ANIDULAFUNGIN

RISK MANAGEMENT PLAN

RMP Version number:	13.1
Data lock point for this RMP:	15 October 2018
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Rationale for submitting an updated RMP:

Support Type II variation for requesting the extended indication to paediatric patients ≥ 1 month of age following completion of Study A8851008 (EMA/H/000788/P46/046). Revise the list of safety concerns based on Study A8851008 completion, and the Request for Supplementary Information (RSI) received on 20 September 2019 with regard to assessment of draft RMP v 13.0, and in line with the GVP Module V (Rev. 2) and the accompanying RMP template (Rev. 2.0.1).

Summary of significant changes in this RMP:

RMP Part/Module	Major Change(s)
PART I. PRODUCT OVERVIEW	Indication and posology updated to reflect the proposed extension for use in individuals from the age of 1 month.
PART II. SAFETY SPECIFICATION	
Module SI. Epidemiology of the Indications and Target Populations	Updated to include paediatric epidemiological data.
Module SII. Non-Clinical Part of the Safety Specification	Revised and aligned with the GVP Module V Rev 2 requirements and based on the RSI.
Module SIII. Clinical Trial Exposure	Updated to data lock point 15 October 2018. Presentation of paediatric exposure data (studies A8851008 and VER002-12).
Module SIV. Populations Not Studied in Clinical Trials	Updated based on new data available following completion of study A8851008, and on RSI and aligned with the GVP Module V Rev 2 requirements.
Module SV. Post-Authorisation Experience	Alignment with the GVP Module V Rev 2 requirements. The post-authorisation exposure was updated.
Module SVI. Additional EU Requirements for the Safety Specification	Alignment with the GVP Module V Rev 2 requirements.
Module SVII. Identified and Potential Risks	Reclassification of the safety concerns in line with the GVP Module V Rev 2, following completion of study A8851008 and on RSI

RMP Part/Module	Major Change(s)
Module SVIII. Summary of the Safety Concerns	The list of safety concerns has been updated based on the reclassification presented in Module SVII.
PART III. PHARMACOVIGILANCE PLAN (INCLUDING POST AUTHORISATION SAFETY STUDIES)	No major changes. Aligned to the current GVP Module V Rev. 2.
PART IV. PLANS FOR POST AUTHORISATION EFFICACY STUDIES	Alignment with the GVP Module V Rev 2 requirements.
PART V. RISK MINIMISATION MEASURES (INCLUDING EVALUATION OF THE EFFECTIVENESS OF RISK MINIMISATION ACTIVITIES)	Updated according to the changes made to the safety concerns in Module VII.
PART VI. SUMMARY OF THE RISK MANAGEMENT PLAN	The text has been updated as per current template accompanying GVP Module V Rev 2.
PART VII. ANNEXES TO THE RISK MANAGEMENT PLAN	The annexes have been revised to match the current template accompanying GVP Module V Rev 2.

Other RMP versions under evaluation:

RMP Version Number	Submitted on	Submitted Within
NA	NA	NA

Details of the currently approved RMP:

RMP Version Number	Approved with procedure	Date of approval (opinion date)
12.1	EMEA/H/C/000788/II/0036	08 March 2018

QPPV name[1]: Francoise Dumas-Sillan, MD

QPPV oversight declaration: the content of this RMP has been reviewed and approved by the marketing authorisation holder´s QPPV. The electronic signature is available on file.

[1] QPPV name will not be redacted in case of an access to documents request; see HMA/EMA Guidance document on the identification of commercially confidential information and personal data within the structure of the marketing-authorisation application; available on EMA website http://www.ema.europa.eu

LIST OF ABBREVIATIONS

AE	Adverse Event
ADR	Adverse Drug Reaction
AMR	Arlington Medical Resources
AUCss	Area Under Concentration
BVL	Ben Venue Laboratories
CEP	Customer Engagement Programmes
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence Interval
CNS	Central Nervous System
CT	Clinical Trial
DOT	Days of Therapy
DTI	Deep Tissue Infection
EC	European Commission
ECMM	European Confederation of Medical Mycology
EMA	European Medicines Agency
EPAR	European Public Assessment Report
EU	European Union
FUM	Follow-up measure
GI	Gastrointestinal
HSCT	Haematopoietic Stem Cell Transplantation
IA	Invasive Aspergillosis
IAR	Infusion-Associated Reaction
IC	Invasive Candidiasis
IC/C	Invasive Candidiasis/Candidaemia
ICU	Intensive Care Unit
IV	Intravenous
LFT	Liver Function Test
MAH	Marketing Authorisation Holder
MedDRA	Medical Dictionary for Regulatory Activities
MIC	Minimal Inhibitory Concentration
NOAEL	No Observed Adverse Event Level
OC	Oesophageal candidiasis
OR	Odds Ratio
PL	Package Leaflet
PS80	Polysorbate 80
PT	Preferred Term
ROW	Rest of the World
RMP	Risk Management Plan
SD	Standard Deviation
SmPC	Summary of Product Characteristics
SCS	Summary of Clinical Safety
TDAR	T-Dependent Antibody Response
TEAEs	Treatment Emergent Adverse Events

UK	United Kingdom
US	United States
UVR	Ultraviolet Radiation
WFI	Water for Injection

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PART I. PRODUCT(S) OVERVIEW

Active substance(s) (INN or common name)	anidulafungin
Pharmacotherapeutic group(s) (ATC Code)	Other antimycotics for systemic use (J02AX06)
Marketing Authorisation Holder / Applicant	Pfizer Limited
Medicinal products to which this RMP refers	1
Invented name(s) in the EEA	ECALTA
Marketing authorisation procedure	Centralised
Brief description of the product:	Chemical class Anidulafungin is a semi-synthetic lipopeptide of the echinocandin class. Anidulafungin is a non-competitive inhibitor of 1, 3-β-D-glucan synthase, an enzyme that is not present in mammalian cells, but which is of crucial importance in fungi. This enzyme is required for synthesis of β-linked glucan, which comprises a major portion of the cell wall carbohydrate in many pathogenic fungi.
	Summary of mode of action Suppression of cell wall glucan production results in osmotically fragile cells that are easily lysed.
	Important information about its composition: NA
Hyperlink to the Product Information:	Please refer to Module 1.3.1 of this submission.
Indication(s) in the EEA	Current: Treatment of invasive candidiasis (IC) in adult patients
	Proposed: Treatment of invasive candidiasis in adults and paediatric patients aged 1 month to <18 years.
Dosage in the EEA	Current: A single 200 mg loading dose should be administered on Day 1, followed by 100 mg daily thereafter. Duration of treatment should be based on the patient's clinical response. In general, antifungal therapy should continue for at least 14 days after the last positive culture.
	Proposed: *Adult population (dosing and treatment duration)* A single 200 mg loading dose should be administered on Day 1, followed by 100 mg daily thereafter. Duration of treatment should be based on the patient's clinical response. In general, antifungal therapy should continue for at least 14 days after the last positive culture. There are insufficient data to support the 100 mg dose for longer than 35 days of treatment. *Paediatric population (1 month to <18 years) (dosing and treatment duration)* A single loading dose of 3.0 mg/kg (not to exceed 200 mg) should be administered on Day 1 followed by a

	daily maintenance dose of 1.5 mg/kg (not to exceed 100 mg) thereafter. Overall antifungal treatment should continue for at least 14 days after the last negative culture (defined as the second of two consecutive negative cultures, separated by at least 24 hours, following the last positive culture) and improvement of clinical signs and symptoms of invasive candidiasis including candidaemia (ICC). Switch to an oral antifungal may occur only after a minimum of 10 days on Ecalta intravenous therapy. The efficacy and safety of Ecalta has not been established in neonates (<1-month-old).
Pharmaceutical form(s) and strengths	Current: Powder and solvent for concentrate for solution for infusion, 100 mg.
	Proposed: N/A
Is/will the product be subject to additional monitoring in the EU?	No

ATC = Anatomic Therapeutic Chemical; EEA = European Economic Area; IC = Invasive Candidiasis; INN = International Non-proprietary Name; N/A = Not Applicable; RMP = Risk Management Plan.

PART II. SAFETY SPECIFICATION

Module SI. Epidemiology of the Indication(s) and Target Population (s)

The United States (US) National Library of Medicine PubMed database was searched for primary research and literature reviews in humans, with abstracts, published in English through November 2018 using the search terms (Invasive candidiasis OR Candidaemia OR Candidemia OR Candidiasis OR Deep tissue candidiasis OR Deep tissue candida infection* OR Disseminated candidiasis OR Invasive fungal infection* OR Invasive yeast infection* OR Deep tissue mycosis OR Invasive mycosis OR Disseminated mycosis Mycoses) AND (epidemiolog* OR incidence OR prevalence OR risk factors OR comorbidity OR morbidity OR mortality). Bibliographies of pertinent papers were reviewed to identify additional relevant literature. Particular focus was placed on identifying studies of European and North American populations.

INDICATION

Ecalta is currently indicated for the treatment of IC in adult patients.

Incidence

Globally, more than 250,000 patients are affected by invasive candidiasis each year, and the incidence of candidaemia ranges from 1 to 14 per 100,000 persons in population-based studies.[1,2]

The incidence of candidaemia has increased in recent years, likely due to more invasive surgeries, increased use of antibiotics, and longer hospital stays.[3] In the US, the incidence of candidaemia has increased since the 1980s, [4] which corresponds with the increasing numbers of patients who are at high risk for fungal infections (eg, due to bone marrow and solid organ transplantation).[5] This trend has also been reported in other regions in Europe. For example, the incidence rate of candidaemia steadily increased in 5 Dutch hospitals from 0.37 in 1987 to 0.72 episodes per 10,000 patient days in 1995.[6] In addition, a Norwegian 13-year prospective nationwide candidaemia study reported higher incidence rates of candidaemia during 2001 to 2003 compared with the early 1990s.[7]

Population-based studies across Europe have reported annual incidence rates of candidaemia ranging from 1.8 to 11 per 100,000 persons. Studies reported specific rates of 1.8, 1.9, 2.4 to 3.9, 4.2, 4.3, 4.9 to 6, 5.0 and 9.6 to 11.0 cases per 100,000 persons in Wales, Finland, Norway, Sweden, Spain (Barcelona), Ireland, Belgium and Denmark, respectively.[7,8,9,10,11,12,13,14,15,16]. Despite the variation in incidence by study, overall, the rate of candidaemia is far higher than other invasive mycoses.[17]

The incidence of candidaemia is higher in the overall hospital setting than in the general population. European surveillance studies reported that the average incidence rate is 1.1 per 1000 hospital admissions. [18] A 2-year European hospital-based surveillance study reported that the incidence of candidaemia was 0.2, 0.32, 0.38, and 0.53 cases per 1000 hospital admissions in France, Sweden, Italy, and Spain, respectively.[19,4]

Within the hospital setting, the incidence of candidaemia varies according to characteristics of the patient population, type of hospital, as well as patient location in the hospital. In 2000, the incidence of candidaemia in Switzerland was 0.36 episodes per 1000 hospital admissions in university hospitals and 0.15 per 1000 admissions in university-affiliated hospitals; the majority of these infections were nosocomial, particularly in intensive care and specialty units.[20] Another study in Swiss hospitals estimated that the incidence rate per 1000 patient days of candidaemia doubled from 0.049 in 2000 to 0.10 in 2010.[18] The overall incidence rate of candidaemia in 25 French hospitals was 0.29 per 1000 admissions, ranging from 0.17 per 1000 admissions in general hospitals to 0.71 per 1000 admissions in cancer referral centres.[21]

One review reported that incidence rates are 5-10 times higher among intensive care unit (ICU) patients than among patients from medical or surgical wards. [18] Another review reported that rates are 10-20 times higher in ICU patients compared with patients in non-ICU settings.[22] One study in 213 ICUs in France (2004-2013) and another in an Italian university hospital (1998-2013) reported that the IR of candidaemia was 0.30 per 1000 patient-days.[23,24] A study in Belgium across 30 hospitals (2013-2014) reported a mean IR of 0.44 per 1000 admissions, or 0.07 per 1000 patients-days.[25] Three Italian studies reported higher mean rates ranging from 1.45 to 3.4 per 1000 admissions in ICUs between 2005 and 2016. [26,27,28] A study in an ICU in France between 2007 and 2016 reported an incidence of 4.49 per 1000 admissions.[29] An even higher mean rate of 9.0 per 1000 admissions was reported by a multicentre study from 2006 to 2008 across 72 ICUs in 14 European countries.[30]

For community acquired candidaemia a 1-year international surveillance programme of bloodstream infections, reported that among 306 *Candida* infections reported, 20% were community acquired.[31] A population-based study in Barcelona indicated that of all *Candida* infections, the proportion of outpatient-acquired candidaemia was 11%.[8]

Prevalence

Candida species are one of the most prevalent opportunistic fungi, causing approximately 43% to 90% of all invasive fungal infections worldwide.[32,33,34,35,36] *Candida* species are the most common fungal pathogens leading to serious health-care associated infections[4] and the third or fourth most frequent cause of nosocomial bloodstream infections in the US.[37,38,39] In Europe, IC accounts for 2-3% of nosocomial infections, [18] and *Candida* species have been reported as the eighth most common cause of bloodstream infections.[40] A recent systematic review estimated that approximately 2400 or 3.6 per 100,000 people are infected with candidaemia each year in France,[41] while another review reported that 46,000 cases of IC occur each year in the US.[4] A study using the Centres for Disease Control and Prevention surveillance program estimated a lower prevalence of 23,000 candidaemia cases in the US in 2017 (95% confidence interval, 20,000-25,000).[42]

Demographics of the population in the authorised indication – age, gender, racial and/or ethnic origin and risk factors for the disease

In virtually all of the population-based surveillance studies across Europe, the highest incidence of candidaemia occurs at the extremes of the age spectrum.

The highest rates of candidaemia were among infants less than 1 year of age and adults over the age of 65 years in Finland, Norway, and Spain.[7,8, 13] For example, in Norway from 1991 to 2003, compared to the overall annual incidence rate of 2.4 cases per 100,000 population, the rate was 10.3 per 100,000 in children aged <1 year old and 8.4 cases per 100,000 in adults aged 80 years and older.[7] In the US in 2017, rates were highest among adults ≥65 years old (0.20 per 1000), followed by adults 45-64 years (0.09 per 1000), and children <1 year (0.07 per 1000). [42]

Globally, *Candida* infections affect males more than females. In a 2-year prospective survey in Sweden, candidaemia was diagnosed more frequently in males (62%).[43] Similarly, in Spain, candidaemia was diagnosed more often in males (65%) than females, mainly in those over 64 years of age.[44] In 2017 in the US, the estimated incidence was higher among males (0.08 per 1000 persons) than females (0.06 per 1000 persons).[42]

By race, population-based studies in the U.S. found that the incidence of candidaemia was highest among blacks, with almost a 2-fold higher incidence for all age groups compared to whites.[45,46] A recent surveillance study in the US reported that rates of candidaemia were higher among blacks (0.13 per 1000 persons) than whites (0.07 per 1000 person).[42] Another recent study using an electronic health record database in the US estimated that African Americans were significantly less likely than the total study population to be infected with the *Candida albicans* species, but more likely to be infected with *Candida parapsilosis* and *Candida tropicalis*; Caucasians were less likely to be infected with *Candida parapsilosis* and *Candida tropicalis*, but more likely to be infected with *Candida albicans*.[47]

Invasive candidiasis is a persistent global public health concern. The burden of IC is tremendous in terms of morbidity, mortality, and economic cost.[48] IC is not a disease seen in normal healthy hosts; rather, there are a large number of reasonably well-characterised risk factors. Some of the risk factors are other diseases or the degree of severity of the underlying illness, while others are induced by various therapies. Major predisposing factors of Invasive Candidiasis/Candidaemia (IC/C) are listed below; many factors represent common interventions or conditions in the intensive care setting.[49,50,51,52,53]

Populations at risk and conditions which place populations at risk: Bone marrow and stem cell transplant recipients, Burns, Haematological malignancies, Human immunodeficiency virus infection/Acquired immunodeficiency syndrome, Recent bacterial infection, Severe trauma, Age (neonates and > 65 years), Solid organ transplant (liver, kidney) recipients, Diabetes mellitus, Cancer patients (with and without neutropenia),Gastrointestinal (GI) perforation, *Candida* colonisation

Health care related factors: Recent chemotherapy or radiation therapy, Steroids and other immunosuppressants, Mechanical ventilation, Prolonged use of broad-spectrum antibiotics, Parenteral hyperalimentation, Multiple blood transfusions, Central intravascular access devices, Surgical procedures (upper GI tract, at higher risk), Indwelling urinary catheters, Prolonged hospitalisation [extended stay (> 3 days) in Intensive Care Unit (ICU) at higher risk], Haemodialysis.

The main existing treatment options

There are multiple treatment options for IC and candidaemia in neutropenic and non-neutropenic adult patients. Available therapies have been reviewed by a panel of European experts and published.[54] The recommendation are graded by strength (from A- strongly supports a recommendation to use to D- supports a recommendation against use) and ranked according to level of scientific evidence (I- strongest to III- weakest).

Echinocandins (anidulafungin, caspofungin and micafungin) were recommended with AI level for initial targeted treatment of Candidaemia and IC in adult patients. Besides anidulafungin, 2 other echinocandin antifungals are approved in the European Community, caspofungin (Cancidas, Merck and Co.) and micafungin (Mycamine, Astellas Pharma Europe).

Anidulafungin is approved in the European Community for treatment of IC in adult non-neutropenic patients.

Caspofungin is approved in the European Community for treatment of IC in adult or paediatric patients, treatment of Invasive Aspergillosis (IA) in adult or paediatric patients who are refractory to or intolerant of amphotericin B, lipid formulations of amphotericin B and/or itraconazole (refractoriness is defined as progression of infection or failure to improve after a minimum of 7 days of prior therapeutic doses of effective antifungal therapy), and empirical therapy for presumed fungal infections (such as *Candida* or *Aspergillus*) in febrile, neutropenic adult or paediatric patients.

Micafungin is approved in the European Community for adults, adolescents ≥16 years of age and elderly for the treatment of IC; treatment of Oesophageal Candidiasis (OC) in patients for whom Intravenous (IV) therapy is appropriate; and prophylaxis of *Candida* infection in patients undergoing allogeneic haematopoietic stem cell transplantation or patients who are expected to have neutropenia (absolute neutrophil count <500 cells/μL) for 10 or more days. For children (including neonates) and adolescents < 16 years of age, micafungin is approved for treatment of IC and prophylaxis of *Candida* infection in patients undergoing allogeneic haematopoietic stem cell transplantation or patients who are expected to have neutropenia for 10 or more days.

A recent analysis of patient-level data from 7 clinical studies (1915 patients) confirmed that treatment with an echinocandin antifungal (Odds Ratio [OR], 0.65; 95% Confidence Interval [CI], .45–.94; P 5 .02) was associated with decreased mortality.[55]

Other options for the treatment IC and candidaemia in non-neutropenic adult patients include amphotericin B liposomal (BI), voriconazole (BI), fluconazole (CI) and amphotericin B lipid complex (CII). Amphotericin B deoxycholate (alone or in combination with fluconazole or flucytosine) and efungumab plus lipid-associated amphotericin B, amphotericin B colloidal dispersion and itraconazole were granted a recommendation against use (DI for the 2 first and DII others). Posaconazole was ranked DIII because of lack of data reported by the authors of the guidelines.

Natural history of the indicated condition in the untreated population, including mortality and morbidity

Candida infections are associated with significant mortality[2] especially relative to other bloodstream infections. In a 3-year analysis of pathogens associated with bloodstream infection in 49 U.S. hospitals, *Candida* species were responsible for approximately 8% of all bloodstream infections, yet they were associated with a 40% crude mortality rate compared to a 21% crude mortality rate associated with coagulase-negative *Staphylococci*, which were responsible for 32% of bloodstream infections.[56]

The severity of candidaemia is confirmed by high crude mortality rates. Crude mortality rates for candidaemia vary from 26% to 61% depending, in part, on the severity of underlying conditions.[2,8,13,19,23,26,56,57,58,59,60,] Attributable mortality of candidaemia is estimated to be 15% to 49%.[2,23,26,57,59,61]

The European Confederation of Medical Mycology (ECMM) survey conducted in 7 European countries reported the crude 30-day mortality rate of candidaemia to be 38%; however, recent studies report rates up to 60%.[2] Slightly higher rates were found in 3 studies in Western European countries. A 1-year population-based survey of patients with candidaemia in Spain reported a mortality rate of 44%.[8] A study at a single tertiary care hospital in Italy found a crude mortality rate of 45% in non-neutropenic patients with candidaemia,[62] while a similar study over a 12-year period in Switzerland found a crude mortality rate of 44%.[63] Crude mortality rates in the UK are lower than those reported in Italy, Spain, and Switzerland. A 2-year study of candidaemia in 6 hospitals in England and Wales reported a crude mortality rate of 26%.[58] Data on mortality rates in Scandinavian countries are limited to 1 study from Finland and 1 from Sweden. In a study of candidaemia patients at a tertiary care hospital in Finland, 12% of patients (12/79) died within 1 week after onset and the 30-day mortality rate was 35%.[13] A similar rate was observed in a study of candidaemia in central Sweden; the crude 30-day mortality rate of candidaemia was 31%.[43] The higher rate in Finland may be related to the differing epidemiological trends of *Candida* infection relative to other countries.

The severity of the underlying medical conditions influences the crude mortality rate. The ECMM hospital-based surveillance survey reported that the highest 30-day mortality rates of candidaemia occurred in patients with solid tumours (49%), haematological malignancy (45%), or in patients treated in ICUs (42%).[19]

Independent risk factors of death from candidaemia include older age (>65 years),[2] procedures associated with intensive care (eg, central venous catheters), [2] and severity of underlying illness. [2,49,64] Delays in initiation of treatment and inappropriate (or inadequate) treatment of fungal infections in patients with candidaemia have a significant impact on mortality. [2,65,66,67,68] Mortality rates were lowest for patients with candidaemia who began antifungal therapy the same day that the culture was performed (15%) compared with patients whose treatment was initiated 3 or more days after culture (41%).[65]

Important co-morbidities

Comorbidities for IC indication were obtained from the studies identified via the literature search described and cited in Module SI. The most important comorbidities are shown in Table 1.

Table 1. Important Comorbidities Found in Target Populations

Indication	Important Comorbidity
IC	HIV/AIDS;[8,19,46,69] diabetes mellitus;[46,70,71,72] illness requiring bone marrow/haematopoietic stem cell transplantation;[73,74,75] illness requiring solid organ transplantation;[74,75] cancer;[8,43,45] surgery or critical illness requiring prolonged hospitalisation;[76,77] ESRD.[78,79]

AIDS=Acquired Immunodeficiency Syndrome; ESRD = End Stage Renal Disease; HIV=Human Immunodeficiency Virus; IC = Invasive Candidiasis.

INDICATION (proposed)

Treatment of invasive candidiasis in adults and paediatric patients aged 1 month to <18 years.[2]

Incidence/Prevalence (Paediatric Population):

Candida species are one of the most common causes of paediatric bloodstream infections in the US and Europe.[80]

Studies in Europe estimate that the incidence of candidaemia and invasive *Candida* among children is between 0.02 and 0.47 per 1000. A study in England and Wales reported the incidence of IC to be 0.02 per 1000 paediatric admissions between 2000 and 2009.[81] A hospital-based study in Poland estimated the annual incidence among children to be 0.35 per 1000 discharges between 2000 and 2010.[82] Similarly, a study in Germany reported an incidence rate 0.47 cases per 1000 discharges between 1998 and 2008.[83]

Studies in the US estimate that the incidence of candidaemia and invasive *candida* is between 0.09 and 0.43 per 1000. A hospital-based study in 2000 in the US reported an incidence of candidaemia of 0.43 per 1000 paediatric admissions.[84] A population-based surveillance study in 25 hospitals conducted between 2008 and 2011 reported an incidence of 0.13 per 1000 in Atlanta and 0.26 in Baltimore.[85] When surveillance continued in the same cities until 2013, the overall incidence in children ages 1-19 years was 0.19 per 1000.[86] A retrospective cohort study in the US reported that the annual incidence rate of candidaemia was 0.12 cases per 1000 patient days in 2010.[87] Another study in the US using an administrative database with data from 43 children's hospitals estimated an incidence rate of IC of 0.09 per 1000 days in 2011.[88]

[2] The underlined text denotes the new proposed indication.

Demographics of the population in the proposed indication – age, gender, racial and/or ethnic origin and risk factors for the disease (Paediatric Population):

A study in the US and Europe reported that among 196 paediatric patients with IC, the average age was 5.7 years (interquartile range, 1.8-14.9), 49% were male, and 52% were white, followed by 27% unknown/mixed/other, 14% Asian, and 7% Black/African American.[80] Another study in England and Wales reported that the incidence of IC between 2000 and 2009 was highest in the <1 year old patients group (0.11 per 1000) and lowest in the 10-14 year old patients (0.0047 per 1000). [81] Risk factors include exposure to chemotherapy, hematopoietic stem cell transplantation, solid organ transplant, primary immunodeficiency, immune-modulating therapy for an autoimmune condition and an acquired immunodeficiency. In addition, neonates and patients in the ICU are also at risk for invasive fungal disease.[90]

The main existing treatment options (Paediatric Population)

Amphotericin B deoxycholate, liposomal amphotericin, amphotericin B lipid complex, fluconazole, micafungin and caspofungin can all be potentially used. Recommendations for the prevention of IC in paediatrics are largely extrapolated from studies performed in adults with concomitant pharmacokinetic data and models in children. For allogeneic haematopoietic stem cell transplantation (HSCT) recipients, fluconazole, voriconazole, micafungin, itraconazole and posaconazole can all be used. Similar recommendations are made for the prevention of IC in paediatrics in other risk groups. With several exceptions, recommendations for the treatment of IC in paediatrics are extrapolated from adult studies, with concomitant pharmacokinetic studies. Amphotericin B deoxycholate, liposomal amphotericin B, amphotericin B lipid complex, micafungin, caspofungin, anidulafungin, fluconazole and voriconazole can all be used.[89]

Natural history of the indicated condition in the untreated population, including mortality and morbidity (Paediatric Population):

While a recent review paper reported an overall paediatric in-hospital mortality rate of candidaemia of 15.8%,[90] most studies report rates between 10 and 25%. [80,83,88] Studies have also reported rates as high as 50% among ICU patients. [80,83] A study in Poland estimated mortality among paediatrics to be 8.5%,[82] while a German study estimated a 30 and 100-day mortality rate of 11.4%. [83]In a US hospital-based study, candidaemia was associated with 10% increased mortality.[84] Mortality risk factors among paediatrics include ICU admission, mechanical ventilation, hypotension or an arterial catheter, and neutropenia.[83]

Important Co-morbidities (Paediatric Population):
Paediatrics with candidaemia have been diagnosed with the following underlying conditions: malignancy (solid tumour or lymphoma) [82, 83,90,91;] hematopoietic stem cell transplantation; [90, 91] congenital malformations/syndromes; [82, 83] metabolic disorders; surgery, trauma, other acute conditions; [83] primary or acquired immunodeficiency; [90, 91] autoimmune condition; [90] and solid organ transplantation (kidney or liver). [82, 83, 90, 91]

Module SII. Non-Clinical Part of the Safety Specification

Table 2. Key Safety Findings and Relevance to Human Usage

Key Safety findings from Non-clinical Studies	Relevance to Human Usage
Toxicity:	
• Genotoxicity	In vitro and in vivo genotoxicity studies with anidulafungin provided no evidence of genotoxic potential.
• Carcinogenicity	No data available.
• Hepatobiliary events	Clinically significant toxicities (increased liver weight, microscopic hepatocellular changes and liver enzyme elevations, all of which were reversible upon drug discontinuation) were observed following 1 to 3 months of IV administration but did not occur until doses of at least 30 mg/kg/day. Data suggest that at high doses (40 mg/kg in monkeys), the effects on the liver can occur quite rapidly. The NOAEL for rat and monkey following repeated dosing for 3 months was 10 mg/kg/day, corresponding to clinical margins of exposure of 0.5-fold (monkey) and 2-fold (rat) the human AUC_{ss} for the 200/100 mg clinical dosing regimen. A 2-month juvenile rat toxicity study revealed effects consistent with those observed in adult rats. No target organs were identified. The NOAEL was the highest dose tested (30 mg/kg/day given subcutaneously) corresponding to a margin of exposure of 4-fold the human AUC_{ss} for the 200/100 mg clinical dosing regimen**.** Potential for hepatic effects are listed in SmPC under Special warnings and precautions for use. See PART II. SVII for discussion of the important identified risk “Hepatobiliary events”.
• Effects on embryo-foetal development	Embryo-foetal development studies were conducted with doses up to 20 mg/kg/day in rats and rabbits (equivalent to 2 and 4 times, respectively, the proposed therapeutic maintenance dose of 100 mg/day on the basis of relative body surface area). Anidulafungin administration resulted in skeletal changes in rat foetuses, including incomplete ossification of various bones and wavy, misaligned or misshapen ribs. These changes were not dose-related and were within the range of the laboratory’s historical control database. Developmental effects observed in rabbits (slightly reduced foetal weights) occurred in the high dose group, a dose that also produced maternal toxicity. Anidulafungin crossed the placental barrier in rats and was detected in foetal plasma. The SmPC states that anidulafungin is not recommended for use during pregnancy unless the benefit to the mother clearly outweighs the potential risk to the foetus. See PART II. SVII and SVIII for removal of the missing information ‘Pregnant women’ from the list of safety concerns.
General safety pharmacology:	
• Exacerbation of infusion-associated reactions (IARs) by anaesthetics	The administration of anaesthetic to rats appeared to exacerbate infusion reactions. Rats were dosed with anidulafungin at 3 dose levels (5, 10, and 30 mg/kg), were anesthetised within 1 hour using a combination of ketamine and xylazine and then were exposed to UVR. Control rats were administered the same doses of anidulafungin but were not anaesthetised nor exposed to UVR. Rats in the high dose group experienced infusion-related reactions (eg, swollen snouts) as a result of anidulafungin administration and when anaesthesia was administered, the clinical signs of infusion reaction were exacerbated (eg, increased snout swelling) and 2 rats died. Some rats in the mid-dose experienced similar infusion-related reactions only after administration of anaesthesia.

Table 2. Key Safety Findings and Relevance to Human Usage

Key Safety findings from Non-clinical Studies	Relevance to Human Usage
	There were no AEs in the low-dose animals in the presence or absence of anaesthesia, and no infusion-related reactions in the mid-dose group in the absence of anaesthesia. The relevance to human usage is unknown. The SmPC provides information to the prescriber in Section 4.4 Special warnings and precautions for use and Section 5.3 Preclinical Safety Data. See PART II. SVII for discussion of the important potential risk 'Exacerbation of infusion-associated reactions by anaesthetics'.

AE = Adverse Event; AUC_{ss} = Area Under Concentration-Time Curve at Steady State; IAR = Infusion-Associated Reaction; IV = Intravenous, NOAEL = No Observed Adverse Event Level; SmPC = Summary of Product Characteristics; TDAR = T-Dependent Antibody Response; UVR = Ultraviolet Radiation.

Module SIII. Clinical Trial Exposure

Cumulatively through 15 October 2018, it is estimated that 2351 subjects have participated in the anidulafungin clinical development programme. Of these 2351 subjects, a total of 1677 received anidulafungin: alone (164) or with placebo (326); with amphotericin (30); with another azole (1091); with tacrolimus (36); or anidulafungin with either placebo or an oral azole (30).

Clinical Trials Exposure in Adult Population[3]

Exposure data in anidulafungin clinical studies presented in Tables 3, 4, 5, 6 and 7 are summarised below:

One (1) pivotal and 2 supportive studies supported the original proposed indication of IC/C. Across these 3 studies, 204 patients with IC/C were administered anidulafungin intravenously as a single loading dose of 200 mg followed by 100 mg daily. These data are referred to in tables and text as the Integrated IC/C Safety Database.

Additional patients with other primary disease conditions (azole-refractory mucosal candidiasis, OC, and IA) were administered anidulafungin at doses up to and including the proposed dose. The data for all indications (IC/C, OC and aspergillosis) are primarily summarised and discussed in Module 2, 2.7.4 Summary of Clinical Safety. When referred to in this document these data are designated in text and tables as the Integrated Phase 2/3 Safety Database.

The total number of patients with IC/C studied at the target dose was appropriate for the size of the target population and the severity of the illness. However, the overall number of patients studied was modest and post-approval experience will be important in confirming and refining the safety profile of anidulafungin (Table 3).

In conducting the clinical programme, restrictions on study entry were minimised to ensure that the population studied was as broad as possible. Inclusion and exclusion criteria were utilised to ensure that the studies were sufficiently controlled to allow interpretation of the data and to protect subject safety while ensuring that the Clinical Trial (CT) population was representative of the target population.

Table 3. Extent of Exposure for Integrated Invasive Candidiasis/Candidaemia Safety Database

	IC/C Safety Data[a]	
	Anidulafungin	**Fluconazole**
Number of IV Doses		
N (subjects)	204	125
Mean	13.3	12.0

[3] One study (VER002-9) included also 2 paediatric patients (aged 16 and 17 years, respectively).

Table 3. Extent of Exposure for Integrated Invasive Candidiasis/Candidaemia Safety Database

	IC/C Safety Data[a]	
	Anidulafungin	**Fluconazole**
Range	1-38	1-36
Duration of IV treatment		
N (subjects)	204	125
Mean	13.5	12.2
Range	1-38	1-37

Source: SCS Table 3-1, Table 3.1.1.1 (overall neutropenic pool), Table 3.1.2.1 (overall DTI pool).

IC/C = Invasive Candidiasis/Candidaemia; SCS = Summary of Clinical Safety.

a. Studies VER002-6, VER002-9, VER002-9b

In the tables below, the following populations are shown:

- IC/C Population (all patients with IC/C treated with 200 mg loading dose followed by 100 mg maintenance dose of anidulafungin):

  a. Randomised, blinded trial population; includes study VER002-9

  b. Integrated IC/C dataset which included both blinded, randomised as well as open-label studies; 200 mg loading dose/100 mg maintenance dose, includes studies VER002-6, VER002-9, VER002-9b:

- All populations: IC/C, OC and IA

  a. All randomised, blinded, CT populations, includes studies VER002-4 and VER002-9 (OC and IC/C, respectively):

  b. Integrated Phase 2/3 dataset which includes both blinded, randomised as well as open-label studies, includes studies VER002-4, VER002-6, VER002-7, VER002-9, VER002-9b, VER002-11, XBAF:

Table 4. Duration of Exposure (by Indication)

Duration of Exposure (at Least)	**Persons**	**Person Time**
IC/C Population (VER002-9): 200 mg loading dose; 100 mg maintenance dose anidulafungin		
Up to and including 14 day	86	874
>14 days up to and including 28 days	42	772
>28 days up to and including 35 days	3	98
Total person time	1744	
IC/C Population (Integrated IC/C Dataset):		
Up to and including 14 day	128	1286
>14 days up to and including 28 days	72	1323
>28 days up to and including 35 days	3	98
>35 days up to and including 49 days	1	38
Total person time	2745	

Table 4. Duration of Exposure (by Indication)

Duration of Exposure (at Least)	Persons	Person Time
IC/C and OC, all doses		
Up to and including 14 day	357	4387
>14 days up to and including 28 days	71	1281
>28 days up to and including 35 days	3	98
Total person time	5766	
Integrated Phase 2/3 Dataset (All doses; IC/C, OC, IA populations)		
Up to and including 14 day	467	5460
>14 days up to and including 28 days	184	3409
>28 days up to and including 35 days	7	220
>35 days up to and including 49 days	7	289
>49 days up to and including 63 days	1	63
>63 days up to and including 77 days	1	70
>77 days up to and including 99 days	2	180
Total person time	9691	

IA = Invasive Aspergillosis; IC/C = Invasive Candidiasis/Candidaemia; OC = Oesophageal Candidiasis.

Table 5. Exposure by Dose (by Indication)

Dose of Exposure	Persons	Person Time
IC/C Population (VER002-9)		
200/100	131	1744
Total	131	1744
IC/C Population (Integrated IC/C Dataset)		
200/100	204	2745
Total	204	2745
IC/C and OC		
200/100	131	1744
100/50	300	4022
Total	431	5766
Integrated Phase 2/3 Dataset (IC/C, OC, IA populations)		
200/100	234	3543
150/75	40	625
100/50	359	4956
70/35	17	242
50/25	19	325
Total	669	9691

IA = Invasive Aspergillosis; IC/C = Invasive Candidiasis/Candidaemia; OC = Oesophageal Candidiasis

Table 6. Exposure by Age Group and Gender (by Indication)

Age Group	Persons		Person Time	
	M	F	M	F
IC/C Population (VER002-9)				
<65 years	37	49	475	650
≥65 years	29	16	407	212
Total	66	65	882	862
IC/C Population (Integrated IC/C Dataset)				
<65 years	64	71	795	956
≥65 years	42	27	608	386
Total.	106	98	1403	1342
IC/C and OC				
<65 years	162	220	2208	2885
≥65 years	31	18	437	236
Total.	193	238	2645	3121
Integrated Phase 2/3 Dataset (IC/C, OC, IA populations)				
<65 years	260	293	3827	4137
≥65 years	67	49	1094	633
Total	330	783	4921	4770

IA = Invasive Aspergillosis; IC/C = Invasive Candidiasis/Candidaemia; OC = Oesophageal Candidiasis

Table 7. Exposure by Ethnic or Racial Origin (by Indication)

Ethnic/Racial Origin	Persons	Person Time
IC/C Population (VER002-9)		
Caucasian/White	93	1291
African-American/Black	26	302
Asian	1	15
Hispanic/Latino	9	129
Other	2	7
Total	131	1744
IC/C Population (Integrated IC/C Dataset)		
Caucasian/White	136	1913
African-American/Black	47	575
Asian	1	15
Hispanic/Latino	16	215
Other	4	27
Total	204	2745
IC/C and OC		
Caucasian/White	137	1909
African-American/Black	172	2216
Asian	47	641
Hispanic/Latino	10	150
Other	65	850
Total	431	5766
Integrated Phase 2/3 Dataset (IC/C, OC, IA populations)		
Caucasian/White	289	4536
African-American/Black	229	3071
Asian	47	641
Hispanic/Latino	34	502

Table 7. Exposure by Ethnic or Racial Origin (by Indication)

Ethnic/Racial Origin	Persons	Person Time
Other	70	941
Total	669	9691

IA = Invasive Aspergillosis; IC/C = Invasive Candidiasis/Candidaemia; OC = Oesophageal Candidiasis

Subjects with neutropenia or Deep Tissue Infection (DTI) were also studied and exposure data are shown below from the relevant CTs. These studies were A8851021 (neutropenic subjects), A8851022 (subjects with DTI), and regional studies A8851011¸ A8851015, A8851016, and A8851019 (subsets of subjects with neutropenia or DTI).

