Cover Page for Protocol

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Title

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

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CP-002

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STATEMENT OF COMPLIANCE

The clinical investigation shall be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki, in compliance with International Conference on Harmonization Good Clinical Practices (ICH-GCP), the International Organization for Standardization (ISO) 14155 International Standard and any regional or national regulations, as appropriate.

All additional requirements imposed by the Institutional Review Boards (IRBs) or US Food and Drug Administration (FDA) will be followed. Any subsequent instruction from either authority will be followed. PolyNovo has indemnity insurance to cover the trial.

The responsibilities of the Clinical Investigator are set forth in the Declaration of Helsinki, ISO 14155-1 and ISO 14155-2, and 21 Code of Federal Regulations (CFR), Part 812, dealing with the investigational device exemptions. The Investigator must also comply with the requirements dealing with informed consent and protection of human subjects including those set out in 32 CFR 219, 10 U.S.C. 980, and, as applicable, 21 CFR Parts 11, 50, 54, 56, 312, 45 CFR Part 46 (Federalwide Welfare Assurance). For trial extensions involving United States Territories, the ICH [E6; 62 Federal Register 25691 (1997)] as well as other applicable federal and state regulations will also apply.

SIGNATURE PAGE

The signature below constitutes the approval of this protocol and the attachments, and provides the necessary assurances that this trial will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality, and according to local legal and regulatory requirements and applicable US federal regulations and ICH guidelines.

Site Investigator:

Signed: _____ Date: _____

Name

Title

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List of Abbreviations

ADL	Activities of Daily Living
AE	Adverse Event/Adverse Effect
BTM	Biodegradable Temporizing Matrix
CFR	Code of Federal Regulations
CRF	Case Report Form
DSMB	Data Safety Monitoring Board
CRO	Contract Research Organization
CTCAE	Common Terminology Criteria for Adverse Events
eCRF	Electronic Case Report Form
FDA	Food and Drug Administration
GCP	Good Clinical Practice
hCG	Human Chorionic Gonadotropin
IB	Investigator's Brochure
ICF	Informed Consent Form
ICMJE	International Committee of Medical Journal Editors
ICH	International Conference on Harmonization
ID	Investigational Device
IDE	Investigational Device Exemption
IRB	Institutional Review Board
MedDRA®	Medical Dictionary for Regulatory Activities
N	Number (typically refers to subjects)
NRS	Numerical Rating Scale
OHRP	Office for Human Research Protections
PHI	Protected Health Information
PI	Principal Investigator
PT	Preferred Term

QA	Quality Assurance
QC	Quality Control
ROM	Range of Motion
SAE	Serious Adverse Event/Serious Adverse Effect
SMC	Safety Monitoring Committee
SOC	System Organ Class
SOP	Standard Operating Procedure
SSG	Split Skin Graft
TAKE	BTM viability or SSG viability and acceptance
TGA	Therapeutic Goods Administration (Australia)
TBSA	Total Body Surface Area
UADE	Unanticipated Adverse Device Effect
UAE	Unanticipated Adverse Effect
mVSS	Modified Vancouver Scar Scale

PROTOCOL SYNOPSIS

Study Title	A Traditional Feasibility Study to Assess the Safety and Effectiveness of the Biodegradable Temporizing Matrix (BTM) in the Treatment of Deep Burn Skin Injuries.
Protocol Number	CP-002
Study Population	Up to 15 subjects, male and female adults (≥18 years and ≤70 years) who have sustained deep dermal/full-thickness burn injuries between 10% and 70% of Total Body Surface Area (TBSA), will be enrolled to ensure 10 subjects are available for evaluation at the 3-month post Split-Skin Graft assessment.
Study Sites	Up to 6 US sites may participate in the study.
Study Duration	Approximately 20 months (includes 3 months startup and 3 months enrollment)
Estimated Time to Complete Enrollment	6 months
Subject Participation Duration	Subjects will be on study for approximately 14 months **Screening:** approximately 1-2 days **Treatment:** approximately 2 months (from admission to hospital through to the end of graft 'take' (remains viable)) **Follow-up:** 12 months
Description of Device	The Biodegradable Temporizing Matrix (BTM) comprises a completely synthetic, sterile, integrating dermal component (porous biodegradable polyurethane foam) and a temporary epidermal barrier component (a non-biodegradable polyurethane sealing membrane). These layers are adhered with a biodegradable polyurethane bonding layer.

Description of Study Design	This is a multi-center, single arm, traditional feasibility study to allow a preliminary assessment of the safety and effectiveness of BTM treatment. Patients with 10-70% TBSA of sustained burns will have BTM devices implanted in areas with deep partial or full thickness burns. At least 5% and a maximum of 50% TBSA of the sustained burns will be treated.
Study Objectives	The Primary objectives of this clinical trial are: • 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 graft (taken) at day 7 - 10 post-SSG, divided by the %TBSA of SSG applied, then multiplied by 100 to express as a percentage*).* The secondary objectives of this clinical trial are: • To assess the incidence and severity of infections in BTM-treated burn wounds. • To assess % 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), and c) scar appearance/quality using the modified Vancouver Scar Scale (mVSS) (Appendix 2).

	• To assess the incidence and severity of pruritus as assessed by Numerical Rating Scale (NRS) (Appendix 2).
Study Endpoints	**Primary Endpoints:** • 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 SSG applied at 7 -10 days after application of the SSG. **Secondary 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 2). • Joint contracture at 1, 2, 3, 6 and 12 months after SSG compared with baseline. This will be assessed by Joint Contracture Severity Scale and Range of Motion (ROM) of joints (Appendix 2). • Scar appearance/quality in BTM -treated wounds as assessed using the Modified Vancouver Scar Scale (mVSS) (Appendix 2) at 2, 3, 6 and 12 months after SSG.

	• Pruritus incidence and severity as assessed by NRS at SSG 'take' and at 1, 2, 3, 6 and 12 months after SSG (Appendix 2).
Safety Assessments	Safety will be assessed throughout the clinical trial. • Physical examinations will be performed at every visit. • Infection assessments will be performed at every visit. • Vital signs will be recorded at every visit. • Adverse events and concomitant medications will be recorded throughout the clinical trial.
Statistical Approach/Rationale for Number of Subjects	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. Unanticipated Adverse Device Effects (UADEs), Adverse Events (AEs) and Serious Adverse Events (SAEs) will be tabulated and summarized by System Organ Class (SOC), preferred term (PT), severity, and relationship to study device. Sample size was determined to gain initial data, while minimizing risk. No formal statistical sample size calculations have been made.
Data Safety Monitoring Board	Study Oversight will be under the direction of a data safety monitoring board (DSMB). The DSMB will operate under the rules of an approved charter that will be written at the organizational meeting of the DSMB. The DSMB's closed session will include two independent clinicians (with training in critical care burn surgery) and an independent biostatistician. For open sessions, the DSMB will also include the trial Principal Investigator (PI), the trial Medical Monitor and PNV representative(s). The DSMB will meet at

	specific time points to assess safety and efficacy and the data may include: summary statistics, AE listings, vital sign data, local infection rate and response to treatment. Additionally, they will evaluate the validity of the endpoints and the ability of the investigators to successfully implant the BTM. Formal meetings of the DSMB will be conducted after 2 subjects complete the 7 - 10 days post SSG time point (collected from the time of BTM application until 7 - 10 days after SSG application). The DSMB will meet again after all 10 subjects complete the 7 - 10 days post SSG time point and finally after all 10 subjects complete the 3 month post SSG follow-up visit. All three safety and efficacy evaluations will guide the study design of the proposed pivotal trial.

1 BACKGROUND INFORMATION AND SCIENTIFIC RATIONALE

1.1 Background Information

Split-skin grafting has been used to treat deep burns for over 140 years. The benefits of this technique include:

i. Application of 'self' (autologous) material.
ii. An inosculatory capacity for rapid 'take' because its harvest transects thousands of blood vessels supplying the papillary dermis and thus (by diffusion) the epidermis.
iii. New vessel growth (angiogenesis) from the wound bed is stimulated by growth factors (Vascular endothelial growth factor) from these vessels.
iv. It contains some dermal supporting elements, a basement membrane and an intact epidermis, thus signaling after application that the wound is 'closed' and that inflammation can abate.
v. No material cost.

The split skin graft technique, however, has multiple limitations. These have been largely overlooked because of the lack of alternatives. These disadvantages include:

i. In certain populations (the elderly, for example), the dermis is thinner and donor site healing is impaired causing pain with recurrent breakdowns and repeated infections.
ii. The use of the split skin graft does not replace 'like with like'.
iii. Skin grafts are thin (generally between 8 and 14 thousandths of an inch) and, when used to replace deep or full thickness skin loss, cannot confer the same degree of robustness to future mechanical, thermal or chemical insult.
iv. Providing a reduced thickness of elastic dermis does not usually allow complete restitution of the supple envelope that uninjured skin provides to facilitate joint mobility and range.
v. Without underlying dermal support the edge of the excised burn, where skin graft meets normal skin, is often depressed and has an obvious appearance.
vi. Because the skin graft contains dermis, a donor site scar (however good) is always created.

Some of these issues can be remediated or delayed by the use of active "temporizing matrices" that temporarily close the debrided burn wound, integrate and provide 'dermal' structure prior to subsequent (delayed) application of split-skin graft. This strategy has

been applied successfully for many years by animal-sourced collagen templates (such as Integra® Dermal Regeneration Template) and has allowed for the reduction of graft contraction and improvement in functional and cosmetic outcomes after split-skin grafting where burn debridement has extended deeply into fat, fascia or muscle[10,11]. In particular, a marked cosmetic improvement is observed when widely meshed graft is applied over the integrated matrix (compared to the unsightly, wide 'chicken-skin' appearance otherwise achieved by applying widely meshed graft on fat). Although a split skin graft donor site is still needed to effect permanent closure, this can be acquired serially, buying time for surgeon and subject.

Collagen-based dermal matrices are underused globally, mainly because of their high cost[12] and their biological composition and delayed neovascularization may contribute to an increased rate of infection[13, 14]. Synthetic alternatives would be expected to reduce cost and susceptibility to infection.

