SYNOPTIC CSR STATISTICAL ANALYSIS PLAN

Protocol: SG021

Protocol Version 4.0 23 MAY 2025

A phase 2, two-part study to assess the safety, antiviral biomarker responses, and efficacy of inhaled SNG001 for the treatment of patients with a confirmed respiratory virus infection undergoing invasive mechanical ventilation

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Prepared for: Synairgen

Prepared by: [redacted]

Approved by	**Signature**	**Date**
[redacted]	[redacted]	

1 Table of Contents

1 Table of Contents 2
2 Abbreviations and Definitions 4
3 Introduction 4
4 Study Objectives, Endpoints and Estimands 4
4.1 Part 1 4
4.1.1 Primary Objective 4
4.1.2 Exploratory Objective 4
4.1.3 Primary Endpoint 4
4.1.4 Exploratory Endpoint 5
5 Study Methods 6
5.1 General Study Design and Plan 6
5.1.1 Part 1 6
5.2 Randomisation and Blinding 6
6 Sample Size 6
7 General Considerations 6
7.1 Analysis and Data Point Sets 7
7.2 Partial Dates 7
8 Summary of Study Data 7
8.1 Adverse Events 7
9 Reporting Conventions 8
10 Technical Details 9
11 Table Shells 9

Table 1: Adverse Event Summary (Safety Set) 9

Table 2: Treatment Emergent Adverse Events by Preferred Term (Safety Set)..... 9

Table 3: Fatal Treatment Emergent Adverse Events by Preferred Term (Safety Set)..... 11

Table 4: Serious Treatment Emergent Adverse Events by Preferred Term (Safety Set)..... 11

2 Abbreviations and Definitions

AE	Adverse Event
CSR	Clinical Trial Report
ICH	International Council for Harmonisation
IDMC	Independent Data Monitoring Committee
MedDRA	Medical Dictionary for Regulatory Activities
PT	Preferred Term
SAP	Statistical Analysis Plan
TEAE	Treatment Emergent Adverse Event

3 Introduction

The purpose of this statistical analysis plan (SAP) is to provide all information that is necessary to perform the required statistical analyses of Synairgen study SG021 for the synoptic clinical study report (CSR). It also describes the tables to be included in the synoptic CSR. The SAP is based upon, and assumes familiarity, with the study protocol, version 4.0, dated 23rd May 2025.

The study was terminated during study Part 1 and therefore this document does not refer to the study part 2. This document was written and finalised following study termination and unblinding. Due to the early termination of the study an synoptic CSR was co0nsidered appropriate and this SAP contains the minimal detail required for the study reporting.

The content of this SAP is compatible with the International Council for Harmonisation (ICH) E9 Guidance document.

4 Study Objectives, Endpoints and Estimands

4.1 Part 1

4.1.1 Primary Objective

To evaluate the safety of SNG001 administration to patients with a confirmed respiratory virus infection undergoing invasive mechanical ventilation (IMV).

4.1.2 Exploratory Objective

[redacted]

4.1.3 Primary Endpoint

The occurrence and severity of adverse events (AEs), serious adverse events (SAEs), including pre-specified respiratory and cardiovascular deteriorations.

4.1.4 Exploratory Endpoint

[redacted]

5 Study Methods

5.1 General Study Design and Plan

Consented participants who test positive for Influenza A (Flu A), Influenza B (Flu B), Respiratory Syncytial Virus (RSV), Rhinovirus (RV), adenovirus, parainfluenza, human metapneumovirus (HMPV) or coronaviruses (including SARS-CoV-2 and seasonal coronaviruses), and are otherwise deemed eligible, will be enrolled into the study and receive the first dose of study medication no later than 48 hours after intubation and commencement of IMV. The study will consist of two parts:

5.1.1 Part 1

The primary objective of Part 1 will be to evaluate the safety of SNG001 administration to participants with a confirmed respiratory virus infection undergoing IMV.

Part 1 (double-blind) will include a low-dose (one syringe) cohort (Cohort 1), followed by an optional second cohort (Cohort 2) that will utilise a two-syringe dose. Each of the cohorts will consist of 12 participants, who will be randomised 3:1 to receive either SNG001 or placebo, in addition to SOC, according to a pre-specified randomisation schedule.

As a precautionary step, sentinel dosing will be conducted, where the initial two participants randomised to Cohort 1 will be randomised 1:1 (i.e. one participant will receive SNG001 and one will receive placebo). Once the first two participants have received a minimum of 2 doses of study medication whilst undergoing IMV, the safety review committee (SRC) consisting, at a minimum, of the Principal Investigator (PI) or delegate, the Chief Investigator and Synairgen's Chief Medical Officer will review the safety data and, if there are no apparent safety concerns, will approve the dosing for the remaining ten participants in Cohort 1.

