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Full Title of Trial	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.
Short Title	Safety and Efficacy of D-PLEX in the Prevention of Sternal Infection Post Cardiac Surgery.
Version & Date of Protocol	Version: 05 Date: 13 August 2017
Sponsor	PolyPid Ltd, 18 HaSivim Street, Petach Tikva, Israel. 495937 Tel: [redacted]
Sponsor Protocol Number	CL-0007, Study D-PLEX-301
Phase of Trial	Phase Ib/II
Site(s)	Multi-site in Israel: [redacted]
Study Principal Investigator & Medical Expert	[redacted] Head, Cardiac Surgery Poria Medical Center, Israel Staff Senior Cardiac Surgeon Chaim Sheba Medical Center Tel -Hashomer, Israel. 52561 Secretary General, Israel Cardiothoracic Surgery Society Tel : [redacted] Fax : [redacted] Mobile : [redacted]

	Email : [redacted]	
Sponsor Representatives	Contact Person:	Clinical Development Manager: [redacted] PolyPid Ltd. 18 HaSivim Street, Petach Tikva. Israel. 495937. Tel: [redacted] Email: [redacted]

PROTOCOL AGREEMENT SIGNATURES

The Principal Investigator and the Sponsor have discussed this protocol. The investigator/s agree to perform the investigations and to abide by this protocol

The investigator agrees to conduct the trial in compliance with the approved protocol, current ICH GCP, Declaration of Helsinki and Israel Ministry of Health (Pharmaceutical Administration), Guidelines for Clinical Trials in Human Subjects 2016, and other regulatory requirements as amended.

Protocol 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.

Protocol version and date: Version: 05,

Date: 13 August 2017

Study Principal Investigator

[redacted], MD

Signature Date

Sponsor Representative

[redacted]

Clinical Project Manager

Signature Date

DOCUMENT HISTORY

Revision	Date reviewed/revised	Changes
Version 05	25 July 2017	Statistic clarification
Version 04	07 March 2017	Change of the study phase to Ib/II, addition of two sites & updates
Version 03	05 December 2016	Changes were done further to FDA requests, wording corrections & clarifications
Version 02 – Addendum 1 (CL-0007-F1/ver. 01)	10 August 2016	Blood test – CRP was added and discrepancies of chemistry test lists were settled
Version 02	16 June 2016	Changes further to MOH requests, wording corrections & clarifications
Version 01	NA	First Issue

DOCUMENT CHANGE HISTORY

Revision	Changes	Reason for changes
Version 05	Sections: 15 Revision of statistical analysis section	Clarification of statistical analysis plan
	Sections: Summary, 5.2, 9.2.12, 9.4.1, 9.5 Remove of MRI imaging	Following further advice from clinical experts, replacement of MRI imaging with clinical evaluation of sternum stability
	Section: Summary Clarification that **approximately** [redacted] subjects will be treated with D-Plex	Randomization plan of 2:1 can't ensure that actual randomization will be exactly 2:1
	Sections: Summary, 9.2.4, 9.4.2, 9.5, 9.6.1 PK samples will be collected from **up to** [redacted] eligible subjects	Correction of typing error
	Sections: Summary, 9.7, 14.1.1	Further to enrollment rate

	Update of study duration	
	Section: 3.3.1, 3.3.3 Updated status & number of enrolled subjects in active studies (103 & 301)	Updated information
	Section: 3.5 Rephrasing	Clarification
Version 04	Sections: Protocol Title, Summary, 6.1, 14.1.1 Change of the study phase to Ib/II according to Israel MOH approval	• The study is comparative (D-PLEX concomitantly with standard of care versus standard of care alone). • Total number of patients was raised to [redacted]. • Safe use of D-PLEX in humans was demonstrated in [redacted] patients administered with D-PLEX in part 1 of the study (no AE related to D-PLEX were reported until now).
	Sections: Summary, 3, 4, 5.1, 6, 9.2.8 Change of "primary sternal infection" to "sternal infection"	D-PLEX indication is for prevention of sternal infection.
	Sections: Summary, 5.1 Efficacy parameters were revised to primary and secondary efficacy endpoints.	Change of the study phase to Ib/II. The primary endpoint provides the most clinically relevant evidence regarding efficacy of D-PLEX.
	Sections: Summary, 5.2 Safety parameters were revised to safety endpoints	Change of the study phase to Ib/II.
	Section: 9.4.2 Added clarification of time point for PK sample collection "day 5 or discharge, whichever comes first"	Clarification of time point
	Section: 9.5	To avoid unnecessary duplication of test.

	Enabling use of X-Ray (or CT/MRI) performed within 3 months before surgery to be used for screening process.	
	Sections: 9.2.4, 9.5 Blood test – LDH was added	LDH test is part of SOC and was previously removed in the protocol text due to typo mistake
	Section: 5.1.1 Addition of the sentence "Patient has at least one of the following"	Clarification of sternum infection diagnosis
	Sections: Summary, 8, 9.6 Addition of [redacted] sites [redacted]	To enhance enrollment
	Sections: Summary, 9.7, 14.1.1 Update of study duration	Further to enrollment rate
	Section: 3.3 Updated number of enrolled subjects in active studies (103 & 301)	Updated information

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LIST OF ABBREVIATIONS

AE	Adverse Event
AR	Adverse Reaction
ASC/AST	Active Surveillance Culture/Testing
BMI	Body Mass Index
β-TCP	β- Tri Calcium Phosphate
CABG	Coronary Artery Bypass Grafting
CDC	Center for Disease Control
COPD	Chronic Obstructive Pulmonary Disease
eCRF	Electronic Case Report Form
CVA	Cerebro Vascular Accident
DPPC	Dipalmitoylphosphatidylcholine
DSPC	Distearoyl Phosphatidylcholine
DSWI	Deep sternal wound infections
EC	Ethics Committee
ECG	Electrocardiogram
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
GRAS	Generally Recognized As Safe
IB	Investigator's Brochure
ICF	Informed Consent Form
IMP	Investigational Medicinal Product
MED	Mediastinitis
MRI	Magnetic Resonance Imaging
PI	Principal Investigator
PK	Pharmacokinetics
PLGA	Poly (DL-lactide-co-glycolide)
PLEX	Polymer- Lipid Encapsulation matrix
PVD	Peripheral Vascular Disease

QA	Quality Assurance
QC	Quality Control
SAR	Serious Adverse Reaction
SAE	Serious Adverse Event
SDV	Source Document Verification
SOC	Standard of Care
SOP	Standard Operating Procedure
SSI	Surgical Site Infection
SSWI	Superficial Sternal Wound Infection
SUSAR	Suspected Unexpected Serious Adverse Reaction
TIA	Transient Ischemic Attack
TX	Treatment
USP	United States Pharmacopeia
VADs	Ventricular Assist Devices

1 TRIAL PERSONNEL

Study Principal Investigator (PI) & Medical Expert

[redacted]

Head, Cardiac Surgery

Poria Medical Center, Israel

Staff Senior Cardiac Surgeon

Chaim Sheba Medical Center

Tel–HaShomer, Israel. 52561

Secretary General, Israel Cardiothoracic Surgery Society.

Email: [redacted]

Tel: [redacted]

Fax: [redacted]

Mobile: [redacted]

Sponsor's Representative

[redacted] PolyPid Ltd.

Clinical Development Manager

Email: [redacted]

Tel: [redacted]

Fax: [redacted]

[redacted] PolyPid Ltd.

Clinical Project Manager

Email: [redacted]

Tel: [redacted]

Fax: [redacted]

2 SUMMARY

Full Title of Trial	A Phase Ib/II Prospective, Multicenter, Two part study; Part 1 - Open Label, Single Arm & Part 2 Randomized, Single-blind, 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.
Short Title	Safety and Efficacy of D-PLEX in the Prevention of Sternal Infection Post Cardiac Surgery.
Investigational Medicinal Product (IMP)	D-PLEX is a new formulation of extended release Doxycycline. Each [redacted] D-PLEX vial contains [redacted] doxycycline [redacted] which is equivalent to [redacted] doxycycline hyclate [redacted] The components of the extended controlled release antibiotic formulation are [redacted] All formulation components which are considered by FDA to be GRAS, are all biodegradable. The D-PLEX will be applied during the cardiac surgery (index procedure), as an adjunct to the standard of care, immediately prior to sternal closure. D-PLEX is supplied as sterile powder to be reconstituted to paste in the operating room, using standard aseptic techniques and is intended for single administration. The D-PLEX dose is dependent 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 of D-PLEX will be used. D-PLEX will be applied directly within the surgical site: between the two halves of the sternum bone and over its surface before wound closure (sewing).

Indication	D-PLEX is indicated for prevention of post cardiac surgery sternal infection.
Standard Of Care (SOC)	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 consistent for all sites that will participate in the clinical program.
Dose Administration	The D-PLEX dose is dependent 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 of D-PLEX will be used.
Duration Of Dosing	D-PLEX is administered as a single application. The active material (i.e., doxycycline) is being constantly released for approximately 4 weeks.
Phase of Trial	Phase Ib/II
Objectives	• To assess the safety of D-PLEX. • To 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 in patients above the age of 18, including high risk patients for infection
Type of Trial	Phase Ib/II, Prospective, Multicenter, Two part study; Part 1 Open Label, Single arm & Part 2 Randomized, single-blinded.
Trial Design & Methods	Phase Ib/II, Prospective, Multicenter, Two part study; Part 1 Open Label, Single arm & Part 2 Randomized, Single-blinded, D-PLEX Concomitantly with Standard Of Care vs. Standard of Care alone. Study population include subjects above the age of 18 years, that undergoing cardiac surgery through mid-sternotomy, including patients with high risk of infection, such as diabetes (Insulin and/or non-insulin dependent), patients with Peripheral Vascular Disease (PVD), Chronic Obstructive Pulmonary Disease (COPD), heavy smokers, Bilateral Mammary artery harvesting, and subjects administered chronic steroid treatment. Subjects who meet the eligibility criteria and provide signed informed consent, will be enrolled into the study and will be treated with D-PLEX concomitantly with standard of care (part 1) or randomized 2:1 to D-PLEX concomitantly with standard of care vs. standard of care only (part 2).

