Official Title: An Open-label Multi-center Study of INO-3107 With Electroporation (EP) in Subjects With HPV-6- and/or HPV-11-associated Recurrent Respiratory Papillomatosis (RRP)

NCT ID: NCT04398433

Document Date: Statistical Analysis Plan Version 2.0 19 December 2022

STATISTICAL ANALYSIS PLAN

STUDY SPONSOR:	Inovio Pharmaceuticals, Inc. 660 W. Germantown Pike, Suite 110 Plymouth Meeting, PA 19462
SPONSOR REPRESENTATIVE:	[redacted]
PROTOCOL TITLE:	An open-label multi-center study of INO-3107 with electroporation (EP) in subjects with HPV-6- and/or HPV-11-associated recurrent respiratory papillomatosis (RRP)
PROTOCOL NUMBER:	RRP-001
PROTOCOL VERSION AND DATE:	Amendment 3: 23 July 2021 Amendment 2: 12 April 2021 Amendment 1: 20 February 2020 Original: 09 January 2020
NAME OF TEST DRUG:	INO-3107
PHASE:	Phase I/II
METHODOLOGY:	Open Label, Multi-Center Trial
ANALYSIS PLAN DATE:	19 December 2022
ANALYSIS PLAN VERSION:	Version 2.0

APPROVAL SIGNATURE PAGE

Protocol Title:	An open-label multi-center study of INO-3107 with electroporation (EP) in subjects with HPV-6- and/or HPV-11-associated recurrent respiratory papillomatosis (RRP)
Sponsor:	Inovio Pharmaceuticals, Inc. 660 W. Germantown Pike, Suite 110 Plymouth Meeting, PA 19462
Protocol Number:	RRP-001
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Veristat, Inc. Author:	[redacted]

Approval Signature	Job Title
DocuSigned by: [redacted] Signer Name: [redacted] Signing Reason: I am the author of this document Signing Time: 20-Dec-2022 | 11:03:00 AM EST [redacted]	[redacted]

Sponsor: Inovio Pharmaceuticals, Inc.
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Sponsor Signatory: [redacted]

Sponsor Approval

By signing this document, I acknowledge that I have read the document and approve of the planned statistical analyses described herein. I agree that the planned statistical analyses are appropriate for this study, are in accordance with the study objectives, and are consistent with the statistical methodology described in the protocol, clinical development plan, and all applicable regulatory guidance and guidelines.

I have discussed any questions I have regarding the contents of this document with the biostatistical author.

I also understand that any subsequent changes to the planned statistical analyses, as described herein, may have a regulatory impact and/or result in timeline adjustments. All changes to the planned analyses will be described in the clinical study report.

Approval Signature	Job Title
DocuSigned by: [redacted] Signer Name: [redacted] Signing Reason: I approve this document Signing Time: 20-Dec-2022 | 8:11:03 AM PST [redacted]	[redacted]

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation	Definition
AE	Adverse event
ATC	Anatomical Therapeutic Chemical
A-O RRP	Adult-Onset RRP
CRF	Case report form
CSR	Clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
DLT	Dose-limiting toxicity
EP	Electroporation
HPV	Human papilloma virus
HPV-6	Human Papillomavirus Type 6
ICH	International Conference on Harmonisation
IM	Intramuscularly
IRB	Institutional Review Board
ITT	Intent-to-treat
J-O RRP	Juvenile-Onset RRP
MedDRA	Medical Dictionary for Regulatory Activities
miRNA	microRNA
mITT	Modified intention to treat
PBMCs	Peripheral blood mononuclear cells
PP	Per-protocol
PT	Preferred term
Rel Day	Relative study day
RRP	Recurrent respiratory papillomatosis
RTF	Rich text format
SAE	Serious adverse event
SAP	Statistical analysis plan
SD	Standard deviation
SOC	System organ class
TEAEs	Treatment-emergent adverse events
WHO	World Health Organization

1. INFORMATION FROM THE STUDY PROTOCOL

1.1. Introduction and Objectives

1.1.1. Introduction

Human papilloma virus (HPV)-associated malignancies are an emerging global epidemic[1]. Additionally, the role of HPV-6 and HPV-11 in the etiology of recurrent respiratory papillomatosis (RRP), the most common benign tumor(s) of the laryngeal epithelium is well-established [2, 3]. Recurrent respiratory papillomatosis is rare; the incidence is estimated at 1.8 per 100,000 adults in the United States [4]. The age of diagnosis ranges from young children to older adults. Although most lesions are benign, some undergo malignant transformation, and patients with RRP have a higher risk of developing laryngeal carcinomas [5].

