Protocol

Study ID: 213514

Official Title of Study: 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

NCT Number-NCT04600752

Approval Date of Document: 19-May-2021

TITLE PAGE

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Protocol Number: 213514/Amendment 01

Compound Number or Name: BRL25000

Study Phase: Phase IV

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

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Regulatory Agency Identifying Number(s): Not Applicable

Approval Date: 19-MAY-2021

SPONSOR SIGNATORY:

Protocol Title: 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

Protocol Number: 213514/Amendment 01

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Dr Puja Kochhar Medical Director Infectious Diseases Classic & Established Products.	**Date**

The signed page is a separate document.

Medical Monitor Name and Contact Information can be found in the Study Reference Manual.

PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

DOCUMENT HISTORY		
Document	**Date**	**DNG Number**
Amendment 1	*19-MAY-2021*	*TMF-13328250*
Original Protocol	*21-AUG-2020*	*2020N430706_00*

Amendment 1 [19-May-2021]

Overall Rationale for the Amendment:

The rationale for this amendment is to address Subject Expert Committee (SEC) recommendation of revising the Phase IV study protocol to include all indications approved by CDSCO in the Marketing Authorization of Augmentin ES. Therefore, the indication is being revised to Acute Respiratory Tract Infections (ARTIs) i.e. inclusion of CABP and ABRS in addition to AOM

Section # and Name	Description of Change	Brief Rationale
Throughout the protocol	Acute otitis media is replaced with Acute respiratory tract infection.	To broaden the indication and include acute respiratory tract infections. Acute respiratory tract infection meaning addition of CABP and ABRS in addition to AOM.
Section 1.1: Synopsis Section 3: Objectives and Endpoints	Added an additional secondary endpoint of Early clinical response at on-therapy visit (Day 3 to 5). Added tables providing definitions of primary and secondary clinical response.	To assess if there is any clinical response early during the treatment period. To clarify the definitions of different responses as part of clinical response.
Section 1.2: Schema	Changed the study schema.	Updated as per the changed study design.
Section 1.3: Schedule of Activities	Added an additional column for interim visit between OT visit and EOT visit Added a row for radiographic evaluations and the respective foot note Added early clinical response at OT	Updated as per the changed study design.
Section 2.2: Background	Added background information about ARTIs	Since the indication is changed from AOM to ARTIs updated this section to include information about ARTIs.
Section 2.3.1: Risk Assessment	Added the risk of exposure to ionizing radiation from X ray and its mitigation strategy	Since X ray is included at Preliminary Visit (if required as per investigator's discretion), the related risk is included.
Section 4.1: Overall Design	Updated details about OT visit. Added the details of additional interim visit.	Updated as per the changed study design.
Section 5: Study Population	Added inclusion criteria for patient with ABRS and CABP. Updated the exclusion criteria	To include the patients with ABRS and CABP.
Section 5.4: Study Procedures	Updated details of OT visit and added details of the Interim visit	Updated as per the changed study design.

Section # and Name	Description of Change	Brief Rationale
	Added radiological evaluation at preliminary visit	
Section 8.1: Efficacy assessment	Added evaluation of early clinical response at OT visit. Added evaluation of primary clinical response at Interim visit.	Updated as per the changed study design.
Section 8.2: Safety Assessment	Added section on Radiographic Evaluations (Section 8.2.4)	To include information about the X ray.
Section 1.1: Synopsis Section 9.2: Sample Size Determination	Sample size is changed from 200 to 270 (without dropouts) and 310 (including dropouts)	Sample size is changed to accommodate the patients with ABRS and CABP along with the AOM patients.
Section 9.4.3: Secondary Endpoint	Added details on estimand	Update estimand strategy
Section 9.2:	A new subsection (Section 9.2.1: Sample Size Sensitivity) is added	To provide details regarding the calculation of the precision of sample size
Appendix 3	Added radiographic evaluations along with the Laboratory evaluations	To include information about the X ray.

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1. PROTOCOL SUMMARY

1.1. Synopsis

Protocol Title: 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.

Short Title: A Phase IV Study to Evaluate the Safety and Efficacy of Augmentin Extra Strength (ES)-600 (amoxicillin/potassium clavulanate 14:1 combination) in Children with Acute Respiratory Tract Infections (ARTIs) in India.

Rationale: Augmentin (ES)-600 is a high-dose amoxicillin/clavulanic acid (AMC/CVA) 14:1 formulation that allows administration at 90/6.4 mg/kg/day in two divided doses, ie, double the previously recommended standard amoxicillin dosage (45 mg/kg/day) without doubling the unit dose of potassium clavulanate in a fixed dose combination formulation, inhibitory activity of CVA against bacterial beta-lactamases is maintained. Optimizing the PK/PD (ie, T>MIC values) of Augmentin (ES)-600 maximizes bacterial eradication such as *Streptococcus pneumoniae* (including penicillin-resistant *S. pneumoniae* (PRSP); MIC 2-4 ug/mL), *Haemophilus influenzae* (*H. influenzae)* and *Moraxella catarrhalis (M. catarrhalis);* principal respiratory pathogens implicated in acute respiratory tract infections (ARTIs) in children. This assures the highest probability of clinical cure and reduce the spread and development of resistance.

The safety profile of AMC/CVA is also well understood. Clinical and post marketing surveillance data has also shown favourable results across all AMC/CVA paediatric and adult formulations. Most adverse events are mild and transient. The most commonly occurring events reported in children are mild transient gastrointestinal effects.

Due to non-availability of Augmentin (ES)-600 in India, most physicians can only use available standard Augmentin 7:1 (45/6.4 mg/kg/day) formulation and double the dose to achieve the guideline recommended higher dose of amoxicillin at 90 mg/kg/day in ARTIs like AOM. However, doubling the dosage using 7:1 formulation causes unnecessary exposure to higher proportionate dose of CVA (12.8 mg/kg/day) as a unit dose of 6.4 mg/kg/day of CVA is only required for efficacy against beta-lactamase producing respiratory pathogens like *H. influenzae* and *M. catarrhalis*. Hence, there is an unmet need for availability of Augmentin (ES)-600 in India.

In this regard, the Indian Regulatory Agency (CDSCO) has granted a marketing authorization on 08 June 2020 for import/marketing of Augmentin (ES)-600 in India to the Sponsor (GlaxoSmithKline), with a post marketing commitment to conduct a

Phase IV study in India, whose purpose is to generate safety data on Augmentin (ES)-600 in paediatric population in India.

To this effect, the current study is designed to assess the safety and clinical efficacy of Augmentin (ES)-600, AMC/CVA (14:1) at 90/6.4 mg/kg/day in two divided doses every 12 hours in children (age between 6 months and 12 years) with ARTIs, including acute otitis media (AOM), acute bacterial rhinosinusitis (ABRS) and community acquired bacterial pneumonia (CABP).

The purpose of this study is to confirm the safety and clinical efficacy profile of Augmentin (ES)-600 in paediatric population in India.

Objectives and Endpoints:

The following are the objectives and endpoints of the study:

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 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) ie, 'success' or 'failure'.

Objectives	Endpoints
	• 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).

[$]A treatment-emergent adverse effect (TEAE) is defined as an AE which has its onset date on or after treatment start date and on or before treatment stop date + 1 day. All adverse events (AEs) experienced during the same period will be monitored. The detail is described in Section 8.3: "Adverse Events and Serious Adverse Events".

**Protocol-defined diarrhoea is:

- 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.

*Efficacy assessment will be made using following criteria:

- **Early or Primary Clinical Response**

Success	Clinical cure	Sufficient resolution or improvement of the signs and symptoms. 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).

- **Secondary Clinical Response**

Success	Persistent clinical cure*	Sufficient resolution of signs/symptoms for those participants who were clinically cured or improved at the end of therapy. No additional antibiotic indicated.
Failure	Clinical recurrence	Reappearance of signs/symptoms for those participants 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).

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

Overall Design:

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

At Preliminary Visit (Day 0) after signing the informed 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 including laboratory and radiographic evaluations, in order to determine whether prospective study participant meets the inclusion criteria. Enrolled participants will receive supervised first dose of study intervention from participant pack, after demonstration of medication reconstitution procedure. In case first dose can be given on Day 0 (after availability of laboratory test result and radiological evaluation [Only if needed by investigator's discretion]), the same will be considered as Day 1. All participants 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. Protocol-defined diarrhoea is:

- 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.

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 use of concomitant medications will also be assessed. The Investigator will assess safety parameters and clinical status whereas study coordinator will check other parameters with coordinated effort.

Participants with worsening of signs and symptoms, severe AE, SAE, or having PDD at OT visit (Day 3 to 5) will be assessed by investigators and withdrawn from study as per investigator's 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 at this visit. However, these participants will return at Follow-Up (FU) visit (Day 22 to 28) for safety assessment.

Participants with worsening of signs and symptoms, severe AE, SAE, or having PDD after OT visit (Day 3 to 5) but prior to EOT visit will be assessed by investigators and withdrawn from study as per investigator's 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 participants will return at FU visit (Day 22 to 28) for safety assessment.

The participants continuing in the study will return for the scheduled 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.

Participants who experience recurrence of signs/symptoms or any new AEs *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 evaluation will be repeated at scheduled FU visit (Day 22 to 28). All participants experiencing recurrence post EOT will be treated according to the Investigator's discretion.

All participants, 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 participants continuing in the study will return for the scheduled 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 participants who were clinical "success" at EOT, but only safety assessment for the

participants who were clinical "failures" at EOT or had disease recurrence after EOT. These participants are, by definition, clinical failures at follow-up visit.

Disclosure Statement: This is a single group open-label treatment study in ARTI in children (age 6 months to 12 years).

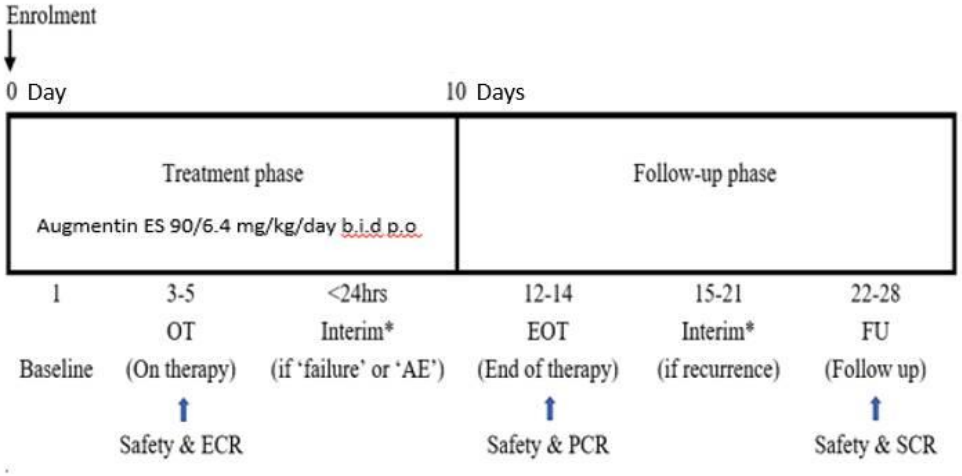
Number of Participants: A total of 310 subjects will be enrolled and dosed.

Note: "Enrolled" means a participant's, or their legally acceptable representative's, agreement to participate in a clinical study following completion of the informed consent process.

Intervention Groups and Duration: The current study is a single arm, open label, non-comparative study. Eligible participants will receive Augmentin (ES)-600 [AMC/CVA 14:1] at 90/6.4 mg/kg/day administered in two divided doses, every 12 hours with food for 10 days.

Data Monitoring or Other Committee: Not Applicable.

1.2. Schema



a. Abbreviations: AE=Adverse event; ECR=Early Clinical Response; PCR=Primary Clinical Response; SAE = Serious Adverse Event, SCR=Secondary Clinical Response.
b. Safety parameter is TEAE (All visits). Efficacy parameter includes ECR (OT visit), PCR (EOT visit), SCR (FU visit) categorized as clinical 'success' or 'failure' as defined in Section 8.1
c. Visit 1 can be completed on the same day as the preliminary Day 0 visit if the laboratory test results and radiological assessment (Only if needed by investigator's discretion) are available on the same day.
d. Participants 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 and treated appropriately (as per Investigator discretion). In such case, the OT visit will be considered as EOT, and all evaluations that are planned at scheduled EOT (Day 12 to 14) will be completed in this visit. However, these participants will return at FU visit (Day 22 to 28) for safety assessment.
e. Participants 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 and treated appropriately (as per Investigator discretion). 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 participants will return at FU visit (Day 22 to 28) for safety assessment.

f. Participants 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 during interim visit at the time of any recurrence (Day 15 to 21) and at scheduled FU visit (Day 22 to 28). At this 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 participants experiencing recurrence post EOT will be treated according to the Investigator's discretion.