	D-PLEX will be administered as a single application during the cardiac surgery (index procedure) immediately prior to sternal closure, as an adjunct to the standard care. Doxycycline pharmacokinetic sampling will be collected from a subgroup of up to [redacted] eligible subjects. Post-operative care will be performed per SOC and will be consistent for all sites. Post-operative resumption of activities are at the discretion of investigator based on subject medical condition. Spontaneous adverse events (AEs) including death will be recorded throughout the study. The study will assess the efficacy and safety of the controlled release antibiotic (doxycycline) by the reduction in the number of sternal infections observed during the study period in any subject above the age of 18 years, including patients with high risk for infection. Additional follow up for prolonged safety assessments only, will be done as follows until 6 months.
Trial Duration Per Participant	It is expected that each subject will be in the study for approximately 6 months.
Estimated total trial duration	Total duration of the study is expected to be approximately 9-12 months from first subject enrolled until last subject completed. Initial enrollment anticipated: Q4 2016 Final enrollment anticipated :Q3 2017 Last 6 months follow up: Q1 2018
Planned trial sites	Multi-center. [redacted]
Total number of participants planned	Anticipated total number of subjects is [redacted]; • [redacted] subjects in part 1 (open label, single arm) • [redacted] subjects in part 2 of the study (single-blinded, randomized to D-PLEX Concomitantly with Standard Of Care vs. Standard of Care alone with randomization rate of 2:1 respectively) A total of approximately [redacted] subjects will be treated with D-PLEX.
Main inclusion/exclusion criteria	**Inclusion criteria (part 1 & 2):**

	Subjects eligible for enrollment in the study must meet all of the following criteria; 1. Male or non-pregnant female above 18 years old 2. Female of childbearing potential should have a negative serum pregnancy test prior to index procedure *Note*: All female of childbearing potential must agree to use a highly effective method of contraception (such as double barrier, oral or parenteral hormonal, intrauterine device and spermicide) consistently and correctly for the duration of the study. 3. Subjects undergoing elective or urgent cardiac surgery, who are preoperative stable hemodynamically 4. Subjects with (20≤BMI≤40) 5. Subjects who sign a written informed consent **Exclusion criteria (part 1 & 2):** Subjects meeting any of the following criteria, are ineligible and must not be enrolled in the study; 1. Subject received any investigational drug within 30 days of start of the study or within 5½ half-lives (pharmacokinetic or pharmacodynamics) prior to enrollment (whichever is longer) 2. Subject that meet any of the following, are ineligible; a. Any preoperative active significant infection b. Antibiotic sensitivity to Doxycycline and/or tetracycline family of drugs c. Known allergies to more than 3 substances.(Allergy questionnaires should be filled during the enrolment process) d. History of allergic/hypersensitivity reaction to any substance having required hospitalization and/or treatment with intra-venous steroids/epinephrine or in the opinion of the investigator the patient is at high risk of developing severe allergic / hypersensitivity reactions. e. History of uncontrolled Asthma (GINA ≥ III) f. History of chronic urticaria 3. Pregnant or breastfeeding women

	4. Subjects who have taken oral or IV doxycycline during the last 4 weeks prior to screening 5. Subjects who undergo cardiac/open chest surgeries, which are classified as emergency 6. Immunocompromised subjects from any reason, at screening 7. Subjects undergone TIA/CVA within the last 3 months prior to enrollment 8. Subjects undergone previously any cardiac surgery through mid-sternotomy 9. In the opinion of investigator, subject is not eligible to participate in the study due to a cognitive status, medical condition or medication status (other than items listed above)
Efficacy Endpoints	<u>Primary Efficacy Endpoint:</u> • Decrease of infection rate as measured by the proportion of subjects with at least 1 identified sternal infection within 90 days post-cardiac surgery. Sternal infection is composed from Deep Sternal Infection (DSWI) and Superficial Sternal Wound Infection (SSWI). <u>Secondary Efficacy Endpoints:</u> • Reduction in Number of readmissions due to Sternal Surgical Site infection. • Reduction in Number of surgical re-interventions due to Sternal Surgical Site infection. • Time to sternal infection post-cardiac surgery. • Decrease of Sternal Infection rate (DSWI and SSWI) during the first 30 days post operation. • Decrease of Sternal infection rate (DSWI and SSWI) between day 30 and 3 months. • Decrease in The total number of sternal infections (DSWI and SSWI) (including several in the same patient) between day 30 and 3 months. • Reduction of Number of hospitalization days due to Sternal Surgical Site infection. Sternal infection will be identified and assessed by the investigator based on predefined criteria in the CDC's Criteria for Surgical Site

	Infection (SSI) & Surveillance Definition for Specific Types of Infections Chapters, January 2016.
Safety Endpoints:	Adverse events, safety laboratory parameters, physical examinations, vital signs. Sternum mechanical dehiscence assessment by X-Ray. Assessment of wound healing and extent of fibrosis/scarring. 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). Safety laboratory parameters: Routine hematology, chemistry, urinalysis and bacterial test (bacterial growth, identification and sensitivity to antibiotics, including to tetracycline).
Statistical methodology and analysis	No formal statistical analysis will be performed. Only descriptive statistics (mean values, standard deviation will be presented).

3 INTRODUCTION

3.1 BACKGROUND

3.1.1 NAME & DESCRIPTION OF THE INVESTIGATIONAL MEDICINAL PRODUCT

Name: D-PLEX

D-PLEX consists of [redacted], and a [redacted] specifically [redacted]

All formulation components which are considered by FDA to be GRAS, are all biodegradable.

Active ingredients: Each [redacted] D-PLEX vial contains [redacted] which is equivalent to [redacted]

Pharmacological Class: Doxycycline pharmacological class: broad spectrum bacteriostatic antibiotics[1].

D-PLEX is a formulation of extended, controlled release doxycycline, intended for local administration.

Intended Use: D-PLEX is indicated for prevention of post cardiac surgery sternal infection.

Intended Users of D-PLEX: The intended users are cardiac surgeons.

For a detailed technical summary of the D-PLEX formulation composition, see Section 5.2 in the D-PLEX Investigator's Brochure, #DV-0079.

3.1.2 RATIONAL FOR PERFORMING RESEARCH WITH THE INVESTIGATIONAL MEDICINAL PRODUCT & THE ANTICIPATED PROPHYLACTIC INDICATION

3.1.2.1 UNMET NEED FOR PREVENTION OF SURGERY STERNAL INFECTION FOLLOWING CARDIAC PROCEDURES

Sternal infections post cardiac surgery are a major cause of post-operative illnesses resulting in increased morbidity and mortality, and hold a major impact on the cost of health.

In North America and Europe two million cardiac surgeries are performed a year, whereas circa 5,000 are conducted in Israel. Cardiac procedures include Coronary Artery Bypass Grafting (CABG) procedures, valve replacement and repair, placement of temporary or permanent implantable cardiac devices, including ventricular assist devices (VADs) and ascending aorta surgeries associated with cardiac procedures. Deep and superficial sternal wound Infection, are rare (0.23 to 5.67 per 100 operations) but the consequences of infection are severe[2].

One of the most dangerous complication following cardiac surgery is Deep Sternal Wound Infection (Mediastinitis). The incidence of deep sternal wound infections ranges between 0.3-3.2% [3,4,5,6,7,8] with mortality rate reaching 40%[3]. In high-risk patients undergoing cardiac surgery, complications are even higher reaching 5-7%[9,10]. Prolonged hospitalization last weeks or months, with repeated surgical interventions and long-term antibiotic treatment, in cases of Osteomyelitis. DSWI affects quality of life, and causes suffering to the patient and family. The financial burden in these patients to the health systems is estimated to be 3-time-fold compared to patients undergoing open cardiac surgery, without any infection[11,12,13].

One of the causes for infection are any bacteria (of local natural flora and/or nosocomial) present at multiple body sites and on the skin surface. Almost two thirds of organisms isolated in patients undergoing cardiac procedures are gram-positive Staphylococci, including *S. aureus*, coagulase-negative staphylococcus. Gram-negative organisms are less commonly isolated in these patients and include *Enterobacter* species, *Pseudomonas aeruginosa*, *Escherichia coli*, *Klebsiella pneumoniae*, *Proteus mirabilis*, and *Acinetobacter* species[14,15,16,17,18,19,20,21].

Multiple studies have found that antimicrobial prophylaxis in cardiac procedures lowers the occurrence of postoperative Sternal Site Infection (SSI) up to fivefold[22].

The *American Society of Health System Pharmacists (ASHP)* has developed guidelines of antimicrobial prophylaxis in surgery. The antibacterial prophylaxis for patients undergoing cardiac procedures, is a single pre-incision dose of cefazolin or cefuroxime with appropriate intraoperative re-dosing if needed. Currently, there is no evidence to support continuing I.V. prophylaxis until all drains or catheters are removed. The currently accepted duration of prophylaxis for cardiac procedures is less than 24 hours, but prophylaxis should be continued for the duration of the procedure[23,24,25,26].

Topical antimicrobials, mainly gentamicin or vancomycin, applied to the sternum during cardiac procedures in combination with I.V. antibiotics to prevent mediastinitis has been evaluated. In the literature, the safety and efficacy of topical antimicrobials have not been clearly established and therefore cannot be recommended for routine use in cardiac procedures[15,27,28]. Randomized control studies in US, of gentamicin collagen sponges failed to show any efficacy in a large prospective study of cardiac surgery in US[10].

In recent years, despite the development of new surgical techniques, new technologies for diagnosing postoperative infection, and wound care technologies, there is no decrease in the occurrence of sternal infections following cardiac surgeries. This is mainly due to the growing number of older patients undergoing cardiac surgery, suffering from other diseases with co-morbidities necessitating longer postoperative hospitalization, caused by postoperative complications [4,7].