Preclinical and pilot studies of INO-3106 have demonstrated tolerability, immunogenicity, and preliminary efficacy. The pilot study of three patients with HPV-6-related-aerodigestive disease, two of whom had RRP, previously required every six-month debridement of their RRP lesions. Treatment extended their inter-surgical times in a meaningful way; one patient sustaining a surgery-free interval for over 900 days, and another for over 500 days, following therapy with INO-3106 on-study [6].

Building on the findings from the INO-3106 study, Inovio is conducting a study of INO-3107. This investigational product has the potential to treat patients with HPV-6 and/or HPV-11-associated RRP, reducing the number of surgical interventions required to control the disease, eradicating the virus in treated patients, thus resulting in a potential disease cure. This treatment not only would reduce exposure to future inevitable surgical intervention but would also remove the signs and symptoms associated with RRP and the potential for malignant transformation and development of HPV-6 or HPV-11-associated cancer. The RRP-001 study will utilize the INO-3107 drug product in adults and adolescents with RRP who are at risk of requiring additional and continuous surgery to manage their disease. We hypothesize that INO-3107 given intramuscularly (IM) followed by electroporation (EP) with CELLECTRA® 2000 will be well-tolerated and provide clinical efficacy in subjects with RRP secondary to HPV-6 and/or HPV-11.

1.1.2. Statistical Analysis Plan Objectives

This is a Phase 1/2 open-label, multicenter trial to evaluate the efficacy, safety, tolerability, and immunogenicity of INO-3107 in subjects with RRP. The statistical analysis plan (SAP) is designed to outline the methods to be used in the analysis of study data to answer the study objective(s). Populations for analysis, data handling rules, statistical methods, and formats for data presentation are provided.

The summary tabulations described in this SAP will provide the basis for the results sections of the clinical study report (CSR) for this trial. This SAP will also outline any differences in the currently planned analytical objectives relative to those planned in the study protocol.

1.1.2.1. Primary Objective

The primary aim of this study is to evaluate the safety and tolerability of INO-3107 with electroporation in subjects with HPV-6 and/or HPV-11-associated RRP.

1.1.2.2. Secondary Objectives

The secondary objectives are the following:

- To evaluate the efficacy of INO-3107, as determined by the frequency of RRP surgical interventions in the year following the first dose of investigational product, compared to the frequency in the year prior to Day 0.
- To evaluate the efficacy of INO-3107 as assessed by changes in the RRP Staging Assessment score over time.
- To evaluate the antigen-specific cellular immune response to INO-3107 given IM, followed by EP.
- To evaluate the immunogenicity of INO-3107 as assessed by pro-inflammatory and immunosuppressive elements present in tumor tissue at study entry and subsequent tissue resections.
- To describe the association of microRNA (miRNA) profile with decreased frequency of surgical intervention.

1.2. Study Design

1.2.1. Synopsis of Study Design

This is a Phase 1/2 open-label, multicenter trial to evaluate the safety, tolerability, immunogenicity, and efficacy of INO-3107 in subjects with RRP. This trial will enroll approximately 30 adults ≥18 years old) who have been diagnosed with either Juvenile-Onset RRP (J-O RRP) as defined by age at first diagnosis <12 years or Adult-Onset RRP (A-O RRP), with age at first diagnosis being ≥ 12 years of age. Subjects will receive treatment with INO-

3107 administered IM injection either by Side Port Needle (n=10 subjects) or standard needle (n=~20), followed by EP at Day 0, and Weeks 3, 6, and 9.

This study will have a safety-run in, during which up to six subjects will be enrolled with a one week waiting period between each. Each subject will be assessed up to Week 6. Once the first three subjects of up to these six have completed Week 6 assessments, in the absence of dose-limiting toxicities (DLT), subject enrollment may begin in full after review of safety data and discussion between the Sponsor's Medical Monitor and the Investigator(s) at the subjects' site(s).