Combining data from the IC/C database, regional studies and studies A8851021 and A8851022 were not feasible, because of differences in databases between Pfizer studies with non-Pfizer studies. Therefore, exposure data are provided separately below for the regional studies, and for subjects with neutropenia or DTI.

Table 8 presents exposure data from subjects in the regional studies A8851011¸ A8851015, A8851016, and A8851019.

Table 8. Exposure in Regional Studies

	N = 595[a]
Duration of antifungal treatment, total (IV and oral) (days)	
N (subjects)	595
Median (days)	14.0
Range (days)	1-67
Duration of IV treatment	
N (subjects)	595
Median (days)	9.0
Range (days)	1-42
Gender, N (subjects)	
Male	327 (55%)
Female	268 (45%)
Age Group, N (subjects)	
<65 years	365 (61.3)
≥65 years	230 (38.7)
Race, N (subjects)	
White	411 (69.1)
Black	64 (10.8)
Asian	72 (12.1)
Other	35 (5.9)
Unspecified	13 (2.2)

Source: Tables 3.1, 4.1 (pooled regional studies) and SCS (Neutropenia, DTI, C.krusei) Table 1

IV = Intravenous; SCS = Summary of Clinical Safety.

a. Regional studies A8851011, A8851015, A8851016, A8851019

Table 9 and Table 10 present exposure data in neutropenic subjects and subjects with DTI from relevant XTs.

Across these studies, patients with neutropenia (n = 53) or DTI (n = 131) were administered anidulafungin intravenously as a single loading dose of 200 mg followed by 100 mg daily.

Table 9. Exposure in Subjects with Neutropenia

	N=53[a]
Duration of antifungal treatment, total (IV and oral) (days)	
N (subjects)	53
Mean (days)	15.0
Range (days)	1-67
Duration of IV treatment	
N (subjects)	53
Mean (days)	10.0
Range (days)	1-42
Gender, N (subjects)	
Male	33
Female	20
Age Group, N (subjects)	
< 65 years	37
≥ 65 years	16
Race, N (subjects)	
White	40
Black	0
Asian	5
Other	8
Unspecified	0

Source: Tables 4.2.1.2 and 5.2.1.1s (Pooled Data); SCS (Neutropenia, DTI, C.krusei) Table 3.

IV = Intravenous; SCS = Summary of Clinical Safety.

a. Study A8851021 and subjects with neutropenia from regional studies A8851011, A8851015, A8851016, A8851019. Three (3) subjects with neutropenia from study VER002-9 were not included in this analysis as they are already captured in the IC/C dataset.

Table 10. Exposure in Subjects with Deep Tissue Infection

	N = 131[a]
Duration of antifungal treatment, total (IV and oral) (days)	
N (subjects)	131
Mean (days)	16.0
Range (days)	1–56
Duration of IV treatment	
N (subjects)	131
Mean (days)	14.0
Range (days)	1–42
Gender, N (subjects)	
Male	75
Female	56
Age Group, N (subjects)	
< 65 years	71
≥ 65 years	60
Race, N (subjects)	
White	106
Black	10
Asian	1
Other	7
Unspecified	7

Source: Tables 4.2.2.2 (Pooled Data) and SCS (Neutropenia, DTI, *C.krusei*) Table 4.

IV = Intravenous; SCS = Summary of Clinical Safety.

a. Study A8851022 and subjects with deep tissue infection from regional studies A8851011, A8851015, A8851016, A8851019

Table 11. Special Populations (Totals)

Total Population	Persons	Person Time
VER002-2: Single IV Dose Hepatic Impairment Study (N = 6 mild; N = 6 moderate; N = 8 severe; 7 control)	27	27
VER002-3: Single IV Dose Renal impairment Study (N = 8 mild; N = 6 moderate, N = 6 severe; N = 6 end stage; N = 8 control)	34	34

IV = Intravenous.

Clinical Trials Exposure in Paediatric Population

Anidulafungin was investigated in 2 completed paediatric clinical studies: A8851008 and VER002-12.

Study A8851008 was a phase 3b study evaluating the safety and tolerability, PK, and efficacy, of anidulafungin for the treatment of IC in paediatric patients 1 month to less than 18 years of age. Subjects who were at high risk for IC (infection susceptibility increased) or who had confirmed IC were included. Within the 9-year study period, 72 subjects were screened, 70 were randomised and 68 subjects were treated. Exposure data for patients receiving anidulafungin are presented in Table 12, Table 13, Table 14, Table 15.

Table 12. Duration of Exposure (by Indication), Study A8851008

	Duration of exposure	Persons	Person Time (patient-days)
Infection Susceptibility Increased	≤ 1 day	0	0
	2-7 days	1	6
	8-14 days	1	9
	15-28 days	0	0
	29-35 days	0	0
	Total	**2**	**15**
Invasive Candidiasis	≤ 1 day	2	2
	2-7 days	7	30
	8-14 days	38	435
	15-28 days	16	336
	29-35 days	3	94
	Total	**66**	**897**
Total For All Indications	≤ 1 day	2	2
	2-7 days	8	36
	8-14 days	39	444
	15-28 days	16	336
	29-35 days	3	94
	Total	**68**	**912**

Table 13. Exposure by Daily Dose (by Indication), Study A8851008

	Daily Dose	Persons	Person Time (patient-days)
Infection Susceptibility Increased	< 1.5 mg/kg[a]	1	9
	≥ 1.5 mg/kg	1	6
	Total	**2**	**15**
Invasive Candidiasis	< 1.5 mg/kg[a]	24	337
	≥ 1.5 mg/kg	42	560
	Total	**66**	**897**
Total For All Indications	< 1.5 mg/kg[a]	25	346
	≥ 1.5 mg/kg	43	566
	Total	**68**	**912**

A single Loading dose equal to 2 times the daily dose was administered on day 1. Dose of Exposure is calculated using average dose and weight from day 2 on.
a. Patients A8851008-1068-1002, A8851008-1081-1001 have no dose information after Day 1.

Table 14. Exposure by Age Group and Gender (by Indication), Study A8851008

	Age Group	Persons		Person Time (patient-days)	
		Male	Female	Male	Female
Infection Susceptibility Increased	1 month to < 2 years	1	1	9	6
	2 to < 12 years	0	0	0	0
	12 to < 18 years	0	0	0	0
	Total	**1**	**1**	**9**	**6**

Table 14. Exposure by Age Group and Gender (by Indication), Study A8851008

	Age Group	Persons		Person Time (patient-days)	
		Male	Female	Male	Female
Invasive Candidiasis	1 month to < 2 years	7	7	105	75
	2 to < 12 years	25	17	347	251
	12 to < 18 years	5	5	61	58
	Total	**37**	**29**	**513**	**384**
Total For All Indications	1 month to < 2 years	8	8	114	81
	2 to < 12 years	25	17	347	251
	12 to < 18 years	5	5	61	58
	Total	**38**	**30**	**522**	**390**

Table 15. Exposure by Ethnic/Racial Origin (by Indication), Study A8851008

	Ethnic/Racial Origin	Persons	Person Time (patient-days)
Infection Susceptibility Increased	Asian	0	0
	Black or African American	0	0
	Other	0	0
	White	2	15
	Total	**2**	**15**
Invasive Candidiasis	Asian	6	49
	Black or African American	1	3
	Other	7	74
	White	52	771
	Total	**66**	**897**
Total For All Indications	Asian	6	49
	Black or African American	1	3
	Other	7	74
	White	54	786
	Total	**68**	**912**

Study (VER002-12) was a phase 1/2 clinical dose-escalation study in immunocompromised paediatric patients with neutropenia, aged 2 to 17 years. The primary objective of the study was to assess the safety, tolerance and PK profile of IV anidulafungin as early empirical therapy for prevention of fungal infections in this patient population. Two age cohorts were included: 2 to 11 years and 12 to 17 years. A total of 25 patients were enrolled: 13 patients received a 1.5 mg/kg loading dose on Day 1 followed by a maintenance dose of 0.75 mg/kg and 12 patients received a 3.0 mg/kg loading dose on Day 1, followed by a 1.5 mg/kg maintenance dose; maintenance doses were initiated on Day 2. A summary of exposure by dose and age group is included in Table 16.

Table 16. Extent of Exposure of Anidulafungin, Study VER002-12

	Anidulafungin 0.75 mg/kg[a] N=13		Anidulafungin 1.5 mg/kg[b] N=12		Total N=25
	Age 2 to 11 (N=6)	Age 12 to 17 (N=7)	Age 2 to 11 (N=6)	Age 12 to 17 (N=6)	
Distribution by Days, n (%)					
<5 days	1 (16.7)	1 (14.3)	0	0	2 (8.0)
5 to 13 days	5 (83.3)	5 (71.4)	5 (83.3)	5 (83.3)	20 (80.0)
≥14 days	0	1 (14.3)	1 (16.7)	1 (16.7)	3 (12.0)
Total days (days)					
Mean (SD)	6.0 (3.0)	8.6 (6.5)	10.0 (6.1)	10.3 (6.6)	8.7 (5.7)
Median	5.0	6.0	8.5	9.5	5.0
Range	4,12	1,21	5,20	5,23	1,23

a. A single loading dose of 1.5 mg/kg was administered on Day 1, followed by the indicated maintenance dose beginning on Day 2

b. A single loading dose of 3.0 mg/kg was administered on Day 1, followed by the indicated maintenance dose beginning on Day 2

SD = standard deviation

Module SIV. Populations Not Studied In Clinical Trials

SIV.1. Exclusion Criteria in Pivotal Clinical Studies within the Development Programme

Table 17. Exclusion Criteria in Pivotal Clinical Studies Within the Development Programme

Criterion	Reason for exclusion	Missing information (Yes/No)	Rationale (if not included as missing information)
Female patients who were pregnant, lactating, or planning a pregnancy during the course of the study, or who were of child bearing potential and not using an acceptable method of birth control. Patients were to continue contraceptive methods during the study and for at least 30 days after receiving their last treatment.	At this time, there are no adequate and well controlled studies with anidulafungin in pregnant women, thus there are limited safety data on the effects of anidulafungin on the unborn foetus.	No	Removed according to the RSI received in September 2019
Neonates <1 month of age	Given the potential toxicity concerns associated with polysorbate 80 (PS80) in neonates, benefit/risk assessment did not support the investigation of anidulafungin in neonates with invasive candidiasis, including candidaemia.	No	Treatment with anidulafungin in neonates (<1-month-old) is not recommended. Treating neonates requires consideration for coverage of disseminated candidiasis including Central Nervous System (CNS); nonclinical infection models indicate that higher doses of anidulafungin are needed to achieve adequate CNS penetration, resulting in higher doses of polysorbate 80, a formulation excipient. High doses of polysorbate have been associated with potentially life-threatening toxicities in neonates as reported in the literature.

CNS = Central Nervous System; IC = Invasive Candidiasis; N/A = Not Applicable; Polysorbate 80 (PS80)

SIV.2. Limitations to Detect Adverse Reactions in Clinical Trial Development Programmes

Table 18. Limitations of Adverse Drug Reaction Detection

Ability to Detect Adverse Reactions	Limitation of Trial Programme	Discussion of Implications for Target Population
Uncommon ADRs	In adult clinical trials, a total of 204 patients received anidulafungin for IC/C at the labelled dose; in addition, 595 patients from regional studies, 56 neutropenic patients[a] and 131 patients with DTI[b] received anidulafungin at the labelled dose. A total of 80 paediatric subjects received anidulafungin at the proposed paediatric dose.	Uncommon or rare ADRs may not be observed in CTs.
Adverse reactions due to prolonged exposure or which have a long latency	The duration of treatment in the adult clinical trials was up to 38 days with most subjects having IV treatment for up to 14 days (n = 128) or 15 to 21 days (n = 60). In addition, 56 neutropenic subjects[a] and 131 patients with DTI[b] received anidulafungin at the labelled dose for up to 42 days. The maximum duration of anidulafungin treatment in the paediatric clinical trials was 35 days.	ADRs due to prolonged exposure or with a long latency have not been identified. There are insufficient data to support the 100 mg dose for longer than 42 days of treatment.

ADR = Adverse Drug Reaction; CT = Clinical Trial; DTI = Deep Tissue Infection; IC/C = Invasive candidiasis/Candidaemia; IV = Intravenous.

a. Subjects with neutropenia include patients from A8851021 (neutropenia) and subjects with neutropenia from the regional studies.

b. Subjects with deep tissue infection (DTI) include patients from A8851022 (DTI) and subjects with DTI from the regional studies.

SIV.3. Limitations in Respect to Populations Typically Under-Represented in Clinical Trial Development Programmes

Table 19. Exposure of Special Populations Included or not in Clinical Trial Development Programmes

Type of special population	Exposure
Pregnant women	Not included in the clinical development program
Breastfeeding women	Not included in the clinical development program
Patients with relevant comorbidities: • Patients with hepatic impairment • Patients with renal impairment • Immunocompromised patients	Please refer to Module SIII, Table 11 and Table 16 for exposure information in these populations.
Population with relevant different ethnic origin	Enrolment in the global clinical studies included patients of all ethnic origins. The clinical efficacy and safety of anidulafungin for the treatment of IC/C was additionally evaluated in a study of 43 patients from Asia (Study A8851016) and 54 patients from Latin America (Study A8851015).
Subpopulations carrying known and relevant genetic polymorphisms	Not included in the clinical development program

Table 19. Exposure of Special Populations Included or not in Clinical Trial Development Programmes

Type of special population	Exposure
Paediatric patients	Paediatric patients were included in two different studies in the clinical development program: 1. A Phase 1/2 study conducted in 25 immunocompromised paediatric patients with neutropenia at risk for invasive fungal infections (VER002-12). None of the paediatric patients enrolled in this study were diagnosed with a fungal infection, thus no assessment of efficacy could be made, although anidulafungin was well tolerated. 2. A completed phase 3b study in which 68 patients 1 month to <18 years of age received anidulafungin for the treatment of IC/C.
Elderly patients	As previously mentioned, the overall size of the database is small. For the IC/C indication, elderly patients (≥65 years of age) comprise 33.8% of the total population, corresponding to 69 patients. An additional 230 (38.7%) patients ≥65 years of age with candidaemia or IC were treated with anidulafungin in studies A8851011¸ A8851015, A8851016, and A8851019 representing a total of 37.5% of patients ≥ 65 years of age. An additional 47 elderly patients with OC and aspergillosis were treated with anidulafungin. About a third of patients in the IC/C studies were 65 years of age or older. Proportionally more severe AEs were reported among elderly patients, but their frequency was similar to that of younger patients, except that respiratory distress was reported by more patients aged 65 and older.
Other Subpopulations	N/A

AE = Adverse Event; CT = Clinical Trial; IC = Invasive Candidiasis; IC/C = Invasive Candidiasis/Candidaemia; OC = Oesophageal Candidiasis.

Module SV. Post-Authorisation Experience

SV.1. Post-Authorisation Exposure

SV.1.1. Method Used to Calculate Exposure

It is estimated that 801,962 patients were exposed to anidulafungin worldwide since the product was first approved through 15 October 2018[4].

Two (2) sources were used for calculating patient exposure: Arlington Medical Resources (AMR)[5] and IMS Midas sales volumes[6]. AMR collects data from a sample of short-term acute care hospitals in US and Key 5 EU countries on usage of antifungal and antibiotic products. The AMR metrics used for this exercise are indication, age, gender, and average Days of Therapy (DOT). The Key 5 EU data are applied to rest of the world (ROW) with the exception of the US, on the assumption that all patients are treated using the same average dosage for the same average duration of time as patients in the major markets of Europe (France, Germany, Italy, Spain and United Kingdom [UK]). AMR percentages of patients are applied to the IMS DOT data to obtain exposure (Patient Days). Patient estimates are then derived from the Patient Days by dividing Patient Days by AMR average DOT per patient.

SV.1.2. Exposure

Table 20. Post-marketing Patient Exposure by Age Group, Gender, and Region, Cumulative through 15 October 2018

	United States		EU and ROW		Total Worldwide	
Age (years)	**Male**	**Female**	**Male**	**Female**	**Male**	**Female**
0-17	0	740	14057	0	14057	740
18-29	741	1750	0	24054	741	25804
30-49	5310	25146	49821	31806	55131	56952
50-64	10243	20347	105,599	113,678	115,843	134,025
65-74	21685	23296	78281	63755	99967	87051
≥75	29181	48330	87381	46761	116,562	95,091
Total	**67161**	**119,607**	**335,139**	**280,054**	**402,300**	**399,662**
Grand Total	**186,768**		**615,193**		**801,962**	

EU= European Union; ROW = Rest of The World.

[4]Please note that DOT data for February 2006 to second quarter 2010, third quarter of 2018 and 1st to 15th October 2018 were not available; thus patient exposure for the RMP period was projected by averaging 4 quarters.

[5] AMR antifungal reports are available for US in 1st and 2nd Half of the year (1H and 2H), while Key 5 EU is 2H only. Most recent data are 1H11 for US and 2H11 for Key 5 EU. These are the sources used for the factoring.

[6] IMS collects sales and units data from >60 countries. Kilogram (KG) sold are used to determine Days of Therapy (DOT) by dividing AMR average gram usage per day to the KG data to determine IMS DOT.

Given the relatively limited availability of market research data for anidulafungin in both the US and EU markets, anidulafungin exposure estimates below are presented by the most common infection type/site (to maximise reliability of available data projections).

Table 21. Post-marketing Patient Exposure by Gender, Region and Infection Type/Site Cumulative through 15 October 2018

	United States		EU and ROW		Total Worldwide	
Indication	**Male**	**Female**	**Male**	**Female**	**Male**	**Female**
Blood Infections	16662	43222	82285	140,435	98947	183,657
Respiratory Infections	21124	32472	129,416	70503	150,540	102,975
Fever of Unknown Origin	0	0	7733	0	7733	0
GI/Biliary Infections	13269	25846	32849	10669	46118	36516
Abdominal Infections	12636	12299	21566	10384	34202	22683
Genitourinary Infections	0	2976	21709	31682	21709	34658
All Other Infections	3470	2792	39582	16381	43052	19173
Total	**67161**	**119,607**	**335,139**	**280,054**	**402,300**	**399,662**
Grand Total	**186,768**		**615,6193**		**801,962**	

EU= European Union; ROW = Rest of the World; GI=Gastrointestinal.

Module SVI. Additional EU Requirements for the Safety Specification

SVI.1. Potential for Misuse for Illegal Purposes

Anidulafungin has no known attributes that make it attractive for intentional overdose, abuse or illegal use.

Module SVII. Identified and Potential Risks

SVII.1. Identification of Safety Concerns in the Initial RMP Submission

Not applicable as this is not an initial version of the RMP.

SVII.1.1. Risks not Considered Important for Inclusion in the List of Safety Concerns in the RMP

Not applicable.

SVII.1.2. Risks Considered Important for Inclusion in the List of Safety Concerns in the RMP

Table 22. Safety Concerns Considered Important for Inclusion in the List of Safety Concerns in the RMP

Risks and Missing Information	Risk-Benefit Impact
Important Potential Risk	
Hepatic impairment and other serious toxicities in neonates < 1 month of age	Given the potential risk of hepatotoxicity associated with polysorbate 80 when an increased amount is used in neonates, there is a theoretical risk of additive or synergistic hepatic effects in neonates when exposed to anidulafungin and polysorbate 80 at higher doses. Neonatal exposure to an increased amount of polysorbate 80 in addition to an increased dose of anidulafungin resulted from the clinical need to use higher doses of anidulafungin to cover documented or suspected Candida meningitis. The proposed label includes a warning about the treatment with anidulafungin in neonates (<1-month-old).

SVII.2. New Safety Concerns and Reclassification with a Submission of an Updated RMP

The MAH reclassified the important identified risks ‘Anaphylaxis and Infusion-associated reactions’, ‘Hepatobiliary events’ and ‘Convulsions’ as identified risks that are not considered important for inclusion in the RMP, in accordance with the guidance in GVP Module V (Rev. 2) and accompanying RMP template Rev. 2.0.1 (Part II: Module SVII), and therefore remove from the list of safety concerns.

The MAH reclassified the important potential risks ‘Exacerbation of Infusion-associated reactions by anaesthetics’ and ‘QT Prolongation/Torsade de Pointes’ as potential risks that are not considered important for inclusion in the RMP, and therefore remove them from the list of safety concerns [GVP Module V (Rev. 2) and accompanying RMP template Rev. 2.0.1].

The MAH removed the Missing Information (MI) ‘Children/Adolescents’ and to add the important potential risk ‘Hepatic impairment and other serious toxicities in neonates < 1 month of age’ based on the completion of Study A8851008. In addition, the missing information ‘Elderly’ is removed from the list of safety concerns in accordance with the guidance in GVP Module V (Rev. 2) and accompanying RMP template Rev. 2.0.1.

The missing information Pregnant women and Resistance are removed from the list of safety concerns following Regulatory Request during the assessment of Type II variation application to extended indication to paediatric patients ≥ 1 month of age.

The rationales for the changes to the list of safety concerns are presented below.

Further details on the safety concerns will be provided in section SVII.3.

Important Identified Risks Removed from the List of Safety Concerns

Anaphylaxis and Infusion-associated reactions

This important identified risk is removed from the list of safety concerns. The MAH believes that 'Anaphylaxis and infusion-associated reactions' can be reclassified as risk not important because it is an adverse reaction already well-known to health professionals, the event does not require additional pharmacovigilance activities or additional risk minimisation measures, and it has no impact on public health. The SmPC provides instruction on maximum infusion rates in Section 4.2, with the reason given to minimize the potential for infusion-associated reactions. In addition, after over 12 years of post-marketing experience, no significant safety issues have been identified. The risk of 'Anaphylaxis and infusion-associated reactions' is still presented in SVII.3.1, including a summary of the cumulative safety data from the global safety database through the current RMP data lock point to further support the evidence for its removal.

Hepatobiliary events

This important identified risk is removed from the list of safety concerns. The MAH believes that 'Hepatobiliary events' can be reclassified as risk not important because it does not require additional pharmacovigilance activities or additional risk minimisation measures. Monitoring of liver function tests (LFTs) is considered part of standard clinical practice in the patient population likely to receive anidulafungin given the indication (ICC) and the risk factors for ICC. Section 4.4 of the SmPC recommends dosage alteration if LFTs worsen during treatment. No causal relationship or mechanism of the risk has been identified. The risk of Hepatobiliary events is still presented in SVII.3.1, including a summary of the cumulative safety data from the global safety database through the current RMP data lock point to further support the evidence for its removal.

Convulsions

This important identified risk is removed from the list of safety concerns. The MAH believes that 'Convulsions' can be reclassified as risk not important because it does not require additional pharmacovigilance activities or additional risk minimisation measures, and it has a low impact on public health. In addition, after over 12 years of post-marketing experience, there is a 1.5% proportional reporting rate. There is no clear evidence that anidulafungin is causally related to the risk of convulsions, and no potential mechanism has been identified. The clinical consequences of convulsions, including those that are serious, occur with a low frequency and are considered acceptable in relation to the severity of the indication treated.

The risk of Convulsions is still presented in SVII.3.1, including a summary of the cumulative safety data from the global safety database through the current RMP data lock point to further support the evidence for its removal.

Important Potential Risks Removed from the List of Safety Concerns

Exacerbation of Infusion-associated reactions by anaesthetics

This important potential risk is removed from the list of safety concerns. The MAH believes that this risk can be reclassified as not important because it does not require additional pharmacovigilance activities or additional risk minimisation measures, and it has a low impact on public health. In addition, after over 12 years of post-marketing experience, no cases were identified either in the clinical programme or in the safety database. The risk of 'Exacerbation of Infusion-associated reactions by anaesthetics' is still presented in SVII.3.1, including a summary of the cumulative safety data from the global safety database through the current RMP data lock point to further support the evidence for its removal.

QT prolongation/Torsades de Pointes

This important potential risk is removed from the list of safety concerns. The MAH believes that 'QT prolongation/Torsades de Pointes' can be reclassified as risk not important because it does not require additional pharmacovigilance activities or additional risk minimisation measures, and it has a low impact on public health. No causal relationship has been confirmed, and no potential mechanism has been identified. In addition, after over 12 years of post-marketing experience, no safety issues have been identified. The risk of QT prolongation/Torsades de Pointes is still presented in SVII.3.1, including a summary of the cumulative safety data from the global safety database through the current RMP data lock point to further support the evidence for its removal.

Important Potential Risk added to the List of Safety Concerns

Hepatic impairment and other serious toxicities in neonates (< 1 month of age)

The classification of the paediatric population including 'Children/adolescents' as missing information is considered no longer appropriate based on availability of new data upon the completion of study A8851008 (see below subsection *Missing Information Removed from the List of Safety Concerns*). Conversely, neonates under 1 month of age have been excluded from the clinical program as the use of anidulafungin in this population may present a different safety profile and therefore warrant remaining among the safety concerns (GVP Module 5 Rev 2). Specifically, the MAH added the important potential risk 'Hepatic impairment and other serious toxicities in neonates < 1 month of age'. This is because of potential toxicity of the excipient PS80 resulting from the higher doses that would be needed for the treatment of invasive candidiasis with CNS involvement in this patient population. The risk is presented in SVII.3.1.

Missing Information Removed from the List of Safety Concerns

Children/Adolescents

The safety concern Children/Adolescents, previously included in the RMP as missing information is removed based on completion of study A8851008:

- safety data are available from study A8851008 and include 68 patients between the ages of 1 month and <18 years
- overall, the adverse events (AEs) reported were in line with the known safety profile of anidulafungin or the pattern of events expected for the patient population
- no new safety concerns were identified for anidulafungin in this population.

Elderly

The safety concern Elderly previously included in the RMP as missing information is removed from the RMP. This is because there is no evidence that the safety profile in these patients would differ from the known safety profile of anidulafungin. It does not require additional pharmacovigilance activities or additional risk minimisation measures, and it has a low impact on public health.

Pregnant women and Resistance

These safety concerns, previously included in the RMP as missing information, are removed from the RMP as per RSI received on 20 September 2019.

SVII.3. Details of Important Identified, Important Potential Risks, and Missing Information

Clinical data including adult population are presented in Annex 7 and are unchanged since last RMP version 12.1. Clinical data from paediatric studies A8851008 and VER002-12 are discussed below and specific Tables pertaining the frequency, seriousness, outcomes and severity of relevant treatment emergent adverse events (TEAEs) are included in Annex 7.

Cumulative post-marketing data through 15 October 2018 are presented in the sections below (MedDRA version 21.0).[7] Tables pertaining seriousness and outcomes by PTs for both CT and non-CT data are included in Annex 7.

[7] MAH safety database contains cases of AEs reported spontaneously, cases reported from regulatory authorities, cases published in the medical literature, and cases of serious adverse events (SAEs) reported from clinical studies and other solicited sources, including marketing programs sponsored by the MAH. CT cases contain all valid serious cases for Pfizer and Non-Pfizer Interventional trials.

SVII.3.1. Presentation of Important Identified Risks and Important Potential Risks

Important Identified Risks:

The following important identified risks are reclassified as "not important" according to the guidance for determination of risks appropriate for inclusion in the RMP as described in GVP Module V (Rev.2) and accompanying RMP template Rev 2.0.1:

- *Anaphylaxis and Infusion-associated reactions* (Table 23)
- *Hepatobiliary events* (Table 24)
- *Convulsions* (Table 25)

The guidance indicates that risks for inclusion in the RMP are likely to impact the risk benefit balance and require pharmacovigilance investigation and/or risk minimisation beyond routine activities.

Table 23. Important Identified Risk: Anaphylaxis and Infusion-Associated Reactions (IARs)

Potential mechanisms	The symptoms are suggestive of a histamine-type of reaction. Plasma histamine levels were evaluated in Study XBAE, however, and there was no clear association between the observed AEs and histamine levels.
Evidence source and strength of evidence	Clinical studies. Reports of anaphylaxis and infusion-associated reactions have been received in the post-marketing setting.
Characterisation of the risk	**Clinical** **Adult Studies:** see Annex 7 (unchanged since last RMP 12.1). **Paediatric studies:** VER002-12 and A8851008. Frequency/Seriousness/Outcomes/Severity In study VER002-12 review of all AE terms of interest identified one 16-year-old male subject with a treatment-related IAR. This subject received low-dosage anidulafungin (1.5 mg/kg loading dose on Day 1 followed by a 0.75 mg/kg daily maintenance dose) and experienced transient flushing (moderate facial erythema and rash) during one infusion. His symptoms resolved with slowing of the infusion rate and no recurrences were observed with the remaining 10 infusions.

Table 23. Important Identified Risk: Anaphylaxis and Infusion-Associated Reactions (IARs)

	No cases of anaphylaxis were reported in study VER002-12. Based on the wide search criteria, adverse event terms in the anaphylaxis SMQ were reported in 1 patient with mild urticaria, drug-induced and 2 patients with mild AEs of urticarial NOS, 1 patient with mild facial oedema, and 2 patients with mild dizziness; all of these events resolved. Additionally, 1 patient was reported to have an AE of moderate hypotension that had on onset post-therapy but was considered possibly related to study-treatment; this event resolved. The above treatment-related AEs reported in study VER002-12 were all mild to moderate in severity and each (facial erythema, rash, hypotension) was reported in 1 of 24 (4.2%) of patients. None of these events were reported as serious adverse events. In study A8851008 following review of these reported events, there were no confirmed cases of anaphylaxis reported for anidulafungin-treated subjects. With regard to IAR, 1 subject experienced an event of moderate generalised pruritus which led to permanent discontinuation of study drug and 1 subject was reported to have mild periorbital oedema that was considered to be related to anidulafungin and resolved; neither of these two events were reported as serious adverse events. The frequency, seriousness, outcome and the severity of PTs of interest are provided in Annex 7 (see Tables 27, 28, 29). **Data from safety database** Cumulative Safety Database Experience (non-CT Cases) In the post-marketing experience, since first approval and through 15 October 2018, 1127 cases were received by the MAH: 136 cases included 222 anaphylaxis and IAR events, corresponding to a 12.1% proportional reporting rate. Included in these 136 cases there were 21 cases for anaphylactic reaction/anaphylactic shock, corresponding to a 1.9% proportional reporting rate. Among these 136 cases, 6 involved paediatric patients with age range between 7 months and 16 years. Anaphylactic shock and Rash were the most frequently reported AEs (2 each). The remaining AEs were Tachypnoea, Dyspnoea, Cyanosis, Bronchospasm and Angioedema. All these events were assessed as serious except for Rash. Of the 222 post-marketing (non-CT) events, 123 (55.4%) were serious. Clinical outcomes were reported as fatal (10), resolved/resolving (152 events), not resolved (11), or unknown (51). The seriousness and clinical outcome of these events, by PT are presented in Annex 7, Table 42. Cumulative Safety Database Experience (CT Cases) In the cumulative period through 15 October 2018, a total of 897 CT cases have been received by the MAH: 192 of these cases contained 217 events matching the anaphylaxis/IAR-search strategy. None of these cases reported anaphylactic reaction or anaphylactic shock.

Table 23. Important Identified Risk: Anaphylaxis and Infusion-Associated Reactions (IARs)

	All of the 217 events from cumulative CT cases were considered SAEs, regardless of whether or not related to anidulafungin. Clinical outcomes were reported as fatal (102), resolved/resolving (52 events), resolved with sequelae (5), not resolved (20), or unknown (38). The clinical outcome of these events is presented by PT in the Annex 7, Table 43. **Background incidence/prevalence** Background incidence/prevalence/mortality data for infusion-related or anaphylactic reactions are available for patients exposed to other echinocandins. Prescribing information for caspofungin indicates that anaphylaxis and possible histamine-mediated symptoms (ie, rash, facial swelling, angioedema, pruritus, sensation of warmth, or bronchospasm) have been reported during administration. Based on randomised CT data, the caspofungin prescribing information document also reported a 20% incidence of caspofungin infusion-related reactions (defined as pyrexia, chills, flushing, hypotension, hypertension, tachycardia, dyspnoea, tachypnea, rash, or anaphylaxis) occurring during infusion or within one hour post-infusion.[92] The prescribing information for micafungin also includes a warning for hypersensitivity reactions (anaphylaxis and anaphylactoid reactions [shock]) and describes possible histamine-mediated symptoms including rash, facial swelling, pruritus and vasodilatation. In a randomised CT for prophylaxis of *Candida* infections in haematopoietic stem cell transplant recipients, the incidence of skin rash (25.9%), pruritus (17.6%), erythema (11.3%), and flushing (11.1%) were reported among micafungin-treated patients. Another randomised study for OC reported an incidence of rash of 5.4% for micafungin-treated patients.[93] Clinical studies were also identified in the literature to characterise the background incidence of infusion-related reactions for other echinocandins. In a randomised trial of patients with candidaemia and other *Candida* infections, the incidence of infusion-related AEs for caspofungin-treated patients was 20.2%.[93] Studies which reported infusion-related mortality estimates for patients treated with other echinocandins were not found.
Risk factors and risk groups	Based on data from a Phase 1 study (XBAE), the symptoms of an IAR occur within minutes of the start of anidulafungin infusion, are transient and resolve without treatment. These characteristics are consistent with non-clinical data. The symptoms appear to be mainly associated with infusion rates >1.6 mg/min. No new risk groups or risk factors have been identified on the basis of available post-marketing data.
Preventability	The rate and concentration of the anidulafungin infusion were reduced for subsequent groups in study XBAE and the slower infusion rate significantly reduced or eliminated the infusion-related AEs. Subsequent to the results of study XBAE, anidulafungin infusion in the clinical programme was kept at rates of 1.11 to 1.16 mg/min and concentrations of 0.5 mg/mL. Based on the low rate of IARs, the careful adjustment of the rate of infusion appears to minimise, if not completely prevent, the occurrence of reactions.
Impact on the risk-benefit balance of the product	Patients may experience symptoms of flushing, shortness of breath, coughing, swollen face, hot feeling spreading to the face, feeling hot and sweaty or symptoms related to anaphylactic reactions or infusion-related reactions and these reactions may be life-threatening.

Table 23. Important Identified Risk: Anaphylaxis and Infusion-Associated Reactions (IARs)

Public health impact	Patients who are treated with anidulafungin are generally severely ill, hospitalised patients. While anaphylaxis can be life-threatening, the potential impact of this risk on public health is expected to be low because these patients are under continual care and health care professionals have been instructed not to exceed the maximum rate of infusion.
MedDRA terms	**SMQ (Broad and narrow)**: Anaphylactic reaction, Angioedema **Preferred Term(s):** PT: Chills; Dizziness; Feeling hot; Hot flush; Hyperhidrosis; Infusion related reaction

AE = Adverse Event; CT = Clinical Trial; IAR = Infusion-Associated Reaction; MAH = Marketing Authorisation Holder; MedDRA = Medical Dictionary for Regulatory Activities; NOS = Not otherwise specified; OC = Oesophageal Candidiasis; PT = Preferred Term; SAE = Serious Adverse Event; SMQ = Standardised MedDRA Query.

Table 24. Important Identified Risk: Hepatobiliary Events

Potential mechanisms	The mechanism for this risk is unknown.
Evidence source and strength of evidence	Clinical and non-clinical studies. Reports of hepatobiliary events have been received in the post-marketing setting.
Characterisation of the risk	**Clinical** **Adult Studies:** see Annex 7 (unchanged since last RMP 12.1). **Paediatric studies:** VER002-12 and A8851008. Frequency/Seriousness/Outcomes/Severity In study VER002-12, all causality AEs related to hepatobiliary events were reported in 2 patients with alanine aminotransferase increased and in the same 2 patients with aspartate aminotransferase increased; these all had an onset subsequent to completion of study treatment and were considered unrelated to study treatment. One event each of alanine aminotransferase increased and aspartate aminotransferase increased resolved, while the others remained ongoing. Additionally, 3 patients were reported to have an AE of liver function test abnormal, 1 of which had an onset subsequent to completion of study treatment. All 3 events were ongoing at the time of last study data collection**.** One patient was reported to have an AE of prothrombin time prolonged that was considered unrelated to study treatment. In study VER002-12, all reported events were mild or moderate in severity, with the exception of two events of aspartate aminotransferase increased and 1 event of alanine aminotransferase increased, which were reported as severe. For one patient, who had events of both aspartate aminotransferase increased and alanine aminotransferase increased, both of these events, which had an onset subsequent to completion of study drug treatment, were considered to be serious adverse events. The overall frequency for both alanine aminotransferase increased, and aspartate aminotransferase increased was 2/24 (8.3%) and for liver function test abnormal was 3/24 (12.5%). The event of prothrombin time prolonged occurred in 1/24 (4.2%) of subjects and was mild in severity.