3.1.2.2 JUSTIFICATION FOR THE USE OF D-PLEX FOR PREVENTION OF SSI FOLLOWING CARDIAC PROCEDURES

Following cardiac surgery the blood supply to the sternal bone is disrupted. Therefore, systemic antibiotics and immune defence cannot sufficiently reach the designated areas, causing these areas to be more susceptible to proliferation of bacteria and subsequent development of infection. In addition, there is a risk of developing antibiotic resistant bacteria in the presence of low local prophylactic antibiotic concentrations, while an increased systemic antibiotic dose may cause systemic toxicity. In an attempt to overcome these problems, some surgeons locally dispense antibiotics before closing the incision. This antibiotic treatment presents a very short release durations of 1-2 hours, and does not prevent development of bacterial infection[15,27,28]. D-PLEX is a new formulation of extended controlled release of Doxycycline, intended to be administered in the sternal surgical site post sternotomy performed in cardiac surgery.

Doxycycline is effective for eradication of most of the bacteria known to cause, sternal infection mainly cocci bacteria which cause at least 80% of the infections[29]. In addition, Doxycycline-PLEX based product (BonyPid-500™), demonstrated efficacy in prevention of infections caused by S. *aureus*[30].

D-PLEX is administered directly at the surgical site and releases doxycycline immediately upon product administration and during approximately 4 weeks following administration, which is the time period in which most of the sternal infections occur[31].

During this period, the expected local Doxycycline concentration is well above the minimal inhibitory concentration (MIC) of sensitive organisms (e.g. *S. aureus*).

By preventing growth of bacteria via high local concentration of doxycycline at the sternal surgical site during the 4 weeks post its administration, D-PLEX is intended to be effective for prevention of post cardiac surgery sternal infection.

3.2 NON-CLINICAL STUDIES

Non-clinical pharmacology and pharmacokinetic studies were performed with D-PLEX in order to demonstrate its relevance to the investigated therapeutic and the possible unfavourable and unintended effects in humans. These studies included:

- A number of *in vitro* development studies with D-PLEX (See IB, section 6.2.1) that demonstrated doxycycline antimicrobial activity post hydration. The studies showed that antibacterial effectiveness of the doxycycline, as incorporated in D-PLEX, and released, is maintained for up to 35 days. The doxycycline release is a high short term initial release (25-30% in the first 24 hours) followed by daily release of 1-3% of the rest of the Doxy reservoir from day 5 up to day 32. Between days 33 and 35 the daily release is below 1% (See IB, section 6.3.2).
- *In vivo*, rat model, study that demonstrated the ability of D-PLEX to significantly reduce bacterial proliferation following induction of a surgical site infection (SSI) attained by intramuscular administration of the test product combined with Staphylococcus aureus (ATCC 25923).
- *In vivo* pharmacokinetic study that demonstrated that after administration of high dose of D-PLEX (more than 100 times higher than the maximum amount allowed to be administered in human) doxycycline was detected in the plasma up to 35 days. This proves the ability of the D-PLEX product to release doxycycline for a period of 35 days in vivo (which is also supportive by the in vitro data). Furthermore, it was observed that after subcutaneously (SC) administration of low dose of D-PLEX (equivalent to twice the maximum amount allowed to be administered in human), doxycycline was detected in the plasma for up to 24 hours only. This indicates that the systemic exposure to doxycycline as consequences of local administration is negligible. In vivo, safety study, rabbit model demonstrated that was no gross pathological findings after administration of D-PLEX in clinically-relevant model (Deep sternal administration).
- *In vivo*, safety study, rabbit model (PLP-002-EF, see IB, section 6.4.1) demonstrated no gross pathological findings after administration of D-PLEX in clinically-relevant sternal model.

Toxicology studies were not performed on D-PLEX. However, the following is regarded as supportive of the non-clinical toxicity of the D-PLEX product:

- The systemic Doxycycline label, which is incorporated in D-PLEX IFU, #L01002ENG, is referred to as supportive of the non-clinical toxicity of doxycycline.
- Two of PolyPid's products (BonyPid-1000™ and BonyPid-500™) toxicology program is referred to as supportive of the non-clinical toxicity of doxycycline and the other constituents used in the D-PLEX product (see IB, section 6.4.2). This support is based on:
    - The amount of doxycycline and polymer-lipid encapsulation matrix (PLEX) components administered in D-PLEX and BonyPid-1000™ are comparable.
    - The amount of β Tri-calcium phosphate (β-TCP) is lower in D-PLEX as compared to BonyPid-1000™.
- The BonyPid-1000™ toxicology program consists of GLP and International Organization for

Standardization (ISO) 10993-1:2009-compliant biocompatibility studies conducted to evaluate BonyPid-1000™-equivalent coated granules without doxycycline, the BonyPid-1000™ product, and BonyPid-1000™ impurities, including 4-epidoxycycline.

- The biocompatibility studies indicate the following:
  - BonyPid-1000™ is not associated with clinically relevant local irritation or sensitization;
  - The slight irritant result obtained was not considered to be biologically relevant;
  - Extracts of BonyPid-1000™ were not acutely toxic, pyrogenic, or genotoxic in a standard battery of assays; and
  - A 13-week subcutaneous implantation study also indicated that there was no evidence of systemic toxicity induced by BonyPid-1000™.

For detailed non clinical studies summary of the D-PLEX, see Section 6 in the D-PLEX Investigator's Brochure, #DV-0079.

3.3 CLINICAL DATA

D-PLEX is indicated for the prevention of sternal wound infection post cardiac surgery.

As of today [redacted] subjects were enrolled to this protocol No AE or SAE were considered to be related to D-PLEX by the investigators. Nevertheless, clinical experience from BonyPid-1000™ can contribute to the understanding of the safety and efficacy of D-PLEX, under the following considerations:

Both products include identical components, except for beta-TCP which differs in its shape, size and function and manufacturer as described:

a) BonyPid-1000™ includes [redacted], which have CE mark approval (CE-0459) and FDA 510(k) clearance (K042340) as a bone void filler.

b) D-PLEX includes [redacted], which is not an approved medical device and does not have any bone healing properties of a bone filler.

c) Both products are tested according to ASTM F1088-04a.

The maximum amount of each component allowed to be administered in both products per patient is the same.

Although they differ in their indications for use[1], both products are administered in the same tissue environment i.e. in bone. Hereinafter is a brief summary of the clinical experience from BonyPid-1000™:

[1] D-PLEX is indicated for prevention of post cardiac surgery sternal wound infection. BonyPid-1000™ is a bone graft substitute intended for filling bone voids or defects that are not intrinsic to the stability of the bony structure. These defects may be surgically created osseous defects or osseous defects created from traumatic injury to the bone. BonyPid-1000™ is resorbed and replaced with bone during the healing process. BonyPid-1000™ contains doxycycline to reduce microbial colonization on the bone void filler of microorganisms sensitive to doxycycline.

Clinical Investigation: Study # BonyPid-1000™ -101

Clinical Investigation: Study # BonyPid-1000™ -102

Clinical Investigation: Study # BonyPid-1000™ -103

3.3.1 BONYPID-1000™- 101 STUDY - FIRST-IN-MAN

BonyPid-101 study was a First in Man Clinical Study to evaluate the safety and the effectiveness of BonyPid-1000™ concomitantly to Standard of Care (SOC) in the treatment of contaminated or infected open fractures and was conducted in Manila, the Philippines. This was a single arm, open label, investigator initiated study using BonyPid-1000™ in open tibia fractures.

Sixteen (16) patients with Gustilo IIIA and IIIB tibia fractures were enrolled. All were treated with standard of care treatment defined as: irrigation and debridement (I&D) of the soft tissues and the target fracture, IV antibiotics and fracture stabilization. BonyPid-1000™ was implanted immediately during the first surgical intervention.

Study Effectiveness Results:

In 15/16 subjects callus formation was demonstrated at week 16 and in 16/16 subjects at week 20.

Study Safety Results:

All clinical adverse events were related to initial injury and complications. No adverse events were assessed as being related to the study device – BonyPid-1000™. No deep infection at the target fracture was reported during the study.

3.3.2 BONYPID-1000™-102 STUDY

BonyPid-102 study was a multicenter study to confirm the safety and the effectiveness of BonyPid- 1000™ concomitantly to Standard of Care (SOC) in the treatment in contaminated or infected open fractures conducted in two sites in Romania. This was a single arm, open label, study using BonyPid-1000™ in long bone fractures.

Three (3) subjects with Gustilo II, IIIA and IIIB tibia and femur fractures were enrolled.

Similarly to study BonyPid-1000™-101, no adverse events related to BonyPid-1000™, were reported.

Study Effectiveness results:

In this study 2/3 subjects have met the efficacy end-point of wound closure and bone union at 24 weeks.

Study Safety results:

No serious adverse events were reported. No adverse events were assessed as being related to BonyPid-1000™. No deep infection at the target fracture was reported during the study.

3.3.3 BONYPID -1000™- 103 STUDY

This study is a prospective, multi-national, multicenter, randomized, two arms, single blinded, Standard of Care (SOC) controlled, with blinded central reading of the x-rays. This study will assess the safety and performance of BonyPid-1000™ in severe open tibia fractures (Gustilo IIIA and IIIB) implanted as an adjunct to SOC and compared to SOC alone.

Fifty one (51) patients were enrolled in the study. Twenty eight (28) continue the study follow up visits.

Until the date of this report, No adverse events were assessed as being related to BonyPid-1000™.

Summarizing the three BonyPid-1000™ clinical studies (101, 102 and 103) in which seventy (70) subjects were enrolled (42 completed and 28 are ongoing) the effectiveness and safety of BonyPid-1000™ has been demonstrated.

3.3.4 SAFETY PROFILE OF DOXYCYCLINE

The antibiotic drug Doxycycline has been on the market for 49 years and its side effects are well established[33].

Information on adverse reactions of doxycycline capsules USP are provided in the D-PLEX IFU.

