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Revision History

Revision	Revision Date	Reason for Revision/Change Request	Revised By
1.0	19-MAR-2017	Original Release	[redacted]
2.0	01-NOV-2017	Updates due to comments from Sponsor	[redacted]
3.0	09-NOV-2017	Updates due to comments from Sponsor	[redacted]

Draft Statistical Analysis Plan

Sponsor: PolyPid Ltd.

Protocol: CL-0007, Study D-PLEX-301

Title:

A Phase Ib/II Prospective, Multicenter, Two part study; Part 1 - Open Label, Single Arm & Part 2 Randomized, Single-blinded Study to assess Safety and Efficacy of D-PLEX Concomitantly with Standard of Care vs. Standard of Care alone in the Prevention of Sternal Infection Post Cardiac Surgery.

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1. DEFINITIONS AND/OR ABBREVIATIONS

AE	Adverse event
AR	Adverse Reaction
BMI	Body Mass Index
CI	Confidence Interval
cm	centimeter
CRF	Case Report Form (may be paper or electronic representation of the data collection tool)
EDC	Electronic Data Capture
ITT	Intent-to-Treat
MedDRA	Medical Dictionary for Regulatory Activities
NA	Not applicable
PT	Preferred Term
QA	Quality Assurance
SAP	Statistical Analysis Plan
SAS	Statistical Analysis Software
SD	Source Documents
SOC	Standard of Care
SOP	Standard Operating Procedure
UNK	Unknown
WHO	World Health Organization

2. PURPOSE

The purpose of this document is to describe in detail the Statistical Analysis Plan of clinical study procedures carried out by Medistat Ltd.

This SAP SOP serves Medistat Ltd. as a guiding document for all statistical analyses performed at the end of each clinical study.

This SAP is specific to PolyPid Ltd, CL-0007, Study D-PLEX-301

This SAP aims to provide details on: sample size calculation, efficacy analyses and safety analyses.

3. SCOPE

This SAP applies to all members of the statistical & data management units in Medistat Ltd.

This SAP includes the main study trial analyses.

4. RESPONSIBILITIES

Medistat Ltd. Responsibilities

The following personnel are responsible for these activities:

Activities	Responsible and accountable	Title
Statistical Analysis Plan (SAP)	[redacted]	Senior Biostatistician & SAS Programmer
Statistical Report and listing appendix	[redacted]	Senior Biostatistician & SAS Programmer
Quality Assurance (QA) of SAP and programs	[redacted]	Senior Biostatistician & SAS Programmer
Quality Assurance (QA) of final statistical report	[redacted]	Quality & Data Assurance Manager

4.1 PolyPid Responsibilities

4.1.1 To review and approve the SAP and related documents prior to database lock.

4.1.2 To review and approve the draft and final statistical report and listing appendix.

5. PROCEDURE

5.1 Introduction

5.1.1 This Statistical Analysis Plan (SAP) is based on the study protocol final version 05, dated 13, August 2017.

5.1.2 This Statistical Analysis Plan (SAP) contains details of the statistical analyses that will be performed, providing a more detailed description of the approach defined in the study protocol. Definitions of variables and populations used for the analyses are also included. The SAP will be finalized and signed prior to hard lock of the database.

5.1.3 General output specifications are provided; examples are given of calculations of derived variables.

5.2 Rationale

5.2.1 The purpose of this study is to assess the safety of D-PLEX. Additionally, the study will assess the anti-infective efficacy of D-PLEX over a period of 3 months (90 days) post operation by preventing primary sternal infection post cardiac surgery.

5.2.2 The D-PLEX dose is dependant on the length of the sternum incision. For subjects with sternum length up to 22cm, two vials of D-PLEX will be used. For subjects with sternum length of 22cm or more, three vials will be used. The SOC is based on The Society of Thoracic Surgeons Practice Guideline Series: Antibiotic prophylaxis in cardiac surgery, part II: antibiotic choice. The SOC will be consitstent for all sites participating the the trial

5.3 Study Objectives and Endpoints

5.3.1 Study Objectivs

5.3.1.1 The purpose of this study is to assess the safety of D-PLEX. Additionally, the study will assess the anti-infective efficacy of D-PLEX over a period of 3 months (90 days) post operation by preventing sternal infection post cardiac surgery.

