Cover Page for SAP

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PolyNovo Biomaterials Pty. Ltd.

CP-002

A Traditional Feasibility Study to Assess the Safety and Effectiveness of the Biodegradable Temporizing Matrix (BTM) Burns in the Treatment of Deep Burn Skin Injuries

Dec 02, 2019

Final Statistical Analysis Plan

Version 2.0

Prepared by:

PPD

929 North Front Street

Wilmington, NC 28401

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Document History – Changes compared to previous version of SAP:

Version	Date	Changes
2.0	02DEC2019	1. Add additional mVSS descriptive summary table by visit regardless of body region and subject in Section 7.2.4. 2. Add additional NRS descriptive summary table by visit regardless of body region and subject in Section 7.2.5. 3. Add descriptive surgeon's assessment of BTM application table by site regardless of wound level and subject in Section 7.2.6. 4. Remove laboratory abnormalities with clinical significance listing since this is not applicable in the study in Section 8.3

List of Abbreviations

BMI	Body Mass Index
BPM	Beats Per Minute/Breaths Per Minute
BSA	Body Surface Area
BTM	Biodegradable Temporizing Matrix
CFR	Code of Federal Regulations
CRF	Case Report Form
CTCAE	Common Terminology Criteria for Adverse Events
DSMB	Data Safety Monitoring Board
eCRF	electronic Case Report Form
FDA	Food and Drug Administration
hCG	human chorionic gonadotropin
IRB	Institutional Review Board
ITT	Intent-to-Treat Population
MedDRA	Medical Dictionary for Regulatory Activities
mmHg	Millimeter of mercury
mVSS	modified Vancouver Scar Scale
NCI	National Cancer Institute
NRS	Numerical Rating Scale
PI	Principal Investigator
PT	Preferred Term
ROM	Range of Motion
SAE	Serious Adverse Event
SD	Standard Deviation
SI	International System of Units
SOC	System Organ Class
SSG	Split Skin Graft
TBSA	Total Body Surface Area

TGA	Therapeutic Goods Administration
UADE	Unanticipated Adverse Device Effect
WHODD	World Health Organization Drug Dictionary

1. Introduction

Split-skin grafting has been used to treat deep burns for over 140 years. However, the split skin graft technique has multiple limitations. These issues have been largely overlooked because of the lack of alternatives. Some of these issues can be remediated or delayed by the use of an active "temporizing matrices" that temporarily closes the debrided burn wound, integrates and provides 'dermal' structure prior to subsequent (delayed) application of a split-skin graft. Collagen-based dermal matrices are underused globally, mainly because of their high cost[12], biological composition, and delayed neovascularization which may contribute to an increased rate of infection[13, 14]. Synthetic alternatives would be expected to reduce cost and susceptibility to infection.

The importance of this trial is that it will provide data regarding the appropriateness/applicability of the safety and efficacy outcomes (endpoints), including operator technique challenges and subject burn wound characteristics that will further support the design of a proposed subsequent pivotal, human multi-center trial of Biodegradable Temporizing Matrix (BTM) when used in the surgical management of significant thermal burn injuries.

The BTM device has been designed to function as an active, temporizing dermal matrix, applied onto deep tissues (fat, muscular fascia, muscle, tendon, etc.), exposed by the process of debridement of deep dermal and full thickness burn injuries. Its design function is to integrate into the wound bed and to produce a vascularized 'neo-dermis' capable of accepting a split skin auto-graft and facilitating survival of that graft to definitively close the wound.

A short-term pilot trial of the biodegradable polyurethane foam portion of the BTM device implanted as a topical negative pressure interface to assess tissue reaction to the presence of this polyurethane foam material in human surgically debrided pressure sores has been completed and the results published[8]. No evidence of irritation, sensitivity, discomfort, itching, rash or any device-related adverse event was observed.

A pilot trial of long term implantation of a prototype BTM into 10 free flap donor sites has also been completed in Adelaide, Australia, assessing ease of application and fixation/speed, completeness of integration, ease of delamination and ability of the integrated matrix to sustain skin graft survival to definitive closure[9]. This study also revealed no evidence of reaction to the implanted BTM foam.

The Australian Therapeutic Goods Administration (TGA) subsequently granted three plastic/burn surgeons approval to use the BTM (with a new seal and bond) as an unapproved device for further long-term evaluation of BTM implantation into free flap donor sites[10]. A prospective pilot study (ACTRN12613001375741) in Australian subjects, under the authority of the TGA is currently being performed with the same BTM device as the second in-human clinical study but with fenestrations added during manufacture (rather than by hand during surgical application). This study is being conducted in subjects with deep-dermal or full thickness burn injuries to between 20% and 50% total body surface area (TBSA). An additional clinical trial is also underway (CT-2015-CTN-00488-02). This is a prospective, non-controlled, open-label study evaluating the use BTM in the treatment of patients with deep burns which require excision and skin grafting.