Furthermore, given the total dose of doxycycline present in D-PLEX (i.e. maximum [redacted]), which is lower than the overall daily dose of systemically administered doxycycline ([redacted]), and it is being gradually released over a period of at least 30 days, it is unlikely that clinically significant systemic levels will be present to give significant side effects. This is further supported by *In vivo*, Rat model, study on D-PLEX administered subcutaneously that has shown negligible systemic concentration (See IB, section 6.2.2).

3.4 RATIONALE & RISKS/BENEFITS

- Major objectives of the plan: Protection of patient safety and welfare while providing best quality medicinal product.
- The quality risk management process includes systematic process of risk assessment (identification, analysis and evaluation), risk control (reduction and acceptance), communication (output, results of the plan) and risk review of events.
- Duration of Plan - during D-PLEX life cycle (all phases in the life of the product from initial development through marketing).

3.4.1 POTENTIAL BENEFITS OF D-PLEX FOR PREVENTION OF POST CARDIAC SURGERY STERNAL INFECTION

a. Prevention of sternal infection, which occurs within 4 weeks post sternotomy.

b. Significant improvement in prevention of sternal infection when used in high risk population (Diabetes, Peripheral Vascular Disease (PVD), Chronic Obstructive Pulmonary Disease (COPD), Obesity and Smoking).

c. Significant improvement in prevention of sternal infection when used in surgical procedures that hold high risk of infection such as: median sternotomy for coronary artery bypass grafting, internal mammary artery harvesting etc.

d. Induces faster recovery and early return to normal activity as compared to SOC post sternotomy.

e. Reduction in the number of surgical re-interventions due to sternal wound infections.

f. Reduction in the number of hospitalizations and/ or shortening hospitalization, thus providing financial savings and reducing hospital load.

g. Potential for reducing comorbidities in vulnerable patients with sternal infection.

h. Used concomitantly with SOC.

i. Ease of administration, no special training is required.

j. Broad spectrum activity of doxycycline.[34]

k. Local administration of high and effective dose of doxycycline during cardiac surgery (which result in local high concentration above the minimal inhibitory concentration for doxycycline sensitive bacteria).

l. Low potential risk for development of bacterial resistance (refer to IB section 4.7.2).

m. Release of local doxycycline over at least 30 days cannot be achieved by systemic or current local solutions (See IB, section 6.3.4).

n. Safe treatment of doxycycline due to:

   i. Local administration of very low dose of doxycycline: Maximal amount of D-PLEX vials allowed is 3 vials per one administration which translates to [redacted] mg doxycycline to be released during at least 30 days. The US approved oral doxycycline daily dose is [redacted] mg.

   ii. Well established safety of local administration of Doxycycline thorough ATRIDOX. ATRIDOX is indicated for adult periodontitis contains [redacted] doxycycline compared to D-PLEX concentration of [redacted] ATRIDOX is administered subgingival locally on similar targets of bone and soft tissue.

o. All PLEX components are widely used in the medicinal or medical device industry, have an established history of safety and acceptable clinical use in contact with bone and/or blood circulation and are biodegradable.

3.4.2 POTENTIAL RISKS OF D-PLEX FOR PREVENTION OF POST CARDIAC SURGERY STERNAL INFECTION

Potential risks associated with addition of new antimicrobial coating as well as repositioning the method of administration from oral/systemic into local administration during sternal cardiac surgery are:

a) Potential contamination of microorganisms and pyrogens by the aseptic product.

b) Potential for local toxicity caused by the drug products, including irritation of the tissues.

c) Individual susceptibility to Doxycycline, leading to allergic reaction.

d) Potential of bacteria resistant to doxycycline (treatment failure) - causing exacerbation of infection.

e) Administration outside of the target organ- sternal surgery site.

f) D-PLEX will be removed from the target organ following repeated I&Ds.

g) Inadequate antibacterial activity of the product.

h) Re-use of D-PLEX, can lead to cross contamination.

i) Potential for permanent tooth discoloration or enamel hypoplasia during tooth development.

j) Tetracycline form stable complex in any bone formation tissue. Reversible decrease in fibula growth rate has occurred in premature infants receiving oral tetracycline.

k) Photosensitivity reaction: exaggerated sun burn reaction.

3.4.3 ASSESSMENT & MANAGEMENT OF RISK

Risks Mitigation process of D-PLEX for prevention of post cardiac surgery sternal infection

a) Potential contamination of microorganisms and pyrogens by the aseptic product.
Mitigation:

- IFU- instruction how to store, administer and use.

b) Potential for local toxicity by the drug product, including irritation of the tissues.

Mitigations:

- At subject level:
  In case of serious of local allergic reaction induced by D-PLEX, removal and irrigation of the product will be done by the surgeon.
- At population level:
  - Close follow up of patients.
  - Safety Monitoring Committee.

c) Individual susceptibility to doxycycline, leading to allergic reaction.

Mitigation:

- Exclude susceptible subjects with known allergy to doxycycline / tetracycline family and/or three different allergens.

d) Potential of bacteria resistant to doxycycline-treatment failure/exacerbation of infection.

Mitigation:

- SOC concomitantly administered with D-PLEX provides systemic antibacterial coverage.

e) Administration outside of the target organ- sternal surgery site.

Mitigations:

- Training of professional surgeons during development phase.
- IFU, clear instructions how to apply.

f) D-PLEX will be removed from the target organ following repeated I&Ds.

Mitigation:

- Apply D-PLEX following I&D procedure as instructed in the IFU.

g) Inadequate anti-bacterial activity of the product

Mitigations:

- Doxycycline assay is tested per batch in release and stability.
- SOC concomitantly administered with D-PLEX provides systemic antibacterial coverage.

h) Re-use of D-PLEX between different patients, can lead to cross contamination.

Mitigations:

- D-PLEX is intended as a single use administration.
- Training of site clinical staff during clinical trials and IFU during marketing.

i) Potential for permanent tooth discoloration or enamel hypoplasia- Tetracycline form stable complex in any bone formation tissue; Reversible decrease in fibula growth rate has occurred in premature infants receiving oral tetracyclines.

Mitigations:

- Exclusion of patients less than 18 years old from the clinical study.
- Exclusion of pregnant or lactating woman from the clinical study.

j) Photosensitivity reaction: exaggerated sun burn reaction.

Mitigations:

- D-PLEX is administered locally at very low dose once in the surgical site.
- Blood levels of doxycycline are negligible, if any. Therefore no potential for photo toxicity is expected.

3.5 SAFETY & EFFICACY SUMMARY

Based on the current data available from the ongoing clinical study with D-PLEX and the 3 Clinical studies with BonyPid-1000™, no major safety concern was observed. Overall, based on risk: benefit assessment, the expected benefits are outweigh the expected risks associated with the use of D-PLEX.

Therefore, clinical trial with D-PLEX in patient undergoing cardiac sternal surgery is warranted.

4 OBJECTIVES

- To assess the safety of D-PLEX.
- To assess the anti-infective efficacy of D-PLEX over a period of 3 months post operation by preventing sternal infection post cardiac surgery in patients above the age of 18, including high risk patients for infection.

5 EFFICACY & SAFETY ENDPOINTS

5.1 EFFICACY ENDPOINTS

The following will be evaluated in this trial:

Primary Efficacy Endpoint

- Decrease of infection rate as measured by the proportion of subjects with at least 1 identified sternal infection within 90 days post-cardiac surgery.
  Sternal infection is composed from Deep Sternal Infection (DSWI) and Superficial Sternal Wound Infection (SSWI).

<u>Secondary Efficacy Endpoints</u>

- Reduction in Number of readmissions due to Sternal Surgical Site infection.
- Reduction in Number of surgical re-interventions due to Sternal Surgical Site infection.
- Time to sternal infection post-cardiac surgery.

- Decrease in Sternal infection rate (DSWI and SSWI) during the first 30 days post operation.
- Decrease in Sternal infection rate (DSWI and SSWI) between day 30 and 3 months.
- Decrease in The total number of sternal infections (DSWI and SSWI) (including several in the same patient) between day 30 and 3 months.
- Reduction in Number of hospitalization days due to Sternal Surgical Site infection.

Sternal infection will be identified by the following predefined criteria as assessed by the investigator:

5.1.1 CDC/NHSN SURVEILLANCE DEFINITIONS FOR SPECIFIC TYPES OF INFECTIONS (JANUARY 2016, p. 17-12)

The patient has at least one of the following:

a. Patient has organisms identified from mediastinal tissue or fluid by a culture or non-culture based microbiologic testing method, which is performed for purposes of clinical diagnosis or treatment [e.g., not Active Surveillance Culture/Testing (ASC/AST)].

b. Patient has evidence of mediastinitis on gross anatomic or histopathologic exam.

c. Patient has at least one of the following signs or symptoms: fever (>38.0°C), chest pain*, or sternal instability*; and at least one of the following:

   i. Purulent drainage from mediastinal area

   ii. Mediastinal widening on imaging test

** with no other recognized cause*

and/or

5.1.2 SUPERFICIAL INCISIONAL PRIMARY (SIP) SSI (Based on PROCEDURE- ASSOCIATED MODULE SSI, JANUARY 2016, p. 9-7):

Infection occurs within 90 days after any NHSN operative procedure (where day 1 = the procedure date)

AND
the patient has at least one of the following:

a. Purulent drainage from the superficial incision.

b. Organisms identified from an aseptically-obtained specimen from the superficial incision or subcutaneous tissue by a culture or non-culture based microbiologic testing

method which is performed for purposes of clinical diagnosis or treatment (e.g., not Active Surveillance Culture/Testing (ASC/AST).

c. Superficial incision that is deliberately opened by a surgeon, attending physician** or other designee and culture or non-culture based testing is not performed.

AND

the patient has at least ***one*** of the following signs or symptoms: pain or tenderness; localized swelling; erythema; or heat. A culture or non-culture based test that has a negative finding does not meet this criterion.

d. Diagnosis of a superficial incisional SSI by the surgeon or attending physician or other designee.

