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Title: Development of a New Critical Pathway for Treatment of Acute Bacterial Skin and Skin Structure Infections

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Development of a New Critical Pathway for Treatment of Acute Bacterial Skin and Skin Structure Infections

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Allergan Signature(s)

Development of a New Critical Pathway for Treatment of Acute Bacterial Skin and Skin Structure Infections

Version 6.0

This study protocol has been subjected to an internal Allergan review. I agree to the terms of this study protocol.

Signature of Principal Investigator

Development of a New Critical Pathway for Treatment of Acute Bacterial Skin and Skin Structure Infections

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Version 6.0

I agree to the terms and conditions relating to this study protocol. I agree to conduct the study according to the protocol and the applicable ICH guidelines and GCP regulations, and to inform all who assist me in the conduct of this study of their responsibilities and obligations.

[redacted]

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List of abbreviations

µL	Microliter
µmol	Micromole
ABSSSI	Acute bacterial skin and skin-structure infection
AE	Adverse event
AIDS	Acquired immune deficiency syndrome
ANC	Absolute neutrophil count
BPM	Beats per minute
cm^2	Square centimeters
CrCl	Creatinine clearance
CRF	Case report form
dL	Deciliter
ED	Emergency department
ESRD	End-stage renal disease
FDA	Food and Drug Administration
g	Gram
GCP	Good Clinical Practice
HCUP	Healthcare Cost and Utilization Project
HIV	Human immunodeficiency virus
hr	Hour
HRQoL	Health-related quality of life
ICF	Informed consent form
ICH	International Conference on Harmonisation
ICU	Intensive care unit
IRB	Institutional review board
IV	Intravenous
kg	Kilogram
L	Liter
mg	Milligram
min	Minute
mL	Milliliter
MRSA	Methicillin-resistant *Staphylococcus aureus*

NIS	National Inpatient Sample
OPAT	Outpatient parenteral antibiotic therapy
PICC	Peripherally-inserted central catheter
q12–24h	Every 12 to 24 hours
q12h	Every 12 hours
q24h	Every 24 hours
q48h	Every 48 hours
q6–12h	Every 6 to 12 hours
q8–12h	Every 8 to 12 hours
q8h	Every 8 hours
SAE	Serious adverse event
SAP	Statistical analysis plan
SF-12	Short Form-12 Health Survey
SIRS	Systemic inflammatory response syndrome
SOP	Standard operating procedure
SSSI	Skin and skin-structure infection
TMP	Trimethoprim
ULN	Upper limit of normal
US	United States

Protocol synopsis

Title of study	Development of a New Critical Pathway for Treatment of Acute Bacterial Skin and Skin Structure Infections
Rationale	Treatment of ABSSSI lacks a clear approach to risk stratification of patients and management upon patient presentation to the emergency department. Lack of a clear approach may cause unnecessary hospital admissions and extended length of stay (LOS) of ABSSSI patients, who otherwise could be treated in an outpatient setting. A paucity of research exists regarding hospital care pathways for treatment of ABSSSI patients and the place of long-acting parenteral antibiotics. Critical pathways, also known as critical paths, clinical pathways, or care paths, are management plans that outline steps, such as the sequence and timing of actions, necessary for a complex process. Therefore, implementation of a new critical pathway may potentially demonstrate benefit compared to usual care for the treatment of ABSSSI for patients who could otherwise be treated in an outpatient healthcare setting. Long-acting parenteral antibiotics may be an important component of the pathway, as a means to increase efficiency of ABSSSI treatment. The new critical pathway under study is defined as (1) use of guideline-based patient identification criteria, and, for those who meet these criteria, (2) use of dalbavancin, a long-acting antibiotic with an abbreviated administration schedule. For appropriate hospitalized patients with ABSSSI, the new critical pathway may demonstrate a potential for decreasing hospital length of stay.
Objectives	To assess the effect of a new critical pathway compared to usual care for the treatment of ABSSSI during initial care (the date of enrollment to 10-14 days) and follow-up (30 days after initial care) on the following outcomes: <u>Primary outcome</u> • Infection-related total admitted hospital days during initial care and follow-up <u>Secondary outcomes</u> • Total admitted hospital days during initial care and follow-up • Infection-related major surgical interventions that required operating room time during initial care and follow-up • Infection-related hospitalizations during initial care and follow-up • Infection-related hospitalizations during initial care and follow-up that resulted in admission to Intensive Care Unit (ICU)

	• All cause hospitalizations in the 30 days post discharge from the hospital • Infection-related ED visits during initial care and follow-up • Infection-related outpatient healthcare visits during initial care and follow-up • Use of a PICC line or central line to administer antibiotic therapy during initial care and follow-up • Infection-related healthcare visits due to PICC line or central line used to administer antibiotic therapy during initial care and follow-up • Response to treatment at end of treatment visit • Serious adverse events (SAEs) during initial care and follow-up • Patient satisfaction with care • Patient work and productivity loss • Patient Health-related Quality of Life (HRQoL)
Population	Study subjects will be recruited among patients who are admitted to the hospital for the treatment of ABSSSI and who require coverage for a known or suspected Gram-positive infection. Among all such individuals, attention will be focused on those who meet all of the inclusion criteria and none of the exclusion criteria.

Inclusion criteria	• Aged ≥18 years • Admitted patients who meet clinical definition for ABSSSI o Present with the following infection types: cellulitis/erysipelas, wound infection, or major cutaneous abscess • Known or suspected infection caused by susceptible isolates of the following Gram-positive microorganisms: *Staphylococcus aureus* (including methicillin-susceptible and methicillin-resistant strains), *Streptococcus pyogenes, Streptococcus agalactiae, Streptococcus dysgalactiae, Streptococcus anginosus group* (including *S. anginosus, S. intermedius, S. constellatus*) and *Enterococcus faecalis* (vancomycin susceptible strains). • Willing and able to return to the hospital or a designated clinic for scheduled visits, or to be in contact with study coordinators through telephone communication as required by the protocol and the antibiotic treatment administered

Exclusion criteria	[redacted] • Known or suspected Gram-negative infections including bacteremia, anaerobic infections, or fungemia, even in the presence of Gram-positive infection • Known or suspected infections that are severe, life-threatening, or are not included in the ABSSSI FDA guidance[1], including the following examples: [redacted]

	[redacted] • Injection drug users presenting with a fever [redacted] • Severe neurological disorder leading to severe immobility or confined to wheelchair or bed (e.g. paraplegia and hemiplegia) • Bilateral lower extremity involvement of the suspected infection (to exclude patients with chronic venous stasis) • Unwilling or unable to follow study procedures
Intervention	The new critical pathway under study is defined as (1) use of guideline-based patient identification criteria, and, for those who meet these criteria, (2) use of dalbavancin, a long-acting antibiotic with an abbreviated administration schedule.
Comparator treatment	Usual care (i.e. investigator choice antimicrobial therapy for a suspected or known Gram-positive infection of susceptible organisms)
Study design	Pre-period versus post-period trial
Study duration and sample size	The duration of the study will not be predetermined, but rather will depend on the number of included sites and eligible subjects at each site. Both the pre- and post-periods will run until approximately 86 subjects are enrolled, or 43 subjects per period. Section 6.3, Sample size, provides information on the minimum number of subjects.
Site	NYP/Weill Cornell Medical Center
Baseline characterization	• Demographics • Comorbidities • Charlson Comorbidity Index • Infection type ○ Cellulitis/erysipelas,

	○ Wound infection, or ○ Major cutaneous abscess • Infection characteristics • Healthcare utilization in prior three months
Outcomes	• Total admitted hospital days during initial care and follow-up • Infection-related total admitted hospital days during initial care and follow-up • Infection-related major surgical interventions that required operating room time during initial care and follow-up • Infection-related hospitalizations during initial care and follow-up • Infection-related hospitalizations during initial care and follow-up that resulted in admission to Intensive Care Unit (ICU) • All cause hospitalizations in the 30 days post discharge from the hospital • Infection-related ED visits during initial care and follow-up • Infection-related outpatient healthcare visits during initial care and follow-up • Use of PICC line or central line to administer antibiotic therapy during initial care and follow-up • Infection-related healthcare visits due to PICC line or central line used to administer antibiotic therapy during initial care and follow-up • Response to treatment at end of treatment visit • Serious adverse events (SAEs) during initial care and follow-up • Patient satisfaction with care • Patient work and productivity loss • Patient Health-Related Quality of Life (HRQoL) [redacted]

	[redacted]
Data analysis	Subject characteristics and outcomes will be summarized and described for all subjects and compared between the pre- and post-periods using appropriate statistical methods with adequate power. Site characteristics will also be summarized and described. Study analyses will be fully described in a separate SAP.
Data Source and Collection	Case-report forms (CRF) will be developed and employed by trained site investigators to prospectively collect information on baseline characteristics and outcomes following subject enrollment in the study.
Safety Reporting	Adverse events (AEs) and serious adverse events (SAEs) will be monitored regularly and all SAEs will be reported by each site to the sponsor.