For moderate to large burn injuries in humans, autologous skin, grafting at a second operation allows significant physiological recovery of the subject prior to graft harvest and application. Reducing the early surgical 'insult' to major burn injury patients is important in patient survival and reduces the risk of loss

of resources (such as harvested applied skin grafts and skin graft donor sites) secondary to physiological insufficiency or deterioration. The cosmetic and functional outcomes of using commercially available dermal matrices before grafting are considerably better than a SSG alone[13].

Two residual risks were identified as part of the BTM device risk assessment. One potential risk is unplanned seal separation/membrane removal; human data shows that the seal can stay for up to 56 days if required[10]. The second potential risk is that the skin graft may not adhere and integrate 'take' due to infection, hematoma, or excessive shear. Clinical results to date show these risks are not common in either small surgical wounds or significant debrided burn wounds[13]. With other burn treatment devices, if infection occurs, it may require removal of the device, or a portion of the device, which prolongs treatment times and risks subject safety.

2. Study objectives

2.1. Primary Objectives

- To obtain preliminary data on the clinical safety and effectiveness of BTM class III medical device.
- To assess the %BTM 'take' rate (%TBSA of BTM that has adhered at time of skin grafting, divided by the %TBSA treated with BTM, then multiplied by 100 to express as a percentage).
- To assess the %SSG (Split Skin Graft) 'take' rate (%TBSA of viable skin taken at day 7 - 10 post-SSG, divided by the %TBSA of SSG applied, then multiplied by 100 to express as a percentage).

2.2. Secondary Objective

- To assess the incidence and severity of infections in BTM-treated burn wounds.
- To assess the percent wound closure in BTM-treated burn wounds.
- To assess the appropriateness of the study endpoints and the study design, including operator ease-of-use and subject characteristics that may impact the device performance.
- To assess the quality of wound healing in subjects treated with BTM, using
  a) the Joint Contracture Severity Scale,
  b) measurements of the Range of Motion (ROM),
  c) scar appearance/quality using the modified Vancouver Scar Scale (mVSS).
- To assess the incidence and severity of pruritus as assessed by Numerical Rating Scale (NRS).

2.3. Overall Study Design and Plan

This is a multicenter, single arm, open-label study to allow a preliminary assessment of the safety and effectiveness of BTM device. Patients with 10-70% TBSA burns will have BTM devices implanted in areas with deep partial or full thickness burns to treat at least 5% and no more than 50%TBSA.

This trial aims to recruit a minimum of ten subjects and up to 15 subjects suffering deep-dermal or full thickness burn injuries to between 10% and 70% TBSA and who are able to provide informed consent, or have a legal representative who is able to make medical decisions on behalf of the subject.

The study will consist of approximately a 1-2 day screening period, a 2 month treatment period, and a 12 months follow-up period. The screening period will start from the day of signing the Informed Consent Form until Day 0 of treatment within 7 days. The treatment period will last approximately 2 months starting from admission to hospital through to the end of graft 'take'. The follow- up period will start from the day after the end of graft take date.

There is no restriction on administration to the subject of their usual medication, or such pharmaceutical treatments felt necessary by the Investigator such as antibiotics or topical aqueous only antimicrobial solutions.

Subjects will be monitored throughout the clinical trial for adverse events/effects. It will be left to the Investigator's clinical judgment to decide whether or not an AE is of sufficient severity to require the participant's removal from the trial, prior to Day 7 after BTM implantation. A participant may also voluntarily withdraw from follow-up treatment after BTM implantation without giving a reason. In either event, a Termination visit assessment will be performed. In the event of AE termination by the Investigator, the subject will be given appropriate medical care until symptoms cease, or until the condition becomes stable.

Evidence of BTM integration (adherence, color, loss of foam pattern, vascularization [illustrated by capillary blanching with pressure and refill when pressure released]) will be assessed every 3-5 days until the SSG procedure. An assessment of the %BTM 'take' rate will be measured by the %TBSA accepting a BTM divided by the total TBSA treated with the BTM device and multiplied by 100 to express as a percentage for each wound site applied with BTM. BTM Take is determined after the sealing membrane is removed from the device. An assessment of the %SSG 'take' rate will be measured by the amount of applied skin graft which remains viable ('takes') expressed as a percentage of the total amount of SSG applied at 7 -10 days after application of the SSG.