1.3. Schedule of Activities (SoA)

Assessments	**Preliminary Visit**	**Visit 1***	**On-therapy Visit[a] (OT)**	**Interim Visit[b] ('Failure' or AE)**	**End of Therapy Visit[c] (EOT)**	**Interim Visit[d] (Recurrence)**	**Follow up Visit[e] (FU)**
Days**	**Day 0***	**Day 1**	**Days 3 to 5**	**Within 24 hours**	**Day 12 to 14**	**Day 15 to 21*****	**Day 22 to 28**
Written dated informed consent	X****						
Inclusion/exclusion	X						
Medical history	X						
Demographics	X						
Vital signs[f]	X		X	X	X	X	X
Physical examination[g]	X		X	X	X	X	X
Laboratory evaluations[h]	X						
Radiographic evaluations[i]	X						
Prior/concomitant medication	X		X	X	X	X	X
Bowel movements	X		X	X	X	X	X
Local examination[j]	X		X	X	X	X	X
Clinical assessment[k]	X		X	X	X	X	X

Assessments	**Preliminary Visit**	**Visit 1***	**On-therapy Visit[a] (OT)**	**Interim Visit[b] ('Failure' or AE)**	**End of Therapy Visit[c] (EOT)**	**Interim Visit[d] (Recurrence)**	**Follow up Visit[e] (FU)**
Baseline signs and symptoms[l]	X						
Dispensing of study intervention		X					
Dispensing of Patient Diary card[m]		X					
Adverse events[n]		X	X	X	X	X	X
Early clinical response			X				
Primary clinical response				X	X		
Secondary clinical response						X	X[o]
Protocol-defined Diarrhoea[p]			X	X	X	X	X
Return of remaining study intervention				X	X		
Collection of Patient Diary card				X	X		
Review of Patient Diary card			X	X	X		
Assessment of compliance				X[q]	X[q]		
Study conclusion							X

[a] Scheduled OT (Safety and early clinical response). If clinical 'failure' or PDD or severe AE/SAE at OT, participant will be withdrawn and treated appropriately. In such case, OT visit will be considered as EOT visit.

[b] Interim visit (< 24 hrs of notification). Only if clinical 'failure' or having PDD or severe AE or SAE occurring after OT visit (Day 3 to 5) but prior to EOT.
[c] Primary clinical response at EOT.
[d] Required only if 'recurrence' occurs between EOT and FU.
[e] Safety and clinical response at follow up.
[f] Vital signs include body temperature, pulse rate, and respiratory rate.
[g] Physical examination will include, measurement of height and weight, assessments of the skin, cardiovascular, respiratory, gastrointestinal and neurological systems.
[h] Laboratory evaluations include hematology, plasma creatinine, aspartate aminotransferase (AST), alanine aminotransferase (ALT) and bilirubin.
[i] Radiographic evaluation will include Chest X ray and X ray of nasal/paranasal sinus (performed for patients presumed to have CABP and ABRS) as per investigators discretion.
[j] Local examination refers to ear, nose/paranasal sinus or chest examination depending upon the primary diagnosis ie, AOM, ABRS or CABP
[k] Includes assessment of disease at baseline and evaluation of clinical improvement or deterioration at other visits during study, as per Investigator's discretion.
[l] Includes baseline signs and symptoms (other than disease under study).
[m] The parent/legal guardian should record the AEs, dosing information, diarrhoea related information in the Dairy Card through the treatment period and until EOT. Patient Diary cards will be appropriately translated for all languages required based on sites participating in the trial.
[n] All AEs will be collected from the signing of the ICF until the follow-up visit at the time points specified.

[o] The secondary clinical response evaluation will be performed at scheduled FU visit only for participants who were treatment successes at the EOT. This is unlike participants with disease recurrence post EOT, whose secondary clinical response evaluation would have already taken place at interim visit, at the time of recurrence.
[p] Incidence of protocol-defined diarrhoea will be assessed (as a secondary endpoint) at EOT (Day 12 to 14), scheduled FU visit (Days 22 to 28) and interim visit, if any.
[q] Not required for the participants who were withdrawn from the study intervention due to worsening, or no improvement, or requirement of additional antibiotics during OT visit (Day 3 to 5).
*In case first dose can be given on Day 0 (after laboratory test result availability), the same will be considered as Day 1.
**Rationale for range: Days 3 to 5; 12 to 14; 15 to 21, and 22 to 28: Basis previous GSK studies. Day 15 to 21 is to cover interim period between EOT and FU to factor any disease recurrence. Refer to Section 5.4 for the details of the evaluation to be performed at each visit.
*** Participants with disease recurrence following the EOT visit (Day 12 to 14), but prior to the scheduled FU visit (Day 22 to 28) will be required to visit the study site twice - once during interim visit at time of recurrence (Day 15 to 21) and again at scheduled FU visit (Day 22 to 28). At interim visit all the evaluations which are to be performed at scheduled FU visit, including primary and secondary endpoint assessments will be performed. However, at scheduled FU visit (Day 22 to 28), all evaluations conducted at interim visit will be repeated, except secondary clinical response.
**** Informed consent to be taken from by the parent/guardian and assent from children between 7 to 12 years.

2. INTRODUCTION

Augmentin is an oral antibacterial combination of the semisynthetic beta-lactam antibiotic, amoxicillin, and the beta-lactamase inhibitor clavulanate potassium. The presence of clavulanate potassium in Augmentin protects amoxicillin from degradation by beta-lactamase enzymes and effectively extends the antimicrobial spectrum of amoxicillin to include many gram-negative aerobic and anaerobic bacteria. It is indicated for use when amoxicillin-resistant pathogens, such as those expressing beta lactamases, are suspected as a cause of respiratory tract and other infections.

Augmentin (ES)-600 is a high-dose amoxicillin/clavulanic acid (AMC/CVA) (14:1) formulation that allows administration at 90/6.4 mg/kg/day in two divided doses, double the previously recommended standard amoxicillin dosage without doubling the unit dose of potassium clavulanate in a fixed dose combination formulation, inhibitory activity of CVA against bacterial beta-lactamases is maintained.[AUGMENTIN ES-600 Prescribing Information, 2019]
Optimizing the PK/PD (ie, T>MIC values) of Augmentin (ES)-600 (14:1) maximizes bacterial eradication such as *Streptococcus pneumoniae* (including penicillin-resistant *S. pneumoniae* (PRSP); MIC 2-4 ug/mL), *Haemophilus influenzae* (*H. influenzae)* and *Moraxella catarrhalis (M. catarrhalis);* principal respiratory pathogens implicated in Acute Respiratory Tract Infections (ARTIs) in children. This assures highest probability of clinical cure, thus reducing the spread and development of resistance. Augmentin (ES)-600 therefore plays an important role in the management of ARTIs in children.

2.1. Study Rationale

Due to non-availability of Augmentin (ES)-600 in India, most physicians can only use available standard Augmentin 7:1 (45/6.4 mg/kg/day) formulation and double the dose to achieve the guideline recommended higher dose of amoxicillin at 90 mg/kg/day in ARTIs in children. However, using the 7:1 formulation causes unnecessary exposure to higher proportionate dose of CVA (12.8 mg/kg/day) as a unit dose of 6.4 mg/kg/day of CVA is only required for efficacy against beta-lactamase producing respiratory pathogens. Hence, there is an unmet need for availability of Augmentin (ES)-600 in India.

The safety profile of AMC/CVA is also well understood. Most adverse events are mild and transient. Main adverse effects (in adults and children) include gastrointestinal (GI) disturbances, including diarrhoea, nausea, vomiting and indigestion (each <5% incidence). [Todd PA et al, 1990] [Huttner A et al, 2020] [Easton J et al, 2003] [Bottenfield GW et al, 1998] [Dietz H et al, 1999]

In this regard, the Indian Regulatory Agency (CDSCO) has granted a marketing authorization on 08 June 2020 for import/marketing of Augmentin (ES)-600 in India to the Sponsor (GlaxoSmithKline), with a post marketing commitment to conduct a

Phase IV study in India, whose purpose is to generate safety data on Augmentin (ES)-600 in paediatric population in India.

To this effect, the current study is designed to assess the safety and clinical efficacy of Augmentin (ES)-600, AMC/CVA (14:1) at 90/6.4 mg/kg/day in two divided doses every 12 hours in children (age between 6 months and 12 years) with ARTIs, including Acute otitis media (AOM), Acute bacterial rhinosinusitis (ABRS) and Community acquired bacterial pneumonia (CABP).

The purpose of this study is to confirm the safety and efficacy profile of Augmentin (ES)-600 in paediatric population in India.

2.2. Background

Acute respiratory tract infections (ARTIs) like acute otitis media, sinusitis and community-acquired pneumonia are a leading cause of infectious disease–related morbidity, hospitalization, and mortality among children worldwide, particularly in low-income countries.[Williams BG et al, 2002] [World Health Organization. World health statistics, 2017b] [World Health Organization. Acute respiratory infections in children, 2017a] Although, in children under 5 years, primary infections with viral pathogens can also predispose to secondary bacterial infections.[Fan J et al, 1998] [Bellau-Pujol S et al, 2005]

The most frequently isolated bacteria in ARTIs include Streptococcus pneumoniae, non-typeable Haemophilus influenzae and Moraxella catarrhalis.[Marom T et al, 2014] These bacteria were increasingly resistant to commonly used antibiotics for ARTI treatment, leading to increase in mortality rates, hospital durations, and health care–associated costs.[Mauldin PD et al, 2010] For instance, the increase in S. pneumoniae of intermediate susceptibility to penicillin-(PISP; penicillin MICs 0.12 to 1.0 μg/mL), and many, but not all, highly resistant serotypes of PRSP (penicillin MICs, ≥2 μg/mL) strains pose serious clinical problems.[Camara M et al, 2017] [Yamanaka N et al, 2008] [Kim SH et al, 2012]

Based on such trends, an increase in the daily dose of amoxicillin from 45 mg/kg to 90 mg/kg was introduced in late 2000 to respond to increasing presence of PRSP. This is because, amoxicillin, with or without clavulanate potassium, has one of the lowest MICs for S. pneumoniae among the available oral beta-lactam agents.[Jacobs MR et al, 1999] [Geng Q et al, 2014] [Pan F et al, 2015] [Li QH et al, 2013] [Fu J et al, 2019] Currently, most treatment guidelines on ARTIs recommend the use of higher doses of amoxicillin with or without clavulanic acid in ARTIs, mostly where PISP/PRSP is suspected.[Dagan R et al, 2001] [Piglansky L et al, 2003] [Arrieta A et al, 2003] [Casellas JM Jr et al, 2005] [Block SL et al, 2006] [Chu CH et al, 2014] [Casey JR et al, 2012] [Hoberman A et al, 2017] [Lieberthal AS et al, 2013]

For instance, in 2013 (reaffirmed in 2019), American Academy of Pediatrics recommended high-dose amoxicillin (80 to 90 mg/kg/day in 2 divided doses) for 5 to 10 days as preferred therapy in AOM.[Lieberthal AS et al, 2013] An alternative recommended first-line treatment is AMC/CVA at 90/6.4 mg per kg/day in 2 divided doses who have received AMC in the previous 30 days or having recurrent/persistent otitis media or who have the otitis-conjunctivitis syndrome.[Lieberthal AS et al, 2013]

In 2012 IDSA recommended "high-dose" AMC/CVA (90 mg/kg/day orally twice daily) for children with ABRS from geographic regions with high endemic rates (≥10%) of invasive PRSP, those with severe infection (eg, evidence of systemic toxicity with fever of 39°C [102°F] or higher, and threat of suppurative complications), attendance at day-care, age <2 years, recent hospitalization, antibiotic use within the past month, or who are immunocompromised.[Anthony W et al, 2012]

High dose amoxicillin (90 mg/kg/day) with or without clavulanic acid has also been recommended in CABP in children age >3 months by American Academy of Pediatrics, British Thoracic Society, especially where higher rates of PRSP exist. Amoxicillin clavulanic acid is the preferred agent when empirical coverage of *H influenzae* and *M catarrhalis* is warranted (30% of *H influenzae* and 100% of *M catarrhalis* produce beta-lactamase).[Messinger AI et al, 2017] [Ostapchuk M et al, 2004]

Overall, the selection of high-dose AMC/CVA (90 mg/kg/day) in ARTIs has been made based on long-term safety of the drug; its efficacy against the key respiratory pathogens and a first choice-to-treat PRSP and beta-lactamase producing strains that have potential to cause disease recurrence or therapy failure.

Safety profile of AMC/CVA is also well understood. The most frequently reported adverse events are GI disturbances, including diarrhoea, nausea, vomiting and indigestion that can be reduced by taking AMC/CVA with food.[Stein GE et al, 1984] [Easton J et al, 2003] High-dose AMC/CVA (90/6.4 mg/kg/day) has shown similar tolerability profile to a conventional twice-daily regimen (45/6.4 mg/kg/day).[Bottenfield GW et al, 1998] Adverse events (AEs) were reported in a total of 50.2% and 47.3% of patients, with protocol-defined diarrhoea in 11% and 8.8% patients. The most frequently reported adverse events in 521 children treated with the high-dose formulation in another study were diaper rash (4.0%), diarrhoea (3.6%), vomiting (2.3%) and other rash (1.3%). Events probably or possibly related to the medication were documented in 14% of patients.

In summary, Augmentin ES-600 (AMC/CVA 14:1) has been developed based on a combination of PK/PD considerations, in vitro, in vivo animal, and clinical data, and primarily intended to treat ARTIs in cases where PRSP is suspected and beta-lactamase producing organism cannot be ruled out. Its safety profile is well understood and is comparable to conventional Augmentin dosing regimens.

