Official Protocol Title:	A Phase II Open-Label, Single-arm Clinical Trial to Study the Safety, Efficacy and Pharmacokinetics of MK-3009 (Daptomycin) in Japanese Pediatric Participants Aged 1 to 17 Years with Complicated Skin and Soft Tissue Infections or Bacteremia caused by Gram-positive cocci
NCT number:	NCT03643952
Document Date:	03-Jun-2020

Title Page

THIS PROTOCOL AMENDMENT AND ALL OF THE INFORMATION RELATING TO IT ARE CONFIDENTIAL AND PROPRIETARY PROPERTY OF MERCK SHARP & DOHME CORP., A SUBSIDIARY OF MERCK & CO., INC., NJ, U.S.A. (MSD).

Protocol Title: A Phase II Open-Label, Single-arm Clinical Trial to Study the Safety, Efficacy and Pharmacokinetics of MK-3009 (Daptomycin) in Japanese Pediatric Participants Aged 1 to 17 Years with Complicated Skin and Soft Tissue Infections or Bacteremia caused by Gram-positive cocci

Protocol Number: 029-01

Compound Number: MK-3009

Sponsor Name and Legal Registered Address:

Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc.
(hereafter referred to as the Sponsor or MSD)

One Merck Drive
P.O. Box 100
Whitehouse Station, New Jersey, 08889-0100, U.S.A.

Regulatory Agency Identifying Number(s):

Not Applicable

EudraCT NUMBER: Not Applicable

Approval Date: 03 June 2020

Sponsor Signatory

Typed Name: Date
Title:

Protocol-specific Sponsor Contact information can be found in the Investigator Trial File Binder (or equivalent).

Investigator Signatory

I agree to conduct this clinical study in accordance with the design outlined in this protocol and to abide by all provisions of this protocol.

Typed Name: Date
Title:

DOCUMENT HISTORY

Document	Date of Issue	Overall Rationale
Amendment 01	03-JUN-2020	In the section 5.3 Beginning and End of Study Definition, the definition of the overall study ends was amended.
Original Protocol	09-APR-2018	Not applicable

PROTOCOL AMENDMENT SUMMARY OF CHANGES

Amendment : 01

Overall Rationale for the Amendment:

Pharmacokinetic analysis and central microbiology reference laboratory analysis are key secondary endpoints in the study; the study is not considered complete until all key data are available for planned endpoint analyses, and these data will only become available 2-3 months after the last patient last visit date.

Summary of Changes Table:

Primary reason(s) for this amendment:

Section # and Name	Description of Change	Brief Rationale
5.3 Beginning and End of Study Definition	The following sentence is added: For purposes of analysis and reporting, the overall study ends when the Sponsor receives the last pharmacokinetic analysis and central microbiology reference laboratory analysis results.	Pharmacokinetic analysis and central microbiology reference laboratory analysis are key secondary endpoints in the study; the study is not considered complete until all key data are available for planned endpoint analyses, and these data will only become available 2-3 months after the last patient last visit date.

Additional change(s) for this amendment:

Section # and Name	Description of Change	Brief Rationale
2 Schedule of Activities (SoA)	Japanese Version Only: To delete the footnote b of 'Clinical Assessment of Infection Site' at Visit 1.	Change based on Protocol Clarification Letter (PCL) on July 12, 2018: corrected minor error.
3.1 Study Rationale	Update the status of pediatric indication in EU (underlined); Daptomycin is also indicated in the EU for adult and pediatric (1 to 17 years of age) patients with *S. aureus* bacteremia (SAB). In adults, use in bacteremia should be associated with RIE or with cSSTI, while in pediatric patients, use in bacteremia should be associated with cSSTI.	Change based on PCL on July 12, 2018: Update the information.
3.1 Study Rationale	English Version Only: To change as follows (underlined); 'Target pathogens: daptomycin susceptible MRSA'	Change based on PCL on July 12, 2018: corrected minor error.
7.1 Treatments Administered	To change the Study Treatment Name to 'Daptomycin for injection' in Table 1.	Change based on PCL on July 12, 2018: updated based on Clinical Supplies Specification.
9 Study Assessments and Procedures	To add the amount of blood collection for analyzing plasma daptomycin concentration as follows; The amount of blood collected from each participant for analyzing plasma daptomycin concentration will be approximately 5 mL total (1 mL per each sampling point).	Change based on PCL on July 12, 2018: determined the procedures for details.

Section # and Name	Description of Change	Brief Rationale
9.1.8 Treatment Administration	English Version Only: To change as follows (underlined); over 60 minutes +/- 10 minutes （1 to 6 years old）	Change based on PCL on July 12, 2018: corrected minor error.
9.2.2 Microbiological Response	Japanese Version Only: To correct the typo in the section title.	Change based on PCL on July 12, 2018: corrected minor error.
9.2.2.1 Pathogen-level microbiological response 9.2.2.2 Subject-level microbiological response 10.4.1 Efficacy / Pharmacokinetic Endpoints	To change the wording from ’gram positive pathogen(s)’ and ‘gram-positive’ to ‘gram-positive cocci’.	Change based on PCL on July 12, 2018: clarified the wording about infecting pathogen.
9.5.4 Neurological Examination	To change the assessment partially as follows; Neurological Examination should be performed according to section 2. The investigators will perform an age appropriate neurological examination including assessments of Mental Status, Cranial Nerve, Muscle Tone (Leg and Arm), Muscle Strength (Leg and Arm), Reflexes (Ankle, Biceps, Knee and Babinski), Coordination and Gait (Finger-to-Nose), Sensory (light touch sense-Forearms and Legs) and Tremor (Upper Extremities). All assessments will be evaluated as normal or abnormal (grading of abnormal and so on if applicable).	Change based on PCL on July 12, 2018 and Nov 1, 2018: update the wording and such during EDC construction.

Section # and Name	Description of Change	Brief Rationale
9.5.7.2 Collection of blood	To change the blood culture as follows (underlined); At EOT (Visit 4), blood culture is required even if the blood cultures until 2 sequential cultures demonstrate no growth is confirmed.	Change based on PCL on July 12, 2018: corrected minor error.
9.5.7.3 Gram stain	To change as follows; Gram stain should be performed at Visit 1, using the collected specimen (infection site) or the bacteria from the specimen culture (Infection site or blood). If the pathogen species are identified by other methods, gram stain is not necessary. Gram stain may be performed at the same day of screening period as the first dose of study drug administration (i.e. Before the first dose of study drug).	Change based on PCL on July 12, 2018: reflected the notes in Section 2 and clarified the requirement of gram stain.
9.5.8 Clinical Assessment of Infection Site	To add the procedures as follows; The investigators will evaluate the clinical assessment of signs and symptoms of cSSTI according to section 2. The signs and symptoms (Erythema, Swelling/Edema, Induration, Localized Warmth, Tenderness on Palpation, Drainage, Fluctuance, Ulceration, Necrotic Tissue, Localized Pain, Redness, Chills and Fever) will be examined and will be evaluated as "Yes" or "No", and grade (Mild, Moderate or Severe, if applicable).	Change based on PCL on July 12, 2018: described the procedures for details based on Section 2.

Section # and Name	Description of Change	Brief Rationale
10.6.3 Summaries of Baseline Characteristics, Demographics, and Other Analyses	English Version Only: To add the sentence as follows (underlined); Population PK analysis may be conducted if needed. <u>If population PK analysis will be conducted, PK data and analysis will be reported separately in a population PK report.</u>	Change based on PCL on July 12, 2018: described population PK analysis for details.
12.4 Appendix 4: Clinical Laboratory Tests	English Version Only: To change about Hematology in table 13 (underlined); WBC count with Differential includes 'Neutrophils, Lymphocytes, Monocytes, <u>Eosinophils</u> and <u>Basophils</u>'.	Change based on PCL on July 12, 2018: corrected minor error.
12.4 Appendix 4: Clinical Laboratory Tests	To change the Laboratory Assessments in table 13 as follows (underlined); Note: 1. Direct bilirubin is tested with blood drawing again if total bilirubin is elevated above the upper limit of normal <u>and the investigator needs further assessments</u>.	Change based on PCL on Nov 1, 2018: clarified the wording about the procedure.

Table of Contents

LIST OF TABLES

LIST OF FIGURES

1. Synopsis

Protocol Title:

A Phase II Open-Label, Single-arm Clinical Trial to Study the Safety, Efficacy and Pharmacokinetics of MK-3009 (Daptomycin) in Japanese Pediatric Participants Aged 1 to 17 Years with Complicated Skin and Soft Tissue Infections or Bacteremia caused by Gram-positive cocci

Short Title:

PII Trial of Daptomycin (MK-3009) in Japanese Pediatric Subjects with cSSTI & Bacteremia

Objectives/Hypotheses and Endpoints:

In Japanese pediatric participants aged 1 to 17 years old with complicated skin and soft tissue infection (cSSTI) or bacteremia caused by Gram-positive cocci:

Objective	**Endpoint**
Primary	
• To assess the safety and tolerability of daptomycin.	• Adverse Events (AEs) - Participant experiencing AE - Participant discontinuing study treatment due to AEs
Secondary	
• To assess the efficacy of administration of daptomycin in participants with methicillin-resistant *S.* aureus (MRSA) infections.	• Clinical response at Test of Cure (TOC) visit • Subject-level microbiological response at Test of Cure (TOC) visit
• To evaluate steady state pharmacokinetics of administration of daptomycin.	• Pharmacokinetic parameters such as AUC_{0-24} , C_{max}, t_{max}, CL_{ss}, V_{ss}, $t_{1/2}$ will be evaluated if evaluable data is obtained.

Overall Design:

Study Phase	Phase II
Clinical Indication	Treatment of cSSTI and bacteremia caused by MRSA
Population	Patients with cSSTI or bacteremia
Study Type	Interventional
Type of Design	Single treatment group (Non-Randomized) (including 4 age sub-groups in each primary disease category)
Type of Control	No treatment control
Study Blinding	Unblinded Open-label
Estimated Duration of Study	The Sponsor estimates that the study will require approximately 2 and a half years from the time the first participant signs the informed consent/assent until the last participant's last study-related phone call or visit.

Number of Participants:

Approximately20 participants will be enrolled.

Treatment Groups and Duration:

Treatment Groups: All age groups: daptomycin intravenous (IV)

	cSSTI (Treatment period: 5-14 days)	Bacteremia (Treatment period: 5-42 days)
12-17 years old	5 mg/kg q 24 hrs infused over 30 minutes	7 mg/kg q 24 hrs infused over 30 minutes
7-11 years old	7 mg/kg q 24 hrs infused over 30 minutes	9 mg/kg q 24 hrs infused over 30 minutes
2-6 years old	9 mg/kg q 24 hrs infused over 60 minutes	12 mg/kg q 24 hrs infused over 60 minutes
1 to < 2 years old	10 mg/kg q 24 hrs infused over 60 minutes	12 mg/kg q 24 hrs infused over 60 minutes

Duration of Participation	Each participant will participate in the study for approximately 31 days (cSSTI) or approximately 59 days (bacteremia) from the time the participant signs the Informed Consent Form (ICF) through the final contact. Within 72 hours of the screening visit, each participant will be allocated to treatment for approximately 5 to up to 14 days (cSSTI) or 42 days (bacteremia). After the end of IV therapy, each participant will be followed for 14 days.

Study governance considerations are outlined in Section 12.1.

2. Schedule of Activities (SoA)

Study Period	Screening	Treatment				Follow up		Notes
Visit Number/Title:	Visit 1 Screening	Visit 2 Initiation of Therapy	Visit 3 On Therapy		Visit 4 End of Therapy (EOT)	Visit 5 Test of Cure (TOC)	Visit 6 Follow Up (FU)	
Scheduled Study Day of Visit:	≤ 72 hours from first dose of study medication	Day 1	Day 3	Day 4 - Day before EOT	Day 5 - 14 [a] Day 5 - 42 [a]	7 days following EOT	14 days following EOT	
Window for Scheduled Visit:			+ 1 Day		+ 1 Day	± 3 Days	+ 3 Days	
Administrative Procedures								
Informed Consent	X							
Participant Identification Card	X							
Inclusion/Exclusion Criteria	X							
Medical History	X							
Prior/Concomitant Medication Review	X	X	X	X	X	X	X	
Treatment Allocation		X						
MK-3009 (daptomycin) Administration [e]		X (q 24 hours)						
Efficacy Procedures								
Clinical Response Assessment					X	X		For procedure, see Section 9.2.1.
Microbiological Response Rating					X	X		For procedure, see Section 9.2.2.
Safety Procedures								
Full physical examination	X						X	
Directed physical examination		X		X Twice a week [h]	X	X		Emphasis on evaluation of weakness, muscle pain, and signs and symptoms related to source of infection.
Height	X							
Weight	X		X					Measure weight if a clinically significant weight change occurred in study therapy.

Study Period	Screening	Treatment				Follow up		Notes
Visit Number/Title:	Visit 1 Screening	Visit 2 Initiation of Therapy	Visit 3 On Therapy		Visit 4 End of Therapy (EOT)	Visit 5 Test of Cure (TOC)	Visit 6 Follow Up (FU)	
Scheduled Study Day of Visit:	≤ 72 hours from first dose of study medication	Day 1	Day 3	Day 4 - Day before EOT	Day 5 - 14 [a] Day 5 - 42 [a]	7 days following EOT	14 days following EOT	
Window for Scheduled Visit:			+ 1 Day		+ 1 Day	± 3 Days	+ 3 Days	
Vital Signs (heart rate, blood pressure, respiratory rate, oral body temperature)	X	X (Daily) [c]				X	X	If the participant's oral body temperature cannot be measured, then it is acceptable to measure the body temperature via non-oral methods, e.g. rectal, forehead, or aural. However, for each participant, the method by which body temperature is measured should be the same throughout the study.
Neurological Examination	X			X Twice a week [h]	X	X		
Assessment of Motor Developmental Skills	X						X	Only for participants who are ≤ 6 years old.
Clinical Assessment of Infection Site	X		X	X Once a week [h]	X	X		Only for participants with cSSTI.
AE Monitoring		X (Daily)				X	X	
Blood for hematology	X [b]			X [c] Once a week [h]	X [c]	X		
Blood for chemistry	X [b]			X [c] Once a week [h]	X [c]	X		

Study Period	Screening	Treatment				Follow up		Notes
Visit Number/Title:	Visit 1 Screening	Visit 2 Initiation of Therapy	Visit 3 On Therapy		Visit 4 End of Therapy (EOT)	Visit 5 Test of Cure (TOC)	Visit 6 Follow Up (FU)	
Scheduled Study Day of Visit:	≤ 72 hours from first dose of study medication	Day 1	Day 3	Day 4 - Day before EOT	Day 5 - 14 [a] Day 5 - 42 [a]	7 days following EOT	14 days following EOT	
Window for Scheduled Visit:			+ 1 Day		+ 1 Day	± 3 Days	+ 3 Days	
Serum CPK	X [b]		X [c]	X [c] Once a week [h]	X [c]	X		
Urine for urinalysis	X [b]					X		Only if the urine sample cannot be collected because of participant's clinical condition, then it is acceptable not to conduct this test.
Urine pregnancy test (β-hCG; Woman of Childbearing Potential only)	X							Serum β-hCG should be measured if the urine pregnancy test is positive.
Infection Site Specimen for Culture	X [d]		X		X	X		Only for participants with cSSTI. For participants in which infection site specimen collection is not medically acceptable, follow up specimen is not required.
Blood Specimen for Culture [e]	X [d]		X	X [f]	X	X	X	At Visit 6 (FU), not necessary if the result at Visit 5 (TOC) is negative.
Gram stain	X							If the pathogen species are identified by other methods, gram stain is not necessary.

