

POLYPID LTD



STATISTICAL ANALYSIS PLAN (SAP)

Phase III, Prospective, Multinational, Multicenter, Randomized, Controlled, Two-arm, Double Blind Study to Assess Efficacy and Safety of D-PLEX Administered Concomitantly with the Standard of Care (SoC), Compared to a SoC Treated Control Arm, in Prevention of Post Abdominal Surgery Incisional Infection.

Study: D-PLEX 312

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Prepared by: Larissa Fertik
Bioforum Biostatistics Dept.



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STATISTICAL ANALYSIS PLAN APPROVAL FORM**Study:** D-PLEX 312**SAP Date:** 25-SEP-2024**SAP Version:** 3

I confirm that I have reviewed this document and agree with the content.

APPROVALS	
Approved by:	
 Medical Director PolyPid Ltd., 18 HaSivim Street, Petach Tikva, Israel 4917002 	Date (dd-Mmm-yyyy)
Approved by:	
 Statistical Consultant Bioforum, 3 Golda Meir St., Weizmann Science Park, Ness Ziona 7414001 Israel 	Date (dd-Mmm-yyyy)

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GLOSSARY OF ABBREVIATIONS

AE	Adverse Event
ASEPSIS	Additional treatment, Serous discharge, Erythema, Purulent exudate, Separation of deep tissue, Isolation of bacteria, Stay duration as inpatient
ATC	Anatomical Therapeutic Chemical
AUC	Area Under the Curve
BMI	Body Mass Index
COPD	Chronic Obstructive Pulmonary Disease
CRF	Case Report Form
CSR	Clinical Study Report
DMC	Data Monitoring Committee
DSSI	Deep Incisional Surgical Site Infection
FAS	Full Analysis Set
FDA	Food and Drug Administration
ICF	Informed Consent Form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IP	Investigational Product
ISAP	Interim Statistical Analysis Plan
ITT	Intention to Treat
IWRS	Interactive Web Randomization System
mITT	Modified Intention to Treat
MedDRA	Medical Dictionary for Regulatory Activities
OR	Operation Room
PI	Principal Investigator
PK	Pharmacokinetics
PLEX	Polymer-Lipid Encapsulation matrix
PP	Per Protocol
PT	Preferred Term
PVD	Peripheral Vascular Disease

SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard Deviation
SE	Standard Error
SoC	Standard of Care
SOC	System Organ Class
SOP	Standard Operating Procedure
SSI	Surgical Site Infection
SSR	Sample Size Re-assessment
SSSI	Superficial Incisional Surgical Site Infection
TEAE	Treatment Emergent Adverse Event
ubSSR	Un-Blinded sample Size Re-assessment
WHO-DD	World Health Organization Drug Dictionary

1. PREFACE

This Statistical Analysis Plan (SAP) describes the planned analysis and reporting for PolyPid study D-PLEX 312, (Phase III, Prospective, Multinational, Multicenter, Randomized, Controlled, Two-arm, Double Blind Study to Assess Efficacy and Safety of D-PLEX Administered Concomitantly with the Standard of Care (SoC), Compared to a SoC Treated Control Arm, in Prevention of Post Abdominal Surgery Incisional Infection), and was written in accordance with SOP 100-60-02 (Statistical Analysis Plan Preparation, Review and Approval, Bioforum's Procedure).

The structure and content of this SAP provides sufficient detail to meet the requirements identified by the FDA and International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH): E9 Guidance on Statistical Principles in Clinical Trials. All work planned and reported for this SAP will follow internationally accepted guidelines, published by the American Statistical Association, and the Royal Statistical Society, for statistical practice.

The following documents were reviewed in preparation of this SAP:

- Clinical Study Protocol D-PLEX 312 Version 08, issued on 25-Sep-2024
- Case Report Forms (CRFs) for Study D-PLEX 312
- ICH E9 Guidance on Statistical Principles for Clinical Trials
- ICH E3 Structure and Content of Clinical Study Reports

The reader of this SAP is encouraged to also read the clinical protocol for details on the conduct of this study, and the operational aspects of clinical assessments and timing for completing a subject in this study.

A separate Interim Statistical Analysis Plan (ISAP) accompanies and completes this document with the full details about the stopping rules and the sample size decision rules for the planned interim analysis.

This SAP describes the statistical analyses as it is foreseen at early stage of the study. The SAP serves as a complement to the protocol and supersedes it in case of differences. In case of major differences between the protocol and SAP, a protocol amendment will be considered. Any deviations from the statistical analyses planned in the protocol will be documented in the SAP and any deviations from the statistical analyses planned in the SAP will be documented in the final clinical study report (CSR).

The SAP may be updated during the study conduct and will be finalized before breaking the blind of the study and before the final database lock.

2. STUDY OBJECTIVES

The primary objectives of this study are as follows:

- To assess the anti-infective efficacy of D-PLEX administered concomitantly with the Standard of Care (SoC) over a period of 30 days post operation, by preventing surgical site infection (SSI), defined as superficial and/or deep infection, in the target incision, compared to the SoC treated control arm.
- To assess the safety of D-PLEX administered concomitantly with the Standard of Care (SoC).

3. STUDY DESIGN

3.1. General Design and Study Schema

This is a Phase III, prospective, multinational, multicenter, randomized, controlled, two-arm, double blind (participant and outcome assessor) study. The study population includes male and female, 18 years old and above at screening, undergoing an elective colorectal surgery involving resection, with or without a stoma formation, that includes at least 1 abdominal incision. The study already enrolled [REDACTED] subjects with abdominal incision ≥ 7 cm (target incision), [REDACTED] of them with incision > 20 cm. Starting from protocol amendment 5, the study will include only subjects with abdominal incision > 20 cm, that will enrich the study population with a longer incision length, following the results of Study D-PLEX 311 and as recommended by the FDA.

Subjects who meet the inclusion criteria and none of the exclusion criteria and who provide a signed Informed Consent Form will be enrolled in the study.

Subjects will be randomized to either the investigational arm (D-PLEX + SoC) or to the control arm (SoC only) in a 1:1 ratio. Subjects will be stratified by incisional length (≥ 7 cm - ≤ 10 cm, > 10 - ≤ 20 cm, > 20 cm), type of SoC prophylactic antibiotic regimens (prophylactic IV antibiotic only; prophylactic IV antibiotic with mechanical bowel preparation or prophylactic IV antibiotic with oral antibiotics combined with mechanical bowel preparation) and by region (US or Europe + Israel). As of protocol amendment #5, stratification according to incision length was no longer performed.

The sponsor, the outcome assessor, the subjects and all staff involved in the collection and recording of the clinical and laboratory data, based on which the independent adjudication committee will perform their assessment, will be blinded to the treatment assignment. The Operating Room (OR) staff will be trained to maintain in confidence the treatment assignment and not to disclose it to other staff members. In addition, all aspects of data management and clean-up will be done using blinded datasets.

Subjects randomized to the investigational arm will be treated with D-PLEX during the surgery (index procedure), as an adjunct to the SoC (see below). D-PLEX will be applied during the closure of the abdominal target incision. D-PLEX will not be readministered if any re-intervention occurs. Subjects randomized to the control arm will receive only prophylactic SoC.

For both arms the prophylactic SoC will be consistent and standardized for all sites in the clinical study and is composed of IV antibiotic immediately prior to surgery, with or without oral antibiotic combined with mechanical bowel preparation (IV antibiotic only, IV antibiotic with mechanical bowel preparation or IV antibiotic with oral antibiotics combined with mechanical bowel preparation). Each site will use the same pre-defined SoC for all its subjects during the study. Post-operative care (excluding prophylactic antibiotics) will be performed per site SoC. Post-operative resumption of activity is at the discretion of the Investigator, based on the subject's medical condition.

Doxycycline pharmacokinetic sampling will be collected in selected sites from all randomized subjects in these sites. About 15 series (15 subjects from the D-PLEX + SoC arm) of 9 samples per set will be analyzed.

Spontaneous Adverse Events (AEs) including death will be recorded throughout the study. Pregnancy will be reported using a specific form and will be followed up until resolution.

The planned clinical program will establish the efficacy and safety of D-PLEX by the reduction in the number of abdominal wall incisional infections observed during 30 days after surgical index procedure. All subjects will be followed until Day 60/termination visit for safety. The occurrence of any Adverse Events (AEs), including death, will be recorded throughout the study. All subjects will be followed for an overall of 60 days for safety.

Visit-specific procedures and assessments are outlined in Table 1 below.