A successful skin graft replacement strategy for extensive wound healing must thus have 2 component parts: 1) a material capable of performing the 'dermal integration/temporary physiological closure' action for up to 4 weeks, and 2) an autologous skin product that can be applied over the dermis to afford permanent wound closure.

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 characteristics that will further support the design of a proposed subsequent pivotal, human multi-center trial of BTM when used in the surgical management of significant thermal burn injuries. The pivotal trial data will facilitate application for marketing of the BTM in the United States by the Food and Drug Administration (FDA) via a Pre-Market Approval pathway.

1.2 BTM Previous Studies

1.2.1 Summary of nonclinical studies

An extensive laboratory, in vitro cell culture and in vivo animal research program has preceded this trial. The results of these studies have been published in peer-reviewed journals and presented at several international scientific conferences[1,2,3]. In addition, biocompatibility studies have been conducted in accordance with ISO 10993 standards.

In vitro studies were performed using prototype versions of the BTM. These studies indicated compatibility of BTM with living cells. A 6-month toxicity study in rats indicated that the test article was well tolerated and there were no findings of toxicity, or abnormal clinical or abnormal histological findings related to the test article.

Additionally, porcine studies demonstrated that the prototype BTM foam integrated rapidly into full-thickness cutaneous porcine wounds, and allowed successful skin grafting over the integrated BTM[4,5,6]. These studies also demonstrated that an unsealed, 2 mm thick foam resulted in unacceptable wound contraction. It was concluded that the foam structure had to be 'sealed' to prevent evaporative water loss and over-deposition of collagen and fibroblast migration. An intermediate version of the BTM was generated with a sealing membrane to limit evaporative loss and resist contraction. A study to compare BTM with Integra® Dermal Regeneration Template, which is a sealed, collagen/glycosaminoglycan dermal matrix, was conducted in pigs[5]. This study demonstrated that identical treatment of the two materials using the same overdressing, resulted in a high rate of infection in the Integra® treated animals (5 of 6) and in no infections (0 of 6) in the BTM-treated animals. Further, after spontaneous loss of the Integra sealing layer, the wounds contracted aggressively. In contrast, the prototype BTM devices did not spontaneously lose their seal or become infected. Further studies were conducted to optimize the sealing membrane and bonding layer[7].

An additional long-term nonclinical toxicology study will be performed concurrently with this traditional feasibility trial as a regulatory requirement.

1.2.2 Summary of clinical trials

A pilot trial of short term, biodegradable polyurethane foam implantation as a topical negative pressure interface to assess tissue reaction to the presence of the 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. Biopsy of the maturing wounds at 6, 9, 12 and 18 months revealed progressive disappearance of the polymer material with infrequent microscopic remnants visible at 12 months on histology and none visible at 18 months. During this study, the investigators noted that the seal was fragile and tore during delamination, making the process of seal removal time-consuming. A new BTM seal and bond were developed to address this issue and assessed in the porcine model described in section 1.2.1. The safety findings in this study indicate a total of 10 device-related adverse events which included blood under BTM seal (n = 3), infection under BTM (n =1), spontaneous delamination due to sub-seal collection (n =1), partial failure of BTM to integrate (16%, 24% and unknown) (n = 3), 80 – 100% spilt skin graft 'take' (n = 2) and seroma (n =1), none of which were classified as serious device related

adverse events

The Australian Therapeutic Goods Administration (TGA) subsequently granted three plastic/burn surgeons approval to use the BTM (with the new seal and bond) as an unapproved device for further long-term evaluation of BTM implantation into free flap donor sites[10]. Twenty-five subjects have subsequently received the BTM device with many of these subjects having greater than 1 year of follow up data available. In these subjects, the BTM seal has been hand fenestrated and this has successfully reduced sub-seal fluid collection. BTM delamination is now rapid, in one piece and with one action. Device attributable adverse events collected from this study include graft failure (partial or full) (n = 4), spontaneous delamination (n = 3) and fluid/blood under seal (n =2).

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 application). This study is being conducted in subjects with deep-dermal or full thickness burn injuries to between 20% and 50% TBSA. Five subjects have completed skin grafting, are being assessed for safety and effectiveness of BTM and will be followed for a year. Three of the 5 subjects have passed the year milestone to date. Results to date have shown BTM-treated areas are soft, pliable and back to normal skin color at the 9-month time point. Since closure of this prospective pilot study, a further 2 subjects with larger TBSA burns have had BTM applied to up to 70% of their TBSA in Australia under a special access scheme. To date, these subjects have tolerated the BTM well with only minor sub-seal hematomas and, occasional, small localized sub-seal fluid collections (clinically infected but not interfering with BTM integration) reported.

Although complete safety data are not yet available from the ongoing prospective pilot study, to date adverse events related to the device in these patients include fluid/blood under the seal (n = 9), infection at the BTM site (n = 1), mild delamination (n =1), BTM integration failure (n = 5), failure of a portion of split skin graft to ‘take’ < 1% TBSA (n =4), split skin graft breakdown (n =2)) and joint contracture (n =3). Histological wound healing associated with BTM implantation, has demonstrated a temporal and progressive dissolution of the foam supporting the expected outcome of complete degradation over time.

An additional clinical trial is also currently 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. This is a 12-month study being performed across Australia and France for the purpose of CE Marking and will include 30 patients (aged 18 – 70 years) across multiple sites. Sixteen patients have been enrolled into this study as of 6 April 2017.

1.3 Rationale

The BTM 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 autograft and facilitating survival of that graft to definitively close the wound. Its route of administration is thus implantation and fixation into an open, debrided wound bed. BTM will be applied to temporarily close debrided deep wounds of between 10 and 70% of the TBSA. Given an average TBSA of 1.71m^2, between 2 and 11 BTM (20 cm x 40 cm) are needed in order to cover 5 - 50% TBSA.

1.4 Potential Risks and Benefits

1.4.1 Potential Risks

Two residual risks were identified as part of the risk assessment and have been subsequently addressed with risk mitigations integrated into the Schedule of Assessments and Procedures (Appendix 1). One potential risk is unplanned seal/membrane removal; human data shows that the seal can stay for up to 43 days if required[10]. The second potential risk is that the skin graft may not 'take' due to infection, hematoma, or excessive shear. Clinical results 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. Experience with BTM to date suggests that infection can be treated either topically or systemically often without requiring the removal of the device. It is anticipated that this may be an advantage that BTM has over existing matrices.

Risk mitigations include:

- A pre-specified plan for periodic subject outcome assessments and reporting prior to enrollment of additional subjects (e.g. the plan will be reviewed by a DSMB)
- Follow-up assessments at regular intervals to monitor subject safety and device effectiveness
- Timely reporting of serious adverse events
- Timely reporting of device performance parameters, which help determine whether the device functions as intended (e.g. measurements of deliverability, stability, handling, visualization, patency, integrity)

- Principal Investigators at the clinical trial sites can receive input (verbal, written, photographs etc.) from experienced burn surgeons regarding BTM if AEs occur

1.4.2 Contraindications

BTM is contraindicated in subjects with a known hypersensitivity to polyurethanes.

1.4.3 Precautions

Solution containing sodium hypochlorite (Dakin's solution) should not come in contact with BTM.

1.4.4 Precautions for use of BTM According to Anatomical Site

1.4.4.1 Palms of hands and soles of feet

No BTM to date has been used to primarily temporize and reconstruct glabrous skin. Due to the uniquely specialized structure and function of the palmar and plantar skin, replacement with skin grafts may lead to a poorer functional and cosmetic outcome. However, these areas have a high capacity for epithelialization under conservative management without the need for tangential debridement, even with surrounding deep burns. An initial conservative approach following appropriate initial antiseptic scrub cleaning and observation over 2 weeks allows areas refractory to conservative management to declare. At this time, BTM use in the glabrous skin is cautioned.

1.4.4.2 Dorsum of hands

Whilst affording effective temporization of the debrided burn wound, application of BTM on the dorsum of hands and fingers delays early mobilization of the fingers in order to allow the BTM to adhere. The thickness of the integrated BTM in its current form may also reduce the elasticity of the reconstructed skin. These properties may reduce resultant active and passive range of motion of the fingers, which can eventually be improved in the compliant and motivated patient, however primary split skin grafting to these areas would enable earlier return to motion exercises. At this time, BTM use in the dorsum of the hands is cautioned.

1.4.4.3 Dorsum of feet

The experience to date in patients with burns to the dorsum of the feet (2 feet, one patient, 6 months follow up) is that BTM facilitates effective temporization and robust cover over the extensor tendons (paratenon preserved) with good functional outcome to date.

1.4.4.4 Face

No BTM to date has been use to primarily temporize and reconstruct the face. Like the glabrous skin, limited areas of deeper burns can epithelialize effectively with conservative measures (soft paraffin application) due to the high vascularity and presence of skin appendages (glands, hair follicles). There may be a role for secondary scar revision or contracture release with BTM, however, like the dorsum of the hands, the current 2 mm thick iteration may be too thick to offer optimal results and its potential effect on the position of sensitively functional structures such as the eyelids and the oral margin is unknown and may be detrimental (causing ectropion, poor oral mobility/competence etc). At this time, BTM use in the face is cautioned.

1.4.4.5 The Neck

To date, one patient has received BTM in the neck for early secondary contracture release in burns. The initial results are encouraging but medium to long term results are unknown. The use of BTM in the neck for primary burns reconstruction is therefore cautioned.

1.4.4.6 Perineum

To date, the BTM has been applied successfully to the buttocks and the thighs. It has not been applied to the perineum or the genital area, therefore the results are not known. The use of BTM in the perineum is therefore cautioned.

1.4.5 Potential Benefits

For moderate to large burn injuries in subjects, 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 sufferers is important in assisting 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], however their composition (collagen/other biological materials) may increase the risk of infection. Given the potential for increased susceptibility to infection and the high cost of existing matrix products, their use is typically restricted to burns >50% of TBSA. The benefits of BTM may include improvements in skin function and cosmesis, and with a much more cost-effective material and strategy than standard dermal matrices.