2.3. Benefit/Risk Assessment

2.3.1. Risk Assessment

The risk/benefit considerations for therapy in ARTIs must also be extended to consider the environmental consequences of using sub-optimally effective antibiotics which may be drivers of the development and spread of antibiotic resistance. There has been clearly a need for alternative dosage regimens and to use measures to control and reduce the emergence of resistant organisms, particularly PRSP.

In this regard, time above MIC (T>MIC) data suggest that doses of AMC at 90 mg/kg/day administered in divided doses every 12 hours may provide concentrations of antibiotic sufficient to kill PRSP with MICs 2-4 µg/mL. This regimen was calculated to provide a T>MIC of 38% for an MIC of 4 µg/mL, in contrast to 23% of T>MIC provided by the current dose of 45/6.4 mg/kg/day given in divided doses every 12 hours. The low toxicity of amoxicillin and experience already gained with higher doses worldwide suggest that the increase in the daily dose of amoxicillin will be unlikely to adversely affect tolerability. In addition, presence of clavulanic acid in Augmentin (ES)-600 would provide coverage against beta-lactamase producing pathogens like as *H. influenzae* and *M. catarrhalis*, that are inherently resistant to amoxicillin. The rationale for dosage and administration is described in Section 4.3.

Overall, the broad spectrum of activity against aerobic and anaerobic Gram-positive and Gram-negative bacteria, together with a good PK/PD profile and well understood safety profile, makes Augmentin (ES)-600 a useful antimicrobial in limiting ARTIs and development of resistance.

The following section outlines the potential risk assessment and mitigation strategy for this protocol (Table 1).

Table 1 Potential Risk and Mitigation Strategy

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Investigational Medicinal Product (IP)		
Hypersensitivity reactions to study treatment and/or beta-lactams	Global data sheet (GDS), , Prescribing Information/potential risk of fatal hypersensitivity (anaphylactoid) reactions have been reported in patients on penicillin therapy. These reactions are more likely to occur in individuals with a history of penicillin hypersensitivity.	Exclusion of subjects with a known hypersensitivity to any component of amoxicillin or clavulanic or beta-lactams, e.g. penicillins and cephalosporins acid and its excipients or history of a serious adverse reaction possibly related to any of these agents. (See exclusion criteria in Section 5.2). In case of anaphylaxis or unanticipated hypersensitivity reaction, participant will be withdrawn and managed as per Investigator's discretion. However, such participants will have to return for safety assessment at scheduled FU visit.
Infectious mononucleosis	GDS, Prescribing Information/ a morbilliform rash has been associated with this condition following the use of amoxicillin.	Exclusion of patients with an infectious mononucleosis. (See exclusion criteria in Section 5.2).
Pseudomembranous colitis and antibiotic associated diarrhoea	GDS/ pseudomembranous colitis has been reported with the use of antibiotics and may range in severity from mild to life-threatening. It is important to consider its diagnosis in patients who develop diarrhoea during or after antibiotic use.	If prolonged or significant diarrhoea occurs or the participant experiences abdominal cramps, treatment should be discontinued immediately, and the participant should be investigated further as per Investigator's discretion.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Hepatic Dysfunction	GDS/ - amoxicillin-clavulanate-associated jaundice/hepatic dysfunction has been rarely reported. GDS/A moderate rise in ALT and AST has been associated with use of - amoxicillin-clavulanate.	Exclusion of patients with current hepatic impairment, or history of jaundice or hepatic impairment due to any component of Amoxicillin/Clavulanic acid. (See exclusion criteria in Section 5.2).
Renal Impairment	GDS/dose needs to be adjusted in patients with creatinine clearance less than 30 mL/min.	Exclusion of patients with known renal insufficiency e.g. plasma creatinine > 1.5 times upper limit of normal range for age. (See exclusion criteria in Section 5.2).
Phenylketonuria	GDS/ amoxicillin-clavulanate suspensions contain aspartame, which is a source of phenylalanine and so should be used with caution in patients with phenylketonuria.	Exclusion of patients with phenylketonuria.
Drug-Drug Interaction Potential	GDS/ In common with other antibiotics, amoxicillin-clavulanate may affect the gut flora, leading to lower oestrogen re-absorption and reduced efficacy of combined oral contraceptives. GDS/ Concomitant use of probenecid is not recommended. Probenecid decreases the renal tubular secretion of amoxicillin. Concomitant use with amoxicillin-clavulanate may result in	This subject population is unlikely to be on OCP. The use of Probenecid is to be prohibited during the study. Patients should be excluded who are on Probenecid.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	increased and prolonged blood levels of amoxicillin, but not of clavulanic acid. GDS/ In the literature there are rare cases of increased international normalised ratio in patients maintained on acenocoumarol or warfarin and prescribed a course of amoxicillin. If co-administration is necessary, the prothrombin time or international normalised ratio should be carefully monitored with the addition or withdrawal of amoxicillin.	This population is unlikely to be on warfarin. If participants are on Warfarin, they should be excluded from study.
Pregnancy/Lactation	GDS/Reproduction studies in animals (mice and rats at doses up to 10 times the human dose) with orally and parenterally administered amoxicillin-clavulanate have shown no teratogenic effects. In a single study in women with pre-term, premature rupture of the fetal membrane (pPROM), it was reported that prophylactic treatment with amoxicillin-clavulanate may be associated with an increased risk of necrotizing enterocolitis in neonates.	Augmentin is not contraindicated in pregnancy. Details of all pregnancies in female participants will be collected at Day 0. Participants will be instructed to notify the Investigator if they become pregnant during study period. Such participants will be immediately withdrawn from the study. Any reported pregnancy must be informed to Sponsor by Investigator within 24 hours of receipt of information and should follow the procedures outlined in Appendix 4.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
		Any abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAE.
Exposure to ionizing radiation from X ray	- Since children demonstrate signs and symptoms of CAP differently than adults and may deteriorate more rapidly than adults, keeping an option of chest X ray in inclusion criteria is critical for investigators to rule out need for hospitalization. - Even if an X ray is only one radiological assay is required. (Only basis for the reference in addition of clinical judgement if needed) - There will be no follow up assay needed. The dose from a single chest X ray should not exceed 20 microsieverts and this corresponds to a lifetime risk of a fatal malignancy of about 1 in 1 million (ICRP 103), which falls into the 'trivial' risk category as defined by ICRP 62. malignancy of approximately 1 in 300,000).	- The study will minimize exposure by using X rays acquired as part of clinical care whenever possible. - Robust study design and CRF will factor in detailed history, lab screening and clinical examination parameters which should reduce the need of radiation exposure in the pediatric age group patients. (It will be considered only if clinicians would like to have additional confirmation in addition of clinical decision) - All procedures will be performed by a qualified technician.

More detailed information about the known and expected benefits and risks and reasonably expected AEs of Augmentin (ES)-600 (14:1) may be found in the Prescribing Information.[AUGMENTIN ES-600 Prescribing Information, 2019]

2.3.2. Benefit Assessment

Amoxicillin-clavulanic acid continues to be a reliable antibiotic for the treatment of ARTIs in children caused by amoxicillin-clavulanate susceptible organisms. Worldwide amoxicillin clavulanic acid has shown to be highly effective clinically in Phase III clinical trials in children including infections caused by PRSP and beta lactamase producing pathogens such as *H. influenzae* and *M. catarrhalis*.

The safety profile is well-defined and supported by over 40-years of post-marketing experience. The most commonly occurring events reported in children are mild transient gastrointestinal effects. Clinical and post marketing surveillance data has also shown a good safety profile that is similar across all AMC/CVA pediatric formulations.

More detailed information about the known and expected benefits and risks and reasonably expected adverse events of Augmentin (ES)-600 may be found in the Prescribing Information.

2.3.3. Overall Benefit: Risk Conclusion

Optimizing the PK/PD (ie, T>MIC values) of Augmentin (ES)-600 maximizes bacterial eradication *Streptococcus pneumoniae* (including penicillin-resistant *S. pneumoniae* (PRSP); MIC 2-4 ug/mL), *Haemophilus influenzae* (*H. influenzae)* and *Moraxella catarrhalis (M. catarrhalis);* principal respiratory pathogens implicated in ARTIs in children. This assures highest probability of clinical cure, thus reducing the spread and development of resistance.

Thus, it can be considered that the investigation of the safety and clinical efficacy of Augmentin (ES)-600 justified in children having ARTIs with a positive benefit/risk ratio.

Considering the measures taken to minimize the risk to participants in this study, the potential risks identified in association with Augmentin (ES)-600 are justified by the anticipated benefits that may be afforded to patients with ARTIs.

3. OBJECTIVES AND ENDPOINTS

The objectives and endpoints of the study are provided in Table 2 below:

Table 2 Objectives and Endpoints

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) ie, '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).

[$]A treatment-emergent adverse effect (TEAE) is defined as an AE which has its onset date on or after treatment start date and on or before treatment stop date + 1 day. All adverse events (AEs) experienced during the same period will be monitored. The detail is described in Section 8.3 "Adverse Events and Serious Adverse Events".

**Protocol-defined diarrhoea is:

- 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.

* Efficacy assessment will be made using following criteria:

- **Early or Primary Clinical Response**

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).

- **Secondary Clinical Response**

Success	Persistent clinical cure*	Sufficient resolution of signs/symptoms for those participants who were clinically cured or improved at the end of therapy. No additional antibiotic indicated.
Failure	Clinical recurrence	Reappearance of signs/symptoms for those participants 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).

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

4. STUDY DESIGN

4.1. Overall Design

This study is an open label, multicentre, non-comparative study. Participants 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 (Section 5.4.2) including laboratory and radiographic evaluations, in order to determine whether prospective study participant meets the inclusion criteria. Enrolled participants will receive supervised first dose of study intervention from the participant pack. Dosing will be accompanied by demonstration/instruction on reconstitution procedure, product handling, storage, and

accountability (Section 6.2). Additional information on the same will be included in Study reference manual.

Visit 1 can be completed on the same day as the preliminary visit (Day 0) if the laboratory test results and radiological evaluation [Only if needed by investigator's discretion] are available on the same day. All participants 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. Protocol-defined diarrhoea is:

- 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.

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.

Participants 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 participants will return at FU visit (Day 22 to 28) for safety assessment.

Participants 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 participants will return at FU visit (Day 22 to 28) for safety assessment.

The participants 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.

Participants 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 participants experiencing recurrence post EOT will be treated according to the Investigator's discretion.

All participants, 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 participants 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 participants who were clinical 'success' at EOT, but only safety assessment for the participants who were clinical 'failures' at EOT or had disease recurrence after EOT. These participants are, by definition, clinical failures at follow-up visit.

4.2. Scientific Rationale for Study Design

As a commitment of receiving Augmentin (ES)-600 marketing authorization from Indian regulators on 08 June 2020, GSK India will have to conduct a Phase IV clinical study in the Indian population. Being a phase IV study, assessment of adverse event profile of Augmentin (ES)-600 would be considered as primary objective. Assessment of clinical efficacy would be considered as secondary objective in this study.

The purpose of this study is to confirm the safety and efficacy profile of Augmentin (ES)-600 in the paediatric population in India, administered at 90/6.4 mg/kg/day in two divided doses for 10 days in ARTIs.

The current study design is a single arm, open-label, non-comparative study, and is based on several GSK-sponsored studies conducted in the past.[SB Report No. HH-1017/BRL-025000/2/CPMS-382] [SB Report No. BRL-025000/RSD-1006FN/3/CPMS-446] [SB Report No. BRL-25000/RSD-1009XZ/3/CPMS-447] [SB Report No BRL-025000/RSD-1016FL/2/CPMS-536] [SEIKEL K et al, 1997]

4.2.1. Participant Input into Design

There was no input from participants/participant organisations into the design of this study.

4.3. Justification for Dose

Augmentin (ES)-600, (AMC/CVA 14:1) was chosen to provide an increased dose of amoxicillin that would be enough to treat ARTIs (AOM, ABRS and CABP) not only due to PSSP/PISP, but also due to PRSP (MIC 2-4 µg/mL). This formulation is also effective against respiratory pathogens like beta-lactamase-positive or negative H. influenzae and M. catarrhalis.[AUGMENTIN ES-600 Prescribing Information, 2019]

High dose amoxicillin with or without clavulanic acid has been recommended as preferred therapy in ARTIs, including AOM (AAP 2013/2019), ABRS (IDSA 2012) and CABP (AAP 2004, BTS etc). The selection of high-dose AMC/CVA has been made based on long-term safety of the drug; its efficacy against the key respiratory pathogens in children and a first intention-to-treat PRSP strains and where beta-lactamase producing organism cannot be ruled out.

The Indian National Treatment Guideline 2016 also mentions use of high-dose AMC/CVA (14:1) at 90/6.4 mg/kg/day in (AOM).[National Treatment Guidelines for Antimicrobial Use in Infectious Diseases, 2019]

Augmentin (ES)-600 is recommended for dosing at 90/6.4 mg/kg/day in two divided doses every 12 hours for 10 days, in children aged 3 months and older. There is no experience in paediatric patients weighing > 40 kg or in adults. There are no clinical data in children under 3 months of age.[AUGMENTIN ES-600 Prescribing Information, 2019]

4.4. End of Study Definition

A participant is considered to have completed the study if he/she has completed all phases of the study including scheduled FU visit (Day 22 to 28) and excludes those who are early treatment failures and do not complete all visits.

