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Study ID: CMO-US-ID-0476

Title: A Pragmatic Trial Designed to Evaluate a New Critical Pathway for Treatment of Patients with Acute Bacterial Skin and Skin Structure Infections – ADVANCE

Statistical Analysis Plan: 05 FEB 2019

[redacted]

Statistical Analysis Plan

Version 1.0 Dated: 05FEB2019

ADVANCE: A Pragmatic Trial Designed to Evaluate a New Critical Pathway for Treatment of Patients with Acute Bacterial Skin and Skin Structure Infections

Protocol Number: CMO-US-ID-0476
Amendment v 3.0 Dated: 11Jan2018

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Allergan

Statistical Analysis Plan - Approval

ADVANCE: A Pragmatic Trial Designed to Evaluate a New Critical Pathway for Treatment of Patients with Acute Bacterial Skin and Skin Structure Infections

Protocol:
Number: CMO-US-ID-0476
Version: 3.0
Date: 11JAN2018

Statistical Analysis Plan
Version: 1.0
Date: 05 February 2019

This Statistical Analysis Plan has been reviewed and approved by the individuals listed below.

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Allergan

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
ABSSSI	acute bacterial skin and skin-structure infections
AE	adverse event
AIDS	acquired immune deficiency syndrome
BMI	body mass index
BP	blood pressure
CCI	Charlson Comorbidity Index
CCR	cost:charge ratio
CI	confidence interval
CRF	case report form
CSR	clinical study report
ED	emergency department
FAS	full analysis set
GFR	Glomerular filtration rate
g/dL	grams per deciliter
HIV	human immunodeficiency virus
HRQoL	health-related quality of life
HRU	health resource utilization
ICU	intensive care unit
LOS	length-of-stay
LTC	long-term care
MedDRA	Medical Dictionary for Regulatory Activities
MIC	minimum inhibitory concentration
MCS	mental component score
MOS	medical outcomes study
mEq/L	milliequivalents per liter
mmHg	milliliter of mercury
mmol/L	millimolar
mg/dL	milligrams per deciliter
MRSA	Methicillin-resistant *Staphylococcus aureus*
OPAT	outpatient parenteral antibiotic therapy
PICC	peripherally inserted central catheter
PCS	physical component score
PRO	patient-reported outcome
SAE	serious adverse event
SAP	statistical analysis plan
SAS	statistical analysis system
SD	standard deviation
SF	short-form
SIRS	Systemic Inflammatory Response Syndrome
SNF	skilled nursing facility
US	United States
WHO	World Health Organization
WPAI	Work Productivity and Activity Impairment Questionnaire

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1.0 Introduction

This statistical analysis plan (SAP) outlines the planned analysis for data collected within Allergan study CMO-US-ID-0476, entitled "A Pragmatic Trial Designed to Evaluate a New Critical Pathway for Treatment of Patients with Acute Bacterial Skin and Skin Structure Infections". This SAP applies to the protocol, Amendment Version 3.0, dated January 11th, 2018, and provides a description of methods for handling the data. The protocol, Amendment Version 3.0, reflects an adjustment to the primary outcome based on the results from the interim analysis.

This pragmatic trial has been developed to assess a new critical pathway for the treatment of ABSSSI; it will include the use of guideline-based criteria to identify patients eligible for outpatient parenteral antibiotic therapy (OPAT), and, for those who meet these criteria, the use of dalbavancin — a novel, single-dose, long-acting, second generation lipoglycopeptide indicated for the treatment of ABSSSI caused by susceptible strains of Gram-positive bacteria.

2.0 Study Objectives

2.1 Primary Objective

The primary objective of the study is to estimate the difference in hospital admission rate at the initial episode of care comparing ABSSSI patients receiving care before implementation of the new critical pathway and after implementation.

2.2 Secondary Objectives

The secondary objectives of this study are to estimate the difference in the following outcomes during initial care (the date of enrollment to 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:

- Total admitted hospital days during initial care and follow-up
- Infection-related total admitted hospital days during initial care and follow-up
- ED length of stay (LOS) at initial episode of care (time from triage to release from ED)
- 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)

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- All cause hospitalizations in the 30 days post discharge from the hospital or release from the ED
- Infection-related ED visits during initial care and follow-up (number of expected, number of unexpected and number of total ED visits during initial care and 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)
- Serious adverse events (SAEs) during initial care and follow-up
- Patient satisfaction with care (patient reported or completed by a caregiver if the patient cannot complete)
- Patient work and productivity loss (patient reported or completed by a caregiver if the patient cannot complete)
- Patient Health-related Quality of Life (HRQoL) (patient reported or completed by a caregiver if the patient cannot complete)

3.0 Study Design

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. The pre-period and post-period will consist of independent groups of patients. During the pre-period, each participating site will implement the first component of the critical pathway through implementation of guideline-based criteria to identify patients at the point of care in the ED, obtain informed consent, and monitor enrolled patients. Sites 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 patient who meets all inclusion and exclusion criteria. Blinding of treating physician to patient enrollment in the study during the pre-period will ensure unbiased provision of usual care. During the post-period, for all patients 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 ED to each study patient who meets all inclusion and exclusion criteria. Sites are expected to transition to the post-period at the enrollment of 50 patients. There is no expectation for all sites to transition to the post-period at the same time.

For both periods of interest, patient follow-up spans the period beginning on the day of study enrollment and ends 44 days thereafter, which incorporates an initial care period of 14 days (reflecting the 10–14-day period during which most antibiotics are anticipated to be required for care of ABSSSI) and a subsequent "follow-up" period of 30 days. Study measures will be collected as described in the protocol and will be based on medical records, unless otherwise indicated.

A schedule of assessments is provided in Appendix A. Follow-up visits will be scheduled for approximately 24 hours after enrollment (post-period only), 48-72 hours after enrollment (post-period only), 14 days after enrollment (both periods), and 44 days after enrollment (both periods). Any additional visits to the visit schedule below will be at the discretion of the patient and treating physician.

The duration of the study was not predetermined; it is dependent on the time required to enroll the necessary number of eligible patients (161 patients per time period; 322 patients enrolled in all).

4.0 Study Measures

4.1 Study Site Characteristics

Study site characteristics consist of counts of all-cause admissions, skin infections, pneumonia, diabetic foot infection, and infective endocarditis recorded at each site. These will be collected in paper admission logs monthly or bimonthly from the sites. These will be entered into an Excel spreadsheet by Mapi's Clinical Operations team, which will then be brought into [redacted] for analysis.

4.2 Baseline Characteristics

The following baseline characteristics will be collected:

- **Demographic data**: Age (in years, derived and described in Appendix B), gender, ethnicity, race, employment status, and location patient presents from (e.g. from home, long-term care [LTC], skilled nursing facility [SNF], nursing home).
- **Comorbidities**: Morbid obesity (derived and described in Appendix B), myocardial infarction, congestive heart failure, peripheral vascular disease, cerebrovascular disease, dementia, chronic pulmonary disease, rheumatologic disease, peptic ulcer disease, mild liver disease, diabetes with/without complications, renal disease, moderate or severe liver disease (Child-Pugh Class B and C), any malignancy (including leukemia and lymphoma), metastatic solid tumor, cancer (active, remitted/cured), alcohol/drug abuse/illicit needle use, malnutrition,

human immunodeficiency virus, other immuno-compromising conditions, altered mental status, lymphedema or chronic venous stasis, and peripheral vascular disease.

- **Charlson Comorbidity Index (CCI)**: A derived variable based on the presence/absence of the comorbidities specified above. The formula by which the CCI is calculated is detailed in Appendix C.
- **Infection type**: Cellulitis/erysipelas, wound infection, major cutaneous abscess
- **Infection and clinical characteristics during the initial assessment in the ED**:
  - Lesion size and location
  - Fever (>100.4˚F; >38.0˚C; or site-specific definition)
  - *Systemic inflammatory response syndrome* (SIRS) (see Appendix B)
  - Blood pressure (BP, in mmHg)
  - Serum creatinine (mg/dL)
  - C-reactive protein (mg/dL)
  - Rapid microbial assay
  - Microbiological culture type (i.e., blood, wound swab, urine) and results thereof
  - Presence of recurrent infection and/or any ABSSSI infections in the prior 6 months
- **Utilization of healthcare services in prior 3 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 (determined by discontinuation of treatment due to worsening or recurrent ABSSSI or the occurrence of an adverse event related to the antibiotic), and receipt of wound care for the presenting infection. The utilization will be based on examination of the patient's medical records.