1.4.6 Warnings

The following complications are possible with the use of BTM. If any of the following conditions occur, the device should be removed: chronic inflammation, allergic reaction, excessive redness, pain or swelling.

BTM should only be applied onto surgically debrided wounds where underlying pathology capable of potentiating the wound has been addressed (e.g. meticulous blood sugar control in diabetic ulceration, compression hosiery/dressings in venous ulceration to combat sustained venous hypertension, etc.). BTM should be applied onto wounds only after effective haemostasis has been afforded.

2 OBJECTIVES

2.1 Study Objectives

The purpose of the trial is to evaluate the safety and effectiveness of the ability of the BTM class III medical device to satisfactorily fulfill the trial endpoints and thus evaluate the appropriateness and applicability of those endpoints for the subsequent pivotal trial. Within the confines of the trial, biodegradable polyurethane will become incorporated into the subjects' wounds to form a neo-dermis. Specifically, temporization of the wound (prevention of contraction and infection), integration and ability to sustain split skin graft 'take' will be evaluated.

Primary Objectives:

The primary objectives of this clinical trial are:

- To obtain preliminary data on the clinical safety and effectiveness of BTM.
- 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 graft (taken) at day 7 - 10 post-SSG, divided by the %TBSA of SSG applied, then multiplied by 100 to express as a percentage*)*.

Secondary Objectives:

The secondary objectives of this clinical trial are:

- To assess the incidence and severity of infections in BTM-treated burn wounds.
- To assess % 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 reflect the impact of the device performance.
- To assess the quality of wound healing in subjects treated with BTM, using Joint Contracture Severity Scale, measurements of the Range of Motion (ROM), and scar appearance/quality scales using the modified Vancouver Scar Scale (mVSS) (Appendix 2).

- To assess the incidence and severity of pruritus as assessed by Numerical Rating Scale (NRS) (Appendix 2).

2.2 Study Outcomes Measures

Primary Endpoints:

- Incidence and type of adverse events occurring after BTM implantation. This will also be reviewed by a Data Safety Monitoring Board (DSMB).

- 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.

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

Secondary/Exploratory Endpoints:

- Incidence and severity of infections at the wound site, 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 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 2).

- Scar appearance/quality in BTM -treated wounds as assessed by Modified Vancouver Scar Scale (mVSS) (Appendix 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.

3 STUDY DESIGN

3.1 Study Population

The study population includes severely ill subjects who have sustained life threatening deep burn injuries and who would usually receive Integra® dermal regeneration template, a similar dermal matrix, xenograft or cadaver allograft, to facilitate functional healing (i.e. those subjects with >10% TBSA full thickness burn injuries). However, beyond the upper end of this range (>70% TBSA full thickness burns), subjects with such injuries experience high subject mortality so that their inclusion in such a trial is not deemed prudent. Instead, this trial aims to recruit a minimum of ten subjects and a maximum of 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.

3.2 Study Design Rationale

The proposed trial is a traditional feasibility trial to assess the appropriateness and applicability of the proposed BTM device outcomes and the measurement of those outcomes for use in a subsequent pivotal trial. Since outcomes for standard of care are defined at each study site, there is no plan to assess those standards of care or their outcomes in this trial design.

3.3 Trial Sites

The intention of this multicenter (up to 6 US sites) trial is to provide data for a feasibility assessment of the BTM medical device.

3.4 Treatment Group(s)

This will be a single-arm study with all feasibility trial subjects receiving BTM. A minimum of ten (10) subjects will be recruited.

3.5 Recruitment Period

Six (6) months

3.6 Duration of Subject Participation

Study participation will last approximately 14 months, divided into an acute care period and a rehabilitation/therapy period.

- **Screening:** approximately 1-2 days (within Day -7 to Day 0)
- **Treatment:** approximately 2 months (from admission to hospital through to the end of graft 'take')
- **Follow-up:** 12 months

3.7 Outcomes

Three primary and seven secondary outcomes have been chosen for this study, with a view to providing both subjective and objective clinical measures/data to demonstrate safety and effectiveness of BTM, as well as, the appropriateness and applicability of both the outcomes and the methods by which they are measured.

3.8 Safety oversight

An independent DSMB will be established to ensure unbiased oversight of the traditional feasibility trial.

4 STUDY ENROLLMENT AND WITHDRAWAL

4.1 Subject Inclusion Criteria

Subjects must fulfill **all** of the following inclusion criteria to be eligible to participate in the study:

1. Provides written informed consent (directly or via legal representative) prior to any clinical trial procedures being performed.
2. Willing to comply with all study procedures and expects to be available for the duration of the study.
3. Male and females ≥ 18 years of age and ≤ 70 years of age.
4. Patients with deep partial or full thickness burns (between 10% and 70% inclusive of their TBSA). The %TBSA will be determined using the rule of nines. For small areas within a particular anatomic region (as defined by the rule of nines), the rule of the palm may be used. Note: The electronic case report form (eCRF) and eCRF completion guidelines detail the localization of each burn region and corresponding wound size with % TBSA.
5. Females, who are non-pregnant (i.e., has a negative urine human chorionic gonadotropin [β-hCG] pregnancy test at Day 0, prior to BTM being applied), non-lactating, or are naturally postmenopausal (i.e., ≥12 months of natural spontaneous amenorrhea), surgically sterile, or who agrees to use effective contraceptive methods throughout the course of the study. Effective contraceptive is defined as:
    - Surgically sterile (bilateral tubal ligation with surgery at least 6 weeks prior to screening, hysterectomy, or bilateral oophorectomy)
    - Intrauterine device (IUD) in place for at least 3 months prior to use of study device
    - Abstinence (not having sexual intercourse)
    - Barrier method (condom or diaphragm) with spermicide for at least 14 days prior to screening and through study completion
    - Stable hormonal contraceptive for at least 3 months prior to study and through study completion

4.2 Subject Exclusion Criteria

Subjects will **not** be included if any one or more of the following conditions exists:

1. Has a known hypersensitivity to polyurethane or silver-containing materials.
2. Multiple traumas (i.e. significant traumatic injury to a solid organ in addition to skin).

3. Presence of a medical condition with a life expectancy of less than 12 months, such as advanced malignancy.
4. Presence of a medical condition that might interfere with treatment evaluation; or require a change in therapy including but not limited to, significant immune deficiency, or skin or vascular diseases in the area of the wound.
5. Has known or suspected pregnancy, planned pregnancy, or lactation (for female subjects).
6. Has exposure to any other investigational agent within the last 6 months.
7. Has clinically significant psychiatric illness (as determined by the Investigator).
8. Has a condition the Investigator believes would interfere with the ability to comply with study instructions, or that might confound the interpretation of the study results or put the subject at undue risk.

4.3 Strategies for Recruitment and Retention

Subjects will be recruited into the clinical trial through the Investigator's burn unit. Subjects may be compensated for their participation as described in the Informed Consent Form (ICF). Once discharged from the burn unit, subjects will be contacted as part of the standard of care (monthly at a minimum) by the investigational site staff to remind them of follow-up visits and ensuring trial compliance.

If the recruitment rate is found to be insufficient, additional sites may be added to increase the rate.

4.4 Enrollment

After burn size, depth assessment and formulation of the immediate surgical plan, the subject/or legal representative will be informed about the trial. After provision of, and the opportunity of the subject/legal representative to read, and understand, a study information sheet, and after the subject/legal representative has been allowed to ask any questions of the Investigator, signed consent, [photographic and standard institutional surgical consent as applicable] will be obtained following reiteration of the trial details. The subject will then be screened for inclusion/exclusion criteria. If all criteria are met, the subject will be enrolled into the trial.

4.5 Subject Withdrawal

Subjects may withdraw voluntarily from the trial at any time without penalty or impact on their treatment or the Investigator or PolyNovo may terminate a subject's participation.

4.5.1 Reasons for Withdrawal

Subjects are free to withdraw from participation in the trial at any time upon request.

An Investigator or PolyNovo may terminate a subject's participation in the trial if:

- Any clinical adverse event (AE), laboratory abnormality, or other medical condition or situation occurs such that continued participation in the trial would not be in the best interest of the subject.
- The subject meets an exclusion criterion (either newly developed or not previously recognized) that precludes further participation.
- Inability or unwillingness to complete the trial or subject noncompliance.
- Adverse event, which is directly attributed to the presence of the implant, where there is no other explanation for the effect.

4.5.2 Handling of Subject Withdrawals or Subject Discontinuation of the Investigational Device

Subjects withdrawn early due to an AE will be followed until medically stable or resolution of the AE.

If withdrawal from the study is requested by the subject, prior to BTM integration (i.e. **before Day 7** post-implantation), the BTM device can be removed and the wound bed closed by the application of an autologous SSG. However, **≥ Day 7** the BTM can be removed, but it is **not recommended**, as integration will likely have occurred to a point such that BTM removal would result in damage to the subject's burn wound. In either case, no data or BTM -related follow-up will be imposed. Physicians are expected to follow subjects according to their institution's standard of care. Investigational Device Exemption (IDE) regulations require investigators to maintain each subject's case history and exposure to the device.

All consented subjects who have been implanted with BTM, even in the event of device failure, will have all lesions followed up as a part of the study until completion or if/when withdrawal from the study is requested by the subject.

If subjects do not complete 3 months follow up **post SSG** implantation for any reason, they will be replaced with further subjects that meet the inclusion/exclusion criteria, to

ensure that the final cohort is (a minimum of) 10 subjects.

In case of withdrawal, the Investigator will promptly inform the Institutional Review Board (IRB) within 5 working days and will provide the reason(s) for the withdrawal. All applicable source documentation will be collected to confirm resolution.

4.6 Premature Termination or Suspension of Trial

This trial may be suspended or prematurely terminated if there is sufficient reasonable cause. Written notification, documenting the reason for trial suspension or termination, will be provided by PolyNovo and agreed upon by the DSMB. If the trial is prematurely terminated or suspended, the Investigator is responsible for promptly informing subjects and the IRB with the reason(s) for the termination or suspension.