Table 24. Important Identified Risk: Hepatobiliary Events

	In study A8851008, the majority of reported hepatobiliary events (11 of 14) were mild to moderate in severity (Annex 7, Table 32). The incidence proportion of hepatobiliary events was highest for the liver related investigations, signs and symptoms SMQ (17.6%) (Annex 7, Table 30). One event of transaminases increased was reported as a serious adverse event. Of a total of 14 reported events, 7 (50.0%) had outcome 'not resolved', 5 reported outcome 'resolved' and 2 'resolved with sequelae' (Annex 7, Table 31). The frequency, seriousness, outcome and the severity of PTs of interest are provided in Annex 7 (see Tables 30, 31, 32). **Data from safety database** Cumulative Safety Database Experience (non-CT Cases) In the post-marketing experience, since first approval and through 15 October 2018, a total of 1127 non-CT cases have been received by the MAH: 96 of these cases contain 119 hepatobiliary related events, corresponding to 8.5% proportional reporting rate. Of the 119 non-CT events, 79 (66.4%) were serious. Fifteen (15) of these events were fatal, 20 events had not resolved, 46 were resolved/resolving; for the remaining 38 events, the outcome was unknown. Among the 96 hepatobiliary cases there were 2 cases that involved 2 neonates reporting the events Blood bilirubin increased and Transaminases increased (the first case) and Liver function test abnormal (the second one). A third case involved a 2-year-old patient who developed Transaminases increased. All these events were serious and resolved/resolving. The seriousness and clinical outcome of these events, by PT, are presented in Annex 7, Table 44. Cumulative Safety Database Experience (CT Cases) In the cumulative CT experience through 15 October 2018, a total of 897 CT cases have been received by the MAH: 39 of these cases contain 44 hepatobiliary related events. All of the 44 hepatobiliary events from CTs were serious regardless of whether or not related to anidulafungin. Clinical outcomes were reported as fatal (10), resolved/resolving (3 events), resolved with sequelae (4), not resolved (17), or unknown (10). The clinical outcome of these events, by PT are presented in Annex 7, Table 45. **Background incidence/prevalence** Often it is extremely difficult to establish causality assessments in critically ill patients as hepatic injury is multifactorial. Although the incidence is unclear, risk of hepatotoxicity is elevated in persons likely to use systemic antifungal agents. In anidulafungin IC/C CTs, the prevalence of elevated hepatobiliary status (defined as either a baseline ALT or AST value greater than 3 × ULN or if the baseline AP is greater than 1.5 × ULN or if the baseline total bilirubin is greater than 1.5 × ULN) was approximately 35% (SCS Table 2-1).

Table 24. Important Identified Risk: Hepatobiliary Events

	No population-based (epidemiologic) studies were found to characterise the incidence of hepatic injury among patients with candidaemia or other forms of *Candida* infection not exposed to anidulafungin; however, data from clinical studies that reported either the baseline prevalence of liver failure or hepatic injury incidence estimates for patients treated with other echinocandins may be informative for risk contextualisation. In a retrospective study of 63 Dutch patients who were admitted to the ICU and subsequently diagnosed with IC (mean duration between ICU admission and echinocandin initiation was 2-3 days, depending on treatment group), 6.3% had liver failure upon ICU admission.[94] It is important to note that the background rate of liver failure for IC patients, in general, may be lower than that observed among ICU patients diagnosed with IC. The review of one hospital-based retrospective study and eleven clinical studies (including randomised CTs and open-label studies) found notable differences in study characteristics (ie, hepatic injury definitions, study region, echinocandin dose). With various hepatic laboratory measures used to define hepatic AEs, the cumulative incidence of treatment-related hepatic AEs from clinical studies ranged from 0.7% to –3.0% for micafungin[95,96] and 1.8% to 7.9% for caspofungin.[97,98] Findings from individual clinical studies are mostly consistent with a published meta-analysis of data from clinical studies of antifungal treatment for definitive infection and empiric use. Pooled cumulative incidence estimates of hepatic enzyme elevations not requiring treatment discontinuation (generally defined as any LFT abnormality or an elevation greater than 2 times the upper limit of normal in any LFT) were 3.0% for micafungin and 7.0% for caspofungin. For hepatic enzyme elevations requiring treatment discontinuation (generally defined as any LFT greater than 5 times the upper limit of normal), pooled incidence estimates were 2.7% for micafungin, and 0.2% for caspofungin.[99] No population-based (epidemiologic) studies were identified to characterise the mortality due to hepatic injury among patients with candidaemia or other forms of *Candida* infection (regardless of echinocandin exposure). To assess the risk of severe hepatotoxicity in hospitalised patients treated with echinocandins (anidulafungin, caspofungin, and micafungin), a retrospective observational cohort study (Post-Authorisation Safety Study - A8851030) was conducted using data obtained from 2 US-based hospital EMRs databases: Humedica and Cerner Health Facts. Relevant data included in these databases-Humedica and Cerner Health Facts - were pooled into a single dataset. Patients ≥18 years of age receiving ≥1 IV infusion of echinocandins during the hospitalisation were included in the study (N = 12678). The date of the treatment initiation was defined as the index date. The baseline period included the time between the hospital admission date and the index date, inclusive, and the observation period included the time from the index date until the earliest event of severe hepatotoxicity, hospital discharge or death. Patients were required to have LFT (ie, AST, ALT, total bilirubin) values both in the baseline and observation periods. LFTs were graded per modified CIT - TCAE in trials of adult pancreatic islet transplantation. Severe hepatotoxicity was defined as the first occurrence of a Grade ≥3 LFT in the observation period. The unadjusted absolute risk (ie, cumulative incidence) of severe hepatotoxicity was calculated as the number of patients with severe hepatotoxicity divided by the total number of patients exposed to each type of echinocandin.

Table 24. Important Identified Risk: Hepatobiliary Events

	The unadjusted incidence rate for each echinocandin group was calculated as the number of patients with severe hepatotoxicity divided by the total person-days of observation in that group and reported per 30 person-days. Adjusted absolute risk and incidence rate of severe hepatotoxicity in each echinocandin group were computed using regression-based indirect standardisation methodology. A total of 12678 eligible patients were identified (anidulafungin: 1700; caspofungin: 4431; micafungin: 6547), among whom 9161 patients had normal to moderately elevated LFT at baseline (anidulafungin: 1012; caspofungin: 3281; micafungin: 4868). At baseline, compared to patients receiving caspofungin and micafungin, more anidulafungin patients had more elevated LFT (proportion LFT Grade ≥3, 40.4% vs 25.9% and 25.6%), critical care admissions (75.3% vs 52.6% and 48.6%), surgeries (41.1% vs 33.7% and 27.1%), use of central venous catheters (43.8% vs 13.3% and 19.3%) and immunosuppressive drugs (14.6% vs 4.4% and 5.9%), and higher rates of comorbidities (eg, organ failures: 69.4% vs 46.7% and 51.5%; sepsis or septic shock: 68.5% vs 46.9% and 47.9%; CVD: 71.1% vs 42.1% and 49.8%; kidney disease: 40.2% vs 17.5% and 21.2%). All comparisons yielded p-values less than 0.05. The unadjusted absolute risk of severe hepatotoxicity was 37.2% (95% CI: 34.3-40.1), 22.4% (95% CI: 21.0-23.8), and 23.3% (95% CI: 22.1-24.4) in the anidulafungin, caspofungin and micafungin groups, respectively. After adjustment, the absolute risk of severe hepatotoxicity decreased to 25.7% (95% CI: 24.7-26.7) in the anidulafungin group and increased to 24.3% (95% CI: 23.4-25.2) and 24.8% (95% CI: 23.9-25.6) in the caspofungin and micafungin groups, respectively. A similar trend was observed in incidence rates after adjustment. The adjusted incidence rate of severe hepatotoxicity was 0.47 (95% CI: 0.44-0.51) in the anidulafungin group, 0.41 (95% CI: 0.38-0.44) in the caspofungin group, and 0.45 (95% CI: 0.43-0.48) in the micafungin group. Baseline clinical features found to be significantly associated with an increased probability of receiving anidulafungin vs caspofungin or micafungin, included higher grade of baseline bilirubin, use of extended-spectrum azoles, having ≥2 fungal infection sites, having critical care admission, using immunosuppressive therapy, using antiretroviral drugs known to have hepatotoxic effects, using a central venous catheter, and the presence of comorbid CVD, hypertension, kidney disease, endocarditis, sepsis or septic shock. Clinical features associated with decreased probability of receiving anidulafungin vs caspofungin or micafungin included emergency admission to the index hospitalisation, use of antibiotics known to have hepatotoxic events and the presence of comorbid gastro-oesophageal reflux disease. Based on real world hospital practice data, the majority of the study analyses showed that adjusted relative risk and incidence rate ratio estimates were not statistically different from 1, suggesting that anidulafungin was not associated with a statistically significantly higher absolute risk or incidence rate for severe hepatotoxicity, as compared to caspofungin and micafungin. It is important to note that the baseline data demonstrated the channelling of anidulafungin treatment towards patients with impaired liver function and higher mortality prognosis based on comorbidity profiles; this is especially notable among patients with Grade 5 hepatotoxicity events. This confounding by indication bias is well-known in epidemiology literature and adjustment is methodologically challenging. Attempts to control for differences in the severity profile of patients in the current study were limited to the information available in the databases. Thus, residual confounding due to unobserved factors is possible.

Table 24. Important Identified Risk: Hepatobiliary Events

	In subgroup analyses on patients with normal or mildly/moderately elevated LFT at baseline (Grades 0-2), which used restriction as a method to homogenise the baseline LFT risk across the treatment groups, no evidence was found to indicate significant differences in the risk of severe hepatotoxicity between patients treated with anidulafungin and patients treated with caspofungin or micafungin. This study was also presented at the 2016 International Society of Pharmacoepidemiology annual conference.[100]
Risk factors and risk groups	Based on non-clinical and Phase 1 data, anidulafungin may have the potential to cause elevations in hepatobiliary laboratory parameters indicative of hepatic damage or dysfunction. Data from Phase 2/3 is less clear and the serious underlying illnesses in the target population may obscure the aetiology of any observed changes in hepatobiliary tests that might be related to anidulafungin. No new risk groups or risk factors have been identified on the basis of available post-marketing data. Hepatic effects associated with anidulafungin do not appear to occur within a specific subpopulation or in patients with specific risk factors; they occur sporadically. Patients with invasive *Candida* infections are at risk of hepatotoxicity due to underlying illness or concomitant medications (eg, parenteral nutrition, analgesics). Persons with HIV are at increased risk of hepatotoxicity due to viral hepatitis co-infection. Patients with diabetes are at increased risk of liver injury to the high burden of non-alcoholic fatty liver disease. Impaired hepatic functioning among those with cancer is elevated and can be the result of tumour metastasis, chemotherapy, infectious disease, or various anti-infective agents. In some patients with serious underlying medical conditions who were receiving multiple concomitant medicines along with anidulafungin, clinically significant hepatic abnormalities have occurred.
Preventability	Patients who develop abnormal LFTs during anidulafungin therapy should be monitored for evidence of worsening hepatic function and evaluated for risk/benefit of continuing anidulafungin therapy.
Impact on the risk-benefit balance of the product	Because patients treated with anidulafungin may develop liver problems during treatment, liver function should be monitored in patients being administered anidulafungin. Given that these patients are generally severely ill and hospitalised, these events can be monitored, and, in most cases, these events are mild or moderate in severity.
Public health impact	Patients who are treated with anidulafungin are generally severely ill, hospitalised patients. The potential impact of the risk of hepatobiliary events on public health is expected to be low because these patients are under continual care. These events are generally mild to moderate in severity and health care professionals have been informed of the need for monitoring of liver function in the SmPC under Special Warnings and Precautions for Use.

Table 24. Important Identified Risk: Hepatobiliary Events

MedDRA terms	**SMQ (Broad and Narrow)**: Cholestasis and jaundice of hepatic origin (SMQ); Hepatic failure, fibrosis and cirrhosis and other liver damage-related conditions (SMQ); Hepatitis, non-infectious (SMQ); Liver infections (SMQ); Liver related investigations, signs and symptoms (SMQ); Liver-related coagulation and bleeding disturbances (SMQ). **Preferred Term(s):** PT: Bilirubinuria; Cholestasis of pregnancy; Hepatitis neonatal; Hyperbilirubinaemia neonatal; Jaundice acholuric; Jaundice extrahepatic obstructive; Jaundice neonatal; Liver transplant rejection; Neonatal cholestasis.

AE = Adverse Event; ALT = Alanine Aminotransferase; AP = Alkaline Phosphatase; AST = Aspartate Aminotransferase; CI = Confidence Interval; CIT-TCAE = Clinical Islet Transplantation study-Terminology Criteria for Adverse Events; CT = Clinical Trial; CVD = Cardiovascular Disease; EMR = Electronic Medical Record; HIV = Human Immunodeficiency Virus; IC = Invasive Candidiasis; IC/C = Invasive Candidiasis/Candidaemia; ICU = Intensive Care Unit; IV = Intravenous; LFT = Liver Function Test; MAH = Marketing Authorisation Holder; MedDRA = Medical Dictionary for Regulatory Activities; PT = Preferred Term; RMP = Risk management Plan; SmPC = Summary of Product Characteristics; SMQ = Standardised MedDRA Query; ULN = Upper Limit of Normal.

Table 25. Important Identified Risk: Convulsions

Potential mechanisms	A potential mechanism for convulsions has not been identified.
Evidence source and strength of evidence	Clinical studies. Reports of convulsions have been received in the post-marketing setting.
Characterisation of the risk	**Clinical** **Adult Studies:** see Annex 7 (unchanged since last RMP 12.1). **Paediatric studies:** VER002-12 and A8851008. Frequency/Seriousness/Outcomes/Severity In study VER002-12, one patient (4.2%) was reported to have an event of convulsions NOS, which was reported as severe, but had an onset subsequent to the completion of anidulafungin treatment and was not considered to be related to anidulafungin; this event resolved. No events in study VER002-12 were reported as serious adverse events. In study A8851008, 3 (4.4%) subjects reported events of convulsion. All 3 subjects had a pre-existing history of seizures and all of these events were considered by the Investigator as unrelated to anidulafungin. One of the events was reported as a serious adverse event and all 3 events resolved. The frequency, seriousness, outcome and the severity of PTs of interest are provided in Annex 7 (see Tables 33, 34, 35).

Table 25. Important Identified Risk: Convulsions

	Data from safety database Cumulative Safety Database Experience (non-CT Cases): In the post-marketing experience, since first approval and through 15 October 2018, a total of 1127 non-CT cases were received by the MAH: 17 of these cases contain 18 events of interest, corresponding to a 1.5% proportional reporting rate. All of the 18 events from non-CT cases were considered serious and there were no paediatric patients involved. Seizure was the most commonly reported event. The clinical outcomes of convulsion related events, by PT are presented in Annex 7, Table 46. There were no fatal cases reported. Cumulative Safety Database Experience (CT Cases) In the cumulative CT experience through 15 October 2018, a total of 897 CT cases have been received by the MAH: 23 of these cases contain 23 convulsion related events. All of the 23 convulsion events from CT cases were considered serious regardless of whether or not related to anidulafungin. Clinical outcomes by PT are summarised in Annex 7, Table 47. **Background incidence/prevalence** The estimated incidence of clinically-recognised seizures in the general ICU is 3.3% over the course of a patient's stay.[101] However, incidence estimates are sensitive to the detection method; studies using continuous electroencephalogram detect many more non-convulsive seizures than ones using other techniques.[102] Using this method, the estimated seizure incidence is nearly 20% among critically ill patients, with greater than 90% of these being non-convulsive.[103] According to a review of the medical causes of seizure, seizures are commonly encountered in patients who do not have a history of epilepsy but have predisposing comorbidities.[104] For example, organ failure, electrolyte imbalance, cancer, systemic disease affecting the nervous system, ischaemic-hypoxic events, metabolic derangements, infection, medication and medication withdrawal, and hypersensitive encephalopathy may lead to the first occurrence of a seizure in a patient. New onset seizures are sequelae of neurological deterioration associated with HIV. Although the incidence is unclear, some experts suggest that seizures occur two to three times more often among those with HIV compared to the general population.[105] Organ transplant recipients are similarly at increased risk of seizures. In a study of liver transplant patients, 5.4% of participants developed seizures in the post-transplant hospital stay.[106] Seizures are a significant concern among patients with cancer especially for brain tumours, which directly increase the risk of seizures.[107] Moreover, cancer patients are often treated with neurotoxic chemotherapy and adjunct anti-infective drugs that increase seizure risk.[108,109] No population-based (epidemiologic) studies were found to characterise the prevalence or incidence of convulsions among patients with candidaemia or other forms of *Candida* infection not exposed to anidulafungin.

Table 25. Important Identified Risk: Convulsions

	Convulsions have been documented in association with other echinocandins. Convulsions have been reported (< 0.5%) during CTs with micafungin[93] and caspofungin. [92] No epidemiologic or clinical studies were found to characterise the mortality associated with seizures among patient populations with candidaemia or other forms of *Candida* infection (regardless of echinocandin exposure).
Risk factors and risk groups	There is no clear evidence that anidulafungin is causally related to the risk of convulsions in the IC/C population studied. Defined groups at risk or risk factors are described in Section 'Background incidence/prevalence' above.
Preventability	Preventability lays in treatment of underlying seizurogenic conditions in seriously ill patients.
Impact on the risk-benefit balance of the product	These events may be serious.
Public health impact	Patients who are treated with anidulafungin are generally severely ill, hospitalised patients. The potential impact of the risk of convulsions on public health is expected to be low because the incidence of convulsive episodes is low and are seen with underlying conditions in patients being treated.
MedDRA terms	**SMQ (Broad and narrow):** Convulsions SMQ.

CI = Confidence Interval; CT = Clinical Trial; HIV = Human Immunodeficiency Virus; IC/C = Invasive Candidiasis/Candidaemia; ICU = Intensive Care Unit; MAH = Marketing Authorisation Holder; MedDRA = Medical Dictionary for Regulatory Activities; PT = Preferred Term; SAE = Serious Adverse Event; SMQ = Standardised MedDRA Query.

Important Potential Risks:

The following important potential risks are reclassified as "not important" according to the guidance for determination of risks appropriate for inclusion in the RMP as described in GVP Module V (Rev.2) and accompanying RMP template Rev 2.0.1:

- *Exacerbation of infusion-associated reactions by anaesthetics* (Table 26)
- *QT prolongation/Torsade de Pointes* (Table 27)

The following safety concern is added as an important potential risk according to the guidance for determination of risks appropriate for inclusion in the RMP as described in GVP Module V (Rev.2) and accompanying RMP template Rev 2.0.1:

- *Hepatic impairment and other serious toxicities in neonates < 1 month of age* (Table 28)

Table 26. Important Potential Risk: Exacerbation of Infusion-associated Reactions by Anaesthetics

Potential mechanisms	A potential mechanism for this risk has not been identified.
Evidence source and strength of evidence	Clinical and non-clinical studies. Reports of exacerbation of infusion-associated reactions by anaesthetics have not been received in the post-marketing setting.
Characterisation of the risk	**Clinical** **Adult Studies:** see Annex 7 (unchanged since last RMP 12.1). **Paediatric studies:** VER002-12 and A8851008. Frequency/Seriousness/Outcomes/Severity There were no events of exacerbation of an infusion-associated reported reaction by anaesthetic reported in study VER002-12. In study A8851008, based on the wide search criteria, adverse events related to potential anaesthetic exacerbation of IAR were identified as summarized in Annex 7. Review of these events did not identify any confirmed cases of anaesthetic exacerbation of IAR. The frequency, seriousness, outcome and the severity of relevant PTs are provided in Annex 7 (see Tables 36, 37, 38). **Data from safety database** Cumulative Safety Database Experience (CT Cases and non-CT Cases) Among all cases reporting IARs, none reported the administration of an anaesthetic as co-suspect medication. When concomitant administration of anaesthetic was reported (eg. barbiturates, benzodiazepine, propofol, fentanyl, lidocaine and ketamine), the implication of these drugs in the clinical manifestations of IARs was not clarified. **Background incidence/prevalence** Data on the background incidence/prevalence/mortality of anaesthetic exacerbation of infusion-associated reactions among patients with candidaemia or other forms of Candida infection (regardless of echinocandin exposure) were not found.
Risk factors and risk groups	Although the clinical relevance of this finding in rats is unknown and there are no known risk groups or factors for this risk. Any patient experiencing an IAR and receiving concurrent anaesthesia might be at risk.

Table 26. Important Potential Risk: Exacerbation of Infusion-associated Reactions by Anaesthetics

Preventability	The rate of IARs in patients is very low therefore the opportunity for an exacerbation of such a reaction is correspondingly low. While the animal data suggests that consequences could be severe, common medical practice would tend to protect against the occurrence of an infusion reaction exacerbation: • Administration of an IV infusion that was not directly needed for the induction or maintenance of anaesthesia simultaneously with a general anaesthetic would generally be avoided. • A patient who experienced an IAR during an anidulafungin administration would likely not be administered general anaesthesia until the reaction had clearly abated. • Placement of an endotracheal tube during anaesthesia would provide protection against occlusion of the airway by oedema, the event believed to be responsible for the rat deaths. • Patients administered anidulafungin are generally critically ill and in a closely supervised hospital setting. If an exacerbation of an infusion reaction occurred, medical intervention would be readily available.
Impact on the risk-benefit balance of the product	See Table 23.
Public health impact	Patients who are treated with anidulafungin are generally severely ill, hospitalised patients. While anaphylaxis can be life-threatening, the potential impact of this risk on public health is expected to be low because these patients are under continual care and health care professionals have been instructed not to exceed the maximum rate of infusion.
MedDRA terms	**SMQ (Broad and narrow)**: Anaphylactic reaction, Angioedema **Preferred Term(s):** PTs: Chills, Dizziness, Feeling hot, Hot flush, Hyperhidrosis, Infusion related reaction and concomitant use of anaesthetics.

CT = Clinical Trial; IAR = Infusion-Associated Reaction; MedDRA = Medical Dictionary for Regulatory Activities; PT = Preferred Term; SMQ = Standardised MedDRA Query.

Table 27. Important Potential Risk: QT prolongation /Torsade de Pointes

Potential mechanisms	Non-clinical data do not provide any insight into any potential mechanism for QT prolongation or torsade de pointes associated with anidulafungin treatment and there is no clear evidence that anidulafungin has any significant potential to prolong QT interval or to contribute to risk for torsade de pointes.
Evidence source and strength of evidence	Non-clinical studies. Reports of QT prolongation/Torsades de Pointes have been received in the post-marketing setting.

Characterisation of the risk	There were no instances of torsade de pointes or confirmed QT prolongation in the anidulafungin development programme. **Clinical** **Adult Studies:** see Annex 7 (unchanged since last RMP 12.1). **Paediatric studies:** VER002-12 and A8851008. Frequency/Seriousness/Outcomes/Severity There were no events of exacerbation of QTc prolongation/Torsades de Pointes reported in study VER002-12. In study A8851008, overall, there were no confirmed cases of QTc-prolongation or Torsades de Pointes reported. One non-serious event of loss of consciousness (moderate in severity) was identified based on the wide search criteria for the risk of QT prolongation/Torsade de Pointes; however, review of this case did not identify any association with QTc prolongation / Torsades de Pointes and anidulafungin. The frequency, seriousness, outcome and the severity of relevant PTs are provided in Annex 7 (see Tables 39, 40, 41). **Data from safety database[8]** Cumulative Safety Database Experience (non-CT Cases): In the post-marketing experience, since first approval and through 15 October 2018, a total of 1127 non-CT cases have been received by the MAH: 19 of these cases contain 19 QT prolongation/Torsade de Pointes SMQ related events, corresponding to a 1.7% proportional reporting rate. All of the 19 events from non-CT cases were considered serious. There were no paediatric patients involved. Clinical outcomes by preferred term are shown in Annex 7, Table 48. Cumulative Safety Database Experience (CT Cases) In the cumulative CT experience through 15 October 2018, a total of 897 cases have been received by the MAH: 93 of these cases contain 97 QT prolongation/Torsade de Pointes SMQ terms. All of the 97 events from CT cases were considered serious regardless of whether or not related to anidulafungin. Clinical outcomes by PT are summarised in Annex 7, Table 49. **Background incidence/prevalence** Patients treated with anidulafungin often are seriously ill with multiple confounding risk factors, such as structural heart disease, electrolyte abnormalities and concomitant medications that may contribute to the development of various cardiac arrhythmias. Published data on the background incidence, prevalence or mortality of QT prolongation or torsade de pointes in patients with candidaemia or other forms of *Candida* infection (regardless of echinocandin exposure) were not found.

Table 27. Important Potential Risk: QT prolongation /Torsade de Pointes

Risk factors and risk groups	There are no clinical or non-clinical data that indicate that anidulafungin has any significant potential to prolong QT interval or to contribute to risk for torsade de pointes.
Preventability	Preventability lies in treatment of underlying comorbidities that may predispose the patient to cardiac arrhythmia.
Impact on the risk-benefit balance of the product	Although QT prolongation or torsade de pointes have not been confirmed to be associated with anidulafungin, patients may develop arrhythmias or cardiac events which may be fatal.
Public health impact	Patients who are treated with anidulafungin are generally severely ill, hospitalised patients. While patients may develop events related to QT prolongation or torsade de pointes (eg, arrhythmias or cardiac events) which may be fatal, the potential impact on public health for this potential risk is expected to be low because no causal relationship between anidulafungin and QT prolongation or torsade de pointes has been confirmed.
MedDRA terms	**SMQ (Broad and narrow)**: Torsade de Pointes/QT prolongation SMQ.

CT = Clinical Trial; MAH = Marketing Authorisation Holder; MedDRA = Medical Dictionary for Regulatory Activities; PT = Preferred Term; SMQ = Standardised MedDRA Query.

[8] The increase of the number of CT and non -CT cases is due to a new PT (Multiple organ dysfunction syndrome) added in the SMQ for QT prolongation that was added at the time of MedDRA version 21.0

Table 28. Important Potential Risk: Hepatic impairment and other serious toxicities in neonates (< 1 month of age)

Potential mechanisms	Treating neonates requires consideration for coverage of disseminated candidiasis including CNS involvement. Nonclinical infection models indicate that higher doses of anidulafungin are needed to achieve adequate CNS penetration, resulting in higher doses of Polysorbate 80 (PS80), a formulation excipient. High doses of PS80 have been associated with potentially life-threatening toxicities in neonates.
Evidence source and strength of evidence	*Candida* meningitis is a serious life-threatening consequence of *Candida* infection in neonates and is associated with high morbidity (i.e., neurologic sequelae) and mortality. In neonates with invasive candidiasis, it has been estimated that 15-20% of cases may have CNS involvement.[110] Owing to the difficulty in rapidly diagnosing CNS infection, neonates with invasive candidiasis are often presumed to have CNS involvement unless proven otherwise. Therefore, when treating neonates with invasive candidiasis, it is often necessary to select an antifungal agent known to have adequate CNS penetration and activity. PS80 is a solubilizing agent used in the current anidulafungin formulation. As described in literature, clinical[110] and non-clinical studies[111, 112, 113] suggest that an approximately 3-fold higher dose than the standard dose of anidulafungin may be needed to achieve the target exposure to treat neonatal candidiasis with CNS involvement. Based on the available data there are concerns regarding the potential risk of hepatic- related adverse events and other possible unknown toxicities resulting from the administration of higher doses of PS80.[114]
Characterisation of the risk	**Clinical** Not applicable: neonates (<1 month) were excluded from the clinical program. **Data from safety database** Cumulative Safety Database Experience (non-CT Cases): In the post-marketing experience through 15 October 2018, a total of 1127 non-CT cases have been received by the MAH: 2 of these cases (0.2% of total non-CT cases) include hepatic events in neonates and both of them were assessed as serious. One case involved a neonate patient who received anidulafungin at an unknown dosage for *Candida* infection and experienced on an unknown date the events of interest Transaminases increased and Blood bilirubin increased (clinical outcome: resolved for both the AEs). The second serious case involved a premature male neonate (32 week of pregnancy) with systemic *Candida*, who experienced Liver function test abnormal during treatment with anidulafungin (1.5 mg/kg/day, iv) administered for 3 weeks and amphotericin B (co-suspect); On the 10th day of treatment with anidulafungin blood cultures were negative and clinical and laboratory workup of the neonate improved. Clinical outcomes by preferred term are shown in Annex 7, Table 50. Cumulative Safety Database Experience (CT Cases): There were no relevant cases.
Risk factors and risk groups	Treating neonates requires consideration for coverage of disseminated candidiasis including CNS; nonclinical infection models indicate that higher doses of anidulafungin are needed to achieve adequate CNS penetration, resulting in higher doses of PS80. Given the potential risk of hepatotoxicity associated with polysorbate 80 when an increased amount is used in neonates, there is a theoretical risk of additive or synergistic hepatic effects in neonates when exposed to anidulafungin and polysorbate 80 at higher doses.

Table 28. Important Potential Risk: Hepatic impairment and other serious toxicities in neonates (< 1 month of age)

Preventability	Treating neonates < 1 month of age with anidulafungin is not recommended.
Impact on the risk-benefit balance of the product	In the neonate age-group, the impact on the risk-benefit balance could be significant. Neonatal exposure to an increased amount of polysorbate 80 in addition to an increased dose of anidulafungin could result in potentially life-threatening toxicities. The proposed label includes a warning about the treatment with anidulafungin in neonates (<1-month-old).
Public health impact	The public health impact is expected to be low as use of anidulafungin in this patient population is not recommended.
MedDRA terms	SMQ (Broad and narrow): Hepatic disorders AND neonates (<1 month of age)

AE = Adverse Event; CNS = Central Nervous system; CT = Clinical Trial; MAH = Marketing Authorisation Holder; MedDRA = Medical Dictionary for Regulatory Activities; PS80 = polysorbate 80; SMQ = Standardised MedDRA Query.

SVII.3.2. Presentation of the Missing Information

The following missing information is removed from the RMP:

- Children/Adolescents
- Elderly
- Pregnant women
- Resistance

Module SVIII. Summary of the Safety Concerns

A summary of the important identified and potential risks and missing information is provided in Table 29.

Table 29. Summary of Safety Concerns

Important identified risks	None
Important potential risks	Hepatic impairment and other serious toxicities in neonates < 1 month of age
Missing information	None

PART III. PHARMACOVIGILANCE PLAN (INCLUDING POST-AUTHORISATION SAFETY STUDIES)

III.1. Routine Pharmacovigilance Activities

Changes in the pharmacovigilance (PV) activities for the safety concerns in the previous RMP (version 12.1 dated 19 October 2017) and listed below are not planned in spite of the MAH's changes to the safety concerns included in the RMP.

In relation to the proposed extended indication of Ecalta in paediatric patients the MAH will perform targeted monthly signal detection activities of paediatric data, for the first 2 years.

Routine pharmacovigilance activities beyond ADRs reporting and signal detection:

Specific adverse reaction follow-up questionnaires for safety concerns:

The MAH has developed a Data Capture Aid for Infusion Associated Reaction, Seizure, Hepatic Events and Lack of Efficacy Events (DCA attached as Appendix 4) which is used by Pfizer to inform follow-up attempts aimed at obtaining relevant information from reporters.

Other forms of routine pharmacovigilance activities for safety concerns:

Not Applicable.

III.2. Additional Pharmacovigilance Activities

There are no category 1–2 studies for Ecalta.

The category 3 Study A8851008 to evaluate anidulafungin for the treatment of IC/C in paediatric patients 1 month to <18 years was completed since the last RMP submission. A population PK/PD analysis, incorporating data from this study as well as two adult studies (A8851019 and A8851011), has also been completed and will be submitted to fulfil FUM 018.

Study A8851008: COMPLETED

Study Title: A Prospective, Open-Label Study to Assess the Pharmacokinetics, Safety and Efficacy of Anidulafungin when used to Treat Children with Invasive Candidiasis, including Candidemia

Rationale and Study Objectives: The primary objective was to assess safety and tolerability of anidulafungin in children treated for IC/C. Secondary objectives included assessment of efficacy (as measured by global response), and PK parameters of anidulafungin and polysorbate 80.

Study design: Phase 3b, open-label, non-comparative

Study population: Paediatric patients 1 month to <18 years

Milestones: CSR completed September 2018

Conclusions:

- Data from this study support the use of anidulafungin as a treatment option for ICC in children aged 1 month to <18 years at the studied dose (3.0 mg/kg loading dose followed by 1.5 mg/kg maintenance dose daily thereafter).
- Overall, the AEs reported were in line with the known safety profile of anidulafungin or the pattern of events expected for the patient population.
- No new safety concerns were identified for anidulafungin.
- The observed global response rates in this paediatric population were generally consistent with those observed in the adult studies.
- Results of polysorbate 80 measurements along with the safety profile from the study supports use of the current formulation of anidulafungin across all age groups.

III.3. Summary Table of Additional Pharmacovigilance Activities

There are no on-going and planned category 1-2 studies for Ecalta. Study A8851008 has been completed since last RMP submission. There are no planned category 3 studies.

PART IV. PLANS FOR POST-AUTHORISATION EFFICACY STUDIES

IV.1. Applicability of Efficacy to all Patients in the Target Population

IV.2. Post-Authorisation Efficacy Studies

There are no post-authorization efficacy studies (PAES) that are a specific obligation by the competent authorities and/or condition of the MA.

PART V. RISK MINIMISATION MEASURES (INCLUDING EVALUATION OF THE EFFECTIVENESS OF RISK MINIMISATION ACTIVITIES)

V.1. Routine Risk Minimisation Measures

The Product information and labelling (SmPC) submitted within this application is updated based on the data from Study A8851008 and is expected to be sufficient for risk minimisation for all safety concerns.

Communication in the SmPC pertaining to the safety concerns that the MAH recategorised will not be changed or removed. The safety concerns that the MAH reclassifed are displayed in strikethrough text. New safety concerns are in italic font.

Table 30. Description of routine risk minimisation measures by safety concern

Safety Concern	Routine risk minimisation activities
Important Identified Risks:	
~~Anaphylaxis and IARs~~	~~SmPC Section 4.2 Posology and method of administration~~ ~~SmPC Section 4.4 Special warnings and precautions for use~~ ~~SmPC Section 4.8 Undesirable effects~~ ~~Section 6.6. Special precautions for disposal and other handling~~
~~Hepatobiliary AEs~~	~~SmPC Section 4.4 Special warnings and precautions for use~~ ~~SmPC Section 4.8 Undesirable effects~~
~~Convulsions~~	~~SmPC Section 4.8 Undesirable effects~~
Important Potential Risks:	
~~Exacerbation of IARs by anaesthetic.~~	~~SmPC Section 4.4 Special warnings and precautions for use~~
~~QT Prolongation/Torsade de Pointes~~	~~None~~
Hepatic impairment and other serious toxicities in neonates < 1 month of age	SmPC Section 4.4 Special warnings and precautions for use
Missing Information	
~~Children and Adolescents~~	~~SmPC Section 4.2 Posology and method of administration~~ ~~SmPC Section 5.2 Pharmacokinetic properties~~
~~Pregnant women~~	~~SmPC Section 4.6 Fertility, pregnancy and lactation~~ ~~SmPC Section 5.3 Preclinical safety data~~
~~Elderly~~	~~SmPC Section 4.2 Posology and method of administration~~ ~~SmPC Section 5.2 Pharmacokinetic properties~~

Table 30. Description of routine risk minimisation measures by safety concern

Safety Concern	Routine risk minimisation activities
~~Resistance~~	~~SmPC Section 5.1 Pharmacodynamic properties~~

AE = Adverse Event; IAR = Infusion-Associated Reaction; SmPC = Summary of Product Characteristics.

V.2. Additional Risk Minimisation Measures

Routine risk minimisation activities as described in V.1 are sufficient to manage the safety concerns of Ecalta. No additional risk minimisation measures are proposed.

V.3. Summary of Risk Minimisation Measures

The safety concerns that the MAH reclassified are displayed in strikethrough text. New safety concerns are in italic font.

Table 31. Summary of the Risk Minimisation Measures by Safety Concern

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Important Identified Risks:		
~~Anaphylaxis and IARs~~	~~Routine risk communication:~~ ~~SmPC Section 4.2 Posology and method of administration~~ ~~SmPC Section 4.4 Special warnings and precautions for use~~ ~~SmPC Section 4.8 Undesirable effects~~ ~~Section 6.6. Special precautions for disposal and other handling~~	~~Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection.~~ ~~IARs follow-up form~~
~~Hepatobiliary AEs~~	~~Routine risk communication:~~ ~~SmPC Section 4.4 Special warnings and precautions for use~~ ~~SmPC Section 4.8 Undesirable effects~~	~~Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection.~~ ~~Hepatic events follow-up form~~
~~Convulsions~~	~~Routine risk communication:~~ ~~SmPC Section 4.8 Undesirable effects~~	~~Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection.~~ ~~Seizure events follow-up form~~
Important Potential Risks:		

Table 31. Summary of the Risk Minimisation Measures by Safety Concern

Safety concern	Risk minimisation measures	Pharmacovigilance activities
~~Exacerbation of IARs by anaesthetic~~	~~Routine risk communication:~~ ~~SmPC Section 4.4 Special warnings and precautions for use~~	~~Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection.~~ ~~IARs follow-up form~~
~~QT Prolongation / Torsade de Pointes~~	~~Not Applicable~~	~~Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection.~~
Hepatic impairment and other serious toxicities in neonates < 1 month of age	Routine risk communication: SmPC Section 4.4 Special warnings and precautions for use	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Hepatic events follow-up form
Missing Information		
~~Children and Adolescents~~	~~Routine risk communication:~~ ~~SmPC Section 4.2 Posology and method of administration~~ ~~SmPC Section 5.2 Pharmacokinetic properties~~	~~Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection.~~
~~Pregnant women~~	~~Routine risk communication:~~ ~~SmPC Section 4.6 Fertility, pregnancy and lactation~~ ~~SmPC Section 5.3 Preclinical safety data~~	~~Routine pharmacovigilance activities. beyond adverse reactions reporting and signal detection: none.~~
~~Elderly~~	~~Routine risk communication:~~ ~~SmPC Section 4.2 Posology and method of administration~~ ~~SmPC Section 5.2 Pharmacokinetic properties~~	~~Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection.~~
~~Resistance~~	~~Routine risk communication:~~ ~~SmPC Section 5.1 Pharmacodynamic properties~~	~~Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:~~ ~~Lack of Efficacy Events follow-up form~~

AE = Adverse Event; IAR = Infusion-Associated Reaction; SmPC = Summary of Product Characteristics.