1 Introduction

1.1 Background

1.1.1 Skin and skin-structure infections

Skin and skin-structure infections (SSSI) are among the most commonly encountered infections in clinical practice, with an estimated 14.2 million outpatient visits for cellulitis and abscess reported in 2005 alone.[2] The number of visits to the emergency department (ED) for SSSI has nearly tripled between 1996 and 2005.[3] In recent years, while some evidence suggests that ED visits for ABSSSI in the United States (US) are stabilizing,[4] the overall burden of these infections to the US healthcare system remains high—between 2000-2012, the incidence of patients with at least 1 SSSI-related hospital, ambulatory care, and ED visit increased by 38%, 46%, and 56%, respectively.[5]

There is evidence that hospital admissions for these infections have also increased substantially in recent years. Based on examinations of the US National Inpatient Sample (NIS), Edelsberg and colleagues reported a 29% increase in admissions to hospitals for SSSI between 2000 and 2004; increases were greatest among patients aged <65 years (37% vs. 14% for those aged ≥65 years), urban hospitals (32% vs. 11% for rural hospitals), and among those with "superficial" infections (e.g., cellulitis, abscess) (33% vs. 24% for deeper/healthcare-associated infections [e.g., post-operative wound infection, infection due to vascular device]).[6] The Healthcare Cost and Utilization Project (HCUP) 2013 report stated that SSSI infections were responsible for over 600,000 hospitalizations annually and were considered the eighth-most rapidly growing cause for hospitalization from 1997- 2011.[7]

1.1.2 Acute bacterial skin and skin structure infections

In an effort to focus on acute infection and increase homogeneity of what had traditionally been a relatively diverse population, in 2013 the US Food and Drug Administration (FDA) provided guidance to manufacturers developing antibiotics for a subgroup of SSSI known as acute bacterial SSSI (ABSSSI). The FDA defined ABSSSI to consist of cellulitis/erysipelas, wound infection, and major cutaneous abscess. To be deemed ABSSSI, the infection should have a lesion surface area ≥75 squared centimeters (cm^2); additional criteria set forth by the FDA[1] were infection-specific and included:

- Spreading areas of redness, edema, and/or induration (cellulitis/erysipelas)
- Purulent drainage from a wound with surrounding redness, edema, and/or induration (wound infection)
- Pus within the dermis or deeper that is accompanied by redness, edema, and/or induration (major cutaneous abscess)

ABSSSI are often caused by Gram-positive pathogens, including but not limited to *Staphylococcus aureus* (both methicillin-resistant [MRSA] and methicillin-susceptible strains [MSSA]) and *Streptococcus pyogenes*.[1]

1.1.3 Treatment of ABSSSI

As with SSSI in general, initial treatment for ABSSSI is typically empiric and based on patient characteristics, clinical presentation, treatment guidelines, knowledge of local pathogen and resistance patterns, and the antimicrobials that are most likely to be effective against them. Given the role of MRSA in this indication, it is not surprising that empiric use of anti-MRSA therapy is fairly common; in one recent evaluation of 13,291 patients hospitalized for community-acquired complicated SSSI (including but not limited to ABSSSI), empiric use of anti-MRSA therapy increased from 61% during 2007 to 73% in 2010[8] ($p<0.01$); Consistent with other research,[9] vancomycin was the most commonly used agent.

Patients requiring parenteral antibiotic treatment for ABSSSI have routinely been admitted to the hospital, regardless of the degree to which they may require other hospital services such as drainage or debridement.[9] In one recent examination of 619 adult patients presenting to 12 US EDs with SSSI, Talan et al noted that for 85% of patients admitted to the hospital (n=94), their doctors indicated that the reason for admission was the requirement for parenteral antibiotic therapy, and for approximately 41% of admitted patients (n=39), this was the only reason for admission.[10] The advent of outpatient parenteral antibiotic therapy (OPAT), which has been shown to be a safe and effective means by which parenteral antibiotic treatment can be administered,[11] has provided an opportunity to rethink this paradigm. Current practice guidelines for the management of ABSSSI in EDs and hospitals have suggested that patients without a need for admission—defined as presence of hemodynamic instability, necrotizing fasciitis, and/or unstable comorbidities—do not require admission and instead could be managed as outpatients. Interestingly, these guidelines note that the presence of systemic signs of infection such as fever, in the absence of the aforementioned risk factors, are not cause in and of themselves for admission.[3] Guidelines for the selection and management of patients receiving OPAT outline other relevant criteria, including psychosocial factors that may threaten the ability to render care on an outpatient basis.[11] Yet, even with recommendations for outpatient care in clinical guidelines, a lack of clear care pathways for ABSSSI patients in the hospital limits use in practice. The development of new antibiotic therapies provides the opportunity to successfully design and implement a new care pathway, due to the accelerated dosing schedules and ease of administration provided by long-acting parenteral antibiotics. Long-acting parenteral antibiotics may be an important component of a care pathway in the hospital for treatment of ABSSSI. Currently, there is a paucity of research that exists regarding a new clinical pathway in the hospital for treatment of ABSSSI patients and the place of long-acting parenteral antibiotics in therapy.

1.1.4 Dalbavancin

Dalbavancin (Dalvance®) is a novel, long-acting, second-generation lipoglycopeptide that is indicated for the treatment of ABSSSI caused by susceptible strains of Gram-positive bacteria, including *Staphylococcus aureus* (both MRSA and MSSA), *Streptococcus pyogenes*, *Streptococcus agalactiae*, *Streptococcus dysgalactiae*, *Streptococcus anginosus* group, and *Enterococcus faecalis* (vancomycin-susceptible strains).[12] In two pivotal clinical trials, the efficacy and safety of two doses of IV dalbavancin administered one week apart (1000 milligrams (mg) for the initial infusion [750 mg for those with renal impairment]

administered over 30 minutes, 500 mg for the second infusion [375 mg] administered over 30 minutes) were shown to be non-inferior to 10–14 continuous days of therapy with vancomycin and linezolid, respectively.[12-14] A subsequent clinical trial demonstrated that the efficacy and safety of a single dose of dalbavancin administered over a 30 minute infusion (1500 mg) was non-inferior to the two-dose regimen.[16] Dalbavancin can be provided through a peripheral line, and does not necessitate central or PICC placement.

1.1.5 New Critical Pathway

Critical pathways, also known as critical paths, clinical pathways, or care paths, are management plans that outline steps, such as the sequence and timing of actions, necessary for a complex process. The definition of the new critical pathway for this study was developed for the treatment of ABSSSI patients who are admitted to the hospital. The new critical pathway is (1) use of guideline-based patient identification criteria, and, for those who meet these criteria, (2) use of dalbavancin, a long-acting antibiotic with an abbreviated administration schedule. Guideline-based patient identification criteria will be developed and applied based on criteria for identification of ABSSSI and existing OPAT guidelines.[3,11]

1.2 Purpose

In addition to a lack of clinical guidelines or critical pathways to inform treatment of ABSSSI patients, many contributing factors are responsible for continuing to admit ABSSSI patients to receive IV antibiotic therapy, who could otherwise be treated in an outpatient healthcare setting. First, physicians may not have experience with or training for use of newer IV antibiotics, including use of long-acting IV antibiotics. Information on use of long-acting IV antibiotics may be limited to clinical trials, which test agents in highly selected populations under optimized settings with limited "real-world" generalizability. Second, physicians may have safety concerns related to adequate patient follow-up with the use of long-acting IV antibiotics. Third, there may be barriers to provision of OPAT, including institutional time spent coordinating care and insurance-related barriers.

