



COVER PAGE

Study Title: A Phase 1b Study of OPT101 in Patients with Type 1 Diabetes

NCT Number: NCT05428943

Date of Last Revision: 14 APR 2024

Date Uploaded to ClinicalTrials.gov: 02 APR 2026



SUMMARY OF CHANGES

Version Number	Effective/ Issue Date	Reason for Revision
1.0	14APR2024	Original Statistical Analysis Plan



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1 GENERAL

1.1 Statistical Overview

This Statistical Analysis Plan (SAP) is based on the final protocol OPT101-100-20 (Version 7.0), dated 12 July 2023. Data analysis will be performed using appropriate statistical methods. Software used will be documented.

The statistical analyses will generally be descriptive in nature. Data collected will be presented using summary tables, data listings, and figures. For categorical variables, the number and percentage of each category within a parameter will be calculated. For continuous variables, the sample size (n), arithmetic mean, median, standard deviation (SD), and the minimum and maximum values, will be presented. Missing data will not be imputed unless otherwise stated.

1.2 Study Design

This study is a randomized, multicenter, placebo-controlled, double blinded study that will be conducted as a multiple ascending doses (MAD) study to measure safety, the immunological, and the clinical effects of 1.1 and 2.8 mg/kg doses of OPT101 that were found to be safe in the OPT-100-30 (IND 150941) Phase 1a study performed in healthy volunteers.

Screening will take place from day -28 to day 0. Eligible subjects will receive up to a total of 8 IV treatments with the 1.1 and 2.8 mg/kg doses or placebo, will be administered to a total of 18 subjects on Days 1, 4, 7, and 14 and then weekly (Days 21, 28, 35, and 42), for a total of 7 weeks.

1.3 Sample Size

The sample size for the dose escalation design is based on the dose escalation rules of the standard 3+3 design. Each cohort contains 3 placebo and 6 active subjects for a total of 18 subjects where subjects were randomized prior to treatment.

1.4 Treatment Group Identification

The following will be used to identify the treatment in applicable data listings, tables and figures:

1.1 mg/kg OPT101

2.8 mg/kg OPT101 Placebo

1.5 Randomization

Prior to the start of the study a block (size 3) randomization list was generated and used to assign subjects to treatment. Any deviations from the initial randomization list will be summarized.



1.6 Blinding

This is a blinded study as the subject, caring staff, and investigator are blinded to the subject treatment group.

1.7 Missing Data

All data analyses will be performed on data available. The number of missing data points in each analysis will be summarized by treatment group. Every attempt shall be made to obtain data per protocol.

1.8 Populations for Analyses

The study population will consist of adult subjects, ≥ 18 years old with Type 1 Diabetes (T1D) diagnosed within the past 20 years. Any subject who withdraws before Day 15 due to unrelated (including unlikely related) AE will be replaced; any subject who withdraws consent or is withdrawn after Day 15 will not be replaced. The specific analysis populations are defined below.

Population	Description
Safety	Safety population consists of all randomized subjects who received at least one dose of IP (treatment or placebo). Subjects will be included in the analysis according to the dose IP received (see Section 1.4).
Pharmacokinetic (PK)	Includes all subjects in the safety population for whom at least one PK parameter can be calculated.
Immunogenicity	Includes all subjects in the safety population for whom at least one immunogenicity parameter can be calculated.
Cytokine	Includes all subjects in the safety population for whom at least one cytokine parameter can be calculated.
Immunological Assessment	Includes all subjects in the safety population for whom at least one immunological parameter can be calculated.

1.9 Planned Interim Analyses

Interim analyses will not be conducted in this trial

2 OBJECTIVES AND ENDPOINTS

2.1 Primary Objective

To assess the safety and tolerability of multiple ascending doses of OPT101 in Type 1 Diabetes patients (≥ 18 years of age).



The study has no specified primary endpoint acceptance criteria. The analyses will focus on summarizing data for safety review. In particular the following endpoints will be addressed with summarized data and table listings.