The end of the study is defined as the date of the last visit of the last participant in the study or last scheduled procedure shown in the Schedule of Activities (SoA) for the last participant in the study.

5. STUDY POPULATION

5.1. Inclusion Criteria

Participants are eligible to be included in the study only if they meet all the below inclusion criteria:

1. Age: 6 months to 12 years of either gender.
2. **Diagnosis of AOM on basis of otoscopic findings as defined below:**
    - Purulent otorrhea of less than 24 hours duration

      OR
    - Middle ear effusion (MEE)
        - Middle ear effusion is evidenced by at least two of the following:
        - Decreased or absent tympanic mobility measured by pneumatic otoscopy,
        - Yellow or white discoloration of the tympanic membrane, or
        - Opacification of the tympanic membrane.

PLUS

At least one of the following indicators of acute inflammation:

- Ear pain within 24 hours, including unaccustomed tugging or rubbing of ear,
- Marked redness of the tympanic membrane, or
- Distinct fullness or bulging of the tympanic membrane.

OR

Child with ABRS with inflammation as bacterial infection who has the following symptoms/signs on the day of or the day before the first dose of the investigational product:

- Redness of the nasal mucosa
- Nasal or postnasal discharge is purulent or mucopurulent
- Pathological shadow in the paranasal sinus on a radiogram (only for reference-based on investigator discretion). Patient with surgical history should be excluded but patient with a pervious surgery more than 365 days before and apparently preserved maxillary sinus mucosa or patient with a previous surgery of nasal polypectomy more than 90 days before may be enrolled in the study.

- Child with ABRS whose severity is classified as moderate or severe (total score ≥4) based on the nasal cavity findings and symptoms as shown below.

		None	Mild/small amount	Moderate or severe
Symptom	Rhinorrhoea	0	1	2
	Bad mood/ productive cough	0	1	2
Nasal cavity finding	Nasal/postnasal discharge	0 (Serous)	2 (Mucopurulent, small amount)	4 (Moderate or larger amount)

The severity of condition will be determined by the total score of the above symptoms/findings:
1 to 3 = mild, 4 to 6 = moderate, 7 to 8 = severe.

OR

Child diagnosed with CABP based on following criteria: (At least three of the four criteria should be met to include in the study)

i. History of documented fever (rectal, ear, or oral temperature ≥38°C or axillary temperature ≥37.5°C) or hypothermia (rectal, ear, or oral temperature <35°C or axillary temperature <34.5°C)

ii. Acute onset or worsening within the previous 5 days of at least two of the following nine clinical signs and symptoms:
   - cough,
   - tachycardia, defined as follows:
     - 6 months to <24 months: ≥160 beats/min
     - 24 months to <10 years: ≥140 beats/min
     - ≥10 years: ≥100 beats/min
   - tachypnea, defined as follows:
     - 6 months to <12 months: ≥50 breaths/min
     - 12 months to <5 years: ≥40 breaths/min
     - ≥5 years: ≥20 breaths/min
   - dyspnea,
   - grunting,
   - sputum production,
   - chest pain,
   - cyanosis,
   - increased work of breathing

iii. At least one of the five following laboratory findings:
   - leukocytosis (>15,000 white blood cells/mm^3),
   - >15% immature neutrophils (bands) regardless of total peripheral white blood cell (WBC),

- leukopenia (4,500 WBC/mm^3) and

iv. Presence with new infiltrates consistent with bacterial pneumonia including new alveolar or lobal infiltrate or consolidation (based on imaging result) - based on investigator's discretion only

3. The participant and parent(s)/legal guardian(s) are willing and able to comply with the study protocol.
4. In accordance with regional/local laws and regulations, the parent(s)/legal guardian(s) has given signed informed, dated consent; and the participant has given written assent, if applicable, to participate in the study.

5.2. Exclusion Criteria

Participants will be excluded from the study if they meet any of the following exclusion criteria:

1. Weight ≥ 40 kg
2. Pre-existing renal insufficiency (eg, plasma creatinine >1.5 times upper limit of normal range for age)
3. Pre-existing liver disease(s) and/or hepatic dysfunction
4. A serious underlying disease as per clinician's judgment.
5. Currently having diarrhea at the time of screening
6. Concomitant infection which would preclude evaluation of the response to study intervention.
7. Concomitant condition precluding evaluation of clinical response (such as acute mastoiditis, facial palsy, bacterial meningitis, and brain tumor) that would preclude evaluation of the response to study intervention.
8. Congenital disorders such as maxillofacial dysplasia.
9. Spontaneous perforation of the tympanic membrane and drainage for longer than 24 hours.
10. Tympanoplastic tube(s) in place, or has anatomic abnormalities associated with recurrent AOM, prolonged middle ear effusion, including cleft palate or repair, high-arched palate, or Down's syndrome.
11. Severe cases of CABP including Hypoxemic, Septic, Ventilator-associated or hospital-acquired pneumonia
12. Need corticosteroid for systemic (inhalational steroids as controller therapy in asthma is allowed)
13. Infectious mononucleosis
14. Evidence of leukopenia and/or thrombocytopenia.
15. History of previous hypersensitivity reaction to penicillins, cephalosporins or other Beta-lactam antibiotics.
16. History of AMC/CVA-associated cholestatic jaundice/hepatic dysfunction.
17. History of phenylketonuria or a known hypersensitivity to aspartame.

18. Received, within 48 hours of study entry, or is scheduled to receive during the study period, any medication which may alter bowel function.
19. Currently receiving or has received more than one dose of systemic antibiotic therapy within one week prior to the initiation of the study.
20. Receipt of an investigational compound (non-FDA and non-DCGI approved) or device within the previous 30 days or five half-lives, whichever is longer, preceding the first dose of study intervention or during the study.
21. Participants with symptoms suggestive of active COVID-19 infection (ie, fever, cough, etc).
22. Participants with known COVID-19 positive contacts within the past 14 days.

5.3. Lifestyle modifications

Lifestyle modifications are not mandated in this study. Advise related to diet and activity will be based on physician's discretion.

5.4. Study Procedure

5.4.1. Schedule of Assessments

Schedule of assessment is presented in Section 1.3.

5.4.2. Screening, Enrolment and Baseline Assessments

Preliminary Visit (Day 0):

A series of screening evaluations will be performed at Preliminary Visit in order to determine whether prospective study participant meet the selection criteria for the study. The following assessments will take place at the Preliminary visit:

- The Investigator or designated study personnel will inform each participant's parent/ guardian of the nature of the study, explain the potential risks, and obtain written informed consent prior to performing any study-related procedures.
- Participant is 6 months to 12 years of age at the time of signing of informed consent by parent(s)/legal guardian(s), as applicable.
- Children between 7 to 12 years to assent prior to performing any study-related procedures.
- The participant and parent(s)/legal guardian(s) are willing and able to comply with the study protocol.
- In accordance with regional/local laws and regulations, the parent(s)/legal guardian(s) has given written informed, dated consent; and the participant (age 7 to 12 years) has given written assent, if applicable, to participate in the study.
- Assessment for eligibility against the inclusion and exclusion criteria.
- Medical history documentation.
- Demographic data (race, age, sex).

- Vital signs (body temperature, pulse rate, and respiratory rate).
- Physical examination (assessments of the skin, cardiovascular, respiratory, gastrointestinal, and neurological systems, height, and weight).
- Laboratory evaluations (hematology, plasma creatinine, aspartate aminotransferase [AST], alanine aminotransferase [ALT] and bilirubin).
- Chest X ray and X ray of nasal/paranasal sinus to be performed for patients presumed to have CABP and ABRS (only for reference, as per investigators discretion).
- Prior/concomitant medications.
- Baseline bowel movements.
- Documentation of the baseline signs and symptoms (other than disease under study).

5.4.3. On Therapy

5.4.3.1. Day 1

- On Day 1 of the treatment period, the parent/guardian of the participant will be provided with the following:
    - Study intervention
    - Patient Diary card
- The parent(s)/legal guardian(s) of the participant will be instructed about study intervention reconstitution, dosing, storage and entering the details in the Patient Dairy card. The first dose will be from the participant pack.
- Any adverse events after signing the inform consent form will be collected.

Note: Visit 1 can be completed on the same day as the preliminary day 0 visit if the laboratory test results are available on the same day.

5.4.3.2. On-therapy Visit (Days 3 to 5)

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 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.

Hence, the following will be evaluated at the OT Visit:

- TEAE (primary endpoint)
- Early Clinical Response (secondary endpoint)

- Incidence of Protocol-defined diarrhea (secondary endpoint)
- Vital signs
- Local examination
- Concomitant medication
- Bowel movements
- Physical examination (assessments of the skin, cardiovascular, respiratory, gastrointestinal, and neurological systems, height and weight)
- Clinical assessment

5.4.3.3. Interim Visit (Within 24 Hours of Notification)

Participants will be called for interim visit within 24 hours of notification to the site for the interim evaluation after OT visit (Day 3 to 5) but prior to EOT, if there is worsening of signs and symptoms, severe AE or SAE, or occurrence of PDD. Failure shall be assessed by the investigator. If the clinical failure or PDD or SAE is diagnosed/confirmed by the Investigator, then the subjects will be withdrawn from the study intervention (as per Investigator) 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 participants will return at FU visit (Day 22 to 28) for safety assessment.

The following will be evaluated at the Interim Visit:

- TEAE (primary endpoint)
- Primary Clinical Response (secondary endpoint)
- Incidence of Protocol-defined diarrhea (secondary endpoint)
- Vital signs
- Local examination
- Concomitant medication
- Bowel movements
- Physical examination (assessments of the skin, cardiovascular, respiratory, gastrointestinal, and neurological systems, height and weight)
- Clinical assessment
- Review of Patient Diary card

5.4.4. End of Therapy Visit (Day 12 to 14)

At the EOT visit the following evaluations will be performed:

- TEAE (primary endpoint)
- Primary clinical response (secondary endpoint)
- Incidence of Protocol-defined diarrhea (secondary endpoint)
- Vital signs
- Concomitant medication

- Bowel movements
- Local examination
- Physical examination (assessments of the skin, cardiovascular, respiratory, gastrointestinal, and neurological systems, height and weight)
- Clinical assessment
- Review of Patient Diary card
- Collection of Patient Diary card
- Assessment of compliance
- Return of study intervention (used and unused)

All participants, including participants who had treatment 'failure' at EOT will be managed as per Investigator's discretion, and their next visit (FU) will be scheduled on Day 22 to 28 (unless there is a recurrence).

5.4.5. Post Therapy

5.4.5.1. Interim Visit (Day 15 to 21)

This visit shall occur between the EOT and Follow up Visit (Days 22 to 28) for participants with recurrence of sign/symptoms after EOT visit. Participants will be required to return to the site at the time of recurrence. At post therapy interim visit, the following evaluations will be performed:

- Follow up of ongoing TEAEs (primary endpoint)
- Recording new AEs
- Secondary clinical response (secondary endpoint)
- Incidence of Protocol-defined diarrhea (secondary endpoint)
- Vital signs
- Concomitant medication
- Bowel movements
- Local examination
- Physical examination (assessments of the skin, cardiovascular, respiratory, gastrointestinal, and neurological systems, height and weight)
- Clinical assessment

The participants evaluated at post therapy interim visit, are required to return at scheduled FU visit (Days 22 to 28) for additional safety (not efficacy) assessment.

5.4.5.2. Follow up Visit (Day 22-28)

All participants including withdrawals will return for a scheduled FU visit. This will occur on Days 22 to 28.

At scheduled FU visit, the following evaluations will be performed:

- TEAE (primary endpoint)

- Secondary clinical response* (secondary endpoint)
- Incidence of Protocol-defined diarrhea (secondary endpoint)
- Vital signs
- Concomitant medication
- Bowel movements
- Local examination
- Physical examination (assessments of the skin, cardiovascular, respiratory, gastrointestinal, and neurological systems, height and weight)
- Clinical assessment

*Except for participants with disease recurrence post EOT, as their secondary clinical response evaluation will be completed at the interim visit (Day 15-21) ie, at the time of recurrence.

At both scheduled EOT and FU visits, the parent or legal guardian will be asked about any AE(s) or concomitant medications. All unused study intervention, empty medication bottles and Patient Diary cards should be returned at any EOT visit, or the FU visit if not returned at the EOT visit. At the time of return, Patient Diary cards will be reviewed by the study coordinator for completeness.

Overall compliance with the study intervention schedule will be monitored using Patient Diary cards. Compliance of between 80% and 120% (and intake of at least four doses on Days 1 and 2) is required for the participant to be considered as evaluable.

5.4.6. Reason of Concluding Study

In this study, a completed participant is one who satisfy all study entry criteria, complete the 10-day treatment phase, and complete scheduled visits ie, OT, EOT, and FU visits. The Investigator has the option of removing a participant from the study prematurely for a variety of reasons, including AE(s), insufficient therapeutic effect, deviation from protocol (including noncompliance to study intervention schedule, dosing regimen or visit schedule), lost to follow-up, or other reason as specified by the Investigator.

5.5. Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently entered in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, any protocol deviations, and any serious adverse events (SAEs). Individuals who do not meet the criteria for participation in this study (screen failure) will not be rescreened.

6. STUDY INTERVENTION

Study intervention is defined as any investigational intervention(s), marketed product(s), placebo, or medical device(s) intended to be administered to a study participant according to the study protocol.