Study Period	Screening	Treatment				Follow up		Notes
Visit Number/Title:	Visit 1 Screening	Visit 2 Initiation of Therapy	Visit 3 On Therapy		Visit 4 End of Therapy (EOT)	Visit 5 Test of Cure (TOC)	Visit 6 Follow Up (FU)	
Scheduled Study Day of Visit:	≤ 72 hours from first dose of study medication	Day 1	Day 3	Day 4 - Day before EOT	Day 5 - 14 [a] Day 5 - 42 [a]	7 days following EOT	14 days following EOT	
Window for Scheduled Visit:			+ 1 Day		+ 1 Day	± 3 Days	+ 3 Days	
Pharmacokinetics								
Blood to collect plasma for daptomycin PK Analysis			X [g]					

a. IV study therapy for cSSTI and/or bacteremia should be administered for a minimum of 5 full days. The total duration of IV study therapy should not exceed 14 days for cSSTI, and should not exceed 42 days for bacteremia.
b. It is acceptable to use local laboratory data for enrollment criteria of laboratory test. The samples for laboratory tests at baseline are collected separately and sent to a central Laboratory as needed.
c. Prior to administration of the study medication.
d. It is acceptable to use a culture sample collected within 120 hours before first study medication.
e. If the blood culture for participant with cSSTI is positive after allocation through the study (including at Visit 1), the participant could continue the study therapy with change of dose regimen for cSSTI to bacteremia upon consultation/discussion with sponsor.
f. After Day 3, performed as clinically indicated or, if pre-study blood culture was positive, repeat blood culture until confirmed negative. For details about blood culture, see Section 9.5.7.2.
g. Perform on the day following the administration of IV study medication for at least 2 consecutive days before blood collection (i.e., PK sampling on the 3rd day of consecutive administration of IV study medication). Only in cases where it is unavoidable, blood should be collected beyond the allowance of visit 3. In all, Sampling at 5 timepoints will occur: Pre-dose, 15 minutes after IV study medication infusion, and at 1 hour post-infusion, 4 hours post infusion, and12 hours post IV study medication infusion.
h. Weekly basis is considered as ‘Day 8 – Day 14’, ‘Day 15 – Day 21’, ‘Day 22 – Day 28’, ‘Day 29 – Day 35’, ‘Day 36 – Day 42’.

3. Introduction

Daptomycin (MK-3009) is a cyclic lipopeptide that represents the class of antibiotics derived from the fermentation of a strain of *Streptomyces roseosporus*.

3.1 Study Rationale

Throughout the world, *Staphylococcus aureus* (including methicillin-resistant *S. aureus*; MRSA) causes a number of invasive diseases, including complicated skin and soft tissue infections (cSSTI) and bacteremia in adult and pediatric populations. Antibacterial agents to treat cSSTI and bacteremia especially caused by MRSA remain as unmet medical needs, especially for the pediatric population.

As of Aug 2017, daptomycin is currently approved for marketing in 62 countries, including the United States (US), the European Union (EU), and Japan.

In the US and the EU, daptomycin is indicated for the treatment of adult and pediatric (1 to 17 years of age) patients with cSSTI caused by gram positive pathogens respectively.

Daptomycin is indicated in the US for the treatment of *Staphylococcus aureus* (*S aureus*) bloodstream infections (bacteremia), including those with right-sided infective endocarditis (RIE) in adult patients and *S aureus* bloodstream infections (bacteremia) in pediatric patients (1 to 17 years of age). Daptomycin is also indicated in the EU for adult and pediatric (1 to 17 years of age) patients with S. aureus bacteremia (SAB). In adults, use in bacteremia should be associated with RIE or with cSSTI, while in pediatric patients, use in bacteremia should be associated with cSSTI.

In Japan, daptomycin is currently indicated the treatment of the infection in adult listed below.

> Target pathogens: daptomycin susceptible MRSA
>
> Target indications: Septicemia, right-sided infective endocarditis, deep skin infections, secondary infections such as Secondary infections such as trauma, burns and surgical wounds, and secondary infections of erosions and ulcers

Therefore, this study is conducted in Japanese pediatric patients based on the dose regimen in non-Japanese pediatric patients that shows the efficacy of daptomycin in clinical studies.

Of the 5 drugs (vancomycin, teicoplanin, arbekacin, linezolid and daptomycin) currently approved in Japan for infection due to *S. aureus* (including MRSA), all except for daptomycin have been indicated for use in the pediatric population. However, these 4 drugs are either recommended to be administered with therapeutic drug monitoring (TDM) (eg, vancomycin) and/or require multiple doses per day (eg, 2-4 times a day). Given the once-daily dosing regimen of daptomycin, the absence of a need for TDM during daptomycin therapy, and the extensive safety and efficacy of daptomycin use in the adult population, the Sponsor is pursuing the clinical development of daptomycin for use in the Japanese pediatric population.

3.2 Background

Refer to the Investigator's Brochure (IB)/approved labeling for detailed background information on MK-3009(daptomycin).

3.2.1 Pharmaceutical and Therapeutic Background

Daptomycin binds preferentially to Gram-positive bacterial membranes, inserts into the membrane and causes a rapid depolarization of membrane potential, which results in inhibition of protein, deoxyribonucleic acid (DNA) and ribonucleic acid (RNA) synthesis, and consequently, bacterial cell death.

Daptomycin for pediatric patients is approved in the US and EU (See Section 3.1) based on the results of safety, efficacy and pharmacokinetics that are provided from pivotal studies as below.

In pediatric patients with cSSTI, P017(DAP-PEDS-07-03) study was conducted to assess the safety, efficacy, and PK of daptomycin versus SOC comparator antibiotics in pediatric subjects between the ages of 1 to 17 years, inclusive, with cSSTI caused by Gram-positive pathogens. A total of 389 participants were treated in the study (257 participants randomized to daptomycin treatment and 132 participants randomized to SOC treatment. In conclusion, Daptomycin administered at doses of 5, 7, 9, or 10 mg/kg for up to 14 days to pediatric subjects with cSSTI aged 12 to 17 years, 7 to 11 years, 2 to 6 years, and 1 to < 2 years, respectively, was shown to be safe and well tolerated and was as effective as SOC therapy.

The P005 (DAP-PEDBAC-11-02) study was conducted to assess the safety, efficacy, and PK of IV daptomycin versus SOC comparator antibiotics in pediatric subjects between the ages of 1 to 17 years, inclusive, with S. aureus bacteremia (SAB). A total of 82 subjects were randomized into the study (55 subjects were randomized to daptomycin treatment and 27 subjects were randomized to comparator treatment. Daptomycin administered intravenously at doses of 7, 9, or 12 mg/kg for up to approximately 6 weeks to pediatric subjects with S. aureus bacteremia aged 12 to 17 years, 7 to 11 years, and 1 to 6 years respectively, was shown to be safe and well tolerated and was as effective as the comparator. No subject < 2 years of age was enrolled. Although not directly studied, simulations based on the pediatric population PK model indicated that doses of 12 mg/kg administered to those 1-2 years of age in bacteremia would result in comparable exposures to pediatric patients 2 to <18 years receiving the age-specific, weight-based doses. Therefore, efficacy and safety from pediatric patients 2 to <18 years can be extended to pediatric patients 1 to <2 years.

In Japan, the clinical study in pediatrics has not been conducted, though phase III study in adults patients (P002) was conducted (with the proportion of participants with infections by Gram-positive coccus was 94.2% [114 of 121 participants] and with infections by MRSA was 64.5% [78 of 121 participants]).

Based on the Phase I study in Japan (P001) and the Phase I studies in the non-Japanese population conducted by Cubist (Protocol DAP-00-02 and DAP-ADT-04-02), the pharmacokinetics in Japanese healthy participants were considered to be similar to non-Japanese healthy participants. Also, the same result about pharmacokinetics in Japanese patients is provided from the Phase III study in Japan (P002). Therefore, it is anticipated that the exposures in Japanese pediatric patients with cSSTI following daptomycin administration

at the evaluated dosing regimens in this study (P029) are comparable to the exposures in non-Japanese pediatric patients with cSSTI (P017) and with SAB (P005) in whom efficacy and safety were established previously. Overall, the dosing regimens evaluated in this study (P029) are appropriate for Japanese pediatric patients with cSSTI or bacteremia.

The purpose of this study is to assess the safety, efficacy and PK of daptomycin in Japanese pediatric participants aged 1 to 17 years with cSSTI or bacteremia.

3.3 Benefit/Risk Assessment

It cannot be guaranteed that participants in clinical studies will directly benefit from treatment during participation, as clinical studies are designed to provide information about the safety and effectiveness of an investigational medicine.

The overall benefit-risk of daptomycin use in the pediatric population has been demonstrated in the non-Japanese pediatric cSSTI and bacteremia studies (Refer to Section 3.2.1).

Additional details regarding specific benefits and risks for participants participating in this clinical study may be found in the accompanying Investigators Brochure (IB) and Informed Consent documents.

4. Objectives/Hypotheses and Endpoints

In Japanese pediatric participants aged 1 to 17 years old with cSSTI or bacteremia caused by Gram-positive cocci:

Objective	**Endpoint**
Primary	
• To assess the safety and tolerability of daptomycin.	• Adverse Events (AEs) - Participant experiencing AE - Participant discontinuing study treatment due to AEs
Secondary	
• To assess the efficacy of administration of daptomycin in participants with MRSA infections.	• Clinical response at Test of Cure (TOC) visit • Subject-level microbiological response at Test of Cure (TOC) visit
• To evaluate steady state pharmacokinetics administration of daptomycin.	• Pharmacokinetic parameters such as AUC_{0-24} , C_{max}, t_{max}, CL_{ss}, V_{ss}, $t_{1/2}$ will be evaluated if evaluable data is obtained.

Objective	Endpoint
Exploratory	
• To assess the efficacy of administration of daptomycin in participants with MRSA infections.	• Clinical response at End Of Therapy (EOT) visit • Subject-level microbiological response at End Of Therapy (EOT) visit
• To assess the efficacy of administration of daptomycin.	• Clinical response at EOT and TOC visit • Subject-level microbiological response at EOT and TOC visit
• To assess the microbiological efficacy of administration of daptomycin per pathogen(s).	• Pathogen-level microbiological response per pathogen(s) at EOT and TOC visit

5. Study Design

5.1 Overall Design

This is an open-label, single-arm study of daptomycin (MK-3009) in Japanese pediatric participants with cSSTI or bacteremia caused by Gram-positive cocci.

Approximately 20 Japanese pediatric participants aged 1 to 17 years old with cSSTI or bacteremia caused by Gram-positive cocci as a infection type will be enrolled into this study. The study enrollment will be stopped when a total of 20 participants are enrolled. Details regarding enrollment distribution by age and diagnoses are provided in Section 5.2.

After a maximum duration of 72-hour screening period, eligible participants will receive a minimum of 5 days to up to a maximum of 14 days (cSSTI) or 42 days (bacteremia) of IV study therapy. While on study therapy, study visits will be performed on Day 1 (initiation of IV study drug), Day 3 (on therapy visit), and at end of therapy (EOT) (Administration of study medication will be witnessed by investigator or qualified designee in the study site, but hospitalization in the treatment period is not mandatory). At Day 3, blood sampling for analyzing plasma daptomycin concentration is conducted from 5 timepoints will occur: Pre-dose, 15 minutes after IV study medication infusion, and at 1 hour post-infusion, 4 hours post infusion, and12 hours post IV study medication infusion. Following the completion of IV study therapy, all participants will be evaluated 7 days following completion of therapy (at test of cure, TOC visit). In addition, a Follow up (FU) visit will be performed in all participants at 14 days after completion of IV study therapy. All participants will remain in the study for a total of up to 31 days (cSSTI) or 59 days (bacteremia).

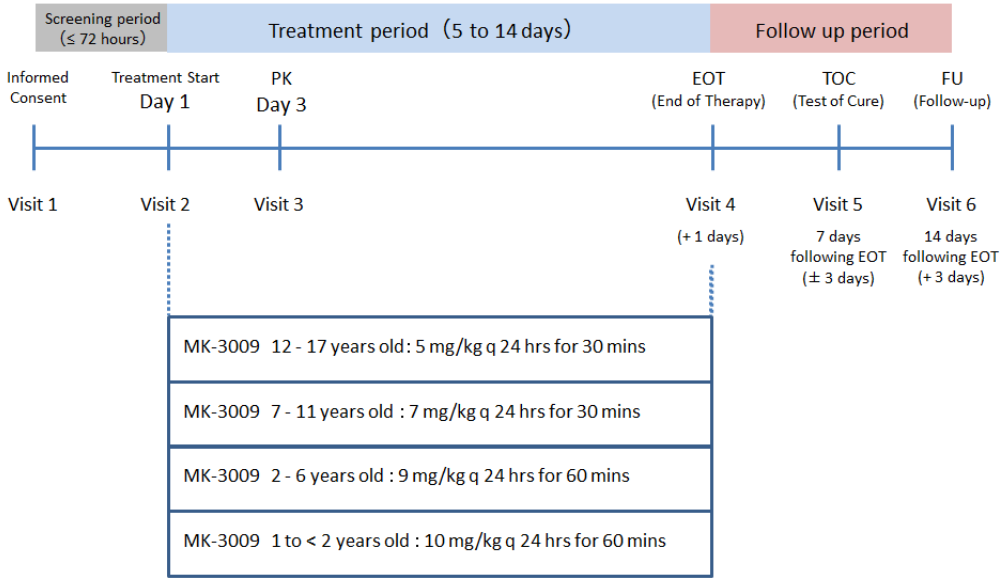
Safety and tolerability will be carefully monitored throughout the study by the Sponsor in accordance with standard procedures.

Specific procedures to be performed during the study, as well as their prescribed times and associated visit windows, are outlined in the Study SoA - Section 2. Details of each procedure are provided in Section 9 – Study Assessments and Procedures.

5.1.1 Study Diagram

The study design is depicted in Figure 1.