Circumstances that may warrant termination include, but are not limited to:

- Determination of unanticipated, significant, or unacceptable risk (e.g. serious adverse device effect) to subjects
- Insufficient adherence to protocol requirements
- Data that are not sufficiently complete and/or evaluable

Halting rules will be included in the DSMB Charter and Statistical Analysis Plan.

5 INVESTIGATIONAL PRODUCT

5.1 Medical Device Description

BTM is a fully synthetic biodegradable dressing that is composed of three layers.

- Dermal component: A 2 mm thick, white, open cell, degradable polyurethane foam (pore sizes of 100-600 µm) with a high degree of porosity (~94%) providing a scaffold for dermal tissue integration
- Epidermal component: A temporary bonding layer designed to adhere the sealing polyurethane film/membrane (65 µm thick) to the dermal foam
- Membrane: A temporary 50 µm thick, transparent, fenestrated, polyurethane sealing membrane designed to physiologically close the wound and limit evaporative water loss

BTM is indicated for primary dermal repair after excision of deep dermal and full thickness thermal burn injury in adults. Usually such definitive epidermal closure is provided by skin autograft. BTM is designed to be implanted into the newly created 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'. After integration, the **combined** bonding layer and sealing membrane is peeled off and discarded, leaving only the implanted foam layer to biodegrade. The timing of the de-lamination is at the discretion of the Investigator based on his/her clinical and surgical judgement. Past clinical experience has placed this de-lamination between Days 21–56, but can be extended beyond 56 days if required. The wound bed is refreshed (e.g. by dermabrasion) and finally closed with a thin SSG.

5.1.1 Supply

All component parts of the BTM are manufactured, assembled packaged and pre-sterilized by PolyNovo Biomaterials Pty Ltd, Port Melbourne, Victoria, Australia. The facility is ISO 13485 compliant and audited to the requirements of 21 CFR Part 820. The investigational device will be supplied to the investigating sites through a product depot vendor.

The proposed device is intended to be supplied in various sizes, including 20 cm × 10 cm, and 20 cm × 40 cm. The devices supplied for this trial will be 20 cm × 40 cm. The dressings are single use, terminally sterilized devices (by gamma-irradiation at 25kGy) that are individually packed in a polymer pouch within an aluminized envelope for

moisture resistance. The packaging is designed to be opened in a surgical setting so as to preserve the sterility of the operating field.

5.1.2 Packaging and Labeling

The BTM device is dry-packed in multilayered, hydration-proof packaging and labeled with details which uniquely identify the product including: date of manufacture; date of expiration; lot number; reference number; and manufacturer information. Labels are affixed to outer foil packaging. The label should be retained for the subject's source records.

5.1.3 Product Storage and Stability

The packaged BTM can be stored vertically or flat on a shelf in a secure location. There are no special storage requirements (e.g. temperature) although perforation of the packaging during storage or transport should be avoided as this will void sterility if penetration of the inner packaging occurs. The shelf life of the device is three (3) years. The device should not be used if the inner packaging has been opened, or obviously tampered with. If the inner packaging is found to be open, report and send the package as found back to PolyNovo.

5.2 Preparation and Administration of Investigational Device

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. It is removed from the outer packaging using sterile technique and opened from one end of the inner packaging to preserve the operating field. Full instructions are available in the Site Manual of Operations. Once opened, the BTM must be used or discarded and cannot be re-stored.

The BTM device is not intended to be used on the hands, face, neck, plantar skin, or perineal area. See Section 1.4.3 for detailed precautions.

Previous clinical use of BTM has demonstrated that integration rate of BTM and primary skin graft 'take' is decreased when BTM is used over bony prominences (such as the olecranon, spine of scapula, calcaneus), as pressure may inhibit integration. Standard pressure area precautions should be taken to ensure successful integration of BTM. In previous clinical use, BTM has been delaminated between Days 21 and 56 after implantation and this range will serve as a guide for this study. The timing of the de-

lamination is at the discretion of the Investigator based on his/her clinical and surgical judgement and could extend beyond 56 days if required.

5.3 Modification of Investigational Device for a Participant

The number of BTM devices required by an individual subject depends on the size of the excised burn wound (between 10 and 70% of the total body surface area). In this traditional feasibility trial, subjects with deep partial or full thickness burns will have BTM devices implanted on at least 5% and a maximum of 50% of their TBSA of the sustained burns to be treated. This maximum is based on clinical experience to date treating burn areas with BTM (1% to 63% TBSA) (unpublished data of ongoing subjects).

5.4 Accountability Procedures for the Investigational Device

PolyNovo's designee, PPD, will distribute, track and account for all investigational devices. Instructions for the investigational device return and/or destruction will be provided in the Site Manual of Operations.

5.5 Assessment of Subject Compliance with Investigational Device

The BTM is directly visualized every three to four days during dressing changes until skin graft 'take'. Inspection of the sealing membrane and of BTM integration is performed during dressing changes for both inpatient and outpatient subjects. The 'take' assessment occurs after the sealing membrane is removed. As subjects with severe burns are typically confined to hospital under supervision, compliance has not been a problem in similar study populations in pilot studies. After skin graft 'take', no compliance issues have occurred to date.

6 STUDY SCHEDULE

6.1 Screening/Enrollment Visit #1 (Day -7 - Day 0)

- Obtain and document informed consent from potential subject/legal representative prior to any study-related procedures being conducted.
- Obtain demographics and review medical history.
- Obtain completion of the Fitzpatrick Skin Typing Test when the subject is able. This is to be completed once from the Screening visit up to and including Visit 6 (1 month post SSG follow-up visit)
- Preliminary review of subject eligibility based on inclusion/exclusion criteria
- Perform full physical examination (and full burn assessment including burn size (%TBSA), depth of burns, and applicable x-rays), record of vital signs, weight and height.
- Review concomitant medications and medication history.
- Assessment of any infection (A clinical diagnosis supported by confirmatory laboratory findings).
- Assessment of adverse events.

6.2 Baseline Visit #2 (Day 0)

- Perform full physical examination (and full burn assessment including burn size (%TBSA), depth of burns and applicable x-rays) with the recording of vital signs.
- Review concomitant medication(s) history.
- Urine pregnancy test (applicable females).
- Assessment of any infection (BTM or non-BTM related) (A clinical diagnosis supported by confirmatory laboratory findings).
- Final review of inclusion/exclusion criteria to determine subject eligibility, prior to application of BTM.
- Under anesthesia, the subject's burn wounds will be excised and debrided. While maintaining hemostasis, the BTM will be applied.

- Assessment of joint contracture severity and ROM of affected joints.
- Assessment of adverse events.
- Photographs of areas where BTM was implanted.

6.3 BTM 'Take' Visit #3 (Every 3 - 5 days from day of BTM application until SSG)

- Perform full physical examination with recording of vital signs results.
- Review concomitant medication(s) history.
- Assessment of any infection (BTM or non-BTM related) (A clinical diagnosis supported by confirmatory laboratory findings).
- Assessment of adverse events.
- Assessment of BTM integration and examination for signs of incomplete spontaneous delamination.

6.4 SSG Visit #4 (1-2 months post BTM)

- Perform full physical examination with recording of vital signs and record results.
- Review concomitant medication(s) history.
- Assessment of any infection (BTM or non-BTM related) (A clinical diagnosis supported by confirmatory laboratory findings).
- Determine BTM integration ('take') rate. This is a visual assessment of the amount of BTM that has integrated ('taken') at the time of SSG, expressed as a percentage of the total amount of BTM applied. Integration is the process where new blood vessels grow into the foam. As it progresses, the foam becomes populated with adipocytes and fibroblast and later blood vessels and blanching or capillary refill may be demonstrated through the seal.
- 'Take' is determined post de-lamination (i.e., following the sealing membrane removal.
- When donor sites are available, the BTM is integrated and it is physiologically optimal for the subject, the BTM device will be delaminated (sealing membrane removed) and a SSG applied which may be meshed (as per surgeon's preference) applied, closed and dressed. Patients can be outpatients prior to skin graft.

Please note: The Investigator will determine when integration is complete. After integration, the **combined** bonding layer and sealing membrane is peeled off and discarded, leaving only the implanted foam layer to biodegrade. The timing of the de-lamination is at the discretion of the Investigator based on his/her clinical and surgical judgement. Past clinical experience has placed this de-lamination between Days 21-56, but can be extended beyond 56 days if required.

- Assessment of adverse events.
- Photographs of areas where BTM was implanted.
- Burn surgeon will complete the Physician's Survey (Appendix 2)

6.5 SSG 'Take' Visit #5 (7 - 10 days post SSG)

- Perform full physical examination with recording of vital signs and record results.
- Review concomitant medication(s) history.
- Assessment of any infection (BTM or non-BTM related) (A clinical diagnosis supported by confirmatory laboratory findings).
- Determination of %Split Skin Graft (SSG) adherence/integration ('take') rate. Calculated as the proportion of the SSG which remains viable ('takes') over area where BTM Burn was applied (post de-lamination or seal removal), expressed as a percentage of the total amount of SSG applied over BTM at 7 -10 days after application of the SSG.
- Assessment of pruritus using the NRS.
- Assessment of adverse events.
- Photographs of areas where BTM was implanted.

6.6 Follow up Visits #6 - 7 (1 - 2 months post SSG)

- Perform full physical examination (and full burn assessment including size (%TBSA) and depth of burns and applicable x-rays) with recording of vital signs, and record results.
- Review concomitant medication(s) history.

- Assessment of any infection (BTM or non-BTM related) (A clinical diagnosis supported by confirmatory laboratory findings).
- Assessment of joint contracture severity and ROM of affected joints
- Assessment of % wound closure.
- Assessment of scar appearance/quality using the mVSS.
- Assessment of pruritus using the NRS.
- Assessment of adverse events.
- Photographs of areas where BTM was implanted.