A new study is therefore required to better understand the "real-world" effectiveness of a new critical pathway that includes use of a long-acting antibiotic for the treatment of ABSSSI. In addition to tangible economic benefits associated with reducing unnecessary admissions, implementation of a new critical pathway may reduce utilization of healthcare services in the inpatient and outpatient care setting, increase patient satisfaction, improve patient health-related quality of life (HRQoL), and reduce patient productivity loss/absenteeism.

2 Study objectives

2.1 Primary objective

Estimate the difference in infection-related total admitted hospital days during initial care (the date of enrollment to 10-14 days) and follow-up (30 days after initial care) comparing ABSSSI patients receiving care before implementation of the new critical pathway and after implementation.

2.2 Secondary objectives

Estimate the difference in the following outcomes during initial care (the date of enrollment to 10-14 days) and follow-up (30 days after initial care) comparing ABSSSI patients receiving care before implementation of the new critical and after implementation:

- Total admitted hospital days during initial care and follow-up
- Infection-related major surgical interventions that required operating room time during initial care and follow-up (number of expected major surgeries, number of unexpected major surgeries, and total number of major surgeries)
- Infection-related hospitalizations during initial care and follow-up
- Infection-related hospitalizations during initial care and follow-up that resulted in admission to Intensive Care Unit (ICU)
- All cause hospitalizations in the 30 days post discharge from the hospital
- Infection-related ED visits during initial care and follow-up (number of expected, number of unexpected and number of total ED visits during follow-up)
- Infection-related outpatient healthcare visits (e.g., physicians' office visits, ED visits, infusion center visits, home health visits) during initial care and follow-up (number of expected visits, number of unexpected and total number of visits)
- Use of a PICC line or central line to administer antibiotic therapy during initial care and follow-up (number of patients who have a PICC or central line placed)
- Infection-related healthcare visits (e.g., hospitalizations, ED visits, other outpatient visits) due to PICC line or central line used to administer antibiotic therapy during initial care and follow-up (number of expected visits, unexpected visits and number of total visits)
- Response to treatment at end of treatment visit
- Serious adverse events (SAEs) during initial care and follow-up
- Patient satisfaction with care (subject reported)
- Patient work and productivity loss (subject reported)
- Patient Health-related Quality of Life (HRQoL) (subject reported)

3 Study design

3.1 Overview

This study will employ a "pre-post" pragmatic design, which will consist of both a pre-period, or an observational baseline period, and a post-period, or an interventional period (Figure 1). During the pre-period, the site will implement the first component of the critical pathway through implementation of guideline-based criteria to identify patients admitted to the hospital, obtain informed consent, and monitor enrolled subjects. The site will initiate

treatment for ABSSSI with "usual care," defined as site- or physician-specific antibiotic treatment of ABSSSI with coverage for a known or suspected Gram-positive infection (e.g., vancomycin, linezolid, and daptomycin) to each study subject who meets all inclusion and exclusion criteria. During the "post" period, for all subjects who provide informed consent and are subsequently enrolled, each participating site will additionally implement the second component of the new critical pathway, use of dalbavancin, at the point of care in the hospital or other designated site to each study subject who meets all inclusion and exclusion criteria.

As the study is pragmatic in design, selection criteria will be minimal and optimized for selection of "real-world" patients who are ideal candidates for treatment in the outpatient healthcare setting, but who are currently admitted to the hospital to receive treatment for ABSSSI. Site training is necessary for both adherence to the protocol and implementation of the new critical pathway, described in greater detail in Section 7, Study sites and administrative structure. Briefly, the investigators on the core study team will provide training to other members of the site study team, including all participating site physicians and other healthcare providers (i.e. nurses, pharmacists, and other staff) on protocol adherence and implementation of the new critical pathway. Protocol training will occur before enrolling subjects in both the pre- and the post-period. Before enrolling subjects in the post-period, training on implementation of the new critical pathway will occur over a two- to four-week period after the date of the last enrolled subject in the pre-period. In addition, ongoing reminders and orientations will be scheduled by the investigators on the core study team as needed during both the pre- and post-period.

For both periods of interest, subject follow-up will begin on the day of study enrollment and end 44 days subsequently. This will reflect the 10 to 14-day period during which antibiotics are anticipated to be required for care of ABSSSI plus an additional 30 days to ascertain outcomes, such as health resource utilization.

3.1.1 Study duration

The duration of the study will not be predetermined, but rather will depend on the number of eligible subjects. Both the pre- and post-periods will run until the minimum number of subjects are enrolled. Refer to Section 6.3, Sample size, for information on the minimum number of subjects.

3.1.2 Rationale of study design

The design of this study allows for the site to understand baseline treatment patterns for ABSSSI, then after this period, to implement an institution-level intervention. Use of this design removes site-level variables as a source of potential confounding and enables comparisons of the new critical pathway to usual care in the same setting(s) and similar subject populations.

The study is designed in a "pragmatic" fashion (i.e., minimal inclusion/exclusion criteria, which will enable an examination of the impact of the new critical pathway under "real-world" conditions, with good generalizability/applicability to clinical practice.

3.2 Antibiotic treatment

3.2.1 Pre-period

During the pre-period, treatment for ABSSSI is initiated with "usual care," defined as investigator's choice of antibiotic therapy (e.g., vancomycin, linezolid, and daptomycin), to each study subject who meets all study selection criteria. It is expected that choice of usual care will be site or physician specific. Dosing of each antibiotic agent should follow recommended guidelines, demonstrated for antibiotic agents in, but not limited to, Table 1 below. All included subjects require Gram-positive antimicrobial coverage for a known or suspected infection caused by susceptible isolates of the following microorganisms: *Staphylococcus aureus* (including methicillin-susceptible and methicillin-resistant strains), *Streptococcus pyogenes, Streptococcus agalactiae, Streptococcus dysgalactiae, Streptococcus anginosus group* (including *S. anginosus, S. intermedius, S. constellatus*) and *Enterococcus faecalis* (vancomycin susceptible strains).

3.2.2 Post-period

During the post-period, all enrolled subjects will receive treatment for ABSSSI with dalbavancin at each participating site. Dalbavancin will be administered as a single IV dose of 1500 mg over 30 minutes (1125 mg over 30 minutes if CrCl <30 mL/min, for those not on regularly scheduled dialysis).[12] Dalbavancin will be provided to sites by study sponsor.

3.2.3 Rationale of dose/regimen of antibiotic treatment

Usual care antibiotic therapy and dalbavancin will each be administered per relevant guidelines/manufacturer instructions (dosing provided in Table 1). Duration of treatment with usual care will be left to the physician's discretion, as recommendations for several agents include a range (e.g., 10–14 days for linezolid).[24]

3.2.4 Rationale for choice of comparator

Usual care will comprise investigator's choice of care and may therefore vary from subject to subject. This was selected to allow for comparisons of the new critical pathway, which includes use of dalbavancin, with "real world" treatment.

3.3 Subject identification

Patients admitted to the hospital with an ABSSSI infection during both the pre- and post-periods will be assessed for inclusion and exclusion criteria. These criteria will be prepared as an annotated checklist for the study coordinator and/or study nurses to implement and document using a CRF. Information obtained through the annotated checklist coupled with physician assessment will define guideline-based patient identification criteria.

3.3.1 Pre-period

During the pre-period, the study coordinator and/or other study nurses will identify patients who may be eligible for the study. All hospital staff may be reminded (through posters or memorandums) to inform the study coordinator and/or other study nurses as soon as an ABSSSI patient is admitted. The study coordinator will implement inclusion and exclusion criteria for the new critical pathway by patient interview and/or chart review. Inclusion criteria includes clinical judgment that patient requires coverage for a known or suspected Gram-positive infection. Patients who meet all inclusion criteria and none of the exclusion criteria based on study coordinator assessment will be enrolled in the study or flagged for further review by core study team physicians, who will make the final enrollment decision. The treating physician will be blinded to protocol content and study enrollment decision. Study coordinator will then complete all additional elements of enrollment, including informed consent, and scheduling of follow-up.