4.3 Primary Outcome

The primary outcome (hospital admission rate) will be assessed during the initial episode of care.

4.4 Secondary Outcomes

Secondary outcomes will be assessed during initial care (the date of enrollment to day 14) and/or follow-up (30 days after initial care), and include:

[redacted]

Measure	Definition	Period of Assessment
Total admitted hospital days	Total LOS during the 44 days of the study (including initial hospitalization)	Initial care and follow-up
Infection-related total admitted hospital days	Total LOS of all infection related hospitalizations during the 44 days of the study (including initial hospitalization)	Initial care and follow-up
ED LOS	Time spent in ED in hours from triage to release (either admitted to the hospital, admitted to observation, or released to home)	Initial episode of care
Infection-related major surgical interventions that required operating room time	Number of all, unexpected and expected infection-related major surgical interventions that required operating room time	Initial care and follow-up
Infection-related hospitalizations	Number of infection-related hospitalizations	Initial care and follow-up
Infection-related hospitalizations that resulted in admission to intensive care unit (ICU)	Number of infection-related hospitalizations resulting in admission to the ICU.	Initial care and follow-up
All cause hospitalizations in the 30 days following discharge from the initial hospitalization or release from the initial ED visit (if not hospitalized)	Number of all hospitalizations for patients discharged from the ED and re-hospitalizations for patients who had an initial hospital admission	Overall, including Initial care and follow-up
Infection-related ED visits	Number of all, unexpected and expected infection-related ED visits	Initial care and follow-up

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Measure	Definition	Period of Assessment
Infection-related outpatient healthcare visits (e.g., physicians' office visits, ED visits, infusion center visits, home health visits)	Number of all, unexpected and expected infection-related outpatient healthcare visits, generated for all patients and repeated by site.	Initial care and follow-up
Use of PICC line or central line to administer antibiotic therapy	Number of PICC line or central line placement for antibiotic therapy	Initial care and follow-up
Infection-related healthcare visits (e.g., hospitalizations, ED visits, other outpatient visits) due to PICC line or central line used to administer antibiotic therapy	Number of all, unexpected and expected infection-related healthcare visits due to PICC line or central line used to administer antibiotic therapy	Initial care and follow-up
Serious adverse events (SAEs)	Number of events, number of patients and percentage of patients experiencing SAEs as described in protocol	Initial care and follow-up
Patient satisfaction with care	Summarize patient satisfaction with care (reported by patient, questionnaire provided in protocol). This will be completed by a caregiver if the patient cannot complete.	Follow-up
Patient work and productivity loss	Number of days with lost/reduced productivity, as measured through the Work Productivity and Activity Impairment (WPAI) questionnaire. This will be completed by a caregiver if the patient cannot complete.	Follow-up

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Measure	Definition	Period of Assessment
Patient HRQoL	Patient reported, as measured through the SF-12[1] (short-form), with acute recall (1-week recall). This will be completed by a caregiver if the patient cannot complete.	Initial care (in person) and follow-up (over phone). Change scores calculated for initial care

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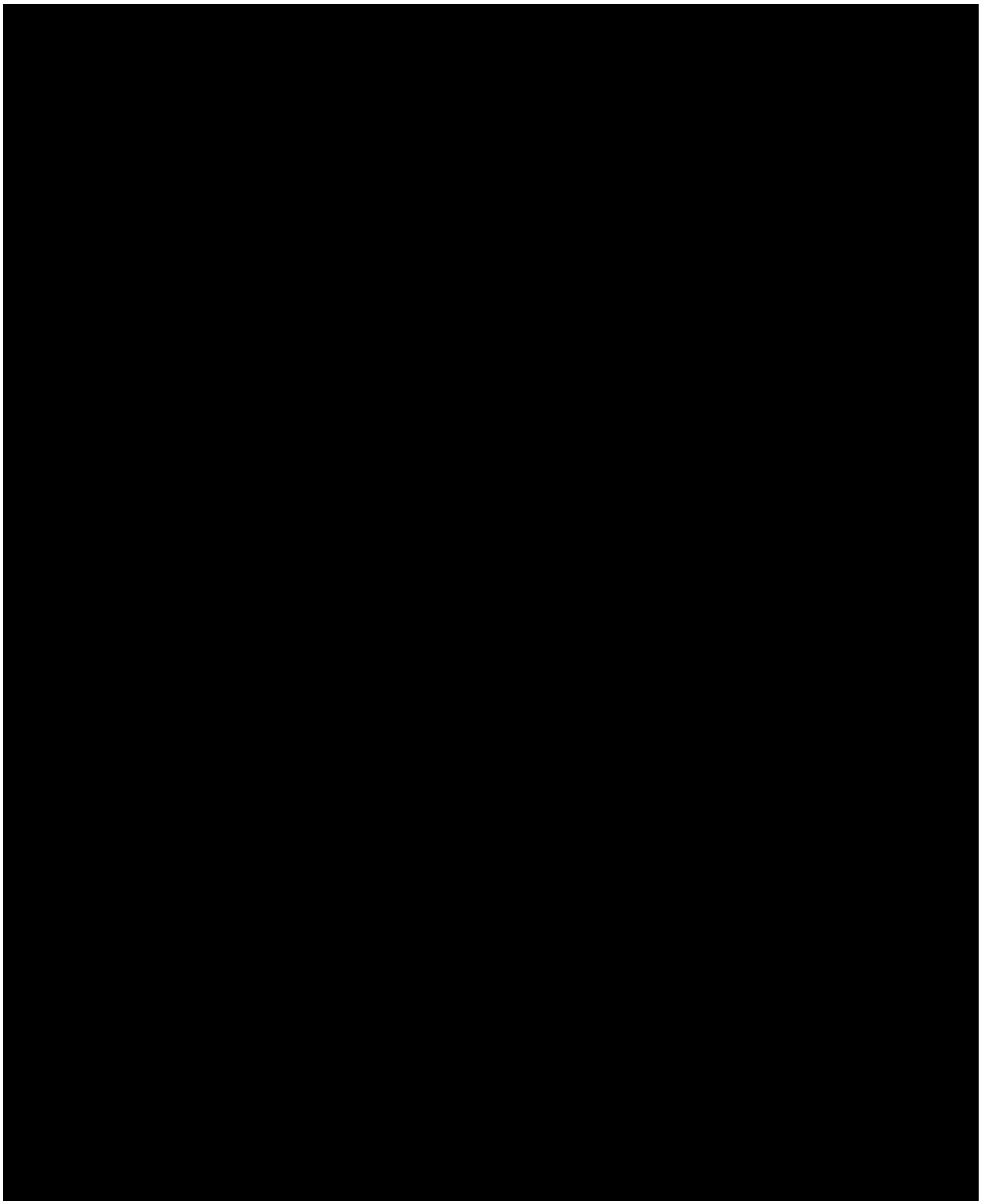