5.3.2 Primary Efficacy Endpoints

5.3.2.1 Infection rate as measured by the proportion of subjects with at least 1 identified sternal infection within 90 days post-cardiac surgery.

5.3.3 Secondary Efficacy Endpoints

5.3.3.1 Number of readmissions due to Sternal Surgical Site infection.

5.3.3.2 Number of surgical re-interventions due to Sternal Surgical Site infection

5.3.3.3 Time to sternal infection post cardiac surgety

5.3.3.4 Sternal Infection rate (DSWI and SSWI) during the first 30 days post operation

5.3.3.5 Sternal infection rate (DSWI and SSWI) between day 30 and 3 months.

5.3.3.6 The total number of sternal infections (DSWI and SSWI) (including several in the same patient) between day 30 and 3 months.

5.3.3.7 Number of hospitalization days due to Sternal Surgical Site infection.

5.3.4 Saftey Endpoints

5.3.4.1 Adverse events, safety laboratory parameters, physical examinations, vital signs.

5.3.4.2 Sternum mechanical dehiscence assessment by X-Ray.

5.3.4.3 Assessment of wound healing and extent of fibrosis/scarring.

5.3.4.4 Bone non-union will be assessed by sternum stability, which will be clinically evaluated by investigators. In case of suspected bone non-union further evaluation will be done according to standard clinical practice (CT imaging).

5.3.4.5 Safety laboratory parameters: Routine hematology, chemistry, urinalysis and bacterial test (bacterial growth, identification and sensitivity to antibiotics, including to tetracycline).

5.4 Overall study design and plan

5.4.1 Study Design

5.4.1.1 This is a phase Ib/II prospective, multicenter, two parts study: part I open label, single arm & part II randomized, single blind.

5.4.1.2 The study population includes any subject above the age of 18 years, who undergoes any cardiac surgery post mid-sternotomy, including patients with high risk for infection, such as Diabetes Mellitus (Insulin and/or non-insulin dependent), Peripheral Vascular Disease (PVD), Chronic Obstructive Pulmonary Disease (COPD), Heavy smokers, Bilateral Mammary artery Harvesting, Chronic Steroid Treatment.

5.4.1.3 Subjects will be enrolled into the study and will be treated with D-PLEX concomitantly with SOC (part 1) or randomized in a 2:1 ratio to D-PLEX concomintantly with SOC or SOC only (part 2).

5.4.2 Schedule of Assessments

Is the table taken form protocol revision 5?

Table 1: Study assessments

Procedures	Visit 1 Screening Day -7 to Day 0	Visit 2 surgery Day 0	Visit 3 Day 1†	Visit 4 Day 5† (or discharge, whichever comes first)	Visit 5 Day 14† (± 3 days)	Visit 6 1 month† (± 3 days)	Visit 7 2 month† (± 7 days)	Visit 8 3 month† (± 7 days)	Visit 9 4 month† (± 7 days)	Visit 10 Termination 6 month† (± 14 days)
Informed Consent	X									
Medical History & Allergy questioner completion	X									
Cardiac History and Status	X									X
General Eligibility Criteria	X	X[8] Confirmation								
Physical Exam	X					X		X		X
12-Lead ECG	X									
Sternum Stability[5]					X	X	X	X	X	X
Chest X-Rays[6]	X[7]							X		
Vital Signs (blood pressure, HR, body temperature)	X	X	X	X	X	X	X	X	X	X
Weight & Height	X									X[11]
Pregnancy Test (serum)	X									
Bacteriological Tests (for culture) [4]		X	X	X	X	X	X	X	X	X

Procedures	Visit 1 Screening Day -7 to Day 0	Visit 2 surgery Day 0	Visit 3 Day 1†	Visit 4 Day 5† (or discharge, whichever comes first)	Visit 5 Day 14† (± 3 days)	Visit 6 1 month† (± 3 days)	Visit 7 2 month† (± 7 days)	Visit 8 3 month† (± 7 days)	Visit 9 4 month† (± 7 days)	Visit 10 Termination 6 month† (± 14 days)
Assessment of Infection (Yes/No) per CDC definition	X	X	X	X	X	X	X	X	X	X
Blood Tests (hematology,chemistry[1])	X		X	X	X	X	X	X	X	X
Doxycycline Pharmacokinetic Sampling[10]		X	X	X	X	X				
Fibrosis/Scarring will be assessed[9]			X	X	X	X	X	X	X	X
Urinalysis [2]	X				X	X	X	X	X	X
Systemic Antibiotic Initiation	X	X	X							
Adverse Events	X	X	X	X	X	X	X	X	X	X
Concomitant Medications	X	X	X	X	X	X	X	X	X	X
Medical Resources Utilization (MRU)			X	X	X	X	X	X	X	X
D-PLEX Administration		X								
Surgical Re-interventions (Yes/No)										
Study Termination										X[3]

Notes:

†. All visits' time points are calculated after surgery (which is considered as Day 0).