6.1. Study Intervention(s) Administered

Table 3 below provides the details of study intervention administered.

Table 3 Study Intervention

ARM Name	Single arm interventional trial
Intervention Name	Augmentin (ES)-600
Type	Drug
Dose Formulation	Suspension
Unit Dose Strength(s)	Each 5 mL of the reconstituted suspension contains: Amoxicillin Trihydrate IP equivalent to Amoxicillin 600 mg Potassium Clavulanate Diluted IP equivalent to Clavulanic Acid 42.9 mg
Dosage Level(s)	90/6.4 mg/kg/day, 12 hourly
Route of Administration	Oral
Use	Experimental
IMP and NIMP	Amoxycillin and Potassium Clavulanate Oral Suspension IP 600 mg/42.9 mg per 5 ml
Sourcing	Provided centrally by the Sponsor
Packaging and Labeling	Study Intervention will be provided in container. Each container will be labelled as required per country requirements.
Current/Former Name(s) or Alias(es)	Augmentin (ES)-600

6.1.1. Medical Devices

- There are no GSK manufactured medical devices (or devices manufactured for GSK by a third party) provided for use in this study.
- Other medical devices (not manufactured by or for GSK) provided for use in this study are: adapta-caps and labelled oral dosing syringes (5 mL).
- Instructions for medical device use are provided in Study Reference Manual.
- All device deficiencies, (including malfunction, use error and inadequate labelling) shall be documented, and reported by the Investigator throughout the study (see Section 8.3.9) and appropriately managed by the sponsor.

6.2. Preparation/Handling/Storage/Accountability

1. The Investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study intervention received and any discrepancies are reported and resolved before use of the study intervention.
2. Only participants enrolled in the study may receive study intervention and only authorized site staff may supply or administer study intervention. All study interventions must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the Investigator and authorized site staff.
3. The Investigator, institution, or the head of the medical institution (where applicable) is responsible for study intervention accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).
4. Further guidance and information for the final disposition of unused study intervention are provided in the Study Reference Manual.

Participants will be dosed at 90/6.4 mg/kg/day in two equally divided doses every 12 hours. The supervised first-dose will be from participant pack. Parents/legal guardians will be demonstrated reconstitution, handling, and storage procedures on Day 0/1. They will then administer the daily dose over the course of the study as per the instruction provided by the Investigator/designee. The amount to be dosed for the participant as per the weight should be according to recommended dosing chart provided in the Study Reference Manual.

The volume of the dose to be administered will be recorded in the Patient Diary card. The two daily doses should be given approximately 12 hours apart immediately at the start of meal in morning and evening. Parents/legal guardians will be instructed on proper dose measurement, dosing techniques, method of reconstitution, and handling and storage of reconstituted study intervention as per the details provided in Study reference manual.

Graduated cylinders will be provided to assist the study co-ordinator with the reconstitution of the study intervention. Adapta-caps and labelled oral dosing syringes

(5 mL) will be provided to assist with dispensing of the reconstituted study intervention. A separate syringe will be used on the study day (Day 1).

Participant will be supplied one unit (prepared) of study intervention after supervised first dose intake on Day 1. For subsequent dosing, participants will reconstitute medication at home as per instructions given on Day 1. Reconstituted suspension should be stored refrigerated at 2°C to 8°C and should not be frozen. The non-reconstituted study intervention should be stored in a dry place in the original package to protect from moisture. Each participant will receive enough study intervention for 10 days of dosing, as appropriate to the treatment regimen and body weight. Each package will be labelled as required per regulatory requirement.

Drug Accountability

The sites will maintain drug accountability and retain all used, partially used, and unused study drug materials until the end of the study. Completed Patient Diary cards will be used by the Investigator to assess compliance.

Missed Doses

The parent/legal guardian should be instructed to administer the study drug on time. If the parent/legal guardian forgets to administer a dose, it should be administered immediately and no later than 3 hours from the scheduled timing of the dose. The next daily dose should be administered on the same time. If more than 3 hours is lapsed beyond scheduled time, that particular dose should be skipped, and the next daily dose should be administered as scheduled.

6.3. Measures to Minimize Bias: Randomization and Blinding

This is a non-comparative open-label study. Therefore, randomization and blinding are not applicable for this study.

6.4. Study Intervention Compliance

Unused clinical supplies and empty medication bottles should be returned from the site for shipment to GlaxoSmithKline Pharmaceuticals.

Participant compliance with the dosing schedule will be monitored using Patient Diary cards that will be completed by the parent/guardian and will be reviewed by the study coordinator on return to the site at EOT visit (Day 12 to 14). Compliance is required to be 80 to 120% through EOT. Noncompliance with the study intervention schedule prior to withdrawal from or completion of the study will be considered a protocol violation.

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%

6.5. Concomitant Therapy

During the trial, concomitant medication(s) necessary for the health of the participant will be permitted (as per physician/Investigator assessment); however, no additional antimicrobial therapy will be allowed. Participants who receive alternate antibiotics because of no improvement, worsening, or recurrence of signs/symptoms will be considered, by definition, clinical “failures".

Medications with the potential to alter bowel habit are to be avoided during the study period. Concomitant use of oral or nasal antihistamines, decongestants, antifungals and/or inhaled steroids (controller therapy for asthma) are permitted during the study. Tubular secretion inhibitors of Augmentin (eg, probenecid) is prohibited. All concomitant medications taken during the study (up to and including the post-therapy FU visit) will be recorded on the eCRF.

6.5.1. Rescue Medicine

Not applicable.

6.6. Dose Modification

Dose-modification or re-treatment is not allowed in the study.

6.7. Intervention after the End of the Study

The participants will not be provided with any intervention after the end of the study.

7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1. Discontinuation of Study Intervention

In rare instances, it may be necessary for a participant to permanently discontinue (definitive discontinuation) study intervention. If study intervention is definitively discontinued, the participant will remain in the study to be evaluated for safety and efficacy. See the SoA (Section 1.3) for data to be collected at the time of discontinuation of study intervention and follow-up and for any further evaluations that need to be completed.

7.2. Participant Discontinuation/Withdrawal from the Study

- A participant may withdraw from the study at any time at his/her own request or may be withdrawn at any time at the discretion of the Investigator for safety, behavioral, compliance or administrative reasons. This is expected to be uncommon.

- 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.
- Participants with worsening of signs and symptoms, severe AE, SAE, or having PDD at OT visit (Day 3 to 5) will be assessed by investigators and withdrawn from study as per investigator's discretion and treated appropriately. In such case, the OT 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 participants will return at FU visit (Day 22 to 28) for safety assessment.
- Participants with worsening of signs and symptoms, severe AE, SAE, or having PDD after OT visit (Day 3 to 5) but prior to EOT visit will be assessed by investigators and withdrawn from study as per investigator's 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 participants will return at FU visit (Day 22 to 28) for safety assessment.
- See SoA for data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed.
- If the participant withdraws consent for disclosure of future information, the Sponsor may retain and continue to use any data collected before such a withdrawal of consent.

If a participant withdraws from the study, he/she may request destruction of any samples taken and not tested, and the Investigator must document this in the site study records.

7.3. Lost to Follow Up

A participant will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow up, the Investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls on 3 consecutive days and, if necessary, a certified letter to the

participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record.

- Should the participant continue to be unreachable, he/she will be considered to have withdrawn from the study.

Discontinuation of specific sites or of the study are handled as part of Appendix 1.

8. STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and their timing are summarized in the SoA.
- Protocol waivers or exemptions are not allowed.
- Immediate safety concerns should be discussed with the Sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study intervention.
- Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The Investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.
- Procedures conducted as part of the participant's routine clinical management (eg, blood count) and obtained before signing of ICF may be utilized for screening or baseline purposes provided the procedure met the protocol-specified criteria and was performed within the time frame defined in the SoA.

8.1. Efficacy Assessments

The efficacy is secondary endpoint in this study and assessed by clinical response.

The *early clinical response* is categorized as treatment "success" or treatment "failure" at OT (Day 3 to 5). A treatment "success" at OT is defined as either "clinical cure" or "improvement". A treatment "failure" is defined as a participant whose clinical outcome is "clinical failure" (due to worsening or non-improvement in symptoms or requirement of additional antibiotic) or "unable to determine" at OT (Day 3 to 5).

The *primary clinical response* is categorized as treatment "success" or treatment "failure" at EOT. A treatment "success" at EOT is defined as either "clinical cure" or "improvement" at scheduled EOT (Day 12-14). A treatment "failure" is defined as a participant whose clinical outcome is "clinical failure" (due to worsening or non-improvement in symptoms) or "unable to determine" at scheduled EOT (Day 12 to 14) or interim visit as EOT.

The *secondary clinical response* is categorized as treatment "success" or treatment "failure" at FU visit. A treatment "success" at FU is defined as "persistent clinical cure" and treatment "failure" (clinical recurrence or unable to determine).

Participants experiencing clinical 'failure' or having PDD or severe AE or SAE after OT visit (Day 3 to 5) but prior to EOT, the *primary clinical response* is categorized as treatment "success" (clinical cure or improvement) or "failure" (worsening or non-improvement in symptoms or "unable to determine") at interim visit (pre EOT).

For participants experiencing disease recurrence post EOT (Day 12 to 14), *secondary clinical response* is categorized as treatment "failure" (clinical recurrence) at post EOT interim visit.

Evaluation of Early Clinical Response at OT visit (Day 3 to 5)

Early clinical response will be evaluated by comparing baseline (pre-treatment) signs/symptoms with those observed at OT visit (ie, Day 3 to 5). The Investigator will evaluate each participant's clinical outcome as follows (Table 4):

Table 4 Parameters of Early Clinical Response

Success	Clinical cure	Sufficient resolution or improvement of the signs and symptoms. 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).

Evaluation of Primary Clinical Response at EOT visit (Day 12 to 14) or Interim visit after OT but prior to EOT (within 24hrs of notification, in case of clinical 'failure' or 'AE')

Primary clinical response will be evaluated by comparing baseline signs/symptoms with those observed at the scheduled EOT visit (ie, Day 12 to 14) or at the time of withdrawal (visit), the Investigator will evaluate each participant's clinical outcome as shown in Table 5.

Table 5 Parameters of Primary Clinical Response

Success	Clinical cure	Sufficient resolution or improvement of the signs and symptoms. No additional antibiotic therapy is indicated.
	Improvement	Improvement, but incomplete resolution of 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).

Note: Participants 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 and treated appropriately (as per Investigator). 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 participants will return at FU visit (Day 22 to 28) for safety assessment.

Evaluation of Secondary Clinical Response at Follow-Up (Day 22 to 28) or Post therapy interim visit (in case of recurrence)

Clinical assessments will be performed at follow-up visit only for participants who were treatment successes at the EOT. By reviewing the clinical information obtained at the follow-up evaluation (Day 22 to 28), the Investigator will determine whether a satisfactory response is maintained, or a relapse has occurred (Table 6).

Table 6 Parameters of Secondary Clinical Response

Success	Persistent clinical cure*	Sufficient resolution of signs/symptoms for those participants who were clinically cured or improved at the end of therapy. No additional antibiotic indicated.
Failure	Clinical recurrence	Reappearance of signs/symptoms for those participants 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).

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

8.2. Safety Assessments

Safety is the primary objective of the study.

The primary endpoint of the study is to assess treatment-emergent adverse events (TEAE) in children with AOM receiving Augmentin (ES)-600 at a dose of 90/6.4 mg/kg/day in two divided doses, administered for 10 days.

Incidence of PDD will be evaluated as secondary endpoint, along with efficacy parameters. protocol-defined diarrhea (PDD) is defined as:

- 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.

Participants who withdraw due to diarrhea or has a documented SAE of diarrhea will be considered to have fulfilled the criteria for PDD and will be analyzed as such, even in the absence of Patient Diary card data.

8.2.1. Physical Examinations

- Physical examination will include, at a minimum, assessments of the skin, cardiovascular, respiratory, gastrointestinal, and neurological systems. Height and weight will also be measured and recorded.
- Investigators should pay special attention to clinical signs related to previous serious illnesses.

8.2.2. Vital Signs

- Body temperature, pulse rate, and respiratory rate will be assessed.
- Pulse measurements will be assessed with a completely automated device. Manual techniques will be used only if an automated device is not available.
- Pulse measurements should be preceded by at least 5 minutes of rest for the participant in a quiet setting without distractions.

8.2.3. Clinical Safety Laboratory Assessments

Refer to Appendix 2 for the list of clinical laboratory tests to be performed and to the SoA for the timing and frequency. The evaluations will be performed at local laboratory at each site.

All protocol-required laboratory assessments, as defined in Appendix 2, must be conducted in accordance with the SoA.

8.2.4. Radiographic Evaluations (X Ray)

An X ray will be performed only at preliminary visit at the study site. Chest X ray and X ray of nasal/paranasal sinus to be performed for patients presumed to have CABP and ABRS. The X ray is not mandatory and performed only for reference, as per investigators discretion. The purpose of radiographic evaluation is only to confirm the diagnosis when CABP or ABRS clinically, reasonably suspected but can't be confirmed with clinical criteria. Since children demonstrates signs and symptoms of CABP differently than adults and may deteriorate more rapidly than adults, keeping an option of chest X ray in the inclusion criteria is critical for investigators to rule out any need for hospitalization.

