF TREATMENT GROUPS

For outputs, treatment groups will be represented as follows:

Treatment Group
Augmentin (ES) – 600

DESCRIPTIVE STATISTICS

If the original data has N decimal places, then the summary statistics will have the following decimal places:

- Minimum and maximum: N;
- Mean, median, lower and upper bounds of two-sided 95% CI: N + 1;
- SD and SE: N + 2

PERCENTAGES

Percentages will be reported to one decimal place. Rounding will be applied, except for percentages < 0.1 but > 0.0 which will be presented as '< 0.1' and percentages < 100.0 but >99.9 which will be presented as '>99.9'.

Where counts are zero, no percentages will appear in the output.

APPENDIX 2. PARTIAL DATE CONVENTIONS

Date Imputation Rule for adverse events and concomitant medication for assigning the event in particular period:

Missing day in a start date, e.g. - -JUN2021, set to the first of the month, 01JUN2021.
Missing month in a start date, e.g., 15- - -2006, set to January, 15JAN2021.
Missing day in a stop date, e.g. - -APR2021, set to the last of the month, 30APR2021.
Missing month in a stop date, e.g., 23- - -2006, set to December, 23DEC2021.
If both day and month are missing, e.g. - - - - -2021, apply both rules giving 01JAN2021 for a partial start date, or 31DEC2021 for a partial stop date

APPENDIX 3. SAS CODE FOR ANALYSES

The following SAS code will be used to analyze the clinical response:

For overall:

```
proc freq data=modeldata;
tables response/ binomial (exact ) alpha=0.05;
output out=_ci95 binomial
run;
```

For indication wise analysis

```
proc freq data=modeldata;
by indication
tables response/ binomial (exact )   alpha=0.05;
output out=_ci95 binomial
run;
```

Note : In the absence of responder category (zero responder), separate category with zero responder in final data set will be added before passing in proc freq using Weight statement with zeroes option as below

SAS code :

```
proc freq data=modeldata ;
by indication;
tables response /  binomial;
weight wgt/zeroes;
 exact binomial;
 run;
```

APPENDIX 4. MAXIMUM RECOMMENDED DOSE BY BODY WEIGHT

Body weight (kg) #	Augmentin 600 for oral suspension (ml) twice in day(BID)	Maximum Recommended Dose Administered by the Oral Route (ml) Twice in day(BID)	Body weight (kg) #	Augmentin 600 for oral suspension (ml) twice in day(BID)	Maximum Recommended Administered by the Oral Route (ml) Twice in day(BID)
			21	8.0	10.5
			22	8.4	11.0
3	1.2	1.5	23	8.6	11.5
4	1.6	2.0	24	9.0	12.0
5	2.0	2.5	25	9.4	12.5
6	2.4	3.0	26	9.8	13.0
7	2.6	3.5	27	10.2	13.5
8	3.0	4.0	28	10.6	14.0
9	3.4	4.5	29	11.0	14.5
10	3.8	5.0	30	11.4	15.0
11	4.2	5.5	31	11.6	15.5
12	4.6	6.0	32	12.0	16.0
13	5.0	6.5	33	12.4	16.5
14	5.4	7.0	34	12.8	17.0
15	5.6	7.5	35	13.2	17.5
16	6.0	8.0	36	13.6	18.0
17	6.4	8.5	37	14.0	18.5
18	6.8	9.0	38	14.4	19.0
19	7.2	9.5	39	14.6	19.5
20	7.6	10.0	40	15.0	20.0

DocuSign

Certificate Of Completion

Envelope Id: PPD
Status: Completed
Subject: Please DocuSign: GSK_213514 SAP Final V1.0.docx
Project Code (Enter 0 for non-billable projects): PPD
IQVIA ID (Login ID): PPD
Business Unit:
DSSR
Source Envelope:
Document Pages: 43
Signatures: 5
Envelope Originator:
Certificate Pages: 6
Initials: 0
PPD
AutoNav: Enabled
EnvelopeId Stamping: Disabled
Time Zone: (UTC-05:00) Eastern Time (US & Canada)

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PPD

Status: Original
7/18/2022 5:40:27 AM
Location: DocuSign

Signer Events	Signature	Timestamp
PPD		Sent: 7/18/2022 5:47:45 AM Viewed: 7/18/2022 6:02:33 AM Signed: 7/18/2022 6:03:18 AM
	With Signing Authentication via DocuSign password With Signing Reasons (on each tab): I am the author of this document	
Electronic Record and Signature Disclosure: Accepted: 7/18/2022 6:04:10 AM PPD Company Name: IQVIA		
PPD IQVIA Biotech DocuSign Part 11 Security Level: Email, Account Authentication (Required), Logged in	PPD Signature Adoption: Pre-selected Style PPD With Signing Authentication via DocuSign password With Signing Reasons (on each tab): I am the author of this document	Sent: 7/18/2022 5:47:47 AM Viewed: 7/18/2022 5:53:41 AM Signed: 7/18/2022 5:54:05 AM
Electronic Record and Signature Disclosure: Not Offered via DocuSign		

Signer Events	Signature	Timestamp
PPD		Sent: 7/18/2022 5:47:47 AM Viewed: 7/18/2022 8:45:24 AM Signed: 7/18/2022 8:49:29 AM
	With Signing Authentication via DocuSign password With Signing Reasons (on each tab): I approve this document	
Electronic Record and Signature Disclosure: Accepted: 7/18/2022 8:45:24 AM PPD Company Name: IQVIA		
PPD		Sent: 7/18/2022 5:47:49 AM Viewed: 7/18/2022 6:28:02 AM Signed: 7/18/2022 6:29:33 AM
	With Signing Authentication via DocuSign password With Signing Reasons (on each tab): I am the author of this document	
Electronic Record and Signature Disclosure: Accepted: 7/18/2022 6:28:02 AM PPD Company Name: IQVIA		
PPD		Sent: 7/18/2022 5:47:49 AM Viewed: 7/20/2022 6:15:25 AM Signed: 7/20/2022 6:16:47 AM
	With Signing Authentication via DocuSign password With Signing Reasons (on each tab): I approve this document	
Electronic Record and Signature Disclosure: Accepted: 7/20/2022 6:15:25 AM PPD Company Name: IQVIA		

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	7/18/2022 5:47:49 AM
Certified Delivered	Security Checked	7/20/2022 6:15:25 AM
Signing Complete	Security Checked	7/20/2022 6:16:47 AM
Completed	Security Checked	7/20/2022 6:16:47 AM

Payment Events	Status	Timestamps

Electronic Record and Signature Disclosure

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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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