Table 1: Study Procedures and Assessments

Procedures	Visit 1 Screening Day -21 to Day 0	Visit 2 surgery - Day 0	Visit 3 Day 1	Visit 4 Day 5 (± 1 day)	Visit 5 Day 14 (± 3 days)	Visit 6 Day 30 (+7 days)	Visit 7 Termination Day 60 (± 7 days)
Informed Consent	X						
Medical History, Charlson co-morbidity index & Allergy questionnaire completion	X						
General Eligibility Criteria	X	X ¹					
Physical Exam	X					X	X
Vital Signs (blood pressure, HR, body temperature)	X	X	X	X	X	X	X
Weight & Height	X						
Pregnancy Test ⁷	X					X ⁷	
HbA1C and Coagulation Tests ³	X						
Assessment of Surgical Site (including SSA questionnaire) ⁵			X	X	X ⁴	X ⁴	X ⁴
Modified Vancouver Scar Scale					X	X	X
Blood Tests (hematology, chemistry ³)	X ²		X	X	X	X	X
Doxycycline PK Sampling ⁸	X	X	X	X	X	X	X
Bacteriology test and photographic picture ⁶			X ⁶	X ⁶	X ⁶	X ⁶	X ⁶
Adverse Events		X	X	X	X ⁴	X ⁴	X ⁴
Concomitant Medications	X	X	X	X	X	X	X
D-PLEX Administration		X					

Notes:

1. Confirmation of Eligibility.
2. Results must be available for PolyPid's MM review prior to randomization.
3. Blood chemistry and hematology: for whole list of tests please refer Section 9.1.11 in the D-PLEX 312 clinical trial protocol. Blood tests should be performed not more than 7 days before surgery. Coagulation tests (PT, INR, PTT) and HbA1C test only at Screening.
4. In case the subject is unable to attend a visit, phone visit should be performed with subject/his community physician/ a first degree relative (as per Sponsor's designated form) to obtain information related to subject's safety and wound assessment. Blood tests and vital signs can be collected in the local clinic/laboratory and the results should be send (blinded with subject study number only) to the Sponsor study manager.
5. Surgical site assessment will be performed only if wound is not dressing.
6. Bacteriology test and photographic picture will be performed in case of suspected infection (in each visit).
7. Pregnancy test (serum or urine dipstick) should be performed within 1 day before surgery. On Day 30 it should be performed in Portugal sites only.
8. Blood samples for PK will be required from about 15 treated subjects at selected sites at the following time-points: pre-D-PLEX application, 2-4 hours, 24 hours, 48 hours, 72 hours, 5 days, 14 days, 30 days and 60 days.

Option for an active open-label extension of the protocol.

In case that the planned unblinded interim analysis with [REDACTED] recruited subjects with incision length >20cm would lead to an early stop of the study for efficacy, an active open-label extension part may be initiated to recruit additional subjects with incision length >20cm for safety monitoring only. During this extension, patients will be recruited to receive D-PLEX + SoC treatment in an open-label design. These subjects will be followed up until day 60/ termination visit, using the standard safety outcomes (adverse events, physical examinations & vital signs, safety laboratory parameters: hematology, chemistry; Incisional wound healing (including Hernia)). Those subjects who will be recruited to this part will be included in the safety analyses only.

3.2. Study Endpoints

3.2.1. Primary Efficacy Endpoint

The primary efficacy endpoint is defined per subject as a binary **treatment-failure** ("Yes" / "No") variable, with "Yes" indicating that a subject had experienced within 30 days post abdominal surgery (up to and including 30 days post index surgery) any Surgical Site Infection (SSI) event in the target incision, as determined by a blinded and independent adjudication committee. SSI is composed of Deep Incisional Surgical Site Infection (DSSI) and/or Superficial Incisional Surgical Site Infection (SSSI). A SSSI is an infection that involves only skin and subcutaneous tissue of the incision and does not include diagnosis/treatment of cellulitis, a stitch abscess alone or a localized stab wound or pin site infection. A DSSI is an infection that involves deep tissues, such as fascia and muscle layers; this also includes infection involving both superficial and deep incision sites.

In addition, the following events occurring within 30 days post abdominal index surgery, will also be considered as **treatment-failure** events:

- Death (from any reason),
- Re-intervention at the target incision site within 30 days of the index operation (regardless of the panel's determination) will be considered a treatment failure for the primary ITT analysis. To note, re-intervention at a different access point than the index wound will not be assessed for SSI.

Subjects who have a valid non-missing observation on Day 30 SSI assessment, performed within the pre-specified visit window, and have not experienced any adjudicated SSI event or death or re-intervention at the target incision within 30 days post abdominal index surgery, will be defined as "No". A valid non-missing observation for Day 30 SSI assessment is any confirmation of such response provided in the window of study Day 27 to study Day 40.

In the rare case of indeterminate SSI outcome (i.e. missing outcome due to other reasons than death resulting in the absence of a valid non-missing Day-30 SSI assessment as required), it will be considered a missing data and will be imputed as **Failure="Yes"** for the primary analysis of this endpoint.

Details on handling of missing primary endpoint data are described further in [Section 5.4](#).

In accordance with the primary objective of the study, the primary analysis of this endpoint is the population of subjects with target incision length >20 cm.

It is noted that formally per the adjudication committee charter, a suspected SSI can be adjudicated as SSI by the committee only by a unanimous decision. In case of a disagreement, the suspected SSI will be considered as not SSI. For the purpose of a sensitivity analysis with regard to this classification of the non-unanimous agreement, a variable similar to the primary endpoint will be created, in which subjects who were assigned as NOT meeting the primary endpoint following such disagreement will be recorded as "YES", meeting SSI.

3.2.2. Secondary Efficacy Endpoints

3.2.2.1. Key Secondary Efficacy Endpoints

The key secondary endpoints are defined as follows:

1. The first key secondary endpoint is infection rate as measured by the proportion of subjects with at least one SSI event in the target incision, occurred within 30 days post abdominal index surgery, and determined by a blinded independent adjudication committee, in the population of subjects with target incision length >20 cm.

This endpoint will be defined per subject as a binary ("Yes" / "No") variable, with "Yes" indicating that a subject has had at least one confirmed (by a blinded independent adjudication committee) SSI event within 30 days post index surgery (up to and including 30 days post index surgery date). Subjects who have a valid non-missing observation of "Day 30 SSI assessment", performed within the pre-specified visit window (the same as defined for the primary endpoint), and have not experienced any adjudicated SSI event within 30 days post index surgery, will be defined as "No".

2. The second key secondary endpoint will be defined the same as the primary endpoint, in the overall population with incision length ≥ 7 cm.
3. The third key secondary endpoint is number (percentage) of subjects with at least one score of ASEPSIS >20 (further to an adjudicated SSI).

This endpoint will be defined per subject as a binary ("Yes" / "No") variable, with "Yes" indicating that a subject has had at least one score of ASEPSIS >20 further to an adjudicated SSI, in the population of subjects with target incision length >20 cm.

3.2.2.2. Additional Secondary Efficacy Endpoints

The current section provides the definitions of the additional secondary efficacy endpoints of the study, general and SSI related. General endpoints will be defined for all subjects in the relevant analysis populations, while SSI related endpoints will be defined only for the sub-population of subjects who experienced at least one adjudicated SSI within 30 days post index surgery. All these endpoints will be evaluated in the population of subjects with target incision length >20 cm.

The general additional secondary efficacy endpoints are defined as follows:

- Incidence of SSSI within 30 days post index surgery.

This endpoint will be defined per subject as a binary ("Yes" / "No") variable, with "Yes" indicating that a subject has had at least one confirmed (by a blinded independent adjudication committee) SSSI event within 30 days post index surgery (up to and including 30 days post index surgery date). Subjects who have a valid non-missing observation on Day 30 SSI assessment, performed within the pre-specified visit window (the same as defined for the primary endpoint), and have not

- experienced any adjudicated SSSI event within 30 days post index surgery, will be defined as "No".
- Incidence of DSSI within 30 days post index surgery.

This endpoint will be defined per subject as a binary ("Yes" / "No") variable, with "Yes" indicating that a subject has had at least one confirmed (by a blinded independent adjudication committee) DSSI event within 30 days post index surgery (up to and including 30 days post index surgery date). Subjects who have a valid non-missing observation on Day 30 SSI assessment, performed within the pre-specified visit window (the same as defined for the primary endpoint), and have not experienced any adjudicated DSSI event within 30 days post index surgery, will be defined as "No".
 - All-cause mortality rate within 30 days post randomization.

In case there are no subjects with unknown survival status at 30 days post randomization, this endpoint will be defined per subject as a binary ("Yes" / "No") variable, with "Yes" indicating that a subject had died (from any reason) within 30 days post randomization. Otherwise, the 30-days mortality rate will be estimated using a time-to-event analysis, by the Kaplan-Meier method. In this case, for each subject survival time will be calculated as days between randomization and death (in the event of death within 30-days) or the time from randomization to the earliest between last date of known to be alive or 30-days, yielding a censored survival time.
 - All-cause mortality rate within 60 days post randomization.

This endpoint will be defined similarly to the 30 days mortality endpoint above, now with the time frame of 60 days post randomization.
 - Time to adjudicated target incisional SSI within 30 days post index surgery.

This endpoint will be defined per subject as the difference between the date of adjudicated SSI and the date of index surgery. Subjects, who have not experienced an adjudicated SSI within 30 days post index surgery, will be handled as follows:

 - Subjects having a valid non-missing Day 30 SSI assessment (within the pre-specified visit window) will be censored at Day 30.
 - Subjects who died within 30 days post index surgery will be censored at the date of death.
 - Subjects having a missing Day 30 SSI assessment (or performed out of the pre-specified visit window) will be censored at the date of the last valid SSI assessment, performed within 30 days post index surgery.
 - Subjects having no valid SSI assessment within 30 days post index surgery will be censored at the date of index surgery (i.e. at Day 0).
 - Number (percentage) of subjects, re-admitted within 30 days post index surgery (for any reason) and experienced adjudicated SSI during this re-admission.

This endpoint will be defined per subject as a binary ("Yes" / "No") variable, with "Yes" indicating that a subject had been re-admitted within 30 days post index surgery (for any reason) and experienced an adjudicated SSI during this re-admission. Subjects who have a valid non-missing observation on Day 30 SSI assessment, performed within the pre-specified visit window (the same as defined for the primary endpoint), and have not been re-admitted within 30 days post index surgery (for any reason) with an adjudicated SSI during this re-admission, will be defined as "No".