PART VI. SUMMARY OF THE RISK MANAGEMENT PLAN

Summary of risk management plan for Ecalta (anidulafungin)

This is a summary of the RMP for Ecalta. The RMP details important risks of Ecalta, how these risks can be minimised, and how more information will be obtained about Ecalta's risks and uncertainties (missing information).

Ecalta's SmPC and its package leaflet give essential information to healthcare professionals and patients on how Ecalta should be used.

This summary of the RMP for Ecalta should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of Ecalta's RMP.

I. The Medicine and What It Is Used For

Ecalta is authorised for treatment of invasive candidiasis in adults and paediatric patients aged 1 month to < 18 years. It contains anidulafungin as the active substance and it is given by IV route of administration.

Further information about the evaluation of Ecalta's benefits can be found in Ecalta's EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage: link to product's EPAR summary landing page on the EMA webpage.

II. Risks Associated With the Medicine and Activities to Minimise or Further Characterise the Risks

Important risks of Ecalta, together with measures to minimise such risks and the proposed studies for learning more about Ecalta's risks, are outlined below.

Measures to minimise the risks identified for medicinal products can be:

- Specific Information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals
- Important advice on the medicine's packaging;
- The authorised pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine's legal status — the way a medicine is supplied to the public (e.g. with or without prescription) can help to minimise its risks.

Together, these measures constitute *routine risk minimisation* measures.

In addition to these measures, information about AEs is collected continuously and regularly analysed, including PSUR assessment so that immediate action can be taken as necessary. These measures constitute *routine pharmacovigilance activities*.

If important information that may affect the safe use of Ecalta is not yet available, it is listed under 'missing information' below.

II.A. List of Important Risks and Missing Information

Important risks of Ecalta are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely administered. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of Ecalta. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g. on the long-term use of the medicine). The MAH reclassified all current potential and identified risks to risks 'not important' and added a new important potential risk i.e. *Hepatic impairment and other serious toxicities in neonates < 1 month of age*. In addition, the MAH removed the following safety concerns which are currently classified as Missing information: *Children/adolescents, Elderly, Pregnant women and Resistance;* the last two were removed in accordance to the Request for Supplementary Information received on 20 September 2019.

Table 32. Summary of Safety Concerns

Important identified risks	None
Important potential risks	Hepatic impairment and other serious toxicities in neonates < 1 month of age
Missing information	None

II.B. Summary of Important Risks

Table 33. Important Potential Risk: Hepatic impairment and other serious toxicities in neonates (< 1 month of age)

Evidence source and strength of evidence	*Candida* meningitis is a serious life-threatening consequence of *Candida* infection in neonates and is associated with high morbidity (i.e., neurologic sequelae) and mortality. In neonates with invasive candidiasis, it has been estimated that 15-20% of cases may have CNS involvement.[110] Owing to the difficulty in rapidly diagnosing CNS infection, neonates with invasive candidiasis are often presumed to have CNS involvement unless proven otherwise. Therefore, when treating neonates with invasive candidiasis, it is often necessary to select an antifungal agent known to have adequate CNS penetration and activity. PS80 is a solubilizing agent used in the current anidulafungin formulation. As described in literature, clinical[110] and non-clinical studies[111, 112, 113] suggest that an approximately 3-fold higher dose than the standard dose of anidulafungin may be needed to achieve the target exposure to treat neonatal candidiasis with CNS involvement. Based on the available data there are concerns regarding the potential risk of hepatic- related adverse events and other possible unknown toxicities resulting from the administration of higher doses of PS80.[114]
Risk factors and risk groups	Treating neonates requires consideration for coverage of disseminated candidiasis including CNS; nonclinical infection models indicate that higher doses of anidulafungin are needed to achieve adequate CNS penetration, resulting in higher doses of PS80. Given the potential risk of hepatotoxicity associated with polysorbate 80 when an increased amount is used in neonates, there is a theoretical risk of additive or synergistic hepatic effects in neonates when exposed to anidulafungin and polysorbate 80 at higher doses.
Risk minimisation measures	Routine risk communication: The risk is communicated through the label (SmPC Section 4.4 Special warnings and precautions for use)

II.C. Post-Authorisation Development Plan

II.C.1. Studies which are Conditions of the Marketing Authorisation

There are no studies which are conditions of the marketing authorisation or specific obligation of Ecalta.

II.C.2. Other Studies in Post-Authorisation Development Plan

There are no studies required for Ecalta.

PART VII. ANNEXES TO THE RISK MANAGEMENT PLAN

Annex 2 – Tabulated summary of planned, ongoing, and completed pharmacovigilance study programme

Annex 3 - Protocols for proposed, ongoing, and completed studies in the pharmacovigilance plan

Annex 4 - Specific Adverse Drug Reaction Follow-Up Forms

Annex 5 - Protocols for proposed and ongoing studies in RMP Part IV

Annex 6 - Details of Proposed Additional Risk Minimisation Activities (if applicable)

Annex 7 - Other Supporting Data (Including Referenced Material)

Annex 8 – Summary of Changes to the Risk Management Plan over Time

REFERENCES:

[1] Arendrup MC, Patterson TF. Multidrug-Resistant Candida: Epidemiology, Molecular Mechanisms, and Treatment. The Journal of infectious diseases 2017;216(suppl_3):S445-s51.

[2] Enoch DA, Yang H, Aliyu SH, et al. The Changing Epidemiology of Invasive Fungal Infections. Methods in molecular biology (Clifton, NJ) 2017;1508:17-65.

[3] Karadag-Oncel E, Kara A, Ozsurekci Y, Arikan-Akdagli S, et al. Candidaemia in a paediatric centre and importance of central venous catheter removal. Mycoses 2015;58(3):140-8.

[4] Suleyman G, Alangaden GJ. Nosocomial Fungal Infections: Epidemiology, Infection Control, and Prevention. Infectious disease clinics of North America 2016;30(4):1023-52.

[5] Pfaller MA, Pappas PG, Wingard JR. Invasive fungal pathogens: Current epidemiological trends. Clin Infect Dis 2006;43(Suppl 1):S3-14.

[6] Voss A, Kluytmans JA, Koeleman JG, et al. Occurrence of yeast bloodstream infections between 1987 and 1995 in five Dutch university hospitals. Eur J Clin Microbiol Infect Dis 1996;15:909-12.

[7] Sandven P, Bevanger L, Digranes A, et al. Candidemia in Norway (1991 to 2003): Results from a nationwide study. J Clin Microbiol 2006;44(6):1977-81.

[8] Almirante B, Rodriguez D, Park BJ, et al. Epidemiology and predictors of mortality in cases of Candida bloodstream infection: Results from population-based surveillance, Barcelona, Spain, from 2002 to 2003. J Clin Microbiol 2005;43(4):1829-35.

[9] Arendrup MC, Fuursted K, Gahrn-Hansen B, et al. Seminational surveillance of fungemia in Denmark: Notably high rates of fungemia and numbers of isolates with reduced azole susceptibility. J Clin Microbiol 2005;43(9):4434-40.

[10] Hesstvedt L, Gaustad P, Andersen CT, et al. Twenty-two years of candidaemia surveillance: results from a Norwegian national study. Clinical microbiology and infection: the official publication of the European Society of Clinical Microbiology and Infectious Diseases 2015;21(10):938-45.

[11] Ericsson J, Chryssanthou E, Klingspor L, et al. Candidaemia in Sweden: a nationwide prospective observational survey. Clinical microbiology and

infection: the official publication of the European Society of Clinical Microbiology and Infectious Diseases 2013;19(4):E218-21.

[12] Health Protection Agency. Laboratory reports of candidemia: England, Wales, and Northern Ireland, 2004. CDR Weekly 2005;15(42).

[13] Poikonen E, Lyytikainen O, Anttila VJ, et al. Candidemia in Finland, 1995-1999. Emerg Infect Dis 2003;9(8):985-90.

[14] Lagrou K, Maertens J, Van Even E, et al. Burden of serious fungal infections in Belgium. Mycoses 2015;58 Suppl 5:1-5.

[15] Dorgan E, Denning DW, McMullan R. Burden of fungal disease in Ireland. Journal of medical microbiology 2015;64(Pt 4):423-6.

[16] Mortensen KL, Denning DW, Arendrup MC. The burden of fungal disease in Denmark. Mycoses 2015;58 Suppl 5:15-21.

[17] Pfaller MA, Diekema DJ. Epidemiology of invasive mycoses in North America. Crit Rev Microbiol 2010;36(1):1-53.

[18] Schmiedel Y, Zimmerli S. Common invasive fungal diseases: an overview of invasive candidiasis, aspergillosis, cryptococcosis, and Pneumocystis pneumonia. Swiss medical weekly 2016;146:w14281.

[19] Tortorano AM, Peman J, Bernhardt H, et al. Epidemiology of candidemia in Europe: Results of 28-month European Confederation of Medical Mycology (ECMM) hospital-based surveillance study. Eur J Clin Microbiol Infect Dis 2004;23(4):317-22.

[20] Marchetti O, Bille J, Fluckiger U, et al. Epidemiology of candidemia in Swiss tertiary care hospitals: Secular trends, 1991-2000. Clin Infect Dis 2004;38(3):311-20.

[21] Richet H, Roux P, Des Champs C, et al. Candidemia in French hospitals: Incidence rates and characteristics. Clin Microbiol Infect 2002;8(7):405-12.

[22] Epelbaum O, Chasan R. Candidemia in the Intensive Care Unit. Clinics in chest medicine 2017;38(3):493-509.

[23] Baldesi O, Bailly S, Ruckly S, et al. ICU-acquired candidaemia in France: Epidemiology and temporal trends, 2004-2013 - A study from the REA-RAISIN network. The Journal of infection 2017;75(1):59-67.

[24] Caggiano G, Coretti C, Bartolomeo N, et al. Candida Bloodstream Infections in Italy: Changing Epidemiology during 16 Years of Surveillance. BioMed research international 2015;2015:256580.

[25] Trouve C, Blot S, Hayette MP, et al. Epidemiology and reporting of candidaemia in Belgium: a multi-centre study. European journal of clinical microbiology & infectious diseases: official publication of the European Society of Clinical Microbiology 2017;36(4):649-55.

[26] Barchiesi F, Orsetti E, Gesuita R, et al. Epidemiology, clinical characteristics, and outcome of candidemia in a tertiary referral center in Italy from 2010 to 2014. Infection 2016;44(2):205-13.

[27] Ghezzi MC, Brunetti G, Visconti V, et al. Candidaemia in a tertiary care academic hospital in Italy. The impact of C. parapsilosis complex on the species distribution and antifungal susceptibility. Journal of medical microbiology 2017;66(7):990-8.

[28] Mencarini J, Mantengoli E, Tofani L, et al. Evaluation of candidemia and antifungal consumption in a large tertiary care Italian hospital over a 12-year period. Infection 2018;46(4):469-76.

[29] Sasso M, Roger C, Sasso M, et al. Changes in the distribution of colonising and infecting Candida spp. isolates, antifungal drug consumption and susceptibility in a French intensive care unit: A 10-year study. Mycoses 2017;60(12):770-80.

[30] Klingspor L, Tortorano AM, Peman J, et al. Invasive Candida infections in surgical patients in intensive care units: a prospective, multicentre survey initiated by the European Confederation of Medical Mycology (ECMM) (2006-2008). Clinical microbiology and infection: the official publication of the European Society of Clinical Microbiology and Infectious Diseases 2015;21(1):87.e1-.e10.

[31] Pfaller MA, Jones RN, Doern GV, et al. International surveillance of bloodstream infections due to Candida species: Frequency of occurrence and antifungal susceptibilities of isolates collected in 1997 in the United States, Canada, and South America for the SENTRY Program. J Clin Microbiol 1998;36(7):1886-9.

[32] Bille J, Marchetti O, Calandra T. Changing face of health-care associated fungal infections. Curr Opin Infect Dis 2005;18(4):314-9.

[33] Farina C, Vailati F, Manisco A, et al. Fungaemia survey: A 10-year experience in Bergamo, Italy. Mycoses 1999;42:543-8.

[34] Lunel FV, Koeleman JGM, Spanjaard L, et al. Trends in fungaemia and antifungal susceptibility on the Netherlands. Netherlands J Med 2006;64(7):236-42.

[35] Sandven P, Bevanger L, Digranes A, et al. Constant low rate of fungemia in Norway, 1991 to 1996. J Clin Microbiol 1998:36(12):3455-9

[36] Bitar D, Lortholary O, Le Strat Y, et al. Population-based analysis of invasive fungal infections, France, 2001-2010. Emerging infectious diseases 2014;20(7):1149-55.

[37] Richards MJ, Edwards JR, Culver DH, et al. Nosocomial infections in medical intensive care units in the United States. Crit Care Med 1999;27(5):887-92.

[38] Wisplinghoff H, Bischoff T, Tallent SM, et al. Nosocomial bloodstream infections in US hospitals: Analysis of 24,179 cases from a prospective nationwide surveillance study. Clin Infect Dis 2004;39:309-17.

[39] McCarty TP, Pappas PG. Invasive Candidiasis. Infectious disease clinics of North America 2016;30(1):103-24.

[40] Ghannoum MA, Kuhn D. Voriconazole better chances for patients with invasive mycoses. Eur J Med Res 2002;7:242-56.

[41] Gangneux JP, Bougnoux ME, Hennequin C, et al. An estimation of burden of serious fungal infections in France. Journal de mycologie medicale 2016;26(4):385-90.

[42] Tsay S, Williams S, Mu Y, et al. 363. National Burden of Candidemia, United States, 2017. Open Forum Infectious Diseases 2018;5(suppl_1):S142-S3.

[43] Klingspor L, Tornqvist E, Johansson A, et al. A prospective epidemiological survey of candidemia in Sweden. Scand J Infect Dis 2004;36:52-5.

[44] Peman J, Canton E, Gobernado M, et al. Epidemiology and antifungal susceptibility of Candida species isolated from blood: Results of a 2-year multicentre study in Spain. Eur J Clin Microbiol Dis 2005;24:23-30.

[45] Hajjeh RA, Sofair AN, Harrison LH, et al. Incidence of bloodstream infections due to Candida species and in vitro susceptibilities of isolates collected from 1998 to 2000 in a population-based active surveillance program. J Clin Microbiol 2004;42(4):1519-27.

[46] Kao A, Brandt M, Pruitt W, et al. The epidemiology of candidemia in two United States cities: Results of a population-based active surveillance. Clin Infect Dis 1999;29:1164-70.

[47] Ricotta E, Lai YL, Kadri SS, et al. 362. Species Distribution and Trends of Invasive Candidiasis in the United States, 2009–2015, Using a Large Electronic Medical Record Database. Open Forum Infectious Diseases 2018;5(Suppl 1):S142-S.

[48] Pfaller MA, Diekema DJ. Epidemiology of invasive candidiasis: A persistent public health problem. Clin Microbiol Rev 2007;20(1):133-63.

[49] Eggimann P, Garbino J, Pittet D. Epidemiology of Candida species infections in critically ill non-immunosuppressed patients. Lancet Infect Dis 2003;3(11):685-702.

[50] Clark TA, Hajjeh RA. Recent trends in the epidemiology of invasive mycoses. Curr Opin Infect Dis 2002;15(6):569-74.

[51] Dixon DM, McNeil MM, Cohen ML, et al. Fungal infections: A growing threat. Public Health Rep 1996;111(3):226-35.

[52] Hidalgo JA, Vazquez JA. Candidiasis. eMedicine Journal. Available: http://www.gimed.info/Candida/Candida.htm. 14 Mar 2006.

[53] Kullberg BJ, Oude Lashof AML. Epidemiology of opportunistic invasive mycoses. Eur J Med Res 2002;7:183-91.

[54] Cornely OA, Bassetti M, Calandra T, et al. ESCMID guideline for the diagnosis and management of candida diseases 2012: Non-neutropenic adult patients. Clin Microbiol Infect 2012;18(Suppl 7):19-37.

[55] Andes DR, Safdar N, Baddley JW, et al. Impact of treatment strategy on outcomes in patients with candidemia and other forms of invasive candidiasis: A patient-level quantitative review of randomized trials. Clin Infect Dis 2012;54(8):1110-22.

[56] Edmond MB, Wallace SE, McClish DK, et al. Nosocomial bloodstream infections in United States hospitals: A three-year analysis. Clin Infect Dis 1999;29(2):239-44.

[57] Gudlaugsson O, Gillespie S, Lee K, et al. Attributable mortality of nosocomial candidemia, revisited. Clin Infect Dis 2003;37:1172-7.

[58] Kibbler CC, Seaton S, Barnes RA, et al. Management and outcome of bloodstream infections due to Candida species in England and Wales. J Hosp Infect 2003;54(1):18-24.

[59] Leleu G, Aegerter P, Guidet B. Systemic candidiasis in intensive care units: A multicenter, match-cohort study. J Crit Care 2002;17(3):168-75.

[60] Pappas P, Rex J, Lee J, et al. A prospective observational study of candidemia: Epidemiology, therapy, and influences on mortality in hospitalized adult and pediatric patients. Clin Infect Dis 2003;37(5):634-43.

[61] Wey SB, Mori M, Pfaller MA, et al. Hospital-acquired candidemia. The attributable mortality and excess length of stay. Arch Intern Med 1988;148(12):2642-5.

[62] Luzzati R, Amalfitano G, Lazzarini L, et al. Nosocomial candidemia in non-neutropenic patients at an Italian tertiary care hospital. Eur J Clin Microbiol Infect Dis 2000;19(8):602-7.

[63] Garbino J, Kolarova L, Rohner P, et al. Secular trends of candidemia over 12 years in adult patients in a tertiary care hospital. Medicine 2002;81(6):425-33.

[64] Cheng MF, Yang YL, Yao TJ, et al. Risk factors for fatal candidemia caused by Candida albicans and non-albicans Candida species. BMC Infect Dis 2005;5(1):22.

[65] Garey KW, Rege M, Pai MP, et al. Time to initiation of fluconazole therapy impacts mortality in patients with candidemia: A multi-institutional study. Clin Infect Dis 2006;43(1):25-31.

[66] Ibrahim EH, Sherman G, Ward S, et al. The influence of inadequate antimicrobial treatment of bloodstream infections on patient outcomes in the ICU setting. Chest 2000;118:146-55.

[67] Kollef MH, Sherman G, Ward S, et al. Inadequate antimicrobial treatment of infections: A risk factor for hospital mortality among critically ill patients. Chest 1999:115:462-74.

[68] Posch W, Heimdorfer D, Wilflingseder D, et al. Invasive candidiasis: future directions in non-culture based diagnosis. Expert review of anti-infective therapy 2017;15(9):829-38.

[69] Tortorano AM, Biraghi E, Astolfi A, et al. European Confederation of Medical Mycology (ECMM) prospective survey of Candidemia: Report from one Italian region. J Hosp Infect 2002;51(4):297-304.

[70] Lortholary O, Charlemagne A, Bastides F, et al. A multicentre pharmacoepidemiological study of therapeutic practices in invasive fungal infections in France during 1998-1999. J Antimicro Chemo 2004;54:456-64.

[71] Bader MS, Lai SM, Kumar V, et al. Candidemia in patients with diabetes mellitus: Epidemiology and predictors of mortality. Scand J Infect Dis 2004;36(11-12):860-4.

[72] Leroy O, Gangneux JP, Montravers P, et al. Epidemiology, management, and risk factors for death of invasive Candida infections in critical care:

A multicenter, prospective, observational study in France (2005-2006). Crit Care Med 2009;37(5):1612-8.

[73] Pappas PG, Morgan J, Hajjeh RA, et al. Prospective surveillance of invasive fungal infections (IFIs) in hematopoietic stem cell (HSCTs) and solid organ transplant recipients (SOTs) in the United States. Chicago, IL: 43rd Annual ICAAC 2003b. Program and abstracts M-1010.

[74] Martino R, Subira M, Rovira M, et al. Invasive fungal infections after allogenic peripheral blood stem cell transplantation: Incidence and risk factors in 395 patients. Br J Haematol 2002;116:475-82.

[75] Datamonitor. Stakeholder insights: Invasive fungal infections. London. 2004. Available: http://www.datamonitor.com/~67ddb354516b484482dace815accbb8d~/products/premium/Report/DMHC1957/001dmhc1957.pdf.

[76] Blumberg H, Jarvis W, Soucie J, et al. Risk factors for candidal bloodstream infections in surgical intensive care unit patients: The NEMIS prospective multicenter study. Clin Infect Dis 2001;33:177-86.

[77] Boo TW, O'Reilly B, O'Leary J, et al. Candidaemia in an Irish tertiary referral hospital: Epidemiology and prognostic factors. Mycoses 2005;48(4):251-9.

[78] Echeverria MJ, Ayarza R, Lopez de Goicoechea MJ, et al. Microbiological diagnosis of peritonitis in patients undergoing continuous ambulatory peritoneal dialysis. Review of 5 years at the Hospital de Galdakao. Enferm Infect Microbiol Clin 1993;11:178-81.

[79] Solomkin JS, Flohr AB, Quie PG, et al. The role of Candida in intraperitoneal infections. Surgery 1980;88:524-30.

[80] Steinbach WJ, Roilides E, Berman D, et al. Results from a prospective, international, epidemiologic study of invasive candidiasis in children and neonates. The Pediatric infectious disease journal 2012;31(12):1252-7.

[81] Oeser C, Lamagni T, Heath PT, et al. The epidemiology of neonatal and pediatric candidemia in England and Wales, 2000-2009. The Pediatric infectious disease journal 2013;32(1):23-6.

[82] Dzierzanowska-Fangrat K, Romanowska E, Gryniewicz-Kwiatkowska O, et al. Candidaemia in a Polish tertiary paediatric hospital, 2000 to 2010. Mycoses 2014;57(2):105-9.

[83] Tragiannidis A, Fegeler W, Rellensmann G, et al. Candidaemia in a European Paediatric University Hospital: a 10-year observational study. Clinical microbiology and infection: the official publication of the

European Society of Clinical Microbiology and Infectious Diseases 2012;18(2):E27-30.

[84] Zaoutis TE, Argon J, Chu J, et al. The epidemiology and attributable outcomes of candidemia in adults and children hospitalized in the United States: a propensity analysis. Clin Infect Dis 2005;41(9):1232-9.

[85] Cleveland AA, Farley MM, Harrison LH, et al. Changes in incidence and antifungal drug resistance in candidemia: results from population-based laboratory surveillance in Atlanta and Baltimore, 2008-2011. Clinical infectious diseases: an official publication of the Infectious Diseases Society of America 2012;55(10):1352-61.

[86] Cleveland AA, Harrison LH, Farley MM, et al. Declining incidence of candidemia and the shifting epidemiology of Candida resistance in two US metropolitan areas, 2008-2013: results from population-based surveillance. PloS one 2015;10(3):e0120452.

[87] Ota KV, McGowan KL. Declining incidence of candidemia in a tertiary inpatient pediatric population. Journal of clinical microbiology 2012;50(3):1048-50.

[88] Fisher BT, Ross RK, Localio AR, et al. Decreasing rates of invasive candidiasis in pediatric hospitals across the United States. Clinical infectious diseases: an official publication of the Infectious Diseases Society of America 2014;58(1):74-7.

[89] Hope WW, Castagnola E, Groll AH, et al. ESCMID* guideline for the diagnosis and management of Candida diseases 2012: prevention and management of invasive infections in neonates and children caused by Candida spp. Clin Microbiol Infect. 2012 Dec;18 Suppl 7:38-52.

[90] Pana ZD, Roilides E, Warris A, et al. Epidemiology of Invasive Fungal Disease in Children. Journal of the Pediatric Infectious Diseases Society 2017;6(suppl_1):S3-s11.

[91] King J, Pana ZD, Lehrnbecher T, et al. Recognition and Clinical Presentation of Invasive Fungal Disease in Neonates and Children. Journal of the Pediatric Infectious Diseases Society 2017;6(suppl_1):S12-s21.

[92] Prescribing Information: CANCIDAS® (caspofungin acetate) for injection, intravenous use. Whitehouse Station, NJ, USA: Merck & Co, Inc. Jun 2010.

[93] Prescribing Information: MYCAMINE® (micafungin sodium) for injection; IV infusion only. Deerfield, IL, USA: Astellas Pharma US, Inc. Jun 2011.

[94] Van der Geest PJ, Hunfeld NG, Ladage SE, et al. Micafungin versus anidulafungin in critically ill patients with invasive candidiasis: A retrospective study. BMC Infect Dis 2016;16:490.

[95] Kuse ER, Chetchotisakd P, da Cunha CA, et al. Micafungin versus liposomal amphotericin B for candidaemia and invasive candidosis: A phase III randomised double-blind trial. Lancet 2007;369(9572):1519-27.

[96] Ostrosky-Zeichner L, Kontoyiannis D, Raffalli J, et al. International, open-label, noncomparative, clinical trial of micafungin alone and in combination for treatment of newly diagnosed and refractory candidemia. Eur J Clin Microbiol Infect Dis 2005;24(10):654-61.

[97] Betts RF, Nucci M, Talwar D, et al. A multicenter, double-blind trial of a high-dose caspofungin treatment regimen versus a standard caspofungin treatment regimen for adult patients with invasive candidiasis. Clin Infect Dis 2009;48(12):1676-84.

[98] Mora-Duarte J, Betts R, Rotstein C, et al. Comparison of caspofungin and amphotericin B for invasive candidiasis. N Engl J Med 2002;347(25):2020-9

[99] Wang JL, Chang CH, Young-Xu Y, et al. Systematic review and meta-analysis of the tolerability and hepatotoxicity of antifungals in empirical and definitive therapy for invasive fungal infection. Antimicrob Agents Chemother 2010;54(6):2409-19.

[100] Vekeman F, Weiss LS, Aram J, et al. Comparative hepatotoxicity of echinocandins in hospitalized patients: A retrospective cohort study. Pharmacoepidemiol Drug Saf 2016;25(Suppl 1):267-8.

[101] Bleck TP, Smith MC, Pierre-Louis S, et al. Neurologic complications of critical medical illnesses. Crit Care Med 1993;21(1):98-103.

[102] Jette N, Hirsch LJ. Continuous electroencephalogram monitoring in critically ill patients. Curr Neurol Neurosci Rep 2005;5(4):312-21.

[103] Claassen J, Mayer SA, Kowalski RG, et al. Detection of electrographic seizures with continuous EEG monitoring in critically ill patients. Neurology 2004;62:1743-8.

[104] Delanty N, Vaughan CJ, French JA. Medical causes of seizure. Lancet 1998;352:383-90.

[105] Mullin P, Green G, Bakshi R. Special populations: The management of seizures in HIV-positive patients. Curr Neurol Neurosci Rep 2004;4(4):308-14.

[106] Saner FH, Sotiropoulos GC, Gu Y, et al. Severe neurological events following liver transplantation. Arch Med Res 2007;38(1):75-9.

[107] Vecht CJ, van Breemen M. Optimizing therapy of seizures in patients with brain tumors. Neurology 2006;67(Suppl 4):S10-13.

[108] Armstrong T, Gilbert MR. Central nervous system toxicity from cancer treatment. Curr Oncol Rpts 2004;6(1):11-9.

[109] Karadeniz C, Oguz A, Canter B, et al. Incidence of seizures in pediatric cancer patients treated with imipenem/cilastatin. Ped Hematol Oncol 2000;17(7):585-90.

[110] Cohen-Wolkowiez, M., Benjamin, D.K, Jr., Piper, L., et al. Safety and pharmacokinetics of multiple-dose anidulafungin in infants and neonates. Clin Pharmacol Ther. 2011;89(5):702-7.

[111] Ripp SL, Aram JA, Bowman CJ et al. Tissue Distribution of Anidulafungin in Neonatal Rats. Birth Defects Res Part B 2012; 95:89-94.

[112] Warn PA, Livermore J, Howard S, et al. Anidulafungin for neonatal hematogenous Candida meningoencephalitis: identification of candidate regimens for humans using a translational pharmacological approach. Antimicrob Agents Chemother. 2012;56(2):708-14

[113] Livermore JL, Felton TW, Abbott J, Sharp A, Goodwin J, Gregson L, et al. Pharmacokinetics and pharmacodynamics of anidulafungin for experimental Candida endophthalmitis: insights into the utility of echinocandins for treatment of a potentially sight-threatening infection. Antimicrob Agents Chemother. 2013;57(1):281-8.

[114] Risk Assessment of Polysorbate 80 in Anidulafungin in the Treatment of Neonates, February 2014

ANNEX 2. TABULATED SUMMARY OF PLANNED, ON-GOING, AND COMPLETED PHARMACOVIGILANCE STUDY PROGRAMME

Table 1 Annex II: Planned and on-going studies

Not applicable.

Table 2 Annex II: Completed studies

Study	Summary of Objectives	Safety Concerns Addressed	Milestones Study Report link
A8851008 (Prospective, open-label, non-comparative, descriptive, multicenter, multinational study) Category 3	To evaluate the safety and efficacy of anidulafungin for the treatment of paediatric patients with invasive candidiasis, including candidaemia	Paediatric patients	September, 2018 Link to final study report
GlobalAntifungal Surveillance Program Category 3	To monitor the in vitro activity of anidulafungin and to detect the emergence of resistance among pathogens causing invasive mycoses	Resistance	03 February 2015 Link to final study report
PASS (A8851030, a non interventional, retrospective cohort study) Category 3	To further characterise the risk of hepatic injury in hospitalized patients treated with echinocandin for Candida infection	Hepatobiliary events	08 June 2015 Link to final study report

ANNEX 3. PROTOCOLS FOR PROPOSED, ON-GOING, AND COMPLETED STUDIES IN THE PHARMACOVIGILANCE PLAN

Part A: Requested protocols of studies in the Pharmacovigilance Plan, submitted for regulatory review with this updated version of the RMP.

Not applicable.

Part B: Requested amendments of previously approved protocols of studies in the Pharmacovigilance Plan, submitted for regulatory review with this updated version of the RMP.

Not applicable.

Part C: Previously agreed protocols for on-going studies and final protocols not reviewed by the competent authority.

Not applicable.

ANNEX 4. SPECIFIC ADVERSE DRUG REACTION FOLLOW-UP FORMS

Table of contents

Overview and Scope

This document describes the special regulatory follow-up commitment for anidulafungin (Eraxis/Ecalta) and specifies case handling requirements for applicable reports. Colleagues and contractors in Worldwide Safety and Regulatory (WSR) are required to follow the guidance described in this document.

Description

Name of Regulatory Authority and Date of Pfizer's Commitment	European Medicines Agency (EMA) Date of Commitment: 15-Mar-2007—Enhanced Follow-up Requirements (Risk Management Plan)
Description of Commitment	A data capture aid (DCA) is to be used to collect information on spontaneous adverse events of interest.
Case Types	• Spontaneous reports—serious or non-serious, labelled or unlabelled • Serious related reports from non-interventional studies and other non-clinical study solicited sources (e.g., compassionate use, some types of Customer Engagement Programs [CEPs], etc.)—labelled or unlabelled. Not required if the serious adverse event (SAE) has been assessed as unrelated
Implementation Details	The following DCAs are to be used to obtain further specific data: • Infusion Associated Reaction • Seizure • Hepatic Events • Lack of Efficacy If the DCA-defined information is not obtained from the initial report, follow-up will be actively pursued.

Refer to the current version of WSR-SRR01-LSOP-SD01 *Special Reporting and Follow-up Event Terms* for event terms that apply.

Revision History

Revision	Effective Date	Summary of Revisions
1.0	16-Jun-2014	New document to replace anidulafungin (Eraxis/Ecalta) content of SJA205-A *Products with Regulatory Follow-up Commitments* 26-Jul-2013.

Instructions for use:

Select questions as needed to obtain any DCA-defined information described below that was not included in the initial report.

AER/Manufacturer Report #: _____

Suspect product: _____

Reported event term prompting special follow-up activities: _____

Infusion Associated Reaction Follow-up Questions

Please provide additional details on a separate page if needed, and reference the question number.

1. Is the reported adverse event a:

☐ New event ☐ Recurrence

Details:

2. Was the infusion rate according to the label instructions or slower?

☐ No (*Specify rate:* _____ mg/min)

☐ Yes

3. Was there concomitant use of anesthesia?

☐ No

☐ Yes *(Provide details, including specifying medications)*

Details:

4. What was time-relationship between the suspected infusion-associated reaction and administration of the product?

Please specify whether the event occurred:

☐ during infusion

☐ within 60 minutes following completion of infusion

☐ within 1-3 hours following completion of infusion

☐ greater than 3 hours following completion of infusion

Details:

5. Did the patient experience any signs and/or symptoms?

☐ No

☐ Yes *(If yes, provide details)*

Details:

6. Were any treatments administered following the reaction?

☐ No

☐ Yes *(If yes, provide details and outcome)*

Details/Outcome:

Additional Infusion-Associated Reaction Follow-up Questions for Daptomycin (Hospira)

Please provide additional details on a separate page if needed, and reference the question number.

[1. Daptomycin] Where was the product vial stored prior to compounding?

[2. Daptomycin] Where was the product prepared? In a sterile environment? *Provide details*

[3. Daptomycin] What diluent was used, and what amount was used to reconstitute the vial?

[4. Daptomycin] On reconstitution, was the vial further diluted/drawn into a syringe immediately or stored for future use? *If stored for future use, for how long and at what temperature?*

[5. Daptomycin] Was the product drawn up into a syringe or diluted further into an infusion bag (type and volume)?

[6. Daptomycin] If the product is being supplied to patients, how many days' supply was shipped?

[7. Daptomycin] Describe the transport conditions of the product to the patient (time and temperature) and storage conditions in the home.

[8. Daptomycin] If the product was stored in the refrigerator prior to administration, was it allowed to come to room temperature?

[9. Daptomycin] Who administered the dose?

- ☐ patient
- ☐ caregiver
- ☐ nurse
- ☐ Other *please specify*

[10. Daptomycin] How was the drug administered?

- ☐ IV push
- ☐ IV infusion
  - ☐ Gravity infusion
  - ☐ IV pump

Please specify time in minutes

[11. Daptomycin] Describe intravenous access:

- ☐ PICC
- ☐ long term central port
- ☐ peripheral vein "hep lock/male adapter plug"

[12. Daptomycin] Were there any concomitant medications given via the same IV access? *If so please provide details*

[13. Daptomycin] Was the IV line flushed with a solution (name of solution) at the beginning or completion of the infusion?

[14. Daptomycin] How many doses of daptomycin Hospira, or daptomycin by another manufacturer, had the patient received prior to experiencing the infusion related adverse events?

- ☐ 1 dose
- ☐ 2 doses
- ☐ Other *please specify*

[15. Daptomycin] Did the patient have a history of the following? *Please select all that apply (Please provide details and indicate whether ongoing)*

- ☐ Prior infusion reactions to a drug of the same chemical class → *If Yes, please provide details, including drug name and symptoms*
  Details
- ☐ Prior infusion reactions to a drug of a different drug class → *If Yes, please provide details, including drug name and symptoms*
  Details
- ☐ Drug allergies, regardless of drug class *(please specify)*
  Details:
- ☐ Other medical conditions *(please specify)*
  Details:

[16. Daptomycin] Did the patient experience infusion related reactions with other brands of daptomycin?

Please provide details including manufacturer.

Revision History

Revision	Effective Date	Summary of Revisions
2.0	27-Jun-2018	Two check boxes added to question 4; new product-specific questions added for Daptomycin Hospira
1.0	07-Mar-2014	New DCA

Seizure Data Capture Aid

Instructions for use:

Select questions as needed to obtain any DCA-defined information described below that was not included in the initial report.

AER/Manufacturer Report #: _____

Suspect product: _____

Reported event term prompting special follow-up activities: _____

Seizure Follow-up Questions

Please provide additional details on a separate page if needed, and reference the question number.

1. Is the reported adverse event a:

☐ New event
☐ Recurrence *(please provide details on previous events)*
☐ Exacerbation of underlying condition *(please provide details)*

Details:

2. Did the patient have a family history of convulsions, seizures,, or seizure activity?

☐ Unknown ☐ No ☐ Yes *(provide details)*

Details:

3. Did the patient have a history of head trauma, head surgery, disease *(e.g., epilepsy, metastatic cancer, CNS infection, degenerative disease, intracranial hemorrhage psychiatric disorders, genetic disorders, metabolic disturbances, cerebrovascular disease, uncontrolled hypertension, hyperpyrexia , kidney disorders, diabetes),* **or other relevant personal history that has or could have affected the patient's neurological system** *(i.e. pyrexia)***?**

☐ Unknown ☐ No ☐ Yes *(provide details)*

Details:

4. If the patient discontinued the product in response to a seizure event, did the patient experience any further seizures after discontinuation?