2.2 Primary Endpoints:

- Rate and type of adverse events after infusion of OPT101 or placebo
- Change in vital signs after infusion of OPT101 or placebo
- Change in plasma histamine levels shortly after infusion of OPT101 or placebo in cases where an infusion reaction occurred.
- Change in laboratory clinical chemistry, hematology and coagulation variables after infusion of OPT101 or placebo
- Development of antidrug antibodies after infusions of OPT101 or placebo
- • Definition of maximum tolerated repeated dose of OPT101

2.3 Secondary Objectives:

- To assess the pharmacokinetics (PK) of OPT101
- To assess the pharmacodynamic (immunologic) effects of OPT101
- To assess the clinical activity of multiple ascending doses of OPT101

2.4 Secondary Endpoints:

- Determination of PK parameters (AUC_{0-t}, C_{max}, CL/F, t_{1/2})
- Change in immunological variables after multiple infusions of OPT101 or placebo
- Change in HbA_{1c}
- Change in daily insulin use
- Change in C-peptide
- Change in fasting plasma glucose
- Change in urine glucose

3 STUDY ANALYSIS VARIABLE SUMMARY

3.1 Demographic and Background Variables

- Date of Informed Consent
- Medical and Surgical History
- Age calculated (date of informed consent – date of birth)/365.25
- Gender
- Race



- Body weight (at each infusion visit)
- Screening Laboratory Tests
- Physical Exam

3.2 Safety Variables

- Prior and Concomitant Medications
- Adverse Events
- Tolerability
- Clinical Laboratory Tests
- Vital Signs
- Electrocardiograms

3.3 Research Variable Categories

- Pharmacokinetic
- Immunogenicity (antibodies)
- Cytokines
- Immunological

4 SUBJECT AND TREATMENT SUMMARIES

4.1 Subject Disposition

The completion status, date of completion or discontinuation, the reason for discontinuation will be listed (Listing X-1). The number of subjects randomized and the frequency and percentage of subjects completing the study, subjects withdrawing early, and primary reason for withdrawal will be summarized by treatment and overall (Table Y-1). The number and percent of subjects in the safety, PK and immunological populations will be summarized by treatment.

4.2 Eligibility Criteria and Protocol Deviations

Listing X-2 will display all enrolled subjects who did not meet an inclusion criterion and all enrolled subjects who met an exclusion criterion.

All reported protocol deviations will be listed (Listing X-3). Randomization deviation will be listed in (Listing X-4).

4.3 Screening Tests

Results of screening tests (serology, serum and urine pregnancy testing for females) will be listed (Listing X-4). The urine drug screen was not collected in the EDC and will not be listed.



4.4 Demographic Data

Demographic information will be listed (Listing X-5). Descriptive statistics will be obtained for the continuous variables age and initial (Visit 1) body weight presented overall (Table Y-2). Frequencies and percentage of subjects will be tabulated by treatment for the categorical variables ethnicity, race, and gender (Table Y-3).

4.5 Medical History

Medical history data will be listed for each subject. Medical history will be coded using Medical Dictionary Regulatory Activities (MedDRA Version 21.0 and higher). Only those body systems where a condition or abnormality has been reported will be listed (Listing X-6).

4.6 Concomitant Medication

Previous and concomitant medications will be coded using the appropriate WHO Drug Dictionary WHO Drug. Prior and concomitant medications will be listed by subject (Listings X7 and X-8, respectively).

4.7 Dose Administration

Listing X-9 will present subject number, treatment, period, study day, and the date and time of dose administration.

5 SAFETY SUMMARIES

The analysis of the safety variables will be conducted using the safety population.

5.1 Adverse Events

All verbatim AE terms reported will be coded according to MedDRA, version 21.0 and higher.

Adverse events will be categorized as:

- Treatment-emergent adverse events (TEAEs) are those AEs that started or worsened in severity after the first administration of IP.
- Non-treatment emergent AEs (NTEAE): AEs that occurred after consent and before the first administration of IP and did not worsen in severity or relationship after exposure to IP.

All AE data will be listed for each subject (Listing X-10). All serious AEs (SAEs) will be listed (Listing X-11). A listing of all AEs leading to treatment discontinuation will be presented, if applicable (Listing X-12).