- Number (percentage) of subjects who experienced at least one surgical re-intervention at target incision due to adjudicated SSI within 30 days post index surgery.

This endpoint will be defined per subject as a binary ("Yes" / "No") variable, with "Yes" indicating that a subject had experienced at least one surgical re-intervention at target incision due to an adjudicated SSI within 30 days post index surgery. Subjects who have a valid non-missing observation on Day 30 SSI assessment, performed within the pre-specified visit window (the same as defined for the primary endpoint), and have not experienced any re-intervention at target incision due to an adjudicated SSI within 30 days post index surgery, will be defined as "No".

The SSI related additional secondary efficacy endpoints will be applied only for subjects with an adjudicated SSI within 30 days post index surgery and are defined as follows:

- Number (percentage) of subjects who had at least one bacterium resistant to Doxycycline grown during bacteriological tests.

This endpoint will be defined per subject as a binary ("Yes" / "No") variable, with "Yes" indicating that a subject had at least one bacterium (grown during bacteriological tests) which is resistant to Doxycycline.

- Number (percentage) of bacteria resistant to Doxycycline out of all bacteria grown during bacteriological tests.

This endpoint will be defined per unique bacterium (grown during bacteriological tests) per subject as a binary ("Yes" / "No") variable, with "Yes" indicating that a unique bacterium is resistant to Doxycycline.

- Number (percentage) of subjects who received IV antibiotic as a treatment for their adjudicated SSI.

This endpoint will be defined per subject as a binary ("Yes" / "No") variable, with "Yes" indicating that a subject received IV antibiotic as a treatment for their adjudicated SSI.

- Number of IV antibiotic treatment days.

This endpoint will be defined per subject as the total number of days on which a subject was treated with IV antibiotic. Subjects who were not treated with IV antibiotic will be assigned a value of 0 days.

- Average of subjects' cumulative ASEPSIS assessment score (AUC).

This endpoint will be defined per subject as Area Under the Curve (AUC) of ASEPSIS assessment scores, calculated using the trapezoidal rule. The analysis will be performed using: 1) all available ASEPSIS measurements throughout the study, 2) only ASEPSIS measurements collected within adjudicated SSI period.

- Number (percentage) of subjects with at least one score of ASEPSIS >20.

This endpoint will be defined per subject in the same way as the third key secondary efficacy endpoint (refer to [Section 3.2.2.1, item 3](#)), and will apply here only for sub-population of subjects with an adjudicated SSI within 30 days post index surgery.

3.2.3. Safety Endpoints

The following safety endpoints will be evaluated:

- Adverse events
- Physical examination
- Vital signs
- Incisional wound healing
- Laboratory tests

The definitions and analyses of these safety measures are provided in [Section 8](#) of this SAP.

3.3. Sample Size and Power Considerations

3.3.1. Original Sample Size Calculation

The updated sample size calculation underlying version 5 of the protocol was based on powering the study with respect to the primary efficacy endpoint, considering the primary analysis of subjects with target incision length >20 cm.

The target sample size for this study relates to number of subjects with incision length >20 cm and is set to a minimum of [REDACTED] to be enrolled and randomized into the study with a maximum of [REDACTED] subjects in total.

The final number of subjects for the Primary Endpoint analysis (with incision length >20 cm) will be determined following an unblinded interim analysis for futility, efficacy and sample size re-estimation, when about [REDACTED] subjects (with incision length >20 cm) will complete their 30 days (1 month) follow-up visit and evaluated for primary endpoint. The study already enrolled about [REDACTED] subjects with incision length ≥ 7 cm, [REDACTED] of them with incision >20 cm.

The maximal sample size for the Primary Endpoint analysis (with incision length >20 cm) was calculated using treatment effect of D-PLEX + SoC from the completed phase 3 clinical study results, and the minimal sample size was based on an optimistic case based on the phase 2 clinical data results. For both the maximal and minimal calculations assumed failure SoC alone were as follows:

- (1) the SSI rate in the SoC arm would be 11%,
- (2) the Failure rate due to re-intervention in the index surgery (included as Failure event in the primary endpoint analysis) = 6.80% and
- (3) the 30-day treatment failure rate due to all-cause mortality rate = 2%.

Thus, the overall treatment failure rate in the SoC alone arm will be: 19.8% (11%+6.8%+2.0%). For the maximal size calculation, it was assumed that D-PLEX + SoC will have effect of 50% on this rate (halving infection rate) relative to SoC alone (thus 5.5% infection rate in D-PLEX + SoC arm), whereas in the minimal sample size calculation the effect was taken as 70% thus leading to 3.3% infection rate in this arm. With the further assumptions regarding D-PLEX + SoC of no effect on mortality and 30% effect on failure due to re-intervention, the assumed overall treatment failure rates for D-PLEX + SoC were 10.06% (3.3%+4.76%+2.0%) for the minimal size and 12.26% (5.5%+4.76%+2.0%) for the maximal size. With these assumptions, a sample of [REDACTED] total subjects provides 90% power to detect level of significance. In order to account for an anticipated 5% lost-to-follow-up rate, a minimum of [REDACTED] subjects ([REDACTED]/treatment arm) with a maximum of [REDACTED] subjects ([REDACTED] per arm).

At the time of this amendment, a total of [REDACTED] subjects with incision length ≥ 7 cm has already been enrolled into the study and thus the overall number of subjects in the study is estimated as the target for incision >20 cm ([REDACTED] to [REDACTED]) plus the [REDACTED] subjects with incision length ≥ 7 cm and <20 cm. In total, a total of [REDACTED] to [REDACTED] subjects with incision length ≥ 7 cm are expected to be enrolled into the study.

To note, the significance level for the above calculation was taken conservatively to account for the planned interim analysis for efficacy (to be performed with a two-sided $\alpha=0.01$). Details on the exact significance level to be used in final analysis are provided in [Section 5.3](#) and [Section 7.2.1](#).

3.3.2. Sample Size Re-assessment

The final sample size of the study will be determined based on results from a pre-specified un-blinded sample size re-estimation (ubSSR) to be conducted when about a total of [REDACTED] subjects with incision >20 cm have been evaluated for the primary endpoint.

The ubSSR analysis will be part of the planned interim analysis, following a group-sequential stopping rules for efficacy and futility, and will be based on the "Promising Zone" approach. Based on this approach, the sample size can be increased up to the maximal size of [REDACTED] subjects in total, only if the comparative result falls in a predefined "Promising Zone".

Thus, the final sample size following the Interim analysis can be either about [REDACTED] (if the study to be stopped due to Efficacy or Futility), or [REDACTED] (if the study is to continue to planned initial size, in case the results falls in the "Un-Favorable" or "Favorable" zones), or increased up to [REDACTED] in total if the results falls in the "Promising Zone", in accordance with the pre-specified comparative unblinded sample size re-estimation plan. The full details of the interim analysis plan and governing rules are detailed in the accompanying Interim Statistical Analysis Plan (ISAP).

3.4. Randomization and Blinding

3.4.1. Randomization

Upon confirmation that the subject fulfils all inclusion criteria and none of the exclusion criteria are met, he/she will be randomized through an Interactive Web Randomization System (IWRS) integrated with the electronic Case Report Form (eCRF).

Subjects will be randomized to either the investigational arm (D-PLEX + SoC) or to the control arm (SoC only) in a 1:1 ratio. Randomization will be stratified by incisional length (≥ 7 cm - ≤ 10 cm, > 10 - ≤ 20 cm, > 20 cm), type of SoC prophylactic antibiotic regimens (prophylactic IV antibiotic only, prophylactic IV antibiotic with mechanical bowel preparation or prophylactic IV antibiotic with oral antibiotics combined with mechanical bowel preparation) and by region (US or Europe + Israel). To note, once the protocol amendment will be applied, randomization to the ≥ 7 cm - ≤ 10 cm and the > 10 - ≤ 20 cm strata will be blocked.

Instructions and training for randomization and stratification process will be provided during site initiation visit. The randomization code will be stored within the IWRS database until unblinding of this study is requested.

3.4.2. Blinding

This is a double blind clinical trial. The sponsor, subjects, outcome assessor and all staff involved in the collection and recording of the clinical and laboratory data, based on which the independent adjudication committee will perform their assessment, will be blind to treatment assignment. In addition, all aspects of data management and clean-up as well as programming for final analysis will be done in blinded datasets. An unblinded statistician, external to the Sponsor, will be tasked with providing unblinded data to the Data Monitoring Committee (DMC) and will have access to the treatment codes via the Interactive Web Response System (IWRS).

The study site personnel, who perform the index surgery (operation room staff), will be trained not to disclose the treatment arm to the blinded investigator, to the subject, his/her family, to other health care providers not present during the surgery or to the study Sponsor representatives.

Wound assessment and other study outcomes throughout the study follow-up visits will be done by a blinded investigator that will not be involved in the surgery.

3.5. Sequence of Planned Analyses

3.5.1. Interim Analyses

One formal comparative interim analysis for an early efficacy or futility stops or unblinded sample size re-estimation is planned, scheduled to be conducted when about a total of [REDACTED] subjects (with incision length >20 cm) will be evaluated for the primary endpoint. The interim analysis will include a group sequential design stopping rule for efficacy or futility, combined with unblinded sample size re-assessment based on the "Promising Zone" approach.