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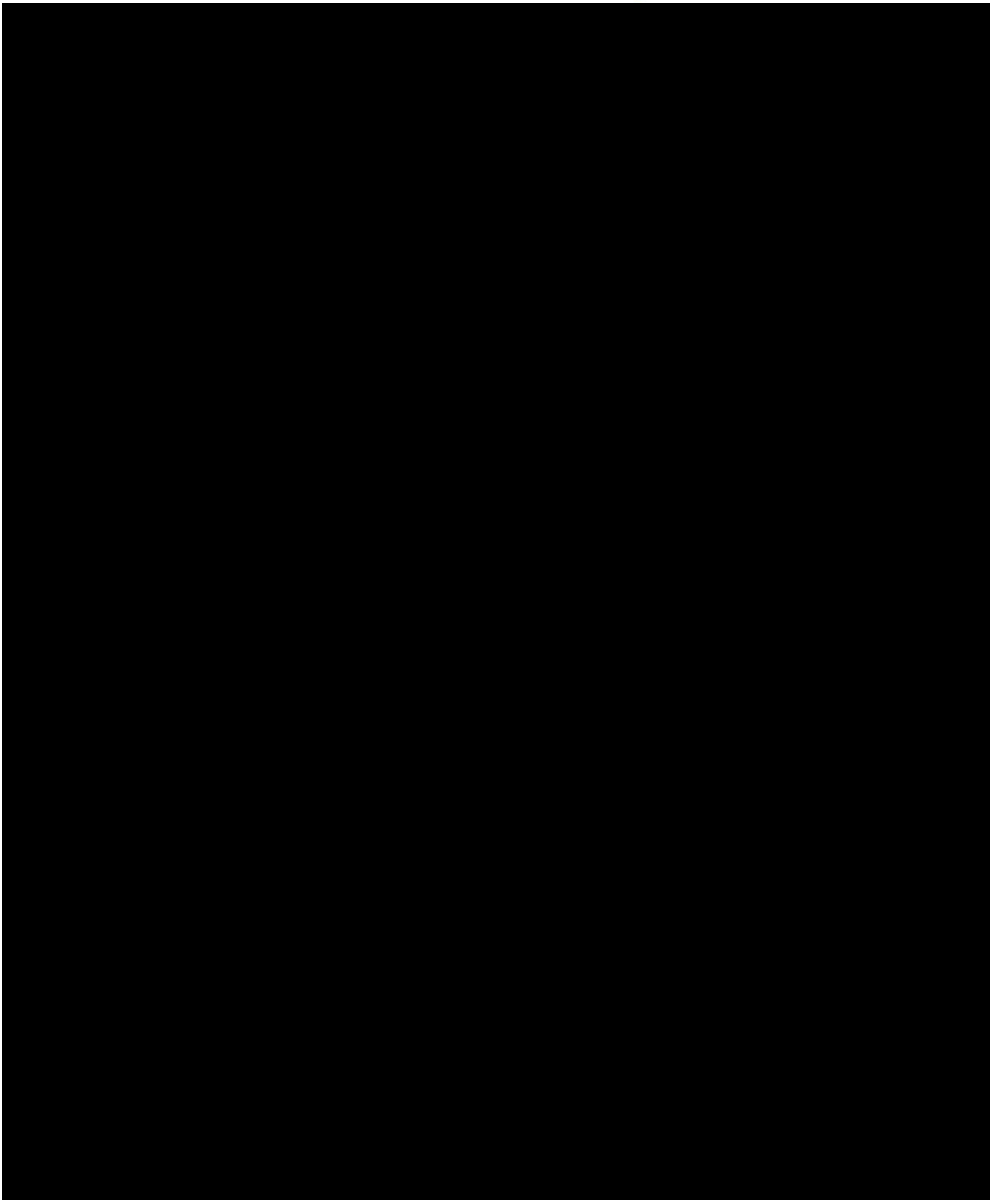

4.7 Safety

At each visit, patients will be queried regarding adverse events (AEs) and SAEs, and medication errors that occurred since the previous visit. Specifically, patients will be asked to volunteer information with a non-leading question

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such as, "How do you feel since your last visit?" Study site personnel will record all pertinent information in the patient's case report form (CRF), as described in details in the protocol.

5.0 Changes in the Protocol Specified Analyses

Infection characteristics described in the protocol including hyperglycemia (>120mg/dL blood glucose or site-specific definition), thrombocytopenia (<150,000 platelet count or site-specific definition), acidosis (<7.35 pH of the blood or site-specific definition or described in medical chart), hyponatremia (<135 mEq/L blood sodium or site-specific definition), uremia (as described in medical chart), and anemia (14-18 g/dL hemoglobin for men or 12-16 g/dL hemoglobin for women or site-specific definition) will not be derived from laboratory values or reported in analysis.

An interim analysis was performed after the enrollment of approximately 75 patients to evaluate the original sample size. It was determined a sample size greater than 322 would be needed for hypothesis testing of the primary outcome of total number of days spent in the hospital. Factors that contributed to the large sample size include:

- The observed variation was larger than the original estimate (SD = 3.0 days).
- The observed attrition rate was larger than the original assumption (10%).

Additionally, the observed mean total LOS was much smaller than the protocol assumption (4.0 days). It was determined that observing a statistically significant reduction in the total number of days spent in the hospital in the post-period was unlikely.

Based on results of the interim analysis, an adjustment was made at the time of the analysis to revise the primary outcome from total admitted hospital days to hospital admission rate at initial episode of care. The initially estimated final enrollment of 322 subjects, including adjustments for attrition, would support one-sided hypothesis testing (two-sample Pearson chi-square test for proportion difference with equal group weights using a normal approximation) with a significance level of 0.05 and at least 80% power assuming hospital admission rate comparing the pre- and post-periods were 38% versus 23%. This change has been reflected in the protocol, Amendment Version 3.0.

6.0 Statistical Plan and Methods

As the data are analyzed, some deviations from expectations and/or assumptions will become apparent (e.g., missing data, distributional assumptions, and small sample sizes in some subgroups of interest). In

instances where these deviations would make the proposed analyses inappropriate/infeasible and/or difficult to interpret, modifications to the analysis plan will be made accordingly, and noted in the final report.

6.1 General Considerations

6.1.1 Analysis populations

Enrolled Set

The enrolled set consists of all patients who have signed informed consent and met all study eligibility criteria. Data will be summarized on disposition and baseline characteristics. Output will be summarized by study period (pre-period vs. post-period). All data listings will be reported for the enrolled set unless specified in Section 5.2.

Full Analysis Set

The full analysis set (FAS) population consists of all enrolled patients. Additionally, patients in the pre-period must receive at least one dose of antibiotics and patients in the post-period must receive at least one dose of dalbavancin for inclusion. All patients in the pre-period and post-period will be analysed. Data will be summarized by study period.

Data from all patients will be aggregated across sites, and all analyses related to protocol outcomes and baseline characteristics will be undertaken on the aggregate pre- and post-periods.

6.1.2 Sample size

Hospital admission rate, which is correlated to total hospital time for the study population, was largely unknown for purposes of sample size estimation. The final enrollment to support hypothesis testing for a primary outcome of total admitted hospital days was initially calculated as 322 subjects (161 subjects in each period). The sample size was evaluated after a planned interim analysis of pre-period data once 75 subjects were enrolled in the pre-period. Based on results of the interim analysis, an adjustment was made at the time of the analysis to revise the primary outcome from total admitted hospital days to hospital admission rate at initial episode of care. The initially estimated final enrollment of 322 subjects, including adjustments for attrition, would support one-sided hypothesis testing (two-sample Pearson chi-square test for proportion difference with equal group
weights using a normal approximation) with a significance level of 0.05 and at least 80% power assuming hospital admission rate comparing the pre- and post-periods were 38% versus 23%.

6.1.3 Rounding

Means and medians will be rounded to one decimal more than that which the variable was recorded. Standard deviations will be rounded to two decimals more than that which the variable was recorded.

Percentages will be rounded to the nearest integer. Percentages for responses to a variable will only include patients with non-missing data, i.e. the denominator will be the number of patients with non-missing data.

P-values will be reported to three decimal places. Probabilities that are <0.001 will be presented as "<0.001."

6.1.4 Handling of outliers

Outliers will be examined using descriptive statistics, making sure that the minimum and maximum of the variable of interest are not unusually small or large and that the standard deviation seems appropriate for the data. If an outlier(s) is detected (e.g; more than 3 SD from the mean), the accuracy of the entry of the data point(s) will be verified (when possible) and corrected if appropriate.

Potential outliers will be identified prior to any statistical analysis. The effect of the any outliers on the analysis will determined by the statistician. Outliers will be included in or excluded from the statistical analyses as appropriate.

6.1.5 Handling of missing and/or incomplete data

Patients will be missing specific data points for a variety of reasons. With the exception of validated instruments, missing values for a given time point will not be imputed and analyses will be conducted using an observed case approach. For validated instruments, missing items will be handled according to instructions from the relevant scoring manuals.