☐ Unknown
☐ No *(please specify duration of the seizure-free period since discontinuation-to-date)*

Details:

☐ Yes *(please provide details, including frequency and latency since product discontinuation)*

Details:

5. Did a health care professional witness the convulsive crisis?

☐ Unknown ☐ No ☐ Yes *(provide details)*

Details:

6. Did the patient have a personal history of convulsions, seizures, or seizure activity?

☐ Unknown ☐ No ☐ Yes *(If yes, please specify the seizure type, triggers, frequency. If the patient was treated with anti-seizure medication(s), please specify and state if treatment was ongoing at the time of therapy, and date of last seizure occurrence prior to start of therapy:*

Details:

7. Was the patient taking any medications that may lower the seizure threshold or may induce seizure if withdrawn quickly?

☐ Unknown ☐ No ☐ Yes *(provide details)*

Details:

8. Did the patient have an ongoing history of alcohol or drug use (prescribed, non-prescribed, and/or illicit) at the time of the event?

☐ Unknown ☐ No ☐ Yes *(provide details)*

Details:

9. Were any relevant neurological examination or diagnostic tests (e.g., EEG, brain imaging studies) performed at the time of the event?

☐ Unknown ☐ No ☐ Yes *(provide details)*

Details:

10. Were any relevant laboratory tests (e.g., CBC, chemistry panel) or toxicology screening performed at the time of the event?

☐ Unknown ☐ No ☐ Yes *(provide details)*

Details:

11. If the patient died, was an autopsy performed? ☐ Unknown ☐ No ☐ Yes *(provide details)* *Details:*	**12. Was any treatment initiated or modified in response to the event(s)?** ☐ Unknown ☐ No ☐ Yes *(provide details)* *Details:*

AER/Manufacturer Report #: _____

Suspect product: _____

Reported event term prompting this questionnaire: _____

Seizure Event Follow-up Questions for Chantix/Champix

Please provide additional details on a separate page if needed, and reference the question number.

[1. Chantix/Champix] Please indicate the patient's smoking status at the time of event onset:

- ☐ Still smoking at same rate, or at higher rate
- ☐ Still smoking, but at a reduced rate
- ☐ Stopped smoking
- ☐ Don't know

[2. Chantix/Champix] If the event(s) listed above resolved, please provide the smoking status at the time of resolution of the event:

- ☐ Still smoking at same rate, or at higher rate
- ☐ Still smoking, but at a reduced rate
- ☐ Stopped smoking
- ☐ Don't know

AER/Manufacturer Report #: _____

Suspect product: _____

Reported event term prompting this questionnaire: _____

Seizure Event Follow-up Questions for Eraxis/Ecalta

Please provide additional details on a separate page if needed, and reference the question number.

[1. Eraxis/Ecalta] Did the event occur during infusion of the medication or within 60 minutes of infusion?

☐ Unknown ☐ No ☐ Yes *(If yes, please specify the infusion rate and whether other symptoms were associated with the seizure) :*

Details:

Revision History

Revision	Effective Date	Summary of Revisions
1.0	14-Mar-2014	New DCA

Hepatic Events Data Capture Aid

Instructions for use:

Select questions as needed to obtain any DCA-defined information described below that was not included in the initial report.

AER/Manufacturer Report #: _____

Suspect product: _____

Reported event term prompting special follow-up activities: _____

Hepatic Events Follow-up Questions

Please provide additional details on a separate page if needed, and reference the question number.

1. Is the reported adverse event a:

☐ New event

☐ Recurrence *(Please specify details of the prior events)*

☐ Exacerbation of existing condition *(please provide details)*

Details:

2. Please provide: name, e-mail address, postal address, and telephone number of any specialist to whom the patient was referred for further evaluation of the reported adverse event(s) *(if applicable based on local privacy regulations):*

3. Please mark whether the patient experienced any of the following signs / symptoms:

☐ Rash	☐ Pruritus	☐ Purpura
☐ Fever	☐ Joint Pain	☐ Abdominal distension
☐ Abdominal Pain	☐ Nausea	☐ Vomiting
☐ Coma	☐ Ascites	☐ Asthenia
☐ Asterixis / "Flapping"	☐ Jaundice	☐ Hepatomegaly
☐ Splenomegaly	☐ Weight gain *(please specify)*_____	

☐ Hepatic encephalopathy

☐ Sepsis *(if yes, describe time to onset and course of the event [e.g., progression and outcome])*_____

☐ Multi-organ failure *(if yes, include time to onset and the course [e.g., progression and outcome])*_____

☐ Other signs / symptoms *(including those related to infections, please specify)* _____

4. Was hepatic function test monitoring (e.g., AST, ALT, Bilirubin) done at the following times?

- **Routine LFTs in year prior to start of drug:**
  ☐ Unknown ☐ No ☐ Yes

If Yes, please provide details of monitoring below and record relevant results in the laboratory data section.

Details:

- **Baseline at start of therapy** ☐ Unknown ☐ No ☐ Yes

If Yes, please provide details of monitoring below and record relevant results in the laboratory data section.

Details:

- **During therapy:** ☐ Unknown ☐ No ☐ Yes

If Yes, please provide details of monitoring below and record relevant results in the laboratory data section:

Details:

- **After therapy:** ☐ Unknown ☐ No ☐ Yes

If Yes, please provide details of monitoring below and record relevant results in the laboratory data section:

Details:

5. Please mark whether the patient was taking any of the following medications / substances at the time of the adverse event or within two weeks prior to the onset of the adverse event: *(Please provide details - specify the products generic names, dates off administration, and dosage)*

- ☐ Antibiotics
- ☐ Anti-arrhythmic drugs
- ☐ ACE inhibitors
- ☐ Potassium supplements
- ☐ Protease inhibitors
- ☐ Retroviral agents
- ☐ Anticoagulants
- ☐ Diuretics
- ☐ Beta blockers
- ☐ Angiotensin II receptor antagonists
- ☐ Potassium-sparing diuretics
- ☐ PDE5 inhibitors
- ☐ Vitamin K antagonists
- ☐ Cyclosporin A
- ☐ Oral contraceptives
- ☐ Dietary supplements
- ☐ Over-the-counter drugs
- ☐ Herbal preparations
- ☐ Recreational drugs (e.g., cocaine, crack cocaine, heroin, methamphetamines)
- ☐ Cytotoxic chemotherapy
- ☐ Disease modifying drugs (e.g. DMARD medications for the treatment of rheumatoid arthritis)
- ☐ Other heart or blood pressure medications
- ☐ Products for the treatment of pulmonary arterial hypertension
- ☐ Other *(please specify)* _____
- ☐ None

Details:

6. Please mark whether the patient had prior to start of therapy any of the following: *(Please provide details and indicate whether ongoing condition or whether occurred in the past)*

- ☐ Hepatic dysfunction
- ☐ Hepatobiliary disease or dysfunction
- ☐ Elevated liver function tests
- ☐ Elevated bilirubin
- ☐ Jaundice
- ☐ Cirrhosis
- ☐ Fatty liver
- ☐ Pancreatitis
- ☐ Gallstones
- ☐ Gall bladder disease
- ☐ Bile duct obstruction
- ☐ Viral hepatitis
- ☐ Congenital heart disease
- ☐ Drug-induced liver toxicity *(please specify drug)* _____
- ☐ Recent travel to other countries *(please specify)*
- ☐ Other *(please specify)* _____
- ☐ Alcohol use *(If checked, complete question 8)*

Details:

- ☐ Parasitic diseases
- ☐ Mycobacterium Avium Complex infection
- ☐ Other non-viral suspected liver infections
- ☐ Cytomegalovirus infection
- ☐ Ischemic hepatitis
- ☐ Cystic fibrosis
- ☐ Granulomatosis
- ☐ Sickle cell anemia
- ☐ Connective tissue disease

- ☐ Lactic acidosis syndrome
- ☐ Blood product transfusions
- ☐ Renal impairment
- ☐ Gilbert's disease
- ☐ Metabolic disease
- ☐ Diabetes mellitus (Type I or II)
- ☐ Heart failure
- ☐ Hypertension
- ☐ Hypertriglyceridemia
- ☐ Portal hypertension
- ☐ Veno-occlusive disease
- ☐ Atherosclerotic / vascular disease
- ☐ Transplant

- ☐ Valvular heart disease
- ☐ Primary malignancy
- ☐ Liver metastases
- ☐ Hepatoma
- ☐ Auto-immune disorder
- ☐ Immune reconstitution disease
- ☐ HIV infection
- ☐ Sepsis
- ☐ Drug toxicity *(please specify)* _____
- ☐ Vitamin deficiency *(please specify)* _____

- ☐ Contact with jaundiced patient
- ☐ Epstein–Barr virus infection
- ☐ Substance abuse/Drug abuse (e.g., recreational/illicit drug use)
- ☐ Alternative medication use (e.g., herbal supplements and vitamins)
- ☐ None

7. Did the patient have a family history of liver disease? *(i.e., genetic conditions)*

☐ Unknown ☐ No ☐ Yes *(please provide details)*

Details:

8. If "Alcohol use" checked above, please answer the following:

How often does the patient drink beverages containing alcohol?
_____*(e.g., monthly, 2-4 times a week, more than 5 times a week, etc)*

How many drinks on a typical day when patient is drinking?:
_____ *(e.g., less than 1 drink, 2 or 3 drinks, more than 3 drinks, etc)*

Please specify the type/brand of alcohol patient typically drinks:
_____ *(e.g., beer)*

If this drinking history is more than one year, please specify duration:
_____

9. Were any of the following laboratory tests / procedures performed? Please specify results with date(s) of test, results with units, and reference ranges. If a test was administered multiple times, please enter the date(s) of test, units, and reference ranges for each test in chronological order.

Laboratory Test / Procedure	Date Performed (DD-MMM-YYYY)	Results with units if applicable	Reference Ranges if applicable
☐ AST			
☐ ALT			
☐ GGT			
☐ Total bilirubin			
☐ Conjugated bilirubin			
☐ Total protein			
☐ Albumin			
☐ Prothrombin time (PT)			
☐ Partial thromboplastin time (PTT)			
☐ International normalized ratio (INR)			
☐ Clotting time			
☐ Alkaline phosphatase			
☐ Hepatitis A serology			
☐ Hepatitis B serology			
☐ Hepatitis C serology			
☐ Cytomegalovirus (CMV) serology			
☐ Epstein Barr serology			
☐ Other serology			
☐ Eosinophil count			
☐ Amylase			
☐ Lipase			
☐ Other pancreatic enzymes tests			
☐ Serum or plasma concentrations for any concomitant drugs			
☐ Liver ultrasound			
☐ Liver biopsy			
☐ Abdominal X-ray			
☐ Abdominal CT			
☐ Abdominal endoscopic retrograde cholangiopancreatography (ERCP)			
☐ Serum ceruloplasmin			
☐ Serum copper			
☐ Serum alpha 1-antitrypsin			
☐ Serum alpha-fetoprotein			
☐ Serum ammonia			
☐ Other relevant lab data *(please specify)*			

Additional Follow-up Questions for Inotuzumab Ozogamicin

Please provide additional details on a separate page if needed, and reference the question number.

[1 Inotuzumab Ozogamicin] Additional Medical History *Please mark all that apply:*

Inflammatory hepatic disease

- ☐ Alcoholic hepatitis date (mm/dd/yyyy) _____
- ☐ Non-alcoholic steatohepatitis (NASH) (mm/dd/yyyy) _____
- ☐ N/A
- ☐ Unknown

Fibrotic hepatic disease

- ☐ Nodular Regenerative Hyperplasia (mm/dd/yyyy) _____
- ☐ Lobular fibrosis (mm/dd/yyyy) _____
- ☐ Extramedullary hematopoiesis with sinusoidal fibrosis (mm/dd/yyyy) _____
- ☐ N/A
- ☐ Unknown

Cholestatic disorders :

- ☐ Jaundice caused by:
  - ☐ Intrahepatic cholestasis ☐ Sepsis
  - ☐ GVHD
  - ☐ N/A
  - ☐ Unknown

☐ **Prior liver biopsy**: ☐ Yes ☐ No
If yes, Date: _____ Findings: _____

☐ **Prior liver irradiation:** (mm/dd/yyyy) _____ Dose_____

☐ **Prior suspected or proven VOD/SOS?** ☐ Yes ☐ No
If yes,(mm/dd/yyyy): _____

[2. Inotuzumab Ozogamicin] Did total bilirubin exceed 2 mg/dL (>34 umol/L) following Inotuzumab Treatment?

☐ Yes ☐ No ☐ Unknown ☐ N/A

If yes,
Date of increase: _____>2 mg/dL (>34 µmol /L) _____
Peak total bilirubin value _____ mg/dL or µmol /L
Date of Peak Value (dd/mmm/yyyy) _____

Was elevated bilirubin and any other hepatic dysfunction associated with severe infection (such as sepsis/septic shock, pneumonia, etc.)?

☐ Yes ☐ No *If yes, please elaborate*

[3. Inotuzumab Ozogamicin] Was an abdominal ultrasound performed to evaluate potential hepatic VOD/SOS?

☐ Yes ☐ No ☐ Unknown ☐ N/A

If Yes, please indicate if any of the following were found (please attach ultrasound results/report and provide details)

- ☐ Hepatomegaly
- ☐ Abnormal portal flow
- ☐ Attenuated hepatic vein flow
- ☐ Reversal of hepatic vein flow
- ☐ Gallbladder wall edema
- ☐ Ascites ☐ mild ☐ moderate ☐ severe

Was therapeutic paracentesis required to manage ascites? ☐ Yes ☐ No
If yes, ☐ once ☐ twice ☐ 3 or more times_____

☐ Increased Resistive Indices (RI) *(please specify RI values)*
Other Details: _____

[4. Inotuzumab Ozogamicin] Was a wedge hepatic vein pressure gradient assessed?

☐ Yes ☐ No ☐ Unknown ☐ N/A

If Yes, please provide results:

[5. Inotuzumab Ozogamicin] Was there evidence of concurrent pleural effusion during hepatic dysfunction?

☐ Yes ☐ No ☐ Unknown ☐ N/A

If yes, please quantify:

[6. Inotuzumab Ozogamicin] Did the patient develop symptomatic peripheral edema during hepatic dysfunction?

☐ Yes ☐ No ☐ Unknown ☐ N/A

[7. Inotuzumab Ozogamicin] Please specify any weight change:

Baseline weight _____ ☐ lbs ☐ kg
Peak weight _____ ☐ lbs ☐ kg
Peak change from baseline *(%)* _____
Date of Peak Value *(dd/mmm/yyyy)* _____
☐ N/A ☐ Unknown
Height _____ in or _____ cm

[8. Inotuzumab Ozogamicin] Did ALT increase >2.5 upper limits of normal (ULN) following Inotuzumab Treatment?

☐ Yes ☐ No ☐ Unknown ☐ N/A

If Yes:

Date of increase >2.5 x ULN) _____

Peak value _____ IU; upper limit of normal: ___ IU

Date of Peak Value (dd/mmm/yy) _____

[9. Inotuzumab Ozogamicin] Did serum creatinine double from baseline during hepatic event? ☐ Yes ☐ No ☐ Unknown ☐ N/A

If Yes:

Baseline value: _____ mg/dl

Peak value: _____ mg/dl; upper limit of normal: ___ IU

Date of Peak Value (dd/mmm/yyyy) _____

Was dialysis required? Yes___ No____

10. [Inotuzumab Ozogamicin] Was right upper quadrant abdominal pain of liver origin reported? ☐ Yes ☐ No ☐ Unknown ☐ N/A

If yes, please specify:

Start date (dd/mmm/yyyy) _____

Stop date (dd/mmm/yyyy) _____

Required treatment for this pain *(please specify)* _____

11. [Inotuzumab Ozogamicin] Prior to this event hepatotoxic chemotherapy and general timeframe of exposure

Mark all that apply:

☐ High dose cytarabine

☐ High dose methotrexate

☐ High dose cyclophosphamide

☐ Asparaginase

☐ Mitoxantrone

☐ Anthracycline (total dose: ____ mg/m^2

☐ Topoisomerase II inhibitors

☐ Prolonged 6-MP and/or methotrexate

☐ Tyrosine kinase inhibitor(s) *(please specify)* _____

☐ Abdominal irradiation

☐ Unknown ☐ N/A

How many HSCTs has this patient received?

☐ Unknown ☐ N/A ☐ 1 ☐ 2 ☐ 3 ☐ more than 3

History of liver failure/severe liver toxicity from any cause? ☐ Yes ☐ No *If yes, please provide date and presumed etiology:*

Was any chemotherapy administered after Besponsa therapy but before HSCT conditioning therapy? ☐ Yes ☐ No *If yes, please provide details:*

[12. Inotuzumab Ozogamicin] HSCT #1: Date: _____

Donor:

- ☐ Autologous HSCT
- ☐ Matched related donor
- ☐ Mismatched related/haploidentical donor
- ☐ Matched unrelated donor
- ☐ Mismatched unrelated donor

Conditioning:

- ☐ Myeloablative
- ☐ Non-myeloablative/reduced intensity

Check all conditioning agents that apply:

- ☐ BCNU or other nitrosourea
- ☐ Melphalan
- ☐ Cyclophosphamide
- ☐ Cytarabine
- ☐ Etoposide
- ☐ Clofarabine
- ☐ Busulfan ☐ IV ☐ Oral ☐ Pharmacokinetic targeted dosing
- ☐ Fludarabine
- ☐ Thiotepa
- ☐ Other: _____

Was total body radiation (TBI) included?

☐ Unknown ☐ N/A ☐ No ☐ Yes – *if yes, please indicate below:*

Date: _____Total Dose: _____Gray

Fractionated? ☐ Yes ☐ No

GVHD prophylaxis: _____

Was sirolimus prescribed post HSCT? ☐ Yes ☐ No

If yes, Start date: _____; Stop date: _____

VOD prophylaxis: ☐ Yes ☐ No ☐ Unknown

If yes, please specify:

Was post HSCT cyclophosphamide given? ☐ Yes ☐ No

HSCT #2: Date: _____

Donor:

- ☐ Autologous HSCT
- ☐ Matched related donor
- ☐ Mismatched related/haploidentical donor
- ☐ Matched unrelated donor
- ☐ Mismatched unrelated donor

Conditioning:

- ☐ Myeloablative
- ☐ Non-myeloablative/reduced intensity

Check all conditioning agents that apply:

- ☐ BCNU or other nitrosourea
- ☐ Melphalan
- ☐ Cyclophosphamide
- ☐ Cytarabine
- ☐ Etoposide
- ☐ Clofarabine
- ☐ Busulfan ☐ IV ☐ Oral ☐ Pharmacokinetic targeted dosing
- ☐ Fludarabine
- ☐ Thiotepa
- ☐ Other: _____

Was total body radiation (TBI) included?

☐ Unknown ☐ N/A ☐ No ☐ Yes – *if yes, please indicate below:*

Total Dose: _____**Gray**

Fractionated? ☐ Yes ☐ No

GVHD prophylaxis: _____

Was sirolimus prescribed post HSCT? ☐ Yes ☐ No;

If yes, Start date: _____; Stop date: _____

VOD prophylaxis: ☐ Yes ☐ No ☐ Unknown

If Yes please specify:

Was post HSCT cyclophosphamide given? ☐ Yes ☐ No

If patient received 3 or more HSCTs, please see end of this section for additional space

[13. Inotuzumab Ozogamicin] Did total bilirubin exceed 2 mg/dL (>34 µmol /L) prior to conditioning therapy?

☐ Yes ☐ No ☐ Unknown ☐ N/A

If yes,

Date of increase: _____>2 mg/dL (>34 µmol /L) _____

Peak total bilirubin value _____ mg/dL or µmol /L

Date of Peak Value (dd/mmm/yyyy) _____

Was elevated bilirubin and any other hepatic dysfunction associated with severe infection (such as sepsis/septic shock, pneumonia, etc)?

☐ Yes ☐ No If yes, please elaborate

[14. Inotuzumab Ozogamicin] Concomitant drugs of interest used during conditioning therapy. *Please mark all that apply:*

- ☐ Itraconazole
- ☐ Other azole(s), please list: _____
- ☐ Norethisterone

[15. Inotuzumab Ozogamicin] Diagnosis *(if applicable)*

Was hepatic VOD/SOS diagnosed?

☐ Unknown ☐ N/A ☐ No ☐ Yes –

If yes, please provide: Date (dd/mmm/yyyy) of diagnosis: _____

Number of days after last dose of **Inotuzumab Ozogamicin** to diagnosis: _____

Number of days from HSCT to diagnosis: _____

VOD/SOS diagnosis was based on *(mark all that apply):*

- ☐ Clinical scenario *(please list criteria):*
- ☐ Abnormal wedge hepatic vein pressure gradient *(please specify)*
- ☐ Radiographic findings *(please describe):*
- ☐ Liver biopsy showed *(please describe)*
- ☐ Autopsy showed *(please describe)*

[16. Inotuzumab Ozogamicin] Was there prior or concurrent evidence of GVHD?

☐ Yes ☐ No ☐ Unknown ☐ N/A

If yes, ☐ acute or ☐ chronic GVHD? Timeframe in relation to hepatic dysfunction? _____

GVHD: organs involved (check all that apply)

☐ Gastrointestinal tract ☐ Skin ☐ Liver

☐ Eyes ☐ Lungs ☐ Other organ(s): _____

GVHD treatment(s):_____

_____

[17 Inotuzumab Ozogamicin] Was there evidence of transfusion-refractory thrombocytopenia with no detectable cause?

☐ Yes ☐ No ☐ Unknown ☐ N/A

[18. Inotuzumab Ozogamicin] Did the patient experience any of the following concurrent with this hepatic event (check all that apply):

☐ Respiratory distress

If yes, was intubation/assisted ventilation required? ☐ Yes ☐ No

If yes, for how many days? _____

☐ Cardiovascular compromise requiring inotropic support

☐ Hepatic Encephalopathy

☐ Renal failure

☐ Admission to an intensive care unit (ICU) for management of hepatic failure?

If yes, for how many days? _____

☐ Unknown

☐ N/A

[19. Inotuzumab Ozogamicin] Outcome of the hepatic event?

☐ Resolved without intervention; Date of resolution: _____

☐ Resolved with intervention *(please specify)*

Defibrotide? ☐ No ☐ Yes Date administered _____

Ursodeoxycholic acid? ☐ No ☐ Yes Date administered _____

If other intervention(s) (list) were provided please list with dates:_____

☐ Event persisted ☐ Event Persisted for >100 days (post HSCT)

☐ Hepatic event was ongoing at time of death, but it was not the cause of death

☐ Hepatic event was the primary cause of death

☐ Hepatic event was a contributing cause of death

Additional Severe Hepatotoxicity Daptomycin Follow-up Questions

Please provide additional details on a separate page if needed, and reference the question number.

[1. Daptomycin] Did the patient present with any of the following signs or symptoms? Check all that apply

- ☐ Dark Urine
- ☐ Pruritus
- ☐ Anorexia
- ☐ Fever
- ☐ Nausea
- ☐ Pale stool
- ☐ Ascites
- ☐ Asthenia
- ☐ Asterixis / "Flapping tremor"
- ☐ Jaundice
- ☐ Fatigue
- ☐ Altered mental status
- ☐ Bleeding (specify location)
- ☐ Abdominal Pain (specify location)
- ☐ Other signs / symptoms *(including those related to infections, please specify)* _____
- ☐ None

[2. Daptomycin] Please mark whether the patient was taking any of the following medications / substances at the time of the adverse event or recently or within the past 6 months prior to the onset of the adverse event: *(Please provide details - specify the products generic names, dates off administration, and dosage)*

- ☐ Valproic acid
- ☐ Tetracycline
- ☐ Metronidazole
- ☐ 6-mercaptopurine
- ☐ Furosemide
- ☐ Acetaminophen/Paracetamol
- ☐ Nicotinic acid
- ☐ Steroids
- ☐ HMG Co-reductase inhibitors (statins)
- ☐ Amiodarone
- ☐ NSAIDS (e.g., ibuprofen)
- ☐ Methotrexate
- ☐ COX II inhibitors (e.g.,
- ☐ Antifungals (e.g., metronidazole)
- ☐ Thiazide Diuretics

[3. Daptomycin] Were any of the following laboratory tests / procedures performed? Please specify results with date(s) of test, results with units, and reference ranges. If a test was administered multiple times, please enter the date(s) of test, units, and reference ranges for each test in chronological order.

Laboratory Test / Procedure	Date Performed (DD-MMM-YYYY)	Results with units if applicable	Reference Ranges if applicable
☐ Hepatitis E serology & PCR			
☐ Erythrocyte Sedimentation Rate (ESR)			
☐ C-reactive protein			
☐ Ferritin			
☐ Fibrinogen			
☐ Haptoglobin			
☐ Liver Transplant (planned or completed)			
☐ Abdominal or hepatobiliary ultrasound			
☐ Autoantibody test			
☐ None			

Revision History

Revision	Effective Date	Summary of Revisions
2.0	09-Apr-2018	Addition of new questions for lack of efficacy for daptomycin products
1.0	22-May-2014	Existing DCA converted to latest DCA format.

Instructions for use:

Select questions as needed to obtain any DCA-defined information described below that was not included in the initial report.

AER/Manufacturer Report #: _____

Suspect product: _____

Reported event term prompting special follow-up activities: _____

Lack of Efficacy (Vaccine) Follow-up Questions

Please provide additional details on a separate page if needed, and reference the question number.

1. What is the primary infection site? ☐ Unknown ☐ Known

→If known, please specify: _____

*Please specify any secondary site(s) (e.g. empyema):*_____

2. Are there predisposing factors? ☐ Unknown ☐ No ☐ Yes

(*e.g. immunosuppression, contact with other infected persons*)

→ If Yes, please specify: _____

3. Was a culture performed?

☐ Unknown ☐ No ☐ Yes

→If Yes, was the culture positive? ☐ Unknown ☐ No ☐ Yes

→If Yes, was serotyping done? ☐ Unknown ☐ No ☐ Yes

→If Yes, please specify organism(s) (and serotype if available): _____

*Please specify the culture source (e.g. blood):*_____

4. Please provide Complete Vaccination Record:

Vaccine	Date Administered (DD-MMM-YYYY)	Dose Number	Manufacturer	Lot Number	Expiration Date

5. Please specify Antipyretic Use (around the date(s) of Vaccination):

Product Name / Strength	Dose / Route of Administration	Date Administered (DD-MMM-YYYY)	Time of Use (e.g., prior to, at the time of, or after Vaccination)
☐ Yes ☐ No ☐ Unknown *If yes, Specify:* _____			

6. Please provide relevant laboratory data:

Culture and Diagnostic Tests	Date performed (DD-MMM-YYYY)	Results	Reference range
☐ Blood culture *(include organism and serotype if available)*			
☐ CSF culture *(include organism and serotype if available)*			
☐ Pleural fluid culture *(include organism and serotype if available)*			
☐ Urine culture *(include organism and serotype if available)*			
☐ Other culture (please specify)			
☐ Chest X-ray			
☐ Other relevant tests (please specify)			

AER/Manufacturer Report #: _____

Suspect product: _____

Reported event term prompting this questionnaire: _____

Lack of Efficacy (Anti-infective) Follow-up Questions

[Anti-infective products] *Please provide additional details on a separate page if needed, and reference the question number.*

1. Was the failure of treatment thought to be due to the development of a resistance to the product?

☐ Unknown ☐ Yes ☐ No → If No, what is the suspected cause?

Details:

2. Was a culture performed <u>at the</u> time of treatment failure? ☐ Unknown ☐ No ☐ Yes

→ if yes, please specify site (blood, CSF, other)_____

→ If Yes, was the culture positive? ☐ No ☐ Yes

→If Yes, please specify organism(s) identified: _____

Was product susceptibility testing performed?

☐ Unknown ☐ No ☐ Yes

→ If Yes, please specify MIC values: _____ mg/L (µg/mL) and whether the interpretation was:

☐ Susceptible(S) ☐ Intermediate (I) ☐ Resistant(R)

3. Was a <u>baseline</u> culture performed? ☐ Unknown ☐ No ☐ Yes

→if yes, please specify site (blood, CSF, other): _____

→ If Yes, was the culture positive? ☐ No ☐ Yes

→ If Yes, please specify organism(s) identified: _____

Was product susceptibility testing performed?

☐ Unknown ☐ No ☐ Yes

→ If Yes, please specify MIC values: _____ mg/L (µg/mL) and whether the interpretation was:

☐ Susceptible(S) ☐ Intermediate (I) ☐ Resistant(R)

4. Please provide relevant laboratory data:

Diagnostic Tests	Date performed (DD-MMM-YYYY)	Results with units	Reference range
☐ Chest X-ray			
☐ Other relevant tests *(please specify)*			

Lack of Efficacy Questions for Reduced Susceptibility to Daptomycin in S.aureus

[Daptomycin cases] *Please provide additional details on a separate page if needed, and reference the question number.*

1. What was the date of primary infection diagnosis?
_____ *DD/MM/YYYY*

2. Was the patient bacteraemic?

☐ No *(please skip to Question 3)*

☐ Yes →

- What was the date of the diagnosis? _____ *DD/MM/YYYY*
- Was a focus of infection identified?

  ☐ Yes *(specify where)*

  ☐ No

3. Was a prosthetic device, intravascular device or intravascular graft present?

☐ No *(please skip to Question 5)*

☐ Yes →

- Was the object suspected or known to be the reservoir for the daptomycin-resistant isolate? ☐ **Yes** ☐ **No**
- Was the object removed/replaced prior to starting with daptomycin? ☐ **Yes** ☐ **No**

4. Was adjunctive surgery (e.g., debridement) indicated?
(Please specify if adjunct surgical intervention was indicated before or after daptomycin initiation)

☐ No *(please skip to Question 5)*

☐ Yes *(please specify type of adjunctive surgery and when it was indicated)* →

- Was the indicated adjunctive surgery performed?
  ☐ No *(please skip to Question 5)*
  ☐ Yes
- Was the indicated adjunctive surgery performed **prior** to starting daptomycin therapy?
  ☐ No *(please skip to Question 5)*
  ☐ Yes
- How many days of daptomycin therapy did the patient receive before it was performed? *(please specify)*

5. Was daptomycin therapy stopped when the daptomycin-resistant isolate was detected?

☐ Yes →

- Was the patient switched to another antibiotic therapy after stopping daptomycin?
  ☐ Yes *(please specify)*

  ☐ No

☐ No →

- Were other antibiotics given as well as daptomycin?
  ☐ Yes *(please specify an include if given concomitantly)*

  ☐ No

6. If the infection resolved, did it resolve on:

☐ daptomycin alone
☐ daptomycin in combination with other antibiotics
☐ Other antibiotics
☐ N/A

Please check the appropriate box above and enter additional antibiotic therapy in the box below. If none, please check here ☐

Additional Antibiotic Therapy Details:

Additional antibiotics administered *(If dose changed during therapy, list each dose separately)*	Indicate whether antibiotic replaced (R) or was concomitant (C) to daptomycin	Route of administration	Dosing Regimen or Daily Dose	Dates of Treatment *(dd/mm/yyyy)* Start date	Stop Date

7. Resistant Pathogen Details

Resistant Pathogen Details *(Please provide details of all isolates obtained from this patient in the table below):*

Pathogen	Date of isolation *(dd/mm/yyyy)*	Source of sample *(e.g., blood, urine, etc.)*	Daptomycin MIC Method[2]	Vancomycin[1] MIC Method[2]	Teicoplanin[1] MIC Method[2]	Linezolid[1] MIC Method[2]

[1] *Write N/A if one or more antibiotics was not tested*

[2] *If agar or broth was used to determine MIC, please specify the medium used (e.g., Mueller-Hinton agar, BHI broth, etc.)*

-For daptomycin, please specify if the medium was supplemented with calcium to 50 mg/L

If the daptomycin-resistant isolate was a Staphylococcus, was it methicillin-resistant?

☐ Yes ☐ No ☐ N/A

Was the daptomycin-resistant isolate sent to a Reference Laboratory for confirmatory testing?

☐ Yes *(please provide details including name of laboratory, city, and country, and results of testing for daptomycin MIC)*

☐ No

Was a baseline isolate obtained (i.e. an isolate obtained prior to starting daptomycin therapy)?

☐ Yes *(please provide details below)*

☐ No

Pathogen	Date of isolation *(dd/mm/yyyy)*	Source of sample *(e.g., blood, urine, etc.)*	Daptomycin Baseline MIC Method[1]

[1] *If agar or broth was used to determine MIC, please specify the medium used (e.g., Mueller-Hinton, agar, BHI broth, etc.)*

8. Other relevant Tests

Diagnostic Tests	Date performed (DD-MMM-YYYY)	Results with units	Reference range
☐ Other relevant tests (please specify)			

AER/Manufacturer Report #: _____

Suspect product: _____

Reported event term prompting this questionnaire: _____

Lack of Effect/Low Recovery (Haemophilia Products) Follow-up Questions

[Haemophilia products] *Please provide additional details on a separate page if needed, and reference the question number.*

1. Is the reported adverse event a:

☐ New event
☐ Recurrence *(please provide details on previous events)*
☐ Exacerbation of underlying condition *(please provide details)*

2. Please mark whether the reported event was any of the following:

☐ Lack of effect ☐ Inhibitor development
☐ Low recovery ☐ Less than expected therapeutic effect (LETE)

3. For the reported event, please specify:

Time from onset of the bleed to administration of the first dose of product: _____

Location and type of bleed treated (e.g., soft tissue, joint, target joint, muscle): _____

Did the bleed occur as the result of trauma? ☐ No ☐ Yes

Was the bleed into a known target joint? ☐ No ☐ Yes

If on Prophylaxis, how long after the last dose of product did the bleed occur? ☐ Hours: _____ ☐ Days: _____

Severity of the bleed: ☐ Mild ☐ Moderate ☐ Severe

Did the bleed resolve following product infusion? ☐ No ☐ Yes

Number of doses required for bleed resolution: _____

Was response as expected for this type of bleed? ☐ Yes ☐ No *If No, please explain*

Number of transfusions required: _____ ☐ None

4. Was a pre-filled syringe used?

☐ No ☐ Yes → If yes, please specify the following:

Lot number: _____*(please include a copy of the sticker, if available)*

Diluent used: ☐ Sodium Chloride ☐ Sterile Water ☐ Provided in kit

Vial Strength: _____IU

How was the product dosage determined?

☐ 0.5 UI/kg times desired FVIII rise times body weight (kg)
☐ 1.2 UI/kg times desired FIX rise times body weight (kg)
☐ 1.4 UI/kg times desired FIX rise times body weight (kg)
☐ Other *(please specify)*

Estimated total cumulative dose exposure: _____

Estimated number of total exposure days: _____

5. Please specify the patient's race:

☐ White
☐ Black
☐ Other *(please specify)*:_____

6. Please mark any of the following relative to the dose regimen at the time the event was detected:

☐ Prophylaxis: IU/kg: _____ Frequency: _____
→ If on prophylaxis, please specify whether
☐ Primary ☐ Secondary ☐ Continual ☐ Intermittent
☐ On Demand: IU/kg: _____ Frequency: _____
☐ Continuous Infusion: Dose regimen: _____
☐ Surgery - Bleeding occurred: ☐ During surgery ☐ After surgery

If surgery, please specify the following:

Type of surgery: _____

Description of event: _____

Estimated blood loss (EBL): _____ mL

Was EBL higher than expected for this type of surgery? ☐ No ☐ Yes

Did the patient require transfusion of RBCs? ☐ No ☐ Yes

→ If Yes, how many units? _____

Were additional (unplanned) factor infusion(s) given during or after surgery?
☐ Unknown ☐ No ☐ Yes

→ If Yes, Dose: _____ Number of infusions: _____

Patient's clinical status immediately post-operative? _____

Did the patient experience any thromboembolic events? ☐ No ☐ Yes

7. If product recovery or half-life study was done, please provide the date, product, dose (IU/kg), Pre/Post Infusion Time Draws, Factor Level (%), and Assay Used (chromogenic substrate, one stage clotting, one stage clotting with lab standard):

Details:

:

8. Please mark whether the patient had a relevant history of any of the following:

☐ Baseline Deficiency: ☐ Severe (<1%) ☐ Moderate (1-5%) ☐ Mild (>5%)
☐ Factor gene mutation *(please specify)*
☐ Known risk factors for thrombosis *(please specify)*
☐ Other relevant medical history *(please specify)*

9. Please mark whether the patient had a relevant family history of any of the following:

☐ Hemophilia ☐ Inhibitors
☐ Allergic reactions to Factor replacement products
☐ Other *(please specify)*

10. Was the patient evaluated for factor inhibitors prior to starting product?

☐ Unknown ☐ No ☐ Yes

→ If Yes, please provide the inhibitor results, date of results (DD-MMM-YYYY), and laboratory cutpoint / normal range (Bethesda Units):

Details:

11. Was the patient switched to another product after the adverse event(s) occurred?

☐ Unknown ☐ No ☐ Yes

→ If No, please provide current dose regimen:_____ and patient response: _____

→ If Yes, please specify product, start/stop date, dose regimen, frequency and reason for switching

Details:

12. Did the bleed resolved with the new product?

☐ Unknown ☐ No ☐ Yes

→ If Yes, please specify the number of doses of the new product required to resolve the bleed: _____

→ If Yes, was the response as expected for this type of bleed?

☐ Yes ☐ No → If No, please explain:

Details:

13. Did the patient experience similar events / symptoms after the switch to another product?

☐ Unknown ☐ No ☐ Yes → If Yes, please explain:

Details:

14. Was an inhibitor test performed after lack of effect, low recovery, or LETE was observed?

☐ Unknown ☐ No ☐ Yes

→ If Yes, please specify the date of the last infusion prior to inhibitor detection (DD-MMM-YYYY): _____

Please provide inhibitor results, including date of results (DD-MMM-YYYY), results (Bethesda Units), and laboratory cutpoint / normal range (Bethesda Units):

Details:

15. Did the patient have a relevant history of Inhibitors?

☐ Unknown ☐ Not tested ☐ No ☐ Yes

→ If Yes, please specify Type of Inhibitor:

☐ Type I ☐ Type II ☐ Unknown ☐ Not tested

→ If Yes, did the patient receive Immune Tolerance Therapy (ITT)?