The outcome of this interim analysis will be either early stopping for efficacy or futility, or continuation to planned final ([REDACTED] subjects with incision length >20 cm) or continue with sample size increased up to maximal size of [REDACTED] only if the comparative result falls in a predefined "Promising Zone".

As specified in [Section 3.3.2](#), the full details about the stopping rules and the sample size decision rules will be detailed in an Interim Statistical Analysis Plan (ISAP) accompanying this document.

The unblinded interim analysis will be performed by an independent DMC statistician who is otherwise not involved in the study, according to the pre-planned interim analysis plan, and comparative information will be kept confidential within the DMC until the study is unblinded. Moreover, should the Interim analysis result lead to study size continuation/increase, the interim information provided to the sponsor will concern sample size only.

3.5.2. Final Analyses and Reporting

- All final, planned analyses identified in this SAP will be performed only after the last subject has completed the study. The randomization codes will not be unblinded until this SAP has been signed and approved.
- Prior to the interim analysis, it is planned to lock the primary endpoint efficacy data of those subjects included in the interim analysis (as per the Interim Analysis section above). Only the primary endpoint will be formally tested as part of the IA.
- In case that the pre-planned efficacy boundary is crossed at the interim analysis and the DMC makes a recommendation to stop the study early, it is expected that following such event a final database will be created to include all randomized subjects, including those recruited during the time of interim analysis conduct, after the IA data lock, and this full database will be the basis of the study report and submission. Any change made between the data used for the interim analysis and final database will be documented and discussed. All study personnel will continue to remain blinded until the final data lock, so that all data cleaning activities for this study will be performed by blinded personnel.

- Importantly, in the case of a successful IA result, the positivity of the study and formal significance testing of the primary endpoint are to be based on the significant interim analysis result for the primary endpoint, and should additional randomized subjects be available in the final full database, it will serve to formally assess the key secondary endpoints where the primary endpoint will only be described and presented along with 95% confidence intervals. No formal statistical testing will be done on the primary endpoint after the successful result from the interim analysis.
- Whereas active open-label extension of the protocol will be initiated to recruit additional patients for safety monitoring to be treated with D-PLEX, these additional subjects will be included in the safety analyses only.
- Any exploratory analyses completed to support study analyses, which were not identified in this SAP, will be documented and reported in appendices to the CSR.

4. ANALYSIS POPULATIONS

The current section describes the analysis populations defined for the study.

4.1. Screened

This population will include all subjects who underwent screening and will be used for summary of disposition and data listings.

4.2. All-Randomized Set

The all-randomized set will include all subjects that had been randomized to receive either D-PLEX + SoC or SoC alone, regardless of their incision length category (>20 cm or not). In this analysis set, treatment will be assigned based on the treatment to which subjects were randomized, regardless of which treatment they actually received. In addition, this analysis set will include subjects even if eventually their abdominal surgery was not performed (after already randomized). Subjects randomized by mistake for whom target incision was not abdominal will not be included.

4.3. Intent to Treat (ITT)

The ITT analysis set will consist of all subjects who have been randomized to receive either D-PLEX + SoC or SoC alone, with a planned target abdominal incision length >20 cm. As the decision to purportedly enrich study population with the >20cm length was made under protocol amendment #5, this cohort will include all patients enrolled before the amendment whose actual target incision length was >20cm. In this analysis set, treatment will be assigned based on the treatment to which subjects were randomized, regardless of which treatment they actually received. In addition, this analysis set will include subjects even if eventually their abdominal surgery was not performed (after already randomized). Further, as all subjects randomized under protocol amendment # 5 are planned by design for a >20cm target incision length, those patients who for any reason ended up with a <20cm incision length would still be included. Subjects randomized by mistake for whom target incision was not *abdominal* will not be included.

4.4. Safety

The safety population will include all subjects randomized and treated with D-PLEX or SoC. In this population, treatment will be assigned based upon the treatment the subjects actually received, regardless of the treatment to which they were randomized, their incision length, if have been ultimately operated or incision site (abdominal or not). Whereas active open-label extension of the protocol will be initiated to recruit additional patients for safety monitoring to be treated with D-PLEX, these additional subjects will be included in the Safety analysis set only.

4.5. Modified Intent to Treat (mITT)

The mITT analysis set is a subset of the ITT set and will consist of all subjects randomized and treated with D-PLEX + SoC or SoC alone who underwent the abdominal (index) surgery with an actual incision length >20 cm and have no eligibility criteria deviation. In this population, treatment will be assigned based upon the treatment to which subjects were randomized, regardless of the treatment they actually received. Exclusion from the mITT population will be determined in a blinded manner prior to database lock and will be based only on observations at baseline.

4.6. Per Protocol (PP)

The PP analysis set is a subset of the mITT set and will consist of all subjects in the mITT who have no major protocol deviations and were assessed for the primary endpoint (i.e. completed the Day 30 assessment or otherwise had prior to that adjudicated post-surgical SSI, or death or re-intervention at the index surgery). The final list of subjects to be excluded from the PP due to major protocol deviation will be finalized blindly before database lock and unblinding of the study.

The analysis of the primary and the first and the third key secondary efficacy endpoints will be performed on the ITT, mITT and PP populations, with the ITT population serving as the primary analysis set. The second key secondary endpoint will be analyzed using the All-Randomized analysis set. Analyses of additional secondary efficacy endpoints will be performed on the populations as described subsequently. Analyses of safety will be performed on the safety analysis set. Baseline subject characteristics and demographics will be summarized for the All-Randomized and ITT populations.

As a general note, all stratified analyses will consider only the two relevant study stratification factors namely region and prophylactic antibiotics, while stratified analysis of the All-Randomized set will also include incision length.

5. GENERAL ASPECTS FOR DATA ANALYSIS

5.1. General

The following is a list of general reporting conventions:

1. Descriptive statistics for continuous variables include n (number of non-missing observations), mean, standard deviation (SD), 25th and 75th percentiles, median, minimum, and maximum.
2. Means and medians will be reported with 1 more digit than the precision of the captured data. Standard deviations and confidence intervals will be reported at 2 more digits than the precision of the data. Minimum and maximum will be reported to the same level of precision as the original observations.
3. Descriptive statistics for categorical variables will include counts (n) and percentages (%) and will be presented in the form of n (%).
4. Percentages will be reported with 1 decimal place.
5. No preliminary rounding should be performed; rounding should only occur after analysis. To round, consider digit to right of last significant digit: if < 5 , then round down; if ≥ 5 , then round up.
6. Unless otherwise noted, all statistical analyses will be conducted with two-sided testing.
7. All data collected will be presented in the by-subject data listings, sorted by subject and by time point, where appropriate.

If departures from these general conventions are present in the specific evaluation sections of this SAP, then those will take precedence over the above general conventions.

5.2. Specification of Baseline Values

In general, Baseline will be defined for each subject as the last available, valid, non-missing assessment before the initiation of study treatment, i.e. before the administration of pre-operative IV antibiotic, given as part of Standard of Care procedures.

5.3. Multiple Comparisons and Multiplicity

The overall study-wise type I error will be 5%.

To protect the study from type I error inflation due to the multiplicity endpoints, the key secondary endpoints will be interpreted inferentially only if a statistically significant treatment effect is detected in the primary endpoint. Type I error will be further controlled for the key secondary endpoints by employing the Hierarchical Approach. To note, as the secondary endpoints are to be tested once (not part of interim analysis), the first secondary endpoint will be tested in full 5% significance level in case the primary endpoint is successful. In accordance with the hierarchy approach, the second key secondary endpoint

will be formally analyzed only in case the first key endpoint will be statistically significant ($p \leq 0.05$), and the third key secondary endpoint will be analyzed only if the second key secondary endpoint is statistically significant ($p \leq 0.05$). The additional secondary endpoints will be used to enhance understanding the beneficial effect of D-PLEX and there is no plan for formal inference for these. Thus, no multiplicity control is further planned beyond the key secondary endpoints.

To account for the option of early stopping for efficacy, the type-1 error spending approach will be utilized. The interim analysis is planned when about [REDACTED] subjects (with incision length >20 cm) in total will be enrolled and have the chance to complete 1-month visit, and an alpha level of 1% (two-sided) regardless of the exact number of subjects included in the analysis will be used. For the strict control of the overall type-1 error, the alpha for the final analysis (in case the study does not stop at interim) will be calculated based on the actual information time of the interim analysis (actual total number of subjects at interim/final size of the ITT population). It is calculated that for an interim analysis performed using [REDACTED] subjects out of final [REDACTED] total size, the information at IA time is 68.9% and the adjusted alpha will be 0.04754 two-sided (0.02377 one-sided).

With regard to the unblinded sample size reassessment, the "Promising Zone" approach (Mehta and Pocock 2011) was chosen to rigidly control study overall type-1 error due to the unblinded comparative size re-estimation at the time of interim analysis, and its planned implementation strictly follows the rules that increase sample size only if comparative results fall in a pre-defined "Promising Zone", thus allowing final analysis to be preserved without further need for statistical adjustment (beyond adjustment due to the interim efficacy analysis as described above).

The planned futility analysis that is part of the interim analysis is concerned with stopping for futility and thus inflation of type 1 error is not introduced as well.

5.4. Handling Withdrawals and Missing Data

5.4.1. Primary Endpoint

As defined for the primary endpoint (refer to [Section 3.2.1](#)), death occurring within the first 30 days post abdominal index surgery is addressed as treatment failure event and thus is not considered as a missing data problem, in either of the primary or sensitivity and supportive primary endpoint analysis.