If, prior to the first three to six subjects completing Week 6, a single subject from the first six experiences a DLT then enrollment will be limited to six subjects until all six subjects have reached Week 6 and are assessed for DLT.

If a second subject within the first 6 experiences a DLT within the first 6 weeks, enrollment will stop, and the Sponsor's Medical Monitor and Investigator(s) at the subjects' site(s) will discuss the case, and a decision will be made whether to cease further enrollment. If a change to the protocol is required, enrollment will only be reinitiated after amendment of the protocol and approval of the amended protocol by the respective study Institutional Review Boards (IRBs).

- Tolerability will be determined by the reported incidence of DLT, which is defined as: Treatment-related NCI CTCAE v5 (CTCAE, version 3.0 Grade ≥ 3) Grade ≥3 non-hematological toxicity that does not respond to supportive therapy and lasts for longer than 48 hours, or Treatment-related CTCAE Grade ≥3 hematological toxicity that does not respond to supportive therapy and lasts for longer than 48 hours

- Treatment-related NCI CTCAE v5.0 Grade ≥3 hematological toxicity that does not respond to supportive therapy and lasts for longer than 48 hours.

Additionally, enrollment and subsequent dosing will be paused until Sponsor discussion with the site Investigator determines that enrollment and dosing may continue, if the following CTCAE v5.0 events occur at any time in the study:

- One Grade 4 or 5 related serious adverse event (SAE);

- Two Grade 3 related SAEs

Enrollment will continue until approximately 30 subjects are enrolled. Safety and tolerability will continue to be assessed throughout the study after tolerability has been established in the first six subjects. If more than two subjects experience a DLT at any time during the study, after the initial six subjects are enrolled, the Sponsor will pause enrollment until further discussion with the site Investigator determines that the study may reopen to enrollment.

Subjects will undergo routine surgical procedure for removal of papilloma(s) during the screening period within 14 days prior to Day 0 dosing (papilloma removal and Day 0dose may be performed same day if other eligibility criteria have been fulfilled). Biopsy tissue will be collected and sent to [redacted] for evaluation of secondary [redacted] endpoints. Archival tissue (slides or blocks) obtained within one year of the screening window may be used, or a biopsy conducted during routine surgery.

Status of disease during the trial will be monitored by the Investigator during laryngoscopy including documentation with Staging Assessment scores. If at any time during the trial, surgical removal (including laser) of papilloma is clinically indicated per PI judgement, the subject may undergo procedure for papilloma removal, but this must be captured on the electronic case report form.

This trial will not use a Data Safety Monitoring Board. As this is an open-label trial, the Sponsor will have access to unblinded safety and tolerability data during the trial. At a minimum, the Sponsor's Medical Monitor will review reported adverse events quarterly.

1.2.2. Stopping Rules

See Study Design Synopsis for details of the safety run in period, during which the first six enrolled subjects will be monitored for DLT. If 2 subjects experience a DLT within the first 6 weeks, enrollment will stop, and the Sponsor's Medical Monitor and Investigator(s) at the subjects' site(s) will discuss the case, and a decision will be made whether to cease further enrollment. If a change to the protocol is required, enrollment will only be reinitiated after amendment of the protocol and approval of the amended protocol by the respective study IRBs.

Enrollment and additional dosing will be paused until Sponsor discussion with the site Investigator determines that enrollment and dosing may continue, if the following CTCAEv5.0 events occur at any time in the study:

- One Grade 4 or 5 related SAE;
- Two Grade 3 related SAEs

There are no pre-defined stopping rules; however, if any of the criteria for pausing are met, as outlined in Section 1.2.1, the Sponsor's Medical Monitor and site Investigator(s) may decide to permanently cease enrollment following review of safety data.

1.2.3. Study Procedures

The schedule of assessments, as outlined in the study protocol, is provided in Table 1-1 .