In case of a safety concern deemed by the SRC to be definitely, probably, or possibly related to the study medication is observed in one of the sentinel participants, sentinel dosing will continue in another two participants.

If a participant in the second group of two patients presents with a safety concern of the same or different nature, the study will be put on hold and the IDMC will review the data and advise on study conduct.

5.2 Randomisation and Blinding

Participants enrolled into Part 1 will be randomised 3:1 to SNG001 or placebo, with 1:1 sentinel dosing for at least the first 2 participants in each cohort.

6 Sample Size

Cohort 1 and the optional Cohort 2 will enrol 12 participants each.

7 General Considerations

7.1 Analysis and Data Point Sets

Analysis sets are defined to identify the subset of participants to be included in the analysis of the estimands:

Analysis Set Name	Participants to be Included
Safety set (SS)	All participants who receive at least one dose of study medication. Participants who receive at least one dose of SNG001 will be summarised under the SNG001 treatment group, patients who only receive doses of Placebo will be summarised under the Placebo treatment group.

7.2 Partial Dates

For adverse events, partial dates will only be imputed for the purposes of determining treatment emergence. The following rules will be applied:

- If only the AE start day is missing and the AE start month is on or after the month of first dose then the AE will be considered treatment emergent.
- If the AE start day and month are missing and the AE start year is on or after the year of first dose, then the AE will be considered treatment emergent.
- If the AE start date is completely missing, then the AE will be considered treatment emergent.

Due to the requirement that dosing is started within 24 hours of consent, AE end dates will not be taken into consideration.

8 Summary of Study Data

For the purpose of the synoptic CSR it is only required to generate summary tables of adverse events.

The frequency and percentages (based on the SS) will be reported. All summary tables will be structured with a column for each treatment in the order; Placebo, SNG001 and will be annotated with the size of the SS.

Table 1: Treatment Group Label Conventions for TFLs Summarising Part 2 only

Output ordered by	Label for use in output	Description
Treatment group	Placebo	Placebo participants
	SNG001	SNG001 participants

For relevant summaries, where similar data are collected on both study Part 1 and study Part 2, both study parts may be presented on the same table, side-by-side and pooled:

8.1 Adverse Events

Adverse events will be recorded from the time informed consent is given until 28 days after the last administration of the study medication. All adverse events will be coded using the latest available version

of the MedDRA and will be categorized by intensity (mild/moderate/severe) and relationship (unrelated/unlikely to be related/possibly related/probably related/definitely related).

A treatment-emergent adverse event (TEAE) is defined as any event not present prior to the administration of study drug, or any unresolved event already present before administration of study drug that worsens in intensity following exposure to the treatment.

Summary tables by preferred term (PT) will contain the cumulative incidence rate and the number of events. A subject who has multiple events in the same PT will be counted only once in the subject counts, but all events will be included. Adverse event summaries will be ordered by decreasing frequency of PT within the SNG001 column.

Summaries of TEAEs by PT will include the following:

- Incidence of TEAEs,
- Incidence of fatal TEAEs,
- Incidence of serious TEAEs.

An overall summary will also be produced which will summarise the number of participants with a TEAE in each of the above categories and the following categories:

- Incidence of any TEAEs by severity,
- Incidence any serious related TEAE,
- Incidence of any related fatal TEAE,
- Incidence of any related TEAE,
- Incidence of any TEAE leading to discontinuation,
- Incidence of any TEAE of note.

For this summary the following relationships will be considered related: 'Definitely related', 'Probably Related' and 'Possibly Related'. 'Unlikely to be Related' and 'Not related' will be considered unrelated. The following intensity categories will be summarised: 'Mild', 'Moderate', 'Severe'. Participants will be counted once under each severity category if multiple events were observed at different severities.

Adverse events which are coded to more than one preferred term will be counted once under each term.

Adverse Events of note are defined as the following:

- Moderate or worse palpitations during the dosing period and up to 24 hours after last dose.
- Severe bronchospasm with 4 hours of investigational agent/placebo administration (symptoms causing inability to perform usual social and functional activities and deemed related to the study product as determined by the site investigator).

9 Reporting Conventions

When reporting relative frequencies or other percentage values, the following rules apply:

- For values where all participants fulfil certain criteria, the percentage value will be displayed as 100.
- For values where the absolute frequency is 0, there will be no percentage presented at all.
- All other percentage displays will use 1 decimal place.