*** The term attending physician for the purposes of application of the NHSN SSI criteria may be interpreted to mean the surgeon(s), infectious disease specialist, other physician on the case, emergency physician or physician's designee (nurse practitioner or physician's assistant).*

5.2 SAFETY ENDPOINTS

The following safety endpoints will be evaluated in this trial:

- Adverse events, physical examinations & vital signs.
- 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).
- Sternum mechanical dehiscence will be evaluated by X-Ray at visit 8 (90 days) and at investigator's discretion
- Fibrosis/Scarring will be assessed by visual wound examination by investigators as an evaluation of wound healing.
- Safety laboratory parameters;
  Routine hematology, chemistry and urinalysis.
- Bacterial growth, identification and sensitivity to antibiotics (especially to tetracycline)

6 TRIAL DESIGN

6.1 OVERALL DESIGN

This is a Phase Ib/II Prospective, Multicentre, Two parts Study; Part 1 Open Label, Single Arm & Part 2 Randomized, Single-Blind, of the Initial Safety and Efficacy of D-PLEX Concomitantly to Standard of Care Study vs. Standard Of Care alone in the Prevention of Sternal Infection Post Operatively Following Cardiac Surgery.

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

Subjects who meet the eligibility criteria and provide signed informed consent will be enrolled in the study.

Subjects will be enrolled into the study and will be treated with D-PLEX concomitantly with SOC (part 1) or randomized 2:1 to D-PLEX concomitantly with standard of care vs. to standard of care only (part 2).

The D-PLEX will be applied during the cardiac surgery (index procedure), as an adjunct to the standard care, immediately prior to sternal closure. Sternum and chest closure will be performed per investigator discretion.

Post-operative care will be performed per SOC that will be consistent for all sites. Post-operative resumption of activity are at the discretion of investigator based on subject medical condition.

Spontaneous adverse events (AEs) will be recorded throughout the study.

The study will assess the efficacy and safety of the controlled release antibiotic (doxycycline) by the reduction in the number of sternal infections observed during the study period in any subject above the age of 18 years, including patients with high risk for infection.

Additional follow up for prolonged safety assessments only, will be done until 6 months.

D-PLEX is a sterile powder, primarily packaged in sterile, depyrogenated inert glass amber vial (6ml vial), with each product vial containing 5g of D-PLEX.

6.2 DESCRIPTION & JUSTIFICATION OF THE DURATION OF TREATMENT, SUBJECT PARTICIPATION AND TRIAL FOLLOW-UP

A number of factors have been considered for determining the 6 months follow up period. Primarily, allowing a sufficient follow up period to demonstrate the initial and sustainability safety and efficacy endpoints of D-PLEX including the safety and efficacy of doxycycline incorporated into D-PLEX.

The anti-infective effect of D-PLEX by preventing sternal infection post cardiac surgery over a period of 1 and 3 months post operation. The prevention of Infection rate is measured by the reduction in the number of sternal infections. 6 months period is a sufficient time to demonstrate the prolonged effect[32].

7 SELECTION OF SUBJECTS

7.1 INCLUSION CRITERIA

Subjects eligible for enrollment in the study must meet all of the following criteria;

a) Male and non-pregnant female subjects above 18 years old.

b) Females of childbearing potential should have a negative serum pregnancy test prior to index procedure.

Note: All females of child bearing age must agree to use a highly effective method of contraception (such as double barrier, oral or parenteral hormonal, intrauterine device and spermicide) consistently and correctly for the duration of the study.

c) Subjects eligible and undergoing elective or urgent cardiac surgery, who are preoperative stable hemodynamically.

d) Subjects with (20≤BMI≤40).

e) Subjects who sign a written consent form.

7.2 EXCLUSION CRITERIA

Subjects who meet any of the exclusion criteria are prohibited from participating in the study.

a) Received any investigational drug within 30 days of start of study or within 5½ half-lives (pharmacokinetic or pharmacodynamics) prior to enrolment (whichever is longer).

b) Are ineligible to receive treatment with:

i. Any preoperative active significant infection.

ii. Antibiotic sensitivity to Doxycycline and/or tetracycline family of drugs.

iii. Known allergies to more than 3 substances. (Allergy questionnaire should be filled during the enrolment process).

iv. History of allergic/hypersensitivity reaction to any substance having required hospitalization and/or treatment with intra-venous steroids/epinephrine or in the opinion of the investigator the patient is at high risk of developing severe allergic / hypersensitivity reactions.

v. History of uncontrolled Asthma (GINA ≥ III).

vi. History of chronic urticarial.

c) Pregnant or breastfeeding women.

d) Subjects who have taken oral or IV doxycycline during the last 4 weeks prior to screening.

e) Subjects who undergo cardiac/open chest surgeries which are classified as emergencies.

f) Immunocompromised subjects for any reason at screening.

g) Subjects that undergo TIA/CVA within the last 3 months prior to enrolment.

h) Subjects that previously underwent any cardiac surgery through mid-sternum.

i) In the opinion of investigator, subject is not eligible to participate in the study due to a cognitive status, medical condition or medication status (other than items listed above.

8 RECRUITMENT

Patient recruitment will be via cardiac surgical admission units at [redacted] Israeli sites: [redacted] Medical Centers.

9 STUDY PROCEDURES & SCHEDULE OF ASSESSMENTS

9.1 INFORMED CONSENT PROCEDURE

The Investigator will prepare an informed consent form (ICF) in accordance with this study protocol and all local and national regulatory requirements. The informed consent form must be submitted to the EC and a copy of the final EC-approved consent form must be submitted to the Sponsor prior to the start of the study at that investigational site.

Prior to any study procedures, all subjects must document their consent, in writing, for study participation and authorization for use and disclosure of health information by signing the Ethics Committee (EC)-approved informed consent form. As part of the consent process, the subject will have the opportunity to ask questions of, and receive answers from, the personnel conducting the study.

It is the responsibility of the Investigator, or a person delegated by the Investigator to obtain written informed consent from each subject prior to participation in the trial, following adequate explanation of the aims, methods, anticipated benefits and potential hazards of the study.

"Adequate time" must be given for consideration by the patient before taking part. The PI must record when the patient information sheet has been given to the patient.

The Investigator or designee will explain the patients are under no obligation to enter the trial and that they can withdraw at any time during the trial, without having to give a reason.

No clinical trial procedures will be conducted prior to taking consent from the participant. Consent will not denote enrolment into trial.

A copy of the signed Informed Consent form will be given to the participant. **The original** signed form will be retained at the study site and a copy placed in the medical notes.

If new safety information results in significant changes in the risk/benefit assessment, the consent form will be reviewed and updated if necessary and subjects will be re-consented as appropriate.

9.2 SCREENING PERIOD - VISIT 1

Patient will be screened for study eligibility at the clinic within 7 days prior to surgery at Day 0 following ICF process and signature. The following screening assessments will be performed:

9.2.1 CARDIAC & MEDICAL HISTORY (ONLY AT SCREENING)

Demographic data and complete cardiac and medical history of past, present illnesses and surgeries as well as medications currently being taken to address current illnesses will be recorded by the investigator. The medical history will include alcohol consumption, tobacco use, diabetic status, and concurrent disease/allergy status.

Subjects with known hypersensitivity to doxycycline and/ or tetracycline family of drugs should be excluded.

Subjects will be permitted to receive concomitant therapy as medically required, except for long term high steroids dose (defined as steroid use for over 3 consecutive months during a 6 month period), immunosuppressive agents and systemic doxycycline (IV/PO).

A record of all concomitant medications will be maintained.

9.2.2 VITAL SIGNS (ALL VISITS)

Systolic/diastolic blood pressure, pulse, temperature will be recorded after 5 minutes of rest.

Weight and height (taken at visit 1 and termination only) will be taken from the subject, or the subject will be asked for this information at screening/admission.

All measurements and the time will be recorded in CRF.

Any abnormal finding, assessed by the investigator as clinically significant, should be recorded as AE in the relevant CRF section.

9.2.3 PHYSICAL EXAMINATION (SCREENING & VISITS 6, 8 & 10)

The investigator will perform a complete physical examination of the major body systems (Eyes, Ears, Nose and Throat; Cardiovascular; Respiratory; Gastrointestinal;

Musculoskeletal/Connective Tissue; Neurological; Endocrine/Metabolic; Hematopoietic/Lymphatic; Dermatologic; Genitourinary) and will assess whether the subject experiences doxycycline reactions or other allergies.

Any abnormal finding with respect to baseline, assessed by the investigator as clinically significant, should be recorded as an adverse event in the relevant CRF section.

9.2.4 LABORATORY EXAMINATIONS

The following laboratory tests will be performed and then analyzed by the respective local laboratories

a. Complete blood count (CBC) with differential white blood cell (WBC) count and platelet count; (all visits, except visit 2).

b. Urinalysis at visits 1 and as per investigator discretion at visits 5 – 10 and termination visit: pH, Specific Gravity, Protein, Glucose, Bilirubin, Ketones, Nitrites, Leukocytes, [At screening & on visits 5-10 (at the discretion of the investigator)].

c. 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.

d. Pregnancy test by serum at screening only, performed by female of child-bearing potential only. All female of child bearing potential must agree to use of a highly effective method of contraception consistently and correctly for the duration of the study.

Doxycycline pharmacokinetic sampling will be collected from a subgroup of up to [redacted] eligible subjects and will be shipped to a central laboratory.

Any abnormal finding with respect to baseline, assessed by the investigator as clinically significant, should be recorded as adverse events in the relevant CRF form.

9.2.5 BACTERIOLOGICAL TESTING - (Should be taken in any case of infection before starting Antibiotic TX)

Bacteriological tests (from sternal bone and/or surrounding soft tissue) will be performed in order to assess infection at the sternum surgical site.

Bacteriological tests from the wound will be taken if there is a wound discharge, at the discretion of the investigator.

The bacteriological swab specimen source (sternal bone or soft tissue) should be indicated on source documents and CRF.