1. Blood chemistry: Glucose, Urea (BUN), AST (SGOT), ALT (SGPT), Total Bilirubin, Alkaline Phosphatase, Calcium, Potassium, Phosphorus, Sodium, Chloride, Total Proteins, Albumin, Serum creatinine, Creatinine phosphokinase (CPK), C-reactive protein (CRP), LDH & Triglyceride. At Screening only PT, PTT, Blood typing
2. Urinalysis, will be done at screening visit and at the discretion at the investigator during the study
3. Termination procedure consists of: Termination Form completion and PI statement.

4. Bacteriology test – growth, identification and sensitivity to antibiotics (specifically to tetracycline) will be done at the discretion of the investigator if there is a suspected sternum infection
5. Sternum stability will be clinically evaluated by investigators
6. Chest X-Rays will be performed at screening and at visit 8 for sternum mechanical dehiscence assessment and at investigator's discretion. In case other chest imaging (i.e. CT/MRI) was performed, X-Ray may not be performed.
7. In case X-Ray (or CT/MRI) scan was performed within 3 months before surgery, and there was no significant change in subject's medical profile, this X-Ray (or CT/MRI) can be used for screening process.
8. Investigator will confirm eligibility before surgery, including bacteriologic tests if needed
9. Fibrosis/Scarring will be assessed by visual wound examination by investigator
10. Doxycycline pharmacokinetic sampling will be collected from a subgroup of up to [redacted] eligible subjects
11. Only weight should be measured at study termination

5.4.3 Randomization, Blinding and Un-blinding

5.4.3.1 Subjects enrolled into part 2 of the study will be randomized into either D-PLEX with SOC or SOC only. The randomization ratio is 2:1. The study is single-blind, so no unblinding procedures are necessary.

5.5 Selection of study population

5.5.1 Study Population

5.5.1.1 The anticipated total number of subjects is [redacted]

5.5.1.2 [redacted] subjects will be enrolled in part 1 (open label, single arm)

5.5.1.3 [redacted] subjects will be enrolled in part 2 (single-blinded, randomized)

5.5.1.4 A total of [redacted] subjects ([redacted] from part 1 and [redacted] from part 2) will be treated with D-PLEX

5.5.2 Rationale of Sample Size Calculation

5.5.2.1 No formal sample size calculation was done for this study. It is anticipated that each site will enroll about [redacted] subjects, for a total of up to [redacted] subjects

5.5.3 Sample Size Justification

5.5.3.1 No formal sample size calculation was performed for this study

5.6 Statistical Analysis Software and Data Management

5.6.1 Data manipulation, tabulation of descriptive statistics, calculation of inferential statistics, and graphical representations will be performed using SAS® version 9.3 or higher for Windows. If the use of other software is warranted, the final statistical methodology report will detail what software was used for what purposes.

5.6.2 Data Management

5.6.3 The OpenClinica system is used in the study for data collecting and management. The system is designed, developed, and implemented by MediStat.

5.6.4 The current study will use an EDC format and a data management plan was prepared by Medistat Ltd.

5.6.5 Edit checks are performed for the purpose of ensuring the accuracy, integrity, and validity of the database. These edit checks may include missing value checks, range checks, consistensy, sequence and protocol adherence checks.

5.6.6 Queries generated from these checks will be stored in the EDC system and are the responsibility of the investigational site to resolve and update the database as appropriate.

5.6.7 Medical Coding

5.6.7.1 Concomitant medications entered into the database are coded using the WHO (World Health Organization) Drug Public Website Dictionary named WHOCC-ATC/DDD index, which employs the Anatomical Therapeutic Chemical classification system.

5.6.7.2 Adverse events are coded using the most updated version of Medical Dictionary for Regulatory Activities (MedDRA) terminology.