2.4. Study Endpoints

2.4.1. Primary Endpoint

- Incidence and type of adverse events occurring after BTM implantation. These data will be reviewed by a Data Safety Monitoring Board (DSMB).
- BTM 'take' rate: amount of BTM that has adhered to the wound bed at the time of skin grafting, expressed as a percentage of the total amount of BTM applied.
- SSG 'take' rate over BTM: applied skin graft which 'takes' expressed as a percentage of the total amount of BTM-treated SSG applied 7 -10 days after application of the SSG.

2.4.2. Secondary/Exploratory Endpoints

- Incidence and severity of infections in BTM-treated areas, and the success of treatment of local infections with BTM in place.
- Clinical assessment of % wound closure.
- Operator ease of use as determined by the physician survey (Appendix 12.2).

- Joint contracture at 1, 2, 3, 6, and 12 months after treatment compared with baseline. This will be assessed by Joint Contracture Severity Scale and Range of Motion (ROM) of joints (Appendix 12.2).
- Scar appearance/quality in BTM -treated subjects as assessed by Modified Vancouver Scar Scale (mVSS) (Appendix 12.2) at 2, 3, 6, and 12 months after SSG.
- Pruritus incidence and severity as assessed by NRS at SSG 'take' and 1, 2, 3, 6, and 12 months after SSG (Appendix 12.2).

2.5. Treatments

The BTM is designed to be implanted into a newly debrided wound bed and stapled or sutured to the edge of the wound. The BTM provides a scaffold to facilitate dermal repair whilst keeping the wound physiologically 'closed to reduce wound contraction'. When integration is complete, typically within 28 to 35 days, the combined bonding layer and sealing membrane is peeled off, or can be left in place longer (>30 days) if more time is required for donor skin graft preparation, and discarded leaving only the implanted foam layer to biodegrade.

The BTM device is not intended to be used on the hands, face, neck, plantar skin, or perineal area.

3. General Statistical Considerations

Continuous variables will be summarized using the appropriate descriptive statistics: number of observations (n), mean, standard deviation (SD), median, minimum, and maximum. Categorical variables will be summarized using the frequency and percentage of observed data. All tabulated data will be presented in subject level listings as source data. In general, no formal inferential statistics are to be performed due to the small sample size unless specified otherwise in the statistical analysis plan.

For the summary statistics of all numerical variables unless otherwise specified, minimum and maximum will be displayed to the same level of precision as reported. Mean and median will be displayed to one level of precision greater than the data collected. The standard deviation or standard error will be displayed to two levels of precision greater than the data collected.

Due to the small sample sizes, all p-values derived from inferential analyses will be considered informative. In general, all significant testing will be two-sided at significance level 0.05. All tests will be made without adjustment for multiplicity or multiple comparisons. P-values will be rounded to four decimal places. If a p-value is less than 0.0001 it will be reported as “<0.0001”. If a p-value is greater than 0.9999 it will be reported as “>0.9999”.

When frequencies are presented, the percentage will be suppressed when the count is zero in order to draw attention to the non-zero counts. A row denoted “Missing” will be included in count tabulations where necessary to account for dropouts or missing data. The denominator for all percentages will be the number of subjects within the analysis population of interest, unless otherwise specified.

Unless otherwise specified, Baseline will be defined as the last non-missing assessment prior to the start of an investigated procedure. Subjects will be identified in the listings by a unique subject number.

All analyses will be conducted using SAS Version 9.2 or higher

3.1. Sample Size

Sample size (N=10) was determined to be adequate to obtain initial data, while minimizing risk to the subjects. No formal statistical sample size calculations have been made.

3.2. Randomization, Stratification, and Blinding

No randomization or stratification will be implemented as this is an open-label study.

3.3. Analysis Populations

Two study populations are defined in this study including Screening, and Intent-to-Treat (ITT).

3.3.1. Screening Population

The Screening Population is defined as the set of subjects who provided informed consent and have at least one screening assessment.

3.3.2. ITT Population

The Intent-to-Treat (ITT) Population consists of all subjects treated with a BTM. All safety and efficacy analyses will be performed using the ITT population.

3.4 DSMB Meetings

Formal meetings of the DSMB will be conducted after 2 subjects complete the 7 to 10 days post SSG time point (calculated from the time of BTM application until 7 to 10 days after SSG application). The DSMB will meet again and all subjects will be reviewed after the 10th subject passes the 7 to 10 days post SSG time point 7-10 day and after the 10th subject passes the 3 month post SSG follow-up visit.