Trial Design for cSSTI



Trial Design for bacteremia

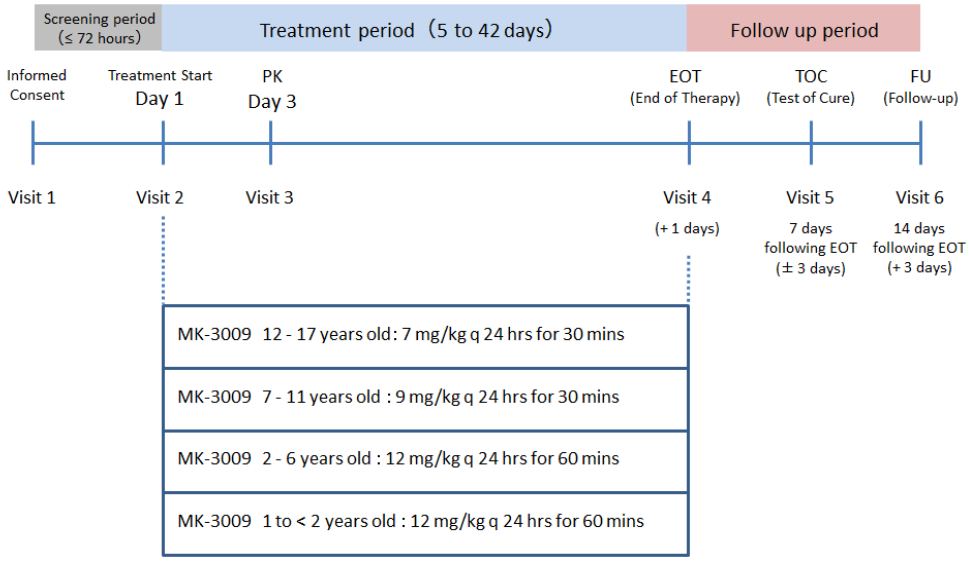


Figure 1 Trial Design

5.2 Number of Participants

Approximately 20 participants will be allocated.

The study will target enrollment of the following minimum number of participants in each infection type category and age groups (see below), but the study enrollment would be stopped when a total of 20 participants are enrolled regardless of enrollment status of each infection type or age groups:

- 6 participants with bacteremia
- 1 participant of 1to < 2 years old and 3 participants each for the higher age categories, regardless of the infection type.

5.3 Beginning and End of Study Definition

The overall study begins when the first participant signs the informed consent/assent form. The overall study ends when the last participant completes the last study-related phone-call or visit, withdraws from the study or is lost to follow-up (ie, the participant is unable to be contacted by the investigator).

For purposes of analysis and reporting, the overall study ends when the Sponsor receives the last pharmacokinetic analysis and central microbiology reference laboratory analysis results.

5.3.1 Clinical Criteria for Early Study Termination

There are no pre-specified criteria for terminating the study early.

5.4 Scientific Rationale for Study Design

5.4.1 Rationale for Population

The Japanese pediatric (1-17 years of age) population will be studied to support the planned licensing of daptomycin for treating cSSTI or bacteremia caused by Gram-positive cocci in Japan.

For the age of participants, same with the studies in non-Japanese pediatric, patients younger than 12 months are excluded from this study due to the risk of potential effects on muscular, neuromuscular, and/or nervous systems (either peripheral and/or central) observed in neonatal dogs with intravenous daptomycin.

5.4.2 Rationale for Endpoints

5.4.2.1 Safety Endpoints

As the primary objective of this study, the safety and tolerability of daptomycin will be assessed by clinical evaluation of adverse events and inspection of other study parameters including vital sign, physical examinations, and standard laboratory safety tests at time points specified in Section 2. Adverse events are graded and recorded according to Section 9.3. Participants may be asked to return for unscheduled visits in order to perform additional safety monitoring.

Other assessments of neurology and motor development are conducted in this study. The safety of daptomycin in the pediatric population in studies conducted outside Japan appears to be comparable to that observed in adults. The main safety concerns for this product include the important identified risks of severe skeletal muscle toxicity, peripheral neuropathy, development of resistance among *S. aureus* isolates during therapy, severe allergic reactions (including pulmonary eosinophilia and severe cutaneous reactions such as DRESS [Drug rash with Eosinophilia and Systemic Symptoms]) and eosinophilic pneumonia; the important potential risks associated with daptomycin include bone marrow toxicity, severe hepatic toxicity, and dysregulation of in vivo coagulation. Therefore, these safety concerns will be monitored closely in this study through clinical assessments and laboratory testing.

5.4.2.2 Efficacy Endpoints

A secondary objective of this study is to assess the efficacy of daptomycin in participants with MRSA infections that is the target pathogen of the Japanese adult indication. Because the targeted infections in this study, i.e. cSSTI and bacteremia, are serious illnesses, the efficacy of treatment should take into account responses in terms of both clinical signs and symptoms and microbiological results. Clinical response and microbiological response are both defined as the efficacy endpoints in this study.

5.4.2.3 Pharmacokinetic Endpoints

A secondary objective of this study is to characterize the PK profile of daptomycin in Japanese pediatric patients. The plasma concentration will be used to determine PK parameters (eg. C_{max}, t_{max}, AUC_{0-24}, CL_{ss} and V_{ss}, $t_{1/2}$ will be assessed if evaluable data is obtained) for daptomycin.

5.4.3 Rationale for population

The Japanese pediatric (1-17 years of age) population will be studied to support the planned licensing of daptomycin for treating cSSTI or bacteremia caused by Gram-positive cocci in Japan.

As was the case for the pediatric daptomycin cSSTI and bacteremia studies in non-Japanese pediatric, patients younger than 12 months are excluded from this study due to the risk of potential effects on muscular, neuromuscular, and/or nervous systems (either peripheral and/or central) observed in neonatal dogs with intravenous daptomycin.

5.5 Justification for Dose

Dosing regimens in Japanese pediatric patients were selected based on matching AUC with adult Japanese patients at the approved 4 mg/kg (cSSTI) or 6 mg/kg (bacteremia) doses. These doses have been demonstrated to be safe and efficacious in Japanese and non-Japanese adult Ph3 studies. In addition, owing to the lack of a role of drug metabolizing enzymes and transporters in daptomycin disposition, ontogenic changes are not expected to influence on PK of daptomycin in pediatric.

Pharmacokinetic assessments in non-Japanese pediatric subjects demonstrated that, in general, body weight-normalized total body clearance in pediatric patients was higher than in

adults and increased with a decrease in age, whereas elimination half-life tends to decrease with a decrease in age. These observations support age-specific, weight-based dosing regimens outlined in the table (see Section 7.4.1). These dosing regimens have been evaluated in non-Japanese pediatric cSSTI or bacteremia safety/efficacy/PK studies and were shown to have comparable safety and efficacy profiles observed in adults, and achieved comparable AUC distribution to those in adult patient populations. Although not directly studied, simulations based on the pediatric population PK model indicated that doses of 12 mg/kg administered to those 1-2 years of age in bacteremia would result in comparable exposures to those 2-6 years.

There is no difference in daptomycin PK between Japanese and non-Japanese (healthy or patients adult).

These results together support the appropriateness of the age-specific, weight-based dosing regimens evaluated in P017 and P005 in Japanese pediatric patients with cSSTI or bacteremia in the current study. See Section 7.4.1 for recommended dosing.

6. Study Population

Male/Female Japanese participants with cSSTI or bacteremia caused by Gram-positive cocci between the ages of 1 to 17 years will be enrolled in this study.

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

6.1 Inclusion Criteria

Participants are eligible to be included in the study only if all of the following criteria apply:

Type of Participant and Disease Characteristics

1. Require treatment for cSSTI or bacteremia.

   NOTE: Participants have to meet the following diagnostic criteria (either for cSSTI or bacteremia). If the participant meets both criteria for cSSTI and bacteremia, the participant must be allocated to group of bacteremia.

   For participant with cSSTI;

   The participant must meet the following two criteria.

   I. Has cSSTI known or suspected to be caused by Gram-positive cocci that requires intravenous antibiotic treatment and diagnosed with either Gram stain or culture. Complicated infections are defined as infections either involving deep soft tissue or requiring significant surgical intervention (e.g. cellulitis, erysipelas, infected ulcers, burns, and major abscesses), or skin and soft tissue infections accompanied by systemic signs and/or symptoms where intravenous antibiotic therapy is warranted.

   II. Has at least 3 of the following clinical signs and symptoms associated with the cSSTI:

      a. Pain;

b. Tenderness to palpation;

c. Temperature >37.0°C axillary or >37.5°C oral or >38.0° C rectal, forehead, or aural;

d. White blood count (WBC) >12,000/mm^3 or ≥10% bands;

e. Swelling and/or induration;

f. Erythema (>1cm beyond edge of wound or abscess);

g. Pus formation.

h. CRP > Upper Limited of Normal.

For participant with bacteremia:

Have proven or probable Gram-positive coccus bacteremia defined as follows:

Proven

Participants with proven bacteremia are those with pathogen identification of Gram-positive cocci at least one blood culture bottle by conventional culture methods or by a rapid diagnostic test in screening period.

Probable

Participants with probable bacteremia are those with a blood culture result demonstrating Gram-positive cocci by Gram stain in screening period.

Demographics

2. Be male or female Japanese aged ≥ 1 to ≤ 17 years on the day of signing informed consent.

Male participants:

3. A male participant must agree to use contraception as detailed in Section 12.2 during the treatment period and for at least 14 days, after the last dose of study treatment and refrain from donating sperm during this period.

Female participants:

4. A female participant is eligible to participate if she is not pregnant (see Section 12.2), not breastfeeding, and at least one of the following conditions applies:
a.) Not a woman of childbearing potential (WOCBP) as defined in Section 12.2
OR
b.) A WOCBP who agrees to follow the contraceptive guidance in Section 12.2 during the treatment period and for at least 14 days after the last dose of study treatment.

Informed Consent/Assent

5. The parent of participant (or a legally acceptable representative if applicable) provides written informed consent for the trial with understanding the study procedures, alternative treatments available, and risks involved with the study, and voluntarily agreement to participate. The participant can provide written assent if participant can do.

Others

6. Agree to allow any bacterial isolates obtained from protocol-required specimens related to the current infection to be provided the Central Microbiology Reference Laboratory for study-related microbiological testing, long-term storage, and other future testing.

6.2 Exclusion Criteria

Participants are excluded from the study if any of the following criteria apply:

Prior/Concomitant Therapy

1. Has received previous systemic antimicrobial therapy that is effective against Gram positive cocci and exceeding 72 hours duration administered at anytime during the 96 hours prior to the first dose of study drug;

   Exception: participant is eligible if the antibiotic is known to be not effective against the causative pathogen (includes clinical failure evaluated by investigator) or if the culture data demonstrate in vitro resistance to prior i.v. antibiotic.

Medical Conditions

2. Has a known infection caused solely by Gram-negative pathogen(s), fungus(i) or virus(es).
3. Has pneumonia (septic emboli in the lung is not an exclusion if clear evidence of source of infection is other than lungs), empyema, meningitis, endocarditis, or osteoarticular infection.
4. Has a history of or current rhabdomyolysis.
5. Is anticipated to require non-study systemic antibiotics that may be potentially effective against Gram-positive pathogen(s).
6. Has shock or hypotension unresponsive to fluids or vasopressors for ≥ 4 hours.
7. Has significant allergy/hypersensitivity or intolerance to daptomycin.
8. Has renal insufficiency (i.e. estimated glomerular filtration rate (eGFR) < 50 mL/min/1.73m^2). The calculus equation of eGFR is referred to section 12.4.
9. Has Creatine Phosphokinase (CPK) elevation ≥ 10 X ULN (upper limit of normal) without symptoms or ≥ 5 X ULN with symptoms such as myalgia, muscle stiffness, muscle weakness at screening.
10. Has a history of clinically significant (as assessed by the Investigator) muscular disease, nervous system or seizure disorder, including unexplained muscular weakness, history of peripheral neuropathy, Guillain-Barre or spinal cord injury; previous uncomplicated febrile seizure allowed.
11. Has a history or current evidence of any condition, therapy, lab abnormality or other circumstance that might expose the participant to risk by participating in the trial, confound the results of the trial, or interfere with the participant's participation for the full duration of the trial.

12. Is a female who is pregnant or is expecting to conceive (or is a male partner of a female who is expecting to conceive), is breastfeeding, or plans to breastfeed prior to completion of the study.

Prior/Concurrent Clinical Study Experience

13. Is currently participating in, or has participated in, any other clinical study involving the administration of investigational or experimental medication (not licensed by regulatory agencies) at the time of the presentation or during the previous 30 days prior to screening or is anticipated to participate in such a clinical study during the course of this trial.
14. Has previously participated in this study at any time.
15. Is or has an immediate family member (eg, spouse, parent/legal guardian, sibling or child) who is investigational site or sponsor staff directly involved with this study.

6.3 Lifestyle Restrictions

6.3.1 Meals and Dietary Restrictions

There are no restrictions in diet or meal.

6.3.2 Caffeine Alcohol, and Tobacco Restrictions

Alcohol and tobacco consumption are not permitted during the entire study period.

6.3.3 Activity

There are no restrictions in activity.

6.4 Screen Failures

Screen failures are defined as participants who consent/assent to participate in the clinical study but are not subsequently entered in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any adverse events or serious adverse events (SAE) meeting reporting requirements as outlined in the data entry guidelines.

6.5 Participant Replacement Strategy

A participant who discontinues from the study will not be replaced.

7. Treatments

Study treatment is defined as any investigational treatment(s), marketed product(s), placebo, or medical device(s) intended to be administered to a study participant according to the study protocol.

Clinical supplies [study treatment(s) provided by the Sponsor] will be packaged to support enrollment as required. Clinical supplies will be affixed with a clinical label in accordance with regulatory requirements.

7.1 Treatments Administered

The study treatment to be used in this study is outlined below in Table 1 Study Treatment.

Table 1 Study Treatment

Study Treatment Name:	Daptomycin for injection
Dosage Formulation:	Lyophilized powder
Unit Dose Strength(s):	500mg
Dosage Level(s):	Once daily administration of 5, 7, 9, 10, or 12mg/kg per infection types and age levels [See Section 7.4.1]
Route of Administration:	IV infusion
Sourcing:	Provided centrally by the Sponsor

All supplies indicated in Table 1 will be provided per the 'Sourcing' row depending upon local country operational requirements. Every attempt should be made to source these supplies from a single lot/batch number. The study site is responsible for recording the lot number, manufacturer, and expiry date for any locally purchased product as per local guidelines unless otherwise instructed by the Sponsor.

Refer to Section 9.1.8 for details regarding administration of the study treatment.

7.2 Method of Treatment Assignment

Participants participating in this trial will be allocated by non-random assignment.