Table 1-1 Schedule of Assessments

Schedule of Events	Screening	Day 0	Week 3 (±4 days)	Week 6 (±4 days)	Week 9 (±4 days)	Week 11 (±1 week)	Week 26 (±2 week)	Week 52 /End of study (±2 weeks)
Informed consent	X							
Medical history, smoking history	X							
Inclusion/Exclusion criteria	X	X						
Demographics	X							
Concomitant medications, AEs	X	X	X	X	X	X	X	X
Physical exam[a]	X	X	X	X	X		X	X
Vital signs	X	X	X	X	X		X	X
Height, weight, BMI		X	X	X	X			
Safety labs[b]	X	X	X	X	X			
Pregnancy test, if applicable[c]	X	X	X	X	X			
INO-3107		X	X	X	X			
Immunology samples	X	X		X	X	X	X	X
[redacted]								
Laryngoscopy and Staging assessment[e]	X[f]			X		X	X	X
Tissue sample[g]	X							X

a. Full physical examination (PE) mandatory at screening and study discharge (Week 52/End of Study visit or relapse), otherwise targeted physical assessment as determined by the Investigator or per subject complaints;
b. Collected within 72 hours prior to dosing such that results are available and assessed against DLT criteria prior to dosing;
c. For women of childbearing potential, a negative serum pregnancy test is required at screening and a negative spot urine pregnancy test is required prior to each study treatment;
[redacted]
e. Staging assessment to be performed during each laryngoscopy and prior to any RRP intervention using the RRP Staging Assessment tool. Video/photographic documentation of laryngoscopy is required.
f. Staging to be performed prior to Routine RRP intervention at Screening, followed by dosing within 14 days.
g. Biopsy tissue should be sent for HPV typing and immunological evaluation at Screening, Week 52, and at any tissue resection, if applicable. Archival tissue collected within 1 year of Day 0 may be sent at screening. Biopsy required with laryngoscopy at Week 52.

1.2.4. Efficacy, Immunogenicity, and Safety Parameters

1.2.4.1. Efficacy Parameters

Efficacy will be measured through the following study parameters.

- Change in the number of RRP surgical interventions in the year following Day 0, compared to the year prior.
- Change in RRP Staging Assessment Score (see Section 1.2.4.1.1.)
- [redacted]
- miRNA profile as related to the reduction in frequency of surgical intervention.

1.2.4.2. Immunogenicity Parameters

The immunogenicity parameters for this study include measurement of [redacted] cell mediated immune responses in blood samples taken at baseline and periodic intervals:

- Secondary Parameters
    - Antigen-specific cellular immune responses assessed by:
        - IFN-γ secreting cells in peripheral blood mononuclear cells (PBMCs) by ELISpot
        - T cell phenotype and lytic potential in PBMCs by flow cytometry
        - [redacted]
    - Assessment of pro-inflammatory and immunosuppressive elements in resected tumor tissue, if available.

[redacted]

- [redacted]
- [redacted]

1.2.4.3. Safety Parameters

Safety evaluations performed during the study include physical examinations, measurement of vital signs, injection site reactions, pain, and concomitant medications/procedures. Safety and tolerability of INO-3107 will be assessed by reported AEs and SAEs as measured and graded by the CTCAE v. 4.0.

Treatment-emergent adverse events (TEAEs) are collected throughout study. All TEAEs that occur within 7 days following each injection will be summarized separately. All adverse events including SAEs, unexpected adverse device effects (UADEs) that relate to the rights, safety, or welfare of subjects, and DLTs, as well as clinically significant changes in laboratory parameters and vital signs from baseline assessments will be assessed.

2. SUBJECT POPULATION

2.1. Population Definitions

The following populations provide the basis for analysis and presentation of data:

- The intention to treat (ITT) population includes all subjects who are eligible.
- The modified intention to treat (mITT) population includes all subjects who receive at least one dose of INO-3107.
- The per-protocol population includes subjects who receive all doses of INO-3107 and have no protocol violations. (Subjects excluded from the PP population based on protocol deviations discovered after or during treatment, will be identified and documented prior to locking of the trial database and excluded from the PP population.)
- The safety population includes all subjects who receive at least one dose of INO-3107.

2.2. Protocol Deviations

At the discretion of the Sponsor, certain protocol deviations, as determined by sponsor review of the data prior to locking of the study database and the conduct of statistical analyses, will result in the removal of a subject's data from the PP population.

The Sponsor or designee will be responsible for producing the final protocol deviation file (formatted as a Microsoft Excel file), in collaboration with Veristat and the data monitoring group as applicable; this file will include a description of the protocol deviation which warrants exclusion from the PP population. This file will be finalized prior to hard database lock.