Unless specified otherwise, all adverse event summaries will include only the TEAEs and adverse event summary counts of AEs will be the number of subjects reporting adverse events and not the number of events reported. A subject with multiple adverse events within a body system is only counted once towards the total of that body system. For subjects with multiple



adverse events of the same preferred term and of different severities, the AE with the highest assessment of severity will be used in the summaries presented by severity. For purposes of the summary tables, AEs will be classified as either being related to study drug or not related.

If a subject has multiple AEs with the same preferred term but occurring after each dose administration (i.e., infusion), then one will be counted for each infusion. AEs that emerge in one infusion and carry over into the next infusion will be attributed to only the infusion in which the AE emerged.

A general summary of all TEAEs (Table Y-4) will show the number and percentage of subjects, as well as the number of events, according to the following categories:

- All treatment emergent adverse events
- Treatment emergent adverse events ‘Related’ to IP
- Mild treatment emergent adverse events
- Moderate treatment emergent adverse events
- Severe treatment emergent adverse events
- Serious treatment emergent adverse events (Life-threatening)
- Treatment emergent adverse events leading to early termination
- Deaths

Other summary tables for adverse events will include:

- Table Y-5: Number and Percentage of Subjects with Treatment Emergent Adverse Events by System Organ Class, Preferred Term, and Treatment
- Table Y-6: Number and Percentage of Subjects with Treatment Emergent Adverse Events ‘Related to the IP’ by System Organ Class, Preferred Term, Severity, and Treatment.
- Table Y-7: Number and Percentage of Subjects with Treatment Emergent Adverse Events ‘Not Related to the IP’ by System Organ Class, Preferred Term, Severity, and Treatment.

5.2 Clinical Laboratory

5.2.1 Chemistry, Hematology, and Coagulation

5.2.1.1 By Subject Listings

A by-subject listing of all observed chemistry, hematology, and coagulation laboratory data will be provided (Listings X-13, X-14, X-15). Laboratory results outside the normal range will be flagged as abnormal not clinically significant (ab-NCS) or as abnormal clinically significant (abCS). Clinically significant laboratory results will be included in the AE listings.

5.2.1.2 Summary By Visit by Treatment Group

The observed values of all safety laboratory assessments for clinical chemistry hematology, and coagulation will be summarized within treatment groups using descriptive statistics showing the



number of observations (n), mean, median, SD, minimum, and maximum value. Table summaries will be presented by treatment for each visit: (Table Y-8, Y-9, Y-10).

5.2.1.3 Change from Screening (Visit 0) to EOS (Visit 9) by Treatment Group

For the chemistry, hematology and coagulation parameters change from screening values to Visit 9 will be derived and listed for each subject (Listing X-16, X-17, X-18).

Change from Screening values for chemistry, hematology and coagulation results will be summarized by treatment and time point (Tables Y-11, Y-12, Y-13).

5.2.1.4 Shift Tables from Screening (Visit 0) to EOS (Visit 9) by Treatment Group

Values for all chemistry, hematology, and coagulation parameters will be categorized as being normal, abnormal – NCS, and Abnormal – CS. For each visit, shift tables will present the frequency and percentage of subjects who have all observations for a visit that are Normal, or one or more observations that are Ab-NCS, or Ab-CS. Specifically for each subject, for each laboratory test at each visit:

- If all values for the test are normal, the subject is categorized as normal.
- If one or more values for the test are abnormal-CS then the subject is categorized as ab-CS.
- If one or more values for the test are abnormal-NCS and none are abnormal-CS then the subject is categorized as Ab-NCS.

Shift tables will be presented by treatment group and Visit (Tables Y-14, Y-15, Y-16).

5.2.2 Urinalysis, i-Stat, and Lipids

Urinalysis test results will be listed (Listing X-19). iStat results will be listed (Listing X-20). Lipid test results will be listed (Listing X-21).

5.2.3 Mixed Meal Tolerance

The mixed meal tolerance variables (HbA1c, c-peptide, and glucose) will be listed by subject, treatment group, and visit. (Listing X-22).

5.2.4 Daily Insulin Use

Daily insulin logs results will be listed by subject, treatment group, and visit. (Listing X-23).