3.3.2 Post-period

During the post-period, the study coordinator and/or other study nurses will identify patients who may be eligible for the study. As in the pre-period, physicians or other appropriate healthcare providers may also identify subjects who are eligible for the study. All hospital staff may be reminded (through posters or memorandums) to inform the study coordinator and/or other study nurses as soon as an ABSSSI subject is admitted to the hospital. The study coordinator or treating physician will implement the checklist and enroll subjects into the study. Study coordinator will then complete enrollment, including informed consent, and scheduling of follow-up.

3.3.3 Subject follow-up

Within both the pre- and post-periods, follow-up for each subject will begin on the day of enrollment (which is anticipated to be the date of treatment initiation) and conclude 44 days thereafter. Follow-up will therefore include the presumed “episode” of antibiotic therapy for ABSSSI (up to 10-14 days) and subsequent 30-day period.

3.3.4 Rationale for subject follow-up

Each subject will be followed for a 10-14-day period (i.e. initial care), which is the longest supported duration of antibiotic therapy for ABSSSI treatment.[15] In order to allow similar opportunity for collection of outcomes in the pre- and the post-period, the post-period similarly assumes 10-14 days. The addition of 30 days after initial care (i.e. follow-up) was thought to comprehensively assess outcomes during a relevant timeframe after the completion of antibiotic therapy. Therefore, 44 days (initial care and follow-up) for each

subject encompasses both the maximum treatment duration and assessment of relevant outcomes in the 30 days following treatment.

3.4 Subject inclusion and exclusion criteria

Study subjects will be recruited among admitted patients with ABSSSI and who require coverage for a known or suspected Gram-positive infection. Among all such individuals, attention will be focused on those who meet all of the inclusion criteria and none of the exclusion criteria.

3.4.1 Inclusion criteria

Eligible study subjects satisfy all of the following inclusion criteria[1,10,24]

- Aged ≥18 years
- Admitted patients who meet clinical definition for ABSSSI[10-11]
    - Present with the following infection types: cellulitis/erysipelas, wound infection, or major cutaneous abscess
- Known or suspected infection caused by susceptible isolates of the following Gram-positive microorganisms: *Staphylococcus aureus* (including methicillin-susceptible and methicillin-resistant strains), *Streptococcus pyogenes, Streptococcus agalactiae, Streptococcus dysgalactiae, Streptococcus anginosus group* (including *S. anginosus, S. intermedius, S. constellatus*) and *Enterococcus faecalis* (vancomycin susceptible strains).
- Willing and able to return to the hospital or a designated clinic for scheduled visits, or be in contact with the study coordinator through telephone communication, as required by the protocol and the antibiotic treatment administered

3.4.2 Exclusion criteria

Study subjects with any of the following criteria will be excluded[1,12-14]

- [redacted]
- Known or suspected Gram-negative infections including bacteremia, anaerobic infections, or fungemia, even in the presence of Gram-positive infection
- Known or suspected infections that are severe, life-threatening, or are not included in the ABSSSI FDA guidance, including the following examples:
    - [redacted]

[redacted]

- Injection drug users presenting with a fever

[redacted]

[a] If the patient is a woman of child-bearing potential, from at least the first dose of study drug until the final visit she must confirm strict abstinence from sexual intercourse with any male or must confirm use of an effective contraceptive method from the following list: A barrier (condoms, diaphragm or cervical cap) with spermicide; Oral or similar contraceptive, which includes, but is not limited to: injectable, implanted, or patch hormone therapy, and intrauterine device (IUD); Documented surgical sterilization at least 4 weeks prior to baseline; Partner vasectomy at least 6 months prior to baseline.

- Severe neurological disorder leading to severe immobility or confined to wheelchair or bed (e.g. paraplegia and hemiplegia)
- Bilateral lower extremity involvement of the suspected infection (to exclude patients with chronic venous stasis)
- Unwilling or unable to follow study procedures

3.5 Early study termination

A premature discontinuation will occur when a subject who signed the informed consent form (ICF) ceases participation in the study, regardless of circumstances, before the completion of all study assessments (i.e., before completing all protocol-stipulated activities). Subjects can be prematurely discontinued from therapy after careful consideration for any one of the following reasons:

- Screen failure
- Failure to receive complete critical pathway by not receiving dalbavancin in the post-period
- Withdrawal of consent (a clear reason will be documented)
- AE (before or after administration of first dose of antibiotic therapy)
- Protocol deviation/violation, including lack of protocol compliance
- Lost to follow-up (every effort will be made to contact the subject)
- Study or site prematurely terminated by the sponsor for any reason
- If a Gram-negative infection including bacteremia, an anaerobic infection, or fungemia develops during the study, or is subsequently found to have been present at baseline, the subject should be removed from study treatment and receive appropriate antibiotic(s) to treat the Gram-negative infection, anaerobic infection, or fungemia.
- Other reasons, such as specified administrative reasons or pregnancy

All subjects who prematurely discontinue from the study, regardless of cause, should have a final assessment at early termination (ET). A final assessment will be defined as either a physical visit or a telephone call that completes the evaluations scheduled for the Final Visit at the end of study (Day 44 visit; refer to Section 4.2, Data collection), or an earlier visit, depending on the visit schedule and when ET occurs. Subjects who do not complete all scheduled visits/procedures will be requested to have an ET Visit. A clear description will be documented and source documentation will be kept by the investigator. The reasons for premature discontinuation from the study will be reflected on the Study Termination page of the CRF.

Within these limits, the specific form of contraception employed are left to the discretion of the patient, and/or the principal investigator, and/or the patient's physician.

4 Measures and data collection

4.1 Study outcomes

4.1.1 Baseline characteristics

Baseline characteristics will be collected following subject enrollment into the study, and will be based on physical examination and medical history. A complete list of baseline characteristics is shown in Table 2.

Table 2. Baseline characteristics

Measure Type	Description
Demographics	Age (in years) Gender Race Employment status Location subject presents from (e.g. from home, LTC, SNF, nursing home)
Comorbidities	Myocardial infarction Congestive heart failure Peripheral vascular disease Cerebrovascular disease Dementia Chronic pulmonary disease Rheumatologic disease Peptic ulcer disease Mild liver disease Diabetes without complications Diabetes with complications Renal disease Moderate or severe liver disease (Child-Pugh Class B and C) Any malignancy, including leukemia and lymphoma Metastatic solid tumor If subject has cancer, whether active vs. remitted/cured Alcohol/drug abuse/illicit needle use Malnutrition HIV

Measure Type	Description
	Immunocompromising conditions other than HIV Altered mental status
Charlson Comorbidity Index[b] (CCI)	Derived variable based on recorded comorbidities: Calculation of the CCI for each subject at baseline to assess the risk of 1 year mortality
Infection type	Cellulitis/erysipelas, wound infection, or major cutaneous abscess
Infection characteristics	Lesion size (as described in Appendix A) and location Thrombocytopenia (<150,000 platelet count or site-specific definition) Hyperglycemia (>120mg/dL blood glucose or site-specific definition) Hyponatremia (<135 mEq/L blood sodium or site-specific definition) Acidosis (<7.35 pH of the blood or site-specific definition or described in medical chart) Uremia (as described in medical chart) Anemia (14-18 g/dL hemoglobin for men or 12-16 g/dL hemoglobin for women or site-specific definition) Fever (>98.6 degrees Fahrenheit or site-specific definition) SIRS criteria[c] at enrollment, including highest or lowest recorded RR and highest or lowest recorded BPM/highest or lowest recorded fever/highest or lowest WBC count or amount of immature cells Highest or lowest recorded BP at enrollment Laboratory results at baseline and during follow-up (e.g. Total white blood cell count, hemoglobin, sodium, glucose, serum creatinine, and C-reactive protein)

[b] Deyo et al 1992

[c] SIRS criteria include abnormalities in temperature, heart rate, respiration, and white blood cell count. Specifically, fever >38.0°C or hypothermia <36.0°C, tachycardia >90 beats/minute , tachypnea >20 breaths/minute or PaCO2 of less than 32mmHg, abnormal white blood cell count leukocytosis >12,000/microliter, leucopoenia <4,000/microliter, or >10% immature cells (bands).[26,27]

Measure Type	Description
	Rapid microbial assay and microbiological culture results and type of culture (i.e. blood, wound swab, urine) at baseline and during follow-up Presence of recurrent infection (evidence from chart review, provider assessment and subject report of a similar ABSSSI in the same location on the body) and any ABSSSI infections in the prior 6 months
Healthcare utilization in prior three months	Hospitalizations and primary reason Surgical interventions and primary reason Admission to the ICU and primary reason ED visits or other outpatient visits (e.g., infusion center and physician's office) and primary reason Use of dialysis Use of any medications for chronic diseases and specifically use of an antibiotic medication Prior antibiotic treatment failure Receipt of wound care for the presenting infection

4.1.2 Primary and secondary outcomes

Primary and secondary outcomes are presented in in Table 3. Outcomes will be assessed during initial care (the date of enrollment to 10-14 days) and follow-up (30 days after initial care) unless otherwise specified.