Where both date and time are collected, partial times (i.e. times with missing minutes or times with missing hours and minutes) will be estimated by a worst-case imputation approach (e.g., impute such that duration is the longest possible value). Analyses will be conducted using an observed case approach for partial or missing dates.

6.1.6 Interim analysis

As documented in the protocol, Amendment Version 3.0, there was an interim analysis of data to check the sample size assumptions based on approximately 75 enrolled pre-period patients. A separate report was completed on the interim analysis. No further interim analysis is planned. The output that was produced for the interim analysis is denoted in the table shells with a ∫ following the title.

6.1.7 Subgroup analyses

Currently no subgroup analyses are planned for this study. If applicable, analyses will be repeated for subgroups of interest. Exploratory analyses will be performed such that selected outputs are repeated by sites if needed.

6.1.8 Statistical software

All analyses will be performed by statisticians/data analysts, in accordance with Good Programming Practices guidelines, and will follow the statistical analysis plan outlined in this document, including the corresponding table shells referenced herein. All analyses will be performed using [redacted]. Table, listing and figure output will be generated and delivered as Adobe Acrobat (PDF) files.

6.1.9 Quality Control

All output will be validated and/or QC'd according to Mapi standard operating procedures. Output tables and figures will be double programmed and undergo statistical review prior to being sent to Allergan.

6.2 Statistical Methods

Descriptive analyses will be performed as follows: for continuous variables, patient counts, percentages, means, 95% confidence intervals (CI) of the means, standard deviations (SD), medians, first (25^{th} percentile) and third (75^{th} percentile) quartiles, minima and maxima, and number missing (where applicable) will be reported. For categorical variables, patient counts and percentages for each category, as well as number missing (where applicable), will be reported. Where applicable, summaries for continuous variables will include frequencies and percentages for discrete categories (e.g., number of ED visits: 0, 1, 2, and so forth).

For applicable categorical measures of baseline characteristics (including demographics, infection characteristics at baseline, comorbid conditions reported at baseline, and prior healthcare resource utilization within past 3 months), the pre-period cohort will be compared with the post-period cohort using chi-square tests or Fisher's exact tests, as appropriate. Differences in proportions of the pre-period and post-period and their corresponding asymptotic 95% confidence interval (CI) will be reported, where applicable. For applicable continuous variables, two-sided Student's t-tests and Mann-Whitney U tests will be used where normality assumptions have, and have not, been met, respectively. Where applicable, differences in descriptive statistics, proportions, and corresponding 95% CI will also be provided between the pre- and post-periods.

Hypothesis testing is specified for outcomes in section 6.2.5. All statistical testing, if done, will be two-sided at the significance level of 0.05 with the exception of the primary outcome, which will be tested with a one-sided Pearson chi-square test for proportion difference with a significance level of 0.05. Secondary outcomes will be analyzed predominantly by descriptive analyses and by number of incidences where applicable. Planned analyses are presented in Sections 6.2.5.2. All planned hypothesis testing and any

unplanned deviation from hypothesis testing for secondary outcomes will be purely exploratory, as adequate power will not likely be present to determine statistical significance. There will be no adjustments made for multiple comparisons.

6.2.1 Patient Disposition

The number and percentage of enrolled and FAS patients, number and percentage of patients who complete the study, and number and percentage of patients who discontinue from the study and reason for withdrawal will be summarized in tables for all patients and repeated by site. This information will also be reflected in a data listing including the patient's enrollment date, early discontinuation or study completion date, and date of death, if applicable. Patients who are excluded from the enrolled set due to not meeting inclusion or exclusion eligibility criteria will be summarized in listings.

Although tables and listings will not reflect screen failures captured with enrollment logs, the clinical study report (CSR) text will address the approximate number of screen failures and the most common reasons for screen failure.

6.2.2 Study Site Characteristics

Study site characteristics will be summarized in a table by the pre-period and post-period. Specifically, number of patients and overall percentages will be described for study site characteristics (skin infection, pneumonia, diabetic foot infection and infective endocarditis admissions relative to all-cause hospital admissions) in a table and proportions amongst the pre-period versus the post-period will be compared by a 2-sample Z-test.

6.2.3 Demographic and Baseline Characteristics

All demographic data will be summarized in tables and listings by the pre-period and post-period for the enrolled and FAS populations. Descriptive statistics will be summarized for age (in years), height at baseline (in cm), weight at baseline (in kg) and BMI at baseline (in kg/m^2). Patient counts and percentages will be summarized for age (e.g., <20 years, 20-29 years, 30-39 years, etc.), race/ethnicity, gender, employment status (e.g., employed, full time, part time, unemployed), admission source (e.g., from home, LTC, SNF, nursing home), and insurance information. This information will be captured in listings with date of birth.

All baseline characteristics for comorbid conditions will be summarized by the pre-period and post-period for the FAS population by patient counts and percentages in tables and include the following measures: morbid obesity, myocardial infarction, congestive heart failure, peripheral vascular disease, cerebrovascular disease, dementia, chronic obstructive pulmonary disease, connective tissue disease, peptic ulcer disease, mild liver disease, moderate or

severe liver disease (Child- Pugh Class B and C), hemiplegia, lymphedema / chronic venous stasis, diabetes mellitus (with and without end-organ damage), moderate to severe chronic kidney disease (e.g., actual measurement and GFR, estimated measurement and GFR, unknown measurement), leukemia and remission status, lymphoma and remission status, metastatic solid tumor and remission status, alcohol abuse, drug abuse including illicit needle use, protein calorie malnutrition, immuno-compromising conditions such as HIV, AIDS, receiving ≥20 mg Prednisone daily (or therapeutically equivalent steroid), receiving TNF inhibitors, receiving any other immune modulating medication including biologics, and receiving chemotherapy. The Charlson Comorbidity Index will be derived and described by descriptive statistics. All data will be reflected in listings.

Healthcare resource utilization within the 3 months prior to study enrollment will be reported in tables by the pre-period and post-period for the FAS population. Number of patients and percentages of occurrences (e.g., none, any, 1, 2, ≥3) and primary reasons for the following will be reported: hospitalizations, admissions to the ICU, surgical interventions, and ED or outpatient visits. Descriptive statistics will also be presented for these variables. Additionally, number of patients and percentages of coded diagnoses terms will be reported for hospitalizations and admissions to the ICU and number of percentages for specified surgical procedures. The number and percentages of patients with minor and major surgical procedures will be displayed. The table will also reflect the number and percentages of patients with dialysis use, prior medications used for chronic diseases, prior use of antibiotics, and wound care for the presenting infection. Listings for hospitalizations will capture the type of visit, primary reason for visit, primary diagnosis (coded and verbatim), admission date and time, discharge date and time, ICU admissions for hospitalizations and discharge disposition. Prior antibiotic medications will be reported in a listing and will include start date and end date, medication named (coded and verbatim), reasons for prescription, dose with units and frequencies, route, and reason for discontinuation.

6.2.4 Infection Characteristics at Baseline

Patient counts and percentages will be summarized by the pre-period and post-period for the FAS population for primary infection type, purulent drainage from primary lesion, primary lesion location, primary lesion size (75cm^2 – 150 cm^2, ≥150 cm^2) number of additional lesion (e.g., 0, 1, 2, ≥3), fever, SIRS (met i.e., ≥2 criteria present, by individual criteria, and by number of criteria met) and recurrent/ABSSSI infection in prior 6 months. Descriptive statistics will be summarized for primary lesion size. Differences in infection characteristics between the pre- and post-period will be assessed using statistical significance testing. All of the aforementioned variables will be reflected in listings.

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6.2.5 Care Pathways Following the Initial Episode of Care

The care patways of patients following the initial episode of care will be summarized using descriptive statistics for the FAS population by the pre- and post-periods and by whether or not the patient was admitted. Variables to summarize will be: Dalvance use, time (hr) in ED at initial episode, time (hr) admitted under observation status, total LOS (days) during the initial hospitalization, total time in ICU (days) during the initial hospitalization, discharge status, and discharge disposition.

6.2.6 Outcomes

6.2.6.1 Primary Outcomes

Primary Outcome: Hospital Admission Rate at Initial Episode of Care

Hospital admission at initial episode of care will include infection-related stays upon discharge from the index ED visit (derived and described in Appendix B). Tables will reflect patient counts and percentages for hospital admission (yes, no) at the initial episode of care by the pre-period and post-period for the FAS population. Summary rows will be repeated by site.