8.3. Adverse Events and Serious Adverse Events

The definitions of an AE or SAE can be found in Appendix 3.

The definitions of device-related safety events, (adverse device effects [ADEs]) and serious adverse device effects (SADEs), can be found in Appendix 5. Device deficiencies are covered in Section 8.3.9.

AEs will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative).

The Investigator and any qualified designees are responsible for detecting, documenting, and reporting events that meet the definition of an AE or SAE and remain responsible for following up AEs that are serious, considered related to the study intervention or the study, or that caused the participant to discontinue the study intervention or study (see Section 7).

8.3.1. Time Period and Frequency for Collecting AE and SAE Information

- All SAEs will be collected from the signing of the informed consent form until the follow-up visit at the time points specified in the SoA (Section 1.3).
- All AEs will be collected from the start of study intervention until the follow-up visit at the time points specified in the SoA (Section 1.3).

- Medical occurrences that begin before the start of study intervention but after obtaining informed consent will be recorded on the Medical History/Current Medical Conditions section of the case report form (eCRF) not the AE section.
- All SAEs will be recorded and reported to the Sponsor or designee immediately and under no circumstance should this exceed 24 hours, as indicated in Appendix 3. The Investigator will submit any updated SAE data to the Sponsor within 24 hours of it being available.
- Investigators are not obligated to actively seek AEs or SAEs after the conclusion of the study participation. However, if the Investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event to be reasonably related to the study intervention or study participation, the Investigator must promptly notify the Sponsor.

8.3.2. Method of Detecting AEs and SAEs

- The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Appendix 3.
- Care will be taken not to introduce bias when detecting AE and/or SAE. Open-ended and non-leading verbal questioning of the participant is the preferred method to inquire about AE occurrence.
- Physical examination may reveal certain AEs not reported by the participant.

8.3.3. Follow-up of AEs and SAEs

After the initial AE/SAE report, the Investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs, will be followed until the event is resolved, stabilized, otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3). Further information on follow-up procedures is given in Appendix 3.

8.3.4. Regulatory Reporting Requirements for SAEs

- Prompt notification by the Investigator to the Sponsor of a SAE is essential so that legal obligations and ethical responsibilities toward the safety of participants and the safety of a study intervention under clinical investigation are met.
- The Sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies (if applicable) about the safety of a study intervention under clinical investigation. The Sponsor will comply with country-

specific regulatory requirements relating to safety reporting to the regulatory authority, Institutional Review Boards (IRB)/Independent Ethics Committees (IEC), and Investigators.

- For all studies except those utilizing medical devices Investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSAR) according to local regulatory requirements and Sponsor policy and forwarded to Investigators as necessary.
- An Investigator who receives an Investigator safety report describing a SAE or other specific safety information (eg, summary or listing of SAEs) from the Sponsor will review and then file it and will notify the IRB/IEC, if appropriate according to local requirements.

8.3.5. Pregnancy

- Details of all pregnancies in female participants will be collected at Day 0.
- Participants will be instructed to notify the Investigator if they become pregnant during study period. Such participants will be immediately withdrawn from the study.
- Any reported pregnancy must be informed to Sponsor by Investigator within 24 hours of receipt of information and should follow the procedures outlined in Appendix 4.
- Any abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAE.

8.3.6. Cardiovascular and Death Events

For any cardiovascular events detailed in Appendix 3 and all deaths, whether they are considered SAEs, specific Cardiovascular (CV) and Death sections of the eCRF will be required to be completed. These sections include questions regarding cardiovascular (including sudden cardiac death) and non-cardiovascular death.

The CV eCRFs are presented as queries in response to reporting of certain CV MedDRA terms. The CV information should be recorded in the specific cardiovascular section of the eCRF within one week of receipt of a CV event data query prompting its completion.

The Death eCRF is provided immediately after the occurrence or outcome of death is reported. Initial and follow-up reports regarding death must be completed within 1 week of when the death is reported.

8.3.7. Disease-Related Events and/or Disease-Related Outcomes Not Qualifying as SAEs

There are no disease related events (DREs) commonly seen in participants with AOM which can be serious/life-threatening.

8.3.8. Adverse Events of Special Interest

There are no adverse events of special interest planned to be monitored.

8.3.9. Medical Device Deficiencies

Medical devices are being provided for use in this study to measure and administer the study intervention. In order to fulfil regulatory reporting obligations worldwide, the Investigator is responsible for the detection and documentation of events meeting the definitions of device deficiency that occur during the study with such devices.

The definition of a Medical Device Deficiency can be found in Appendix 5.

NOTE: Incidents fulfilling the definition of an AE/SAE will also follow the processes outlined in Section 8.3.3 and Appendix 3 of the protocol.

8.3.9.1. Time Period for Detecting Medical Device Deficiencies

- Medical device deficiencies will be detected, documented, and reported during all periods of the study in which the medical device is used.
- If the Investigator learns of any device deficiency at any time after a participant has been discharged from the study, and such device deficiency is considered reasonably related to a medical device provided for the study, the Investigator will promptly notify the Sponsor.

The method of documenting Medical Device Incidents is provided in Appendix 5.

8.3.9.2. Follow-up of Medical Device Deficiencies

- Follow-up applies to all participants, including those who discontinue study intervention or the study.
- The Investigator is responsible for ensuring that follow-up includes any supplemental investigations as indicated to elucidate the nature and/or causality of the deficiency.
- New or updated information will be recorded on the originally completed form with all changes signed and dated by the Investigator.

8.3.9.3. Prompt Reporting of Medical Device Deficiencies to Sponsor

- Device deficiencies will be reported to the Sponsor within 24 hours after the Investigator determines that the event meets the protocol definition of a device deficiency.
- The Medical Device Deficiency Report Form will be sent to the Sponsor by fax. If fax is unavailable, then email should be utilized.
- The Sponsor will be the contact for the receipt of device deficiency reports.

8.3.9.4. Regulatory Reporting Requirements for Medical Device Incidents

- The Investigator will promptly report all deficiencies occurring with any medical device provided for use in the study for the Sponsor to fulfill the legal responsibility to notify appropriate regulatory authorities and other entities about certain safety information relating to medical devices being used in clinical studies.

The Investigator, or responsible person according to local requirements (eg, the head of the medical institution), will comply with the applicable local regulatory requirements relating to the reporting of device deficiencies to the IRB/IEC.

8.4. Treatment of Overdose

For this study, any dose of Augmentin (ES)-600 greater than 90/6.4 mg/kg/day within a 24-hour time period will be considered an overdose.

Sponsor does not recommend any specific treatment for an overdose.

In the event of an overdose, the Investigator should:

5. Contact the Medical Monitor immediately.
6. Document the quantity of the excess dose as well as the duration of the overdosing in the eCRF.

Further decision regarding dose interruptions or modifications will be made by the Investigator in consultation with the Medical Monitor based on the clinical evaluation of the participant.

8.5. Pharmacokinetics

Pharmacokinetic parameters are not evaluated in this study.

8.6. Pharmacodynamics

Pharmacodynamic parameters are not evaluated in this study.

8.7. Genetics

Genetics are not evaluated in this study.

8.8. Biomarkers

Biomarkers are not evaluated in this study.

8.9. Immunogenicity Assessments

Immunogenicity assessments are not evaluated in this study.

8.10. Health Economics OR Medical Resource Utilization and Health Economics.

Health Economics/Medical Resource Utilization and Health Economics parameters are not evaluated in this study.

9. STATISTICAL CONSIDERATIONS

9.1. Statistical Hypotheses

No formal hypothesis is considered.

9.2. Sample Size Determination

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 Table 7 below. These prevalence values are based on all ARTIs in India.

Table 7 Prevalence for Division of Sample Size

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.

9.2.1. Sample Size Sensitivity

The sensitivity of the precision is calculated with respect to 5 different proportions estimated as presented below in Table 8.

Table 8 Sample Size Sensitivity for Precision

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%)

9.3. Populations for Analyses

The following populations are defined (Table 9):

Table 9 Analysis Population

Population	Description
Enrolled	All participants who sign the ICF
Intent-to-Treat	All participants who are enrolled and receive at least 1 administration of the investigational product (Augmentin [ES]-600) will be included in the analysis.

9.4. Statistical Analyses

The statistical analysis plan will include a more technical and detailed description of the statistical analyses described in this section. This section is a summary of the planned statistical analyses of the most important endpoints including primary and key secondary endpoints.

9.4.1. General Considerations

Descriptive statistics will be provided for baseline characteristics, efficacy, and safety data. Descriptive statistics on continuous measurements will include means, medians, standard deviations, and ranges, while categorical data will be summarized using counts and percentages. Graphical summaries of the data may also be presented. No subgroup analysis will be conducted.

9.4.2. Primary Endpoint(s)

Statistical analyses on safety endpoints will be conducted using participants from the Intent-to-Treat (ITT) population.

Adverse Events

The primary safety endpoint is the incidence of participants reporting at least one TEAE combined across all the indications.

The primary estimand is the percentage of participants reporting at least one TEAE regardless of withdrawal from the study resulting in loss to follow-up. The while-on-treatment strategy will be used, which will count and analyse adverse event occurred during treatment effect (During treatment Period + lag time of 1day).

Apart from the TEAE, overall adverse events would be reported as collected (Treatment Policy).

The primary safety endpoint will be summarized using number and percentage of participants reporting any TEAEs and participants with at least one TEAE with corresponding exact 95% CI.

Participant incidence of all TEAEs will be tabulated by system organ class (SOC) and preferred term (PT). The number and percentage of participants reporting adverse events will be evaluated and will also be tabulated by relationship to study drug.

All summaries will be reported as overall summaries and also stratified by indication.

Further details will be provided in the Statistical Analysis Plan (SAP).

9.4.3. Secondary Endpoint(s)

Statistical analyses on efficacy endpoints will be conducted using participants from the Intent to treat population. All the displays will be created as overall summaries and as stratified by indication.

Early Clinical Response

The estimand is the proportion of successful clinical responses. The intercurrent events expected for this endpoint are:

- Discontinuation of study treatment due to AE
- Discontinuation of study treatment due to lack of efficacy
- Use of rescue medication
- Discontinuation of study treatment due to any other reason

The estimand strategies for the above intercurrent events are

- A **composite strategy** would be used if intercurrent event **'Discontinuation of study treatment due to AE' Discontinuation of study treatment due to lack of efficacy**' and '**Use of rescue medication**'occur. That is, if a subject discontinues the study treatment due to AE or due to lack of efficacy or uses rescue medication, the subject will be imputed as a failure.
- A treatment policy would be used if intercurrent event 'Discontinuation of study treatment due to any other reason' occurs. That is, if a subject discontinues the study treatment due to any other reason (other than AE, lack of efficacy or use of rescue medication), the data for that subject will be analysed as collected

The proportion of clinical response OT (Days 3 to 5) (defined as: A treatment success is defined as either "clinical cure" or "improvement" at end of therapy and treatment failure is defined as a participant whose clinical outcome was "clinical failure" or "unable to determine") with corresponding 95% CI will be calculated. A full description of statistical analysis methods will be mentioned in SAP of study.

Primary Clinical Response

The estimand is the proportion of successful clinical responses. The intercurrent events expected for this endpoint are:

- Lack of compliance (<80%)
- Discontinuation of study treatment due to lack of efficacy
- Discontinuation of study treatment due to AE
- Use of rescue medication
- Discontinuation of study treatment due to any other reason

The estimand strategies for the above intercurrent events are

- A **principal stratum** strategy will be used in case of **'Lack of compliance (<80%)'**. That is, only those subjects who have more than 80% compliance would be considered in the calculation of proportion.
- A **composite strategy** would be used if intercurrent events **'Discontinuation of study treatment due to lack of efficacy' and 'Discontinuation of study treatment due to AE' and 'Use of rescue medication'** occur. That is, if a

subject discontinues the study treatment due to lack of efficacy or due to AE or uses rescue medication, the subject will be imputed as a failure.

- A treatment policy would be used if intercurrent event 'Discontinuation of study treatment due to any other reason' occurs. That is, if a subject discontinues the study treatment due to any other reason (other than AE, lack of efficacy or use of rescue medication), the data for that subject will be analysed as collected.

The proportion of clinical response at EOT (defined as: A treatment success is defined as either "clinical cure" or "improvement" at end of therapy and treatment failure is defined as a participant whose clinical outcome was "clinical failure" or "unable to determine") with corresponding exact 95% CI will be calculated. A full description of statistical analysis methods will be mentioned in SAP of study.

Secondary Clinical Response

No intercurrent event is defined for this endpoint as no events are expected to occur during the follow-up period. The data will be analyzed as collected.

The proportion of clinical response (defined as any of the following: treatment success is defined as a "persistent clinical cure" and Treatment failure is defined as a participant whose clinical outcome was "clinical recurrence" or "unable to determine") with corresponding exact 95% CI will be calculated.

Protocol-defined diarrhoea (PDD)

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

The number and percentage of participants reporting incidence of PDD with corresponding exact 95% CI will be calculated and tabulated.

9.4.4. Other Safety Analyse(s)

Safety data including clinical assessments, physical examination findings will be presented in tabular and/or graphical format and summarized descriptively according to GSK's Integrated Data Standards Library (IDSL) standards. Complete details will be documented in the SAP.