All protocol deviations will be presented in a data listing.

3. GENERAL STATISTICAL METHODS

3.1. Sample Size Justification

Formal power calculation was not performed for this study, as the primary statistics are descriptive. For the safety endpoints, among n=30, we hypothesize that the true serious adverse event incidence is <12%, if no additional SAEs are observed.

3.2. General Methods

All data listings that contain an evaluation date will contain a relative study day (Rel Day). Pre-treatment and on-treatment study days are numbered relative to the day of the first dose of study medication (Day 0) which is designated as Rel Day 1. The preceding day is Rel Day -1, the day before that is Rel Day -2, etc. There is no Rel Day 0.

All output will be incorporated into Microsoft Word (.rtf) files, or Adobe Acrobat PDF files, sorted and labeled according to the International Conference on Harmonisation (ICH) recommendations, and formatted to the appropriate page size(s).

Tabulations will be produced for appropriate demographic, baseline, efficacy, immunogenicity, and safety parameters. For categorical variables, summary tabulations of the number and percentage of subjects within each category (with a category for missing data) of the parameter will be presented. For continuous variables, the number of subjects, mean, median, standard deviation (SD), minimum, and maximum values will be presented. Summarizations will be presented for all subjects in the specified population as described in the next section of this SAP. These summary statistics will be presented with 2-sided confidence intervals (CI) on selected parameters, as described in the sections below.

3.3. Computing Environment

All statistical analyses will be performed using SAS statistical software Version 9.4, unless otherwise noted. Medical history and adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) Version 23.0 or higher. Concomitant medications will be coded using the B3 World Health Organization (WHO) Drug Global Dictionary, March 2020.

3.4. Baseline Definition

For all analyses, baseline will be defined as the most recent measurement prior to the first administration of study drug.

3.5. Methods of Pooling Data

Data will be pooled across study sites .

3.6. Adjustments for Covariates

No formal statistical analyses that adjust for possible covariate effects are planned.

3.7. Multiple Comparisons/Multiplicity

Multiplicity is not of concern for this study with a descriptive interpretation.

3.8. Subpopulations

All safety, efficacy, and immunogenicity data will be analyzed separately and combined for subjects by number of prior surgical interventions (≤2, 3-5, and ≥6), [redacted] and overall.

3.9. Withdrawals, Dropouts, Loss to Follow-up

A subject will be considered to have completed the trial when they have completed all study visits through Week 52. Subjects may withdraw consent at any time for any reason or be dropped from the trial at the discretion of the Investigator should any untoward effect occur. In addition, the Investigator or the Sponsor has the right to discontinue a subject from the trial at any time.

The Investigator must notify the Sponsor within 24 hours when a subject has been discontinued/withdrawn due to an AE. Any AEs and/or SAEs present at the time of discontinuation/withdrawal should be followed in accordance with the safety requirements outlined in the protocol. Subjects who are withdrawn or discontinued from the study will not be replaced.

3.10. Missing, Unused, and Spurious Data

When tabulating AE data, partial dates will be handled as follows in order to determine treatment emergence. If any of the day, month, or year is missing, the onset date will be set to the earliest date that is consistent with any non-missing date information, unless the non-missing date information is the same as study treatment start. In this case, in order to conservatively report the event as treatment-emergent, the onset date will be assumed to be the date of start of treatment. A completely missing onset date will be coded as the day of start of treatment.

A prior medication is defined as any medication that was used and has a stop date before the start of the trial (before Dose #1 on Day 0). A concomitant medication is defined as any medication that has a stop date that is on or after the date of first dose of study drug. For prior and concomitant medications, partial start dates will not be imputed, as stop dates determine prior versus concomitant. Partial stop dates will be assumed to be the latest possible date consistent with the partial date.

3.11. Visit Windows

Once eligibility has been confirmed, the subject's Day 0 dose will be scheduled within 14 days after the next planned surgical intervention. If timing allows, the Day 0 dose may be given on the same day immediately following the next planned surgical intervention. Visit dates and windows must be calculated from Day 0, unless otherwise noted. All subjects will be followed until the Week 52 visit.