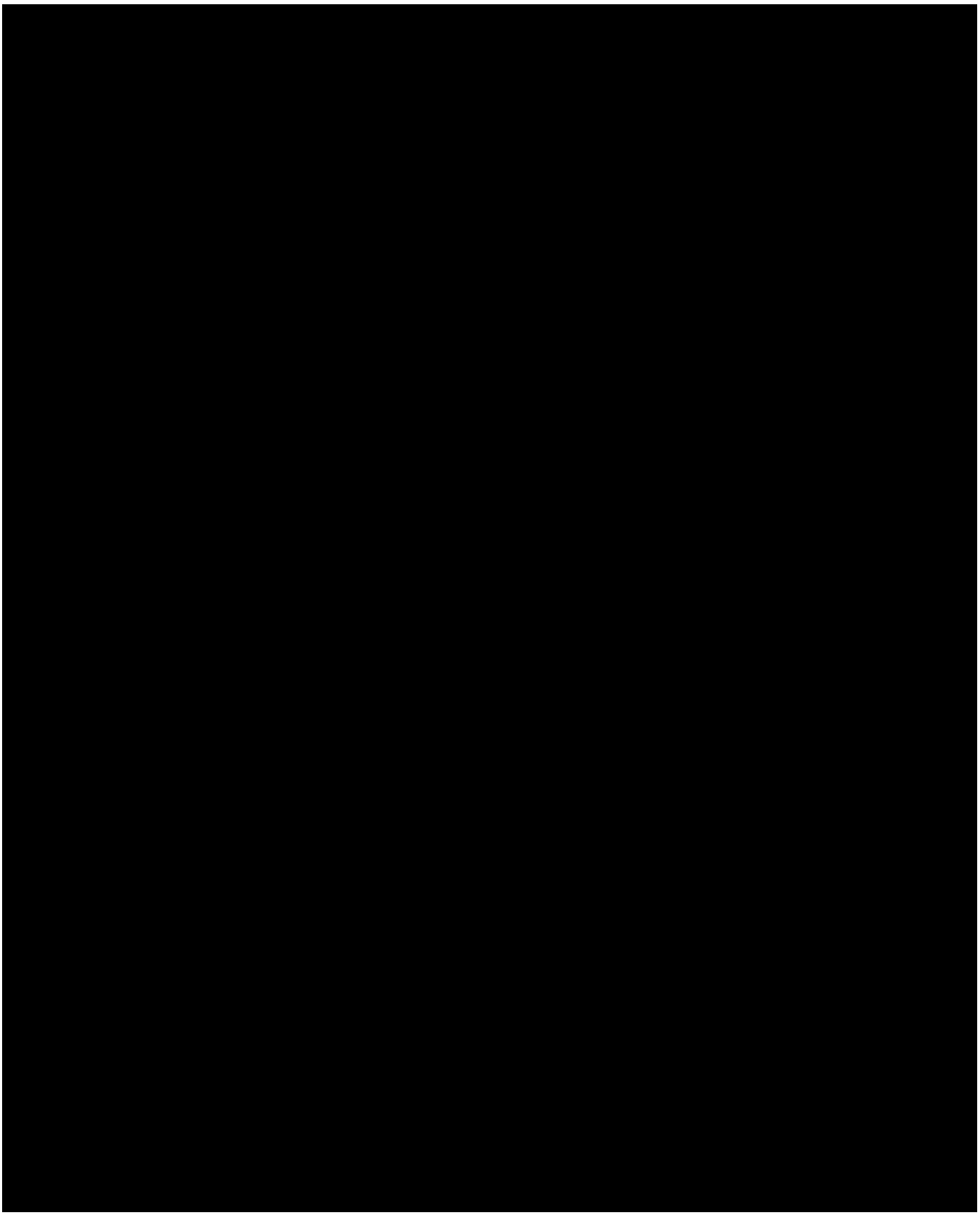
Table 3. Primary and secondary outcomes

Measure	Description
Infection-related total admitted hospital days during initial care and follow up	Includes days during the initial hospitalization and all other hospitalizations
Total admitted hospital days during initial care and follow up	Includes days during the initial hospitalization and all other infection-related hospitalizations
	Number of major unexpected surgeries
	Number of major expected surgeries

Measure	Description
Infection-related major surgical interventions that required operating room time during initial care and follow up	Number of all major surgical interventions unexpected or expected
Infection-related hospitalizations during initial care and follow up	Number of infection-related hospitalizations
Infection-related hospitalizations during initial care and follow-up that resulted in admission to Intensive Care Unit (ICU)	Number of infection-related hospitalizations resulting in admission to the ICU.
All cause hospitalizations in the 30 days post discharge from the hospital	Number of all hospitalizations for subjects including re-hospitalizations
Infection-related ED visits during initial care and follow up	Number of unexpected visits to ED
	Number of expected visits to ED
	All visits (unexpected and expected) to ED
Infection-related outpatient healthcare visits (e.g., physicians' office visits, ED visits, infusion center visits, home health visits) during initial care and follow up	Unexpected visits, by site (e.g., physicians' office visits, ED visits, infusion center visits, home health visits)
	Expected visits, by site (e.g., physicians' office visits, ED visits, infusion center visits, home health visits)
	All visits (unexpected and expected), by site (e.g., physicians' office visits, ED visits, infusion center visits, home health visits)
Use of PICC line or central line to administer antibiotic therapy during initial care and follow up	PICC line or central line placement for antibiotic therapy
Infection-related healthcare visits (e.g., hospitalizations, ED visits, other outpatient visits) due to PICC line or central line used to administer antibiotic therapy during initial care and follow up	Unexpected visits due to PICC line (i.e. complications)
	Expected visits due to PICC line (i.e. initial placement, monitoring of PICC line)
	All visits due to PICC line (both unexpected and expected visits)
Response to treatment at end of therapy visit	Response to treatment (healthcare provider assessment) comparing response at the 10-14 day visit (end of therapy visit). Response to treatment will be defined

Measure	Description
	through an assessment of erythema (erythema to be assessed as defined in Appendix 11.1: Measurement of lesion characteristics) and the absence of fever at 10-14 days. Response to treatment will specifically be defined as: **Complete response** Resolution of all baseline signs and symptoms, including fever, erythema, pain, and tenderness. **Partial response** Resolution of fever, pain, and tenderness, but with residual erythema **Failure** Persistence of fever, pain, and/or tenderness with or without residual erythema
Serious adverse events (SAEs) during initial care and follow-up	All SAEs as defined in Section 5 Safety assessments
Patient satisfaction with care (subject reported)	Patient satisfaction with care (Subject-reported, Section 11.2- questionnaire similar to the final implemented version)
Patient work and productivity loss (subject reported)	Number of days with lost/reduced productivity during follow-up, as measured through Work Productivity and Activity Impairment Questionnaire (Section 11.4)[30]
Patient Health-Related Quality of Life (HRQoL) (subject reported)	Health-related quality of life (subject reported), as measured through the Medical Outcomes Study Short Form-12 (SF-12), with acute recall (1 week recall) (Section 11.5)[31]

[redacted]