9.5. Interim Analyses

No interim analysis is planned for the study.

9.6. Data Monitoring Committee (DMC) or Other Review Board

Not applicable.

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1. Appendix 1: Regulatory, Ethical, and Study Oversight Considerations

10.1.1. Regulatory and Ethical Considerations

- This study will be conducted in accordance with the protocol and with:
    - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
    - Applicable ICH Good Clinical Practice (GCP) Guidelines
    - Applicable laws and regulations
- The protocol, protocol amendments, ICF, Investigator Brochure, and other relevant documents (eg, advertisements) must be submitted to an IRB/IEC by the Investigator and reviewed and approved by the IRB/IEC before the study is initiated.
- Any amendments to the protocol will require IEC/IRB approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.
- The Investigator will be responsible for the following:
    - Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/EC
    - Notifying the IRB/IEC of SAE or other significant safety findings as required by IRB/IEC procedures
    - Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations

10.1.2. Financial Disclosure

Investigators and sub-Investigators will provide the Sponsor with sufficient, accurate financial information as requested to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities.

Investigators are responsible for providing information on financial interests during the study and for 1 year after completion of the study.

10.1.3. Informed Consent Process

- The Investigator or his/her representative will explain the nature of the study to the participant or his/her legally authorized representative (defined in ICH-GCP as an individual, juridical or other body authorized under applicable law to consent, on behalf of a prospective individual, to the individual's participation in the clinical trial) and answer all questions regarding the study.
- Participants must be informed that their participation is voluntary. Participants or their legally authorized representative will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB/IEC or study center.
- The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- Participants between age 7 to 12 years will sign the most current version assent form during participation in the study. Procedure of obtaining assent will conform to ICH-GCP regulations, details of which will be mentioned in the assent form.
- Participants must be re-consented to the most current version of the ICF(s) during their participation in the study.
- A copy of the ICF(s) must be provided to the participant or the participant's legally authorized representative.

GSK (alone or working with others) may use participant's coded study data and samples and other information to carry out this study; understand the results of this study; learn more about the study intervention or about the study disease; publish the results of these research efforts; work with government agencies or insurers to have the the study intervention approved for medical use or approved for payment coverage.

10.1.4. Data Protection

- Participants will be assigned a unique identifier by the Sponsor. Any participant records or datasets that are transferred to the Sponsor will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.

- The participant must be informed that his/her personal study-related data will be used by the Sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant who will be required to give consent for their data to be used as described in the informed consent.
- The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the Sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

10.1.5. Committees Structure

Not applicable.

10.1.6. Dissemination of Clinical Study Data

- Where required by applicable regulatory requirements, an Investigator signatory will be identified for the approval of the clinical study report. The Investigator will be provided reasonable access to statistical tables, figures, and relevant reports and will have the opportunity to review the complete study results at a GSK site or other mutually agreeable location.
- GSK will also provide the Investigator with the full summary of the study results. The Investigator is encouraged to share the summary results with the study participants, as appropriate.
- The procedures and timing for public disclosure of the protocol and results summary and for development of a manuscript for publication for this study will be in accordance with GSK Policy.
- GSK intends to make anonymized patient-level data from this trial available to external researchers for scientific analyses or to conduct further research that can help advance medical science or improve patient care. This helps ensure the data provided by trial participants are used to maximum effect in the creation of knowledge and understanding
- A manuscript will be progressed for publication in the scientific literature if the results provide important scientific or medical knowledge.

10.1.7. Data Quality Assurance

- All participant data relating to the study will be recorded on printed or electronic eCRF unless transmitted to the Sponsor or designee electronically (eg, laboratory data). The Investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the eCRF.
- The Investigator must maintain accurate documentation (source data) that supports the information entered in the eCRF.

- The Investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.
- Monitoring details describing strategy (eg, risk-based initiatives in operations and quality such as Risk Management and Mitigation Strategies and Analytical Risk-Based Monitoring), methods, responsibilities and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in the Monitoring Plan.
- The Sponsor or designee is responsible for the data management of this study including quality checking of the data.
- The Sponsor assumes accountability for actions delegated to other individuals (eg, Contract Research Organizations).
- Study monitors will perform ongoing source data verification to confirm that data entered into the eCRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.
- Records and documents, including signed ICF, pertaining to the conduct of this study must be retained by the Investigator for 25 years from the issue of the final Clinical Study Report (CSR)/ equivalent summary unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the Sponsor. No records may be transferred to another location or party without written notification to the Sponsor.

10.1.8. Source Documents

- Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the Investigator's site.
- Data reported on the eCRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The Investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.
- Definition of what constitutes source data can be found in Study Reference Manual.

10.1.9. Study and Site Start and Closure

The study start date is the date on which the clinical study will be open for recruitment of participants.

The first act of recruitment is the first participant in and will be the study start date.

GSK or its designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of GSK. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The Investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the Sponsor or Investigator may include but are not limited to:

- Failure of the Investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the Sponsor's procedures, or GCP guidelines
- Inadequate recruitment of participants by the Investigator
- Discontinuation of further study intervention development

If the study is prematurely terminated or suspended, the Sponsor shall promptly inform the Investigators, the IECs/IRBs, the regulatory authorities, and any contract research organization(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The Investigator shall promptly inform the participant and should assure appropriate therapy and/or follow-up of the participant.

10.1.10. Publication Policy

- The results of this study may be published or presented at scientific meetings. If this is foreseen, the Investigator agrees to submit all manuscripts or abstracts to the Sponsor before submission. This allows the Sponsor to protect proprietary information and to provide comments.
- The Sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the Sponsor will generally support publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating Investigator will be designated by mutual agreement.
- Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

10.2. Appendix 2: Clinical Laboratory and Radiographic Tests

- The tests detailed in Table 10 will be performed at the local laboratory.
- Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 5 of the protocol.
- Additional tests may be performed at any time during the study as determined necessary by the Investigator or required by local regulations.

Table 10 Protocol-Required Safety Laboratory Assessments

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)		

10.3. Appendix 3: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

10.3.1. Definition of AE

AE Definition
• An AE is any untoward medical occurrence in a clinical study participant, temporally associated with the use of a study intervention, whether or not considered related to the study intervention. • NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a study intervention.

Events Meeting the AE Definition
• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the Investigator (ie, not related to progression of underlying disease). • Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition. • New conditions detected or diagnosed after study intervention administration even though it may have been present before the start of the study. • Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction. • Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae. • The signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfill the definition of an AE or SAE. Also, "lack of efficacy" or "failure of expected pharmacological action" constitutes an AE or SAE.

Events NOT Meeting the AE Definition
• Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the Investigator to be more severe than expected for the participant's condition. • The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition. • Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE. • Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital). • Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

10.3.2. Definition of SAE

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met (eg, hospitalization for signs/symptoms of the disease under study, death due to progression of disease).

A SAE is defined as any untoward medical occurrence that, at any dose:
○ Results in death
○ Is life-threatening The term 'life-threatening' in the definition of 'serious' refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.
Requires inpatient hospitalization or prolongation of existing hospitalization • In general, hospitalization signifies that the participant has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AE. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious.

- Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.

Results in persistent or significant disability/incapacity

- The term disability means a substantial disruption of a person's ability to conduct normal life functions.
- This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

Is a congenital anomaly/birth defect

Other situations:

- Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.
- Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

10.3.3. Definition of Cardiovascular Events

Cardiovascular Events (CV) Definition:

Investigators will be required to fill out the specific CV event page of the CRF for the following AEs and SAEs:

- 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

10.3.4. Recording and Follow-Up of AE and SAE

AE and SAE Recording

- When an AE/SAE occurs, it is the responsibility of the Investigator to review all documentation (eg, hospital progress notes, laboratory, and diagnostics reports) related to the event.
- The Investigator will then record all relevant AE/SAE information in the eCRF.
- It is **not** acceptable for the Investigator to send photocopies of the participant's medical records to GSK in lieu of completion of the GSK /AE/SAE eCRF page.
- There may be instances when copies of medical records for certain cases are requested by GSK. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to GSK.
- The Investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of Intensity

The Investigator will make an assessment of intensity for each AE and SAE reported during the study and assign it to 1 of the following categories:

- Mild: An event that is easily tolerated by the participant, causing minimal discomfort, and not interfering with everyday activities.
- Moderate: An event that causes sufficient discomfort and interferes with normal everyday activities.
- Severe: An event that prevents normal everyday activities. An AE that is assessed as severe should not be confused with an SAE. Severe is a category utilized for rating the intensity of an event; and both AE and SAE can be assessed as severe.

  An event is defined as 'serious' when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe.

Assessment of Causality

- The Investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE.
- A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- The Investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration will be considered and investigated.
- The Investigator will also consult the Investigator's Brochure (IB) and/or Product Information, for marketed products, in his/her assessment.
- For each AE/SAE, the Investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred, and the Investigator has minimal information to include in the initial report to GSK. However, **it is very important that the Investigator always make an assessment of causality for every event before the initial transmission of the SAE data to** GSK**.**
- The Investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of AE and SAE

- The Investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by GSK to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- If a participant dies during participation in the study or during a recognized follow-up period, the Investigator will provide GSK with a copy of any post-mortem findings including histopathology.
- New or updated information will be recorded in the originally completed eCRF.

- The Investigator will submit any updated SAE data to GSK within 24 hours of receipt of the information.

10.3.5. Reporting of SAE to GSK

SAE Reporting to GSK via Electronic Data Collection Tool

- The primary mechanism for reporting SAE to GSK will be the electronic data collection tool.
- If the electronic system is unavailable, then the site will use the paper SAE data collection tool (see next section) in order to report the event within 24 hours.
- The site will enter the SAE data into the electronic system as soon as it becomes available.
- The Investigator or medically-qualified sub-Investigator must show evidence within the eCRF (eg, check review box, signature, etc.) of review and verification of the relationship of each SAE to IP/study participation (causality) within 72 hours of SAE entry into the eCRF.
- After the study is completed at a given site, the electronic data collection tool will be taken off-line to prevent the entry of new data or changes to existing data.
- If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the electronic data collection tool has been taken off-line, then the site can report this information on a paper SAE form (see next section) or to the medical monitor by telephone.
- Contacts for SAE reporting can be found in Study Reference Manual.

SAE Reporting to GSK via Paper CRF

- Facsimile transmission of the SAE paper CRF is the preferred method to transmit this information to the **medical monitor**.
- In rare circumstances and in the absence of facsimile equipment, notification by telephone is acceptable with a copy of the SAE data collection tool sent by overnight mail or courier service.
- Initial notification via telephone does not replace the need for the Investigator to complete and sign the SAE CRF pages within the designated reporting time frames.
- Contacts for SAE reporting can be found in Study Reference Manual.

10.4. Appendix 4: Contraceptive Guidance and Collection of Pregnancy Information

10.4.1. Definitions:

Woman of Childbearing Potential (WOCBP)

A woman is considered fertile following menarche and until becoming post-menopausal unless permanently sterile (see below).

If fertility is unclear (eg, amenorrhea in adolescents or athletes) and a menstrual cycle cannot be confirmed before first dose of study intervention, additional evaluation should be considered.

Women in the following categories are not considered WOCBP

7. Premenarchal
8. Premenopausal female with 1 of the following:
    - Documented hysterectomy
    - Documented bilateral salpingectomy
    - Documented bilateral oophorectomy

    For individuals with permanent infertility due to an alternate medical cause other than the above, (eg, mullerian agenesis, androgen insensitivity), Investigator discretion should be applied to determining study entry.

    Note: Documentation can come from the site personnel's: review of the participant's medical records, medical examination, or medical history interview.

9. Postmenopausal female
    - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.
        - A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, confirmation with more than one FSH measurement is required.
    - Females on HRT and whose menopausal status is in doubt will be required to use one of the non-estrogen hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must

discontinue HRT to allow confirmation of postmenopausal status before study enrolment.

10.4.2. Contraception Guidance

• **CONTRACEPTIVES[a] ALLOWED DURING THE STUDY INCLUDE:**
• **Highly Effective Methods[b] That Have Low User Dependency** *Failure rate of <1% per year when used consistently and correctly.*
• Implantable progestogen-only hormone contraception associated with inhibition of ovulation[b]
• Intrauterine device (IUD)
• Intrauterine hormone-releasing system (IUS) [b]
• Bilateral tubal occlusion
• Vasectomized partner *Note: Vasectomized partner is a highly effective contraceptive method provided that the partner is the sole sexual partner of the woman of childbearing potential and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used. Spermatogenesis cycle is approximately 90 days.*
• **Highly Effective Methods[b] That Are User Dependent** *Failure rate of <1% per year when used consistently and correctly.*
• Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation[c] • oral • intravaginal • transdermal • injectable
• Progestogen-only hormone contraception associated with inhibition of ovulation[c] • oral • injectable
• Sexual abstinence • *Note: Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.*

• **ACCEPTABLE METHODS[d]**
• Progestogen-only oral hormonal contraception where inhibition of ovulation is not the primary mode of action
• Male or female condom with or without spermicide[e]
• Cervical cap, diaphragm, or sponge with spermicide
• A combination of male condom with either cervical cap, diaphragm, or sponge with spermicide (double-barrier methods)[c]
a. Contraceptive use by men or women should be consistent with local regulations regarding the use of contraceptive methods for those participating in clinical studies. b. Failure rate of <1% per year when used consistently and correctly. Typical use failure rates differ from those when used consistently and correctly. c. If locally required, in accordance with Clinical Trial Facilitation Group (CTFG) guidelines, acceptable contraceptive methods are limited to those which inhibit ovulation as the primary mode of action. d. Considered effective, but not highly effective - failure rate of ≥1% per year. Periodic abstinence (calendar, sympto-thermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhoea method (LAM) are not acceptable methods of contraception. e. Male condom and female condom should not be used together (due to risk of failure with friction).