5.3 Vital Signs

5.3.1.1 By Subject Listings



The observed data for heart rate, blood pressure (systolic and diastolic), respiratory rate, and pulse oximetry level will be listed by subject, treatment, visit, and time point (Listings X-24).

5.3.1.2 Change from Pre-infusion Listing

For each infusion (Visits 1 to 8) the change from pre-infusion for blood pressure (systolic and diastolic) and respiratory rate will be derived and listed by subject, treatment, and time point (Listing X-25).

5.3.1.3 Summary of Change from Pre-infusion by Treatment Group

For systolic blood pressure, diastolic blood pressure and respiratory rate the observed and change from pre-infusion data will be summarized by treatment and time point. Summaries will include tables of descriptive statistics showing the number of observations (n), mean, SD, median, minimum, and maximum value (Tables Y-15 and Y-16).

5.4 12-Lead Safety ECG

The overall qualitative assessment as well as the raw quantitative results for: PR interval, QRS interval, RR interval, QT interval, QTcF (corrected QT according to Fridericia), and heart rate will be listed by subject, treatment, and visit (Listing X-26).

5.5 Physical Examination

All abnormal physical examination findings will be listed (Listing X-27). Weight collected at dose time points will be listed (Listing X-28).

6 PHARMACOKINETIC CONCENTRATIONS AND PARAMETERS

6.1 The analysis of the PK data will be conducted using the PK population.

With the exception of the minimum and maximum statistic for C_{max} and summaries of PK concentrations, descriptive statistics for PK concentrations and all PK parameters will be reported. The minimum and maximum statistics for C_{max} and summaries of PK concentrations will reflect the. Summary PK for T_{max} will be presented with.

The coefficient of variation for all PK data will be reported. Descriptive statistics and statistical analyses will be. All tables, listings and figures for OPT101 will be presented in units of ng/mL.

6.2 Concentrations

Pharmacokinetic concentration data for OPT101 will be listed by subject, treatment, and period. (Listing X-29).

Concentrations for OPT101 will be summarized by treatment and nominal time (Table 21). In these tabular summaries the following statistics will be presented at each nominal time point: n,



arithmetic mean, SD, median, minimum, maximum, 10th, 25th, 75th and 90th percentiles, coefficient of variation percentage (CV%), geometric mean, and geometric CV%.

6.3 PK Parameters

All derived PK parameters for OPT101 will be listed by subject, treatment, sequence, and period (Listing X-30).

Derived PK parameters for OPT101 that reflect reliability and validity, will be listed for each subject (Listing X-31)

The following descriptive statistics will be presented in PK parameter summary tables by treatment: n, arithmetic mean, SD, median, minimum, maximum, 10th, 25th, 75th and 90th percentiles, coefficient of variation (CV%), geometric mean, geometric CV% (Tables Y-17).

6.4 Graphical Presentation of PK Data

PK concentrations will be presented graphically by treatment and time point. Graphical presentations of the OPT101 plasma concentrations will include:

- Subject Profiles for OPT101 Concentration Time Data
- Subject Profiles for OPT101 Concentration Time Data - Semi-Logarithmic Scale
- Combined Subject Profiles for OPT101 Concentration Time Data
- Mean ($\pm$ SD) OPT101 Concentration Time Data
- Mean OPT101 Concentration Time Data - Semi-Logarithmic Scale

Combined subject profiles are presented as spaghetti plots.

6.5 PK Concentration Values Below the Limit of Quantification (BLQ)

7 IMMUNOGENICITY, CYTOKINE AND IMMUNOLOGICAL ASSESSMENT

7.1 Immunogenicity

The number and percentage of subjects with presence (Table Y-18).

7.2 Cytokine Analysis

Serum levels will be summarized descriptively for each assessment time point by subject and treatment (Table Y-19).



7.3 Immunological Assessment

The percent and number of peripheral blood will be summarized descriptively for each assessment time point by subject and treatment (Table Y-20).