4. Subject Disposition

4.1. Disposition

The number and percentage of subjects in the Screening and ITT Populations will be summarized by sites for screening population.

The number and percentage of subjects who discontinue the study early will be presented for the ITT population. Reasons for early discontinuation will be summarized in categories recorded in the eCRFs.

A listing of subject disposition and population data will be also presented for the Screening population.

4.2. Protocol Deviations

A protocol deviation is any noncompliance with the clinical trial protocol, Good Clinical Practices, Manual of Operations, or other applicable requirements. Noncompliance may be due to the subject, Investigator, or trial staff. Protocol deviations will be categorized into major and non-major deviations. Major deviations are departures from the protocol that impact subject safety or data integrity.

The protocol deviations/violations will be identified and assessed by the clinical monitor of the sponsor or designee following company standard operational procedure.

A summary table by types of protocol deviation and a by-subject listing with protocol deviations will be provided based on the ITT population.

5. Demographics and Baseline Characteristics

5.1. Demographics

Demographic data consists of age in years (Equation 1), age group which will be categorized as: young adults (18 to 35 years), middle-aged adults (36 to 55 years), and older adults (≥55 years), sex, race, and ethnicity. The subject level Baseline characteristics consist of Baseline height in cm, Baseline weight in kg, body mass index (BMI) in kg/m^2, Fitzpatrick Skin Type Scale, Burn Etiology, and %TBSA Affected by Deep Dermal/Full-Thickness. A summary of demographics and subject level Baseline characteristics will be presented for the ITT population using either descriptive statistics or frequency and percentages. Age will be calculated as:

Equation 1:

Age = greatest integer $\leq$ [(informed consent date – date of birth + 1) / 365.25].

Wound level Baseline characteristics such as depth and size in %TBSA will be summarized by frequency and percentages and descriptive statistics respectively for the ITT population.

All other Baseline characteristics for safety and efficacy assessments will be summarized in efficacy and safety reports respectively if applicable.

5.2. Medical History

A summary of medical and surgical history will be presented by body system as recorded in the eCRF. A by-subject listing will be also provided.

5.3. Inclusion and Exclusion Criteria

Subjects who meet all of the protocol defined inclusion criteria and none of the exclusion criteria will be enrolled into the study. Inclusion/exclusion criteria data will be presented in a listing for the Screening Population.

6. Treatments and Medications

6.1. Prior and Concomitant Medications/Non-Drug Therapies/Burn Therapies

All medications taken within 30 days prior to the date of study screening will be recorded in the eCRF. Concomitant medication will be coded according to the World Health Organization Drug Dictionary (WHODD, version 01SEP2015). A prior medication is defined as any medication that has a stop date before the date of implantation of BTM. A concomitant medication is defined as any medication that has a stop date during the treatment-emergent period or beyond.

The number and percentage of subjects who used prior or concomitant medications will be summarized by preferred term for the ITT population. A listing for prior or concomitant medications will also be provided.

Imputation for missing medication stop dates can be found in Appendix 12.3.

Medications with missing stop dates after imputation will be classified as both prior and concomitant.

Furthermore, Non-Drug Therapies and Burn Therapies will be presented in a listing.

6.2. Study Treatments

The sole investigational device in this traditional feasibility trial is the BTM. It is supplied with the seal factory-fenestrated and in pieces 20 cm × 40 cm. These can either be cut to size (for smaller wounds) or joined side-to-side (not overlapped) by stapling at seams (in large wounds). No special preparation of the BTM is necessary.

6.2.1. Extent of Exposure (Time to delaminate)

There is no Extent of Exposure analysis applicable for this study.

6.2.2. Treatment Compliance and Modifications

There is no Treatment Compliance analysis applicable for this study.

7. Efficacy Analysis

All efficacy analyses will be conducted using the ITT population. Wound and subject level listings will be presented primarily for all efficacy endpoints. The summary tables will be provided by body regions captured in the eCRFs if applicable. Tables for value change or shift from baseline by visits or other time points will also be given for efficacy points with both baseline and multiple post baseline values.

7.1. Primary Efficacy Endpoint

The primary efficacy endpoints include the BTM 'take' rate and SSG 'take' rate.