The primary analysis will consist of hypothesis testing using a one-sided, two-sample Pearson chi-square test for proportion difference with a normal approximation. An appropriate alternative method will be selected if a major violation to an assumption is present.

Because the baseline characteristics of the pre-period may differ from those of the post-period, a secondary analysis using a multivariate logistic regression analyses will be implemented. This model will assume mutual independence between the sites.

Clinically relevant baseline characteristics of interest for the adjusted analysis include the following variables: age, gender (Male, Female), race (White/Caucasian, Black or African American, Other), employment status (Full-Time, Part-Time, None), insurance plan type (Private commercial plan, Government funded, Uninsured, Other), Charlson Comorbidity Index, lesion surface area (<75cm cm2, =>75 cm2 – 150 cm2, >150 cm2), infection type (Wound infection, Cellulitis/erysipelas, Abscess), prior health resource use (Yes, No, Unknown), prior antibiotic treatment failure (Yes, No, Unknown), presence of SIRS criteria (<2 or >=2), presence of recurrent infection in prior 6 months (Yes, No, Unknown), any health resource use in prior 3 months (Yes, No, Unknown), as well as is patient was immunocompromised (Yes, No, Unknown). Patients will be defined as immunocompromised if they have evidence of any of the following at baseline: Connective tissue disease, diabetes mellitus, leukemia, or malignant lymphoma. Categorical variables will be collapsed where possible. The primary predictor variable will be a pre/post-period indicator, and potentially other selected characteristics will be forced into the model based on clinical rationale and distributions observed in the

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data (specifically imbalance between the pre- and post-periods). The stepwise selection of variables in the logistic regression will be done. The retention criteria in the model will be set as 0.1. The final model results will be presented in a table.

6.2.5.2 Secondary Outcomes

Secondary Outcomes: Total Number of Days Spent in Hospital

Total number of days spent in the hospital will be calculated by two methods for the FAS population. First, LOS will be calculated by inpatient stays only and second, LOS will be calculated by inpatient stays including time spent in prolonged observation status (>1 day). Descriptive statistics for total number of days spent in hospital will be shown in a table by initial care, follow-up, and overall for the pre-period and post-period, and depicted graphically overall using box plots. Patient counts and percentages will be given for the primary outcome (e.g., 0 day, 1 day … > 5 days). Descriptive statistics in the table will be repeated by patients who complete the study or are admitted for comparison. No formal hypothesis testing will take place.

Secondary Outcomes: Infection-Related Total Admitted Hospital Days

Infection-related total admitted hospital days will be calculated by two methods by the pre-period and post-period for the FAS population. First, LOS will be calculated by inpatient only stays and second, LOS will be calculated by inpatient stays including time spent in prolonged observation status (>1 day). The infection-related total admitted hospital-days will be assessed using a similar approach described for the primary analysis and will limit to patients who had infection-related hospital stays. Tables will reflect descriptive statistics for infection-related hospital stays and depicted graphically overall using box plots. Summaries will be repeated for only patients that are admitted. No formal hypothesis testing will take place.

Secondary Outcomes: ED Length of Stay at Initial Episode of Care

Tables will reflect descriptive statistics for ED length of stay at the initial episode of care by the pre-period and post-period for the FAS population. No formal hypothesis testing will take place.

Secondary Outcomes: Infection-Related Major Surgical Interventions that Required Operating Room Time

Infection-related major surgical interventions that required operating time will be displayed in tables by initial care, follow-up, and overall by the pre-period and post-period for the FAS population. Patient counts and percentages will be reported for no, any, expected, and unexpected surgical interventions. No formal hypothesis testing will take place.

Secondary Outcomes: Infection-Related Hospitalizations

Infection-related hospitalizations will be displayed in tables by initial care, follow-up, and overall by the pre-period and post-period for the FAS

population. Patient counts and percentages will be reported for none, any, 1, 2, and ≥3 infection-related hospitalizations. No formal hypothesis testing will take place.

Secondary Outcomes: Infection-Related Hospitalizations that Resulted in Admission to Intensive Care Unit (ICU)

Infection-related hospitalizations that resulted in admission to ICU will be displayed in tables by initial care, follow-up, and overall by the pre-period and post-period for the FAS population. Patient counts and percentages will be reported for none, any, 1, 2, and ≥3 infection-related hospitalizations that resulted in admission to ICU. No formal hypothesis testing will take place.

Secondary Outcomes: All Cause Hospitalizations in the 30 Days Post-Discharge from the Hospital or Release from ED

All-cause hospitalizations in the 30 days post-discharge from the hospital will be displayed in tables by the pre-period and post-period for the FAS population. Patient counts and percentages will be reported for none, any, 1, 2, and ≥3 all-cause hospitalizations in the 30 days post-discharge from the ED. No formal hypothesis testing will take place.

Secondary Outcomes: Infection-Related ED Visits

Infection-related ED visits will be displayed in tables by initial care, follow-up, and overall by the pre-period and post-period for the FAS population. Patient counts and percentages will be reported for none, any, 1, 2, and ≥3 infection-related ED visits. These categories will be repeated for all, expected, and unexpected ED visits. No formal hypothesis testing will take place.

Secondary Outcomes: Infection-Related Outpatient Healthcare Visits

Infection-related outpatient healthcare visits will be displayed in tables by initial care, follow-up, and overall by the pre-period and post-period for the FAS population. Patient counts and percentages will be reported for none, any, 1, 2, and ≥3 infection-related outpatient healthcare visits. These categories will be repeated for all, expected, and unexpected outpatient healthcare visits. No formal hypothesis testing will take place.

Secondary Outcomes: Use of PICC Line or Central Line to Administer Antibiotic Therapy

Use of PICC line, central line or no line to administer antibiotic therapy will be displayed in tables by initial care, follow-up, and overall by the pre-period and post-period for the FAS population. Patient counts and percentages will be presented. No formal hypothesis testing will take place.

Secondary Outcomes: Infection-Related Healthcare Visits Due to PICC Line or Central Line Used to Administer Antibiotic Therapy

Infection-related healthcare visits due to PICC line or central line used to administer antibiotic therapy will be displayed in tables by initial care, follow-up, and overall by the pre-period and post-period for the FAS population. Patient counts and percentages will be reported for none, any, 1, 2, and ≥3 infection-related outpatient healthcare visits. These categories will be repeated for all, expected, and unexpected outpatient healthcare visits. No formal hypothesis testing will take place.

Secondary Outcomes: Serious Adverse Events

Serious adverse events will be reported in a table as presented in section 6.2.9. No formal hypothesis testing will take place.

Secondary Outcomes: Patient Satisfaction with Care

Descriptive statistics for the patient satisfaction questionnaire will be reported within a table by the pre-period and post-period for the FAS population. No scoring or formal hypothesis testing will take place. A listing will display the date of visit the assessment occurred, questions answered, and the response to each question for each patient.

Secondary Outcomes: Patient Work and Productivity Loss

Descriptive statistics for the WPAI questionnaire will be reported in a table by the pre-period and post-period for the FAS population. Summaries will describe the distribution of scores derived at day 14. Scores will be calculated and summarized following the WPAI Score Guidelines (see Appendix D). A listing will display the date of visit the assessment occurred, component scores (absenteeism, impairment while working, overall work impairment, activity impairment), questions answered, and the response to each question for each patient. No formal hypothesis testing will take place.

Secondary Outcomes: Patient HRQoL

Descriptive statistics for the SF-12 will be reported within a table by the pre-period and post-period for the FAS population. Summaries will describe the distribution of scores derived at baseline and day 14, as well as the distribution of changes in scores from baseline. Scores will be calculated and summarized following the SF-12 scoring manual (see Appendix E). A listing will display the date of visit the assessment occurred, component scores (mental health and physical), questions answered, and the response to each question for each patient.