10.4.3. Collection of Pregnancy Information:

Female Participants who become pregnant

- The Investigator will collect pregnancy information on any female participant, who becomes pregnant while participating in this study.
- The initial information will be recorded on the appropriate form and submitted to GSK within 24 hours of learning of a participant's pregnancy.
- Participant will be followed to determine the outcome of the pregnancy. The Investigator will collect follow up information on participant and neonate, which will be forwarded to GSK Generally, follow-up will not be required for longer than 6 to 8 weeks beyond the estimated delivery date.
- Any termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for procedure.
- While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be reported as an AE or SAE.
- A spontaneous abortion (occurring at < 22 weeks gestational age) or still birth (occurring at > 22 weeks gestational age) is always considered to be an SAE and will be reported as such.
- Any SAE occurring as a result of a post-study pregnancy which is considered reasonably related to the study intervention by the Investigator, will be reported to

GSK as described in Appendix 3. While the Investigator is not obligated to actively seek this information in former study participants, he or she may learn of an SAE through spontaneous reporting.

Any female participant who becomes pregnant while participating will discontinue study intervention or be withdrawn from the study.

10.5. Appendix 5: Medical Device Adverse Events (AEs), Adverse Device Effects (ADEs), Serious Adverse Events (SAEs) and Device Deficiencies: Definition and Procedures for Recording, Evaluating, Follow-up, and Reporting

- The definitions and procedures detailed in this appendix are in accordance with ISO 14155.
- Both the Investigator and the Sponsor will comply with all local medical device reporting requirements.

- The detection and documentation procedures described in this protocol apply to all GSK medical devices provided for use in the study (see Section 6.1.1 for the list of GSK medical devices).

10.5.1. Definition of AE and ADE

AE and ADE Definition
• An AE is defined as any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory finding) in study participants, users, or other persons, whether or not related to the investigational medical device. This definition includes events related to the investigational medical device or comparator and events related to the procedures involved except for events in users or other persons, which only include events related to investigational devices. • An adverse device effect (ADE) is defined as an adverse event related to the use of an investigational medical device. This definition includes any adverse events resulting from insufficient or inadequate instructions for use, deployment, implantation, installation, or operation, or any malfunction of the investigational medical device as well as any event resulting from use error or from intentional misuse of the investigational medical device. • A treatment emergent adverse effect (TEAE) is defined as, an AE with its onset date on or after treatment start date and on or before treatment stop date + 1 day.

10.5.2. Definition of SAE, SADE and USADE

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met (eg, hospitalization for signs/symptoms of the disease under study, death due to progression of disease).

An SAE is an AE that:
a. Led to death
b. Led to serious deterioration in the health of the participant, that either resulted in: 1. A life-threatening illness or injury. The term ‘life-threatening' in the definition of serious' refers to an event in which the participant was at risk of death at the

time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe 2. A permanent impairment of a body structure or a body function, 3. Inpatient or prolonged hospitalization, planned hospitalization for a pre-existing condition, or a procedure required by the protocol, without serious deterioration in health, is not considered an SAE 4. Medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function
c. Led to fetal distress, fetal death or a congenital abnormality or birth defect
SADE definition
• A SADE is defined as an adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event.
USADE definition
• A USADE is a serious adverse device effect which by its nature, incidence, severity or outcome has not been identified in the current version of the risk analysis report (see Section 2.3).

10.5.3. Definition of Device Deficiency

Device Deficiency definition
• A device deficiency is an inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety, or performance. Device deficiencies include malfunctions, use errors, and inadequate labeling.

10.5.4. Recording and Follow-Up of AE and/or SAE and Device Deficiencies

AE, SAE, and Device Deficiency Recording
• When an AE/SAE/device deficiency occurs, it is the responsibility of the Investigator to review all documentation (eg, hospital progress notes, laboratory reports, and diagnostics reports) related to the event. • The Investigator will then record all relevant AE/SAE/device deficiency information in the participant's medical records, in accordance with the Investigator's normal clinical practice, and on the appropriate form of the CRF. • It is not acceptable for the Investigator to send photocopies of the participant's medical records to GSK in lieu of completion of the AE/SAE/device deficiency CRF page.

- There may be instances when copies of medical records for certain cases are requested by GSK. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to GSK.
- The Investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.
- For device deficiencies, it is very important that the Investigator describes any corrective or remedial actions taken to prevent recurrence of the incident.
- A remedial action is any action other than routine maintenance or servicing of a medical device where such action is necessary to prevent recurrence of a device deficiency. This includes any amendment to the device design to prevent recurrence.

Assessment of Intensity

- The Investigator will make an assessment of intensity for each AE/SAE/device deficiency reported during the study and assign it to one of the following categories:
- Mild: An event that is easily tolerated by the participant, causing minimal discomfort and not interfering with everyday activities.
- Moderate: An event that causes sufficient discomfort and interferes with normal everyday activities.
- Severe: An event that prevents normal everyday activities. An AE that is assessed as severe should not be confused with a SAE. Severe is a category utilized for rating the intensity of an event; and both AEs and SAEs can be assessed as severe.
- An event is defined as ‘serious’ when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe.
- Other measures to evaluate AEs and SAEs may be utilized (eg, National Cancer Institute Common Terminology Criteria for Adverse Events [NCI-CTCAE]).

Assessment of Causality

- The Investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE/device deficiency
- A “reasonable possibility” of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- The Investigator will use clinical judgment to determine the relationship.

- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration will be considered and investigated.
- The Investigator will also consult the Product Information, in his/her assessment.
- For each AE/SAE/device deficiency, the Investigator must document in the medical notes that he/she has reviewed the AE/SAE/device deficiency and has provided an assessment of causality.
- There may be situations in which an SAE has occurred and the Investigator has minimal information to include in the initial report to GSK. However, it is very important that the Investigator always make an assessment of causality for every event before the initial transmission of the SAE data to GSK.
- The Investigator may change his/her opinion of causality in light of follow-up information and send a SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of AE/SAE/device deficiency

- The Investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by GSK to elucidate the nature and/or causality of the AE/SAE/device deficiency as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- New or updated information will be recorded in the originally completed CRF.
- The Investigator will submit any updated SAE data to GSK within 24 hours of receipt of the information.

10.5.5. Reporting of SAEs

SAE Reporting to GSK via an Electronic Data Collection Tool

- The primary mechanism for reporting an SAE to GSK will be the electronic data collection tool.
- If the electronic system is unavailable, then the site will use the paper SAE data collection tool (see next section) in order to report the event within 24 hours.
- The site will enter the SAE data into the electronic system as soon as it becomes available.
- After the study is completed at a given site, the electronic data collection tool will be taken off-line to prevent the entry of new data or changes to existing data.

- If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the electronic data collection tool has been taken off-line, then the site can report this information on a paper SAE form (see next section) or to the GSK medical monitor by telephone.
- Contacts for SAE reporting can be found in Study Reference Manual.

SAE Reporting to GSK via Paper CRF

- Facsimile transmission of the SAE paper CRF is the preferred method to transmit this information to the GSK medical monitor.
- In rare circumstances and in the absence of facsimile equipment, notification by telephone is acceptable with a copy of the SAE data collection tool sent by overnight mail or courier service.
- Initial notification via telephone does not replace the need for the Investigator to complete and sign the SAE CRF pages within the designated reporting time frames.
- Contacts for SAE reporting can be found in Study Reference Manual.

10.5.6. Reporting of SADEs

SADE Reporting to GSK

NOTE: There are additional reporting obligations for medical device incidents that are potentially related to SAEs that must fulfil the legal responsibility to notify appropriate regulatory authorities and other entities about certain safety information relating to medical devices being used in clinical studies.

- Any device deficiency that is associated with an SAE must be reported to GSK within 24 hours after the Investigator determines that the event meets the definition of a device deficiency.
- GSK shall review all device deficiencies and determine and document in writing whether they could have led to an SAE. These shall be reported to the regulatory authorities and IRBs/IECs as required by national regulations.
- Contacts for SAE reporting can be found in Study Reference Manual.

10.6. Appendix 6: COVID-19 Considerations

10.6.1. Overall Rationale for This Appendix

COVID-19 pandemic may impact the conduct of clinical studies. Challenges may arise from quarantines, site closures, travel limitations, interruptions to the supply chain for the investigational product or other considerations if site personnel or study participants become infected with COVID-19. These challenges may lead to difficulties in meeting protocol-specified procedures, including administering or using the investigational product or adhering to protocol-mandated visits and laboratory/diagnostic testing.

This protocol appendix outlines measures that may be applicable for any site impacted by the COVID-19 pandemic. The purpose of the appendix is to provide information on the measures to be taken to protect participants' safety, welfare and rights, and promote data integrity.

These measures will remain in place until study completion.

10.6.2. Study Procedures During Covid-19 Pandemic

During the special circumstances caused by the current COVID-19 pandemic, you should consider specific public health guidance, the impact of any travel restrictions implemented by local/regional health authorities and local institutions, and individual benefit /risk when making enrolment and treatment decisions for trial participants.

As outlined in Section 8, Protocol waivers or exemptions are not allowed and every effort should be made to adhere to protocol-specified assessments for participants on study intervention, including follow up however when not possible, for the duration of these special circumstances, the following measures may be implemented for enrolled participants.

- Clinical investigators should document in site files and in participant notes as appropriate how restrictions related to COVID-19 led to the changes in study conduct and duration of those changes and indicate which trial participants are impacted and how those trial participants are impacted (as per the current local COVID-19 related regulatory guidance).
- Missing protocol required data/visits due to COVID-19 should be noted in participant notes and recorded as a COVID-19 protocol deviation.

Protocol Defined Procedures/Visits:

- The protocol defined interval for the collection of samples during the follow-up visit (see Section 1.3: Schedule of Activities), may be extended up to a maximum length of 14 days.

Data Management/Monitoring:

- If a situation arises where on-site monitoring is no longer permitted, GSK will consider remote Source Data Verification/Source Document Review (SDV/SDR)

where permitted by the clinical site/institution. Remote SDV/SDR will be proposed to study sites to meet a participant and/or critical quality need, eg, to assess participant safety or to ensure data integrity. In case of remote SDV/SDR, GSK will work with the site to ensure participant privacy.

- eCRF/CRF Final or Interim Sign off Process: The Principal Investigator (PI) is responsible for ensuring that the data within the eCRF casebook and any other data sources utilized during the study for each study participant is complete and consistent with source documents throughout the study (ICH GCP 4.9.1 and 4.9.2). The PI may sign/re-sign the eCRF from any computer/location by accessing InForm (or other eDC platform) using his/her unique eCRF log-in credentials. The PI may delegate this activity to another medically qualified and trained sub-investigator and this must be documented on the Delegation of Responsibilities (DoR) Log. It is recommended that the PI identifies a sub-investigator as a back-up for eCRF signatures. The sub-investigator must be appropriately trained on the protocol and eCRF requirements (with training documented), and the DoR log updated accordingly.
- Essential Document Sign Off Process: If an Investigator is unable to print and sign essential documents such as Protocol /Amendment signature page, then Email approval can be accepted by replying to the relevant email that is sent by GSK.

10.7. Appendix 7: Abbreviations and Trademarks

Abbreviation	**Definition**
ABRS	Acute bacterial rhinosinusitis
ADE	Adverse Device Effects
AE	Adverse event
ALT	Alanine aminotransferase
AMC	Amoxicillin
AOM	Acute otitis media
ARTI	Acute respiratory tract infection
AST	Aspartate aminotransferase
CABP	Community acquired bacterial pneumonia
CARTI	Community acquired respiratory tract infections
CIOMS	Council for International Organizations of Medical Sciences
CV	Cardiovascular
CVA	Clavulanic acid
eCRF	Electronic case report form
EOT	End of Therapy
ES	Extra strength
FU	Follow up
GCP	Good Clinical Practice
HCP	Healthcare professional
HRT	Hormonal replacement therapy
ICF	Informed consent form
IEC	Independent Ethics Committee
IRB	Institutional Review Board

Abbreviation	Definition
MEE	Middle ear effusion
MIC	Minimum inhibitory concentration
OT	On-therapy
PD	Pharmacodynamics
PDD	Protocol-defined diarrhea
PI	Principal Investigator
PISP	Penicillin-intermediate resistant *S. pneumoniae*
PK	Pharmacokinetics
PRSP	Penicillin resistance *S. pneumoniae*
SADE	Serious adverse device effects
SAE	Serious adverse events
SoA	Schedule of Activities
SUSAR	Suspected unexpected serious adverse reactions
TEAE	Treatment-emergent adverse events
TM	Tympanic membrane

Trademark Information

Trademarks of the GlaxoSmithKline group of companies
None

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