To note, re-intervention at the target incision occurring within the first 30 days post abdominal index surgery, will be addressed as treatment failure event ("Yes") in all sensitivity and supportive analyses of the primary efficacy endpoint, unless otherwise specified (see [Section 7.2.2](#)).

As specified in [Section 3.2.1](#), in the primary analysis of the primary endpoint, missing data will be imputed as follows: Subjects, who have missing primary efficacy endpoint data due to other reasons than death (i.e. missing Day 30 SSI assessment regardless of reason or

performed out of pre-specified visit window) and have not already been identified as treatment failures due to having experienced any adjudicated SSI event or any re-intervention in the target incision, will be imputed as treatment failures ("Yes").

For the determination of a Failure="No" response, a valid non-missing observation for Day 30 SSI assessment is any confirmation of such response provided in the window of study Day 27 to study Day 40.

For the purpose of the sensitivity analyses to the primary efficacy endpoint analysis, missing data (arising from other reasons than death) will be imputed as follows:

When using ITT population:

1. Using Multiple Imputation (MI) technique
2. Imputing as not treatment failure ("No")

The MI technique will be performed in 3 steps:

1. Step 1- Imputation: missing data will be filled in using 50 different sets of values, to produce 50 imputed datasets. The imputed datasets will consist of 50 copies of the original ITT set, with the observed values being the same across all copies, and with imputed values varying from one copy to another. The logistic regression method as implemented in the MI procedure in SAS (the MONOTONE LOGISTIC statement) will be used for this step. The variables that will be included in the imputation model will be as follows: treatment group, stratification factors, age and gender. In case of complete separation issues, the baseline factors list (except treatment) may be reduced.
2. Step 2- Analysis: each dataset will be analyzed separately using the same analytical approach defined for the primary analysis (namely, the CMH test).
3. Step 3- Pooling: The results from the 50 imputed datasets will be combined into one result using Rubin's rules which accounts for the uncertainty associated with imputed values. This pooling will be performed using the MIANALYZE procedure in SAS. A normalizing Wilson-Hilferty transformation will be applied to the CMH statistic and the resulted normal variable will be further standardized prior to pooling, following the method proposed in Ratitch et al.

When using mITT and PP populations: no imputation will be performed (i.e., a complete case analysis will be used).

5.4.2. Secondary Endpoints

There will be no imputation of missing data for the first and the third key secondary endpoints and the other (non-key) study endpoints, i.e., a complete case analysis will be used, unless otherwise noted for a specific analysis.

The second secondary endpoint is defined exactly as the primary endpoint, yet in the overall All-Randomized population. Therefore, for consistency, the same imputation rules as defined for the primary endpoint for missing data will be applied here as well.

For the key secondary efficacy endpoints, sensitivity analysis for missing data due to reasons other than death may be performed, depending on the number of these cases, using the same methods specified above for the primary endpoint.

There is no planned sensitivity analysis for missing data in other secondary endpoints. Time to adjudicated SSI within 30 days post index surgery endpoint will handle the missing values as censored, as detailed in the definition of this endpoint in [Section 3.2.2.2](#).

5.5. Study days and visit windows

The day of initiation of study treatment in this study is defined as the day of index surgery (Day 0). Study days will be numbered relative to the day of index surgery (i.e. ..., -2, -1, 0, 1, 2, ...), with Day -1 being the day before index surgery, Day 0 being the day of index surgery, Day 1 being 1 day post index surgery.

In general, the study data will be summarized as collected at the scheduled study visits regardless of visit window violations. For by-visit summaries, if there are multiple assessments at a post-baseline visit, then the last non-missing assessment at that visit will be used for the summary.

For the primary efficacy endpoint definition, the pre-specified visit window for Day 30 follow-up visit will be used, as described in [Section 3.2.1](#) above.

5.6. Strata Pooling

The planned stratified analyses of the ITT population are to employ the stratification factors of type of SoC prophylactic antibiotic regimen factor (3 levels) and geographical region (2 levels), whereas in the stratified analysis of the All-Randomized population, the type of SoC prophylactic antibiotic regimen, geographical region, and Incision length factor (3 level) are to be used.

In the stratified analyses involving the CMH test, data in a stratum will not contribute to the calculation of the test statistic and the p-value if a row sum or column sum is 0 in the contingency table. To ensure that all data is used if this occurs, data from the two geographical regions will be pooled, thus the analysis will not be stratified by Region. If a row sum or column sum is still 0 after this pooling, data will be pooled between the two types of SoC category with the smallest number of patients. If a row sum or column sum is still 0, all SoC antibiotic regimen will be pooled (i.e the test will not be stratified in the ITT analyses). In the application of CMH test in the all-randomized set, pooling strategy will continue similarly with incision length factor (where pooling can be done first with adjacent level before pooling the three levels if needed).

6. STUDY POPULATION

6.1. General

Study population summaries will be presented by treatment group and overall unless otherwise noted. Subject disposition will include all screened subjects. All other study population summaries will be based on the All-Randomized and the ITT population unless otherwise noted.

6.2. Subject Disposition

The subject disposition will be summarized as follows and presented for each treatment group and overall, unless otherwise specified. The percentages will be calculated from the All-Randomized and the ITT population, unless otherwise specified.

- The number of all screened subjects (i.e. the number of subjects in the Screened population), presented only for overall group
- The number (%) of subjects who failed screening (% calculated from the Screened population), including the distribution of reasons for failing the screening, presented only for overall group
- The number (%) of subjects screened but not randomized, if applicable (% calculated from the Screened population), presented only for overall group
- For randomized subjects:
 - The number of randomized subjects
 - The number (%) of subjects randomized but not treated, if applicable (% calculated from the number of randomized subjects)
 - The number (%) of subjects randomized by mistake with non-abdominal target incision, if applicable (% calculated from the number of randomized subjects)
 - The number (%) of subjects randomized with abdominal target incision (% calculated from the number of randomized subjects)
- The number of subjects in the Safety population (i.e. treated subjects) – whereas active open-label extension of the protocol will be initiated to recruit additional patients for safety monitoring to be treated with D-PLEX, a separate count of these subjects and of those randomized subjects (along with % calculated from the number of randomized subjects) will be provided.
- For the All-Randomized population:
 - The number of subjects in the All-Randomized population
 - The number (%) of subjects who completed the study
 - The number (%) of subjects who discontinued the study prematurely, including the distribution of reasons for premature discontinuation

- Descriptive statistics of the number of days in the study
- For the ITT population:
 - The number of subjects in the ITT population
 - The number (%) of subjects in the mITT population
 - The number (%) of subjects in the PP population
 - The number (%) of subjects who completed the study
 - The number (%) of subjects who discontinued the study prematurely, including the distribution of reasons for premature discontinuation
 - Descriptive statistics of the number of days in the study

6.3. Demographics and Baseline Characteristics

Demographics and baseline characteristics will be summarized by treatment group and overall using All-Randomized, ITT and Safety populations. Summaries will be presented with the appropriate descriptive statistics as specified in [Section 5.1](#) above.

The following will be provided:

- Demographics:
 - Age (years) (continuous)
 - Gender: Male, Female (categorical)
 - Childbearing Potential: Yes, No (categorical, females only)
 - Ethnicity: Hispanic or Latino, Not Hispanic or Latino, Unknown, Not Stated (categorical)
 - Race: White, American Indian or Alaska native, Asian, Black or African American, Native Hawaiian or Other Pacific Islander, Other (categorical)
 - Region: USA, Europe+ Israel (categorical)
 - Height (cm) (continuous)
 - Weight (kg) (continuous)
 - BMI (kg/m²) (continuous)
- Allergy History:
 - Any known allergy: Yes, No (categorical)
 - Any known allergy to Doxycycline and/or to the tetracycline family of drugs: Yes, No (categorical)
 - Any hospitalization due to drug/food allergy reaction: Yes, No (categorical)
 - Taking antihistamine drugs in the last year for any reason: Yes, No (categorical)

- Suffering from allergic type symptoms: Yes, No (categorical)
- Substance Use (only subjects for whom Substance Use data had been collected):
 - Cigarettes (Tobacco):
 - Usage: Current, Former, Never (categorical)
 - Number of Pack-Years (continuous)
 - Alcohol:
 - Usage: Current, Former, Never (categorical)
 - Frequency: Daily, Occasionally, Almost Never (categorical)
 - Recreational Drugs Abuse:
 - Usage: Current, Former, Never (categorical)
 - Drug Type: Amphetamines, Barbiturates, Benzodiazepines, Cocaine, Methadone, Methamphetamines, Opiate, Phencyclidine, Tricyclic Antidepressants, Cannabinoids, Other, Unknown/Not reported (categorical)
- Charlson Co-Morbidity Index (CCI), total score
- Is this a COVID-19 patient: Confirmed Positive, Suspected, Unlikely, Confirmed Negative, Not Done.
- Indication for Index Surgery: Cancer, Inflammatory Bowel Disease (IBD), Other (categorical)

The following baseline factors are identified as prognostic factors that may be associated with primary outcome for which group balance will be reviewed: age, gender, comorbid conditions (Yes/No) associated with increased risk of SSI (as listed in [Section 6.5](#)), Charlson co-morbidity index, indication for index surgery. If any of these baseline factors are deemed imbalanced then the factor will be included as an extra adjusting covariate in the relevant sensitivity analysis models for the primary and key secondary efficacy endpoints.