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6.2.7 Hospitalizations, Emergency Department Visits and Observational Unit Stays

The number and percent of patients who were admitted to hospital or not admitted to the hospital following their initial evaluation in the ED will be

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tabulated in a frequency table by the pre-period and post-period for the FAS population. Patients' care pathways, including time spent in each setting of care (ED, observation unit, initial hospitalization, and ICU), will be summarized with descriptive statistics. The number and percentage of patients will be reported for treatment with dalbavancin, alive or dead at discharge, and discharge disposition location. All of the aforementioned variables will be reflected in listings.

6.2.8 Clinical Assessments

Vital signs including temperature (°C), method of collection of temperature, heart rate (beats per minute), respiratory rate (breaths per minute), systolic BP (mmHg), diastolic BP (mmHg), height (cm), weight (kg) and BMI (kg/m^2) will be summarized at baseline and the 48-72 hours after enrollment follow-up visit (post-period only).

Height is collected in both inches (in) and centimeters (cm) and will be reported in centimeters in the analysis. If height is reported in inches then it will be converted as follows:

Height (cm) = reported value (inches) * 2.54

Weight is collected in both pounds (lbs) and kilograms (kg) and will be reported in kilograms in the analysis. If weight is reported in pounds then it will be converted as follows:

Weight (kg) = reported value (lbs) * 0.4536

Temperature is collected in both degrees Celsius and Fahrenheit and will be reported in degrees Celsius in the analysis. If temperature is reported in degrees Fahrenheit then it will be converted as follows:

Temperature (°C) = (reported value (°F) – 32) / 1.8

Clinical assessments will be summarized with descriptive statistics for baseline and the 48-72 hour visit (post-period only) by the pre-period and post-period for the FAS population. Values will be summarized in tables and listings, and in listings, reported with the visit date and change form baseline for follow-up values.

6.2.9 Antibiotic Treatments and Concomitant Medications

Concomitant medications taken three months prior to study start will be coded using the WHODRUG dictionary, Version B2 201609 or later, and the number and percentage of patients will be summarized in tables. Antibiotic usage during the study will also be coded using the WHODRUG dictionary, Version B2 201609 or later, and summarized in tables. The most current WHODRUG

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dictionary will be used at the time of analysis. These prior non-antibiotic medications used for chronic conditions will be reported in listings, including the medication name (coded), reason for prescription, route, and start date and end date. All medications will be summarized using descriptive statistics by the pre-period and post-period for the FAS population. For post-period patients, discharge to complete care in an outpatient setting on the same day Dalvance was provided and reasons for not being discharged to an outpatient setting will be summarized by patient counts and percentages.

6.2.10 Safety Assessments

The reporting period for adverse events (AEs) begins from the time of the signing of the Patient Authorization throughout the patient's enrollment in the study. AE information will be collected in an ongoing fashion through patient reporting AEs to their healthcare provider.

All AEs will be coded and summarized by the pre-period and post-period for the FAS population by system organ class and preferred term based on the MedDRA coding dictionary Version 20.0 or later; the most current MedDRA coding dictionary will be used at the time of analysis. AEs will be summarized by relationship to treatment as yes, there is evidence to suggest a causal relationship between the study drug (any antibiotic given for ABSSSI from enrollment, including the pre-period or post-period) and adverse event, and no, there is no evidence to suggest a causal relationship between the study drug and adverse event. For severity, the most severe case of an AE by a patient will be reported, with order of most severity as: Severe>Moderate>Mild.

A listing of adverse events will also be given for each patient and will include the reported term, seriousness, severity, relationship to treatment, action taken with medication, event outcome and date for each event reported.

6.2.11 Laboratory and Microbiology

All laboratory and microbiological assessments will be summarized for baseline and follow-up visits in tables with descriptive statistics by the pre-period and post-period for the FAS population. Laboratory results will be reported for the scheduled baseline and 42-78 hour visits, with the latter laboratory results for post-period patients only. The first microbiology result for each patient at baseline and follow-up, respectively, will be summarized for each time period. Where more than one unit is collected within analysis, values will be converted to a common unit and displayed for analysis. Laboratory conversions to standard international units are reported in the table below:

Laboratory Unit	**Standard International Unit**	**Factor**

Sodium mEq/L	Sodium mmol/L	x1
Potassium mEq/L	Potassium mmol/L	x1
Bicarbonate mEq/L	Bicarbonate mmol/L	X1

A listing of laboratory and microbiological assessments will also be given for each patient and will include the time period the assessment was taken (e.g., initial care, follow-up), date of assessment, laboratory test, reported laboratory value, reported laboratory unit, specimen type, method of collection, if any isolated were grown from the specimen, the organism grown, if this organism was tested for susceptibility, what antibiotics were used for susceptibility, the level of susceptibility (sensitive, resistant, intermediate, indeterminate) and the minimum inhibitory concentration (MIC) with corresponding unit.

6.2.12 Healthcare Costs

Total costs of care for each study patient over the 44-day period of interest will be estimated by multiplying estimates of utilization of healthcare services collected during the conduct of this study by corresponding unit costs. Unit costs will include: cost of day in hospital, cost of day in ICU, emergency department visit, healthcare visits, surgical procedures, imaging tests, catheter placement (PICC line/central line) and microbial culture. Further detail can be found in Section 4.6 of this document.

Summary statistics for total costs of care will be estimated for the pre-period and post-period for the FAS population.

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7.0 List of Potential Tables/Listings/Figures

Table shells are included in the file 055123_ADVANCE_SAP_ Table Shells_v 1.0_20181204.docx.

§ Denotes output that can be produced at interim analysis. ∫ Denotes the minimum output necessary to support sample size confirmation. * Denotes output to be produced only for the sample size confirmation described in the protocol.

Table 1 Disposition of Study Patients by Site and All Patients: Enrolled Set§∫
Table 2 Study Site Characteristics §
Table 3.1 Patient Demographics at Baseline by All Patients: Enrolled Set§
Table 3.2 Patient Demographics at Baseline by Site 10X: Full Analysis Set
Table 4 Comorbid Conditions Reported at Baseline: Full Analysis Set§
Table 5 Healthcare Resource Utilization at Previous 3 Months: Full Analysis Set§
Table 6 Infection characteristics and clinical characteristics during the initial assessment in the ED: Full Analysis Set§
Table 7.1 Care Pathways of Patients Following Initial Episode of Care: Full Analysis Set§
Table 9 Use of Antibiotics by Patients During the Study: Full Analysis Set§
Table 10 Primary Outcome: Hospital Admission Rate at Initial Episode of Care Full Analysis Set§∫
Table 11 Primary Outcome: Primary Outcome: Hospital Admission Rate at Initial Episode of Care Multivariate Analysis Full Analysis Set§∫
Table 12.1 Secondary Outcome: Total LOS during Initial Care and Follow-up: Full Analysis Set§∫
Table 12.XX Secondary Outcome: Total LOS during Initial Care and Follow-up: Full Analysis Set: Site XXX§∫
Table 13.1 Secondary Outcomes by All Patients: Full Analysis Set§
Table 13.2 Secondary Outcomes: Infection-related outpatient healthcare visits by Site 101: Full Analysis Set
Table 13.XX Secondary Outcomes: Infection-related outpatient healthcare visits by Site 10X: Full Analysis Set
Table 14 Secondary Outcome: Serious Adverse Events by SOC and PT: Full Analysis Set§
Table 15 Secondary Outcomes: Patient Satisfaction with Care: Full Analysis Set §
Table 16 Secondary Outcomes: Patient Work and Productivity Loss: Full Analysis Set§
Table 17 Secondary Outcomes: Patient Health-Related Quality of Life (SF-12): Full Analysis Set
Table 18 Other Outcomes: Full Analysis Set§
Table 19 Adverse Events- Overall Summary: Full Analysis Set§
Table 20 All Adverse Events by SOC and PT: Full Analysis Set§
Table 21 Adverse Events with Possible Causal Relationship to Study Drug by SOC and PT: Full Analysis Set§
Table 22 Adverse Events Leading to Study Discontinuation by SOC and PT: Full Analysis Set§
Table 23 Adverse Events Leading to Death by SOC and PT: Full Analysis Set§
Table 24 Laboratory Values: Full Analysis Set§
Table 25 Microbial Assessments: Full Analysis Set§
Table 26 Vital Signs: Full Analysis Set§
Table 27 Summary of Cost Analyses over 44 Day Period: Full Analysis Set
Table 28 Sample Size Confirmation ∫*
Table 29 Sample Size Confirmation with Variations of Power and Statistical Significance *
Table 30 Secondary Outcome: ED LOS during Initial Care and Follow-up: Full Analysis Set*

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8.0 References

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9. Ware JE, Sherbourne CD. The MOS 36-item short-form health survey (SF-36): I. Conceptual framework and item selection. *Med Care.* 1992;30(6):473-483.