5.6.7.3 Medical history and cardiac history is coded using the most updated version of Medical Dictionary for Regulatory Activities (MedDRA) terminology

5.6.8 Handling of Missing data

5.6.8.1 No imputations will be performed

5.6.9 Protocol Deviations

5.6.9.1 Departures from the protocol should be avoided unless required for the safety of the subject. Protocol deviations and, if possible, the reason for occurrence will be documented by the study monitor.

5.6.9.2 The Investigator must report any protocol deviation to the Sponsor and, if required, to the Institutional Ethics Committee in accordance with local regulations, within reasonable time. All violations and deviations must be recorded in the study site's electronic system and signed by the Investigator (or designee).

5.7 Subject Population for analyses

5.7.1 The ITT/ Safety population will include all subjects (open label and randomized) who underwent a cardiac surgical procedure and received D-PLEX or SOC for prevention of infections.

5.7.2 All safety analyses will be performed on the ITT population.

5.8 Statistical Analysis

5.8.1 General

5.8.2 All measured variables and derived parameters will be listed individually and, if appropriate, tabulated by descriptive statistics. For categorical variables summary tables will be provided giving sample size, absolute and relative frequency. For continuous variables summary tables will be provided giving sample size, arithmetic mean, standard deviation, median, minimum and maximum of variables.

5.8.3 The data is analyzed using the SAS ® version 9.3 or higher (SAS Institute, Cary North Carolina, USA). Analyses presented in the clinical report but not mentioned in the SAP are unplanned or ad-hoc analyses.

5.8.4 Statistical methods presented in the SAP may be slightly different from those that are presented in the protocol. Differences are clearly stated and the SAP supersedes the protocol only with regard to the way data will be handled and analysed.

5.8.5 Definition of baseline

5.8.5.1 Baseline is defined as the last non-missing value prior to the patient start of treatment (screening or surgery visit).

5.8.6 End of Study

5.8.6.1 The end-of-study visit is defined as Visit 10 termination visit

5.8.7 Incomplete dates

5.8.7.1 All incomplete dates will be entered in the database as they were recorded in the CRF/SD. Thereafter, for calculation purposes, the incomplete dates will be completed using pre-defined rules.

5.8.7.2 If a day or month are missing, or if the recorded day contradicts other dates, a query will be issued to the investigational site.

5.8.7.3 If a day or month is recorded as UNK it will be replaced by the first day of the month or January, respectively, provided this does not contradict any other dates recorded. If both day and month are recorded as UNK it will be replaced by the first day of month and January.

5.8.8 Disposition of subjects (Table 14.1-1.1)

5.8.8.1 The number of subjects that are randomized into the study, the number of subjects in the ITT population, and the number of study completers will be presented.

5.8.8.2 The reasons for early termination/ withdrawal will be summarized.

5.8.9 Demographic and Baseline data (Tables 14.1.2-1 -14.1.2-5)

5.8.9.1 Baseline and demographic data will be summarized in appropriate tables using the ITT population. The data includes demographic characteristics (age and gender), medical history, cardiac history, smoking history, and sternal length at screening

5.8.10 Efficacy Analysis

5.8.10.1 No formal statistical analysis will be performed. Only descriptive statistics will be presented

5.8.10.2 The primary efficacy endpoint is the rate of sternal infection post cardiac surgery. Rate will be summarized by treatment

5.8.10.3 The time to first sternal infection will be calculated as the difference between date of cardiac surgery and date of sternal infection, as indicated in the EDC system, in days.

5.8.10.4 The number of readmissions will be tabulated and summarized per subject. Subjects with no readmissions will be indicated as such in the table

5.8.10.5 The number of sujbects with surgical re-intervention will be tabulated.

5.8.10.6 Sternal infection rates (DSWI and SSWI) will be summarized by timepoints (the first 30 days and >30 days through 3 months).

5.8.10.7 The total number of subjects with infections will be summarized by timepoints (the first 30 days and >30 days through 3 months).

5.8.10.8 Number of hospitalizaiton days due to infection will be summarized per subject.

5.8.11 Safety analysis.

5.8.11.1 Safety data will be summarized for the ITT population.

5.8.11.2 Adverse events will be coded according to coding dictionaries (the most updated version of MedDRA) and presented in tables by System Organ Class and Preferred Term (PT) and by treatment group.

5.8.11.3 The incidence of AEs, as well as the intensity and relationship to study drug will be summarized by treatment group.