6.4. Stratification Factors for Randomization

Stratification factors for randomization will be summarized by treatment group and overall using All-Randomized and ITT populations. Summaries will be presented with the appropriate descriptive statistics as specified in [Section 5.1](#) above.

The following will be provided:

- Incisional length (categorical): ≥ 7 cm - ≤ 10 cm, >10 - ≤ 20 cm, >20 cm,
- Type of SoC prophylactic antibiotic regimens (categorical): prophylactic IV antibiotic only, prophylactic IV antibiotic with mechanical bowel preparation or

- prophylactic IV antibiotic with oral antibiotics combined with mechanical bowel preparation,
- Region (Categorical): US or Europe + Israel.

If error in randomization (selecting the wrong category of the factor) occurs, both the as-randomized and the corrected factor (actual, as presented in the CRF) will be presented. To note, incisional length factor will be presented only for All-Randomized population summary.

6.5. Medical History

Medical history data will be summarized by treatment group and overall using Safety population. All medical history terms will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). The number and percentage of subjects with at least one medical history term will be summarized by System Organ Class (SOC) and by Preferred Term (PT) within SOC for each treatment group and overall. The number of events will also be summarized. The table will be sorted by overall descending frequency of SOC and then, within a SOC, by overall descending frequency of PT.

Additional summary table will be provided for the following comorbid conditions (associated with increased risk of SSI): Diabetes, Chronic Obstructive Pulmonary Disease (COPD)/Smoking, Obesity/Overweight, Hypertension, and Peripheral Vascular Disease (PVD). The number and percentage of subjects will be presented for each comorbid condition by treatment group and overall using All-Randomized, ITT and Safety populations.

All medical history data will be listed.

6.6. Prior Medications

All medications will be classified using the Anatomical Therapeutic Chemical (ATC) classification codes and preferred terms (PT) from the World Health Organization Drug Dictionary (WHO-DD). Medications with a stop date before the date of index surgery will be considered prior medications. In case of partial or missing stop dates, the imputation rules, described further in concomitant medications [Section 8.7.1](#), will be applied.

Prior medications data will be summarized by treatment group and overall using Safety population. The number and percentage of subjects with at least one medication term will be summarized by ATC Level 4 category and by PT within an ATC Level 4 for each treatment group and overall. The table will be sorted by overall descending frequency of ATC Level 4 and then, within an ATC Level 4, by overall descending frequency of PT.

In addition, all prior medications data will be listed.

6.7. Physical Examination

Physical examination findings at baseline (Normal, Abnormal NCS, Abnormal CS) will be summarized by treatment group and overall using Safety population. Summaries will be presented with the appropriate descriptive statistics as specified in [Section 5.1](#) above.

6.8. Protocol Deviations

All protocol deviations in the study will be listed. Summary of deviations according to predefined categories will also be provided by treatment group and overall.

7. EFFICACY ANALYSES

7.1. General

The analysis of the primary efficacy endpoint will be performed on the ITT, mITT and PP populations, with the ITT population serving as the primary analysis population. The first and the third key secondary endpoints will be analyzed using the same sets as the primary endpoint, and the second key secondary endpoint will be analyzed using the All-Randomized population. General additional secondary efficacy endpoints will be analyzed using the ITT and mITT populations, unless otherwise noted for a specific endpoint. SSI related additional secondary efficacy endpoints will be analyzed on the sub-population of subjects who experienced at least one adjudicated SSI within 30 days post index surgery.

Summaries will be presented by treatment group, unless otherwise noted.

7.2. Primary Efficacy Analysis

The primary objective of the study is to assess the anti-infective efficacy of D-PLEX + SoC over a period of 30 days post operation, by preventing surgical site infection (SSI), defined as superficial and/or deep infection, in the index (target) incision, compared to the SoC alone control arm, in the population of subjects with target incision length >20 cm.

7.2.1. Primary Analysis

The primary efficacy analysis will be based on the ITT population and will compare the proportions of treatment failures (as defined in [Section 3.2.1](#) above) between D-PLEX + SoC and SoC alone treatment groups.

The primary population for the primary analysis is the subjects with target incision >20 cm, per the ITT set definition.

The number and proportion of subjects with treatment-failure event will be tabulated per treatment group. A ■■■% confidence interval (based on the Clopper-Pearson method) will be constructed for each proportion. The Cochran Mantel-Haenszel (CMH) test will compare the proportion of treatment-failure between the two groups using the study stratification factors used for randomization and corresponding risk difference estimate will be presented with ■■■% confidence interval (using the method of Mantel-Haenszel stratum weights, as applied in the COMMONRISKDIFF option in the SAS FREQ procedure).

The following generic SAS syntax will be used:

```
ODS OUTPUT CommonPdiff=cmh_pdiff(WHERE=(method="Mantel-Haenszel"))
CMH=cmh_pval(WHERE=(AltHypothesis="Row Mean Scores Differ"));
PROC FREQ DATA=eff ORDER=internal;
TABLES STRATAA*STRATAB*TRTP*AVALC / CMH COMMONRISKDIFF(COLUMN=2);
RUN;
```

The following hypotheses will be tested for a significant difference in the treatment-failure proportions between D-PLEX + SoC (P_{D-PLEX}) and SoC (P_{SoC}) treatment:

$$H_0: P_{D-PLEX} = P_{SoC}$$

vs.

$$H_1: P_{D-PLEX} \neq P_{SoC}$$

For final analysis, the interim analysis adjusted significance level will be used for this test, refer to [Section 5.3](#) for details. In the case of small number of events (less than 5 events in any treatment group), the Fisher's exact test will be used.

In addition, the number and percentage of each of the failure types comprising the primary efficacy endpoint will be presented by treatment group. The denominator for percentages will be the number of ITT subjects in each treatment group. The mutually exclusive failure type categories are:

1. Death

1.1. Death and Adjudicated DSSI Event

1.2. Death and Adjudicated SSSI Event

1.3. Death and Re-intervention

1.4. Death, without Adjudicated SSI Event or Re-intervention

2. Adjudicated SSI Event (Total)

2.1. Adjudicated DSSI Event

2.2. Adjudicated SSSI Event

3. Re-intervention

4. Missing Day 30 SSI Assessment.

In this table, subjects experiencing more than one type of treatment failure event will be counted only in the highest in the hierarchy type (based on the above order). To note, adjudicated DSSI and SSSI events, all-cause mortality, and re-interventions will be analyzed further as a part of the additional secondary efficacy analyses.

7.2.2. Sensitivity and Supportive Analyses

Sensitivity and supportive analyses for the primary endpoint analysis will address the following aspects:

- Repeat the primary analysis using the mITT and PP populations.
- To account for the possibility of errors in values of stratification factors used for randomization, the primary analysis will supportively be repeated using the correct values.
- Difference between the treatment groups when controlling for possible imbalance in important baseline factors will be analyzed by evaluating the odds ratio obtained

from estimating a multiple logistic regression model. The list of baseline variables provided at the end of [Section 6.3](#).

- Rather than treating re-intervention at the target incision site as treatment failure, taking the SSI outcome according to the determination of the independent adjudication committee.
- Sensitivity analysis for the imputation of missing data due to other reasons than death (please refer to [Section 5.4](#)).
- Sensitivity analysis, in which subjects who were assigned as NOT meeting the primary endpoint due to a disagreement within the adjudication committee (as described in [Section 3.2.1](#)), will now be considered as treatment failure.
- Sensitivity analysis, in which any suspected SSI event (regardless of adjudication committee decision) will be considered as treatment failure (in addition to the primary endpoint treatment failure events, as detailed in [Section 3.2.1](#)).

All analyses of the primary endpoint are based on the blinded and independent adjudication committee decisions (except for the last two sensitivity analyses). The investigator assessment of SSI will be described and listed, as detailed in [Section 8.5](#). In addition, the subjects for which non-unanimous decision on SSI status led to a final decision of SSI='NO', will be flagged and listed.

7.3. Secondary Efficacy Analyses

7.3.1. Key Secondary Efficacy Analyses

This section describes the analysis of the key secondary endpoints. The same sensitivity analyses as defined for the primary endpoint will be performed for the key secondary efficacy endpoints, as applicable. Sensitivity analyses for missing data in these endpoints are described in [Section 5.4.2](#). In accordance with the type 1 error control strategy specified for this study, the key secondary endpoints are to be tested once (not part of interim analysis), using an hierarchical approach (as described in [section 5.3](#)), and based on the Final Analyses and Reporting plan as described in [section 3.5.2](#).

7.3.1.1. First Key Secondary: SSI Rate within 30 Days Post Index Surgery

The number and proportion of subjects with SSI event as defined in the first key secondary endpoint above, will be tabulated per treatment group. A 95% confidence interval will be constructed for each proportion. A Cochran Mantel-Haenszel (CMH) test will compare the proportion of SSI between the two groups, using the study stratification factors used for randomization, and corresponding risk difference estimate will be presented with 95% confidence interval (using the method of Mantel–Haenszel stratum weights, as applied in the COMMONRISKDIFF option in the SAS FREQ procedure, generic SAS syntax detailed in [Section 7.2.1](#) above). In the case of small number of events (less than 5 events in any study arm), the Fisher exact test will be used.

This first key secondary efficacy endpoint will be formally tested only if the primary efficacy endpoint analysis showed statistically significant difference between the groups in the favor of D-PLEX + SoC as determined in the planned interim analysis or at planned final analysis. .