Bacterial growth, identification and bacteria sensitivity to antibiotics (specifically to tetracycline) will be assessed by the respective local laboratories.

Any abnormal finding, assessed by the investigator as clinically significant, should be recorded as AE in the relevant CRF section.

9.2.6 ELECTROCARDIOGRAM (ECG) - (Only at screening)

A standard 12-lead electrocardiogram (ECG) will be performed at screening, to identify subjects who have undiagnosed clinically significant anomalies that the investigator believes would preclude study participation.

The ECG review is under the investigator's responsibility.

Any abnormal finding, assessed by the investigator as clinically significant, should be recorded under the medical history section in the relevant CRF form and source documents.

9.2.7 CHEST X-RAYS (at Screening and at visit 8)

Routine chest X-Ray will be performed to all subjects at screening visit or on surgery day (pre-operative), at visit 8 and at investigator's discretion.

9.2.8 ASSESSMENT of STERNAL INFECTION (at all visits)

Sternal infection will be identified as assessed by investigator by the following predefined criteria in the CDC's Criteria for Surgical Site Infection (SSI) & Surveillance Definition for Specific Types of Infections Chapters, January 2016 (see 5.1.1 & 5.1.2).

9.2.9 ALLERGY QUESTIONNAIRE (at screening only)

An allergy questionnaire will be filled at screening as part of subject's medical history.

9.2.10 ADVERSE EVENTS (All visits)

Adverse events will be recorded starting from visit 1 and throughout the study. Pre-existing conditions (present before start of the AE collection period) are considered "concurrent medical conditions" and should NOT be recorded as AEs. However, if the subject experiences a worsening or complication of such a concurrent condition, the worsening or complication should be recorded as an AE. Investigators should ensure that the AE term recorded captures the change in the condition (e.g. "worsening of….").

9.2.11 MEDICAL RESOURCE UTILIZATION (MRU)

All MRU information pertaining to unscheduled (not scheduled per protocol) hospitalizations (i.e. total hospitalization days), unscheduled clinic visits, unscheduled laboratory tests, and unscheduled procedures will be collected during the follow-up period.

9.2.12 STERNUM STABILITY ASSESSMENT

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).

9.3 SURGERY – INDEX PROCEDURE - VISIT 2

Subjects will be enrolled into the study and will be treated with D-PLEX concomitantly with SOC or SOC alone.

<u>The SOC is based on:</u>

The Society of Thoracic Surgeons practice guideline series: antibiotic prophylaxis in cardiac surgery, part II: antibiotic choice;

1. In patients for whom cefazolin is the appropriate prophylactic antibiotic for cardiac surgery, administration within 60 minutes of the skin incision is indicated. The pre-operative prophylactic dose of cefazolin for a patient of greater than 60 kg body weight is recommended to be 2g.
2. When surgical incision remains open in the operating room, to patients with normal renal function, a second dose of 1g should be administered every 3 to 4 hours. If it is apparent that cardiopulmonary bypass will be discontinued within 4 hours, it is appropriate to delay until perfusion is complete to maximize effective blood levels.
3. In patients for whom vancomycin is an appropriate antibiotic for cardiac surgery, a dose of 1 to 1.5 g or a weight adjusted dose of 15 mg/kg administered intravenously slowly over 1 hour, with completion with 1 hour of the skin incision, is recommended. A second dose of vancomycin of 7.5 mg/kg may be considered during cardiopulmonary bypass, although its usefulness is not well established.
4. For patients who receive an aminoglycoside (usually gentamycin, 4 mg/kg) in addition to vancomycin before cardiac surgery, the initial dose should be administered within 1 hour of the skin incision. Re-dosing an aminoglycoside during cardiopulmonary bypass is not indicated and may be harmful.

The standard of care will be consistent for all sites that will participate in the clinical study.

The D-PLEX will be applied during the cardiac surgery (index procedure), as an adjunct to the standard care, immediately prior to sternal closure.

D-PLEX is supplied as sterile powder to be reconstituted to paste in the operating room, using standard aseptic techniques and is intended for single administration.

The D-PLEX dose is dependent 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 of D-PLEX will be used.

D-PLEX will be applied directly within the surgical site: between the two halves of the sternum bone and over its surface before wound closure (sewing)

For more details, please refer to the IFU- D-PLEX IFU.

9.4 SUBSEQUENT VISITS AND ASSESSMENTS – VISITS 3 - 10

Post-operative care will be performed per SOC. Post-operative resumption of activity are at the discretion of investigator based on subject medical condition.

The subsequent follow up visits (visits 3-5) will take place at 1 day, 5 days and, 14 days post index procedure. These visits are usually performed after this kind of surgery.

The additional follow up visits (visits 6-10) will take place at 1 month, 2 months, 3 months, 4 months and 6 months post index procedure and are required by the study, i.e. in addition to the routine visits usually performed after this kind of surgery.

During these visits the following procedures will be performed: Vital signs, Assessment of infection, Laboratory examinations (Haematology & Chemistry) and Adverse Events. Urinalysis will be performed only at the discretion of the investigator. Bacteriology cultures will be taken at the discretion on the investigator if there is a wound discharge. AB initiation will continue from screening to V3. Physical examination will be performed only at visits 6, 8 and 10.

Follow up assessments will be done over a total of 6 clinic visits until final assessment at 6 months ±14 days. Table 1 details all scheduled/ planned assessment at these visits.

9.4.1 SAFETY ENDPOINTS TO BE ASSESSED DURING THE STUDY

Collection of adverse events

Physical examinations, vital signs

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).

X-Ray: to assess sternum mechanical dehiscence

Fibrosis/Scarring will be assessed by visual wound examination by investigator

Safety laboratory parameters: Routine hematology, chemistry

Urinalysis will be done on screening visit and at the discretion of the investigator

Bacteriology test – growth, identification and sensitivity to antibiotics (specifically to tetracyclines) will be collected at the investigator discretion if there is a wound discharge

9.4.2 DOXYCYCLINE PHARMACOKINETICS

- Doxycycline PK sampling will be collected from a subgroup of up to [redacted] eligible subjects
- Samples of [redacted] blood will be collected for each PK time point, prepared and shipped to central laboratory

Visit / Day	Time after surgery	Comments
Surgery - Day 0 (Visit 2)	1. Pre-application of D-PLEX 2. After D-PLEX Application; ½ hour 1 hour 2 hours 4 hours 12 hours	Subject hospitalized
Day 1	24 hours	Subject hospitalized
Day 2	48 hours	Only if subject still hospitalized
Day 3	72 hours	Only if subject still hospitalized
Day 5 (Visit 4)	Day 5	Or discharge from hospital, whichever comes first
Day 14 (Visit 5)	Day 14	
Month 1 (Visit 6)	Month 1	

9.5 TABLE OF STUDY ASSESSMENTS

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

9.6 METHODS

9.6.1 LABORATORY PROCEDURES

The following samples will be processed at Local Hospital Labs at each of the [redacted] Israeli sites [redacted] as part of safety laboratory parameter assessment: Physical exam, vital signs, ECG, Bacteriological tests, deep and superficial assessment of infection, laboratory measurements, wound assessments.

Doxycycline pharmacokinetic sampling will be collected from a subgroup of up to [redacted] eligible subjects and will be shipped to a central laboratory.

9.7 DEFINITION OF END OF TRIAL

Total duration of the study is expected to be approximately 9-12 months from first subject enrolled until last subject completed. The end of the trial will be the 6 months final follow visit for the last enrolled patient.

The last six (6) months follow up expected to be in: Q4 2017.

9.8 DISCONTINUATION/WITHDRAWAL OF PARTICIPANTS & 'STOPPING RULES'

While study withdrawal is not encouraged, subjects may choose to withdraw from the study at any time, with or without reason and without prejudice to further treatment. However, a subject's participation in any clinical trial is voluntary and the subject has the right to withdraw at any time without penalty or loss of benefit.

In the event that a subject withdraws from the study, every effort should be made to have the subject return for a final study follow-up assessment and the information identified for collection at the 6 months follow-up visit will be obtained to the extent possible. Withdrawn subjects will not be replaced (the justified sample size considers an estimated allowance for attrition).

The reason for withdrawal will be recorded (if given) on the appropriate eCRF and subject's medical records in all cases of withdrawal. If more than one reason is cited for withdrawal, study personnel should identify the most significant reason.

The Investigator may discontinue a subject from participation in the study if the Investigator feels that the subject can no longer fully comply with the requirements of the study or if any of the study procedures are deemed potentially harmful to the subject.

The sponsor may suspend or prematurely terminate this study either in an individual investigation site, or the entire study for significant and documented reasons.

EC or regulatory authority may suspend or prematurely terminate participation in the study at the investigation sites for which they are responsible.

If suspicion of an unacceptable risk to subjects arises during the study, or when so instructed by the EC or regulatory authorities, the sponsor shall suspend the clinical investigation while the risk is assessed. The sponsor shall terminate the study if an unacceptable risk is confirmed.

Data that has already been collected on withdrawn subjects will be retained and used for analysis but no new data will be collected after withdrawal.

Subjects who withdraw from the study will not be replaced.

Stopping Rules:

Not applicable at this stage of development.

10 NAME & DESCRIPTION OF ALL DRUGS USED IN THE TRIAL

D-PLEX is the investigational medicinal product to be administered in this study. A comprehensive description is provided in Section 3.1.1. No additional drugs will be administered as part of the requirements of this clinical study.

10.1 TREATMENT OF SUBJECTS

Investigational Medicinal Product – **D-PLEX.**

The D-PLEX will be applied during the cardiac surgery (index procedure), as an adjunct to the standard care, immediately prior to sternal closure.

D-PLEX is supplied as sterile powder to be reconstituted to paste in the operating room, using standard aseptic techniques and is intended for single administration.

The D-PLEX dose is dependent 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 of D-PLEX will be used.

D-PLEX will be applied directly within the surgical site: between the two halves of the sternum bone and over its surface before wound closure (sewing).

For more details, please refer to the IFU- D-PLEX IFU.