☐ No ☐ Yes

→ If Yes, was ITT successful?

☐ Ongoing ☐ No ☐ Yes

→ If Yes, please provide ITT Product Brand Name, start/stop dates, dose regimen, and number of exposure days

Details:

16. Please specify prior Factor replacement products that the patient has received: *(specify product, dose/regimen, total cumulative dose, start/stop dates, estimated or known number of Exposure Days)*

17. Did the patient experience lack of effect, low recovery, less than expected therapeutic effect, or inhibitor development with the other products?

☐ Unknown ☐ No ☐ Yes

→ If Yes, please mark all that apply:

☐ Lack of effect ☐ Inhibitor Development
☐ Low Recovery ☐ Less than expected therapeutic effect (LETE)

18. If product recovery or half-life study was done with any *other* product, please provide the date, product, dose (IU/kg), Pre/Post Infusion Time Draws, Factor Level (%), and Assay Used (chromogenic substrate, one stage clotting, one stage clotting with lab standard):

Details:

Lack of Efficacy (Injectable contraceptives) Follow-up Questions

Please provide additional details on a separate page if needed, and reference the question number.

1. Which medicine did you inject?

☐ DMPA-SC pre-filled syringe (PFS) ☐ DMPA-SC pre-filled injector (PFI) ☐ Unknown

2. Was this the first time the medicine was injected?

☐ Yes ☐ No ☐ Unknown

If No, how many injections have you received up to now? *Please specify*:

If No, was the site of injection changed after the previous administration?

☐ Yes ☐ No ☐ Unknown

3. Did you inject the medicine yourself?

☐ Yes
☐ No
☐ Unknown
☐ Not Applicable

If Yes, did your health care provider instruct you how to self-inject?

☐ Yes ☐ No ☐ Unknown

If No, who injected the medicine?

☐ Medical Doctor ☐ Nurse ☐ Other *(please specify):*

4. Was the medicine administered according to the recommended dose?

☐ Yes ☐ No ☐ Unknown

5. Was the medicine administered according to the recommended schedule?

☐ Yes ☐ No ☐ Unknown

6. What route of administration was used?

☐ Subcutaneous ☐ Intramuscular ☐ Intravenous ☐ Other *(please specify):*

7. Was the medicine injected in the abdomen or front upper thigh?

☐ Yes → please specify if abdomen or front upper thigh: _____
☐ No → please specify where the medicine was injected: _____
☐ Unknown

8. Were the instructions for use followed to prepare the injection?

☐ Yes ☐ No ☐ Unknown

9. Was the medicine at room temperature?

☐ Yes ☐ No ☐ Unknown

10. Was the skin cleaned at the injection area?

☐ Yes ☐ No ☐ Unknown

11. Was the skin without any lesions at the injection area?

☐ Yes ☐ No ☐ Unknown

12. Was the medicine injected over a period of 5-7 seconds?

☐ Yes ☐ No ☐ Unknown

13. Was the dose administration successful?

☐ Yes ☐ No ☐ Unknown

If No, was any problem noticed with the injector?

☐ Leakage ☐ Occlusion
☐ Needle issue ☐ Other injector malfunction *(please specify):*

14. After administration of the medicine, did an unintended pregnancy occur?

☐ Yes ☐ No

15. Which type of test was performed to confirm pregnancy?

Please specify:

Lack of Efficacy (Cardiovascular) Follow-up Questions

Please provide additional details on a separate page, if needed and reference the question number.

1. Is the reported lack of efficacy a:

☐ New event
☐ Recurrence *(please provide details on previous events)*
☐ Exacerbation of underlying condition *(please provide details)*

Details:

2. Was the event confirmed by a health care professional?

☐ Unknown ☐ No ☐ Yes

3. Please specify whether the patient received any of the following treatments and provide details:

☐ Conservative management ☐ Surgery
☐ PTCA / Stent ☐ Thrombolytics
☐ Intravenous medications ☐ Electrical therapy
☐ Cardioversion ☐ Pacemaker
☐ Automated implantable cardiac defibrillator (AICD)
☐ Other *(please specify)*

Details:

4. Did an arrhythmia occur? Please specify

☐ Atrial ☐ Ventricular ☐ Junctional ☐ Unknown

5. Was an electrophysiology (EP) study done to identify the source of the arrhythmia?:

☐ Yes ☐ No ☐ Unknown

6. Did the patient have a <u>family history</u> of cardiovascular/cerebrovascular disease, sudden death, premature coronary artery disease (before 55 years old), transient ischaemic attack, stroke, or other relevant medical event?

☐ Unknown ☐ No ☐ Yes → *If Yes, please provide details*

7. Please provide the name, address and phone number of any specialist to whom the patient was referred for the lack of drug effect:

Details:

8. Please specify whether the patient experienced any of the following symptoms :

☐ Chest discomfort / chest pain
☐ Edema
☐ Dyspnea
☐ Cardiac failure
☐ Diaphoresis
☐ Heartburn and/or indigestion
☐ Chest pain radiating (please specify)
☐ Palpitations
☐ Other *(please specify)*

Details:

9. Did any cerebrovascular events occur?

☐ Bilateral blindness
☐ Ipsilateral blindness
☐ Visual field defects
☐ Contralateral hemiparesis,
☐ Sensory loss
☐ Aphasia
☐ Dysarthria
☐ Anosognosia
☐ Spatial disorientation
☐ Memory impairment
☐ Bulbar signs
☐ Cerebellar signs
☐ Ataxia
☐ Nausea,
☐ Dizziness,
☐ Headache
☐ Gaze paresis
☐ Other (please specify)

Details:

10. Specify whether the patient had a history of the following: *(Please provide details and indicate whether ongoing)*

- ☐ Atherosclerotic/vascular disease/angina/myocardial infarction/coronary artery disease
- ☐ Cerebrovascular accident (CVA)/transient ischemic attack (TIA)
- ☐ Cardiac arrhythmias/dysrhythmias/bradycardia/torsades de pointes/ventricular tachycardia/ventricular fibrillation/premature ventricular contractions/sick sinus syndrome/supraventricular tachycardia
- ☐ Valvular heart disease/mitral stenosis/aortic stenosis/mitral regurgitation/aortic regurgitation/mitral valve prolapse
- ☐ Cardiomegaly/cardiomyopathy
- ☐ Congenital heart defects (patent foramen ovale, patent ductus arteriosus, etc.)
- ☐ Heart failure/congestive heart failure/Cardiac insufficiency
- ☐ Left ventricular hypertrophy
- ☐ Right ventricular hypertrophy
- ☐ Acquired long QT syndrome/congenital long QT syndrome
- ☐ Pacemaker/automated implantable cardiac defibrillator (AICD)
- ☐ Hypercholesterolemia/hyperlipidemia/Hypertriglyceridemia/unspecified CV disease or arteriosclerosis
- ☐ Hypertension
- ☐ Hypotension
- ☐ Blood coagulation disorders/bood platelet disorder
- ☐ Myeloproliferative disorders and the hyperviscosity syndrome
- ☐ Inherited clotting disorder (e.g. thrombophilic and/or hypofibrinolytic coagulation disorders)
- ☐ Dizziness/fainting/presyncope/syncope/vertigo
- ☐ Peripheral vascular disease
- ☐ Diabetes mellitus
- ☐ Hyperthyroidism
- ☐ Ablation
- ☐ Renal disorder
- ☐ Smoking/acohol/substance abuse/Illicit drug use
- ☐ Other risk factors (social, occupational, environmental) *(please specify)*
- ☐ Other relevant history *(please specify)*

Details:

11. Was the patient taking any medication within <u>one month</u> preceding up to the time of the event: *(Please specify the product, generic name, indication, dates of administration, and dosage)*

Please specify:

Details:

12. Were any of the following performed? *Please specify results, including baseline results if available, with units, date of test, and reference ranges. Use additional pages, if needed*:

Diagnostic Test	Date Performed DD-MMM-YYYY	Results with units if applicable	Baseline Results		Reference Ranges if applicable
			Date Performed DD-MMM-YYYY	Results with units if applicable	
☐ QTc interval before and after product initiation (please indicate how the interval was measured)					
☐ CK *(before, during and after treatment)*					
☐ CK–MB *(before, during and after treatment)*					
☐ Troponin I level *(before, during and after treatment)*					
☐ Troponin T level *(before, during and after treatment)*					
☐ Serum potassium					
☐ Serum magnesium					
☐ Serum calcium					
☐ Blood urea nitrogen (BUN)					
☐ Serum creatinine					
☐ Creatinine clearance					
☐ Cardiac ejection fraction					
☐ Blood pressure					
☐ Heart rate					
☐ Cardiac catheterization					
☐ Echocardiogram					
☐ Electrocardiogram (ECG)					
☐ Stress test *(specify type)*					
☐ Angiogram *(pre/post surgery, if applicable)*					
☐ Autopsy (if applicable)					
☐ Ventilation / perfusion scan					
☐ Holter monitor					
☐ Toxicology screen					
☐ Hypercoagulability profile					
☐ Serum or plasma concentrations of concomitant medications					

Revision History

Revision	Effective Date	Summary of Revisions
4.0	09-Apr-2018	Addition of new questions for lack of efficacy for daptomycin products
3.0	16-May-2016	Addition of new questions for lack of efficacy cases for cardiovascular products
2.0	25-Feb-2016	Addition of new product-specific questions for DMPA-SC cases
1.0	18-Mar-2014	New DCA

ANNEX 5. PROTOCOLS FOR PROPOSED AND ON-GOING STUDIES IN RMP PART IV

Not applicable. There are no post-authorization efficacy studies (PAES) (neither proposed nor on-going) that are a specific obligation by the competent authorities and/or condition of the MA.

ANNEX 6. DETAILS OF PROPOSED ADDITIONAL RISK MINIMISATION ACTIVITIES (IF APPLICABLE)

Not applicable.

ANNEX 7 OTHER SUPPORTING DATA (INCLUDING REFERENCED MATERIALS)

TABLE OF CONTENTS

LIST OF TABLES

Annex 7.1. Part II: Module SVII.3 Details of Important Identified, Important Potential Risks (Clinical data-Adult population)

In the sections below, clinical data are presented by studies including adult population.

Adult studies: clinical data are presented for 1) integrated database,[*] 2) the IC/C safety database (for registration), [†]3) relevant studies in neutropenic subjects,[‡] and 4) relevant studies in subjects with DTI. [§]These data are presented for all important identified and potential risks with one exception: anaphylaxis, IARs, and exacerbation of infusion-related reactions are not presented for the integrated data because of differences in the criteria for identifying cases for these risks in the original trials versus completed trials (A8851021, A8851022 and regional studies).

Important Identified Risk: Anaphylaxis and Infusion-Associated Reactions

Frequency with 95% CI

Anaphylaxis

Anaphylaxis is a known safety issue which emerged in the postmarketing period. No cases of anaphylaxis have been reported during clinical trials (ICC safety database, in neutropenic subjects, or in subjects with DTI).

Infusion-Associated Reactions

Symptoms of flushing, shortness of breath, coughing, swollen face, hot feeling spreading to the face, feeling hot and sweaty were associated with anidulafungin infusion in a Phase 1 study (XBAE).

In the Phase 2/3 ICC studies, the anidulafungin adverse event data were coded using MedDRA Version 8.1. No specific code for systemic-type infusion reaction exists within MedDRA, thus retrospective identification of infusion reactions in the ICC Safety Database is challenging. The retrospective identification of infusion reactions is further complicated because the time of occurrence of adverse events was not captured in most Phase 2 and 3 studies, thus a temporal relationship to anidulafungin infusion cannot be established for specific adverse events. To maximize the opportunity to identify potential anidulafungin-related infusion reactions, the following search strategy was pursued.

[*] Studies include: IC/C Safety Database, A8851021 (neutropenic subjects), A8851022 (subjects with deep tissue infection, and regional studies A8851011, A8851015, A8851016, and A8851019.

[†] Studies include: VER002-6, VER002-9, VER002-9B.

[‡] Studies include: A8851021, neutropenic subject in registrational study VER 002-9 and regional studies A8851011, A8851015, A8851016, and A8851019.

[§] Studies include: A8851022 and subjects with deep tissue infection regional studies A8851011, A8851015, A8851016, and A8851019.

The listings of unique adverse event terms (SCS Listings 30-1.1 and 30-1.1A) was reviewed and revealed 5 unique terms that appeared to directly imply that a symptom occurred during a study drug infusion:

Unique Verbatim (Investigator) Adverse Event Terms Associated with Infusion-Related Reactions (Phase 2/3 Safety Database)

Adverse Event Verbatim Term	Coded Preferred Term
c/o feeling hot 2 hours into infusion	Feeling hot
Chills during study drug infusion	Chills
Flush on face during 3 first minutes of infusion	Flushing
Post-infusion diaphoresis	Hyperhydrosis
Pt became light headed during first infusion	Dizziness

These 5 events were experienced by 4 subjects (2 administered anidulafungin, 2 administered fluconazole). The individual cases were reviewed and all of these events were probable infusion reactions.

The Phase 2 and 3 data (integrated) were searched using an algorithmic approach described in the Standardized MedDRA Query (SMQ) for Anaphylactic Reaction. A case must have included 1 of the following:

A narrow term such as anaphylactic reaction, anaphylactic shock, anaphylactoid reaction, circulatory collapse or Type 1 hypersensitivity

An upper airway/respiratory term AND an angioedema/urticaria/pruritus/flush term

A cardiovascular/hypotension term AND an upper airway/respiratory term OR an angioedema/urticaria/pruritus/flush term

Nine (9) subjects were identified that met algorithmic criteria. The case data were reviewed for each of these subjects. Five (5) subjects were treated with anidulafungin, and 4 were treated with fluconazole.

Based on the case review, 1 subject experienced a possible infusion reaction of rash (VER002-0006-024-011) and another experienced probable infusion reactions of mild hypotension and mild flushing (XBAF-302-219). The other 7 subjects experienced events that appeared to be more likely due to other causes, such as underlying disease, than anidulafungin infusion.

A list of MedDRA preferred terms was compiled by reviewing SCS Table 5-1.1 and selecting preferred terms based on the collective information from the preclinical data, from the infusion reactions described in study XBAE, using the PTs correlating to the unique investigator terms that implied infusion reactions, and the adverse events identified by SMQ algorithm:

Angioneurotic edema
Chills
Cough
Hyperhydrosis
Hypersensitivity
Orbital edema

Drug hypersensitivity
Dyspnea
Dyspnea exacerbated
Dizziness
Erythema
Face edema
Feeling hot
Flushing
Hot Flush
Productive Cough
Rash erythematous
Respiratory distress
Swelling face
Swollen tongue
Tachypnea
Urticaria
Wheezing

These terms are non-specific and information was not available to determine if a temporal relationship existed between these events and anidulafungin infusion. To bring specificity to the search, only treatment-related events (investigator assessment) were selected.

ICC Dataset

When this comprehensive search strategy was applied to the ITT population treatment-related adverse events of flushing, hot flush, and urticaria were identified in the anidulafungin-treated subjects (Table 1). The total number of events was small, thus it is difficult to draw firm conclusions.

Table 1. Incidence of Treatment-Related Possible Infusion-Associated Adverse Events by Decreasing Frequency: ICC Safety Database

Preferred Term	Anidulafungin (N = 204)	
Number (%) of patients with at least 1 possible infusion-associated treatment-related adverse event	4 (2.0)	95% CI (0.5%, 4.9%)
Flushing	3 (1.5)	
Hot Flush	1 (0.5)	
Urticaria	1 (0.5)	
Chills	0	
Dizziness	0	
Feeling hot	0	
Hyperhydrosis	0	

Source: Table 21.21 (Pooled data)

Subjects with Neutropenia or Deep Tissue Infection

To identify cases potentially indicating infusion-associated reactions in relevant studies in neutropenic subjects and subjects with deep tissue infections, rather than using drug-related events (the methodology to identify these cases in ICC population), the all-causality AEs identified per the defined search strategy [Anaphylactic reaction, Angioedema SMQs (Broad and narrow) and PTs (Infusion related reaction, Hot flush, Chills, Dizziness, Feeling hot and Hyperhidrosis)] were filtered for latency (event had to occur during the anidulafungin infusion or within 60 minutes following completion of the anidulafungin infusion).

The results of this search are shown in Table 2 for neutropenic subjects and Table 3 for subjects with DTI. These frequencies do not reflect true rates of infusion-associated

reactions and are based on the wide search criterion used to identify all possible cases, given the various symptoms that may represent an infusion-associated reaction. A thorough review of the data suggests that majority of these AEs were associated with the underlying diseases or their complications rather than reflecting true IARs.

Table 2. Incidence of Treatment-Emergent Adverse Events Potentially Suggestive of Infusion-Associated Reactions: Events Occurring During Infusion or up to One Hour Afterwards: Patients with Neutropenia

Preferred term	Neutropenic Subjects[a] N=56[b]	
Total number (%) of subjects experiencing at least 1 AE that is potentially suggestive of anaphylaxis or infusion-associated reaction	12 (21.4)	95% CI (11.6%, 34.4%)
Acute respiratory failure	1 (1.8)	
Cardiac arrest	2 (3.6)	
Cough	2 (3.6)	
Drug hypersensitivity	1 (1.8)	
Dyspnoea	2 (3.6)	
Hypotension	1 (1.8)	
Oedema	2 (3.6)	
Rash	3 (5.4)	
Wheezing	1 (1.8)	

Sources: Table 21.13 (Pooled data)
Abbreviations: N = number of subjects
a: Protocols included in analysis: Neutropenic subjects from A8851011, A8851015, A8851016, A8851019 and A8851021. In addition to the above mentioned protocols, 3 subjects with neutropenia from study VER002-9 were included in this analysis.
Includes data up to 30 days after last dose of study drug.

Table 3. Incidence of Treatment-Emergent Adverse Events Potentially Suggestive of Infusion-Associated Reactions: Events Occurring During Infusion or up to One Hour Afterwards: Patients with Deep Tissue Infection

Preferred term	Subjects with Deep Tissue Infection[a] N=131	
Total number (%) of subjects experiencing at least 1 AE that is potentially suggestive of anaphylaxis or infusion-associated reaction	23 (17.6)	95% CI (11.5%, 25.2%)
Acute respiratory failure	3 (2.3)	
Bronchial oedema	1 (0.8)	
Bronchospasm	2 (1.5)	
Cardiac arrest	4 (3.1)	
Chills	1 (0.8)	
Cough	1 (0.8)	
Dyspnoea	1 (0.8)	
Erythema	1 (0.8)	
Generalised oedema	2 (1.5)	
Hypotension	4 (3.1)	
Oedema	2 (1.5)	
Oedema peripheral	1 (0.8)	
Pruritus	1 (0.8)	
Rash	2 (1.5)	
Respiratory failure	2 (1.5)	
Scrotal oedema	1 (0.8)	

Sources: Table 21.14 (Pooled data)
Abbreviations: N = number of subjects
a: Protocols included in analysis: Subjects with deep tissue from A8851011, A8851015, A8851016, A8851019 and A8851022.
Includes data up to 30 days after last dose of study drug.

Seriousness/outcomes

ICC Dataset

None of the infusion-related reactions in the ICC Dataset were reported as serious adverse events. There were no events identified as infusion reactions in the ICC Dataset that had an outcome of 'ongoing', 'other', 'unknown', or 'death'; all events had an outcome of 'recovered.'

Subjects with Neutropenia or Deep Tissue Infection

A thorough review of the data in subjects with neutropenia or DTI suggest that majority of these AEs were associated with the underlying diseases or their complications rather than reflecting true infusion-associated reactions. Of the remaining AEs that were potential symptoms of infusion-associated reactions and likely due to administration of anidulafungin, none were serious and most resolved.

Severity and nature of risk

Treatment-related AEs identified using the search strategy above were considered as potential infusion-associated reactions in ICC dataset and all events identified as infusion-associated reactions were either mild or moderate in the ICC safety database (see Table 4).

In the studies with neutropenic subjects and subjects with deep tissue infections, infusion-associated reactions were filtered for latency of during infusion or up to 1 hour later (Table 5 and Table 6). None of the severe cases were true IARs. Severe cases of anaphylactic reactions including shock were observed in post-marketing reports.

Table 4. Incidence and Outcome of Treatment-Related Possible Infusion-Associated Adverse Events: ICC Dataset

	Anidulafungin 100 mg (N = 204)		
Preferred Term	**Overall n**	**Mild n (%)**	**Moderate n (%)**
Chills	0	0	0
Dizziness	0	0	0
Feeling hot	0	0	0
Flushing	3	2 (1.0)	1 (0.5)
Hot flush	1	1 (0.5)	0
Hyperhydrosis	0	0	0
Urticaria	1	0	1 (0.5)

Source: phase2_3 Table RMP-AE-2.1.1

Table 5. Incidence and Outcome of Treatment-Emergent Adverse Events Potentially Suggestive of Infusion Associated Reactions: Events Occurring During Infusion or up to One Hour Afterwards: Patients with Neutropenia

	Neutropenic Subjects[a] N=56			
Preferred term	**N (%)**	**Mild**	**Mod**	**Sev**
Acute respiratory failure	1 (1.8)	0	0	1
Cardiac arrest	2 (3.6)	0	0	2
Cough	2 (3.6)	1	1	0
Drug hypersensitivity	1 (1.8)	1	0	0
Dyspnoea	2 (3.6)	1	0	1
Hypotension	1 (1.8)	0	0	1
Oedema	2 (3.6)	2	0	0
Rash	3 (5.4)	2	1	0
Wheezing	1 (1.8)	1	0	0

Source: Table 19.1.1.1a (Pooled Data)
Terms searched: SMQ (Broad and narrow) - Anaphylactic reaction, Angioedema; Preferred Term(s) - Infusion related reaction, Hot flush, Chills, Dizziness, Feeling hot, Hyperhidrosis.
Abbreviations: N = number of subjects
a: Protocols included in analysis: A8851011, A8851015, A8851016, A8851019 and A8851021.
Includes data up to 30 days after last dose of study drug.
When a dictionary other than MedDRA was used, percentages of gender specific events are calculated using the corresponding gender count as denominator.
MedDRA version 16.0 coding dictionary applied.

Table 6. Incidence and Outcome of Treatment-Emergent Adverse Events Potentially Suggestive of Infusion Associated Reactions: Events Occurring During Infusion or up to One Hour Afterwards: Patients with Deep Tissue Infection

	Subjects with Deep Tissue Infection[a] N=131			
Preferred term	**N (%)**	**Mild**	**Mod**	**Sev**
Acute respiratory failure	3 (2.3)	0	1	2
Bronchial oedema	1 (0.8)	0	1	0
Bronchospasm	2 (1.5)	1	1	0
Cardiac arrest	4 (3.1)	0	0	4
Chills	1 (0.8)	0	1	0
Cough	1 (0.8)	1	0	0
Dyspnoea	1 (0.8)	1	0	0
Erythema	1 (0.8)	1	0	0
Generalised oedema	2 (1.5)	1	1	0
Hypotension	4 (3.1)	0	3	1
Oedema	2 (1.5)	1	1	0
Oedema peripheral	1 (0.8)	1	0	0
Pruritus	1 (0.8)	0	1	0
Rash	2 (1.5)	2	0	0
Respiratory failure	2 (1.5)	0	1	1
Scrotal oedema	1 (0.8)	1	0	0

Source: Table 19.1.2.1a (Pooled Data).
Terms searched: SMQ (Broad and narrow) - Anaphylactic reaction, Angioedema; Preferred Term(s) - Infusion related reaction, Hot flush, Chills, Dizziness, Feeling hot, Hyperhidrosis.
Abbreviations: N = number of subjects
a: Protocols included in analysis: A8851011, A8851015, A8851016, A8851019 and A8851022.
Includes data up to 30 days after last dose of study drug.
When a dictionary other than MedDRA was used, percentages of gender specific events are calculated using the corresponding gender count as denominator.
MedDRA version 16.0 coding dictionary applied.

Important Identified Risk: Hepatobiliary Events

Frequency with 95% CI

In the Phase 2/3 studies, dose-related elevations in hepatobiliary laboratory tests were not as clearly identified as they were in Phase 1. However, these patients often had severe underlying illness and were receiving many concurrent medications, complicating the interpretation of the data. Many of the patients who had hepatobiliary abnormalities during the study also had abnormalities present at baseline. The frequencies of post-baseline hepatobiliary abnormalities were similar in the total anidulafungin and total fluconazole treatment groups; within each treatment group, the proportions of patients experiencing post-baseline hepatobiliary abnormalities were not grossly different between patients treated for ≤14 days and those treated for > 14 days (SCS Table 21-1).

To aid in the review of adverse events that could possibly be indicative of hepatic damage or dysfunction, the MedDRA Hepatic Disorders SMQ was used to search the anidulafungin

adverse event Safety Database. This SMQ employs a comprehensive search of all terms possibly related to disorders of the liver, irrespective of whether they are possibly related to drug effects. It includes a number of sub-searches on some specific liver related topics and searches for terms for potentially drug related liver disorders. This SMQ is quite broad and contains 11 stand-alone topics. For the purposes of searching the ICC Safety Database, 6 of these SMQs were used. These were selected on the basis of their relevance to the population studied and the types of hepatic disorders of interest for anidulafungin. Laboratory test result adverse events that could be related to hepatic disorders are included in the SMQs, an advantage to searching strictly on the basis of adverse events directly related to hepatic disorders.

Hepatic Disorders SMQ

SMQ Code	SMQ Term
20000008*	Liver related investigations, signs and symptoms
20000009*	Cholestasis and jaundice of hepatic origin
20000010*	Hepatitis, non-infectious
20000011	Liver neoplasms, malignant and unspecified
20000012	Liver neoplasms, benign
20000013*	Hepatic failure, fibrosis and cirrhosis and other liver damage-related conditions
20000014	Congenital, familial, neonatal and genetic disorders of the liver
20000015*	Possible liver-related coagulation and bleeding disturbances
20000016*	Liver infections
20000017	Events specifically reported as alcohol-related
20000018	Pregnancy-related hepatic disorders

* SMQs used to search ICC Safety Database

Integrated Database (ICC + Regional Studies + A8851021 + A8851022)

Table 7 shows all-causality hepatobiliary disorders in the integrated clinical studies (ICC studies, regional studies, study A8851021, and A8851022).

Table 7. Incidence of All-Causality Hepatobiliary Adverse Events: Integrated Data (ICC Studies + Regional Studies + A8851021 + A8851022)

MedDRA Preferred Term	Anidulafungin (n=840)	
Total number of subjects experiencing at least 1 hepatobiliary AE	149 (17.7)	95% CI (15.2%, 20.5%)
Alanine aminotransferase abnormal	2 (0.2)	
Alanine aminotransferase increased	17 (2.0)	
Ascites	15 (1.8)	
Aspartate aminotransferase abnormal	1 (0.1)	
Aspartate aminotransferase increased	16 (1.9)	
Blood alkaline phosphatase abnormal	2 (0.2)	
Blood alkaline phosphatase increased	46 (5.5)	
Blood bilirubin increased	8 (1.0)	
Blood fibrinogen decreased	1 (0.1)	
Cholecystitis	5 (0.6)	
Cholestasis	8 (1.0)	
Chronic hepatic failure	1 (0.1)	
Gamma-glutamyl-transferase increased	7 (0.8)	
Gastric varices	1 (0.1)	
Hepatic cyst	1 (0.1)	
Hepatic encephalopathy	2 (0.2)	
Hepatic enzyme increased	7 (0.8)	
Hepatic failure	6 (0.7)	
Hepatic function abnormal	1 (0.1)	
Hepatic lesion	1 (0.1)	
Hepatocellular injury	2 (0.2)	
Hepatomegaly	2 (0.2)	
Hepatosplenomegaly	1 (0.1)	
Hepatotoxicity	1 (0.1)	
Hyperammonaemia	1 (0.1)	
Hyperbilirubinaemia	6 (0.7)	
Hypoalbuminaemia	14 (1.7)	
International normalized ratio increased	7 (0.8)	
Ischaemic hepatitis	1 (0.1)	
Jaundice	8 (1.0)	
Jaundice cholestatic	1 (0.1)	
Liver abscess	4 (0.5)	
Liver disorder	2 (0.2)	
Liver function test abnormal	8 (1.0)	
Pneumobilia	2 (0.2)	
Prothrombin time abnormal	1 (0.1)	
Prothrombin time prolonged	2 (0.2)	
Transaminases increased	3 (0.4)	

Source: Table 21.9 (Pooled data)

ICC Dataset

Table 8 shows all-causality hepatobiliary disorders in the ICC database.

Table 8. Incidence of All-Causality Hepatobiliary Adverse Events: ICC Safety Database

Preferred Term	Anidulafungin (N = 204)	
Patients with at least 1 hepatic adverse event	53 (26.0)	95% CI (20.1%, 32.6%)
Alanine aminotransferase abnormal	1 (0.5)	
Alanine aminotransferase increased	10 (4.9)	
Ascites	5 (2.5)	
Aspartate aminotransferase increased	8 (3.9)	
Blood alkaline phosphatase abnormal	1 (0.5)	
Blood alkaline phosphatase increased	27 (13.2)	
Blood bilirubin increased	6 (2.9)	
Blood fibrinogen decreased	1 (0.5)	
Cholestasis	1 (0.5)	
Gamma-glutamyl-transferase increased	4 (2.0)	
Hepatic enzyme increased	3 (1.5)	
Hepatic failure	1 (0.5)	
Hepatic function abnormal	1 (0.5)	
Hepatomegaly	1 (0.5)	
Hyperbilirubinemia	1 (0.5)	
Hypoalbuminemia	4 (2.0)	
Ischaemic hepatitis	1 (0.5)	
Jaundice	2 (1.0)	
Liver function test abnormal	5 (2.5)	
Prothrombin time abnormal	1 (0.5)	
Transaminases increased	1 (0.5)	

Source: Table 21.12 (Pooled data)

Subjects with Neutropenia or Deep Tissue Infection

The defined search criteria were also used to identify hepatobiliary events in relevant studies in subjects with neutropenia or deep tissue infections (Table 9 and Table 10, respectively).

Table 9. Incidence of All Causality Hepatobiliary Adverse Events: Patients with Neutropenia

Preferred term	Neutropenic Subjects[a] N=56	
Number (%) of Subjects with at least one Adverse Event	12 (21.4)	95% CI (11.6%, 34.4%)
Alanine aminotransferase increased	3 (5.4)	
Ascites	1 (1.8)	
Aspartate aminotransferase increased	2 (3.6)	
Blood alkaline phosphatase increased	5 (8.9)	
Blood bilirubin increased	1 (1.8)	
Cholestasis	1 (1.8)	
Gamma-glutamyltransferase increased	2 (3.6)	
Hyperbilirubinaemia	2 (3.6)	
Hypoalbuminaemia	2 (3.6)	
Liver disorder	1 (1.8)	
Liver function test abnormal	2 (3.6)	

Source: Table 21.10 (Pooled data)
Abbreviations: N = number of subjects
a: Protocols included in analysis: A8851011, A8851015, A8851016, A8851019 and A8851021. In addition to the above mentioned protocols, 3 subjects with neutropenia from study VER002-9 were included in this analysis.
Includes data up to 30 days after last dose of study drug.
MedDRA version 16.0 coding dictionary applied.

Table 10. Incidence of All Causality Hepatobiliary Adverse Events: Patients with Deep Tissue Infection

Preferred term	Subjects with Deep Tissue Infection[a] N=131	
Number (%) of Subjects with at least one Adverse Event	26 (19.8)	95% CI (13.4%, 27.7%)
Ascites	2 (1.5)	
Aspartate aminotransferase increased	2 (1.5)	
Blood alkaline phosphatase increased	10 (7.6)	
Cholestasis	3 (2.3)	
Hepatic encephalopathy	1 (0.8)	
Hepatic enzyme increased	3 (2.3)	
Hepatic failure	3 (2.3)	
Hyperbilirubinaemia	1 (0.8)	
Hypoalbuminaemia	2 (1.5)	
Jaundice	1 (0.8)	
Liver disorder	1 (0.8)	
Liver abscess	2 (1.5)	
Prothrombin time prolonged	1 (0.8)	

Source: Table 21.11 (Pooled data)
Abbreviations: N = number of subjects
a: Protocols included in analysis: A8851011, A8851015, A8851016, A8851019 and A8851022.
Includes data up to 30 days after last dose of study drug.
MedDRA version 16.0 coding dictionary applied.

In clinical studies with anidulafungin, altered tests of hepatic enzymes were reported. In Phase 1 studies, 9.4% (19/202) and 5.9% (12/202) patients experienced AST or ALT elevations, respectively (SCS Table 5-1.1B). Most of these events occurred in Study VER002-15 (5 events of raised ALT, 3 events of raised AST), an interaction study with tacrolimus, which is known to be associated with abnormal liver function tests. Eight (8) additional events occurred in Study VER002-5, which was a dose escalation study of IV anidulafungin using loading/maintenance doses of 150/75, 200/100 and 260/130 mg (each for 10 days). The events in Study VER002-5 all were associated with administration of the highest dose.

Seriousness/outcomes

Integrated Database (ICC + Regional Studies + A8851021 + A8851022)

Hepatobiliary adverse events reported as serious adverse events in the integrated clinical studies are shown in Table 11. The events of hepatic failure and chronic hepatic failure (2 subjects, each) resulted in death, but the investigator deemed that these events were unrelated to anidulafungin. International normalized ratio increased and pneumobilia (1 subject, each) had outcomes of ongoing and liver function test (1 subject) had an outcome of unknown. All other serious adverse events resolved.

Table 11. Incidence of All-Causality Hepatobiliary Adverse Events Reported as Serious Adverse Events: Integrated Data (ICC Studies + Regional Studies + A8851021 + A8851022)

MedDRA Preferred Term	Anidulafungin (N=840)
Ascites	2 (0.2%)
Cholecystitis	2 (0.2%)
Chronic hepatic failure	2 (0.2%)
Hepatic enzyme increased	1 (0.1%)
Hepatic failure	2 (0.2%)
Hepatic function abnormal	1 (0.1%)
Hypoalbuminaemia	1 (0.1%)
International normalized ratio increased	1 (0.1%)
Liver function test abnormal	1 (0.1%)
Pneumobilia	1 (0.1%)

SAEs are from the project database.
Source: SCS Table 9-1.1 (original dossier); Table 16.6 (Regional Studies Pooled Data); CSR A8851021, Table 50; CSR A8851022, Tables 51 and 52.

Table 12. Incidence and Outcome of All-Causality Hepatobiliary Adverse Events: Integrated Data (ICC Studies + Regional Studies + A8851021 + A8851022)

MedDRA Preferred Term	Anidulafungin (N=840)		
		Recovered	Ongoing
	N (%)	n (%)	n (%)
Alanine aminotransferase abnormal	2 (0.2)	2 (0.2)	0
Alanine aminotransferase increased	17 (2.0)	13 (1.5)	4 (0.5)
Ascites	15 (1.8)	(10 1.2)	5 (0.6)
Aspartate aminotransferase abnormal	1 (0.1)	1 (0.1)	0
Aspartate aminotransferase increased	16 (1.9)	13 (1.5)	3 (0.4)
Blood alkaline phosphatase abnormal	2 (0.2)	1 (0.1)	1 (0.1)
Blood alkaline phosphatase increased	46 (5.5)	22 (2.6)	24 (2.9)
Blood bilirubin increased	8 (1.0)	6 (0.7)	2 (0.2)
Blood fibrinogen decreased	1 (0.1)	1 (0.1)	0
Cholecystitis	5 (0.6)	4 (0.5)	1 (0.1)
Cholestasis	8 (1.0)	5 (0.6)	3 (0.4)
Chronic hepatic failure	1 (0.1)	0	1 (0.1)
Gamma-glutamyl-transferase increased	7 (0.8)	4 (0.5)	3 (0.4)
Gastric varices	1 (0.1)	0	1 (0.1)
Hepatic cyst	1 (0.1)	0	1 (0.1)
Hepatic encephalopathy	2 (0.2)	2 (0.2)	0
Hepatic enzyme increased	7 (0.8)	6 (0.7)	1 (0.1)
Hepatic failure	6 (0.7)	1 (0.1)	5 (0.6)
Hepatic function abnormal	1 (0.1)	0	1 (0.1)
Hepatic lesion	1 (0.1)	1 (0.1)	0
Hepatocellular injury	2 (0.2)	2 (0.2)	0
Hepatomegaly	2 (0.2)	1 (0.1)	1 (0.1)
Hepatosplenomegaly	1 (0.1)	0	1 (0.1)
Hepatotoxicity	1 (0.1)	1 (0.1)	0
Hyperammonaemia	1 (0.1)	0	1 (0.1)
Hyperbilirubinaemia	6 (0.7)	5 (0.6)	1 (0.1)
Hypoalbuminaemia	14 (1.7)	6 (0.7)	8 (1.0)
International normalized ratio increased	7 (0.8)	6 (0.7)	1 (0.1)
Ischaemic hepatitis	1 (0.1)	0	1 (0.1)
Jaundice	8 (1.0)	4 (0.5)	4 (0.5)
Jaundice cholestatic	1 (0.1)	0	1 (0.1)
Liver abscess	4 (0.5)	3 (0.4)	1 (0.1)
Liver disorder	2 (0.2)	1 (0.1)	1 (0.1)
Liver function test abnormal	8 (1.0)	5 (0.6)	3 (0.4)
Pneumobilia	2 (0.2)	2 (0.2)	0
Prothrombin time abnormal	1 (0.1)	1 (0.1)	0
Prothrombin time prolonged	2 (0.2)	1 (0.1)	1 (0.1)
Transaminases increased	3 (0.4)	1 (0.1)	2 (0.2)

Source: Table 21.4 (Pooled data)

ICC Dataset

Four subjects in the ICC Dataset had hepatobiliary SAEs (2 events of liver function test abnormal and 1 event each of cholecystitis and hepatic function abnormal). Overall, in the ICC Dataset, there were no hepatobiliary events that had an outcome of 'other', 'unknown', or 'death'; all events had an outcome of 'recovered' or 'ongoing'. The frequency for these events and outcomes is presented in Table 13.