7.3.1.2. Second Key Secondary: Treatment-Failure Event Rate within 30 Days Post Index Surgery in the All-Randomized population

The number and proportion of subjects with treatment-failure event as defined in the second key secondary endpoint (namely, the treatment failure as used for the primary endpoint), will be analyzed similarly as the primary endpoint, this time using the All-Randomized analysis set. To note, the analysis will also stratify for the category of the incision length according to the pre-defined classification of: 7 to ≤ 10 cm, >10 to ≤ 20 cm and >20 cm. This endpoint will be formally tested only if the first key secondary endpoint is significant, using two-sided α % significance level.

Descriptive statistics of this endpoint in the group of subjects with incision length of 7 to ≤ 20 cm and in the smaller groups of 7 to ≤ 10 cm in length, >10 to ≤ 20 cm length will also be provided alongside the analysis of this endpoint, for the purpose of providing further considerations for interpretation of its outcome. These subgroupings will be based on the subjects randomized before application of amendment # 5 (as in this amendment decision to randomize only incision length >20 cm length was taken), based on the actual incision length performed.

7.3.1.3. Third Key Secondary: ASEPSIS >20 Rate

The third key secondary efficacy endpoint (as defined in [Section 3.2.2.1, item #3](#)) will be analyzed using the same methods as described for the first key secondary efficacy endpoint (refer to [Section 7.3.1.1](#) above).

This third key secondary efficacy endpoint will be formally tested only if the first and the second key secondary efficacy endpoints showed statistically significant difference between the groups in the favor of D-PLEX + SoC, using two-sided 5% significance level.

7.3.2. Additional Secondary Efficacy Analyses

The current section describes the analyses to be performed on the additional secondary efficacy endpoints, as defined in [Section 3.2.2.2](#).

General additional secondary efficacy endpoints will be analyzed using the ITT and mITT populations, unless otherwise noted for a specific endpoint. The following analyses will be provided:

- Incidence of SSSI within 30 days post index surgery.

This endpoint will be analyzed using the same methods as described for the first key secondary efficacy endpoint (refer to [Section 7.3.1.1](#) above). The analysis will be performed using the ITT, mITT and PP populations.

- Incidence of DSSI within 30 days post index surgery.

This endpoint will be analyzed using the same methods as described for the first key secondary efficacy endpoint (refer to [Section 7.3.1.1](#) above). The analysis will be performed using the ITT, mITT and PP populations.

- All-cause mortality rate within 30 days post randomization.

In case there are no subjects with unknown survival status at 30 days post randomization, this endpoint will be analyzed using the same methods as described for the first key secondary efficacy endpoint (refer to [Section 7.3.1.1](#) above). Otherwise, time to event survival analysis methods will be employed in which subjects with unknown survival status will be censored on the last date of known to be alive. In this later case, Day 30 mortality rates, along with 95% confidence intervals, will be estimated from Kaplan-Meier curves and Z test will be used to compare these rates between the treatment groups.

- All-cause mortality rate within 60 days post randomization.

This endpoint will be analyzed using the same methods as described above for the all-cause mortality rate within 30 days post randomization endpoint, while changing 30 days to 60 days.

- Time to adjudicated SSI within 30 days post index surgery.

Time to adjudicated SSI will be estimated using Kaplan-Meier (KM) method. A graphical representation of the data will be done using KM curves. The corresponding restricted mean times (by Day 30) with 95% confidence intervals will be estimated. In addition, the number of censored observations will be provided by treatment group. The treatment groups will be compared with a stratified log rank test, using the study stratification factors used for randomization (as specified in [Section 3.4.1](#) above). In addition, cumulative incidence plot, treating death as competing event, will be provided. Descriptive statistics of the days to adjudicated SSI within 30 days will be provided based on those subjects experiencing the event, in each group.

- Number (percentage) of subjects, re-admitted within 30 days post index surgery (for any reason) and experienced adjudicated SSI during this re-admission.

This endpoint will be analyzed using the same methods as described for the first key secondary efficacy endpoint (refer to [Section 7.3.1.1](#) above).

- Number (percentage) of subjects who experienced at least one surgical re-intervention due to adjudicated SSI within 30 days post index surgery.

This endpoint will be analyzed using the same methods as described for the first key secondary efficacy endpoint (refer to [Section 7.3.1.1](#) above).

SSI related additional secondary efficacy endpoints will be analyzed on the sub-population of subjects who experienced at least one adjudicated SSI within 30 days post index surgery. The following analyses will be provided:

- Number (percentage) of subjects who had at least one bacterium resistant to Doxycycline grown during bacteriological tests.

This endpoint will be tabulated by treatment group, presenting the number and percentage of subjects in each category ("Yes" / "No"). Chi square test (or Fisher's exact test, as applicable) will be used to compare the treatment groups, and corresponding risk difference estimate will be presented with 95% confidence interval.

- Number (percentage) of bacteria resistant to Doxycycline out of all bacteria grown during bacteriological tests.

This endpoint will be tabulated by treatment group, presenting the number and percentage of bacteria in each category ("Yes" / "No").

In addition, the analysis will be repeated for the number (percentage) of bacteria resistant to SoC intravenous antibacterial drugs (cephalosporins and/or metronidazole) out of all bacteria grown during bacteriological tests.

- Number (percentage) of subjects who received IV antibiotic as a treatment for their adjudicated SSI.

This endpoint will be analyzed using the same methods as described above for the number (percentage) of subjects who had at least one bacterium resistant to Doxycycline grown during bacteriological tests endpoint.

In addition, the analysis will be repeated for the number (percentage) of subjects who received Oral / Other / Any antibiotics for their adjudicated SSI.

- Number of IV antibiotic treatment days.

This endpoint will be summarized by treatment group, using the appropriate descriptive statistics as specified in [Section 5.1](#) above. A Wilcoxon Rank Sum Test will be conducted to assess for treatment group differences.

- Average of subjects' cumulative ASEPSIS assessment score (AUC).

This endpoint will be summarized by treatment group, using the appropriate descriptive statistics as specified in [Section 5.1](#) above. A Wilcoxon Rank Sum Test will be conducted to assess for treatment group differences.

- Number (percentage) of subjects with at least one score of ASEPSIS >20.

This endpoint will be analyzed using the same methods as described above for the number (percentage) of subjects who had at least one bacterium resistant to Doxycycline grown during bacteriological tests endpoint.

7.4. Sub-group Analysis

The primary efficacy endpoint will be analyzed using All-Randomized population by actual incision length with the following categories: ≥ 7 to ≤ 10 cm, >10 to ≤ 20 cm, ≥ 7 to ≤ 20 cm and >20 cm. Subgroup analyses will be performed using the same methods specified for the primary analysis. To note, only the two relevant study stratification factors namely region and prophylactic antibiotics will be used in each subgroup.

8. SAFETY ANALYSES

8.1. General

Safety analyses will be based on Safety population. All summaries will be presented by treatment group, unless otherwise noted. As defined for the Safety analysis set (section 4.4), whereas active open-label extension of the protocol will be initiated to recruit additional patients for safety monitoring to be treated with D-PLEX, these additional subjects will be included in the Safety analysis along with the subjects randomized D-PLEX.

8.2. Adverse Events

All adverse events (AEs) will be coded using the Medical Dictionary for Regulatory Activities (MedDRA, version 23.1). Only Treatment Emergent Adverse Events (TEAEs) will be summarized. TEAEs are defined as all AEs that start on or after the date of the index surgery. If the AE start date is incomplete, unless it is clear that the date is prior to index surgery, it will be conservatively imputed as follows for the purpose of determining TEAE flag:

- If the start date is completely missing, the start date will be equal to the date of the index surgery. However, if the stop date is not missing and is before the date of the index surgery, then the stop date will be used instead.
- If the start day is missing, but the month and year are not missing and are equal to the month and year of the index surgery, then the day of the index surgery will be used.
- If the start day is missing, but the month and year are not missing and are not equal to the month and year of the index surgery, then the first day of the month will be used.
- If the start day and month are missing, then the day and the month of the index surgery will be used.

Please note, AE summary tables will include also all suspected SSI Events, reported by investigator on Suspected SSI Events form.

Every AE will be graded by the investigator as mild, moderate, or severe and will be assessed by the investigator for its relationship to the Investigational Product (IP) (related, possibly related, unlikely related, not related), and for relationship to other causes (concurrent illness, surgical intervention, other, none). AEs assessed for relationship to the IP as "Unlikely Related" or "Not Related" will be summarized under "Not Related" category; AEs assessed for relationship to the IP as "Related" or "Possibly Related" will be summarized under "Related" category; AEs with missing assessment for relationship to the IP will be conservatively included in "Related" category.

When reporting by System Organ Class (SOC) and PT, the reports will present the SOC in alphabetical order; while PTs within the SOC will be presented in order of overall

decreasing frequency of occurrence. A patient with multiple AEs (different PTs) coded to the same SOC will be counted only once for that SOC, but will be counted each time for different PTs within that SOC. A patient with separate events of the same PT will be counted only once in the frequency tables for that PT.