6.7 Final Follow up Visits

The following assessments will be performed at Visit 8, 11 and 17 (3, 6 and 12 months' post SSG):

- Perform full physical examination with recording of vital signs, weight, and urine pregnancy test (applicable females) and record results.
- Review concomitant medication(s) history.
- Assessment of any infection (BTM or non-BTM related) (A clinical diagnosis supported by confirmatory laboratory findings).
- Assessment of joint contracture severity and ROM of the affected joints.
- Assessment of % wound closure.
- Assessment of scar appearance/quality using the mVSS.
- Assessment of pruritus using the NRS.
- Assessment of adverse events.
- Photographs of areas where BTM was implanted.

A follow-up phone call will be performed at Visit 9 and 10, and Visits 12 to 16 (4, 5 and 7 to 11 months' post SSG) to collect AEs and changes to concomitant medications.

6.8 Early Termination Visit

- Perform full physical examination with recording of vital signs, weight, and urine pregnancy test (applicable females) and record results.
- Review concomitant medication(s) history.
- Assessment of any infection (BTM or non-BTM related) (A clinical diagnosis supported by confirmatory laboratory findings).
- Assessment of joint contracture severity and ROM of the affected joints.
- Assessment of % wound closure.
- Assessment of scar appearance/quality using mVSS.
- Assessment of pruritus using the NRS.
- Assessment of adverse events.
- Photographs of areas where BTM was implanted.

6.9 Unscheduled Visit

Unscheduled visits will only be recorded if the subject has:

a. Missed a scheduled appointment/visit and the Investigator wishes to have a time-point appraisal done in a delayed fashion, or

b. Has developed problems/issues requiring investigation/evaluation.

Assessments include:

- Perform full physical examination with recording of vital signs, weight, and urine pregnancy test (applicable females) and record results.
- Review concomitant medication(s) history.
- Assessment of any infection (BTM or non-BTM related) (A clinical diagnosis supported by confirmatory laboratory findings).
- Assessment of joint contracture severity and ROM of the affected joints.
- Assessment of % wound closure.

- Assessment of scar appearance/quality using mVSS.
- Assessment of pruritus using the NRS.
- Assessment of adverse events.
- Photographs will be taken.

7 STUDY PROCEDURES/EVALUATIONS

7.1 Study Procedures/Evaluations

- Medical history including concomitant and medication history will be collected and recorded. A review of permitted and prohibited medications per Inclusion/Exclusion (I/E) criteria will be performed and demographic data recorded. Demographic data will be collected.
- The Fitzpatrick Skin Typing Test, as detailed in Appendix 2[20], will be collected when the patient is able.
- Full Physical examination to include the following organ 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 will be conducted at all visits. 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.
- A full burn assessment including burn size (%TBSA) by region, depth of burns, % of BTM applied and x-rays (where applicable) will be conducted. **All burn assessments** (*Appendix 2* including: ROM, mVSS, and NRS) **will be conducted per burn wound region/site**. NOTE: The Maximum BTM that may be applied is 50% of the TBSA.
- Vital signs [blood pressure (supine), respiratory rate, pulse, and temperature] will be assessed to ensure subject meets eligibility for trial enrollment and will be conducted at all subsequent visits.
- Clinical Assessment of any infection will be performed using institutional standard of care procedures. Microbiological assessment of infection will only be performed if there is clinical suspicion of infection or if routine surveillance swabs are part of the institutional standard of care for subjects with severe burns.
- 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 SSG procedure. *Patients can be outpatients prior to skin grafting.*
- An assessment of the %BTM ‘take’ rate will be measured by the %TBSA of BTM that has adhered at the time of skin grafting divided by the total %TBSA treated

with the BTM device and multiplied by 100 to express as a percentage (Section 11.3).

- 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 (Section 11.3).
- An assessment of the quality of the wound will be measured using active Range of Motion (ROM) of affected joints when possible and severity of joint contracture (Appendix 2). The details regarding the assessment of the grading for mild, moderate and severe contractions are also included in Appendix 2.
- An assessment of % wound closure for each BTM-treated burn wound.
- Scar appearance/quality will be assessed using the modified Vancouver Scar Scale (mVSS) (Appendix 2).
- Pruritus incidence and severity will be assessed by the Numerical Rating Scale (NRS) (Appendix 2). [The eCRF will also capture duration, NRS scale (intensity), disability, and distribution on the body.]
- Physicians will be surveyed to assess Ease of Use. The eCRF will capture ease of BTM application, delamination, time, and overall impressions.
- Subjects will be called monthly to collect adverse events and changes to medications and any non-trial visits with a physician regarding their burn or burn treatment (specify physician type: general practitioner, physical therapist, other: specify).

7.2 Assessment of Concomitant Medications/Treatments/Therapies

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.

Cessation or continuation of pre-existing anti-platelet or anticoagulation treatment in patients with indwelling vascular stents, atrial fibrillation or prosthetic heart valves, for example, is to be determined by the treating surgical team according to local perioperative guidelines. Likewise, thromboprophylaxis measures, including chemoprophylaxis with low molecular weight heparin, for example, is not restricted by the use of the BTM, and should follow the local guidelines or Surgeon's preference.

Any perioperative event indicating the commencement of a course of anticoagulation or antiplatelet medication is not contraindicated by use of BTM, however, as with any large acute surgical wound, resultant haematoma formation under the BTM should be anticipated as a complication and the surgical team should remain vigilant for this at dressing changes. This may necessitate removal and replacement of the involved section of BTM.

There is no restriction on administration to the subject of additional therapies required to aid wound healing (including, but not limited to, occupational therapy, scar therapy, and physiotherapy) and should be commenced as per local standard of care guidelines.

7.3 Assessment of Adverse Events/Effects

Adverse events and adverse effects will be assessed at each visit.

7.4 Laboratory Evaluations

7.4.1 Clinical Laboratory Evaluations

There are no specific laboratory investigations for this traditional feasibility trial. All clinical laboratory evaluations will be managed by the site according to standard of care, except safety laboratory tests.

Safety Laboratory Tests

In women of childbearing potential, a urine sample will be collected to test for β-HCG to exclude pregnancy. The pregnancy test will be performed 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 at 3, 6 and 12 month Post SSG visits.

Efficacy Laboratory Tests
NA

Burn-specific evaluations at the discretion of the treating Investigator may include:
Hematology: hemoglobin, hematocrit, white blood cells (WBC) with differential count, platelet count.

Biochemistry: creatinine, total bilirubin, alanine aminotransferase (ALT), aspartate aminotransferase (AST).

Urinalysis: dipstick urinalysis, including protein, hemoglobin and glucose; if dipstick result is abnormal, complete microscopic urinalysis is required.

Microbiology: blood cultures, wound swab, discharge/exudate, device or tissue

7.4.2 Special Photographic/Video Procedures

Digital photographs and if attainable, video footage of specific results, will be collected at Visit 2, Visits 4 and 5, Visits 6 to 8, Visit 11, Visit 17, Unscheduled Visit and Early Termination (ET) Visit with a digital camera provided by the Sponsor. Special instructions for the acquisition, timing, file preparation, handling, and storage of digital images will be included in a separate **Manual of Operations**.

At each visit requiring digital photographs, clinical sites are to capture photographs of each burn lesion before and after the BTM device implantation (as applicable), as well as before and after split skin grafting and throughout wound closure. Photography is also part of the study design to capture potential issues with the burn wound(s). De-lamination is only to be photographed (before and after) to document adverse events or other device issues. Investigators are encouraged to take images to support the standard of care and the data capture requirements of the trial.

Please refer to the Manual of Operations for photography specifications.

8 ASSESSMENT OF SAFETY

Subjects will be monitored throughout the clinical trial for adverse events/effects. Subjects will be instructed on the need to inform the Investigator and/or clinical trial staff of any AEs that may occur at any time during the clinical trial.

Adverse events considered related to the investigational device (ID), as judged by a medically qualified Investigator or PolyNovo, will be followed either until resolution or the event is considered medically stable.

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. A participant may also voluntarily withdraw from treatment until Day 7 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.

8.1 Specification of Safety Parameters

The following information will be recorded in the eCRF for all Adverse Events:
description, date/time of onset and end date, severity, assessment of relatedness to the ID, other suspect drug or device, and action taken. Follow-up information should be provided until resolution or as appropriately deemed by the Investigator.

8.1.1 Adverse Events

An adverse event is any untoward or unfavorable medical occurrence in a human subject, including any abnormal sign (for example, abnormal physical exam or laboratory finding), symptom, or disease, temporally associated with the subject's participation in the research, whether or not it is considered related to the subject's participation in the research.

8.1.2 Serious Adverse Events

A serious adverse event (SAE) is one that meets one or more of the following criteria:

- Results in death

- Is life-threatening (places the subject at immediate risk of death from the event as it occurred)
- Results in subject hospitalization or prolongation of existing hospitalization
- Results in a persistent or significant disability or incapacity
- Results in a congenital anomaly or birth defect
- An important medical event that may not result in death, be life threatening, or require hospitalization may be considered an SAE when, based upon appropriate medical judgment, the event may jeopardize the subject and may require medical or surgical IP to prevent one of the outcomes listed in this definition.

8.2 Time Period and Frequency for Event Assessment and Follow-Up

Adverse events, SAEs will be recorded in the data collection system throughout the trial and the subject followed until resolution or they are considered medically stable.

The PI will record all adverse events with start dates occurring any time after informed consent is obtained until 7 days (for AEs) or 30 days (for SAEs) after the last day of trial participation. At each visit, the Investigator will inquire about the occurrence of AE/SAEs since the last visit. Events will be followed for outcome information until resolution or stabilization.

8.3 Characteristics of an Adverse Event

8.3.1 Causal Relationship to Investigational Device

To assess a causal relationship of an event to trial ID, the following guidelines are applicable:

1. Related (Possible, Probable, Definite)
    a. The event is known to occur with the ID.
    b. There is a temporal relationship between the ID and event onset.
    c. The event abates when the ID is discontinued.

d. The event reappears upon a re-challenge with the ID.

2. Not Related (Unlikely, Not Related)

e. There is no temporal relationship between the IP and event onset.

f. An alternative etiology has been established.