Table 13. Incidence and Outcome of All-Causality Hepatobiliary Adverse Events Reported as Adverse Events: ICC Safety Database

	Anidulafungin (N = 204)		
Preferred Term	**Overall n**	**Recovered n (%)**	**Ongoing n (%)**
Ascites	5	2 (1.0)	3 (1.5)
Blood alkaline phosphatase abnormal	1	0	1 (0.5)
Blood alkaline phosphatase increased	27	10 (4.9)	17 (8.3)
Blood bilirubin increased	6	4 (2.0)	2 (1.0)
Blood fibrinogen decreased	1	1 (0.5)	0 (0.0)
Cholestasis	1	0	1 (0.5)
Hepatic candidiasis	0	0	0
Hepatic encephalopathy	0	0	0
Hepatic enzyme increased	3	2 (1.0)	1 (0.5)
Hepatic failure	1	0	1 (0.5)
Hepatic function abnormal	1	0	1 (0.5)
Hepatic pain	0	0	0
Hepatitis C	0	0	0
Hepatomegaly	1	0	1 (0.5)
Hyperbilirubinemia	1	1 (0.5)	0
Hypoalbuminemia	4	0	4 (2.0)
Ischemic hepatitis	1	0	1 (0.5)
Jaundice	2	2 (1.0)	0
Liver disorder	0	0	0
Liver function test abnormal	5	2 (1.0)	3 (1.5)
Prothrombin time abnormal	1	1 (0.5)	0
Prothrombin time prolonged	0	0	0
Transaminases increased	1	1 (0.5)	0

Source: phase2_3 Table RMP-AE-2.2.3

Subjects with Neutropenia or Deep Tissue Infection

Of the 12 neutropenic subjects who experienced hepatobiliary events, 1 subject reported an SAE (Liver Function Test (LFT) abnormal. This patient experiencing an abnormal LFT received concomitant medications that were hepatotoxic and were reported as co-suspects. The patient was hospitalized, but the final outcome of the event was listed unknown.

Of the 26 subjects with DTI, 2 subjects reported SAEs of hepatic failure. Both were due to underlying disease conditions and had an outcome of death.

Severity and nature of risk

Integrated Database (ICC + Regional Studies + A8851021 + A8851022)

For the integrated studies, most hepatobiliary adverse events were reported as either mild or moderate (Table 14).

Table 14. Incidence and Severity of All-Causality Hepatobiliary Adverse Events: Integrated Data (ICC Studies + Regional + A8851021 + A8851022)

		Anidulafungin (n=840)		
		Severity*		
MedDRA Preferred Term	**N (%)**	**Mild**	**Moderate**	**Severe**
Alanine aminotransferase abnormal	2 (0.2)	1	1	0
Alanine aminotransferase increased	17 (2.0)	16	0	1
Ascites	15 (1.8)	7	6	2
Aspartate aminotransferase abnormal	1 (0.1)	1	0	0
Aspartate aminotransferase increased	16 (1.9)	14	2	0
Blood alkaline phosphatase abnormal	2 (0.2)	0	2	0
Blood alkaline phosphatase increased	46 (5.5)	28	17	1
Blood bilirubin increased	8 (1.0)	4	2	2
Blood fibrinogen decreased	1 (0.1)	1	0	0
Cholecystitis	5 (0.6)	1	3	1
Cholestasis	8 (1.0)	3	3	2
Chronic hepatic failure	1 (0.1)	0	0	1
Gamma-glutamyltransferase increased	7 (0.8)	1	3	3
Gastric varices	1 (0.1)	0	1	0
Hepatic cyst	1 (0.1)	1	0	0
Hepatic encephalopathy	2 (0.2)	1	1	0
Hepatic enzyme increased	7 (0.8)	5	2	0
Hepatic failure	6 (0.7)	0	1	5
Hepatic function abnormal	1 (0.1)	0	0	1
Hepatic lesion	1 (0.1)	1	0	0
Hepatocellular injury	2 (0.2)	0	2	0
Hepatomegaly	2 (0.2)	1	1	0
Hepatosplenomegaly	1 (0.1)	0	0	1
Hepatotoxicity	1 (0.1)	0	1	0
Hyperammonaemia	1 (0.1)	0	1	0
Hyperbilirubinaemia	6 (0.7)	2	4	0
Hypoalbuminaemia	14 (1.7)	4	7	3
International normalised ratio increased	7 (0.8)	1	5	1
Ischaemic hepatitis	1 (0.1)	0	0	1
Jaundice	8 (1.0)	3	4	1
Jaundice cholestatic	1 (0.1)	1	0	0
Liver abscess	4 (0.5)	2	0	2
Liver disorder	2 (0.2)	1	1	0
Liver function test abnormal	8 (1.0)	2	4	2
Pneumobilia	2 (0.2)	0	1	1
Prothrombin time abnormal	1 (0.1)	1	0	0
Prothrombin time prolonged	2 (0.2)	2	0	0
Transaminases increased	3 (0.4)	2	1	0

Table 14. Incidence and Severity of All-Causality Hepatobiliary Adverse Events: Integrated Data (ICC Studies + Regional + A8851021 + A8851022)

		Anidulafungin (n=840)		
		Severity*		
MedDRA Preferred Term	**N (%)**	**Mild**	**Moderate**	**Severe**

* If the same subject in a given treatment had more than one occurrence in the same preferred term event category, only the most severe occurrence is taken.
Source: Table 21.1 (Pooled data)

ICC Dataset

Severe Hepatic Injuries

A Hepatic Expert Report was prepared by an external hepatologist (summarized in SCS Section 2.7.4.2.1.6.1), and a Hepatic Safety Summary was compiled. The Expert Report reviewed any cases of patients from Studies VER002-4, -5, -6, -7, -9, -11, -12, and -15 who met a conservative definition of 'Hy's Rule'; patients who experienced both an elevation in ALT (> 2 × ULN) and a concomitant or up to 1 month delayed elevation in bilirubin (at least 1.5 × ULN). Ten (10) such patients from anidulafungin treatment groups and 8 from fluconazole groups were identified and reviewed. The primary findings of the report were that:

There were proportionately more Hy's Rule cases receiving fluconazole compared to anidulafungin. This likely reflects liver injuries that can occur from multiple etiologies in desperately ill patients.

There was 1 Hy's Rule case among the anidulafungin treated patients that was considered to be related to anidulafungin treatment. The onset of hepatic injury appeared to be gradual allowing for recognition of the process at an early stage.

The report concluded that the "risk of irreversible liver injury from short term treatment (< 2 weeks) with anidulafungin appears to be low, and in line with the risk from systemic fluconazole treatment in the patient populations studied." The expert report also concluded that it was reasonable to provide caution to physicians to monitor for evidence of abnormal or worsening hepatic function in patients who develop abnormal ALT during anidulafungin therapy.

All Hepatobiliary Adverse Events in the ICC Dataset

The majority of hepatic events were mild or moderate in severity (see Table 15). There were 9 events classified as severe and 1 event classified as life-threatening in the anidulafungin arm. It should be noted that 'life-threatening' was an option for classification of severity only in Study VER002-6. There is no new information about the severity or nature of the risk from anidulafungin based on available post-marketing information.

Table 15. Incidence and Severity of All-Causality Hepatobiliary Adverse Events: Integrated Data ICC Safety Database

	Anidulafungin (N = 204)				
Preferred Term	**Overall n**	**Mild n (%)**	**Moderate n (%)**	**Severe n (%)**	**Life Threatening n (%)**
Ascites	5	2 (1.0)	2 (1.0)	1 (0.5)	0
Blood alkaline phosphatase abnormal	1	0	1 (0.5)	0	0
Blood alkaline phosphatase increased	27	18 (8.8)	8 (3.9)	1 (0.5)	0
Blood bilirubin increased	6	3 (1.5)	1 (0.5)	2 (1.0)	0
Blood fibrinogen decreased	1	1 (0.5)	0	0	0
Cholestasis	1	0	1 (0.5)	0	0
Hepatic candidiasis	0	0	0	0	0
Hepatic encephalopathy	0	0	0	0	0
Hepatic enzyme increased	3	2 (1.0)	1 (0.5)	0	0
Hepatic failure	1	0	0	0	0
Hepatic function abnormal	1	0	0	1 (0.5)	0
Hepatic pain	0	0	0	0	0
Hepatitis C	0	0	0	0	0
Hepatomegaly	1	0	1 (0.5)	0	0
Hyperbilirubinemia	1	0	1 (0.5)	0	0
Hypoalbuminemia	4	1 (0.5)	2 (1.0)	1 (0.5)	0
Ischemic hepatitis	1	0	0	1 (0.5)	0
Jaundice	2	0	2 (1.0)	0	0
Liver disorder	0	0	0	0	0
Liver function test abnormal	5	2 (1.0)	1 (0.5)	2 (1.0)	0
Prothrombin time abnormal	1	1 (0.5)	0	0	0
Prothrombin time prolonged	0	0	0	0	0
Transaminases increased	1	1 (0.5)	0	0	0

Life Threatening option for classification of severity only in Study VER002-6
Source: phase2_3 Table RMP-AE- 2.1.3

Subjects with Neutropenia or Deep Tissue Infection

For the subjects with neutropenia or deep tissue infection, most hepatobiliary adverse events were either mild or moderate in severity (see Table 16 and Table 17, respectively).

Table 16. Incidence and Severity of All Causality Hepatobiliary Adverse Events: Subjects with Neutropenia

	Neutropenic Subjects[a] N=56			
Preferred term	**N (%)**	**Mild**	**Mod**	**Sev**
Alanine aminotransferase increased	3 (5.4)	2	0	1
Aspartate aminotransferase increased	2 (3.6)	1	1	0
Ascites	1 (1.8)	0	1	0
Blood alkaline phosphatase increased	5 (8.9)	2	3	0
Blood bilirubin increased	1 (1.8)	1	0	0
Cholestasis	1 (1.8)	0	1	0
Gamma-glutamyltransferase increased	2 (3.6)	0	1	1
Hypoalbuminaemia	2 (3.6)	0	2	0
Hyperbilirubinaemia	2 (3.6)	1	1	0
Liver disorder	1 (1.8)	1	0	0
Liver function test abnormal	2 (3.6)	0	2	0

Source: Table 19.2.1.1 (Neutropenic subjects).
Abbreviations: N = number of subjects
a: Protocols included in analysis: A8851011, A8851015, A8851016, A8851019 and A8851021.
Includes data up to 30 days after last dose of study drug.
When a dictionary other than MedDRA is used, percentages of gender specific events are calculated using the corresponding gender count as denominator.
MedDRA version 16.0 coding dictionary applied.

Table 17. Incidence and Severity of All Causality Hepatobiliary Adverse Events: Subjects with Deep Tissue Infection

	Subjects with Deep Tissue Infection[b] N=131			
Preferred term	**N (%)**	**Mild**	**Mod**	**Sev**
Aspartate aminotransferase increased	2 (1.5)	2	0	0
Ascites	2 (1.5)	1	1	0
Blood alkaline phosphatase increased	10 (7.6)	6	4	0
Cholestasis	3 (2.3)	2	1	0
Hepatic encephalopathy	1 (0.8)	1	0	0
Hepatic enzyme increased	3 (2.3)	2	1	0
Hepatic failure	3 (2.3)	0	1	2
Hypoalbuminaemia	2 (1.5)	1	1	0
Hyperbilirubinaemia	1 (0.8)	1	0	0
Jaundice	1 (0.8)	0	1	0
Liver disorder	1 (0.8)	0	1	0
Liver abscess	2 (1.5)	1	0	1
Prothrombin time prolonged	1 (0.8)	1	0	0

Source: Table 19.2.2.1 (subjects with DTI).
Abbreviations: N = number of subjects
a: Protocols included in analysis: A8851011, A8851015, A8851016, A8851019 and A8851022.
Includes data up to 30 days after last dose of study drug.
When a dictionary other than MedDRA is used, percentages of gender specific events are calculated using the corresponding gender count as denominator.
MedDRA version 16.0 coding dictionary applied.

Important Identified Risk: Convulsions

Frequency with 95% CI

During the anidulafungin development program, convulsions were 1 of 2 treatment-related serious adverse events that occurred in more than 1 patient; a detailed summary of convulsions was prepared (Summary of Seizures Occurring During Anidulafungin Development) and additional discussion of convulsions is found in Module 2; 2.7.4 Summary of Clinical Safety, Section 2.7.4.2.1.6.3.

Integrated Database (ICC + Regional Studies + A8851021 + A8851022)

In the integrated studies, convulsions were reported in 17 (2.0%) of subjects and grand mal convulsion in 2 (0.2%) subjects (Table 18).

Table 18. All Causality Treatment Emergent Convulsions: Integrated Data (ICC Studies + Regional Studies + A8851021 + A8851022)

MedDRA Preferred Term		**Anidulafungin (n=840)**
Total number of subjects experiencing at least 1 convulsion AE	17 (2.0)	95% CI (1.2%, 3.2%)
Convulsion	16 (1.9)	

Table 18. All Causality Treatment Emergent Convulsions: Integrated Data (ICC Studies + Regional Studies + A8851021 + A8851022)

MedDRA Preferred Term	Anidulafungin (n=840)
Grand mal convulsion	2 (0.2)

Source: Table 21.19 (Pooled Data)

ICC Dataset

In the ICC Safety Database, there were 6 convulsions (MedDRA preferred terms convulsion and grand mal convulsion) experienced by 5 patients in the anidulafungin group and 2 convulsions (experienced by 2 patients) in the fluconazole group). Four (4) of the events were considered serious adverse events for anidulafungin.

Three (3) of the 6 anidulafungin convulsions were assessed by the investigator as possibly treatment-related; both convulsions occurring in the fluconazole group were assessed as unlikely related to treatment.

Four (4) of the convulsions reported in the anidulafungin group occurred after anidulafungin was discontinued; 3 occurred more than 6 days after the last dose of anidulafungin was administered (when anidulafungin levels would be expected to be negligible), 1 occurred approximately 18 hours after the last dose. Both convulsions in the fluconazole group occurred while the patient was still on fluconazole.

Because of the low numbers of seizures in the ICC Safety Database, the Phase 2/3 Safety Database was also examined (this dataset combines the ICC population with other populations studied). In the Phase 2/3 Safety Database there were an additional 5 convulsions (5 patients) and 1 grand mal convulsion reported for anidulafungin and 3 convulsions (3 patients) reported for fluconazole. The frequency was similar between the treatment groups in the Phase 2/3 Safety Database. One (1) of the convulsions in the anidulafungin group occurred 4 days, and 1 occurred 1 day after the last administration of study drug while all fluconazole convulsions occurred during fluconazole treatment.

Table 19. All Causality Treatment Emergent Convulsions: ICC and Phase 2/3 Safety Databases

Preferred Term	Anidulafungin (N = 204)	ICC Safety Database	Phase 2/3 Safety Database Anidulafungin (N = 669)
Total number of subjects experiencing at least 1 convulsion AE	5 (2.5)	95% CI (0.8%, 5.6%)	
Convulsion			
All causality adverse event	5 (2.5)		9 (1.3)
Treatment-related adverse event	3 (1.5)		5 (0.7)
All causality serious adverse event	4 (2.0)		5 (0.7)
Treatment-related serious adverse event	3 (1.5)		4 (0.6)
Grand mal convulsion			
All causality adverse event	1 (0.5)		2 (0.3)
Treatment-related adverse event	0		0
All causality serious adverse event	0		0
Treatment-related serious adverse event	0		0

Source: SCS Tables 5-1.1, 5-1.1A, 7-1.1, 7-1.1A, 9-1.1, 9-1.1A, 10-1, 10-1A, Table 21.20

Subjects with Neutropenia or Deep Tissue Infection

The defined search criteria were also used to identify convulsions events in relevant studies in subjects with neutropenia or with deep tissue infections and in the overall population. Convulsions were reported in 2 neutropenic subjects (3.6%; 95% CI [0.4%, 12.3%]). No events of convulsion were reported in subjects with DTI.

Seriousness/outcomes

Integrated Database (ICC + Regional Studies + A8851021 + A8851022)

Of the subjects who reported convulsions, 10 of these subjects had convulsions that were serious adverse advents and all but two of these subjects recovered. Of the two subjects who did not recover, 1 had an underlying medical condition (metastatic lymphoma) and the other discontinued from the study and died two weeks after the event.

Table 20 shows the outcomes for all convulsion adverse events in the integrated studies.

Table 20. Incidence and Outcome of All-Causality Convulsion Adverse Events: Integrated Data (ICC Studies + Regional Studies + A8851021 + A8851022)

	Anidulafungin (N = 840)		
	Overall	Recovered	Ongoing
Preferred Terms	n	n (%)	n (%)
Convulsion	16 (1.9)	13 (1.5)	3 (0.4)
Grand mal convulsion	2 (0.2)	2 (0.2)	0

Source: Table 21.4 (Pooled Data)

ICC Dataset

In the ICC population, 1 patient had a treatment-related serious adverse event of seizure that resulted in death (VER002-6-011-001 Narrative). All other adverse events of convulsion/grand mal convulsion had an outcome of 'recovered'. Convulsions that occurred in anidulafungin-treated patients of other populations studied (oesophageal candidiasis and invasive aspergillosis) all had outcomes of 'recovered' (phase2_3 Table RMP-AE-2.2.9).

Subjects with Neutropenia or Deep Tissue Infection

In the relevant studies in subjects with neutropenia, two subjects reported convulsions. One convulsion events was a treatment-related serious adverse event, which did not resolve despite anidulafungin being discontinued. The other event had an outcome of "still present", but was due to brain lymphoma. None of the subjects with DTI reported convulsion.

Severity and nature of risk

Integrated Database (ICC + Regional Studies + A8851021 + A8851022)

The incidence and severity of convulsions in the integrated clinical studies are presented in Table 21. Most events were mild or moderate in severity.

Table 21. Incidence and Severity of All-Causality Convulsion Adverse Events: Integrated Data (ICC Studies + Regional Studies + A8851021 + A8851022)

	Anidulafungin (n=840)			
		Severity		
MedDRA Preferred Term	**N (%)**	**Mild**	**Moderate**	**Severe**
Convulsion	16 (1.9)	2	10	4
Grand mal convulsion	2 (0.2)	1	1	0

Source: Table 21.1 (Pooled data)

The incidence and severity of convulsions in the ICC population are presented in Table 22. Two of the 5 cases were severe. The severity of convulsions occurring in the Phase 2/3 Safety Dataset may be found in phase2_3 Table RMP-AE-2.1.9; the severity does not differ markedly from that observed in the ICC Safety Dataset.

In the relevant studies in subjects with neutropenia, of the two subjects with convulsions (neutropenia subjects), both were of moderate severity. None of the subjects with DTI reported convulsions.

Table 22. Incidence and Severity of All-Causality Convulsion Adverse Events: ICC Safety Dataset

	Anidulafungin (N = 204)			
Preferred Term	**N**	**Mild n (%)**	**Moderate n (%)**	**Severe n (%)**
Convulsion	5	1 (0.5)	2 (1.0)	2 (1.0)
Grand mal convulsion	1	0	1(0.5)	0

Source: phase 2, 3 Table RMP-AE-2.1.7

Important Potential Risk Exacerbation of Infusion-associated Reactions by Anesthetics

Frequency with 95% CI

There are no known instances in humans where an exacerbation of an infusion-associated reaction by anesthetic has occurred.

Seriousness/outcomes

Infusion-associated adverse events were identified as a risk and are described in detail above, *Seriousness and outcome* paragraph.

Severity and nature of risk

Based on the experience in rats, an exacerbation of an infusion-associated reaction could range from mild to life threatening.

Important Potential Risk: QT prolongation /Torsade de Pointes

Frequency with 95% CI

There were no instances of torsade de pointes or confirmed QT prolongation in the anidulafungin development program.

Although a thorough QT study as defined by ICH E14 guidance was not performed with anidulafungin, a thorough clinical evaluation of the potential for anidulafungin to cause QT prolongation was conducted in addition to standard preclinical evaluations. These assessments are described in detail in Section 2.5.5.8 of the Clinical Overview (Module 2, 2.5) and Section 2.7.4.4 of the Summary of Clinical Safety (Module 2, 2.7.4). As described in the latter, there were 3 anidulafungin-treated patients who had adverse events of "electrocardiogram QT prolonged" reported.

These events were reported as adverse events on the basis of site-read ECG. When these ECG tracings were assessed by personnel at the central cardiac laboratory, QT prolongation was not confirmed, and these adverse events do not represent true ECG changes.

MedDRA includes a level 2 sub-SMQ (under Cardiac Arrhythmia SMQ) for Torsade de Pointes/QT prolongation. The Torsade de Pointes/QT prolongation sub-SMQ was used to search the anidulafungin ICC Safety Database for adverse events that could reflect a risk for or an outcome of torsade de pointes in the populations below.

No adverse events specific to QT prolongation or torsade de pointes were identified in the anidulafungin integrated population using this search strategy except for the 4 'Electrocardiogram QT prolonged' adverse events (3 in the ICC dataset and 1 in subjects with deep tissue infection).

For the 3 subjects in the ICC dataset, these ECG changes were not confirmed by central laboratory review as discussed above; all other preferred terms identified are defined as 'broad' by the SMQ and have potential in identifying cases of torsade de pointes/QT prolongation but are non-specific and may be caused by many other conditions, particularly in a population with severe underlying illness as in the ICC program.

One subject with DTI experienced an event of Electrocardiogram QT prolonged and ventricular tachycardia due to hypokalaemia (1 subject with DTI experienced ventricular arrhythmia, but it was associated with a septic shock and hemorrhagic shock).

AEs that could be associated with QT prolongation are shown for the integrated studies (Table 23), the ICC dataset (Table 24), subjects with neutropenia (Table 25), and subjects with deep tissue infection (Table 26).

Table 23. All-Causality Treatment-Emergent Adverse Events That Could be Associated with QTc Prolongation/Torsades de Pointes: Integrated Data (ICC Studies + Regional Studies + A8851021 + A8851022)

MedDRA Preferred Term	Anidulafungin (n=840)	
Number (%) of patients with at least 1 Torsade de Pointes / QT prolongation adverse event (MedDRA SMQ)	61 (7.3)	95% CI (5.6%, 9.2%)
Cardiac arrest	26 (3.1)	
Cardio-respiratory arrest	17 (2.0)	
Electrocardiogram QT prolonged	4 (0.5)	
Loss of consciousness	4 (0.5)	
Sudden death	1 (0.1)	
Syncope	2 (0.2)	
Ventricular arrhythmia	2 (0.2)	
Ventricular fibrillation	2 (0.2)	
Ventricular tachycardia	7 (0.8)	

Source: Table 21.15 (Pooled data)
* If the same subject in a given treatment had more than one occurrence in the same preferred term event category, only the most severe occurrence is taken.

Table 24. All-Causality Treatment-Emergent Adverse Events That Could be Indicative of QTc Prolongation/Torsades de Pointes: ICC Safety Database

Preferred Term	Anidulafungin (N = 204)	
Number (%) of patients with at least 1 Torsade de Pointes / QT prolongation adverse event (MedDRA SMQ)	23 (11.3)	95% CI (7.3%, 16.4%)
Cardiac arrest	7 (3.4)	
Cardio-respiratory arrest	6 (2.9)	
Electrocardiogram QT prolonged	3 (1.5)	
Loss of consciousness	1 (0.5)	
Syncope	2 (1.0)	
Ventricular arrhythmia	1 (0.5)	
Ventricular fibrillation	1 (0.5)	
Ventricular tachycardia	2 (1.0)	

Source: Table 21.16 (Pooled data)

Table 25. All-Causality Treatment-Emergent Adverse Events That Could be Indicative of QTc Prolongation/Torsades de Pointes: Subjects with Neutropenia

Preferred term	Neutropenic Subjects[a] N=56	
Number (%) of subjects with at least one event	4 (7.1)	95% CI (2.0%, 17.3%)
Cardiac arrest	3 (5.4)	
Cardio-respiratory arrest	1 (1.8)	

Source: Table 21.17 (Pooled data)
Abbreviations: N = number of subjects
a: Protocols included in analysis: A8851011, A8851015, A8851016, A8851019 and A8851021.
In addition to the above mentioned protocols, 3 subjects with neutropenia from study VER002-9 were included in this analysis.
Includes data up to 30 days after last dose of study drug.
When a dictionary other than MedDRA is used, percentages of gender specific events are calculated using the corresponding gender count as denominator.
MedDRA version 16.0 coding dictionary applied.

Table 26. All-Causality Treatment-Emergent Adverse Events That Could be Indicative of QTc Prolongation/Torsades de Pointes: Subjects With Deep Tissue Infection

Preferred term	Subjects with Deep Tissue Infection[a] N=131	
Number (%) of subjects with at least one event	8 (6.1)	95% CI (2.7%, 11.7%)
Cardiac arrest	4 (3.1)	
Cardio-respiratory arrest	1 (0.8)	
Electrocardiogram QT prolonged	1 (0.8)	
Loss of consciousness	1 (0.8)	
Ventricular arrhythmia	1 (0.8)	
Ventricular tachycardia	1 (0.8)	

Source: Table 21.18 (Pooled data)
Abbreviations: N = number of subjects
a. Protocols included in analysis: A8851011, A8851015, A8851016, A8851019 and A8851022.
Includes data up to 30 days after last dose of study drug.
When a dictionary other than MedDRA is used, percentages of gender specific events are calculated using the corresponding gender count as denominator.
MedDRA version 16.0 coding dictionary applied.

Seriousness/outcomes

There were no confirmed instances of QT prolongation, torsade de pointes or related events in the anidulafungin clinical development program. As described above, 3 reported instances of "Electrocardiogram QT prolonged" in anidulafungin-treated patients in the ICC dataset were not confirmed by the central laboratory, were not serious and all resolved. For the 1 subject with DTI who experienced an event of Electrocardiogram QT prolonged, the event was not serious and resolved.

Severity and nature of risk

For the 3 anidulafungin-treated subjects who reported instances of "Electrocardiogram QT prolonged" in the ICC dataset, all events were mild in severity. For the 1 subject with DTI who experienced an event of Electrocardiogram QT prolonged, the event was moderate in severity.

Annex 7.2. Supporting Tables to Part II: Module SVII.3 Details of Important Identified, Important Potential Risks (Clinical data-Paediatric Study A8851008)

Important Identified Risk Anaphylaxis and Infusion-Associated Reactions

Search terms (MedDRA version 20.1): Anaphylactic reaction or Angioedema (SMQ), broad and narrow scope; PT: Chills; Dizziness; Feeling hot; Hot flush; Hyperhidrosis; Infusion related reaction

Table 27. Important Identified Risk - Frequency with 95% CI for Anaphylaxis and Infusion-associated reactions. Study A8851008 - Safety Population

Group of Risk Terms	Number of events	N	Incidence proportion (%)	Incidence proportion (%) [95% CI] Lower Limit	Upper Limit
Anaphylactic reaction (SMQ)	21	68	30.9	20.2	43.3
Acute respiratory failure	1	68	1.5	0.0	7.9
Bronchospasm	1	68	1.5	0.0	7.9
Cough	1	68	1.5	0.0	7.9
Dyspnoea	1	68	1.5	0.0	7.9
Erythema	2	68	2.9	0.4	10.2
Eyelid oedema	1	68	1.5	0.0	7.9
Hypotension	4	68	5.9	1.6	14.4
Laryngospasm	1	68	1.5	0.0	7.9
Oedema	1	68	1.5	0.0	7.9
Periorbital oedema	2	68	2.9	0.4	10.2
Pruritus generalised	1	68	1.5	0.0	7.9
Rash	6	68	8.8	3.3	18.2
Rash generalised	1	68	1.5	0.0	7.9
Respiratory distress	2	68	2.9	0.4	10.2
Respiratory failure	1	68	1.5	0.0	7.9
Shock	1	68	1.5	0.0	7.9

Table 27. Important Identified Risk - Frequency with 95% CI for Anaphylaxis and Infusion-associated reactions. Study A8851008 - Safety Population

Group of Risk Terms	Number of events	N	Incidence proportion (%)	Incidence proportion (%) [95% CI] Lower Limit	Upper Limit
Tachypnoea	1	68	1.5	0.0	7.9
Urticaria	1	68	1.5	0.0	7.9
Angioedema (SMQ)	9	68	13.2	6.2	23.6
Eyelid oedema	1	68	1.5	0.0	7.9
Generalised oedema	2	68	2.9	0.4	10.2
Oedema	1	68	1.5	0.0	7.9
Oedema peripheral	2	68	2.9	0.4	10.2
Penile oedema	1	68	1.5	0.0	7.9
Periorbital oedema	2	68	2.9	0.4	10.2
Scrotal oedema	1	68	1.5	0.0	7.9
Urticaria	1	68	1.5	0.0	7.9
Hyperhidrosis	1	68	1.5	0.0	7.9

Data from the Clinical Database.
MedDRA version 20.1.
Please note that for the same patient, multiple events could be reported.
If a patient had more than one adverse event within a preferred term, that patient is counted once in the overall incidence for that preferred term.
Confidence limits are computed using exact (Clopper-Pearson) method.
PFIZER CONFIDENTIAL Date of Reporting Dataset Creation: Date of Table Generation: 15JAN2019 (15:56)

Table 28. Important Identified Risk - AEs by Outcome and Seriousness by Preferred Search Terms for Anaphylaxis and Infusion-associated reactions. Study A8851008 - Safety Population

Group of Risk Terms	Number of events (SAEs)	Serious %	Resolved %	Resolved with sequelae %	Not resolved %	Unknown %
Anaphylactic reaction (SMQ)	21(3)	3(14.29)	17(80.95)	2(9.52)	2(9.52)	0(0.00)
Acute respiratory failure	1(1)	1(100.0)	0(0.00)	1(100.0)	0(0.00)	0(0.00)
Bronchospasm	1(0)	0(0.00)	1(100.0)	0(0.00)	0(0.00)	0(0.00)
Cough	1(0)	0(0.00)	1(100.0)	0(0.00)	0(0.00)	0(0.00)
Dyspnoea	1(0)	0(0.00)	1(100.0)	0(0.00)	0(0.00)	0(0.00)
Erythema	2(0)	0(0.00)	2(100.0)	0(0.00)	0(0.00)	0(0.00)
Eyelid oedema	1(0)	0(0.00)	1(100.0)	0(0.00)	0(0.00)	0(0.00)
Hypotension	4(0)	0(0.00)	3(75.00)	0(0.00)	1(25.00)	0(0.00)
Laryngospasm	1(0)	0(0.00)	0(0.00)	1(100.0)	0(0.00)	0(0.00)
Oedema	1(0)	0(0.00)	1(100.0)	0(0.00)	0(0.00)	0(0.00)
Periorbital oedema	2(0)	0(0.00)	2(100.0)	0(0.00)	0(0.00)	0(0.00)
Pruritus generalised	1(0)	0(0.00)	1(100.0)	0(0.00)	0(0.00)	0(0.00)

Table 28. Important Identified Risk - AEs by Outcome and Seriousness by Preferred Search Terms for Anaphylaxis and Infusion-associated reactions. Study A8851008 - Safety Population

Group of Risk Terms	Number of events (SAEs)	Serious %	Resolved %	Resolved with sequelae %	Not resolved %	Unknown %
Rash	6(0)	0(0.00)	4(66.67)	0(0.00)	2(33.33)	0(0.00)
Rash generalised	1(0)	0(0.00)	1(100.0)	0(0.00)	0(0.00)	0(0.00)
Respiratory distress	2(1)	1(50.00)	2(100.0)	0(0.00)	0(0.00)	0(0.00)
Respiratory failure	1(1)	1(100.0)	1(100.0)	0(0.00)	0(0.00)	0(0.00)
Shock	1(0)	0(0.00)	1(100.0)	0(0.00)	0(0.00)	0(0.00)
Tachypnoea	1(0)	0(0.00)	1(100.0)	0(0.00)	0(0.00)	0(0.00)
Urticaria	1(0)	0(0.00)	1(100.0)	0(0.00)	0(0.00)	0(0.00)
Angioedema (SMQ)	9(0)	0(0.00)	7(77.78)	0(0.00)	2(22.22)	0(0.00)
Eyelid oedema	1(0)	0(0.00)	1(100.0)	0(0.00)	0(0.00)	0(0.00)
Generalised oedema	2(0)	0(0.00)	1(50.00)	0(0.00)	1(50.00)	0(0.00)
Oedema	1(0)	0(0.00)	1(100.0)	0(0.00)	0(0.00)	0(0.00)
Oedema peripheral	2(0)	0(0.00)	2(100.0)	0(0.00)	0(0.00)	0(0.00)
Penile oedema	1(0)	0(0.00)	0(0.00)	0(0.00)	1(100.0)	0(0.00)
Periorbital oedema	2(0)	0(0.00)	2(100.0)	0(0.00)	0(0.00)	0(0.00)
Scrotal oedema	1(0)	0(0.00)	0(0.00)	0(0.00)	1(100.0)	0(0.00)
Urticaria	1(0)	0(0.00)	1(100.0)	0(0.00)	0(0.00)	0(0.00)
Hyperhidrosis	1(0)	0(0.00)	1(100.0)	0(0.00)	0(0.00)	0(0.00)
Total	22(3)	3(13.64)	16(72.73)	2(9.09)	4(18.18)	0(0.00)

Data from the Clinical Database.
MedDRA version 20.1.
Please note that for the same patient, multiple events could be reported.
If a patient had more than one adverse event within a preferred term, that patient is counted once.
If a patient had the same preferred term more than once, most negative outcome is taken based on this order: Unknown, Resolved, Resolved with Sequelae, Not Resolved.
In the total row, each patient is counted only once.
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Table 29. Important Identified Risk - Severity and nature of risk by Search Terms for Anaphylaxis and Infusion-associated reactions. Study A8851008 - Safety Population

Group of Risk Terms	Number of events (SAEs)	Mild (%)	Moderate (%)	Severe (%)
Anaphylactic reaction (SMQ)	21(3)	12(57.14)	6(28.57)	3(14.29)

Table 29. Important Identified Risk - Severity and nature of risk by Search Terms for Anaphylaxis and Infusion-associated reactions. Study A8851008 - Safety Population

Group of Risk Terms	Number of events (SAEs)	Mild (%)	Moderate (%)	Severe (%)
Acute respiratory failure	1(1)	0(0.00)	0(0.00)	1(100.0)
Bronchospasm	1(0)	0(0.00)	1(100.0)	0(0.00)
Cough	1(0)	1(100.0)	0(0.00)	0(0.00)
Dyspnoea	1(0)	0(0.00)	1(100.0)	0(0.00)
Erythema	2(0)	2(100.0)	0(0.00)	0(0.00)
Eyelid oedema	1(0)	1(100.0)	0(0.00)	0(0.00)
Hypotension	4(0)	2(50.00)	1(25.00)	1(25.00)
Laryngospasm	1(0)	0(0.00)	1(100.0)	0(0.00)
Oedema	1(0)	1(100.0)	0(0.00)	0(0.00)
Periorbital oedema	2(0)	2(100.0)	0(0.00)	0(0.00)
Pruritus generalised	1(0)	0(0.00)	1(100.0)	0(0.00)
Rash	6(0)	6(100.0)	0(0.00)	0(0.00)
Rash generalised	1(0)	1(100.0)	0(0.00)	0(0.00)
Respiratory distress	2(1)	0(0.00)	1(50.00)	1(50.00)
Respiratory failure	1(1)	0(0.00)	0(0.00)	1(100.0)
Shock	1(0)	0(0.00)	1(100.0)	0(0.00)
Tachypnoea	1(0)	0(0.00)	1(100.0)	0(0.00)
Urticaria	1(0)	1(100.0)	0(0.00)	0(0.00)
Angioedema (SMQ)	9(0)	7(77.78)	1(11.11)	1(11.11)
Eyelid oedema	1(0)	1(100.0)	0(0.00)	0(0.00)
Generalised oedema	2(0)	0(0.00)	1(50.00)	1(50.00)
Oedema	1(0)	1(100.0)	0(0.00)	0(0.00)
Oedema peripheral	2(0)	2(100.0)	0(0.00)	0(0.00)
Penile oedema	1(0)	1(100.0)	0(0.00)	0(0.00)
Periorbital oedema	2(0)	2(100.0)	0(0.00)	0(0.00)
Scrotal oedema	1(0)	1(100.0)	0(0.00)	0(0.00)
Urticaria	1(0)	1(100.0)	0(0.00)	0(0.00)
Hyperhidrosis	1(0)	1(100.0)	0(0.00)	0(0.00)
Total	22(3)	13(59.09)	5(22.73)	4(18.18)

Data from the Clinical Database.
MedDRA version 20.1.
Please note that for the same patient, multiple events could be reported.
If a patient had more than one adverse event within a preferred term, that patient is counted once.
If a patient had the same preferred term more than once, the most severe is taken.
In the total row, each patient is counted only once.
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Important Identified Risk Hepatobiliary Events