7.2.1 Stratification

For this single treatment group design, eligible participants will be pre-stratified by age category (12-17, 7-11, 2-6 and 1 to <2 years of age) and infection type (cSSTI, bacteremia) prior to treatment assignment. The target number of participants for age categories and bacteremia as outlined in Section 5.2.

7.3 Blinding

This study is an open-label study; therefore, the Sponsor, investigator and participant will know the treatment administered.

7.4 Preparation/Handling/Storage/Accountability

7.4.1 Dose Preparation

The dose is assigned according to weight and infection type in each age group as Table 2.

Table 2 Dose Preparation

	cSSTI	Bacteremia	Infusion Volume	Infusion Duration
12-17 years old	5 mg/kg q 24 hrs	7 mg/kg q 24 hrs	50 mL saline	30 minutes
7-11 years old	7 mg/kg q 24 hrs	9 mg/kg q 24 hrs	50 mL saline	30 minutes
2-6 years old	9 mg/kg q 24 hrs	12 mg/kg q 24 hrs	25 mL saline	60 minutes
1 to < 2 years old	10 mg/kg q 24 hrs	12 mg/kg q 24 hrs	25 mL saline	60 minutes

Time window for dosing interval (q 24 hours): +/- 2 hours

Time window for infusion duration: +/- 5 minutes for 30 minutes, +/- 10 minutes for 60 minutes

The dose of each participant should be determined based on the body weight measured at Visit 1. If the body weight fluctuates by more than 10% during the treatment period and the investigator determines that it is a clinically significant fluctuation, the dose may be recalculated and modified.

If a participant with cSSTI is diagnosed with bacteremia after allocation (i.e. the blood culture for participant with cSSTI is positive after allocation through the study [including at Visit 1]), the participant could continue the study treatment with change of dose regimen from dosing for cSSTI to dosing for bacteremia upon consultation/discussion with sponsor.

7.4.2 Handling, Storage and Accountability

The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study treatment received and any discrepancies are reported and resolved before use of the study treatment.

Only participants enrolled in the study may receive study treatment and only authorized site staff may supply or administer study treatment. All study treatments must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff.

The investigator, institution, or the head of the medical institution (where applicable) is responsible for study treatment accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).

For all study sites, the local country Sponsor personnel or designee will provide appropriate documentation that must be completed for drug accountability and return, or local discard and destruction if appropriate. Where local discard and destruction is appropriate, the

investigator is responsible for ensuring that a local discard/destruction procedure is documented.

The study site is responsible for recording the lot number, manufacturer, and expiry date for any locally purchased product as per local guidelines unless otherwise instructed by the Sponsor.

The investigator shall take responsibility for and shall take all steps to maintain appropriate records and ensure appropriate supply, storage, handling, distribution and usage of study treatments in accordance with the protocol and any applicable laws and regulations.

7.5 Treatment Compliance

Interruptions from the protocol specified treatment plan for compliance < 80% (actual number of study administration is < 80% of actual number of days for treatment period) require consultation between the investigator and the Sponsor and written documentation of the collaborative decision on participant management.

7.6 Concomitant Therapy

Medications or vaccinations specifically prohibited in the exclusion criteria are not allowed during the ongoing study. If there is a clinical indication for any medication or vaccination specifically prohibited, discontinuation from study therapy or vaccination may be required. The investigator should discuss any questions regarding this with the Sponsor Clinical Director. The final decision on any supportive therapy or vaccination rests with the investigator and/or the participant's primary physician. However, the decision to continue the participant on study treatment requires the mutual agreement of the investigator, the Sponsor and the participant.

The following concomitant medications/therapies are prohibited in this study:

(From first study drug administration to TOC)

- Non-study systemic (oral, intravenous or suppository) antibacterial treatments with indications for Gram-positive coccus identified as baseline causative pathogen.
- Any medication administration via intramuscular (IM) injection.

Aztreonam as adjunctive antimicrobial therapy for Gram-negative aerobic pathogens may be initiated at the discretion of the investigator depending on the clinical circumstances and the likely or proven pathogens at a given site.

7.6.1 Rescue Medications and Supportive Care

No rescue or supportive medications are specified to be used in this study.

7.7 Treatment After the End of the Study

There is no study-specified treatment following the end of the study.

7.8 Clinical Supplies Disclosure

This study is open-label; therefore, the participant, the study site personnel, the Sponsor and/or designee are not blinded. Study treatment (name, strength or potency) is included in the label text; random code/disclosure envelopes or lists are not provided.

8. Discontinuation/Withdrawal Criteria

8.1 Discontinuation of Study Treatment

Discontinuation of study treatment does not represent withdrawal from the study.

As certain data on clinical events beyond study treatment discontinuation may be important to the study, they must be collected through the participant's last scheduled follow-up, even if the participant has discontinued study treatment. Therefore, all participants who discontinue study treatment prior to completion of the protocol-specified treatment period will still continue to participate in the study as specified in Section 2.

Participants may discontinue study treatment at any time for any reason or be dropped from the study treatment at the discretion of the investigator should any untoward effect occur. In addition, a participant may be discontinued from study treatment by the investigator or the Sponsor if study treatment is inappropriate, the study plan is violated, or for administrative and/or other safety reasons. Specific details regarding procedures to be performed at study treatment discontinuation are provided in Section 9.1.9.

A participant must be discontinued from study treatment but continue to be monitored in the study for any of the following reasons:

- The participant or participant's legally acceptable representative requests to discontinue study treatment.
- The participant or participant's legally acceptable representative requests to discontinue study treatment.
- The participant has a medical condition or personal circumstance which, in the opinion of the investigator and/or sponsor, placed the participant at unnecessary risk from continued administration of study treatment.
- The participant has a confirmed positive serum pregnancy test.
- Non-compliance, such that the Investigator did not permit further study participation.
- Rhabdomyolysis with or without renal failure not attributed to known causes such as trauma or burns.
- Guillain-Barre syndrome.
- Elevated blood creatine phosphokinase (CPK) to levels ≥ 10X ULN not related to trauma, burns or muscle infection.
- Elevated blood creatine phosphokinase (CPK) to levels ≥ 5X ULN with muscle symptoms such as but not limited to weakness or myalgia not related to an underlying disease (e.g. muscle infection).

- Decreased renal function (eGFR is < 30 mL/min/1.73m^2) at any time after screening. The calculus equation of eGFR is referred to section 12.4.

For participants who are discontinued from study treatment but continue to be monitored in the study, all visits and procedures, as outlined in the SoA, should be completed.

Discontinuation from study treatment is "permanent." Once a participant is discontinued, he/she shall not be allowed to restart study treatment.

8.2 Withdrawal from the Study

A participant must be withdrawn from the study if the participant or participant's legally acceptable representative withdraws consent from the study.

If a participant withdraws from the study, they will not receive study treatment or be followed at scheduled protocol visits.

Specific details regarding procedures to be performed at the time of withdrawal from the study are outlined in Section 9.1.9. The procedures to be performed should a participant repeatedly fail to return for scheduled visits and/or if the study site is unable to contact the participant are outlined in Section 8.3.

8.3 Lost to Follow Up

If a participant fails to return to the clinic for a required study visit and/or if the site is unable to contact the participant, the following procedures are to be performed:

- The site must attempt to contact the participant and reschedule the missed visit. If the participant is contacted, the participant should be counseled on the importance of maintaining the protocol-specified visit schedule.
- The investigator or designee must make every effort to regain contact with the participant at each missed visit (eg, phone calls and/or a certified letter to the participant's last known mailing address or locally equivalent methods). These contact attempts should be documented in the participant's medical record.
- Note: A participant is not considered lost to follow-up until the last scheduled visit for the individual participant. The missing data for the participant will be managed via the pre-specified statistical data handling and analysis guidelines.

9. Study Assessments and Procedures

- Study procedures and their timing are summarized in the SoA.
- Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.
- The Investigator is responsible for assuring that procedures are conducted by appropriately qualified or trained staff. Delegation of study site personnel responsibilities will be documented in the Investigator Trial File Binder (or equivalent).
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log

to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.

- Procedures conducted as part of the participant's routine clinical management (eg, blood count) and obtained before signing of ICF may be utilized for screening or baseline purposes provided the procedure met the protocol-specified criteria and were performed within the time frame defined in the SoA.
- Additional evaluations/testing may be deemed necessary by the investigator and or the Sponsor for reasons related to participant safety. In some cases, such evaluation/testing may be potentially sensitive in nature (eg, HIV, Hepatitis C, etc.), and thus local regulations may require that additional informed consent, and assent if applicable, be obtained from the participant. In these cases, such evaluations/testing will be performed in accordance with those regulations.

The amount of blood collected from each participant for clinical safety laboratory assessment over the duration of the study will be approximately 13mL to 33mL depending on the treatment period of each participant. The amount of blood collected from each participant for analyzing plasma daptomycin concentration will be approximately 5 mL total (1 mL per each sampling point).

Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

9.1 Administrative and General Procedures

9.1.1 Informed Consent/Assent

The investigator or qualified designee must obtain documented consent, and assent if applicable, from each potential participant or each participant's legally acceptable representative prior to participating in a clinical study. If there are changes to the participant's status during the study (eg, health or age of majority requirements), the investigator or qualified designee must ensure the appropriate consent/assent is in place.

9.1.1.1 General Informed Consent/Assent

Consent/assent must be documented by the participant's dated signature or by the participant's legally acceptable representative's dated signature on a consent/assent form along with the dated signature of the person conducting the consent discussion.

A copy of the signed and dated consent/assent form should be given to the participant before participation in the study.

The initial informed consent/assent, any subsequent revised written informed consent/assent and any written information provided to the participant must receive the IRB/IEC's approval/favorable opinion in advance of use. The participant or his/her legally acceptable representative should be informed in a timely manner if new information becomes available that may be relevant to the participant's willingness to continue participation in the study. The communication of this information will be provided and documented via a revised consent/assent form or addendum to the original consent/assent form that captures the

participant's dated signature or by the participant's legally acceptable representative's dated signature.

Specifics about a study and the study population will be added to the consent/assent form template at the protocol level.

The informed consent will adhere to IRB/IEC requirements, applicable laws and regulations and Sponsor requirements. The assent, as applicable will adhere to IRB/IEC requirements, applicable laws and regulations and Sponsor requirements.

9.1.2 Inclusion/Exclusion Criteria

All inclusion and exclusion criteria will be reviewed by the investigator or qualified designee to ensure that the participant qualifies for the study.

9.1.3 Participant Identification Card

All participants will be given a Participant Identification Card identifying them as participants in a research study. The card will contain study site contact information (including direct telephone numbers) to be utilized in the event of an emergency. The investigator or qualified designee will provide the participant with a Participant Identification Card immediately after the participant provides written informed consent/assent. At the time of treatment allocation/randomization, site personnel will add the treatment/randomization number to the Participant Identification Card.

The participant identification card also contains contact information for the emergency unblinding call center so that a health care provider can obtain information about study treatment in emergency situations where the investigator is not available.

9.1.4 Medical History

A medical history will be obtained and the evaluation of a participant's medical history in terms of study eligibility will be evaluated by the investigator or qualified. All medical conditions including infections will be documented at Visit1 on the appropriate eCRF.

9.1.5 Prior and Concomitant Medications Review

9.1.5.1 Prior Medications

The investigator or qualified designee will review prior medication use, and record prior medication taken by the participant within 30 days before starting the study.

9.1.5.2 Concomitant Medications

The investigator or qualified designee will record medication, if any, taken by the participant during the study.

9.1.6 Assignment of Screening Number

All consented participants will be given a unique screening number that will be used to identify the participant for all procedures that occur prior to treatment allocation. Each

participant will be assigned only one screening number. Screening numbers must not be re-used for different participants.

9.1.7 Assignment of Treatment/Randomization Number

All eligible participants will be allocated, by non-random assignment, and will receive a treatment/randomization number. The treatment/randomization number identifies the participant for all procedures occurring after treatment allocation/randomization. Once a treatment/randomization number is assigned to a participant, it can never be re-assigned to another participant.

A single participant cannot be assigned more than 1 treatment/randomization number.

9.1.8 Treatment Administration

Trial dosage and regimen of study drug are described in Section 7.4.1. The first dose will be administered at Visit 2.

All IV study therapy infusions should be administered over 30 minutes +/- 5 minutes (7 to 17 years old) or 60 minutes +/- 10 minutes (1 to 6 years old). The IV study therapy must NOT be administered simultaneously through the same infusion line/lumen with any other drugs. If another IV drug is required either prior to or after study drug and only 1 line is available, an appropriate volume of saline flush must be used between IV infusions. Administration of study medication will be witnessed by the investigator and/or qualified designee.

IV study therapy should be administered for a minimum of 5 days to up to a maximum of 14 days (cSSTI) or 42 days (bacteremia). Administration of trial medication will be witnessed by the investigator and/or qualified designee.

Further details on the preparation, storage, and administration of the intravenous study antibiotics are provided in a separate Pharmacy Binder.

9.1.8.1 Timing of Dose Administration

The IV study drug infusion will be administrated once daily every 24 (+/- 2) hours.

9.1.9 Discontinuation and Withdrawal

Participants who discontinue study treatment prior to completion of the treatment period should be encouraged to continue to be followed for all remaining study visits.

When a participant withdraws from participation in the study, all applicable activities scheduled for the final study visit should be performed (at the time of withdrawal). Any adverse events which are present at the time of withdrawal should be followed in accordance with the safety requirements outlined in Section 9.3.

9.1.10 Participant Blinding/Unblinding

This is an open label study; there is no blinding for this study.

9.1.11 Calibration of Equipment

The investigator or qualified designee has the responsibility to ensure that any device or instrument used for a clinical evaluation/test during a clinical study that provides information about inclusion/exclusion criteria and/or safety or efficacy parameters shall be suitably calibrated and/or maintained to ensure that the data obtained is reliable and/or reproducible. Documentation of equipment calibration must be retained as source documentation at the study site.

9.2 Efficacy Assessments

9.2.1 Clinical Response

At the EOT and TOC, the investigator will determine the subject's clinical response based on consideration of the subject's signs and symptoms compared with those present at baseline using the following categories as Table 3:

Table 3 Definition of clinical assessment

Cure	Resolution of clinically significant signs and symptoms associated with admission infection (i.e., return to pre-infection Baseline). No further antibiotic therapy required for the infection type under study.
Improvement	Partial resolution of clinical signs or symptoms of infection such that no further antibiotic therapy is required for the infection type under study.
Failure	Inadequate clinical response to therapy – additional antibiotic therapy required for infection type under study.
Not evaluable	None of the above. (e.g. Subject was not available to be examined and assessed.)

"Cure" and "Improved" will be considered a "Clinical success" (satisfactory clinical responses).

Any subjects who still require further antibiotic therapy at TOC will be considered a "Failure".