5.8.11.4 Concomitant medication verbatim terms (as recorded on the CRFs) will be coded to Anatomical Therapeutic Chemical (ATC) Level 2 and 4, and generic name, using the World Health Organization (WHO) dictionary.

5.8.11.5 Physical examination, vital signs, and laboratory parameters will be summarized and tabulated by parameter and visit

5.8.12 Interim Analysis

5.8.12.1 No interim analysis will be performed

6. RELATED DOCUMENTS (OPTIONAL)

6.1 Internal Documents

6.1.1 CL-00007 Data management plan for EDC 27NOV2016

6.1.2 IMP Protocol_D-PLEX 301 v5_ (Clean) FINAL

6.2 External documents

7. RELATED FORMS (OPTIONAL)

Not Applicable

8. REFERENCES

Not Applicable

9. APPENDICES (OPTIONAL)

APPENDIX I: TABLE SHELLS

PolyPid: CL-0007 (Study D-PLEX -301)

14.1.1 Subject Disposition

Table 14.1.1-1: Subject Disposition

14.1.2 Demographic Data and Baseline Assessments

Table 14.1.2-1: Demographic Data

Table 14.1.2-2: Medical History*

Table 14.1.2-3: Cardiac History and Current Status

Table 14.1.2-4: Smoking and Alcohol History

Table 14.1.2-5: Sternum Length at Screening

14.2.1: Primary Efficacy Parameters

Table 14.2.1.1: Sternal Infections after Surgery

14.2.2: Secondary Efficacy Parameters

Table 14.2.2.1a: Number of subject with readmissions due to sternal site infection

Table 14.2.2.1b: Number of Surgical re-interventions due to sternal site infection

Table 14.2.2.2a: Number of subject with readmissions due to sternal site infection

Table 14.2.2.2b: Number of Surgical re-interventions due to sternal site infection

Table 14.2.2.3a: Number of subjects with surgical re-interventions due to sternal site infection

Table 14.2.2.3b: Number of Surgical re-interventions due to sternal site infection

Table 14.2.2.4: Time to first sternal infection after Surgery

Table 14.2.2.5: Sternal Infections within 30 days of surgery

Table 14.2.2.6: Sternal Infections from >30 days to 3 months (90 days) after surgery

Table 14.2.2.7: Frequency of Infections months after surgery

Table 14.2.2.8: Number of hospitalization days due to sternal site infection

14.3 Safety Data

14.3.1 Adverse Events

Table 14.3.1-1: Summary of Adverse Events by SOC and PT

Table 14.3.1-2: Frequency of any Adverse Events

APPENDIX II: LISTINGS SHELLS

PolyPid: CL-0007 (Study D-PLEX -301)

16.2.1 Subject Disposition

Listing 16.2.1-1: Subject Disposition

Listing 16.2.1-2: Visit dates per subject (Part 1 of 2)

Listing 16.2.1-2: Visit dates per subject (Part 2 of 2)

16.2.3 Subjects Excluded from the Efficacy Analysis

Listing 16.2.3-1: Inclusion Criteria

Listing 16.2.3-2: Exclusion Criteria

16.2.4 Demographic Data and Baseline Assessments

Listing 16.2.4-1: Demographic Data

Listing 16.2.4-2: Medical History

Listing 16.2.4-3: Cardiac History and Current Status

Listing 16.2.4-4: Smoking and Alcohol History

Listing 16.2.4-5: Sternum Length at Screening

16.2.5 Compliance/Exposure/Drug Concentration Data

Listing 16.2.5-1: Index Procedure (part 1 of 2)

Listing 16.2.5-1: Index Procedure (part 2 of 2)

16.2.6 Individual Efficacy/PK/PD Response Data

Listing 16.2.6-1: Assessment of Sternal Infection (part 1 of 2)

Listing 16.2.6-1: Assessment of Sternal Infection (part 2 of 2)

Listing 16.2.6-2: Hospitalization Record

Listing 16.2.6-3: PK Log

16.2.7 Adverse Event Listings

Listing 16.2.7-1: Adverse Events (Part 1 of 4)

Listing 16.2.7-1: Adverse Events (Part 2 of 4)

Listing 16.2.7-1: Adverse Events (Part 3 of 4)

Listing 16.2.7-1: Adverse Events (Part 4 of 4)

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Listing 16.2.8-3: Height, Weight, and BMI

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