10 Technical Details

Statistical evaluation will be performed by Veramed Limited.

The datasets will not follow analysis dataset model (ADaM) data specifications.

All analyses will be performed using SAS version 9.4.

11 Table Shells

Table 1: Adverse Event Summary (Safety Set)

	Placebo + SoC N=XX n (%)	**SNG001 + SoC N=XX n (%)**
Any TEAE	XX (XX.X%)	XX (XX.X%)
Mild	XX (XX.X%)	XX (XX.X%)
Moderate	XX (XX.X%)	XX (XX.X%)
Severe	XX (XX.X%)	XX (XX.X%)
Any serious TEAE	XX (XX.X%)	XX (XX.X%)
Any serious related TEAE	XX (XX.X%)	XX (XX.X%)
Any fatal TEAE	XX (XX.X%)	XX (XX.X%)
Any related fatal TEAE	XX (XX.X%)	XX (XX.X%)
Any TEAE related to study treatment	XX (XX.X%)	XX (XX.X%)
Any TEAE leading to discontinuation of study treatment	XX (XX.X%)	XX (XX.X%)
Any TEAE of note	XX (XX.X%)	XX (XX.X%)

n: Number of participants with an event, N: Total number of participants dosed, SoC: Standard of care, TEAE: Treatment emergent adverse event.
Percentages are calculated using the total number of participants in each treatment group (N).
A TEAE is defined as any event beginning or worsening or becoming serious on or after the first dose of study drug in the respective period.

Table 2: Treatment Emergent Adverse Events by Preferred Term (Safety Set)

	Placebo + SoC N=XX n (%) e	**SNG001 + SoC N=XX n (%) e**
Any TEAE	XX (XX.X%) XX	XX (XX.X%) XX
Preferred Term 1	XX (XX.X%) XX	XX (XX.X%) XX
Preferred Term 2	XX (XX.X%) XX	XX (XX.X%) XX
Preferred Term 3	XX (XX.X%) XX	XX (XX.X%) XX

e: Number of events, MedDRA: Medical Dictionary for Regulatory Activities, n: Number of participants with an event, N: Total number of participants dosed, SoC: Standard of care, TEAE: Treatment emergent adverse event.
Percentages are calculated using the total number of participants in each treatment group (N).

A TEAE is defined as any event beginning or worsening or becoming serious on or after the first dose of study drug in the respective period.
Adverse events were coded using MedDRA, version 27.1.

Table 3: Fatal Treatment Emergent Adverse Events by Preferred Term (Safety Set)

	Placebo + SoC N=XX n (%) e	**SNG001 + SoC N=XX n (%) e**
Any TEAE	XX (XX.X%) XX	XX (XX.X%) XX
Preferred Term 1	XX (XX.X%) XX	XX (XX.X%) XX
Preferred Term 2	XX (XX.X%) XX	XX (XX.X%) XX
Preferred Term 3	XX (XX.X%) XX	XX (XX.X%) XX

e: Number of events, MedDRA: Medical Dictionary for Regulatory Activities, n: Number of participants with an event, N: Total number of participants dosed, SoC: Standard of care, TEAE: Treatment emergent adverse event.
Percentages are calculated using the total number of participants in each treatment group (N).
A TEAE is defined as any event beginning or worsening or becoming serious on or after the first dose of study drug in the respective period.
Adverse events were coded using MedDRA, version 27.1.

Table 4: Serious Treatment Emergent Adverse Events by Preferred Term (Safety Set)

	Placebo + SoC N=XX n (%) e	**SNG001 + SoC N=XX n (%) e**
Any TEAE	XX (XX.X%) XX	XX (XX.X%) XX
Preferred Term 1	XX (XX.X%) XX	XX (XX.X%) XX
Preferred Term 2	XX (XX.X%) XX	XX (XX.X%) XX
Preferred Term 3	XX (XX.X%) XX	XX (XX.X%) XX

e: Number of events, MedDRA: Medical Dictionary for Regulatory Activities, n: Number of participants with an event, N: Total number of participants dosed, SoC: Standard of care, TEAE: Treatment emergent adverse event.
Percentages are calculated using the total number of participants in each treatment group (N).
A TEAE is defined as any event beginning or worsening or becoming serious on or after the first dose of study drug in the respective period.
Adverse events were coded using MedDRA, version 27.1.

[redacted]

[redacted]

[redacted]

[redacted]

E
P