For subjects whose clinical course cannot be clearly defined as "Improved", a clinical outcome of "Failure" will be rendered. Subjects who discontinue study drug therapy before Day 3 will be considered "Not evaluable" unless otherwise deemed a clinical "failure". "Clinical failure" will be carried through as "failure" for purposes of evaluation.

9.2.2 Microbiological Response

9.2.2.1 Pathogen-level microbiological response

At the EOT and TOC, Each subject's Baseline Infecting Pathogen(s) will be assessed by investigator according to the following criteria, which are hierarchical and mutually exclusive as Table 4:

Table 4 Definition of pathogen-level microbiological response

Eradication	Absence of the Baseline Infecting Pathogen
Presumed eradication	Absence of material to culture in a subject deemed a clinical cure (cSSTI only)
Persistent	Continued presence of the Baseline Infecting Pathogen
Presumed persistent	Absence of material to culture in a subject deemed a clinical failure (cSSTI only)
Not evaluable	None of the above (e.g. Study data are not available)

Proportion of the microbiological success per pathogen will be analyzed based on these results (see stat section 10.6).

Super infection and new infection will be also assessed by investigator separately from the baseline infection evaluation as Table 5.

Table 5 Definition of Super infection and new infection

Super infection	Presence of new gram-positive cocci pathogen(s) other than baseline infecting pathogen during treatment period
New infection	Presence of new gram-positive cocci pathogen other than baseline infecting pathogen or superinfecting pathogen after EOT

9.2.2.2 Subject-level microbiological response

At the EOT and TOC, the Subject's Microbiological Response will be derived from the Pathogen-Level Microbiological Response for all of the subject's Baseline Infecting Pathogens and from the presence or absence of a Superinfecting Pathogen or New infecting pathogen (gram-positive cocci). The Subject's Microbiological Response will be categorized as Table 6:

Table 6 Definition of subject-level microbiological response

Success	Absence or presumed absence* of the ALL Baseline Infecting Pathogen(s) And No gram-positive cocci superinfection (EOT) or gram-positive new infection (TOC)
Failure	Presence of any Baseline Infecting Pathogen(s) Or Gram-positive cocci superinfection (EOT) or gram-positive new infection (TOC)
Not evaluable	None of the above (e.g. Study data are not available)

*: Only applicable for cSSTI

9.3 Adverse Events (AE), Serious Adverse Events (SAE) and Other Reportable Safety Events

The definitions of an adverse event (AE) or serious adverse event (SAE), as well as the method of recording, evaluating, and assessing causality of AE and SAE and the procedures for completing and transmitting AE, SAE and other reportable safety event reports can be found in Section 12.3

AE, SAEs, and other reportable safety events will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative).

The investigator, who is a qualified physician, and any designees are responsible for detecting, assessing, documenting, and reporting events that meet the definition of an AE or SAE as well as other reportable safety events. Investigators remain responsible for following up AE, SAEs and other reportable safety events for outcome according to Section 9.3.3.

9.3.1 Time Period and Frequency for Collecting AE, SAE and Other Reportable Safety Event Information

All AEs, SAEs and other reportable safety events that occur after the consent form is signed but before treatment allocation/randomization must be reported by the investigator if the participant is receiving placebo run-in or other run-in treatment, if the event causes the participant to be excluded from the study, or is the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, or a procedure.

From the time of treatment allocation/randomization through 14 days following cessation of treatment, all AEs, SAEs and other reportable safety events must be reported by the investigator.

Additionally, any SAE brought to the attention of an investigator at any time outside of the time period specified in the previous paragraph must be reported immediately to the Sponsor if the event is considered to be drug-related.

Investigators are not obligated to actively seek AE or SAE or other reportable safety events in former study participants. However, if the investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event to be reasonably related to the study treatment or study participation, the investigator must promptly notify the sponsor.

All initial and follow-up AEs, SAEs and other reportable safety events will be recorded and reported to the sponsor or designee within the timeframes as indicated in Table 7.

Table 7 Reporting Time Periods and Timeframes for Adverse Events and Other Reportable Safety Events

Type of Event		**Reporting Time Period:** **Consent to Randomization/ Allocation**	**Reporting Time Period:** **Randomization/ Allocation through Protocol-Specified Follow-up Period**	**Reporting Time Period:** **After the Protocol Specified Follow-up Period**		**Timeframe to Report Event and Follow-up Information to SPONSOR:**
Non-Serious Adverse Event (NSAE)		Report if: - due to protocol-specified intervention - causes exclusion - participant is receiving placebo run-in or other run-in treatment	Report all	Not required		Per data entry guidelines
Serious Adverse Event (SAE)		Report if: - due to protocol-specified intervention - causes exclusion - participant is receiving placebo run-in or other run-in treatment	Report all	Report if: - drug/vaccine related. (Follow ongoing to outcome)		Within 24 hours of learning of event
Pregnancy/ Lactation Exposure		Report if: - due to intervention - causes exclusion	Report all	Previously reported – Follow to completion/termination; report outcome		Within 24 hours of learning of event
Event of Clinical Interest (require regulatory reporting)		Report if: - due to intervention - causes exclusion	Report - Potential DILI - Require regulatory reporting	Not required		Within 24 hours of learning of event
Event of Clinical Interest (Do not require regulatory reporting)		Report if: - due to intervention - causes exclusion	Report - non-DILI ECIs and those not requiring regulatory reporting	Not required		Within 5 calendar days of learning of event
Cancer		Report if: - due to intervention - causes exclusion	Report all	Not required		Within 5 calendar days of learning of event

Type of Event		Reporting Time Period: Consent to Randomization/ Allocation	Reporting Time Period: Randomization/ Allocation through Protocol-Specified Follow-up Period	Reporting Time Period: After the Protocol Specified Follow-up Period		Timeframe to Report Event and Follow-up Information to SPONSOR:
Overdose		Report if: - receiving placebo run-in or other run-in medication	Report all	Not required		Within 5 calendar days of learning of event

9.3.2 Method of Detecting AE, SAE and Other Reportable Safety Events

Care will be taken not to introduce bias when detecting AE and/or SAE and other reportable safety events. Open-ended and non-leading verbal questioning of the participant is the preferred method to inquire about AE occurrence.

9.3.3 Follow-up of AE, SAE and Other Reportable Safety Event Information

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All AE, SAE and other reportable safety events including pregnancy and exposure during breastfeeding, ECI, Cancer and Overdose will be followed until resolution, stabilization, until the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 8.3). In addition, the investigator will make every attempt to follow all non-serious AEs that occur in randomized participants for outcome. Further information on follow-up procedures is given in Section 12.3.

9.3.4 Regulatory Reporting Requirements for SAE

- Prompt notification (within 24 hours) by the investigator to the sponsor of SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study treatment under clinical investigation are met.
- The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study treatment under clinical investigation. All Adverse Events will be reported to regulatory authorities, IRB/IECs and investigators in accordance with all applicable global laws and regulations, ie, per ICH Topic E6 (R1) Guidelines for Good Clinical Practice.
- Investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSAR) according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.
- An investigator who receives an investigator safety report describing an SAE or other specific safety information (eg, summary or listing of SAE) from the sponsor will file

it along with the Investigator's Brochure and will notify the IRB/IEC, if appropriate according to local requirements.

9.3.5 Disease-Related Events and/or Disease-Related Outcomes Not Qualifying as AEs or SAEs

Not applicable.

9.3.6 Pregnancy and Exposure During Breastfeeding

Although pregnancy and infant exposure during breastfeeding are not considered adverse events, any pregnancy or infant exposure during breastfeeding in a participant (spontaneously reported to the investigator or their designee) that occurs during the study are reportable to the Sponsor.

All reported pregnancies must be followed to the completion/termination of the pregnancy. Pregnancy outcomes of spontaneous abortion, missed abortion, benign hydatidiform mole, blighted ovum, fetal death, intrauterine death, miscarriage and stillbirth must be reported as serious events (Important Medical Events). If the pregnancy continues to term, the outcome (health of infant) must also be reported.

9.3.7 Events of Clinical Interest (ECI)

Selected non-serious and serious adverse events are also known as Events of Clinical Interest (ECI) and must be reported to the Sponsor.

Events of clinical interest for this study include:

1. an elevated AST or ALT lab value that is greater than or equal to 3X the upper limit of normal and an elevated total bilirubin lab value that is greater than or equal to 2X the upper limit of normal and, at the same time, an alkaline phosphatase lab value that is less than 2X the upper limit of normal, as determined by way of protocol-specified laboratory testing or unscheduled laboratory testing.*

*Note: These criteria are based upon available regulatory guidance documents. The purpose of the criteria is to specify a threshold of abnormal hepatic tests that may require an additional evaluation for an underlying etiology. The study site guidance for assessment and follow up of these criteria can be found in the Investigator Trial File Binder (or equivalent).

If laboratory tests meet this ECI criteria above in patients BEFORE receiving MK-3009, investigators need to report that as ECI within 24 hours of leaning the event to the SPONSOR, however the process to identify the etiology (stage 1 and stage 2 testing) should be evaluated as clinically indicated. Instead, the Liver Functional Test in the participant should be periodically monitored and discontinuation of MK-3009 should be considered if necessary.

9.4 Treatment of Overdose

In this study, an overdose is defined as follows.

Dose regimen: more than once daily, or the administration interval is less than 12 hours even once daily

Dosage: more than the protocol-specified dose of study medication. (Please see Table 2)

If overdose is suspected, carefully observe the condition of the participant and provide supportive treatment as necessary. In adults, daptomycin is slowly removed from the body by hemodialysis (about 15% removal of the dose in 4 hours) or peritoneal dialysis (about 11% removal in 48 hours).

Decisions regarding dose interruptions or modifications will be made by the investigator in consultation with the Sponsor based on the clinical finding of the participant.

9.5 Safety

Details regarding specific safety procedures/assessments to be performed in this study are provided below. The clinical laboratory test can be found in Section 12.4.

Planned time points for all safety assessments are provided in the SoA.

9.5.1 Physical Examinations

All physical examinations must be performed by the investigators.

A full physical examination, performed at Visit1 and Visit6 includes the following assessments:

- general appearance
- head
- eyes
- ears/nose/ throat
- neck
- lymph nodes
- skin
- lungs
- heart
- abdomen
- musculoskeletal
- neurologic evaluations

(If clinically indicated)

- Breast
- rectal
- genitourinary/pelvic exams

Directed physical examination, performed at Visit2, Visit4, Visit5 and in treatment period (twice a week) includes the following assessments:

Emphasis on evaluation of:

- weakness
- muscle pain
- signs and symptoms related to source of infection.

Any abnormal or clinically significant findings from the physical examinations must be recorded on the appropriate eCRF.

9.5.2 Vital Signs

Blood pressure (systolic/diastolic), pulse rate, respiratory rate and oral temperature will be assessed.

- If the participant's oral body temperature cannot be measured, then it is acceptable to measure the body temperature via non-oral methods, e.g. rectal, forehead, or aural. However, for each participant, the method by which body temperature is measured should be the same throughout the study.
- Participants should be resting in a seated or semi-recumbent position for at least 10 minutes prior to having vital sign measurements obtained. And clinical laboratory test should be performed after the measurement of vital signs.
- Vital signs should be measured prior to administration of the study medication.

9.5.3 Height and weight

The height should be measured at Visit1.

The weight should be measured at Visit1 and Visit3. And the weight should be measured and recorded if a clinically significant weight change occurred in study therapy.

9.5.4 Neurological Examination

Neurological Examination should be performed according to section 2.

The investigators will perform an age appropriate neurological examination including assessments of Mental Status, Cranial Nerve, Muscle Tone (Leg and Arm), Muscle Strength (Leg and Arm), Reflexes (Ankle, Biceps, Knee and Babinski), Coordination and Gait (Finger-to-Nose), Sensory (light touch sense-Forearms and Legs) and Tremor (Upper Extremities). All assessments will be evaluated as normal or abnormal (grading of abnormal and so on if applicable).

9.5.5 Assessment of Motor Developmental Skills

Motor developmental skills should be assessed for the participants 6 years and under.

The investigators will perform an assessment of motor developmental skills using the questionnaire (e.g. washes and dries hands, balances on one foot for 2 seconds. Reference: American Academy of Pediatrics' Bright Futures). For the assessment at Visit1, the investigators may assess based on the information on developmental skills immediately prior to cSSTI or bacteremia provided by participant's parents.

9.5.6 Clinical Safety Laboratory Assessments

Refer to Section 12.4 for the list of clinical laboratory tests to be performed and to the SoA for the timing and frequency.

- The investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the CRF. The laboratory reports must be filed with the source documents. Clinically significant abnormal laboratory findings are those which are not associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.
- All protocol-required laboratory assessments, as defined in Section 12.4, must be conducted in accordance with the laboratory manual and Section 2.
- If laboratory values from non-protocol specified laboratory assessments performed at the institution's local laboratory require a change in study participant management or are considered clinically significant by the investigator (eg, SAE or AE or dose modification), then the results must be recorded in the appropriate CRF (eg, SLAB).
- For any laboratory tests with values considered clinically significantly abnormal during participation in the study or within 14 days after the last dose of study treatment, every attempt should be made to perform repeat assessments until the values return to normal or baseline or if a new baseline is established as determined by the investigator.
- In cases of technical difficulties or age of participant, it is acceptable that the laboratory tests of urinalysis is not conducted according to the determines of investigators.

9.5.7 Microbiological Culture

All microbiological Cultures should be performed at the local microbiology laboratory according to recognized methods and per each laboratory's standard procedures according to section 2.

Any suspected causative bacterial pathogens that are isolated from local microbiological cultures must be collected and available for submission to the Central Microbiology Reference Laboratory. Suspected causative bacterial pathogens should also be stored at the local microbiology laboratory if possible future testing is needed. Relevant culture data, including date of collection, specimen type (including method of collection), and pathogen

identification (to the species level, if identified) must be collected on the appropriate eCRF. Submission of suspected causative bacterial pathogen is needed for allocated participant only.

Additional details regarding bacterial specimen collection, processing, handling, and shipment will be provided by the Sponsor in a separate microbiology laboratory manual.

9.5.7.1 Collection of Infection-Site Specimens

Infection-site specimens for culture should be obtained from the participant with cSSTI specified in protocol (refer to Section 2). For collection of infection-site specimen at Visit 1, if the culture specimen collected within 120 hours before the first administration of study drug already exists, the same specimen may be used. For participants in which infection site specimen collection is not medically acceptable, follow up specimen is not required.

All specimens collected for culture must be collected via valid sampling technique (aspirate, biopsy, deep swab, etc; superficial swab not acceptable) by investigators or qualified designee, and specimens should be collected as much as possible. If there is no appropriate site to collect the specimens (e.g. cellulitis) specimens are to be collected according to standard practice at the site.