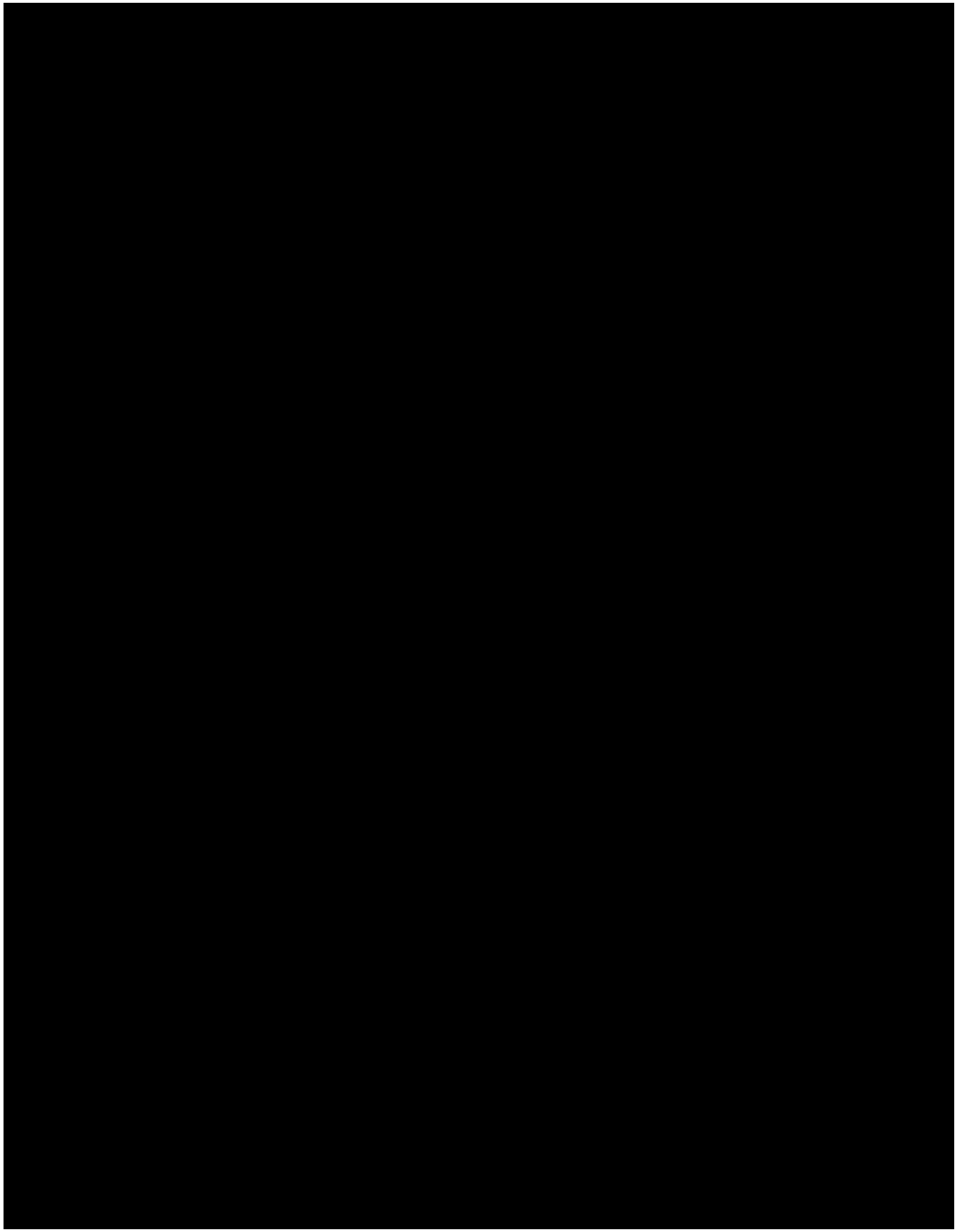
4.2 Data collection

Information on baseline characteristics, outcomes, and other measures will be collected following subject enrollment in the study and will be based on the medical record and CRFs that will be developed exclusively for use in this study.

Data collection will involve the use of the site's electronic data capture (EDC) system through use of CRFs, to which only authorized personnel will have access. Subject's data are to be entered into the EDC system by the investigator or designee using their assigned EDC user account. After data entry into the EDC system by the investigator or designee, a combination of manual and programmatic edit checks will be used to review the data for completeness, logic, and adherence to study protocol. As a result of these edits checks, data monitoring, and reviews, queries may be electronically issued to the site and should be answered electronically via the EDC system.

4.2.1 Data collection schedule

Table 5 describes expected follow-up. Follow-up visits will be scheduled between 48-72 hours after hospital discharge, 10-14 days after enrollment (end of treatment visit, both periods), and 44 days after enrollment (both periods). 48-72 hours after hospital discharge, both pre- and post-period patients will be called via telephone. A limited physical visit will be conducted 10-14 days after enrollment. However, for subjects unable to be seen back at the site, a telephone interview will suffice. Research data will be collected through follow-up visits at between days 10-14 through an in-person visit (end of treatment visit; if patient cannot be seen back at site, telephone call can occur up to 21 days from enrollment) and at 44 days (telephone call can occur up to 51 days from enrollment), through a telephone interview of the subject in both the pre- and post-periods. Additionally, electronic medical chart data will be reviewed at the 10-14 day and 44 day time points from enrollment. Any additional visits to the visit schedule below will be at the discretion of the subject and treating physician.



[redacted]

4.2.2 Patient Diary Aid

Patients will be provided with a bound, paper diary to record specific information about their health status on days in which they have an interaction with a health care provider. The diary is intended only as an aid to help patients remember details about health care appointments, medications, and medical tests. The diary will not be collected by or returned to study staff.

5 Safety assessments

At each visit, subjects are to be queried regarding any adverse events (AEs) or serious adverse events (SAEs) that have occurred since the previous visit. Subjects will be asked to volunteer information with a nonleading question such as, "How do you feel since your last visit?" Study site personnel will record all pertinent information in the subject's CRF. All AEs will be recorded on the appropriate AE reporting page of the subject's CRF whether or not they are considered causally related to the study drug (any antibiotic given for ABSSSI from enrollment, including the pre-period).

For every AE, the investigator will:

- Provide an assessment of the seriousness of the event (i.e., is it an SAE?), as well as the severity and causal relationship
- Document all actions taken with regard to the study drug
- Detail any other treatment measures taken for the AE
- Document the outcome of the AE

In addition, subjects will be reminded, as described in the ICF to notify site personnel of any AEs occurring from the time the subject signed the ICF until the final follow-up visit. Any AEs that are ongoing at the time of the final protocol-defined study visit will be followed until the condition returns to pre-study status, has resolved or stabilized, or can be explained as being unrelated to the study drug. If a follow-up visit is deemed necessary for appropriate safety surveillance, it will take place within 30 days of the final protocol-defined study visit.

5.1 Adverse events

An AE is any untoward medical occurrence in a patient or clinical trial subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment.

An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a product, whether or not considered related to the product. The definition of an AE includes:

- Worsening of a pre-existing condition or underlying disease
- Events associated with the discontinuation of the use of a product(s), (e.g., appearance of new symptoms)

Please note hospital admissions and/or medical/surgical procedures scheduled prior to consenting, but occurring during the study will not be captured as AEs, but will be listed in the medical history if related to a pre-existing condition. AEs or abnormal test findings will be followed until the event (or its sequelae) or the abnormal test finding resolves or stabilizes at a level acceptable to the sponsor/investigator.

5.2 Causality assessment

For each AE, the investigator will provide an assessment of causal relationship to the study drug. The causality assessment will be recorded on the appropriate AE reporting page of the subject's CRF. Causal relationship will be assessed by answering the following question:

Is there a reasonable possibility the study drug caused the event?