7.1.1. BTM 'take' rate

Amount of BTM that is viable (taken) at the time of skin grafting, expressed as a percentage of the total amount of BTM applied.

$$\%BTM\ 'Take' rate = \left(\frac{\%TBSA\ covered\ by\ BTM\ that\ has\ adhered\ at\ time\ of\ SSG}{\%TBSA\ treated\ with\ BTM}\right)\ x\ 100$$

Wound level BTM 'take' rate will be captured in the eCRFs and the subject level one will be calculated by dividing the total 'take' %TBSA by total BTM treated %TBSA for each given subject. Both subject and wound level BTM 'take' rate will be present in a listing.

Evidence of BTM integration, i.e. adherence, color, loss of foam pattern, and vascularization, if available, will be listed by BTM-treated lesions.

Descriptive table of BTM 'take' rate at both subject and wound level by age group and gender will be reported as appropriate.

7.1.2. SSG 'take' rate

Applied skin graft which remains viable ('taken') expressed as a percentage of the total amount of BTM-treated SSG applied 7 -10 days after application of the SSG.

$$\%SSG\ 'Take' rate = \left(\frac{\%TBSA\ of\ viable\ SSG\ applied\ over\ BTM}{\%TBSA\ of\ treated\ SSG applied\ over\ BTM}\right) x\ 100$$

Same analysis approach as BTM 'take' rate will be conducted for SSG 'take' rate.

7.2. Secondary/Exploratory Efficacy Endpoint

7.2.1. Clinical assessment of wound closure at BTM-treated wound site

Assessments of wound closure such as wound closure percentage, wound closure status, dressing requirement or any other aspects of clinical interest will be presented primarily at each visit using wound level listing. A descriptive table will be provided for wound closure percentage by visit. Another table will report count and percentages of wound closure status (yes or no) by visits. The count and percentages for the wounds which were assessed as 'closed' (yes) at least once will be presented in the same table as well.

7.2.2. Operator ease-of-use as determined by the physician survey

Listing of physician survey scores will be provided with individual score and total score for the four questions.

7.2.3. Joint Contracture Severity and Degree of Motion

Assessments on joint contracture such as joint contracture severity, degree of motion, range of motion test and the cause of the contracture will be presented primarily at each visit using joint level listing. Shift table from baseline to the worst post baseline and from baseline to '7-10 days post SSG time point' in terms of joint contracture severity will also be given at joint level.

7.2.4. Modified Vancouver Scar Scale

Assessments of Modified Vancouver Scar Scale (mVSS) such as pigmentation, vascularity, pliability, height and the corresponding individual and total scores will be presented primarily at each visit using wound level listing. Summary table will be provided for individual and total score respectively by body region and visit using descriptive statistics. Additional descriptive summary table will be provided for individual and total score respectively by visit regardless of body region and subject.

7.2.5. Pruritus assessed by numerical rating scale and disability

Assessments of pruritus such as duration (hours per day), Numerical Rating Scale (NRS) score and disability will be presented primarily at each visit using wound level listings. A table will be provided for summary statistics of NRS score by visit at wound level. Additional descriptive summary table will be provided for NRS score by visit regardless of body region and subject. Another table will report count and percentages of disability by visits at wound level as well.

7.2.6. Surgeon's assessment of BTM application

Surgeon's assessment of BTM application such as BTM is easy to use, BTM is easy to apply, BTM is easy to delaminate, BTM is a product I would use for burn patients and total scores will be presented primarily at each visit using wound level listings. The result of surgeon's assessment of BTM application will be summarized by site regardless of wound level and subject.

8. Safety Analysis

Specific assessments to evaluate treatment device safety include the following: the frequency and type of adverse events, clinically significant laboratory abnormality, and vital signs. All analyses of safety will be conducted using the ITT population.

8.1. Adverse Events

An AE can be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of an investigational product, whether or not considered related to the product. All AEs encountered during the study will be reported in detail in the CRF, starting at the time of the first screening/eligibility assessment and ending at the end of the study for each subject. Pre-existing conditions that worsen during a study are to be reported as AEs. Clinically significant changes in physical examination, standard of care laboratory safety tests, and vital signs will also be defined as AEs and recorded appropriately. All AEs will be coded using the MedDRA Dictionary (MedDRA, Version 18.1 or higher).

A study-specific subset of AE events called Unanticipated Adverse Device Effect (UADE) will be introduced to the safety analysis of this study. UADE is defined as “any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death, was not previously identified in a nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects” (21 CFR 812.3). The UADE will be identified by the Principal Investigator (PI) on site and reported in the CRFs.

Imputation for missing AE onset dates can be found in Appendix 13.3.