In addition, the data regarding to surgical intervention and indwelling/replacement/removal of prosthetic object (e.g. catheter, stent) should be recorded and collected on the appropriate eCRF. Additional unscheduled cultures should also be performed for obtained specimen at the time of any surgical intervention.

9.5.7.2 Collection of blood

For each blood culture collection, two sets of blood cultures (total 4 bottles: 2 for aerobic culture and 2 for anaerobic culture), i.e., one set each from two separate venipuncture (or 1 venipuncture and 1 catheter) sites are recommended. However, if in the opinion of the investigator and owing to the safety of the participant or age of participant, it is acceptable that the number of sets or bottles for blood culture is not satisfied with protocol.

At Visit1, blood culture is required in all participants. For blood collection at Visit 1, if the culture specimen collected within 120 hours before the first administration of study drug already exists, the same specimen may be used. At EOT (Visit 4), blood culture is required even if the blood cultures until 2 sequential cultures demonstrate no growth is confirmed. In the follow-up period, blood cultures are performed at TOC (Visit 5) and FU (Visit 6), but if the result is negative at TOC (Visit 5), blood culture should not be required at FU (Visit 6).

Participants with positive blood cultures at Visit1 (screening) should have follow-up blood cultures until 2 sequential cultures demonstrate no growth is confirmed.

For participants with negative blood cultures at Visit1 (screening), i.e. participants with no evidence of bacteremia, the follow-up blood culture is not required and should also be performed at the investigator discretion as clinically indicated.

9.5.7.3 Gram stain

Gram stain should be performed at Visit 1, using the collected specimen (infection site) or the bacteria from the specimen culture (Infection site or blood). If the pathogen species are identified by other methods, gram stain is not necessary. Gram stain may be performed at the

same day of screening period as the first dose of study drug administration (i.e. Before the first dose of study drug).

9.5.8 Clinical Assessment of Infection Site

The investigators will evaluate the clinical assessment of signs and symptoms of cSSTI according to section 2. The signs and symptoms (Erythema, Swelling/Edema, Induration, Localized Warmth, Tenderness on Palpation, Drainage, Fluctuance, Ulceration, Necrotic Tissue, Localized Pain, Redness, Chills and Fever) will be examined and will be evaluated as "Yes" or "No", and grade (Mild, Moderate or Severe, if applicable).

9.6 Pharmacokinetics

9.6.1 Blood Collection for Plasma daptomycin

Blood sampling for analyzing plasma daptomycin concentration is conducted on Visit 3. And blood sampling is performed after at least 2 consecutive daptomycin dosing. In order to avoid the missing of collecting the blood sample, it is acceptable to collect the blood sample beyond the allowance of Visit 3 (+1 day).

Total 5 points of blood sampling is recommended for all age groups as Table 8.

Table 8 Blood sampling points and their allowances

Blood sampling points	Allowance
Pre-dose	Within 2 hours prior of daptomycin dosing
15 min after the end of infusion	+/- 5 min
1 hour after the end of infusion	+/- 10 min
4 hours after the end of infusion	+/- 30 min
12 hours after the end of infusion	- 2 hours

However, if in the opinion of the investigator and owing to the safety of the participant or age of participant, number of blood samples as below may be collected to support PK analysis with consultation with the Sponsor.

- 7 to 17 years old participants: All 5 points.
- 1 to 6 years old participants: At least 3 points at 15 minutes, 1 or 4 hours and 12 hours post-infusion

The blood sample for daptomycin PK evaluation is collected through a separate line in a contralateral arm/leg from the infusion line/lumen used for study drug or infusion solution dosing.

If the blood sample should be collected through the same infusion line/lumen used for study drug or infusion solution dosing due to the subject condition, the infusion line/lumen is required to be flushed by the appropriate volume of saline solution.

The sample collection, storage and shipment instructions of the plasma sample are referred to the operations/laboratory manual.

9.7 Pharmacodynamics

Pharmacodynamics will not be evaluated in this study.

9.8 Biomarkers

Biomarkers are not evaluated in this study.

9.9 Future Biomedical Research Sample Collection

Future Biomedical Research Samples will not be collected in this study.

9.10 Visit Requirements

Visit requirements are outlined in Section 2 – Schedule of Activities (SoA). Specific procedure-related details are provided above in Section 9 – Study Assessments and Procedures.

9.10.1 Screening

Approximately 72 hours prior to first dose, potential participants will be evaluated to determine that they fulfill the entry requirements as set forth in Section 6.1 and 6.2. Regarding the evaluation and procedures prescribed in Section 2, if there is data obtained in the screening period (72 hours before the first dose of study administration), even if the data obtained before obtaining the consent of participating in the trial, eligibility may be evaluated using such data. Screening procedures before allocation may be repeated multiple times after consultation with the Sponsor.

9.10.2 Treatment Period

IV study therapy should be administered for a minimum of 5 days, i.e., 5 dose of daptomycin based on the q24h dosing regimen. The total duration of IV study therapy should NOT exceed 14 days (cSSTI) or 42 days (bacteremia).

Assessments and procedures while on IV study therapy will be completed at the indicated times and intervals as per the Schedule of Activities (Section 2). All study assessments are recommended to be performed at approximately the same time of day for the study participant (e.g. every morning) for each calendar day.

The EOT visit will be completed within 1 day after the last dose of IV study therapy.

9.10.3 Follow up period (Post-treatment)

TOC visit [7 (+/-3) days after completion of IV study therapy] and FU visit [14 (+3) days after completion of IV study therapy] must be completed for each participant.

10. Statistical Analysis Plan

This section outlines the statistical analysis strategy and procedures for the study. Changes to analyses made after the protocol has been finalized, but prior to the database lock, will be documented in a supplemental SAP (sSAP) and referenced in the Clinical Study Report (CSR) for the study. Post hoc exploratory analyses will be clearly identified in the CSR.

10.1 Statistical Analysis Plan Summary

Key elements of the statistical analysis plan are summarized below; the comprehensive plan is provided in Sections 10.2-10.12.

Study Design Overview	An open-label, single-arm phase II study to assess safety, efficacy and pharmacokinetics of daptomycin in Japanese pediatric participants with cSSTI or bacteremia
Treatment Assignment	All participants enrolled in the treatment period will receive open-label treatment with daptomycin. The dose level will vary depending on the age category and infection type of individual participants (See Section 7.4.1).
Analysis Populations	The primary analysis populations for efficacy, pharmacokinetics and safety are as follows. Efficacy Modified intent-to-treat population with positive culture of MRSA at baseline (MITT-MRSA) Pharmacokinetics Pharmacokinetics (PK) population Safety All Participants as Treated (APaT) population
Primary Endpoint(s)	Safety parameters including AEs, laboratory tests, vital signs
Secondary Endpoint(s)	1. Clinical response to daptomycin at the TOC visit 2. Subject-level microbiological response to daptomycin at the TOC visit 3. Pharmacokinetic parameters of daptomycin
Statistical Methods for Key Efficacy and Pharmacokinetics Analyses	Efficacy The proportions of participants achieving clinical success and microbiological success, respectively, will be calculated by visit, along with corresponding 95% confidence intervals (CIs) by the method of Clopper and Pearson [1]. The analysis will be performed separately by infection type (cSSTI, bacteremia). Participants who have both cSSTI and bacteremia will be included in the analysis of both infection types. The analysis of the proportion of participants in the MITT-MRSA population achieving clinical success at the TOC visit is of primary interest for efficacy. Pharmacokinetics Descriptive statistics of pharmacokinetic parameters will be provided.
Statistical Methods for Key Safety Analyses	The proportions of participants will be calculated for broad clinical and laboratory AE categories [e.g., any AE, a drug-related AE, a serious AE (SAE), a drug-related SAE, discontinuation of study treatment due to an AE], as well as specific AEs (system organ classes and preferred terms). Change from baseline in laboratory tests and vital signs will be summarized.
Interim Analyses	No interim analysis is planned.
Multiplicity	No multiplicity adjustment is planned.
Sample Size and Power	A total of 20 participants will be enrolled in the treatment period. If a particular AE or other safety event of interest is not observed in any of the 20 participants, then the true incidence of that event is 11% or less with 90% confidence.

10.2 Responsibility for Analyses/In-House Blinding

The statistical analysis of the data obtained from this study will be the responsibility of the Clinical Biostatistics department of the Sponsor. This trial is being conducted as a non-randomized, open-label study, i.e., participants, investigators, and Sponsor personnel will be aware of participant treatment assignments after each participant is enrolled and treatment is assigned.

10.3 Hypotheses/Estimation

The objectives of the study are stated in Section 4.

10.4 Analysis Endpoints

Efficacy, pharmacokinetics and safety endpoints that will be evaluated in the study are listed below.

10.4.1 Efficacy / Pharmacokinetic Endpoints

Efficacy

The efficacy endpoints will be clinical response and microbiological response at the EOT and TOC visits. At a particular visit, clinical success and microbiological success for a participant will be defined as follows.

Clinical success: a clinical response of "Cure" or "Improvement" at that visit.

Microbiological success (subject-level): microbiological responses of "Eradication" or "Presumed Eradication" (i.e., pathogen-level microbiological success) at that visit for all pathogens identified at baseline, without any superinfection or new infection by gram-positive cocci pathogen(s).

A list of efficacy endpoints is provided below.

Table 9 List of efficacy endpoints

Secondary	The following endpoints in the MITT-MRSA population: • Clinical response at the TOC visit • subject-level microbiological response at the TOC visit
Exploratory	1. The following endpoints in the MITT-MRSA population: • Clinical response at the EOT visit • Subject-level microbiological response at the EOT visit 2. The following endpoints in the MITT and MITT Gram-Positive populations • Clinical response at the EOT and TOC visits • Subject-level microbiological response at the EOT and TOC visits 3. By-pathogen microbiological response at EOT and TOC visits in the MITT, MITT Gram-Positive and MITT-MRSA populations

Further details are in Section 9.2.

Pharmacokinetics

Pharmacokinetic endpoints include the following pharmacokinetic parameters: AUC_{0-24}, C_{max}, t_{max}, CLss, Vss, $t_{1/2}$ if evaluable data is obtained.

10.4.2 Safety Endpoints

Refer to Section 5.4.2.1.

10.5 Analysis Populations

The analysis populations for efficacy, pharmacokinetics and safety are defined below. The composition of the respective populations will be made and documented in a separate memo prior to the database lock.

10.5.1 Efficacy / Pharmacokinetics Analysis Populations

Efficacy

The modified intent-to-treat (MITT) population, which consists of all enrolled participants who receive at least one dose of study treatment, will be used for the analysis of efficacy data in this study. Subsets of the MITT population consisting of those participants with positive culture of any Gram-positive coccus (cocci) and MRSA at baseline will be defined as the MITT-Gram Positive and MITT-MRSA populations, respectively. The primary population for efficacy analysis will be the MITT-MRSA population.

Pharmacokinetics

The Pharmacokinetics (PK) population will be used for the analysis of pharmacokinetic data in the study. The PK population consists of all enrolled participants who meet the following:

- The participant receives at least 3 consecutive IV infusions of study treatment
- The participant has at least 1 PK sample following study drug administration on the PK sampling day
- The participant does not have any major protocol violation affecting the PK profile.

10.5.2 Safety Analysis Populations

The APaT population will be used for the analysis of safety data in this study. The APaT population consists of all enrolled participants who receive at least one dose of study treatment.

10.6 Statistical Methods

10.6.1 Statistical Methods for Efficacy Analysis

The proportions of participants achieving clinical success and microbiological success, respectively, will be calculated by visit, along with corresponding 95% CIs by the method of Clopper and Pearson. The analysis will be performed separately by infection type (cSSTI, bacteremia). Participants who have both cSSTI and bacteremia will be included in the analysis of both infection types.

Missing data and the assessment of "Not Evaluable" will be considered failure. The exception to this will be:

- [cSSTI only] Even if culture is missing at a particular timepoint, microbiological success will be presumed from clinical success (i.e., presumed eradication)

A clinical response of "Failure" at the EOT visit will be carried forward to the TOC visit. A microbiological response of "Persistent" at the EOT visit will be carried forward to the TOC visit.

Table 10 summarizes key efficacy analysis.

Table 10 Analysis Strategy for Key Efficacy Variables

Endpoint / Variable (Description / Timepoint)	Statistical Method	Analysis Population	Missing Data Approach
Secondary objectives			
Clinical success at the TOC visit	Clopper-Pearson	MITT-MRSA	Missing = Failure†
Microbiological success at the TOC visit	Clopper-Pearson	MITT-MRSA	Missing = Failure†
† [cSSTI only] Even if culture is missing at a particular timepoint, microbiological success will be presumed from clinical success (i.e., presumed eradication)			

10.6.2 Statistical Methods for Safety Analysis

Safety and tolerability will be assessed by clinical review of all relevant parameters including AEs, vital signs and laboratory tests.

The proportions of participants will be calculated for broad clinical and laboratory AE categories [e.g., any AE, a drug-related AE, a serious AE (SAE), a drug-related SAE, discontinuation of study treatment due to an AE], specific AEs (system organ classes and preferred terms) and participants whose laboratory measurement exceeds predefined limits of change.

Summary statistics for baseline, on-treatment, and change from baseline values will be provided for continuous measures such as vital signs and laboratory tests.

The analysis of safety data will include all enrolled participants regardless of the infection type. A supplemental analysis by infection type will also be performed; in this analysis, those participants who have both cSSTI and bacteremia and treated with the daptomycin dose for bacteremia will be considered to be participants with bacteremia.

10.6.3 Summaries of Baseline Characteristics, Demographics, and Other Analyses

Demographic and baseline characteristics

The number and percentage of participants screened, enrolled, the primary reasons for screening failure, and the primary reason for study/study therapy discontinuation will be displayed. Demographic variables (e.g., age, gender), primary and secondary diagnoses, and prior and concomitant therapies will be summarized by descriptive statistics or categorical tables.

Pharmacokinetics

PK parameters of daptomycin obtained from individual participants will be listed.

The following PK parameters of daptomycin (AUC_{0-24}, C_{max}, t_{max}, CL_{ss}, V_{ss} and $t_{1/2}$ if evaluable data is obtained) will be determined by non-compartmental PK analysis if at least 3 PK samples are available, and these PK parameters will be summarized by descriptive statistics. If less than 3 PK samples are available, the plasma concentration including C_{max} (or end of infusion) will be described. The derived PK parameters of daptomycin will be reported for each infection type and age categories. Population PK analysis may be conducted if needed. If population PK analysis will be conducted, PK data and analysis will be reported separately in a population PK report.

10.7 Interim Analyses

No interim analysis is planned.

10.8 Multiplicity

No multiplicity adjustment is planned.

10.9 Sample Size and Power Calculations

A total of 20 participants will be enrolled in the treatment period. If a particular AE or other safety event of interest is not observed in any of the 20 participants, then the true incidence of that event is 11% or less with 90% confidence.