It is expected that all visits should occur according to the protocol schedule. All data will be tabulated per the scheduled visit as recorded on the case report form (CRF) even if the assessment is unscheduled (outside of the visit window). For example, a visit that occurs after the scheduled Week 6 visit, but before the scheduled Week 9 visit, will be reported (tabulated) with the Week 6 data. In data listings, the relative day of all dates will be presented.

3.12. Interim Analyses

No formal interim analyses are planned for this study. An analysis of the first 21 subjects [redacted] was conducted.

4. STUDY ANALYSES

4.1. Subject Disposition

Subject disposition will be tabulated by the number of prior surgeries, [redacted] and overall, for the number of eligible subjects, enrolled subjects, treated subjects, and subjects who completed study follow up visits through Week 52. In addition, the number of subjects who withdrew prior to completing the study and reason(s) for withdrawal will be tabulated.

The number of patients in each analysis population (ITT, mITT, PP, and SP) will be presented. Unless specified, percentages will be based on number of eligible subjects (i.e., ITT population).

By-subject data listings of study completion information, including reason(s) for premature study withdrawal, not participating, and inclusion/exclusion criteria not met, will be provided.

4.2. Demographics and Baseline Characteristics

Demographics, baseline characteristics, and medical history will be summarized by number of prior surgeries, [redacted] and overall. Age, height, weight, and BMI will be summarized using descriptive statistics (e.g., number, mean, standard deviation, median, minimum, and maximum). The number and percentage of subjects in each sex, race, and ethnicity category also will be presented. Childbearing potential and contraception method (when applicable) will be tabulated. Medical history, prior RRP treatment, and HPV type prior to study will be summarized. These tabulations will be presented on the mITT and safety populations. by MedDRA System Organ Class (SOC) and Preferred Term (PT) (v 25.0).

No formal statistical comparisons will be performed for these characteristics. All baseline data will be provided in by-subject listings.

4.3. Efficacy and Immunogenicity Evaluation

Efficacy and immunogenicity analyses will be conducted using the mITT Population. The Per Protocol population will provide supportive analyses.

The following efficacy evaluations will be conducted. Statistical methods and analysis of populations are described below.

4.3.1. Efficacy Analyses

The parameters that follow will be analyzed to support the conclusions of the primary analysis. For categorical endpoints, frequency and percentages will be calculated. For continuous variables, means, medians, or changes in percentage will be summarized. Where appropriate, 95% confidence intervals will be calculated (see specific analysis discussed subsequently). Analyses will be summarized and presented by number of prior surgical interventions (≤2, 3-5, and ≥6), [redacted] and overall.

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- Secondary analyses
    - Frequency of RRP surgical interventions in the year following intervention, compared to the frequency in the year prior will be presented as median difference with 95% CI based on non-parametric methodology.
    - Percent reduction in RRP surgical intervention as a categorical variable (categories consist of percent ranges), with frequency and percentages.
    - Change in surgical interval for prior to intervention to post will be presented along with median, mean, and 95% confidence intervals.
    - Change in stage as measured by the RRP Staging Assessment. Median changes and associated 95% confidence intervals will be computed.
    - The relationship of microRNA (miRNA) profiles with frequency of surgical intervention will be described using regression analysis.

[redacted]

In addition to these tabulations, by-subject listings will be provided for all efficacy endpoints.

4.3.2. Immunology Analyses

The following parameters will be presented:

- Secondary Immunogenicity Analyses
    - Cellular immune responses will be measured using ELISpot results from PBMCs. Median increase from baseline to each assessment point will be calculated along with associated 95% confidence intervals.
    - Immune response as determined by change in T cell phenotype and lytic markers measured using flow cytometry of PBMCs [redacted] Median increases and associated 95% confidence intervals will be calculated.
    - Assessment of pro-inflammatory and immunosuppressive elements in resected tumor tissue [redacted]

[redacted]

4.4. Safety Analyses

Safety analyses will be conducted using the Safety Population, and will be tabulated by number of prior surgeries, [redacted] and overall. The primary analysis of this trial is the safety analysis of TEAEs, tolerability, and change in safety lab parameters.

4.4.1. Study Drug Exposure

Study drug exposure will be tabulated by the number of doses received and presented by number of prior surgeries, [redacted] and overall.

The location of the EP injection, guide usage, and whether there was a second EP attempt will also be summarized. Study drug exposure for each subject will also be presented in a data listing.