8.3.2 Anticipated SAEs

The PPD Medical Monitor in consult with the PI will be responsible for determining whether an SAE is anticipated or not anticipated. A serious adverse event will be considered **not** anticipated if the nature, severity, or frequency of the event is not consistent with the risk information previously described in the IB.

8.3.3 Severity of Event

The Common Terminology Criteria for Adverse Events v4.03 or higher (CTCAE) will be used to assess the causal relationship of AEs to the ID. Grades 1-5 are defined below:

1 Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.

2. Moderate; minimal, local or non-invasive intervention indicated; limiting age-appropriate instrumental activities of daily living (ADL)*.

3. Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL**.

4. Life-threatening consequences; urgent intervention indicated.

5. Death related to AE.

Activities of Daily Living (ADL)
*Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

**Self-care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

8.4 Adverse Event Reporting Procedures

8.4.1 Unanticipated Problem Reporting to IRB and PPD

Incidents or events not described in the Investigators Brochure are considered unanticipated. Investigators should include the following information when reporting an adverse event, or any other incident, experience, or outcome as an unanticipated problem to the IRB:

- appropriate identifying information for the research protocol, such as the title, Investigator's name, and the IRB project number;
- a detailed description of the adverse event, incident, experience, or outcome;
- an explanation of the basis for determining that the adverse event, incident, experience, or outcome represents an unanticipated problem;
- a description of any changes to the protocol or other corrective actions that have been taken or are proposed in response to the unanticipated problem.

To satisfy the requirement for prompt reporting, unanticipated problems will be reported using the following timeline:

- Unanticipated problems that are SAEs will be reported to the PolyNovo within 24 hours and to the IRB within 1 week of the Investigator becoming aware of the event.
- Any other unanticipated problem will be reported to PolyNovo within 1 week and to the IRB within 2 weeks of the Investigator becoming aware of the problem.
- All unanticipated problems should be reported to appropriate institutional officials (as required by an institution's written reporting procedures), the supporting agency head (or designee) within one month of the IRB's receipt of the report of the problem from the Investigator as applicable.
- **Unanticipated adverse device effect** (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).

- An evaluation of a UADE must be conducted immediately and the results of the evaluation reported to the FDA, the IRB, and all participating investigators within 10 working days after the sponsor first receives notice of the effect (21 CFR 812.46(b), 812.150(b)(1)).

All unanticipated problems will be reported to the centralized reporting system:

24 Hour Product Safety Fax Hotline (US): [redacted] or [redacted]

General questions about SAE reporting can be directed to the PPD Safety Hotline (available 8:00AM – 5:00PM Eastern Time):

US: [redacted]

8.4.2 Serious Adverse Event Reporting to PPD

Any AE meeting the Serious Adverse Event criteria specified below:

1. In the view of either the Investigator or PolyNovo, the adverse events results in any of the following outcomes:

    a. Death

    b. A life-threatening adverse event if, in the view of either the Investigator or PolyNovo, its occurrence places the subject or subjects at immediate risk of death. It does not include an adverse event or suspected adverse reaction that, had it occurred in a more severe form, might have caused death

    c. Inpatient hospitalization or prolongation of existing hospitalization

    d. Persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or

    e. A congenital anomaly/birth defect

    f. An important medical event, according to FDA 21 CFR Part 312, Section 32 may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate medical judgement, they may jeopardize the patient or subject

and may require medical or surgical intervention to prevent of the outcomes listed in this definition.

2. Suspected - reasonable possibility that the device caused the adverse event

3. Unanticipated - the event is not described in the Investigator brochure or is not listed at the specificity or severity that has been observed

will be submitted on an AE/SAE form to PolyNovo's centralized safety system via PPD Product Safety/Pharmacovigilance electronic data capture system (includes initials and follow-ups). The investigator is also responsible for submitting any supporting source documentation to the safety fax line below.

SAE Reporting Contact Information:

24 Hour Product Safety Hotline Fax Line (US): [redacted] or [redacted]

General questions about SAE reporting can be directed to the PVG safety hotline: [redacted] (available 24/7)

The Investigator/co-Investigator will complete a Serious Adverse Event Form and submit via electronic data capture within the following timeline:

- All SAEs whether related or unrelated, anticipated or unanticipated will be recorded on the SAE Form and submitted to Product Safety within 24 hours of site awareness.

8.4.3 Reporting of SAEs, AEs and UADEs to FDA

PolyNovo complies with 21 CFR Part 312 and Part 812 for mandatory reporting of safety events to the Food and Drug Administration (FDA).

8.4.4 Reporting of Pregnancy

Any pregnancy and spontaneous miscarriage occurring during the clinical trial and the outcome of the pregnancy should be recorded and followed up for congenital abnormality or birth defect, at which point it would fall within the definition of "serious".

8.4.5 Reporting Device Deficiencies

Immediate notification by telephone will be made to the CEO of PolyNovo of any device deficiency. The defective material will be replaced in its wrapper and kept for transport to PolyNovo for critical analysis. A second material will be utilized for the surgery. If all

materials are found to be defective, the donor site wound will be closed with an autologous split skin graft and the subject will be withdrawn from the trial.

PolyNovo Biomaterials Pty Ltd, 2/320 Lorimer Street, Port Melbourne 3207, Victoria, Australia.

Phone: [redacted]

Phone: [redacted]

Email: [redacted]

9 STUDY OVERSIGHT

9.1 Data Safety Monitoring Board (DSMB)

Study oversight will be under the direction of a data safety monitoring board (DSMB). The DSMB will operate under the rules of an approved charter that will be written at the organizational meeting of the 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, the trial Medical Monitor and PNV 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 - 10 days post SSG time point (collected from the time of BTM application until 7 - 10 days after SSG application). Based on the data and safety reviews, the DSMB will determine whether to authorize enrollment of the remaining subjects.The DSMB will meet again after all 10 subjects complete the 7 - 10 days post SSG time point (from the time of BTM application until 7 - 10 days after SSG application) and after all 10 subjects complete the 3 month post SSG follow-up visit. The DSMB will perform no further reviews during the treatment period unless a serious adverse device-related event occurs. In collaboration with the Investigator, the DSMB will also assess safety of study procedures in the protocol in individual subjects. At this time, each data element that the DSMB needs to assess will be clearly defined. The DSMB will advise PolyNovo of its findings in a written report.

9.2 Medical Monitoring

It is the responsibility of the PI to oversee the safety of the trial. This safety monitoring will include careful assessment and appropriate reporting of adverse events as defined in Section 7, as well as the construction and implementation of a site data and safety-monitoring plan (see Section 13.1, Site Audits and Monitoring). Medical monitoring will include a regular assessment of the number and type of serious adverse events.

10 CLINICAL MONITORING

This trial will be monitored according to an approved Monitoring Plan based on the objectives, purpose, design and complexity of the trial. The Investigator will allocate adequate time for all monitoring visits and between visits to facilitate the requirements of the study and study timelines. The Investigator will also ensure that the monitor or other compliance or quality assurance reviewer is given direct access to all study-related documents and study related facilities (e.g. pharmacy, diagnostic laboratory, etc.), phone, fax and internet and has adequate space to conduct the monitoring visit.

Site monitoring is conducted to ensure that the rights of human subjects are protected, that the trial is implemented in accordance with the protocol and/or other operating procedures, and that the trial uses high quality data collection processes. The monitor will evaluate study processes based on PolyNovo or designee standards, ICH E6 and all applicable, regulatory guidelines.

Clinical monitoring includes the following visit types:

- Pre-Study Qualification - of the Investigator, the investigational site, staff, and facility. Monitors ensure the latest version of the approved protocol for the trial is available for review and discussion, handling of Informed Consent Forms (ICF), processes for AE and SAE reporting and contact information, CRF completion and maintenance, source documentation requirements, and ID accountability requirements.

- Initiation - of the investigational site to formally begin the clinical trial. Monitors review goals, obligations, protocol procedures (with particular attention to inclusion/exclusion criteria, enrollment goals, adverse event definitions, primary efficacy variables and GCP compliance), informed consent procedure, AE/SAE reporting, CRF completion, error correction and the need for adequate source documentation, maintenance of the investigational binder and site visit log, status of ID and requirements for accountability, and any other issue as deemed important to the conduct of the trial.

- Interim - monitors review AE/SAE reporting, CRF completion, error correction and the need for adequate source documentation, maintenance of the investigational binder and site visit log, status of ID and requirements for accountability, and any other issue as deemed important to the conduct of the trial.

- Close-out - monitors conduct a complete review of the Investigator site files to ensure that all necessary CVs are present and current, all applicable versions of the protocol are present and filed appropriately, all applicable versions of the ICF are present, IRB approval letters are present, all SAEs have been reported to PolyNovo and the IRB, documentation of submission of protocol deviations to the IRB and PolyNovo are present, notification and/or final report to the IRB present, a copy of the monitoring log is obtained, a copy of the Delegation of Responsibilities log is obtained, all CRFs have been completed and appropriately filed, ID reconciliation records are completed and appropriately filed, ID shipment and return invoices are present and appropriately filed, maintenance and retention of trial records are discussed, regulatory agency inspection process is discussed.

10.1 Site Monitoring Plan

A comprehensive and stand-alone monitoring plan will be established, which will ensure subject safety is maintained and quality data is obtained. The monitoring plan will emphasize the level of review for all subjects ensuring that human subject protection and trial procedures are of the highest quality and meet the protocol requirements, it will include source documents expected to be reviewed e.g. charts, lab data, photographs. The plan will delineate completion of the electronic case report forms (eCRFs), timely query resolution, definition and classification of a protocol deviation/violation, correct documentation of the study, device accountability, management and issue resolution, site communication and training. The monitoring plan will also define types of visits and frequency of monitoring, whether they are on-site monitoring activities or remote monitoring (e.g. Risk Based Monitoring) and institute strong quality control measures.

11 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 also be presented in subject level listings as source data. In general, no inferential statistics are to be performed due to the small sample size unless specified otherwise in the statistical analysis plan.

11.1 Study Hypotheses

No statistical hypothesis is specified for this study as this is a feasibility study with approximately 10 subjects and there is no between-treatment comparison.