Yes: There is evidence to suggest a causal relationship between the study drug and adverse event; i.e.:

- There is a reasonable temporal relationship between the study drug and the event, and/or
- The event is unlikely to be attributed to underlying/concurrent disease, other study drugs, or other factors, and/or
- Positive dechallenge and/or rechallenge exist

No: There is no evidence to suggest a causal relationship between the study drug and adverse event, i.e.:

- There is no reasonable temporal relationship between the study drug and the event, or
- The subject did not take the study drug, or
- The event is likely to be attributed to underlying/concurrent disease, other study drugs, or other factors, or
- The event is commonly occurring in the (study) population independent of study drug exposure

5.3 Severity assessment

The investigator will provide an assessment of the severity of each AE by recording a severity rating on the appropriate AE reporting page of the subject's CRF. *Severity,* which is a description of the intensity of manifestation of the AE, is distinct from *seriousness,* which implies a subject outcome or AE-required treatment measure associated with a threat to life or functionality. Severity will be assessed according to the following scale:

Mild: Minor awareness of signs or symptoms that are easily tolerated without specific medical intervention

Moderate: Discomfort that interferes with usual activities and may require minimal intervention

Severe: Significant signs or symptoms that are incapacitating with an inability to work or perform routine activities and/or that require medical intervention

5.4 Serious adverse events

An SAE is any untoward medical occurrence that at any dose:

- Results in death
- Is life-threatening (i.e., the subject was, in the opinion of the investigator, at immediate risk of death at the time of the event, it does not refer to an event that hypothetically might have caused death if more severe)
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect
- Is an important medical event that might not be immediately life threatening or result in death or hospitalization but might jeopardize the subject or might require intervention to prevent one of the other outcomes listed above. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization or development of dependency or abuse.

In general, hospitalization signifies that the participant has been detained (usually involving at least an overnight stay) at the hospital for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting.

Emergency room visits that do not result in hospitalization should be evaluated for one of the other serious outcomes to determine whether they qualify as SAEs.

5.5 Medication error

Medication error refers to any unintended error in the dosing and/or administration of the study drug as per instructions in the prescribing information. Medication errors generally fall into 4 categories as follows:

- Wrong drug
- Wrong dose (including dosing regimen, strength, form, concentration, amount);
- Wrong route of administration;
- Wrong subject (i.e. not administered to the intended subject).

Medication Errors include occurrences of overdose and underdose of the study drug.

5.6 Procedure for collection of adverse events and serious adverse events

All nonserious AEs and SAEs that occur in a subject from the time he or she signs the ICF until the final follow-up visit will be assessed and recorded on the source documents and CRF, regardless of causal relationship to the study drug.

5.7 Procedure for serious adverse event reporting

All SAEs that occur in a subject from the time he or she signs the ICF until the final follow-up visit will be reported to the sponsor within 24 hours of awareness of the event using the provided SAE Report Form. The completed SAE Report Form will be sent directly to the sponsor by emailing [redacted]. In addition to completing the SAE Report Form, each SAE will be entered on the appropriate page of the CRF. The investigator will assess the causality for each SAE.

When death occurs with an SAE, the cause of death will be reported as an SAE. "Fatal" will be reported as the outcome for these events.

The sponsor will contact the investigator, if necessary, to clarify any of the event information. The investigator will provide any follow-up information for the event to the sponsor on an updated SAE report form as soon as it becomes available.

If the investigator is notified of a SAE that occurs post-study period, that he or she wishes to report to the sponsor (e.g., an event suspected to be causally related to the study drug), the event will be reported through the process described above.

Where appropriate, if required by local regulations or procedures, the investigator will report these events to the Institutional Review Board (IRB)/Ethics Committee (EC) and/or national regulatory authority in addition to the sponsor.

5.8 Procedure for medication error reporting

Medication errors with or without an associated AE will be recorded as medication errors in the CRF. SAEs associated with medication errors will be reported to the sponsor as described in Section 5.7.

5.9 Procedures for reporting pregnancies/lactation exposure

Occurrences of pregnancy/lactation exposure in a subject should be reported within 24 hours. In cases where a pregnancy/lactation exposure occurs with a SAE, the SAE report form should be used to report the SAE and the Pregnancy Reporting form should be used to report the pregnancy.

When a pregnancy occurs without any concurrent SAE, the Pregnancy Reporting form will be submitted alone. The pregnancy will be followed through to outcome of pregnancy, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications. Any pregnancy discovered from the time of consent to follow-up will be reported.

5.10 Potential Hy's Law cases

Every subject that meets potential Hy's law criteria,

- ALT or AST >/=3xULN AND
- Total Bilirubin >/=2xULN AND
- Alkaline Phosphatase <2xULN

occurring anytime from the time he or she signs the ICF for the trial until the final follow up visit, investigators will notify the sponsor immediately when all the above criteria have been met. A potential Hy's law case will be sent directly to the sponsor by emailing IR-clinical-SAE@allergan.com on an AE of Special Interest Form along with the SAE Report Form as soon as possible (within 24 hours of learning of the potential Hy's law). The CRF for potential Hy's law cases will be completed within seven calendar days. Every effort to determine the cause of the liver enzyme abnormalities will be made, and close monitoring will be initiated in conjunction with the medical monitor and in accordance with the FDA "Guidance for Industry: Drug Induced Liver Injury- Pre-Marketing Clinical Evaluation" July 2009.

6 Data analysis

Frequency and proportion of subjects deemed eligible and ineligible for study enrollment based on each of the inclusion/exclusion criteria will be summarized. The frequency and proportion of subjects who successfully complete the study, withdraw, were lost-to-follow-up, and who terminated the study early, will also be reported. Subject characteristics at baseline will be summarized and described for all enrolled subjects and compared between the pre- and post-periods. Site characteristics will also be described. Descriptive statistics (count, mean, standard deviation, range for quantitative variables, and counts and percentages for categorical variables) will be reported for all outcomes. The difference in study outcomes between the pre- and post-period will be assessed using appropriate statistical methods, accounting for study site, with adequate power. The primary outcome will be tested for simple superiority, and subsequently, tested for non-inferiority with a 10% margin between the pre- and post-periods.

The primary analysis of differences in LOS is performed using a 2-sided hypothesis test of the modified intent-to-treat principle such that all evaluable patients are included in the analysis. Patients are evaluable if they received at least one dose of antimicrobial therapy for their ABSSSI. Differences in length of stay are measured by Mann-Whitney U test.

The secondary endpoints in this study are intended for hypothesis testing and are not powered for statistical significance. Differences in continuous variables of secondary endpoints will be measured by Mann-Whitney U test, while difference in proportions will be analyzed by Fisher's exact test

All analyses will be specified in a detailed statistical analysis plan (SAP) that will be prepared subsequently and before database lock. The SAP will include table and figure shells.

6.1 Cost

Cost data will not be collected in the study. As these data often vary by site and insurer, representative unit cost estimates for each healthcare service/medication identified during the collection of outcome measures will be identified. Total costs of care for each study subject will then be estimated by multiplying utilization of healthcare services collected via the CRF by the corresponding unit costs; mean/median total costs of care during the pre- and post-periods will then be estimated and compared. The approach to the pre-post comparison and unit costs will be defined in the SAP.

6.2 Handling of missing data

The SAP will define how missing values and information from subjects lost to follow-up will be handled. Site procedures will be developed to minimize the amount of missing data however, as this is a pragmatic trial, missing data is expected. Certain outcomes are based on data availability from sites (e.g. laboratory values will be summarized for subjects who had data collected).

The extent of missing values will be examined to assess completeness of data among the study cohort. In addition, the characteristics of participants with and without missing data will be examined to assess whether participant characteristics have any relationship to incompleteness.

6.3 Sample size and sample size considerations

The sample size was estimated for a two-sided hypothesis test (two-sample equal-variance T-test) with a significance level of 0.05 comparing total hospital time (number of days) between the pre- and post-periods with 80% power. Assuming an average hospital length of stay of 4.0 days (inclusive of all enrolled subjects), with a standard deviation of 3.0 days, and a 2 day reduction in length of stay between the pre- and post-periods, it was estimated that 37 subjects in each arm of the trial (total enrollment of 74) would be required to demonstrate a mean reduction in hospital stay of 2 day. The final enrollment, including adjustments for attrition came to 86 subjects (43 patients in each period).

However, average length of stay and variance, which is correlated to the primary outcome of total hospital time for the study population, is largely unknown. The estimated sample size will be targeted, yet a subsequent sample size calculation will be undertaken through an interim analysis. The average length of stay and variance for the site will be determined once an estimated 25 subjects have been enrolled in the pre-period. Based on a revised sample size calculation at the time of the interim analysis, any adjustments to targeted sample size will be finalized.