The following summaries will be provided:

- An overall summary of TEAEs, presenting the overall incidence (number and percentage) of subjects, by treatment group, for the following categories:
 - Subjects with at least one TEAE
 - Subjects with at least one severe TEAE
 - Subjects with any IP related TEAE
 - Subjects with at least one serious TEAE
 - Subjects with at least one serious related TEAE
 - Subjects with any TEAE resulting in death
 - Subjects with at least one Adverse Event of Special Interest (AESI)
 - Subjects with any TEAE with action taken marked as Surgical re-Intervention with same incision as in the Index Surgery.
- Tabulations of the number and percentage of subjects with at least one TEAE, as well as the number of events, summarized for each treatment group by System Organ Class (SOC) and by Preferred Term (PT) within SOC, will be provided for the following events:
 - All TEAEs
 - Serious TEAEs
 - Treatment-Related TEAEs
 - Adverse Event of Special Interest
 - TEAEs resulting in death
 - TEAEs with action taken marked as Surgical re-Intervention with same incision as in the Index Surgery
 - TEAEs by maximal Severity (Mild, Moderate, Severe)
 - TEAEs by maximal relationship to Treatment (Not Related, Related)

In addition, all AEs will be listed, regardless of whether they were treatment emergent. In addition, a listing of all SAEs will be provided. If there are any death, a by-patient listing of deaths will also be provided. A listing of AESI will also be provided.

8.3. Physical Examination

Physical examinations (PE) will be performed at screening, Day 30 and Day 60 visits. As noted in the protocol, any abnormal finding with respect to baseline, assessed by the Investigator as clinically significant, should be recorded as an Adverse Event in the relevant eCRF section.

In order to display any changes in body system findings over time, PE findings (Normal, Abnormal NCS, Abnormal CS) will be summarized using the appropriate descriptive statistics as specified in [Section 5.1](#) above, presenting:

- By-visit summary table;
- Shift table from baseline to each post-baseline scheduled visit.

In addition, all abnormal physical examination results will be listed.

8.4. Vital Signs

Vital signs (body temperature, systolic blood pressure, diastolic blood pressure and heart rate) are collected at screening and at Day 0 (before surgery, unless they were taken for screening occurring on the same day), Day 1, Day 5, Day 14, Day 30 and Day 60 (termination) visits. It should also be collected at unscheduled (UN) visits. Each measurement will be assessed by the investigator as clinically significant (CS) or not clinically significant (not CS).

Vital signs measurements will be summarized using the appropriate descriptive statistics as specified in [Section 5.1](#) above, as follows:

- By-visit summaries will be presented on the raw and change from baseline values for each vital sign parameter (continuous).
- The number and percentage of subjects with not CS and CS values will be tabulated by visit, for each parameter. In addition, the number and percentage of subjects with not CS and CS values will be tabulated per parameter for any time during study time point, where a subject may be counted both as having CS value and as having not CS value, if experienced both events during the study.

Results obtained at unscheduled visit will not be included in by-visit summaries, but will be included in any time during study summaries, and data listings.

In addition, all clinically significant vital signs data will be listed.

8.5. Incisional Wound Healing

Incisional wound healing will be assessed by a blinded investigator using Modified Vancouver Scar Scale questionnaire. Assessment is scheduled at Day 1, Day 5, Day 14, Day 30 and Day 60 (termination) visit. Assessment will also be performed at UN visits.

Data will be summarized using the appropriate descriptive statistics as specified in [Section 5.1](#) above. By-visit summaries for responses to the Modified Vancouver Scar Scale

questionnaire (categorical and continuous) will be provided. In addition, the sum of continuous scores will be calculated and summarized.

Incisional wound healing will also be addressed using adverse events data. Treatment emergent adverse events (TEAEs) related to incisional wound healing will be determined by medical review. Tabulations of the number and percentage of subjects with at least one TEAE related to incisional wound healing, as well as the number of events, will be provided for each treatment group by System Organ Class (SOC), by Preferred Term (PT) within SOC, and by Lowest Level Term (LLT) within SOC and PT.

All incisional wound healing data will be listed. Only scheduled visits will be summarized in by-visit analysis, but unscheduled visits will be presented in data listings.

To note, in accordance with the protocol amendment, in this study, an adverse event term of special interest (AESI) has been defined as "Incision site impaired healing". As such, AEs reported as AESI will be summarized along with AEs summaries, as detailed in [Section 8.2](#).

8.6. Laboratory Tests

Laboratory data (Hematology and Chemistry) will be summarized using the appropriate descriptive statistics as specified in [Section 5.1](#) above, using the Safety population.

The following will be provided:

- By-visit summaries on the raw and change from baseline values, if applicable, for each laboratory parameter.
- Shift tables presenting the changes in laboratory values (Low, Normal, High) from baseline to each post-baseline scheduled visit, if applicable, for each laboratory parameter.

In addition, all laboratory data will be listed. A separate listing of abnormal tests will also be provided.

8.7. Other Safety Measures

8.7.1. Concomitant Medications

Per the protocol, all currently used concomitant medications, as well as all medications taken/prescribed to the subject throughout the study will be recorded in the electronic Case Report Form (eCRF). All medications will be classified using the Anatomical Therapeutic Chemical (ATC) classification codes and preferred terms (PT) from the World Health Organization Drug Dictionary (WHO-DD, WHODrug-Global-B3).

Medications with start date or stop date on or after the date of index surgery or ongoing at study completion will be considered concomitant medications. In case of partial or missing dates, the following imputation rules will be applied.

If the medication start date is incomplete, then it will be imputed as follows for the purpose of determining concomitant use:

- If the start date is completely missing, the start date will be equal to the date of index surgery. However, if the stop date is not missing and is before the date of index surgery, then the stop date will be used instead.
- If the start day is missing, the first day of the month will be used.
- If the start day and month are missing, then the first day of the first month (January) will be used.

If the medication stop date is incomplete, then it will be imputed as follows for the purpose of determining concomitant use:

- If the stop date is completely missing and the medication is not ongoing, the stop date will be equal to the date of completion/withdrawal.
- If the stop day is missing, the last day of the month will be used.
- If the stop day and month are missing, then the last day of the last month (December) will be used.

All concomitant medications data will be summarized by treatment group and overall using the Safety population. The number and percentage of subjects with at least one medication term will be summarized by ATC Level 4 category and by PT within an ATC Level 4 for each treatment group and overall. The table will be sorted by overall descending frequency of ATC Level 4 and then, within an ATC Level 4, by overall descending frequency of PT.

In addition, summaries of antibiotics that were taken prior to and after the index surgery will be provided:

- Two separate tables will be produced (one for antibiotics taken prior to the index surgery and the other for antibiotics taken after the index surgery) in the same format as for all concomitant medications table, described above.
- An overall summary table of antibiotics, summarized by treatment group and overall, presenting the incidence (number and percentage) of subjects with antibiotics taken prior to and after the index surgery, overall and by route of administration.

All concomitant medications data will be listed.

8.7.2. Surgery Characteristics

Surgery characteristics will be summarized using both ITT and Safety analysis population. The summaries will be provided by treatment group and overall, using the appropriate descriptive statistics as specified in [Section 5.1](#) above. The following will be provided:

- Preoperative IV Antibiotic Given Prior to Surgery: Yes, No (categorical)
- Oral Antibiotic Given Prior to Surgery: Yes, No (categorical)

- Mechanical Bowel Preparation Performed: Yes, No (categorical)
- Surgery Performed: Yes, No (categorical)
- Type of Surgery: Right Hemicolectomy, Left Hemicolectomy, Transverse Colectomy, Sigmoidectomy, Subtotal Colectomy, Total Colectomy, Proctocolectomy, Low Anterior Resection, Rectum Resection, Rectosigmoid Resection, Hartman's Procedure, Cecectomy, Abdominoperineal Resection, Other (categorical)
- Length of Surgical Index Incision (cm) (continuous)
- Length of Surgical Index Incision: ≥ 7 to ≤ 10 cm, >10 to ≤ 20 cm and >20 cm (categorical)
- Anastomosis Performed: Yes, No (categorical)
- Type of Anastomosis Performed: Ileocolonic, Ileorectal, Ileoanal, Colocolonic, Colorectal, Coloanal, Other (categorical)
- Surgery Included Stoma: Yes, No (categorical)
- Any Complications Encountered During the Surgery: Yes, No (categorical).

All surgery characteristics data will be listed.

8.7.3. Measures of Treatment Compliance

D-PLEX treatment will be administered during a single operative session directly visualized by the Investigator and recorded in the subject's source documents. The number and percentage of subjects receiving each D-PLEX dose (1, 2 or 3 vials) will be summarized, for the All-Randomized population and the Safety populations.

All study drug administration data will be listed.

9. PHARMACOKINETIC (PK) ANALYSES

The PK population will consist of all subjects who have been treated with D-PLEX, and have had PK sampling. All PK data will be listed. Details for PK endpoints and analyses will be provided prior to breaking the blind and prior to the database lock.

10. STATISTICAL SOFTWARE

All summary tables, figures, listings and statistical analyses will be generated using SAS[®] software, version 9.3 or later.

11. LIST OF TABLES, FIGURES AND LISTINGS

The list of summary tables, figures and listings will be provided in a separate document.

12. REFERENCES

1. Ratitch, B., Lipkovich, I., O’Kelly, M., 2013 “Combining Analysis Results from Multiply Imputed Categorical Data”, proceedings of the Pharmaceutical SAS Users Group Conference (PharmaSUG 2013), paper SP03.
2. Rubin, D.B. 1987. Multiple Imputation for Nonresponse in Surveys. New York: John Wiley and Sons.
3. Mehta CR, Pocock SJ. Adaptive Increase in Sample Size when Interim Results are Promising: A Practical Guide with Examples. Statist. Med. 2000; 00:1–62011.