4.4.2. Adverse Events

All adverse events (AEs) will be coded using the MedDRA coding system (v. 25.0 or higher) and displayed in tables and data listings by SOC and PT. AEs will be summarized for the safety population by number of prior surgeries, [redacted] and overall. Tables will describe the incidence of AEs. In these tabulations, each subject will contribute only once (i.e., the most related occurrence or the most intense occurrence) to each of the incidences in the analysis, regardless of the number of episodes. Multiple occurrences of the same AE will be counted only once following a worst-case approach with respect to severity and relationship to study treatment.

Adverse events with onset after the administration of study medication through 30 days following the last dose, are considered treatment emergent adverse events (TEAEs). The frequency and 95% Clopper-Pearson CIs of TEAEs will be calculated. An overall summary of TEAEs will include the number and percentage of subjects with any TEAE, any TEAE assessed by the Investigator as related to treatment, any TEAE by severity grade, any SAE, any pre-treatment AE, any AE leading to discontinuation of treatment, and any AE leading to death and separately for events occurring within 7 days of any dose and regardless of when they occurred. AEs and SAEs that are not TEAEs or serious TEAEs will be presented in listings:

- All TEAEs
- All TEAEs by most recent dose*
- All TEAEs by severity grade
- All TEAE considered treatment-related
- All TEAEs by most recent dose and severity grade *
- All AEs that occur any time within 52 Weeks on Study
- All treatment related TEAEs by most recent dose *

*TEAEs of this type will also be presented within 7 days.

All adverse events occurring on-study will be provided in by-subject data listings along with subject deaths, SAEs, Grade 3/4 level events and DLTs, and AEs leading to withdrawal.

4.4.3. Laboratory Data

Clinical laboratory values will be expressed in SI units. Laboratory values will be summarized for each clinical laboratory parameter, including hematology and serum chemistry. For women of childbearing potential, a serum pregnancy test will be assessed at screening, and urine pregnancy tests prior to each dose administration.

The mean change from baseline and corresponding 95% CI, and shifts in CTCAE grade, to each on-study evaluation will be summarized for each clinical laboratory parameter.

All laboratory data will be provided in data listings. A subset listing will be presented for all clinically significant laboratory values.

4.4.4. Vital Signs and Physical Examination

Vital sign values as well as changes from baseline (shift table) will be summarized by scheduled visit for subjects in the safety population. Descriptive statistics will be tabulated by number of prior surgeries, [redacted] and overall. Vital sign measurements will be presented for each subject in a data listing.

Physical examinations performed will be summarized in tables by scheduled visit. Reasons for physical examinations not done will be presented in a data listing.

4.4.5. Prior and Concomitant Medications and Procedures

Prior medications and/or procedures are those used or performed before the start of trial, i.e. before Day 0 dosing. Concomitant medications and/or procedures are those used or performed during the trial (on or after the first dose). Concomitant medications also include any that did not end prior to first dose of the study treatment, are missing an end date, or are ongoing, and will be included. Concomitant procedures, defined as continuing or new procedures and treatments undergone by the subject at or after first (Day 0) dosing, will be included.

Partial stop dates of concomitant medications and procedures will be assumed to be the latest possible date consistent with the partial date; start dates will not be imputed. Data for all concomitant medications will be summarized with counts and percentages by WHO Drug Anatomical Therapeutic Chemical (ATC) classification and preferred term, for the mITT population. The use of concomitant medications and procedures will be presented in a by-subject data listing.

5. CHANGES TO PLANNED ANALYSES

- The analysis of frequency of RRP interventions will be based on a median change instead of a mean fold-change due to the nature of the data.
- There will be no formal interim analysis; however, a subset analysis of the first 21 subjects will be conducted

[redacted]

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7. REVISION HISTORY

Protocol Version 1.0	09 January 2020
Protocol Version 2.0	20 February 2020
Protocol Version 3.0	12 April 2021
Protocol Version 4.0	23 July 2021

7.1. Statistical Analysis Plan Version 0.1: 13 April 2022

Statistical Analysis Plan Version 0.2 with Shell Tables/Listings added 29 June 2022

Statistical Analysis Plan Version 1.2 with updated Shells on 21 November 2022.

Statistical Analysis Plan Version 2.0 with updated Shells to include all subjects on 15 December 2022.