10.2 CONCOMITANT MEDICATION

Medication(s)/Treatment(s) Permitted

- Concomitant Medications
  - All concomitant medications will be recorded in the case report form (eCRF).
- Antibiotics Treatment per SOC Allowed in this Protocol

- Subjects will receive IV antibiotics, followed by oral antibiotics (as needed), according to the SOC.
- Any additional concomitant medication for the treatment of concurrent illnesses are allowed at the discretion of the treating physicians.

Medications prohibited during the trial

- Additional antibiotics, except those listed as part of the SOC post sternotomy, or approved by the study investigator.
- Long term high steroids dose (defined as steroid use for over 3 consecutive months during a 6 month period).
- Immunosuppressive agents.
- Doxycycline IV/PO administration is not allowed in this protocol during the entire trial period.

10.3 PREPARATION, HANDLING, & LABELING OF INVESTIGATIONAL MEDICINAL PRODUCT (IMP)

The investigational medicinal product is manufactured aseptically at Nextar, at a Grade A (ISO 5) clean room. The investigational medicinal product will be provided to the investigational site by PolyPid Ltd., once a signed Investigator Agreement and documentation of Ministry of Health and Ethics Committee approval of the protocol and consent forms have been received.

D-PLEX is provided sterile and primarily packaged in sterile, depyrogenated inert glass amber vial [redacted] and each product vial contains [redacted]g of D-PLEX. The sterile vial is packaged in an aluminium packaging. All packaging will bear the following statement per Israel Ministry of Health regulations:

"**For Clinical Trial Use Only**" in Hebrew and/or in English.

Preparation and labelling of the investigational medicinal products are completed in accordance with the relevant GMP guidelines.

Information on the Storage and Handling of the IMP can be found in D-PLEX IFU.

10.4 DRUG ACCOUNTABILITY

The Investigator or designee (i.e., pharmacist) is responsible for ensuring adequate accountability of all used and unused study drug. This includes acknowledgment of receipt of each shipment of study product (quantity and condition) and subject dispensing records and returned or destroyed study product. Dispensing records will document quantities received

from PolyPid and quantities dispensed to subjects, including lot number, date dispensed, subject identifier number, subject initials, and the initials of the person dispensing the medication.

At study initiation, the monitor will evaluate the site's standard operating procedure for study drug disposal/destruction in order to ensure that it complies with PolyPid requirements. Drug may be returned or destroyed on an ongoing basis during the study as appropriate. At the end of the study, following final drug inventory reconciliation by the monitor, the study site will dispose of and/or destroy all unused study drug supplies, including empty containers, according to these procedures. If the site cannot meet PolyPid requirements for disposal, arrangements will be made between the site and PolyPid or its representative for destruction or return of unused study drug supplies.

All drug supplies and associated documentation will be periodically reviewed and verified by the study monitor over the course of the study.

Investigators will be notified in writing of enrolment completion. All unused D-PLEX vials must be returned to the Sponsor when enrolment is complete according to sponsor instructions.

11 RECORDING & REPORTING OF ADVERSE EVENTS & REACTIONS

11.1 DEFINITIONS

Term	Definition
Adverse Event (AE)	Any untoward medical occurrence in a patient or clinical trial subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment.
Adverse Drug Reaction (ADR)	Any untoward and unintended response in a subject to an investigational medicinal product which **is related** to any dose administered to that subject. *This includes medication errors, uses outside of protocol (including misuse and abuse of product)*
Serious adverse event (SAE), serious adverse drug reaction (SADR) or unexpected serious adverse reaction	Any adverse event, adverse reaction or unexpected adverse reaction, respectively, that: • results in death, • is life-threatening, • requires hospitalisation or prolongation of existing hospitalisation,

Term	Definition
	• results in persistent or significant disability or incapacity, or • consists of a congenital anomaly or birth defect
Important Medical Event	These events may jeopardize the subject or may require an intervention to prevent one of the above characteristics/consequences. Such events should also be considered 'serious'.
Unexpected adverse reaction	An adverse reaction the nature and severity of which is not consistent with the information about the medicinal product in question set out: (a) in the case of a product with a marketing authorization, in the summary of product characteristics for that product, (b) in the case of any other investigational medicinal product, in the investigator's brochure relating to the trial in question.
SUSAR	Suspected Unexpected Serious Adverse Reaction

11.2 RECORDING ADVERSE EVENTS

All spontaneous adverse events will be recorded in the medical records and eCRF following consent. Reporting of AEs will also be performed on Day-1 to Day 0.

If the investigator suspects that the subjects' disease has progressed faster due to the administration of the investigational medicinal product (IMP), D-PLEX then he will record and report this as an unexpected adverse event.

Clinically significant abnormalities in the results of objective tests (e.g. infection status, laboratory variables, ECG, etc) will also be recorded as adverse events. If the results are not expected as part of disease or IMP, these will also be recorded as unexpected.

All adverse events will be recorded with clinical symptoms and accompanied with a simple, brief description of the event, including dates as appropriate.

All adverse events will be recorded and will be reportable to sponsor up to and including 6 months, at Visit 10

11.3 ASSESSMENT OF ADVERSE EVENTS

Each adverse event will be assessed for the following criteria:

11.3.1 SEVERITY

Category	Definition
Mild	The adverse event does not interfere with the volunteer's daily routine, and does not require intervention; it causes slight discomfort.
Moderate	The adverse event interferes with some aspects of the volunteer's routine, or requires intervention, but is not damaging to health; it causes moderate discomfort.
Severe	The adverse event results in alteration, discomfort or disability which is clearly damaging to health.

11.3.2 CAUSALITY

The assessment of relationship of adverse events to the administration of IMP is a clinical decision based on all available information at the time of the completion of the case report form. The following categories will be used to define the causality of the adverse event:

Category	Definition
Definitely:	There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out.
Probably:	There is evidence to suggest a causal relationship, and the influence of other factors is unlikely.
Possibly	There is some evidence to suggest a causal relationship (e.g. the event occurred within a reasonable time after administration of the trial medication). However, the influence of other factors may have contributed to the event (e.g. the patient's clinical condition, other concomitant events).
Unlikely	There is little evidence to suggest there is a causal relationship (e.g. the event did not occur within a reasonable time after administration of the trial medication). There is another reasonable explanation for the event (e.g. the patient's clinical condition, other concomitant treatments).
Not related	There is no evidence of any causal relationship.
Not Assessable	Unable to assess on information available.

11.3.3 EXPECTEDNESS

Category	Definition
Expected	An adverse event that is classed in nature as serious and which is consistent with the information about the IMP listed in the Investigator Brochure **or clearly defined in this protocol.**
Unexpected	An adverse event that is classed in nature as serious and which is not consistent with the information about the IMP listed in the Investigator Brochure.

The reference document to be used to assess expectedness against the IMP is the D-PLEX Investigator's Brochure.

11.3.4 SERIOUSNESS

Seriousness as defined for an SAE in section 11.1.

Collection, recording and reporting of adverse events (including serious and non-serious events and reactions) to the sponsor will be completed according to the sponsor's SOP 0031.

11.4 PROCEDURES FOR RECORDING & REPORTING SERIOUS ADVERSE EVENTS

All serious adverse events will be recorded in the hospital notes and the eCRF, and the sponsor's SAE log.

All serious adverse events will need to be reported to the sponsor within 24 hours of knowledge, according to local regulations.

In case the eCRF is not available, the Principal Investigator will complete the sponsor's serious adverse event form and the form will be faxed to the sponsor on [redacted], within one working day of his becoming aware of the event. The Principal Investigator will respond to any SAE queries raised by the sponsor as soon as possible.

Reporting to the sponsor will be completed as per the sponsor's SOP and using the PolyPid SAE form.

11.4.1 NOTIFICATION OF DEATHS

All deaths will be reported to the sponsor irrespective of whether the death is related to disease progression, the IMP, or an unrelated event. Deaths should be reported within 24 hours of knowledge to the sponsor.

11.4.2 REPORTING OF SUSARs

The sponsor will notify the Investigator of all SUSARs. SUSARs that are fatal or life-threatening must be notified to the Investigator within 7 days after the sponsor has learned of them. Other SUSARs must be reported to the Investigator within 15 days after the sponsor has learned of them.

Investigator will forward SUSARs that occurred at his centre to the EC in a timely manner. All other SUSARs will be forwarded to EC periodically (at least every 6 months).

11.4.3 DEVELOPMENT OF SAFETY UPDATE REPORTS

The sponsor will provide the main EC and the Ministry of Health with a Safety Report which will be written in conjunction with the trial team and the Sponsor's office.

11.4.4 OVERDOSE

Guidance on the recognition and treatment of possible overdose and adverse drug reactions

Overdose of D-PLEX is defined as using more than 3 vials of D-PLEX per patient (i.e. more than [redacted] gr per patient). Overdose of D-PLEX will be recognized by the report of number of vials used as documented by the operation room (O.R.) team.

Information on adverse drug reactions of D-PLEX are provided in the D-PLEX IFU.

In case of an overdose or adverse drug reactions and per surgeon decision, the implanted D-PLEX can be removed by re-exploring the surgical incision and washing out the D-PLEX.

All overdoses should be recorded and notified to the sponsor.
If an SAE is associated with the overdose the PI should ensure the overdose if fully described in the SAE report form.

11.4.5 REPORTING URGENT SAFETY MEASURES

If any urgent safety measures are taken the PI/Sponsor shall immediately and in any event no later than 3 days from the date the measures are taken, give written notice to the Israel

Ministry of Health and the relevant EC of the measures taken and the circumstances giving rise to those measures.

11.4.6 THE TYPE & DURATION OF THE FOLLOW-UP OF SUBJECTS AFTER ADVERSE EVENTS

All AE/ SAEs should be followed up until resolution or permanent outcome of the event.

SAE- If information is not available at the time when the first report becomes available, the investigator should fill out a follow-up SAE report at a later date and send to the Sponsor. (Per the instructions of EDC completion).