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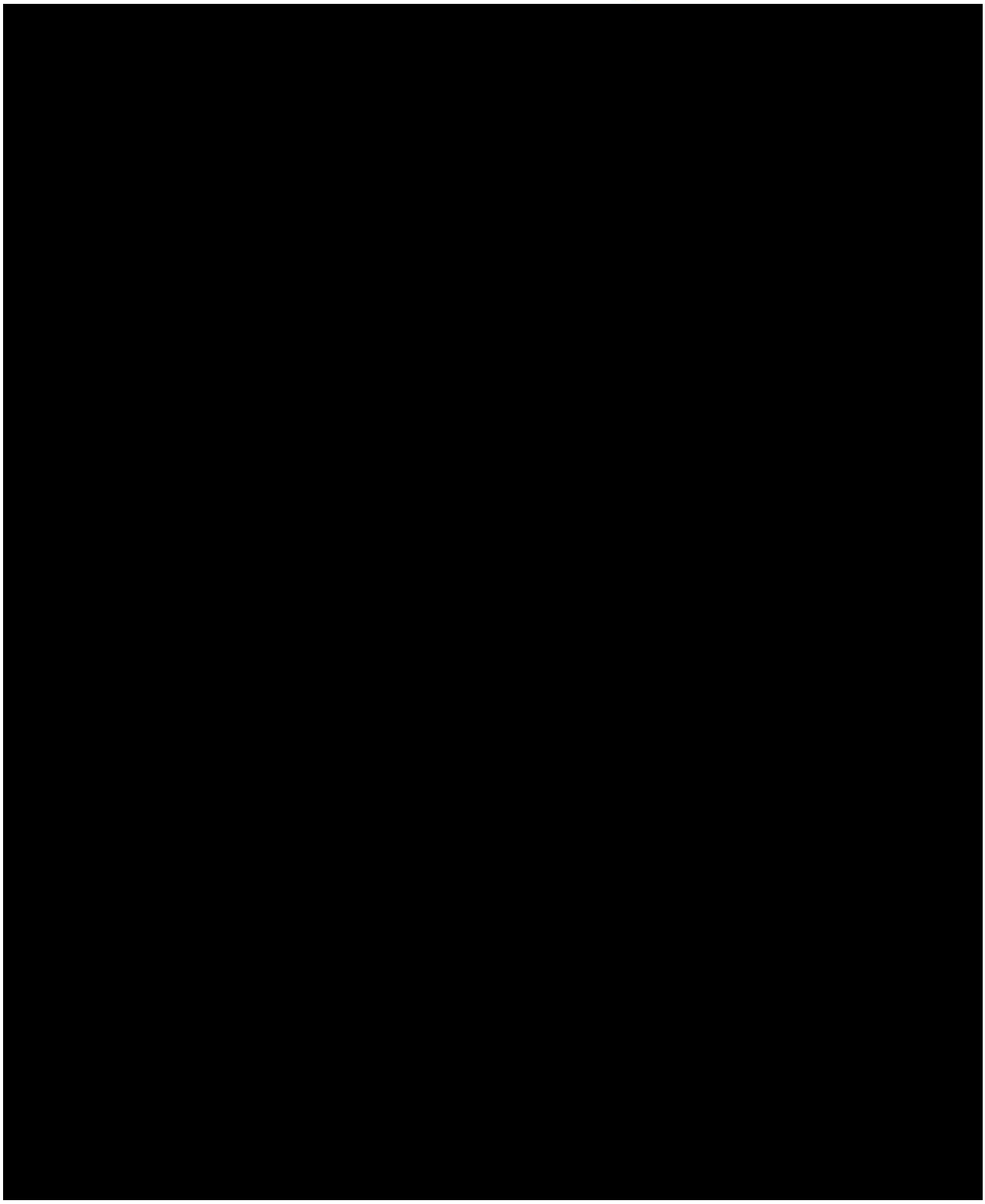

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Appendix B: Derived Variables

Analysis Section (Visit)	**Variable (Units)**	**Definition**
General (Baseline)	Enrollment date	Informed consent date
General (Baseline)	Baseline date	Initial ED admission date
General (Initial Care)	Initial care indicator	If enrollment date ≤ date ≤ enrollment date + 13 days then = Yes Else = No
General (Follow-up)	Follow-up indicator	If enrollment date + 14 ≤ date ≤ enrollment date + 43 days then = Yes Else = No
Demographics (Baseline)	Age (years)	Round down to nearest integer((Initial ED admission date – date of birth + 1)/365.25), when both dates are available.
Demographics (Baseline)	BMI	weight (kg)/ [height(m)]^2 Where necessary, height and weight will be converted to proper units.
Infection Characteristics (Baseline)	CCI	Will be scored as described in Appendix C. Includes variables for raw score and 10 year survival probability.
Infection Characteristics (Baseline)	Fever	If temperature>38 ° C then =Yes Else =No
Infection Characteristics (Baseline)	Morbid Obesity	If baseline BMI ≥ 40 then =Yes Else =No
Infection Characteristics (Baseline)	SIRS Criteria Met	SIRS criteria include abnormalities in temperature, heart rate, respiration, and white blood cell count. Specifically included are: • Fever of more than> 38.0°C or hypothermia with temperature< 36.0°C

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Analysis Section (Visit)	Variable (Units)	Definition
		• Tachycardia with heart rate > 90 beats/minute or • Tachypnea with respiratory rate of > 20 breaths/minute or $PaCO_2$ of less than 32mmHg • Abnormal white blood cell count: leukocytosis >12,000/microliter, leucopoenia <4,000/microliter, or >10% immature cells (bands).[3,4] If 2 or more criteria present = Yes Else = No
Antibiotic Medications (Initial Care and Follow-up)	Days Received Antibiotic Medication	∑ (Medication end date – Medication start date +1), when both dates are available. If dates overlap (e.g., end date and next start date are identical) then subtract 1 from summation for each occurrence.
Primary Outcome	Hospital Admission At Initial Episode of Care	<u>If discharge destination from the initial episode of care = Hospital and the reported hospitalization where discharge date = hospital date is infection-related then = Yes,</u> <u>Else = No</u>
Secondary Outcomes (All visits)	Hospitalization LOS (days)	<u>For all-cause:</u> ∑ (Hospitalization end date – Hospitalization start date +1), when both dates are available. If ongoing at end of study or discontinuation date, use study completion date or discontinuation date as end date. For outcomes, LOS will be computed two ways: only in-patient hospitalizations visits and inpatient hospitalizations visits with prolonged observation

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Analysis Section (Visit)	Variable (Units)	Definition
		status (e.g., time in observation status exceeds 1 day). For infection-related: Subset all-cause hospitalization time for patients with infection-related hospitalization stays
Secondary Outcomes (End of Study Visit)	Completers Flag	If "Did the patient complete the study?" = 1 on the end of study visit CRF page and date of study completion does not equal missing, then =Yes, Else = No This flag will be used to repeat certain primary and secondary outcomes that could be influenced by early discontinuation (e.g., LOS)

Secondary and Other Outcomes (Initial episode of care)	ED LOS (hours)
	Observation Status LOS (hours)
		Impute with estimated time where applicable for partial times.
		if admission date = discharge date then
		LOS (hours) = discharge time – admission time
		
		else
		LOS (hours) = sum all hours over stay, with a full day counting as 24 hours

Secondary Outcomes (Follow-up)	WPAI	Scores and coded variables will be derived as described in Appendix D.
Secondary Outcomes (Initial Care and Follow-up)	SF-12	SF-12 sub-scores and total scores will be compiled using the Health Outcomes Scoring Software 5.0 by QualityMetric Inc. Further detail can be found in Appendix E.
Adverse Events (Baseline, Initial Care and Follow-up)	Highest severity AE	Severity of most severe AE for the patient with order of severity: Severe>Moderate>Mild Patients who only have AEs reported with missing severity,