11.2 Safety Review

Adverse events will be coded using the MedDRA Dictionary (December 2015 or later) and severity using Common Terminology Criteria for Adverse events (CTCAE) version 4.03 or higher. The number and percentage of subjects experiencing at least one AE will be presented by System Organ Class (SOC) and Preferred Term (PT). Separate summaries will be provided for all AEs, device related AEs, Serious AEs (SAE), AEs leading to withdrawal and AEs leading to death.

The frequency and severity of infections and recurrence of infections will be tabulated. Clinical evaluation of erythema (redness), edema (swelling) and pain will be presented in a listing for all subjects and visits.

Vital signs (blood pressure (supine), respiratory rate, pulse, height, weight and temperature) will be summarized by visit and presented in a listing.

Physical examination data collected at each visit will be presented in a listing.

11.3 Effectiveness Review

BTM /integration ‘take’ rate is measured at time of skin grafting and is defined in the formula below:

Effectiveness for %BTM ‘take’ rate and %SSG ‘take’ rate will be calculated 7 - 10 days after application of SSG and are defined in the formulas below:

%BTM 'Take' rate =

$$\left(\frac{\%\text{TBSA covered by BTM that has adhered at time of SSG}}{\%\text{TBSA treated with BTM}}\right) \times 100$$

%SSG 'Take' rate =

$$\left(\frac{\%\text{TBSA of viable SSG applied over BTM}}{\%\text{TBSA treated SSG}}\right) \times 100$$

Baseline range of motion (ROM) of joints (evaluated immediately after eschar removal) will be compared with follow-up measurements and will be summarized using n, mean, SD, median, minimum, and maximum by joint and presented in a listing.

Joint Contracture Severity Scale will be summarized using n and percent to summarize by severity category and presented in a listing.

Wound Closure will be summarized using n and percent and presented in a listing.

Modified Vancouver Scar Scale (mVSS) evaluated at 2, 3, 6 and 12 months after SSG will be summarized using number of observations (n) in each category by visit and presented in a listing.

Severity of pruritus as assessed by the Numerical Response Scale (NRS) at SSG 'take' (7 - 10 days after application of SSG) and 1, 2, 3, 6, and 12 months post SSG will be summarized using n, mean, SD, median, minimum, and maximum by visit and presented in a listing.

11.4 Final Analysis Plan

Full details of the planned analyses will be addressed in the statistical analysis plan (SAP), including specified subset of outputs for the DSMB.

In general, no inferential statistics are to be performed due to the small sample size and single arm study design unless specified otherwise in the statistical analysis plan. All statistical analyses will be based on treated population, which includes all subjects treated with BTM. No interim analysis is planned.

12 SOURCE DOCUMENTS AND ACCESS TO SOURCE DATA/DOCUMENTS

Source data are all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source documents are where data are first recorded, and from which subjects' CRF/eCRF data are obtained. These include, but are not limited to, hospital records, clinical and office charts, laboratory notes, memoranda, or evaluation checklists, pharmacy records, diaries, microfiches, videos, radiographs, correspondence, recorded data from automated instruments, or other data collection events, copies or transcriptions certified after verification as being accurate and complete, photographs or digital photo files, x-rays, and subject files and records kept at the pharmacy, at the laboratories, and medico-technical departments involved in the clinical trial.

The protocol does not permit entering data directly into electronic data capture. Case Report Form entries will NOT be considered source data [the site of the original recording of written or electronic record of trial data]. All documents will be stored securely in confidential conditions. On all trial-specific documents, other than the signed consent, the participant will be referred to by the subject's number/code, not by name.

Each participating site will maintain appropriate medical and research records for compliance with ICH E6, and regulatory and institutional requirements for the protection of confidentiality of subjects. Each site will permit authorized representatives of PolyNovo and regulatory agencies to examine (and when required by applicable law, to copy) research records for the purposes of quality assurance reviews, audits, and evaluation of the trial safety, progress and data validity.

13 QUALITY CONTROL AND QUALITY ASSURANCE

Investigator(s)/institution(s) will permit trial-related monitoring, audits, IRB/Internal Ethics Committee review, and regulatory inspection(s) by providing direct access to source data/documents. Each site should have standard operating procedures (SOPs) and/or a quality management plan that describe:

- How data will be evaluated for compliance with the protocol and for accuracy in relation to source documents.
- The documents to be reviewed (e.g. CRF/eCRFs, clinic notes, device accountability records, laboratory reports, specimen tracking logs, diaries/questionnaires, digital images, video recordings, surgery or procedure records), who is responsible, and the frequency for reviews.
- Who will be responsible for addressing quality assurance issues (correcting procedures that are not in compliance with protocol) and quality control issues (correcting errors in data entry).
- Staff training methods and how such training will be tracked.

13.1 Site Audits and Monitoring

Ten percent of clinical investigational sites will be audited for compliance and quality standards. As detailed in Section 13.1, monitoring will be performed according to ICH GCP as clinical sites are qualified, initiated and closed for trial participation. Data will be evaluated for compliance with the protocol and accuracy in relation to source documents. Following written standard operating procedures, the monitors will verify that the clinical trial is conducted and data are generated, documented and reported in compliance with the protocol, GCP and the applicable regulatory requirements. Clinical trial sites are required to make trial source documents and records available for inspection by both auditors and monitors.

14 ETHICS/PROTECTION OF HUMAN SUBJECTS

14.1 Ethical Standard

The Investigator will ensure that this trial is conducted in full conformity with the principles set forth by the United States (US) Food, Drug, and Cosmetic Act codified in 21 CFR and in the International Conference on Harmonization Good Clinical Practice guidelines (ICH GCP E6); the ethical requirements of the European Union Directive 2001/20/EC, and all applicable international standards, government regulations and Institutional research policies and procedures. This clinical trial is to be conducted in accordance with the ethical principles that have their origins from the Declaration of Helsinki.

14.2 Institutional Review Board (IRB)

Subjects in a clinical trial are afforded protection by the process of the clinical investigational plan being reviewed by the Institutional Review Board of each Institution at which the trial is to be conducted. This body of people (both medical/paramedical and lay) scrutinize the research protocol, ensuring that the protocol, subject information and the trial ICF promise a risk-minimized trial and protection of the subject's rights and confidentiality.

Each participating institution must provide for the review and approval of this protocol and the associated ICF, surgical consent (as applicable), HIPPA authorization (as applicable), and subject information sheets by an Office for Human Research Protections (OHRP) registered IRB. Any amendments to the protocol, ICF or subject information sheets must also be approved before they are utilized. In the United States, only institutions holding a current US Federal-wide Assurance issued by OHRP may participate.

14.3 Informed Consent Process

Informed consent is a process that is initiated prior to the individual agreeing to participate in the trial and continues throughout study participation. Extensive discussion of risks and possible benefits of participation will be provided to subjects and their families, if applicable. An ICF describing in detail the study procedures and risks will be given to the subject or his/her legal representative. Consent forms will be IRB-approved, and the subject is required to read and review the document or have the document read to him or her. The Investigator or designee will explain the research study to the subject and answer any questions that may arise. The subject will sign the informed consent document prior to any study-related assessments or procedures. Subjects will be given

the opportunity to discuss the trial with their family or legal representative or think about it prior to agreeing to participate. They may withdraw consent at any time throughout the course of the study. A copy of the signed informed consent document will be given to the subject or their legal representative for their records. The rights and welfare of the subjects will be protected by emphasizing to them that the quality of their clinical care will not be adversely affected if they decline to participate in this trial.
If non-English speakers will be enrolled, a translated ICF will be available and an appropriate person will conduct the consent process. Each investigational site will be provided both types of ICF models. Each institution may revise or add information to the ICF to comply with their consent processes, but may not remove procedural or risk content from the model ICF. All changes to the ICF must be approved in writing by PPD prior to consenting of subjects.

The consent process will be documented in the clinical research record.

14.3.1 Consent in critical care

If the subject is awake and oriented, they will be apprised of the extent and severity of their burn and the usual treatment plan at the institution. They will then be verbally informed about the trial objectives, followed by an in-depth discussion of what the BTM intervention means for the subject (e.g. potential risks).

If the subject is unable to give Informed Consent for any reason, but the Investigator/Co-Investigator feels that a better outcome will be gained from using BTM, open discussion may be held with subject's legal representative. If, after the opportunity to digest the information and to ask questions, those parties agree with the Investigator/Co-Investigator, consent can be signed by the subject's legal representative.

14.3.2 Vulnerable populations

The nature of the burn injuries studied entails risk of burn-related morbidity and mortality, which increases as burn size as a percentage of TBSA increases. However, the majority of these injuries are sustained by young men in their mid-20s who are fit and well prior to their injury. No truly vulnerable population (i.e., children less than 18 years of age, pregnant women, and paraplegics) will be recruited into this traditional feasibility trial.

14.4 Subject Confidentiality

Subject confidentiality is strictly held in trust by the participating investigators, their staff, PolyNovo, and their agents. This confidentiality is extended to cover testing of biological samples, procedures and any trial information relating to participating subjects. The trial protocol, documentation, data, and all other information generated will be held in strict confidence. The subject will be identified only an ID number on the CRF, data listings, reports, summaries and in any paper/electronic format or database. No information concerning the trial or the data will be released to any unauthorized third party without prior written approval of the PolyNovo.

All documents will be stored securely and only accessible by trial staff and authorized personnel. Clinical information will not be released without written permission of the subject, except as necessary for monitoring by IRB, FDA, PolyNovo, applicable regulatory authority or PolyNovo's designee. The trial will anonymize data as soon as it is practical to do so. The trial protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the trial or the data will be released to any unauthorized third party without prior written approval of PolyNovo.

PolyNovo and its authorized representatives may inspect all documents and records required to be maintained by the Investigator, including but not limited to, medical records (office, clinic, or hospital) for the subjects in this trial. The clinical trial site will permit access to such records.

Photographic data will be de-identified. Since facial burns are not included in the protocol, there will be no reason to take facial images, which might identify subjects.

14.5 Future Use of Stored Specimens

Not applicable - there are no stored specimens in this trial.