It is the responsibility of investigators to inform their Ethics Committee of SAEs (whether IMP related or not) as required by their Ethics Committee procedure.

Any SUSAR related to the IMP (D-PLEX) will need to be reported to the Sponsor irrespective of how long after IMP administration the reaction has occurred.

11.4.7 NOTIFICATION OF SERIOUS BREACHES TO GCP AND/OR PROTOCOL VIOLATION

The Investigator is responsible for ensuring the study is conducted in accordance with the procedures and evaluations described in this protocol.

A “serious breach” is a breach which is likely to effect to a significant degree –

(a) The safety or physical or mental integrity of the subjects of the trial; or

(b) The scientific value of the trial.

The sponsor of a clinical trial shall notify the licensing authority in writing of any serious breach of:

(i) The conditions and principles of GCP in connection with that trial; or (ii) The protocol relating to that trial, as amended from time to time, within 7 days of becoming aware of that breach.

The sponsor will be notified immediately of any case where the above definition applies during the trial conduct phase. The sponsor’s SOP on the ‘Notification of violations, urgent safety measures and serious breaches’ will be followed.

12 DATA MANAGEMENT & QUALITY ASSURANCE

12.1 CONFIDENTIALITY

The Electronic Case Report Form (eCRF) will not bear the subject's name or other personal identifiable data. The subject's initials, date of birth and trial identification number, will be used for identification.

12.2 DATA COLLECTION TOOLS & SOURCE DOCUMENT IDENTIFICATION

Primary data collection based on source-documented hospital and/or clinic chart reviews will be performed clearly and accurately by site personnel trained on the clinical investigation plan and eCRF completion. The Sponsor or designee will provide clinical monitoring throughout the study.

It will be the responsibility of the investigator to ensure the accuracy of all data entered in the eCRFs.

12.3 DATA HANDLING & ANALYSIS

The procedures for data review and query management are described in the *Data Management Plan* and the *Edit Checks Specification Table*. Data will be reviewed throughout the study according to this document.

Data will be collected using eCRFs that are specifically designed for this study. The data collected on the eCRFs will be captured in a clinical data management system (CDMS) that meets the technical requirements described in *21 CFR Part 11* and *EMA regulations*. The CDMS will be fully validated to ensure that it meets the scientific, regulatory, and logistical requirements of the study before it is used to capture data from this study. Before using the CDMS, all users will receive training on the system and study-specific training. After they are trained, users will be provided with individual system access rights.

Data will be collected at the investigational center by appropriately designated and trained personnel, and eCRFs must be completed for each screened subject according to their source documents. In no case the eCRF could be considered as data source for this trial.

Subject identity should not be discernible from the data provided on the eCRF.

A comprehensive validation check program will verify the data and automatically generate discrepancies for resolution by the investigator.

Data will be verified using the data source by the study monitor, and reviewed for consistency by Data Management using both automated logical checks and manual review.

All data collected will be approved by the investigator at the investigational center. This approval acknowledges the investigator's review and acceptance of the data as being complete and accurate.

13 RECORD KEEPING & ARCHIVING

The Investigator shall arrange for the retention of study records for at least 15 years after completion or discontinuation of the study. Subject files and other source data shall be kept for the maximum period of time permitted by the hospital or institution.

The investigator should ensure that the following records are maintained:

a) Subject files containing copies of completed case reports and supporting documentation and a copy of the signed, Informed Consent form.

b) Investigator files containing copies of the documents required for the initiation of the study (signed Investigator's Agreement, Curricula Vitae for the principal and all sub-investigators, copy of the EC approval of the protocol and Informed Consent form), copies of correspondence received from and sent to CRO/Sponsor. In addition to these records required by regulations, CRO/Sponsor requests that the investigator keep a copy of the Financial Agreement between CRO/Sponsor and the investigator.

c) Files containing copies of the Investigational Medicinal Product Accountability Log (IPAL) or an equivalent form approved by CRO/Sponsor, instructions for the use of the IPAL and instructions for use (IFU) inserts and/or the Investigator's Brochure.

These documents should be retained for a longer period, if required by local or national regulations. No records will be destroyed without the written consent of the Sponsor. It is the responsibility of the Sponsor to inform the investigator when these documents no longer need to be retained.

14 STATISTICAL CONSIDERATIONS

No formal statistical analysis will be performed. Only descriptive statistics (mean values, standard deviation will be presented).

14.1 SAMPLE SIZE & RECRUITMENT

14.1.1 PLANNED RECRUITMENT RATE

Total duration of the study is expected to be approximately 9-12 months from first subject enrolled until last subject completed.

It is expected that each subject will be in the study for approximately 6 months

Initial enrolment anticipated: Q4 2016
Final enrollment anticipated: Q3 2017
Last 6 months follow up: Q1 2018

This is a phase Ib/II clinical study, a total of up to [redacted] subjects, will be enrolled across [redacted] Israeli sites.

15 EFFICACY AND SAFETY ASSESSMENT

Efficacy assessment will be applied when all the subjects complete 3 months in the study. The primary efficacy endpoint (the reduction in the number of sternal infections observed) will be evaluated and summarized in appropriate tables.

The data will be locked before the statistical analysis will be performed. Sponsor will remain blinded to individual patient treatment and all data will be presented as aggregated per treatment arm, as long as the last patient has not completed the safety follow up period. No listings will be issued in order to maintain safety evaluation by Sponsor throughout safety follow-up period.

A complete statistical report including safety and efficacy endpoints will be prepared when all the subjects complete their follow-up period and all safety and efficacy additional data was completed.

16 NAME OF COMMITTEES INVOLVED IN TRIAL

The Executive Committee including PolyPid Safety Officer will review and adjudicate any AE and SAE considered as related to investigational medicinal product or SAE leading to death or life threatening.

Executive Committee: A committee responsible for overseeing the conduct of the study from various aspects:

a) Review, classification and adjudication of Adverse Events and Serious Adverse Events, as defined in the clinical protocol.

b) Recommending on study specific needs such as special training to site staff.

c) Reviewing the study results.

It comprises of physician members from disciplines relevant to the study, who are not participating in the study and will not have any conflict interest with the study sponsor. The Executive Committee is responsible to schedule periodic meetings and ad hoc meeting upon PolyPid request and study needs.

This committee adjudicates AE/SAE as defined in the protocol and classifies the adjudicated AEs as to their relation to the IMP/procedure.

17 DIRECT ACCESS TO SOURCE DATA DOCUMENTS

As required, the principal investigator shall obtain permission for direct access to source documents from the subject, hospital administration and national regulatory authorities before starting the clinical investigation.

The investigator will permit trial-related monitoring, audits, EC review, and regulatory inspection(s), providing direct access to source data/documents. Trial participants are informed of this during the informed consent discussion. Participants will consent to provide access to their medical notes.

18 ETHICS & REGULATORY REQUIREMENTS

The protocol, informed consent form and Authorization for the Use and Disclosure of Health Information or country specific confidentiality requirements must be reviewed and approved by the respective EC and the Sponsor before subject enrolment. Changes to the protocol must be approved in writing by the Sponsor and the EC (as applicable) before the change is implemented.

Prior to subject enrolment, a signed copy of the EC approval letter addressed to the investigator must be submitted to the Sponsor, certifying study approval. Investigators are responsible for submitting and obtaining initial approval and continuing approval from the EC and forwarding copies of the approval letters to the Sponsor. The original letters are to be kept in the investigational center's Regulatory Binder designated for this study.

The investigator will notify the Sponsor within five (5) working days of withdrawal of EC approval.

19 MONITORING REQUIREMENT FOR THE TRIAL

A trial specific monitoring plan will be established for the study. The trial will be monitored with the agreed plan.

The Sponsor and/or designee will monitor the study over its duration according to the pre-specified monitoring plan. The study monitor will visit each site at appropriate intervals to review investigational data for accuracy and completeness and ensure compliance with the clinical investigation plan. The study monitor may inspect all documents and required records that are maintained by the Investigator/Site, including medical records (office, clinic, or hospital) for the subjects in this study. Source documentation must be available to substantiate proper informed consent procedures, adherence to clinical investigation plan procedures, adequate reporting and follow-up of adverse events, accuracy of data collected on case report forms, and device information. A monitoring visit sign-in log will be maintained at the site. The Investigator and/or research coordinator will be available for monitoring

visits. It is expected that the Investigator/Site will provide the study monitor with a suitable working environment for review of study-related documents.

20 INSURANCE

The Sponsor will provide insurance or indemnify (legal and financial coverage), the Investigatory/Institution against claims arising from the study, insurance covering the cost of treatment of the subjects in the event of clinical-investigation-related injuries, in accordance with national regulations, except for claims that arise from malpractice, negligence, or non-compliance with the protocol. The certificate of insurance and coverage will be provided upon request.

21 PUBLICATION POLICY

All data generated from this study are the property of PolyPid and shall be held in strict confidence along with all information furnished by PolyPid, subject to the right of the Investigator or any member of his/her staff to publish the results in accordance with the publication procedure to be defined in the clinical trial agreement.

Independent analysis and/or publication of these data by the Investigator or any member of his/her staff are permitted subject to obtaining the prior written consent of PolyPid.

Written permission to the Investigator will be contingent on the review by PolyPid of the statistical analysis and manuscript and will provide for nondisclosure of PolyPid confidential or proprietary information. In all cases, the parties agree to submit all manuscripts or abstracts to all other parties 30 days prior to submission. This will enable all parties to protect proprietary information and to provide comments based on information that may not yet be available to other parties.

22 STATEMENT OF COMPLIANCE

The trial will be conducted in compliance with the approved protocol, Declaration of Helsinki, ICH GCP and the applicable Israel Ministry of Health regulatory requirement(s).

The clinical investigation shall not begin until the required approval or favorable opinion from the EC has been obtained and, if applicable, any local or national regulatory authority approvals or notifications have been obtained.

The Sponsor has obtained clinical investigation insurance that will cover expenses in the event of any physical injury resulting from research procedures.

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