In order to collect data from the broadest range of categories of participants possible, the study will target enrollment of the following minimum number of participants in each category:

- 6 participants with bacteremia
- 1 participant of 1 to <2 years old and 3 participants each for the higher age categories, regardless of the infection type.

The recruitment will continue until a total of 20 participants have been enrolled in the treatment period regardless of the age category or infection type.

The 95% CIs for efficacy analysis under various sample sizes are shown below.

Table 11 Precision estimates for efficacy analysis

Number of participants included in analysis	Number of participants achieving success	95% CI of percentage of participants achieving success
5	3	(14.7%, 94.7%)
	4	(28.4%, 99.5%)
10	6	(26.2%, 87.8%)
	7	(34.8%, 93.3%)
	8	(44.4%, 97.5%)
	9	(55.5%, 99.7%)
15	9	(32.3%, 83.7%)
	10	(38.4%, 88.2%)
	11	(44.9%, 92.2%)
	12	(51.9%, 95.7%)
	13	(59.5%, 98.3%)
	14	(68.1%, 99.8%)

10.10 Subgroup Analyses

No subgroup analysis is planned.

10.11 Compliance (Medication Adherence)

For each subject, treatment compliance will be calculated as follows.

$$\text{Compliance (\%)} = \frac{\text{Number of completed IV doses}}{\text{Number of expected IV doses}} \text{ x100}$$

Descriptive statistics of treatment compliance will be calculated for the respective efficacy analysis populations.

10.12 Extent of Exposure

The extent (number of days) of exposure to study treatment will be evaluated for the APaT population.

11. References

1. Clopper CJ, Pearson ES. The use of confidence or fiducial limits illustrated in the case of the Binomial. Biometrika; 26: 404-13.
2. The Guidance of renal function evaluation for pediatric Chronic Kidney Disease. Labor and Welfare Research grant subsidy Overcoming research project on refractory diseases, the year 2013 (Japan Pediatric CKD Research Group). Feb 28, 2014.

12. Appendices

12.1 Appendix 1: Study Governance Considerations

Merck Code of Conduct for Clinical Trials

Merck*
Code of Conduct for Clinical Trials

I. Introduction

A. Purpose

Merck, through its subsidiaries, conducts clinical trials worldwide to evaluate the safety and effectiveness of our products. As such, we are committed to designing, implementing, conducting, analyzing and reporting these trials in compliance with the highest ethical and scientific standards. Protection of participant safety is the overriding concern in the design of clinical trials. In all cases, Merck clinical trials will be conducted in compliance with local and/or national regulations and in accordance with the ethical principles that have their origin in the Declaration of Helsinki.

B. Scope

Such standards shall be endorsed for all clinical interventional investigations sponsored by Merck irrespective of the party (parties) employed for their execution (eg, contract research organizations, collaborative research efforts). This Code is not intended to apply to trials which are observational in nature, or which are retrospective. Further, this Code does not apply to investigator-initiated trials which are not under the control of Merck.

II. Scientific Issues

A. Trial Conduct

1. Trial Design

Except for pilot or estimation trials, clinical trial protocols will be hypothesis-driven to assess safety, efficacy and/or pharmacokinetic or pharmacodynamic indices of Merck or comparator products. Alternatively, Merck may conduct outcomes research trials, trials to assess or validate various endpoint measures, or trials to determine participant preferences, etc.

The design (ie, participant population, duration, statistical power) must be adequate to address the specific purpose of the trial. Research participants must meet protocol entry criteria to be enrolled in the trial.

2. Site Selection

Merck selects investigative sites based on medical expertise, access to appropriate participants, adequacy of facilities and staff, previous performance in Merck trials, as well as budgetary considerations. Prior to trial initiation, sites are evaluated by Merck personnel to assess the ability to successfully conduct the trial.

3. Site Monitoring/Scientific Integrity

Trial sites are monitored to assess compliance with the trial protocol and general principles of Good Clinical Practice. Merck reviews clinical data for accuracy, completeness and consistency. Data are verified versus source documentation according to standard operating procedures. Per Merck policies and procedures, if fraud, misconduct or serious GCP-non-Compliance are suspected, the issues are promptly investigated. When necessary, the clinical site will be closed, the responsible regulatory authorities and ethics review committees notified and data disclosed accordingly.

B. Publication and Authorship

To the extent scientifically appropriate, Merck seeks to publish the results of trials it conducts. Some early phase or pilot trials are intended to be hypothesis-generating rather than hypothesis testing. In such cases, publication of results may not be appropriate since the trial may be underpowered and the analyses complicated by statistical issues of multiplicity.

Merck's policy on authorship is consistent with the requirements outlined in the ICH-Good Clinical Practice guidelines. In summary, authorship should reflect significant contribution to the design and conduct of the trial, performance or interpretation of the analysis, and/or writing of the manuscript. All named authors must be able to defend the trial results and conclusions. Merck funding of a trial will be acknowledged in publications.

III. Participant Protection

A. IRB/IEC review

All clinical trials will be reviewed and approved by an independent IRB/IEC before being initiated at each site. Significant changes or revisions to the protocol will be approved by the IRB/IEC prior to implementation, except that changes required urgently to protect participant safety and well-being may be enacted in anticipation of IRB/IEC approval. For each site, the IRB/IEC and Merck will approve the participant informed consent form.

B. Safety

The guiding principle in decision-making in clinical trials is that participant welfare is of primary importance. Potential participants will be informed of the risks and benefits of, as well as alternatives to, trial participation. At a minimum, trial designs will take into account the local standard of care. Participants are never denied access to appropriate medical care based on participation in a Merck clinical trial.

All participation in Merck clinical trials is voluntary. Participants are enrolled only after providing informed consent for participation. Participants may withdraw from a Merck trial at any time, without any influence on their access to, or receipt of, medical care that may otherwise be available to them.

C. Confidentiality

Merck is committed to safeguarding participant confidentiality, to the greatest extent possible. Unless required by law, only the investigator, sponsor (or representative) and/or regulatory authorities will have access to confidential medical records that might identify the research participant by name.

D. Genomic Research

Genomic Research will only be conducted in accordance with informed consent and/or as specifically authorized by an Ethics Committee.

IV. Financial Considerations

A. Payments to Investigators

Clinical trials are time- and labor-intensive. It is Merck's policy to compensate investigators (or the sponsoring institution) in a fair manner for the work performed in support of Merck trials. Merck does not pay incentives to enroll participants in its trials. However, when enrollment is particularly challenging, additional payments may be made to compensate for the time spent in extra recruiting efforts.

Merck does not pay for participant referrals. However, Merck may compensate referring physicians for time spent on chart review to identify potentially eligible participants.

B. Clinical Research Funding

Informed consent forms will disclose that the trial is sponsored by Merck, and that the investigator or sponsoring institution is being paid or provided a grant for performing the trial. However, the local IRB/IEC may wish to alter the wording of the disclosure statement to be consistent with financial practices at that institution. As noted above, publications resulting from Merck trials will indicate Merck as a source of funding.

C. Funding for Travel and Other Requests

Funding of travel by investigators and support staff (eg, to scientific meetings, investigator meetings, etc.) will be consistent with local guidelines and practices including, in the U.S., those established by the American Medical Association (AMA).

V. Investigator Commitment

Investigators will be expected to review Merck's Code of Conduct as an appendix to the trial protocol, and in signing the protocol, agree to support these ethical and scientific standards.

* In this document, "Merck" refers to Merck Sharp & Dohme Corp. and Schering Corporation, each of which is a subsidiary of Merck & Co., Inc. Merck is known as MSD outside of the United States and Canada. As warranted by context, Merck also includes affiliates and subsidiaries of Merck & Co., Inc."

Financial Disclosure

Financial Disclosure requirements are outlined in the US Food and Drug Administration Regulations, Financial Disclosure by Clinical Investigators (21 CFR Part 54). It is the Sponsor's responsibility to determine, based on these regulations, whether a request for Financial Disclosure information is required. It is the investigator's/subinvestigator's responsibility to comply with any such request.

The investigator/subinvestigator(s) agree, if requested by the Sponsor in accordance with 21 CFR Part 54, to provide his/her financial interests in and/or arrangements with the Sponsor to allow for the submission of complete and accurate certification and disclosure statements. The investigator/subinvestigator(s) further agree to provide this information on a Certification/Disclosure Form, commonly known as a financial disclosure form, provided by the Sponsor. The investigator/subinvestigator(s) also consent to the transmission of this information to the Sponsor in the United States for these purposes. This may involve the transmission of information to countries that do not have laws protecting personal data.

Data Protection

Participants will be assigned a unique identifier by the sponsor. Any participant records or datasets that are transferred to the sponsor will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.

The participant must be informed that his/her personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant.

The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

Confidentiality of Data

By signing this protocol, the investigator affirms to the Sponsor that information furnished to the investigator by the Sponsor will be maintained in confidence, and such information will be divulged to the institutional review board, ethics review committee (IRB/IEC) or similar or expert committee; affiliated institution and employees, only under an appropriate understanding of confidentiality with such board or committee, affiliated institution and employees. Data generated by this study will be considered confidential by the investigator, except to the extent that it is included in a publication as provided in the Publications section of this protocol.

Confidentiality of Participant Records

By signing this protocol, the investigator agrees that the Sponsor (or Sponsor representative), IRB/IEC, or regulatory authority representatives may consult and/or copy study documents in order to verify worksheet/case report form data. By signing the consent form, the participant agrees to this process. If study documents will be photocopied during the process of

verifying worksheet/case report form information, the participant will be identified by unique code only; full names/initials will be masked prior to transmission to the Sponsor.

By signing this protocol, the investigator agrees to treat all participant data used and disclosed in connection with this study in accordance with all applicable privacy laws, rules and regulations.

Confidentiality of IRB/IEC Information

The Sponsor is required to record the name and address of each IRB/IEC that reviews and approves this study. The Sponsor is also required to document that each IRB/IEC meets regulatory and ICH GCP requirements by requesting and maintaining records of the names and qualifications of the IRB/IEC members and to make these records available for regulatory agency review upon request by those agencies.

Publication Policy

The results of this study may be published or presented at scientific meetings. The sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the sponsor will generally support publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating investigator will be designated by mutual agreement.

If publication activity is not directed by the sponsor, the investigator agrees to submit all manuscripts or abstracts to the sponsor before submission. This allows the sponsor to protect proprietary information and to provide comments.

Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

Compliance with Study Registration and Results Posting Requirements

Under the terms of the Food and Drug Administration Amendments Act (FDAAA) of 2007 and the European Medicines Agency (EMA) clinical trial Directive 2001/20/EC, the Sponsor of the study is solely responsible for determining whether the study and its results are subject to the requirements for submission to http://www.clinicaltrials.gov, www.clinicaltrialsregister.eu or other local registries. MSD, as Sponsor of this study, will review this protocol and submit the information necessary to fulfill these requirements. MSD entries are not limited to FDAAA or the EMA clinical trial directive mandated trials. Information posted will allow participants to identify potentially appropriate studies for their disease conditions and pursue participation by calling a central contact number for further information on appropriate study locations and site contact information.

By signing this protocol, the investigator acknowledges that the statutory obligations under FDAAA, the EMA clinical trials directive or other locally mandated registries are that of the Sponsor and agrees not to submit any information about this study or its results to those registries.

Compliance with Law, Audit and Debarment

By signing this protocol, the investigator agrees to conduct the study in an efficient and diligent manner and in conformance with this protocol; generally accepted standards of Good Clinical Practice (eg, International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use Good Clinical Practice: Consolidated Guideline and other generally accepted standards of good clinical practice); and all applicable federal, state and local laws, rules and regulations relating to the conduct of the clinical study.

The Code of Conduct, a collection of goals and considerations that govern the ethical and scientific conduct of clinical investigations sponsored by MSD, is provided in this appendix under the Merck Code of Conduct for Clinical Trials.

The investigator agrees not to seek reimbursement from participants, their insurance providers or from government programs for procedures included as part of the study reimbursed to the investigator by the Sponsor.

The investigator will promptly inform the Sponsor of any regulatory authority inspection conducted for this study.

The Investigator agrees to provide the Sponsor with relevant information from inspection observations/findings to allow the Sponsor to assist in responding to any citations resulting from regulatory authority inspection, and will provide the Sponsor with a copy of the proposed response for consultation before submission to the regulatory authority.

Persons debarred from conducting or working on clinical studies by any court or regulatory authority will not be allowed to conduct or work on this Sponsor's studies. The investigator will immediately disclose in writing to the Sponsor if any person who is involved in conducting the study is debarred or if any proceeding for debarment is pending or, to the best of the investigator's knowledge, threatened.

Data Quality Assurance

All participant data relating to the study will be recorded on printed or electronic CRF unless transmitted to the sponsor or designee electronically (eg, laboratory data). The investigator or qualified designee is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.

Detailed information regarding Data Management procedures for this protocol will be provided separately.

The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.

The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.

Study documentation will be promptly and fully disclosed to the Sponsor by the investigator upon request and also shall be made available at the study site upon request for inspection, copying, review and audit at reasonable times by representatives of the Sponsor or any

regulatory authorities. The investigator agrees to promptly take any reasonable steps that are requested by the Sponsor or regulatory authority as a result of an audit or inspection to cure deficiencies in the study documentation and worksheets/case report forms.

The sponsor or designee is responsible for the data management of this study including quality checking of the data.

Study monitors will perform ongoing source data review and verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

Records and documents, including signed ICF, pertaining to the conduct of this study must be retained by the investigator for 15 years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor.

Source Documents

Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.

Data reported on the CRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

Study and Site Closure

The sponsor or its designee may stop the study or study site participation in the study for medical, safety, regulatory, administrative, or other reasons consistent with applicable laws, regulations, and GCP.

In the event the Sponsor prematurely terminates a particular study site, the Sponsor will promptly notify that study site's IRB/IEC.

12.2 Appendix 2: Contraceptive Guidance and Pregnancy Testing

Definitions

Woman of Childbearing Potential (WOCBP)

A woman is considered fertile following menarche and until becoming post-menopausal unless permanently sterile (see below)

Women in the following categories are not considered WOCBP:

- Premenarchal
- Premenopausal female with 1 of the following:
  - Documented hysterectomy
  - Documented bilateral salpingectomy
  - Documented bilateral oophorectomy

  Note: Documentation can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.
- Postmenopausal female
  - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.
    - A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, confirmation with two FSH measurements in the postmenopausal range is required.
  - Females on HRT and whose menopausal status is in doubt will be required to use one of the non-hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

Contraception Requirements

Male Participants

Male participants with female partners of childbearing potential are eligible to participate if they agree to one of the following during the protocol defined time frame in section 6.1:

- Be abstinent from penile-vaginal intercourse as their usual and preferred lifestyle (abstinent on a long term and persistent basis) and agree to remain abstinent.
- Use a male condom plus partner use of an additional contraceptive method when having penile-vaginal intercourse with a woman of childbearing potential who is not currently pregnant.
  - The following are not acceptable methods of contraception:

- Periodic abstinence (calendar, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhoea method (LAM).
- Male and female condom cannot be used together.