An overview summary of the number and percentage of subjects with any AE, SAE, AE related to study device, AE leading to early termination, and AE leading to death will be provided with ITT population. A repeated analysis will be conducted for the subset of UADEs.

8.1.1. Incidence of Adverse Events

Summaries of the total number of AEs and the number and percentage of subjects with at least one AE will be provided for the ITT population by system organ class (SOC) and preferred term (PT). At each level of subject summarization, a subject is counted once if the subject reported more than one event. A repeated analysis will be conducted for the subset of UADEs.

All AEs will be presented in a listing for the screening population.

8.1.2. Relationship of Adverse Events to Study Device

The investigator will provide an assessment of the relationship of the event to the study device. The possible relationships defined in the protocol are “Not Related” and “Related”. The “Related” category will be further classified into possible, probable, and definite. The “Not related” category will be further classified into unlikely and not related.

The AEs categorized by SOC and PT will be summarized by relationship to study device in a manner similar to that described in Section 9.1.1 for the ITT population.

AEs that are missing a relationship will be presented in the summary table as "Related" but will be presented in the data listing with a missing relationship.

A repeated analysis will be conducted for the subset of UADEs.

8.1.3. Intensity Grade of Adverse Event

The NCI CTCAE (version 4.03 or higher) will be used for grading AEs.

The AEs categorized by SOC and PT will be summarized by intensity grade in a manner similar to that described in Section 9.1.1.

In the intensity grade table, if a subject reported multiple occurrences of the same SOC or PT, only the highest intensity grade will be counted. Missing intensity grade will be imputed as 'Grade 3' in tables but will be presented in the data listing with a missing severity.

A repeated analysis will be conducted for the subset of UADEs.

8.1.4. Serious Adverse Events

The seriousness of an AE should be assessed by the PI at site or PolyNovo (Sponsor) from the severity of the AE.

The SAEs will be categorized and presented by SOC and PT with overall population in a manner similar to that described in Section 9.1.1.

All SAEs will be presented in a listing as well.

A repeated analysis will be conducted for the subset of SAE UADEs.

8.1.5. Adverse Events Leading to Early Termination

It will be left to the Investigator's clinical judgment to decide whether or not an AE is of sufficient severity to require the participant's removal from treatment, prior to Day 7 after BTM implantation.

All AEs including UADEs leading subject to study discontinuation will be presented in a listing.

8.1.6. Death

All subjects who have an AE with an outcome of death will be presented in a listing.

8.2. The incidence and severity of infections at BTM-treated wound site

Assessments of the infections, such as severity, pattern, type or any other aspects of clinical interest will be presented primarily at each visit using wound level listing. The summary of infection incidents by visit and severity will be presented in a table. The number of wounds at each severity category including 'having no infection' will also be summarized by visit. Wounds with multiple infections will be counted once at the severity category determined by the highest level infection the wound has. For each subject, the ratio of the number of infected wounds to the total number of wounds will be calculated and a table summarizing those subject's ratios using descriptive statistics will also be provided. Shift table from baseline to the worst post

baseline and from baseline to '7-10 days post SSG time point' in terms of severity will also be given at wound level respectively.

8.3. Clinical Laboratory Evaluations

There is no specific laboratory investigation for this traditional feasibility trial. All clinical laboratory evaluations will be managed by the site as per standard of care.

8.4. Vital Sign Measurements

Summary tables presenting observed values and changes from baseline will be provided overall for vital sign data, including systolic blood pressure (mmHg), diastolic blood pressure in mmHg, Heart rate in bpm, Respiratory rate in bpm, temperature in °C. A by visit summary table for vital sign using descriptive summary statistics will be provided. All vital sign data will be presented in a listing by subject and visit.

8.5. Physical Examination

The number and percentage of subjects with each physical examination outcome will be summarized overall by body system, and visit.

For all the visits, the physical examination includes the following body systems: skin, head, eyes, ears, nose, throat, neck (to include lymph nodes), back, chest, lungs, heart, abdomen, gastrointestinal tract, legs, musculoskeletal system, neurologic, and vascular system. Height and weight will be recorded only at Visit 1 (-7 to Day 0) for TBSA calculation. Weight will be recorded at follow-up visits and early termination.

Physical examination results for all subjects will be presented in a listing.

8.6. Electrocardiogram

No ECG data collection is planned for the study.

8.7. Female Reproductive Status and Pregnancy Test Results

In women of childbearing potential, a urine sample will be collected to test for β-hCG, to exclude pregnancy. The pregnancy test will be done on Day 0 (Visit 2) prior to device implantation and results must be available prior to administration of investigational device. Urine pregnancy test will also be performed 1, 3, 6, and 12 month Post SSG visits. The urine pregnancy test results will be presented in a listing.