8 PLANED TABLES

Table Y-1	Subject Disposition
Table Y-2	Demographics - Continuous Variables
Table Y-3	Demographics - Categorical Variables
Table Y-4	Summary of Treatment Emergent Adverse Events
Table Y-5	Number and Percentage of Subjects with Treatment Emergent Adverse Events by System Organ Class, Preferred Term, and Treatment
Table Y-6	Number and Percentage of Subjects with Treatment Emergent Adverse Events 'Related to IMP' by System Organ Class, Preferred Term, Severity, and Treatment
Table Y-7	Number and Percentage of Subjects with Treatment Emergent Adverse Events 'Not Related to IMP' by System Organ Class, Preferred Term, Severity, and Treatment
Table Y-8	Clinical Laboratory Chemistry Summary of Observed Values
Table Y-9	Clinical Laboratory Hematology Summary of Observed Values
Table Y-10	Clinical Laboratory Coagulation Summary of Observed Values
Table Y-11	Clinical Laboratory Chemistry Summary of Change From Screening Values
Table Y-12	Clinical Laboratory Hematology Summary of Change From Screening Values
Table Y-13	Clinical Laboratory Coagulation Summary of Change From Screening Values
Table Y-14	Clinical Laboratory Chemistry Shift From Screening to V9

Table Y-15	Clinical Laboratory Hematology Shift From Screening to V9
Table Y-16	Clinical Laboratory Coagulation Shift From Screening to V9
Table Y-15	Vital Signs Summary of Observed Values
Table Y-16	Vital Signs Summary of Change From Screening
Table Y-17	Summary of OPT101 Pharmacokinetic Parameters
Table Y-18	Summary of Immunogenicity



Table Y-19	Summary of Cytokines
Table Y-20	Summary of Immunological Assessments

9 PLANED FIGURES

Figure Z-1	Subject Profiles for OPT101 Plasma Concentration Time Data
Figure Z-2	Subject Profiles for OPT101 Plasma Concentration Time Data - SemiLogarithmic Scale
Figure Z-3	Combined Subject Profiles for OPT101 Plasma Concentration Time Data
Figure Z-4	Mean ($\pm$ SD) OPT101 Plasma Concentration Time Data
Figure Z-5	Mean OPT101 Plasma Concentration Time Data - Semi-Logarithmic Scale
Figure Z-6	Individual OPT101 PK Parameters with Geometric Means and 95% Confidence Intervals.

10 PLANED LISTINGS

Listing X-1	Subject Disposition
Listing X-2	Enrolled Subjects Who Did Not Meet All Eligibility Criteria
Listing X-3	Protocol Deviations
Listing X-4	Exclusion Tests
Listing X-5	Demographics
Listing X-6	Medical History
Listing X-7	Prior Medications
Listing X-8	Concomitant Medications
Listing X-9	Study Drug Administration
Listing X-10	Adverse Events



Listing X-11	Serious Adverse Events
Listing X-12	Adverse Events Leading to Discontinuation
Listing X-13	Clinical Laboratory Chemistry – Observed Values
Listing X-14	Clinical Laboratory Hematology – Observed Values
Listing X-15	Clinical Laboratory Coagulation – Observed Values
Listing X-16	Clinical Laboratory Chemistry- Change From Screening Values
Listing X-17	Clinical Laboratory Hematology – Change From Screening Values
Listing X-18	Clinical Laboratory Coagulation – Change From Screening Values
Listing X-19	Clinical Laboratory Urinalysis – Observed Values
Listing X-20	iStat Results – Observed Values
Listing X-21	Clinical Laboratory – Lipid panel
Listing X-22	Mixed Meal Tolerance Test
Listing X-23	Daily Insulin Use
Listing X-24	Vital Signs Observed Values
Listing X-25	Vital Signs Change from PreInfusion
Listing X-26	12 Lead Safety ECG Observed Values
Listing X-27	Physical Examination Abnormal Findings
Listing X-28	Weight
Listing X-29	OPT101 Concentration-Time Data
Listing X-30	OPT101Pharmacokinetic Parameters
Listing X-31	Pharmacokinetic Diagnostic Parameters

11 VERSION HISTORY

Version	Section(s) changed	Details of change
1.0	New Document	N/A