- A combination of male condom with either cap, diaphragm or sponge with spermicide are considered acceptable, but not highly effective, birth control methods.
- Note: Men with a pregnant or breastfeeding partner must agree to remain abstinent from penile-vaginal intercourse or use a male condom during each episode of penile penetration.

Female Participants

Female participants of childbearing potential are eligible to participate if they agree to use one of the contraception methods described in Table 12 consistently and correctly during the protocol-defined time frame in Section 6.1.

Table 12 Contraceptive Methods

Acceptable Contraceptive Methods *Failure rate of >1% per year when used consistently and correctly.*
● Male or female condom with or without spermicide ● Cervical cap, diaphragm or sponge with spermicide
Highly Effective Contraceptive Methods That Are User Dependent [a] *Failure rate of <1% per year when used consistently and correctly.*
● Combined (estrogen- and progestogen- containing) hormonal contraception [b] ○ Oral ○ Intravaginal ○ Transdermal ○ Injectable
● Progestogen-only hormonal contraception [b] ○ Oral ○ Injectable
Highly Effective Methods That Have Low User Dependency *Failure rate of <1% per year when used consistently and correctly.*
● Progestogen- only contraceptive implant [b, c] ● Intrauterine hormone-releasing system (IUS) [b] ● Intrauterine device (IUD) ● Bilateral tubal occlusion
● Vasectomized partner A vasectomized partner is a highly effective contraception method provided that the partner is the sole male sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used.

● Sexual abstinence Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatment. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.)
Notes: Use should be consistent with local regulations regarding the use of contraceptive methods for participants of clinical studies. a) Typical use failure rates are lower than perfect-use failure rates (ie, when used consistently and correctly). b) If hormonal contraception efficacy is potentially decreased due to interaction with study treatment, condoms must be used in addition to the hormonal contraception during the treatment period and for at least [X days, corresponding to time needed to eliminate study treatment plus 30 days for study treatments with genotoxic potential] after the last dose of study treatment . c) If locally required, in accordance with Clinical Trial Facilitation Group (CTFG) guidelines, acceptable hormonal contraceptives are limited to those which inhibit ovulation.

Pregnancy Testing

WOCBP should only be included after a negative highly sensitive urine or serum pregnancy test.

Pregnancy testing will be performed whenever an expected menstrual cycle is missed or when pregnancy is otherwise suspected.

12.3 Appendix 3: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

Definition of AE

AE Definition
● An AE is any untoward medical occurrence in a patient or clinical study participant, temporally associated with the use of study treatment, whether or not considered related to the study treatment. ● NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a study treatment. ● NOTE: for purposes of AE definition, study treatment (also referred to as Sponsor's product) includes any pharmaceutical product, biological product, vaccine, device, diagnostic agent or protocol specified procedure whether investigational (including placebo or active comparator product) or marketed, manufactured by, licensed by, provided by or distributed by the sponsor for human use in this study.

Events Meeting the AE Definition
● Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECG, radiological scans, vital signs measurements), including those that worsen from baseline, or are considered clinically significant in the medical and scientific judgment of the investigator. ● Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition. ● New conditions detected or diagnosed after study treatment administration even though it may have been present before the start of the study. ● Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction. ● Signs, symptoms, or the clinical sequelae of a suspected overdose of either study treatment or a concomitant medication. ● For all reports of overdose (whether accidental or intentional) with an associated adverse event, the AE term should reflect the clinical symptoms or abnormal test result. An overdose of study treatment without any associated clinical symptoms or abnormal laboratory results is reported using the terminology "accidental or intentional overdose without adverse effect." ● Any new cancer or progression of existing cancer.

Events NOT Meeting the AE Definition
● Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE. ● Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital). ● Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen. ● Surgery planned prior to informed consent to treat a pre-existing condition that has not worsened. ● Refer to section 9.3.5 for protocol specific exceptions

Definition of SAE

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met

A SAE is defined as any untoward medical occurrence that, at any dose:
a. Results in death
b. Is life-threatening ● The term 'life-threatening' in the definition of 'serious' refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.
c. Requires inpatient hospitalization or prolongation of existing hospitalization ● Hospitalization is defined as an inpatient admission, regardless of length of stay, even if the hospitalization is a precautionary measure for continued observation. (Note: Hospitalization for an elective procedure to treat a pre-existing condition that has not worsened is not a serious adverse event. A pre-existing condition is a clinical condition that is diagnosed prior to the use of an MSD product and is documented in the patient's medical history.
d. Results in persistent or significant disability/incapacity ● The term disability means a substantial disruption of a person's ability to conduct normal life functions. ● This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

e. Is a congenital anomaly/birth defect

- in offspring of participant taking the product regardless of time to diagnosis

f. Other important medical events:

- Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.

  Examples of such events include invasive or malignant cancers, 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 drug dependency or drug abuse.

Additional Events Reported

Additional Events which require reporting

- In addition to the above criteria, adverse events meeting either of the below criteria, although not serious per ICH definition, are reportable to the Sponsor.
- Is a cancer;
- Is associated with an overdose.

Recording AE and SAE

AE and SAE Recording

- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory, and diagnostics reports) related to the event.
- The investigator will record all relevant AE/SAE information on the Adverse Event case report forms/worksheets at each examination.
- It is **not** acceptable for the investigator to send photocopies of the participant's medical records to the Sponsor in lieu of completion of the AE CRF page.
- There may be instances when copies of medical records for certain cases are requested by the Sponsor. In this case, all participant identifiers, with the exception of the participant number, will be blinded on the copies of the medical records before submission to the Sponsor.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. In such cases, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of Intensity

- An event is defined as 'serious' when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe.
- The investigator will make an assessment of intensity for each AE and SAE (and other reportable safety event) reported during the study and assign it to 1 of the following categories:
  - Mild: An event that is easily tolerated by the participant, causing minimal discomfort and not interfering with everyday activities. (for pediatric studies, awareness of symptoms, but easily tolerated)
  - Moderate: An event that causes sufficiently discomfort and interferes with normal everyday activities. (for pediatric studies, definitely acting like something is wrong)
  - Severe: An event that prevents normal everyday activities. An AE that is assessed as severe should not be confused with an SAE. Severe is a category utilized for rating the intensity of an event; and both AE and SAE can be assessed as severe (for pediatric studies, extremely distressed or unable to do usual activities).

Assessment of Causality

- Did the Sponsor's product cause the adverse event?
  - The determination of the likelihood that the Sponsor's product caused the adverse event will be provided by an investigator who is a qualified physician. The investigator's signed/dated initials on the source document or worksheet that supports the causality noted on the AE form, ensures that a medically qualified assessment of causality was done. This initialed document must be retained for the required regulatory time frame. The criteria below are intended as reference guidelines to assist the investigator in assessing the likelihood of a relationship between the test product and the adverse event based upon the available information
  - **The following components are to be used to assess the relationship between the Sponsor's product and the AE;** the greater the correlation with the components and their respective elements (in number and/or intensity), the more likely the Sponsor's product caused the adverse event:
    - **Exposure:** Is there evidence that the participant was actually exposed to the Sponsor's product such as: reliable history, acceptable compliance assessment (pill count, diary, etc.), expected pharmacologic effect, or measurement of drug/metabolite in bodily specimen?
    - **Time Course:** Did the AE follow in a reasonable temporal sequence from administration of the Sponsor's product? Is the time of onset of the AE compatible with a drug-induced effect (applies to studies with investigational medicinal product)?
    - **Likely Cause:** Is the AE not reasonably explained by another etiology such as

underlying disease, other drug(s)/vaccine(s), or other host or environmental factors

- **Dechallenge:** Was the Sponsor's product discontinued or dose/exposure/frequency reduced?
  - If yes, did the AE resolve or improve?
    - If yes, this is a positive dechallenge.
  - If no, this is a negative dechallenge.

  (Note: This criterion is not applicable if: (1) the AE resulted in death or permanent disability; (2) the AE resolved/improved despite continuation of the Sponsor's product; (3) the study is a single-dose drug study); or (4) Sponsor's product(s) is/are only used one time.)
- **Rechallenge:** Was the participant re-exposed to the Sponsor's product in this study?
  - If yes, did the AE recur or worsen?
    - If yes, this is a positive rechallenge.
  - If no, this is a negative rechallenge.

  (Note: This criterion is not applicable if: (1) the initial AE resulted in death or permanent disability, or (2) the study is a single-dose drug study); or (3) Sponsor's product(s) is/are used only one time.)

NOTE: IF A RECHALLENGE IS PLANNED FOR AN ADVERSE EVENT WHICH WAS SERIOUS AND WHICH MAY HAVE BEEN CAUSED BY THE SPONSOR'S PRODUCT, OR IF RE-EXPOSURE TO THE SPONSOR'S PRODUCT POSES ADDITIONAL POTENTIAL SIGNIFICANT RISK TO THE PARTICIPANT THEN THE RECHALLENGE MUST BE APPROVED IN ADVANCE BY THE SPONSOR CLINICAL DIRECTOR, AND IF REQUIRED, THE INSTITUTIONAL REVIEW BOARD/INDEPENDENT ETHICS COMMITTEE.

- **Consistency with Study treatment Profile:** Is the clinical/pathological presentation of the AE consistent with previous knowledge regarding the Sponsor's product or drug class pharmacology or toxicology?

- The assessment of relationship will be reported on the case report forms /worksheets by an investigator who is a qualified physician according to his/her best clinical judgment, including consideration of the above elements.
- Use the following scale of criteria as guidance (not all criteria must be present to be indicative of a Sponsor's product relationship).
  - Yes, there is a reasonable possibility of Sponsor's product relationship: There is evidence of exposure to the Sponsor's product. The temporal sequence of the AE onset relative to the administration of the Sponsor's product is reasonable. The AE is more likely explained by the Sponsor's product than by another cause.

- No, there is not a reasonable possibility of Sponsor's product relationship: Participant did not receive the Sponsor's product OR temporal sequence of the AE onset relative to administration of the Sponsor's product is not reasonable OR the AE is more likely explained by another cause than the Sponsor's product. (Also entered for a participant with overdose without an associated AE.)

- For each AE/SAE, the investigator must document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.

- There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to the Sponsor. However, it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to the Sponsor.

- The investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.

- The causality assessment is one of the criteria used when determining regulatory reporting requirements

Follow-up of AE and SAE

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by Sponsor to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- New or updated information will be recorded in the CRF.
- The investigator will submit any updated SAE data to the Sponsor within 24 hours of receipt of the information.

Reporting of AE, SAE, and Other Reportable Safety Events to the Sponsor

AE, SAE, and Other Reportable Safety Event Reporting to Sponsor via Electronic Data Collection Tool

- The primary mechanism for reporting to the Sponsor will be the electronic data collection (EDC) tool.
  - Electronic reporting procedures can be found in the EDC data entry guidelines (or equivalent).
  - If the electronic system is unavailable for more than 24 hours, then the site will use the paper AE Reporting form.
    - Reference section 9.3.1 – Time Period and Frequency for Collecting AE and SAE and Other Reportable Safety Event Information for reporting time requirements

- The site will enter the SAE data into the electronic system as soon as it becomes available.
- After the study is completed at a given site, the electronic data collection tool will be taken off-line to prevent the entry of new data or changes to existing data.
- If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the electronic data collection tool has been taken off-line, then the site can report this information on a paper SAE form or by telephone (see next section).
- Contacts for SAE reporting can be found in the Investigator Trial File Binder (or equivalent).

SAE Reporting to the Sponsor via Paper CRF

- If the electronic data collection tool is not operational, facsimile transmission or secure e-mail of the SAE paper CRF is the preferred method to transmit this information to the Sponsor.
- In rare circumstances and in the absence of facsimile equipment, notification by telephone is acceptable with a copy of the SAE data collection tool sent by overnight mail or courier service.
- Initial notification via telephone does not replace the need for the investigator to complete and sign the SAE CRF pages within the designated reporting time frames.
- Contacts and instructions for SAE reporting and paper reporting procedures can be found in the Investigator Trial File Binder (or equivalent).

12.4 Appendix 4: Clinical Laboratory Tests

- The tests detailed in Table 13 will be performed by the central laboratory (chemistry) or local laboratory (hematology and urinalysis). (Chemistry at Visit1 only, there is possibility that the tests will also be performed by the local laboratory).
- If the test for chemistry is performed by local laboratory at Visit 1 to confirm the eligibility before Visit 2, it is recommended that the sample for central analysis is obtained at the same time.
- The local laboratory results of hematology and urinalysis must be entered into the CRF.
- If the local laboratory results are used to make either a study treatment decision or response evaluation, the results must be entered into the CRF.
- Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 6.1 and 6.2 of the protocol.
- Additional tests (by the local or central laboratory) may be performed at any time during the study as determined necessary by the investigator to assess the clinical conditions of participant or required by local regulations.

Table 13 Protocol-Required Safety Laboratory Assessments

Laboratory Assessments	Parameters			
Hematology	Platelet Count	WBC count with Differential:		
	RBC Count	Neutrophils	Eosinophils	
	Hemoglobin	Lymphocytes	Basophils	
	Hematocrit	Monocytes		
Chemistry	Aspartate aminotransferase (AST)	Alanine aminotransferase (ALT)	Alkaline phosphatase (ALP)	Total bilirubin
	Direct bilirubin [1]	Sodium (Na)	Potassium (K)	Chloride (Cl)
	Calcium (Ca)	Glucose [2]	Blood Urea Nitrogen (BUN)	Creatinine
	Creatine Phosphokinase (CPK)	Total Protein	Albumin	
Routine Urinalysis	• Specific gravity • pH, glucose, protein, blood			
Other Screening Tests	• [Serum or urine] β human chorionic gonadotropin (β hCG) pregnancy test (as needed for women of childbearing potential). Serum β hCG is tested only when the result of urine β hCG pregnancy test is positive.			

Note:
1. Direct bilirubin is tested with blood drawing again if total bilirubin is elevated above the upper limit of normal and the investigator needs further assessments.
2. Indicate if fasting, or nonfasting at blood drawing. Blood glucose meter at bedside could be used to measure glucose depending on a participants' condition. However, for each participant, the method by which glucose is measured should be the same throughout the study.

Investigators must document their review of each laboratory safety report.

eGFR is calculated basically refer to the equation as follows [2].

eGFR=110.2*(y/serum Cr)+2.93

boys: $y=-1.259*H^5+7.815*H^4-18.57*H^3+21.39*H^2-11.71*H+2.628$

girls: $y=-4.536*H^5+27.16*H^4-63.47*H^3+72.43*H^2-40.06*H+8.778$