9. Interim Analysis

No interim analysis is planned.

10. Data Safety Monitoring

Study oversight will be under the direction of a data safety monitoring board (DSMB). The DSMB's closed sessions will be composed of two independent clinicians (with training in critical care burn

surgery) and an independent biostatistician. For open sessions, the DSMB will also include the trial PI, trial Medical Monitor and PolyNovo representative(s).

The DSMB will meet at specific time points to assess safety and efficacy data. They will review the safety data that may include: summary statistics, AE listings, vital sign data, local infection rate and response to treatment. Formal meetings of the DSMB will be conducted after 2 subjects complete the 7 to 10 days post SSG time point (calculated as the time of BTM application until 7 to 10 days after SSG application). The DSMB will meet again and all subjects will be reviewed after the 10^{th} subject passes the 7 to 10 days post SSG time point (calculated as the time of BTM application until 7 to 10 days after SSG application) and after the 10^{th} subject passes the 3 month post SSG follow-up visit.

Documentation of the patient data reviewed at each meeting, including the individual DSMB member's confirmation of their data review and the findings and actions of the DSMB, will be included in the Trial Master File. The DSMB findings that impact the safety of patients in this study will be immediately reported to the local Institutional Review Boards (IRBs). The results of the 3^{rd} DSMB meeting will be complied in a formal report that will be provided to the FDA.

A DSMB Charter outlining the DSMB composition and responsibilities will be in place prior to the first scheduled meeting.

11. References

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12. Appendices

12.1.SCHEDULE OF ASSESSMENTS AND PROCEDURES

Assessment/ Procedure	Screening	Baseline	BTM 'Take'	SSG	SSG 'Take'	Follow-up Visits			Unscheduled/ Early Termination Visit
	Visit 1	Visit 2	Visit 3 Every 3 – 5 days until SSG	Visit 4 ~1 – 2 m[a]	Visit 5 7 - 10 days post SSG	Visit 6/7 ~1 & 2m post SSG[b]	Visit 8/11/17 ~3 m, 6m, 12m post SSG	Visit 9/10/12-16 ~4 - 11m post SSG[c]	
	Day -7 to Day 0	Day 0	~Day 3 – Day 56	Month 1 – Month 2	Month 1 – Month 2	Month 2 – Month 4	Month 4 – Month 14	Month 5 - Month14	
Informed consent	X								
Medical History & Demographics	X								
Fitzpatrick Skin Typing Test	Once between Screening and the 1 Month post SSG follow up (Visit 6)								
Inclusion/exclusion criteria assessment	X	X							
Physical exam and vital signs	X	X	X	X	X	X	X		X

Assessment/ Procedure	Screening	Baseline	BTM 'Take'	SSG	SSG 'Take'	Follow-up Visits			Unscheduled/ Early Termination Visit
	Visit 1	Visit 2	Visit 3 Every 3 – 5 days until SSG	Visit 4 ~1 – 2 m[a]	Visit 5 7 - 10 days post SSG	Visit 6/7 ~1 & 2m post SSG[b]	Visit 8/11/17 ~3 m, 6m, 12m post SSG	Visit 9/10/12-16 ~4 - 11m post SSG[c]	
	Day -7 to Day 0	Day 0	~Day 3 – Day 56	Month 1 – Month 2	Month 1 – Month 2	Month 2 – Month 4	Month 4 – Month 14	Month 5 - Month14	
Assessment of Concomitant Medications/Therapies	X	X	X	X	X	X	X	X	X
β-hCG pregnancy test (urine)		X					X		X
Assessment of infection [d]	X	X	X	X	X	X	X		X
Anesthesia, burn excision, hemostasis, BTM app		X							
BTM 'take' rate				X					
BTM integration assessment			X						

Assessment/ Procedure	Screening	Baseline	BTM 'Take'	SSG	SSG 'Take'	Follow-up Visits			Unscheduled/ Early Termination Visit
	Visit 1	Visit 2	Visit 3 Every 3 – 5 days until SSG	Visit 4 ~1 – 2 m[a]	Visit 5 7 - 10 days post SSG	Visit 6/7 ~1 & 2m post SSG[b]	Visit 8/11/17 ~3 m, 6m, 12m post SSG	Visit 9/10/12-16 ~4 - 11m post SSG[c]	
	Day -7 to Day 0	Day 0	~Day 3 – Day 56	Month 1 – Month 2	Month 1 – Month 2	Month 2 – Month 4	Month 4 – Month 14	Month 5 - Month14	
Delamination and grafting				X					
SSG 'take'					X				
Joint Contracture Severity Scale and (ROM)		X				X	X		X
Wound Closure						X	X		X
Pruritus Scale (NRS)					X	X	X		X
Photographs		X		X	X	X	X		X
mVSS						X	X		X
Assessment of AEs	X	X	X	X	X	X	X	X	X
Physician's survey				X					