6.4 Data monitoring and quality control

Before any subject enters the study, a representative of the sponsor will meet with the investigator and core study team to review the procedures to be followed during the study. Functionality training for electronic data capture (EDC) provided through REDCap or other suitable data platform will be provided via in-person training or computer to investigators and authorized designees on recording the data in the CRFs using the EDC system. All

subject information and data will be considered private health information and kept confidential in compliance with HIPAA (Health Insurance Portability and Accountability Act of 1996). After the first subject is enrolled, the sponsor will periodically monitor the progress of the study by teleconference and/or conducting on-site visits. The sponsor may request and review query statuses, possibly warranting more frequent communication and/or site visits with the investigator and the study site staff. The investigator will make available to the sponsor source documents (written notes and electronic medical records, if used), signed consent forms, and all other study-related documents. The investigator and the study site staff will be responsible for data entry of subject data into the CRFs via the EDC system, resolving data queries generated via the EDC system and providing missing or corrected data. The investigator will be responsible for approving all data entry and all changes performed on the data, and endorsing the subject data within the EDC system.

Quality control will be implemented and maintained throughout the conduct of the study. Data collection will involve the use of the EDC system provided by the site, to which only authorized personnel will have access. Subject's data will be entered into the EDC system by the investigator or designee using their assigned EDC user account as specified in Section 4.2 Data collection.

7 Study site and study administrative structure

7.1 Core study team

The core study team will consist of primary investigators and sponsor representatives. The primary investigators on the core study team will be responsible for training of the site study teams, responsible for adherence to the protocol, monitoring and reporting as consistent with regulation and law, and coordinating and participating in training sessions for the site study teams. The site investigators on the core study team is responsible for coordinating training of the site study teams for both protocol adherence and implementation and operationalization of the new critical pathway, including site-specific considerations. Training will occur before enrollment in the pre- and post-periods for adherence to the protocol. Training will additionally occur for implementation of the new critical pathway during the 2-4 weeks after the last subject is enrolled during the pre-period of the study.

7.2 Site study team

The site study team at each site will consist of the primary site investigators and study administrators, including hospital staff (including physicians, nurses, and/or pharmacists), who will be responsible for adhering to the protocol for both the pre- and post-periods. The site study team will be further supported by the core study team. The site study team will be responsible for participating in training sessions and/or engagement in communication from site investigators on the core study team, in regards to study background/rationale, site procedures to identify and enroll subjects who are eligible for the study during the pre- and post-periods, data collection, and follow-up of subjects. Specifically, for the post-period, training on the implementation of the new critical pathway is vital. Training will include site procedures, such as how to obtain study drug during the post-period from the hospital pharmacy and the location to administer study drug. This will ensure adherence to the protocol and that operationalization of the study is consistent during both study periods.

8 Ethical considerations

8.1 Regulatory and ethical compliance and protection of human subjects

To ensure safety of participating subjects, this study will be conducted in compliance with the protocol, the rules and regulations of each institutional review board (IRB), informed consent regulations, and standard operating procedures (SOP) of the sponsor, and the site. This study will adhere to all applicable local regulatory requirements and be governed according to local laws and regulations. The following rules, regulations, and practices will be adhered to: Good Clinical Practice (GCP) guidelines, International Conference on Harmonisation (ICH) Guidelines, Declaration of Helsinki, and the Belmont Report.

8.2 Subject confidentiality

All necessary measures will take place to ensure subject confidentiality. Only site study team members will know the identity of participating subjects, however no identifying information will be collected on any study-related documents. Any data provided to the sponsor will be provided by using the unique subject ID. The sponsor will not have access to any subject identification log. Any data reported or published will be presented as aggregated data, and no individual data will be reported to reduce any risk of subject identification.

8.3 Informed consent procedures

Patients, after being given an explanation of the study, will give voluntary and written informed consent and HIPAA (Health Insurance Portability and Accountability Act of 1996) authorization (in compliance with 21 CFR, Parts 50 and 312) or other appropriate documentation, according to local regulatory requirements, before participating in any study-related procedures.

Informed consent will be obtained from each subject prior to the beginning of any study-specific activities, and will include consent to collection of clinical, economic and humanistic outcomes. This may involve gathering data through chart review or directly eliciting information from subjects. Informed consent during the post-period, or interventional period, will involve consent to treatment through a new critical pathway and consent to collection of clinical, economic and humanistic outcomes. Each eligible subject will have the opportunity to read and review the approved informed consent form (ICF) and have the opportunity to ask questions to the participating Study Investigator, Study Coordinator, or other study team member. Signed copies of the ICF and the HIPAA or other locally applicable form will be given to the subject, and both documents will be placed in the investigator's study files.

The participating subject may withdraw participation and/or informed consent at any time throughout the conduct of the study. Withdrawing participation will relieve the subject from any future data collection time points; withdrawing consent will relieve the subject from any future data collection time points and remove any historic study data collection.

8.4 Responsibilities of the investigator and IRB

The responsibilities of investigators include creation of and maintenance of a core study team (Please refer to Section 7 for more information), adhering to protocol requirements, including

educational requirements for implementation of the intervention in the post-period, and ultimately, are the institutional leads to support protocol implementation. The study team will be responsible for timely reporting, where appropriate, to the institutional IRB. The investigators must demonstrate reasonable efforts to obtain qualified patients for the study.

The responsibilities of the IRB include adhering to institutional requirements, performing an objective review of the acceptability of the study protocol and analysis plan (i.e. research) in terms of institutional requirements, commitments, regulations, applicable law, and professional conduct and practice, provide continued monitoring and review of research, review of key events (protocol amendments, protocol deviations, adverse events, or non-compliance), review of any required progress reports, and to report any required information to appropriate authorities and/or organizations.

8.5 Publication

All data generated in this study are the property of the sponsor. An integrated clinical and statistical analysis report will be prepared at the completion of the study.

Publication of the results by the investigator will be subject to mutual agreement between the investigator and the sponsor and will follow the sponsor's SOP on publications.

9 Protocol deviations and violations

A *protocol deviation* is any change, divergence, or departure from the study design or procedures that is under the investigator's responsibility and oversight (as defined by regulations) without prior written IRB approval or favorable opinion of an appropriate amendment and that does not have a major impact on the subject's rights, safety, or well-being, or on the integrity and authenticity of the study data. Deviations may include, but are not limited to, departure from inclusion/exclusion criteria, dosing, duration of treatment, failure to perform the required assessments at specified time points, scheduling of visits not in accordance with specifications, or subject safety. Deviating from the protocol is permitted only if absolutely necessary for the safety or clinical management of the subjects and will immediately be reported to the sponsor. Protocol deviations will be reported to the sponsor either verbally or electronically within 5 working days from the day of discovery.

A *protocol violation* is a form of protocol deviation that has a major impact on the subject's rights, safety, or well-being, or on the integrity and authenticity of the study data. Protocol violations will be reported to the sponsor within 24 hours, if possible. The IRB will be notified within the time period dictated by the IRB associated with this study.

9.1 Protocol amendments

Any amendment to this protocol will be provided to the investigator in writing by the sponsor. No protocol amendment will be implemented (with the exceptions noted below) before it has been approved by the IRB and the signature page, signed by the investigator, has been received by the sponsor. If the protocol is amended to eliminate or reduce the risk to subjects, the amendment will be implemented before IRB review and approval. However, the IRB will be informed in writing of such an amendment, and approval will be obtained within reasonable time limits.

10 References

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11 Appendices

11.1 Measurement of lesion characteristics

Measurements are to be taken while the infected area is in a nondependent position, e.g., if infection was on the leg, the subject was lying down, not sitting or standing. All types of infections are to be measured as measurement of erythema upon enrollment and any subsequent physical follow-up visits. Maximal dimensions of erythema, both width and length, are to be recorded in centimeters. Investigators should attempt to find the infection edge that best distinguished erythema from non-erythematous skin. Erythema is to be measured in the dimension of maximal length. The maximal width is to be measured perpendicular to the axis of the maximal length. The maximal width measurement does not have to be in the center if the area of erythema is irregular. The length of the infection is to be multiplied by perpendicular width of wound.