15 DATA HANDLING AND RECORD KEEPING

The investigators are responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported in accordance with ICH E6. All source documents should be completed in a neat, legible manner to ensure accurate interpretation of data. The investigators will maintain adequate case histories of trial subjects, including accurate case report forms (CRF/eCRFs) and source documentation.

15.1 Data Management Responsibilities

Data collection and complete and accurate documentation are the responsibility of the trial staff under the supervision of the site Principal Investigator. All source documents, photographs and laboratory reports must be reviewed by the trial team and data entry staff, which will ensure that they are accurate and complete. Unanticipated problems and adverse events must be reviewed by the Investigator or designee.

The contract research organization (CRO), Pharmaceutical Products Development (PPD) will be responsible for data management, quality review, analysis, and reporting of the trial data.

15.2 Data Capture Methods

A centralized electronic data capture system will be utilized for this clinical trial. Electronic case report forms (eCRFs) will be utilized to capture all data and from which all source data are entered. Investigational sites with defined users will be given access using a password for entry and specific permissions will be given depending on the delegation of responsibilities at the site. Sites are expected to enter data as it relates to the Schedule of Assessments and Procedures (Appendix 1) for each subject within 24 hours of the subject time point.

15.3 Source Documents/Types of Data

Data for this trial may include safety, laboratory, scar appearance and quality using photography, pruritus scale (NRS), mVSS, ROM joint contracture severity and outcome measures (e.g. microbiology and virology).

15.4 Schedule and Content of Reports

The CRO will provide monthly reports on activities like: monitoring, enrollment, safety and data collection/cleaning, and reports for the data safety monitoring board as well as the final clinical study report.

15.5 Study Records Retention

Study documents should be retained for a minimum of 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents should be retained for a longer period, however, if required by local regulations. No records will be destroyed without the written consent of the PolyNovo, if applicable. It is the responsibility of the PolyNovo to inform the Investigator when these documents no longer need to be retained.

15.6 Protocol Deviations

A protocol deviation is any non-compliance with the clinical trial protocol, Good Clinical Practices, or Manual of Operations and other applicable requirements. The non-compliance may be on the part of the subject, the Investigator, or trial staff. As a result of deviations, corrective actions are to be developed and implemented promptly.

All deviations from the protocol must be addressed in the subject source documents and promptly reported to the PolyNovo or delegated CRO and the local IRB, according to their requirements.

16 PUBLICATION POLICY

The results of the clinical investigation may be submitted for publication.

PolyNovo requires Investigators to submit for consideration all manuscripts, case studies and presentation materials for PolyNovo review prior to submission to any peer-reviewed journal or meeting as per the Clinical Trial Agreement. The data will be formulated into the results section of a manuscript, maintaining full subject confidentiality. Photographic consent for publication is secured from each subject at enrollment. The manuscript will be submitted to a peer-reviewed journal. Additional manuscripts relating to video data may be submitted to a peer-reviewed online journal, e.g. ePlasty, or to the 'online' section of a 'paper' journal such as the Journal of Burn Care and Research.

In order to publish in peer-reviewed journals, the trial MUST be registered with a Clinical Trial Registry. Additionally, PolyNovo requires Investigators to submit final peer-reviewed journal manuscripts that arise from PolyNovo research to the digital archive PubMed Central upon acceptance for publication.

The International Committee of Medical Journal Editors (ICMJE) member journals have adopted a clinical trials registration policy as a condition for publication. The ICMJE defines a clinical trial as any research project that prospectively assigns human subjects to IP or concurrent comparison or control groups to study the cause-and-effect relationship between a medical IP and a health outcome. Medical Investigational Products include drugs, surgical procedures, devices, behavioral treatments, process-of-care changes, and the like. Health outcomes include any biomedical or health-related measures obtained in subjects or participants, including pharmacokinetic measures and adverse events. The ICMJE policy requires that all clinical trials be registered in a public trials registry such as ClinicalTrials.gov, which is managed by the National Library of Medicine. PolyNovo will register this clinical trial with www.clinicaltrials.gov.

17 LITERATURE REFERENCES

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References pertinent to the justification for the study

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15**.** Brusselaers N, Pirayesh A, Hoeksema H, et al. Burn Scar Assessment: A systematic Review of Different Scar Scales. Journal of Surgical Research. 2010;164:e115-e123.

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18 APPENDICES

Appendix 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 & 2 m post SSG[b]	Visit 8/11/17 ~3, 6 & 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 & vital signs	X	X	X	X	X	X	X		X
Assessment of Concomitant Medications/Therapies	X	X	X	X	X	X	X	X	X
B-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					

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 & 2 m post SSG[b]	Visit 8/11/17 ~3, 6 & 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	
BTM integration assessment			X						
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; FU = follow up; 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.

Appendix 2: SCALES[15-20]

All detailed procedures for each scale are 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

Table 1. Range of motion severity ratings by joint muscle action

		Contracture Severity		
Joint	Muscle Action	Mild	Moderate	Severe
Shoulder	Flexion	120–180	60–119	<60
	Extension	32–50	16–31	<16
	Abduction	120–180	60–119	<60
	Adduction	32–50	16–31	<16
Elbow	Flexion	93–140	46–92	<46
	Extension	−140–93	−46–92	>−46
	Pronation	53–80	26–52	<26
	Supination	53–80	26–52	<26
Hip	Flexion	67–100	34–66	<34
	Extension	20–30	10–19	<10
	Abduction	26–40	13–25	<13
	Adduction	13–20	7–12	<7
Knee	Flexion	100–150	50–99	<50
	Extension	−150–100	−99–50	>−50

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

Fitzpatrick Skin Typing Test:

PolyNovo Protocol CP-002

Protocol Version _____ Protocol Date:_____

Fitzpatrick Skin Typing Test – Genetic Disposition

Patient Number: _____ Date Administered: _____

Visit #: _____ Administered by: _____

Administer questionnaires strictly according to instructions in PolyNovo PRO and Scales Training Manual. The gray highlighted box can be completed by the subject or study staff.

What is the color of your eyes?

0 – Light Blue, Gray, or Green
1 – Blue, Gray, or Green
2 – Blue
3 – Dark Brown
4 – Brownish Black

What is the natural color of your hair?

0 – Sandy Red
1 – Blond
2 – Chestnut/Dark Blond
3 – Dark Brown
4 – Black

What is the color of your non-exposed skin?

0 – Reddish
1 – Very Pale
2 – Pale with Beige Tint
3 – Light Brown
4 – Dark Brown

Do you have freckles on unexposed areas?

0 – Many
1 – Several
2 – Few
3 – Incidental
4 - None

Enter the number that best describes you below.

Eye Color	Hair Color	Skin Color	Freckles	Total

Subject Initials :_____ Date:_____/_____/_____

DD/MMM/YYYY

(This section to be completed by the subject to validate their assessment)

PolyNovo Fitzpatrick Skin Typing Test Form V1.0 26Aug2016

PolyNovo Protocol CP-002

Protocol Version _____ Protocol Date:_____

Fitzpatrick Skin Typing Test-Reaction to Sun Exposure

Patient Number: _____ Date Administered: _____

Visit #: _____ Administered by: _____

Administer questionnaires strictly according to instructions in PolyNovo PRO and Scales Training Manual. The gray highlighted box can be completed by the subject or study staff.

What happens when you stay in the sun too long?

0 – Painful redness, blistering, peeling
1 – Blistering followed by peeling
2 – Burns sometimes followed by peeling
3 – Rare burns
4 – Never had Burns

To what degree do you turn brown?

0 – Hardly or not at all
1 – Light color tan
2 – Reasonable tan
3 – Tan very easy
4 – Turn Dark Brown Quickly

How deeply do you tan?

0 – Not at all or very little
1 – Lightly
2 – Moderately
3 – Deeply
4 – Very Deeply

How does your face react to the sun?

0 – Very Sensitive
1 – Sensitive
2 – Normal
3 – Very Resistant
4 – Never had a Problem

Enter the number that best describes you below.

What happens when you stay in the sun too long?	What happens when you stay in the sun too long?	How deeply do you tan?	How does your face react to the sun?	Total

Subject Initials :_____ Date:_____/_____/_____

DD/MMM/YYYY

(This section to be completed by the subject to validate their assessment)

PolyNovo Fitzpatrick Skin Typing Test Form V1.0 26Aug2016

PolyNovo Protocol CP-002

Protocol Version _____ Protocol Date:_____

Fitzpatrick Skin Typing Test-Tanning Habits

Patient Number: _____ Date Administered: _____

Visit #: _____ Administered by: _____

Administer questionnaires strictly according to instructions in PolyNovo PRO and Scales Training Manual. The gray highlighted box can be completed by the subject or study staff.

When did you last expose your body to sun (or artificial sunlamp)?

0 – More than 3 months ago

1 – 2 to 3 months ago

2 – 1 to 2 months ago

3 – Less than a month ago

4 – Less than 2 weeks ago

Enter the number that best describes you below.

When did you last expose your body to sun (or artificial sunlamp)?

Subject Initials :_____ Date:_____/_____/_____

DD/MMM/YYYY

(This section to be completed by the subject to validate their assessment)

PolyNovo Fitzpatrick Skin Typing Test Form V1.0 26Aug2016

PolyNovo Protocol CP-002

Protocol Version _____ Protocol Date:_____

Fitzpatrick Skin Typing Test-Totals

Patient Number: _____ Date Administered: _____

Visit #: _____ Administered by: _____

This section should be completed by the study staff. It is not considered a deviation if the subject totals the page; however site staff are required to initial below to confirm the Skin Type Score and Fitzpatrick Skin Type Category are properly recorded.

Genetic Disposition Total	Reaction to Sun Exposure Total	Tanning Habits Score	Total Skin Type Score

Total Skin Type Score	Fitzpatrick Skin Type
0-7	I
8-16	II
17-25	III
26-30	IV
Over 30	V-VI

Using the chart above enter the Fitzpatrick Skin Type (Roman Numerals) _____

PolyNovo Fitzpatrick Skin Typing Test Form V1.0 26Aug2016