AE = adverse event; ~ = approximately; BTM = biodegradable temporizing matrix; β-hCG = human chorionic gonadotropin; m = months; Numerical Rating Scale (NRS), mVSS modified Vancouver Scar Scale; ROM = range of motion; SSG = split-skin graft; wk = weeks

The visit windows are intended as a guide to the investigators standard of care.

[a] Note that in cases of multiple BTM implantations subjects will continued to be reviewed every 3-5 days until final SSG

[b] Note that post SSG follow-up visits will occur once the final SSG has been applied

[c] Follow-up performed via telephone (not in-person visits).

[d] Assessment of infection includes clinical diagnosis supported by confirmatory laboratory findings.

12.2.SCALES

All detailed procedures for each scale will be included in the **Site Manual of Operations**.

Pruritus:

Numerical Rating Scale (NRS):

0	1	2	3	4	5	6	7	8	9	10
No Itch										Worst Imaginable Itch

Range of Motion (ROM):

ROM measurement (measured with goniometer for each affected joint)

Joint Contracture Severity Scale

1=mild
2=moderate
3=severe

Modified Vancouver Scar Scale (mVSS):

Measured for each lesion

Pigmentation:

0 – Normal color (resembles nearby skin)
1 – Hypopigmentation
2 – Hyperpigmentation
3 – Combination/Mixed

Vascularity:

0 – Normal

1 – Pink (slightly increased in local blood supply)

2 – Red (significant increase in the local blood supply)

3 – Purple (excessive local blood supply)

Pliability

0 – Normal

1 – Supple (flexible with minimal resistance)

2 – Yielding (giving way to pressure)

3 – Firm (solid/inflexible, not easily moved, resistant to manual pressure)

4 – Banding (rope-like, blanches with extension of scar, does not limit range of motion)

5 – Contracture (permanent shortening of scar producing deformity or distortion, limits range of motion)

Height (mm) of burn lesion

0 – Normal (flat)
1 - <2
2 - >2 and <5
3 - ≥5

Total Score: _____

Surgeon's Assessment of BTM Application:

BTM is easy to use:

1 – Strongly Agree
2 – Agree
3 – Neutral
4 – Disagree
5 – Strongly Disagree

BTM is easy to apply:

1 – Strongly Agree
2 – Agree
3 – Neutral
4 – Disagree

5 – Strongly Disagree

BTM is easy to delaminate:

1 – Strongly Agree
2 – Agree
3 – Neutral
4 – Disagree
5 – Strongly Disagree

BTM is a product I would use for burn patients:

1 – Strongly Agree
2 – Agree
3 – Neutral
4 – Disagree
5 – Strongly Disagree

12.3. Missing AE onset dates imputation

For the purpose of inclusion in AE tables, incomplete AE onset dates will be imputed as follows:

Missing day only:

- If the month and year are the same as the BTM implantation month and year, then the date of the BTM implantation will be assigned to the missing day.
- If the month and year are before the month and year of the BTM implantation, then the last day of the month will be assigned to the missing day.
- If the month and year are after the month and year of the BTM implantation, then the first day of the month will be assigned to the missing day.

Missing day and month or missing month only:

- If the year is the same as the BTM implantation, and the end date (after any imputation) is prior to the BTM implantation, then the date of the BTM implantation will be assigned to the missing fields.
- If the year is before the year of BTM implantation, then December 31 will be assigned to the missing fields.
- If the year is after the year of BTM implantation, then January 1 will be assigned to the missing fields.

If year is missing, onset date will not be imputed. If the end date is non-missing and the imputed onset date is after the end date, the onset date will be imputed by the end date.

For the purpose of inclusion in prior and concomitant medication tables, incomplete medication stop dates will be imputed as follows:

- If only the day is missing, then 15th will be assigned to the missing day.
- If only the month is missing, then June will be assigned to the missing month.
- If both day and month are missing, then June 15th will be assigned to the missing month and day.
- If year is missing, stop date will not be imputed.

If the imputed medication stop date is before the medication start date, the stop date will be imputed by the end date.