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Analysis Section (Visit)	Variable (Units)	Definition
		highest severity AE will be reported as missing

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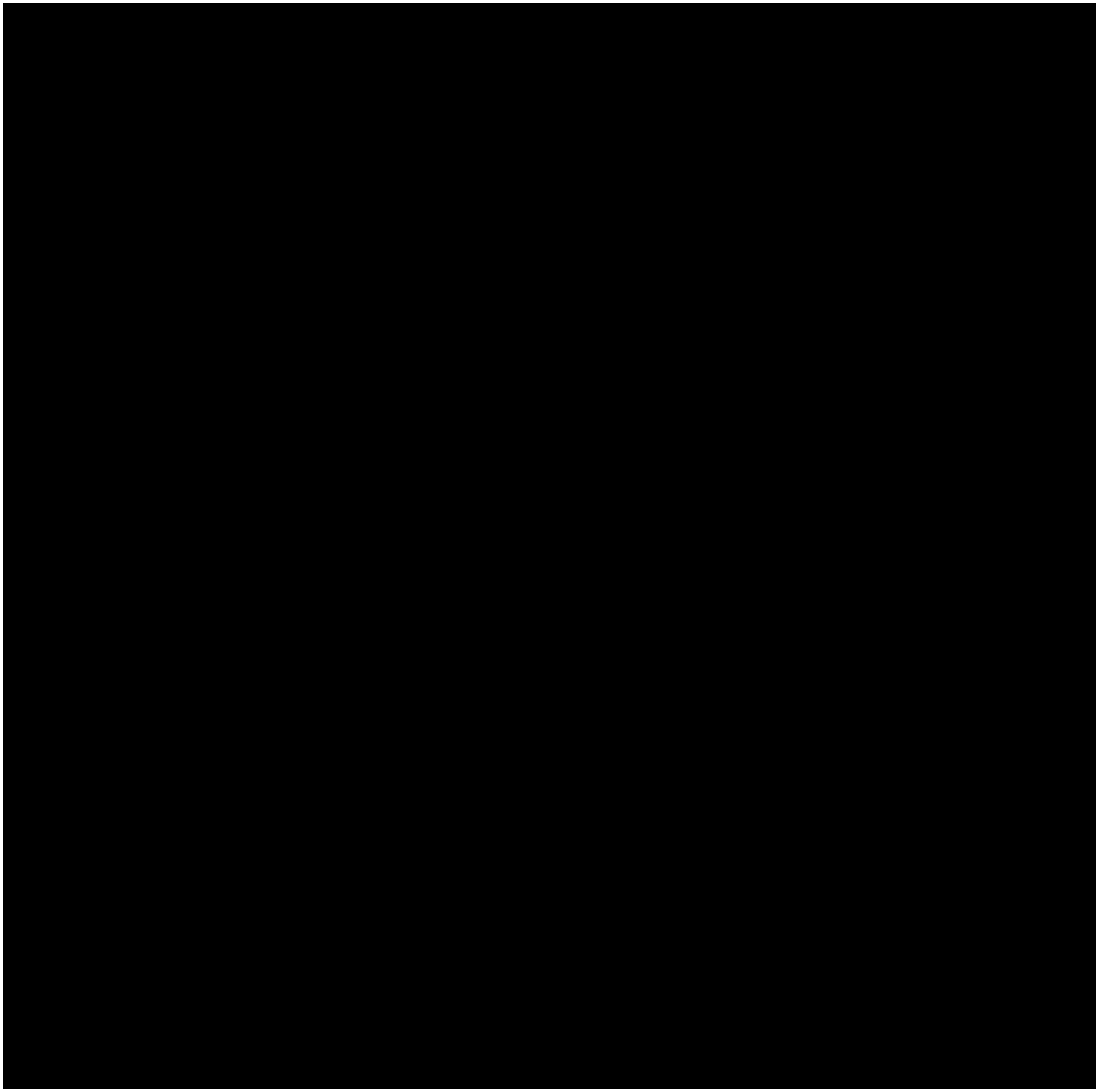

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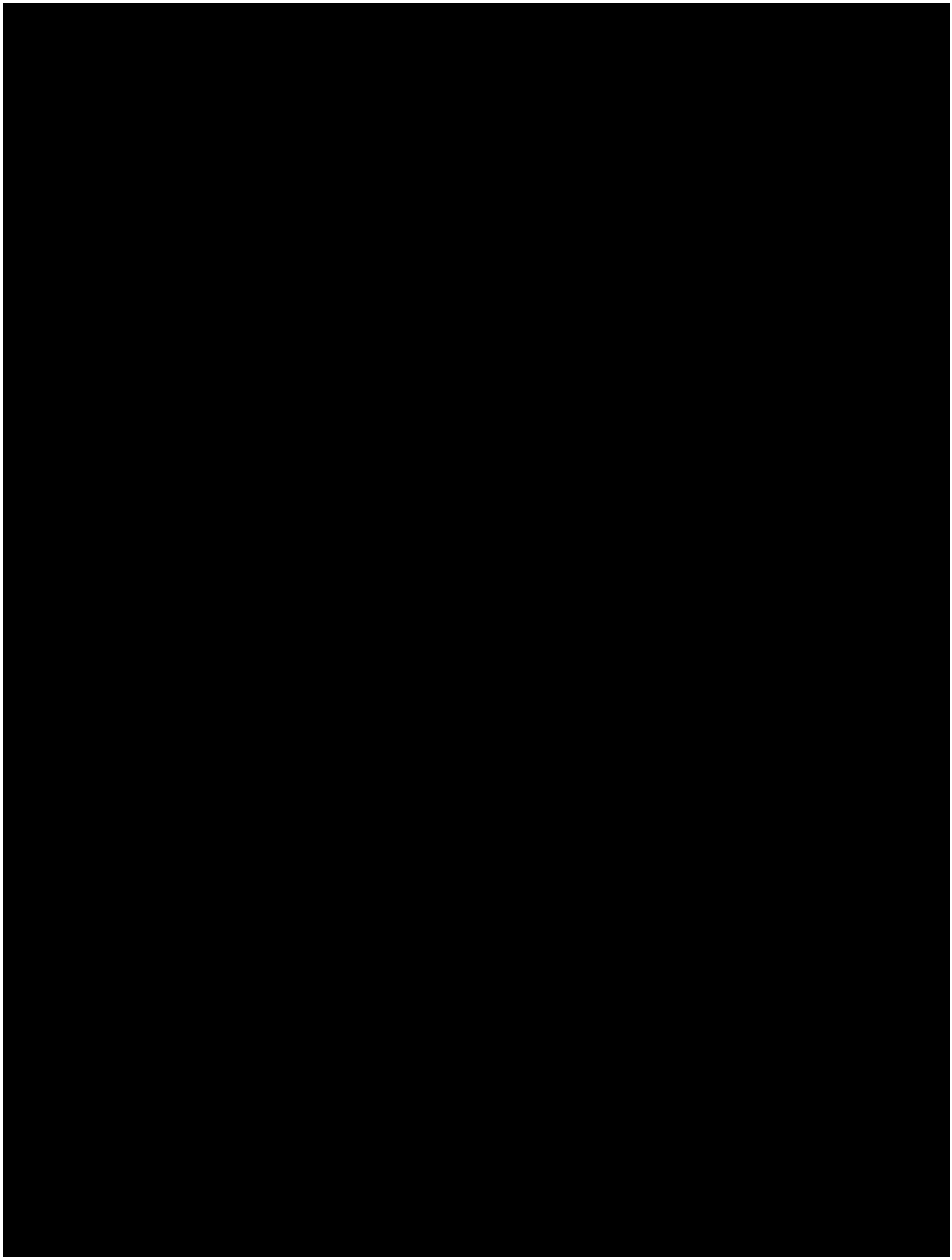

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Appendix F: Revision History

Version	Issue Date	Summary of Changes
1.0	05FEB2019	N/A (first version)

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