Search terms (MedDRA version 20.1): Cholestasis and jaundice of hepatic origin (SMQ); Hepatic failure, fibrosis and cirrhosis and other liver damage-related conditions (SMQ); Hepatitis, non-infectious (SMQ); Liver infections (SMQ); Liver related investigations, signs and symptoms (SMQ); Liver-related coagulation and bleeding disturbances (SMQ), Broad and narrow scope. PT: Bilirubinuria; Cholestasis of pregnancy; Hepatitis neonatal; Hyperbilirubinaemia neonatal; Jaundice acholuric; Jaundice extrahepatic obstructive; Jaundice neonatal; Liver transplant rejection; Neonatal cholestasis

Table 30. Important Identified Risk - Frequency with 95% CI for Hepatobiliary events. Study A8851008 - Safety Population

Group of Risk Terms	Number of events	N	Incidence proportion (%)	Incidence proportion (%) [95% CI] Lower Limit	Upper Limit
Cholestasis and jaundice of hepatic origin (SMQ)	3	68	4.4	0.9	12.4
Cholestasis	1	68	1.5	0.0	7.9
Hyperbilirubinaemia	2	68	2.9	0.4	10.2
Ocular icterus	1	68	1.5	0.0	7.9
Hepatitis, non-infectious (SMQ)	1	68	1.5	0.0	7.9
Hepatitis acute	1	68	1.5	0.0	7.9
Liver infections (SMQ)	1	68	1.5	0.0	7.9
Liver abscess	1	68	1.5	0.0	7.9
Liver related investigations, signs and symptoms (SMQ)	12	68	17.6	9.5	28.8
Alanine aminotransferase increased	6	68	8.8	3.3	18.2
Aspartate aminotransferase	4	68	5.9	1.6	14.4
Gamma-glutamyltransferase increased	2	68	2.9	0.4	10.2
Hepatomegaly	1	68	1.5	0.0	7.9
Hyperbilirubinaemia	2	68	2.9	0.4	10.2
Hypoalbuminaemia	1	68	1.5	0.0	7.9
Liver function test abnormal	1	68	1.5	0.0	7.9
Liver function test increased	1	68	1.5	0.0	7.9
Transaminases increased	3	68	4.4	0.9	12.4
Liver-related coagulation and bleeding disturbances (SMQ)	1	68	1.5	0.0	7.9
Prothrombin time prolonged	1	68	1.5	0.0	7.9

Table 30. Important Identified Risk - Frequency with 95% CI for Hepatobiliary events. Study A8851008 - Safety Population

Group of Risk Terms	Number of events	N	Incidence proportion (%)	Incidence proportion (%) [95% CI] Lower Limit Upper Limit

Data from the Clinical Database.
MedDRA version 20.1.
Please note that for the same patient, multiple events could be reported.
If a patient had more than one adverse event within a preferred term, that patient is counted once in the overall incidence for that preferred term.
Confidence limits are computed using exact (Clopper-Pearson) method.
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Table 31. Important Identified Risk - AEs by Outcome and Seriousness by Preferred Search Terms for Hepatobiliary events. Study A8851008 - Safety Population

Group of Risk Terms	Number of events (SAEs)	Serious %	Resolved %	Resolved with sequelae %	Not resolved %	Unknown %
Cholestasis and jaundice of hepatic origin (SMQ)	3(0)	0(0.00)	1(33.33)	0(0.00)	2(66.67)	0(0.00)
Cholestasis	1(0)	0(0.00)	0(0.00)	0(0.00)	1(100.0)	0(0.00)
Hyperbilirubinaemia	2(0)	0(0.00)	1(50.00)	0(0.00)	1(50.00)	0(0.00)
Ocular icterus	1(0)	0(0.00)	0(0.00)	0(0.00)	1(100.0)	0(0.00)
Hepatitis, non-infectious (SMQ)	1(0)	0(0.00)	1(100.0)	0(0.00)	0(0.00)	0(0.00)
Hepatitis acute	1(0)	0(0.00)	1(100.0)	0(0.00)	0(0.00)	0(0.00)
Liver infections (SMQ)	1(0)	0(0.00)	0(0.00)	0(0.00)	1(100.0)	0(0.00)
Liver abscess	1(0)	0(0.00)	0(0.00)	0(0.00)	1(100.0)	0(0.00)
Liver related investigations, signs and symptoms (SMQ)	12(1)	1(8.33)	5(41.67)	2(16.67)	5(41.67)	0(0.00)
Alanine aminotransferase increased	6(0)	0(0.00)	4(66.67)	1(16.67)	1(16.67)	0(0.00)
Aspartate aminotransferase increased	4(0)	0(0.00)	2(50.00)	2(50.00)	0(0.00)	0(0.00)
Gamma-glutamyltransferase increased	2(0)	0(0.00)	1(50.00)	1(50.00)	0(0.00)	0(0.00)
Hepatomegaly	1(0)	0(0.00)	1(100.0)	0(0.00)	0(0.00)	0(0.00)
Hyperbilirubinaemia	2(0)	0(0.00)	1(50.00)	0(0.00)	1(50.00)	0(0.00)
Hypoalbuminaemia	1(0)	0(0.00)	0(0.00)	0(0.00)	1(100.0)	0(0.00)

Table 31. Important Identified Risk - AEs by Outcome and Seriousness by Preferred Search Terms for Hepatobiliary events. Study A8851008 - Safety Population

Group of Risk Terms	Number of events (SAEs)	Serious %	Resolved %	Resolved with sequelae %	Not resolved %	Unknown %
Liver function test abnormal	1(0)	0(0.00)	0(0.00)	0(0.00)	1(100.0)	0(0.00)
Liver function test increased	1(0)	0(0.00)	1(100.0)	0(0.00)	0(0.00)	0(0.00)
Transaminases increased	3(1)	1(33.33)	2(66.67)	0(0.00)	1(33.33)	0(0.00)
Liver-related coagulation and bleeding disturbances (SMQ)	1(0)	0(0.00)	0(0.00)	0(0.00)	0(0.00)	1(100.0)
Prothrombin time prolonged	1(0)	0(0.00)	0(0.00)	0(0.00)	0(0.00)	1(100.0)
Total	14(1)	1(7.14)	5(35.71)	2(14.29)	7(50.00)	0(0.00)

Data from the Clinical Database.
MedDRA version 20.1.
Please note that for the same patient, multiple events could be reported.
If a patient had more than one adverse event within a preferred term, that patient is counted once.
If a patient had the same preferred term more than once, most negative outcome is taken based on this order: Unknown, Resolved, Resolved with Sequelae, Not Resolved.
In the total row, each patient is counted only once.
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Table 32. Important Identified Risk - Severity and nature of risk by Search Terms for Hepatobiliary events. Study A8851008 - Safety Population

Group of Risk Terms	Number of events (SAEs)	Mild (%)	Moderate (%)	Severe (%)
Cholestasis and jaundice of hepatic origin (SMQ)	3(0)	1(33.33)	1(33.33)	1(33.33)
Cholestasis	1(0)	1(100.0)	0(0.00)	0(0.00)
Hyperbilirubinaemia	2(0)	0(0.00)	1(50.00)	1(50.00)
Ocular icterus	1(0)	1(100.0)	0(0.00)	0(0.00)
Hepatitis, non-infectious (SMQ)	1(0)	1(100.0)	0(0.00)	0(0.00)
Hepatitis acute	1(0)	1(100.0)	0(0.00)	0(0.00)
Liver infections (SMQ)	1(0)	1(100.0)	0(0.00)	0(0.00)
Liver abscess	1(0)	1(100.0)	0(0.00)	0(0.00)
Liver related investigations, signs and symptoms (SMQ)	12(1)	2(16.67)	7(58.33)	3(25.00)

Table 32. Important Identified Risk - Severity and nature of risk by Search Terms for Hepatobiliary events. Study A8851008 - Safety Population

Group of Risk Terms	Number of events (SAEs)	Mild (%)	Moderate (%)	Severe (%)
Alanine aminotransferase increased	6(0)	0(0.00)	5(83.33)	1(16.67)
Aspartate aminotransferase increased	4(0)	1(25.00)	2(50.00)	1(25.00)
Gamma-glutamyltransferase increased	2(0)	0(0.00)	2(100.0)	0(0.00)
Hepatomegaly	1(0)	1(100.0)	0(0.00)	0(0.00)
Hyperbilirubinaemia	2(0)	0(0.00)	1(50.00)	1(50.00)
Hypoalbuminaemia	1(0)	0(0.00)	1(100.0)	0(0.00)
Liver function test abnormal	1(0)	1(100.0)	0(0.00)	0(0.00)
Liver function test increased	1(0)	0(0.00)	1(100.0)	0(0.00)
Transaminases increased	3(1)	1(33.33)	1(33.33)	1(33.33)
Liver-related coagulation and bleeding disturbances (SMQ)	1(0)	1(100.0)	0(0.00)	0(0.00)
Prothrombin time prolonged	1(0)	1(100.0)	0(0.00)	0(0.00)
Total	14(1)	4(28.57)	7(50.00)	3(21.43)

Data from the Clinical Database.
MedDRA version 20.1.
Please note that for the same patient, multiple events could be reported.
If a patient had more than one adverse event within a preferred term, that patient is counted once.
If a patient had the same preferred term more than once, the most severe is taken.
In the total row, each patient is counted only once.
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Important Identified Risk Convulsions

Search terms (MedDRA version 20.1): Convulsions (SMQ), Broad and narrow scope.

Table 33. Important Identified Risk - Frequency with 95% CI for Convulsions. Study A8851008 - Safety Population

Group of Risk Terms	Number of events	N	Incidence proportion (%)	Incidence proportion (%) [95% CI] Lower Limit	Upper Limit
Convulsions (SMQ)	3	68	4.4	0.9	12.4
Seizure	3	68	4.4	0.9	12.4

Table 33. Important Identified Risk - Frequency with 95% CI for Convulsions. Study A8851008 - Safety Population

Group of Risk Terms	Number of events	N	Incidence proportion (%)	Incidence proportion (%) [95% CI] Lower Limit Upper Limit

Data from the Clinical Database.
MedDRA version 20.1.
Please note that for the same patient, multiple events could be reported.
If a patient had more than one adverse event within a preferred term, that patient is counted once in the overall incidence for that preferred term.
Confidence limits are computed using exact (Clopper-Pearson) method.
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Table 34. Important Identified Risk - AEs by Outcome and Seriousness by Preferred Search Terms for Convulsions. Study A8851008 - Safety Population

Group of Risk Terms	Number of events (SAEs)	Serious %	Resolved %	Resolved with sequelae %	Not resolved %	Unknown %
Convulsions (SMQ)	3(1)	1(33.33)	3(100.0)	0(0.00)	0(0.00)	0(0.00)
Seizure	3(1)	1(33.33)	3(100.0)	0(0.00)	0(0.00)	0(0.00)
Total	3(1)	1(33.33)	3(100.0)	0(0.00)	0(0.00)	0(0.00)

Data from the Clinical Database.
MedDRA version 20.1.
Please note that for the same patient, multiple events could be reported.
If a patient had more than one adverse event within a preferred term, that patient is counted once.
If a patient had the same preferred term more than once, most negative outcome is taken based on this order: Unknown, Resolved, Resolved with Sequelae, Not Resolved.
In the total row, each patient is counted only once.
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Table 35. Important Identified Risk - Severity and nature of risk by Search Terms for Convulsions. Study A8851008 - Safety Population

Group of Risk Terms	Number of events (SAEs)	Mild (%)	Moderate (%)	Severe (%)
Convulsions (SMQ)	3(1)	2(66.67)	0(0.00)	1(33.33)
Seizure	3(1)	2(66.67)	0(0.00)	1(33.33)
Total	3(1)	2(66.67)	0(0.00)	1(33.33)

Table 35. Important Identified Risk - Severity and nature of risk by Search Terms for Convulsions. Study A8851008 - Safety Population

Group of Risk Terms	Number of events (SAEs)	Mild (%)	Moderate (%)	Severe (%)

Data from the Clinical Database.
MedDRA version 20.1.
Please note that for the same patient, multiple events could be reported.
If a patient had more than one adverse event within a preferred term, that patient is counted once.
If a patient had the same preferred term more than once, the most severe is taken.
In the total row, each patient is counted only once.
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Important Potential Risk Exacerbation of Infusion-associated Reactions by Anesthetics

Search terms (MedDRA version 20.1): Anaphylactic reaction or Angioedema SMQs Broad and narrow scope. PTs: Chills, Dizziness, Feeling hot, Hot flush, Hyperhidrosis, Infusion related reaction and concomitant use of anesthetics.

Table 36. Important Potential Risk - Frequency with 95% CI for Exacerbation of Infusion-associated Reactions by Anesthetics. Study A8851008 - Safety Population

Group of Risk Terms	Number of events	N	Incidence proportion (%)	Incidence proportion (%) [95% CI] Lower Limit	Upper Limit
Anaphylactic reaction (SMQ)	15	68	22.1	12.9	33.8
Bronchospasm	1	68	1.5	0.0	7.9
Cough	1	68	1.5	0.0	7.9
Dyspnoea	1	68	1.5	0.0	7.9
Erythema	1	68	1.5	0.0	7.9
Eyelid oedema	1	68	1.5	0.0	7.9
Hypotension	4	68	5.9	1.6	14.4
Oedema	1	68	1.5	0.0	7.9
Periorbital oedema	1	68	1.5	0.0	7.9
Pruritus generalised	1	68	1.5	0.0	7.9
Rash	4	68	5.9	1.6	14.4
Rash generalised	1	68	1.5	0.0	7.9
Respiratory distress	2	68	2.9	0.4	10.2
Respiratory failure	1	68	1.5	0.0	7.9
Shock	1	68	1.5	0.0	7.9
Tachypnoea	1	68	1.5	0.0	7.9
Urticaria	1	68	1.5	0.0	7.9
Angioedema (SMQ)	8	68	11.8	5.2	21.9
Eyelid oedema	1	68	1.5	0.0	7.9
Generalised oedema	2	68	2.9	0.4	10.2
Oedema	1	68	1.5	0.0	7.9
Oedema peripheral	1	68	1.5	0.0	7.9

Table 36. Important Potential Risk - Frequency with 95% CI for Exacerbation of Infusion-associated Reactions by Anesthetics. Study A8851008 - Safety Population

Group of Risk Terms	Number of events	N	Incidence proportion (%)	Incidence proportion (%) [95% CI] Lower Limit	Upper Limit
Penile oedema	1	68	1.5	0.0	7.9
Periorbital oedema	1	68	1.5	0.0	7.9
Scrotal oedema	1	68	1.5	0.0	7.9
Urticaria	1	68	1.5	0.0	7.9
Hyperhidrosis	1	68	1.5	0.0	7.9

Data from the Clinical Database.
MedDRA version 20.1.
Please note that for the same patient, multiple events could be reported.
If a patient had more than one adverse event within a preferred term, that patient is counted once in the overall incidence for that preferred term.
Confidence limits are computed using exact (Clopper-Pearson) method.
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Table 37. Important Potential Risk - AEs by Outcome and Seriousness by Preferred Search Terms for Exacerbation of Infusion-associated Reactions by Anesthetics. Study A8851008 - Safety Population

Group of Risk Terms	Number of events (SAEs)	Serious %	Resolved %	Resolved with sequelae %	Not resolved %	Unknown %
Anaphylactic reaction (SMQ)	15(2)	2(13.33)	13(86.67)	0(0.00)	2(13.33)	0(0.00)
Bronchospasm	1(0)	0(0.00)	1(100.0)	0(0.00)	0(0.00)	0(0.00)
Cough	1(0)	0(0.00)	1(100.0)	0(0.00)	0(0.00)	0(0.00)
Dyspnoea	1(0)	0(0.00)	1(100.0)	0(0.00)	0(0.00)	0(0.00)
Erythema	1(0)	0(0.00)	1(100.0)	0(0.00)	0(0.00)	0(0.00)
Eyelid oedema	1(0)	0(0.00)	1(100.0)	0(0.00)	0(0.00)	0(0.00)
Hypotension	4(0)	0(0.00)	3(75.00)	0(0.00)	1(25.00)	0(0.00)
Oedema	1(0)	0(0.00)	1(100.0)	0(0.00)	0(0.00)	0(0.00)
Periorbital oedema	1(0)	0(0.00)	1(100.0)	0(0.00)	0(0.00)	0(0.00)
Pruritus generalised	1(0)	0(0.00)	1(100.0)	0(0.00)	0(0.00)	0(0.00)
Rash	4(0)	0(0.00)	2(50.00)	0(0.00)	2(50.00)	0(0.00)
Rash generalised	1(0)	0(0.00)	1(100.0)	0(0.00)	0(0.00)	0(0.00)
Respiratory distress	2(1)	1(50.00)	2(100.0)	0(0.00)	0(0.00)	0(0.00)
Respiratory failure	1(1)	1(100.0)	1(100.0)	0(0.00)	0(0.00)	0(0.00)
Shock	1(0)	0(0.00)	1(100.0)	0(0.00)	0(0.00)	0(0.00)
Tachypnoea	1(0)	0(0.00)	1(100.0)	0(0.00)	0(0.00)	0(0.00)
Urticaria	1(0)	0(0.00)	1(100.0)	0(0.00)	0(0.00)	0(0.00)

Table 37. Important Potential Risk - AEs by Outcome and Seriousness by Preferred Search Terms for Exacerbation of Infusion-associated Reactions by Anesthetics. Study A8851008 - Safety Population

Group of Risk Terms	Number of events (SAEs)	Serious %	Resolved %	Resolved with sequelae %	Not resolved %	Unknown %
Angioedema (SMQ)	8(0)	0(0.00)	6(75.00)	0(0.00)	2(25.00)	0(0.00)
Eyelid oedema	1(0)	0(0.00)	1(100.0)	0(0.00)	0(0.00)	0(0.00)
Generalised oedema	2(0)	0(0.00)	1(50.00)	0(0.00)	1(50.00)	0(0.00)
Oedema	1(0)	0(0.00)	1(100.0)	0(0.00)	0(0.00)	0(0.00)
Oedema peripheral	1(0)	0(0.00)	1(100.0)	0(0.00)	0(0.00)	0(0.00)
Penile oedema	1(0)	0(0.00)	0(0.00)	0(0.00)	1(100.0)	0(0.00)
Periorbital oedema	1(0)	0(0.00)	1(100.0)	0(0.00)	0(0.00)	0(0.00)
Scrotal oedema	1(0)	0(0.00)	0(0.00)	0(0.00)	1(100.0)	0(0.00)
Urticaria	1(0)	0(0.00)	1(100.0)	0(0.00)	0(0.00)	0(0.00)
Hyperhidrosis	1(0)	0(0.00)	1(100.0)	0(0.00)	0(0.00)	0(0.00)
Total	16(2)	2(12.50)	12(75.00)	0(0.00)	4(25.00)	0(0.00)

Data from the Clinical Database.
MedDRA version 20.1.
Please note that for the same patient, multiple events could be reported.
If a patient had more than one adverse event within a preferred term, that patient is counted once.
If a patient had the same preferred term more than once, most negative outcome is taken based on this order: Unknown, Resolved, Resolved with Sequelae, Not Resolved.
In the total row, each patient is counted only once.
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Table 38. Important Potential Risk - Severity and nature of risk by Search Terms for Exacerbation of Infusion-associated Reactions by Anesthetics. Study A8851008 - Safety Population

Group of Risk Terms	Number of events (SAEs)	Mild (%)	Moderate (%)	Severe (%)
Anaphylactic reaction (SMQ)	15(2)	8(53.33)	5(33.33)	2(13.33)
Bronchospasm	1(0)	0(0.00)	1(100.0)	0(0.00)
Cough	1(0)	1(100.0)	0(0.00)	0(0.00)
Dyspnoea	1(0)	0(0.00)	1(100.0)	0(0.00)
Erythema	1(0)	1(100.0)	0(0.00)	0(0.00)
Eyelid oedema	1(0)	1(100.0)	0(0.00)	0(0.00)
Hypotension	4(0)	2(50.00)	1(25.00)	1(25.00)
Oedema	1(0)	1(100.0)	0(0.00)	0(0.00)
Periorbital oedema	1(0)	1(100.0)	0(0.00)	0(0.00)

Table 38. Important Potential Risk - Severity and nature of risk by Search Terms for Exacerbation of Infusion-associated Reactions by Anesthetics. Study A8851008 - Safety Population

Group of Risk Terms	Number of events (SAEs)	Mild (%)	Moderate (%)	Severe (%)
Pruritus generalised	1(0)	0(0.00)	1(100.0)	0(0.00)
Rash	4(0)	4(100.0)	0(0.00)	0(0.00)
Rash generalised	1(0)	1(100.0)	0(0.00)	0(0.00)
Respiratory distress	2(1)	0(0.00)	1(50.00)	1(50.00)
Respiratory failure	1(1)	0(0.00)	0(0.00)	1(100.0)
Shock	1(0)	0(0.00)	1(100.0)	0(0.00)
Tachypnoea	1(0)	0(0.00)	1(100.0)	0(0.00)
Urticaria	1(0)	1(100.0)	0(0.00)	0(0.00)
Angioedema (SMQ)	8(0)	6(75.00)	1(12.50)	1(12.50)
Eyelid oedema	1(0)	1(100.0)	0(0.00)	0(0.00)
Generalised oedema	2(0)	0(0.00)	1(50.00)	1(50.00)
Oedema	1(0)	1(100.0)	0(0.00)	0(0.00)
Oedema peripheral	1(0)	1(100.0)	0(0.00)	0(0.00)
Penile oedema	1(0)	1(100.0)	0(0.00)	0(0.00)
Periorbital oedema	1(0)	1(100.0)	0(0.00)	0(0.00)
Scrotal oedema	1(0)	1(100.0)	0(0.00)	0(0.00)
Urticaria	1(0)	1(100.0)	0(0.00)	0(0.00)
Hyperhidrosis	1(0)	1(100.0)	0(0.00)	0(0.00)
Total	16(2)	9(56.25)	4(25.00)	3(18.75)

Data from the Clinical Database.
MedDRA version 20.1.
Please note that for the same patient, multiple events could be reported.
If a patient had more than one adverse event within a preferred term, that patient is counted once.
If a patient had the same preferred term more than once, the most severe is taken.
In the total row, each patient is counted only once.
PFIZER CONFIDENTIAL Date of Reporting Dataset Creation: Date of Table Generation: 15JAN2019 (16:28)

Important Potential Risk QT Prolongation/Torsade de Pointes

Search terms (MedDRA version 20.1): Torsade de pointes/QT prolongation (SMQ), broad and narrow scope.

Table 39. Important Potential Risk - Frequency with 95% CI for QT Prolongation/Torsade de Pointes. Study A8851008 - Safety Population

Group of Risk Terms	Number of events	N	Incidence proportion (%)	Incidence proportion (%) [95% CI] Lower Limit	Upper Limit
Torsade de pointes/QT prolongation (SMQ)	1	68	1.5	0.0	7.9

Table 39. Important Potential Risk - Frequency with 95% CI for QT Prolongation/Torsade de Pointes. Study A8851008 - Safety Population

Group of Risk Terms	Number of events	N	Incidence proportion (%)	Incidence proportion (%) [95% CI] Lower Limit	Upper Limit
Loss of consciousness	1	68	1.5	0.0	7.9

Data from the Clinical Database.
MedDRA version 20.1.
Please note that for the same patient, multiple events could be reported.
If a patient had more than one adverse event within a preferred term, that patient is counted once in the overall incidence for that preferred term.
Confidence limits are computed using exact (Clopper-Pearson) method.
PFIZER CONFIDENTIAL Date of Reporting Dataset Creation: Date of Table Generation: 10JAN2019 (21:34)

Table 40. Important Potential Risk - AEs by Outcome and Seriousness by Preferred Search Terms for QT Prolongation/Torsade de Pointes. Study A8851008 - Safety Population

Group of Risk Terms	Number of events (SAEs)	Serious %	Resolved %	Resolved with sequelae %	Not resolved %	Unknown %
Torsade de pointes/QT prolongation (SMQ)	1(0)	0(0.00)	1(100.0)	0(0.00)	0(0.00)	0(0.00)
Loss of consciousness	1(0)	0(0.00)	1(100.0)	0(0.00)	0(0.00)	0(0.00)
Total	1(0)	0(0.00)	1(100.0)	0(0.00)	0(0.00)	0(0.00)

Data from the Clinical Database.
MedDRA version 20.1.
Please note that for the same patient, multiple events could be reported.
If a patient had more than one adverse event within a preferred term, that patient is counted once.
If a patient had the same preferred term more than once, most negative outcome is taken based on this order: Unknown, Resolved, Resolved with Sequelae, Not Resolved.
In the total row, each patient is counted only once.
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Table 41. Important Potential Risk - Severity and nature of risk by Search Terms for for QT Prolongation/Torsade de Pointes. Study A8851008 - Safety Population

Group of Risk Terms	Number of events (SAEs)	Mild (%)	Moderate (%)	Severe (%)
Torsade de pointes/QT prolongation (SMQ)	1(0)	0(0.00)	1(100.0)	0(0.00)

Table 41. Important Potential Risk - Severity and nature of risk by Search Terms for for QT Prolongation/Torsade de Pointes. Study A8851008 - Safety Population

Group of Risk Terms	Number of events (SAEs)	Mild (%)	Moderate (%)	Severe (%)
Loss of consciousness	1(0)	0(0.00)	1(100.0)	0(0.00)
Total	1(0)	0(0.00)	1(100.0)	0(0.00)

Data from the Clinical Database.
MedDRA version 20.1.
Please note that for the same patient, multiple events could be reported.
If a patient had more than one adverse event within a preferred term, that patient is counted once.
If a patient had the same preferred term more than once, the most severe is taken.
In the total row, each patient is counted only once.
See table z for search criteria.
PFIZER CONFIDENTIAL Date of Reporting Dataset Creation: Date of Table Generation: 10JAN2019 (21:36)

Annex 7.3. Supporting Tables to Part II: Module SVII.3 Details of Important Identified, Important Potential Risks (Safety database CT and PM data)

Table 42. Anaphylaxis and Infusion-Associated Reactions (IARs)- Adverse Events Seriousness/Outcomes - Number of Events Preferred Term (Non-Clinical Trials)

PT	No. of Events (% of Total PTs)	No. Serious Events (% of PT)	No. Events with Criterion of Hospitalisation (% of PT)	Distribution of Event by Outcome[a]			
				Fatal	Resolved/Resolving	Not Resolved	Unknown/No Data
All PTs	**222 (100)**	**123 (55.4)**	**18 (8.1)**	**10 (4.5)**	**152 (68.5)**	**11 (5)**	**51 (23)**
Respiratory failure	9 (4.1)	9 (100)	2 (22.2)	5 (55.6)	3 (33.3)	0	1 (11.1)
Rash	37 (16.7)	8 (21.6)	1 (2.7)	0	22 (59.5)	2 (5.4)	14 (37.8)
Dyspnoea	23 (10.4)	18 (78.3)	3 (13)	0	18 (78.3)	0	5 (21.7)
Cardiac arrest	3 (1.4)	3 (100)	0	2 (66.7)	1 (33.3)	0	0
Hypotension	14 (6.3)	10 (71.4)	1 (7.1)	2 (14.3)	9 (64.3)	1 (7.1)	2 (14.3)
Respiratory distress	1 (0.5)	1 (100)	0	0	1 (100)	0	0
Erythema	15 (6.8)	5 (33.3)	0	0	11 (73.3)	3 (20)	1 (6.7)
Pruritus	15 (6.8)	3 (20)	1 (6.7)	0	10 (66.7)	3 (20)	3 (20)
Acute respiratory failure	1 (0.5)	1 (100)	0	0	1 (100)	0	0
Anaphylactic reaction	12 (5.4)	12 (100)	0	0	10 (83.3)	0	2 (16.7)
Hypersensitivity	11 (5)	7 (63.6)	2 (18.2)	0	9 (81.8)	0	2 (18.2)
Anaphylactic shock	9 (4.1)	9 (100)	5 (55.6)	0	6 (66.7)	0	3 (33.3)
Respiratory arrest	1 (0.5)	1 (100)	0	1 (100)	0	0	0
Bronchospasm	4 (1.8)	3 (75)	1 (25)	0	2 (50)	0	2 (50)
Cough	1 (0.5)	1 (100)	0	0	1 (100)	0	0
Cyanosis	5 (2.3)	4 (80)	0	0	4 (80)	0	1 (20)
Hyperhidrosis	6 (2.7)	3 (50)	0	0	6 (100)	0	0
Tachypnoea	4 (1.8)	3 (75)	0	0	3 (75)	0	1 (25)
Blood pressure decreased	4 (1.8)	1 (25)	0	0	2 (50)	0	2 (50)
Shock	1 (0.5)	1 (100)	0	0	0	0	1 (100)
Chest discomfort	4 (1.8)	3 (75)	0	0	4 (100)	0	0
Chills	2 (0.9)	1 (50)	0	0	2 (100)	0	0

Table 42. Anaphylaxis and Infusion-Associated Reactions (IARs)- Adverse Events Seriousness/Outcomes - Number of Events Preferred Term (Non-Clinical Trials)

PT	No. of Events (% of Total PTs)	No. Serious Events (% of PT)	No. Events with Criterion of Hospitalisation (% of PT)	Distribution of Event by Outcome[a]			
				Fatal	Resolved/Resolving	Not Resolved	Unknown/No Data
All PTs	**222 (100)**	**123 (55.4)**	**18 (8.1)**	**10 (4.5)**	**152 (68.5)**	**11 (5)**	**51 (23)**
Circulatory collapse	2 (0.9)	2 (100)	0	0	2 (100)	0	0
Rash generalised	4 (1.8)	0	0	0	2 (50)	0	2 (50)
Dizziness	1 (0.5)	1 (100)	0	0	1 (100)	0	0
Feeling hot	3 (1.4)	2 (66.7)	0	0	3 (100)	0	0
Flushing	3 (1.4)	1 (33.3)	0	0	3 (100)	0	0
Oedema	2 (0.9)	1 (50)	0	0	1 (50)	0	1 (50)
Oedema peripheral	1 (0.5)	0	0	0	1 (100)	0	0
Urticaria	3 (1.4)	0	0	0	1 (33.3)	0	2 (66.7)
Angioedema	2 (0.9)	2 (100)	1 (50)	0	1 (50)	0	1 (50)
Choking sensation	2 (0.9)	1 (50)	0	0	1 (50)	0	1 (50)
Drug hypersensitivity	2 (0.9)	0	0	0	0	0	2 (100)
Generalised erythema	2 (0.9)	1 (50)	0	0	1 (50)	0	1 (50)
Pruritus generalised	2 (0.9)	0	0	0	0	1 (50)	1 (50)
Rash erythematous	2 (0.9)	0	0	0	2 (100)	0	0
Rash pruritic	1 (0.5)	1 (100)	0	0	1 (100)	0	0
Swelling	1 (0.5)	0	0	0	0	1 (100)	0
Swelling face	1 (0.5)	0	0	0	1 (100)	0	0
Eyelid oedema	1 (0.5)	1 (100)	1 (100)	0	1 (100)	0	0
Hot flush	1 (0.5)	0	0	0	1 (100)	0	0
Laryngeal oedema	1 (0.5)	1 (100)	0	0	1 (100)	0	0
Lip oedema	1 (0.5)	1 (100)	0	0	1 (100)	0	0
Throat tightness	1 (0.5)	0	0	0	1 (100)	0	0
Type I hypersensitivity	1 (0.5)	1 (100)	0	0	1 (100)	0	0

Table 42. Anaphylaxis and Infusion-Associated Reactions (IARs)- Adverse Events Seriousness/Outcomes - Number of Events Preferred Term (Non-Clinical Trials)

PT	No. of Events (% of Total PTs)	No. Serious Events (% of PT)	No. Events with Criterion of Hospitalisation (% of PT)	Distribution of Event by Outcome[a]			
				Fatal	Resolved/Resolving	Not Resolved	Unknown/No Data
All PTs	**222 (100)**	**123 (55.4)**	**18 (8.1)**	**10 (4.5)**	**152 (68.5)**	**11 (5)**	**51 (23)**

a. For the event count, the multiple Lowest Level Terms (LLTs) that code to the same MedDRA PTs within a case, or the PTs duplicated during migration from legacy databases for matching the original assessment are counted once. For the outcome count, the multiple LLTs that code to the same PT within a case or the PTs duplicated during migration from legacy databases (possibly with different outcome), are counted and presented individually. Therefore, for selected PTs the total count of event outcomes may exceed from the total number of events.
PT = Preferred Term.

Table 43. Anaphylaxis and Infusion-Associated Reactions (IARs)- Adverse Events Seriousness/Outcomes - Number of Events Preferred Term (Clinical Trials)

PT	No. Serious Events (% of PT)	No. Events with Criterion of Hospitalisation (% of PT)	Distribution of Event by Outcome[a]				
			Fatal	Resolved/Resolving	Resolved with Sequelae	Not Resolved	Unknown/No Data
All PTs	**217 (100)**	**83 (38.2)**	**102 (47)**	**52 (24)**	**5 (2.3)**	**20 (9.2)**	**38 (17.5)**
Respiratory failure	53 (100)	20 (37.7)	26 (49.1)	13 (24.5)	1 (1.9)	11 (20.8)	2 (3.8)
Rash	1 (100)	0	0	0	0	0	1 (100)
Dyspnoea	14 (100)	11 (78.6)	2 (14.3)	5 (35.7)	0	1 (7.1)	6 (42.9)
Cardiac arrest	33 (100)	3 (9.1)	25 (75.8)	5 (15.2)	2 (6.1)	0	1 (3)
Hypotension	22 (100)	13 (59.1)	3 (13.6)	12 (54.5)	0	1 (4.5)	6 (27.3)
Respiratory distress	21 (100)	11 (52.4)	7 (33.3)	5 (23.8)	1 (4.8)	3 (14.3)	5 (23.8)
Erythema	2 (100)	0	0	0	0	0	2 (100)
Cardio-respiratory arrest	16 (100)	2 (12.5)	15 (93.8)	1 (6.3)	0	0	0
Pruritus	1 (100)	1 (100)	0	0	0	0	1 (100)
Acute respiratory failure	13 (100)	7 (53.8)	8 (61.5)	2 (15.4)	1 (7.7)	2 (15.4)	0

Table 43. Anaphylaxis and Infusion-Associated Reactions (IARs)- Adverse Events Seriousness/Outcomes - Number of Events Preferred Term (Clinical Trials)

PT	No. Serious Events (% of PT)	No. Events with Criterion of Hospitalisation (% of PT)	Distribution of Event by Outcome[a]				
			Fatal	Resolved/Resolving	Resolved with Sequelae	Not Resolved	Unknown/No Data
All PTs	**217 (100)**	**83 (38.2)**	**102 (47)**	**52 (24)**	**5 (2.3)**	**20 (9.2)**	**38 (17.5)**
Hypersensitivity	1 (100)	1 (100)	0	0	0	0	1 (100)
Respiratory arrest	7 (100)	2 (28.6)	5 (71.4)	2 (28.6)	0	0	0
Bronchospasm	2 (100)	0	0	2 (100)	0	0	0
Cough	5 (100)	5 (100)	0	0	0	1 (20)	4 (80)
Cyanosis	1 (100)	0	0	0	0	0	1 (100)
Tachypnoea	2 (100)	1 (50)	0	0	0	1 (50)	1 (50)
Blood pressure decreased	1 (100)	0	0	0	0	0	1 (100)
Shock	4 (100)	0	4 (100)	0	0	0	0
Chills	2 (100)	0	1 (50)	1 (50)	0	0	0
Circulatory collapse	2 (100)	0	2 (100)	0	0	0	0
Dizziness	2 (100)	2 (100)	0	1 (50)	0	0	1 (50)
Oedema	1 (100)	0	0	0	0	0	1 (100)
Oedema peripheral	2 (100)	2 (100)	1 (50)	0	0	0	1 (50)
Rash pruritic	1 (100)	1 (100)	0	0	0	0	1 (100)
Swelling	1 (100)	0	0	1 (100)	0	0	0
Swelling face	1 (100)	0	0	1 (100)	0	0	0
Asthma	1 (100)	1 (100)	0	0	0	0	1 (100)
Endotracheal intubation	1 (100)	0	1 (100)	0	0	0	0
Infusion related reaction	1 (100)	0	0	1 (100)	0	0	0
Obstructive airways disorder	1 (100)	0	1 (100)	0	0	0	0
Tracheostomy	1 (100)	0	0	0	0	0	1 (100)
Wheezing	1 (100)	0	1 (100)	0	0	0	0

Table 43. Anaphylaxis and Infusion-Associated Reactions (IARs)- Adverse Events Seriousness/Outcomes - Number of Events Preferred Term (Clinical Trials)

PT	No. Serious Events (% of PT)	No. Events with Criterion of Hospitalisation (% of PT)	Distribution of Event by Outcome[a]				
			Fatal	Resolved/Resolving	Resolved with Sequelae	Not Resolved	Unknown/No Data
All PTs	**217 (100)**	**83 (38.2)**	**102 (47)**	**52 (24)**	**5 (2.3)**	**20 (9.2)**	**38 (17.5)**

a. For the event count, the multiple Lowest Level Terms (LLTs) that code to the same MedDRA PTs within a case, or the PTs duplicated during migration from legacy databases for matching the original assessment are counted once. For the outcome count, the multiple LLTs that code to the same PT within a case or the PTs duplicated during migration from legacy databases (possibly with different outcome), are counted and presented individually. Therefore, for selected PTs the total count of event outcomes may exceed from the total number of events.

PT = Preferred Term.

Note: Events displayed in the table are those reported in CT cases involving anidulafungin only; all the events are presented regardless they were related or not to anidulafungin therapy.

Table 44. Hepatobiliary Events Seriousness/Outcomes-Number of Events Preferred Term (Non-Clinical Trial)

PT	No. of Events (% of Total PTs)	No. Serious Events (% of PT)	No. Events with Criterion of Hospitalisation (% of PT)	Distribution of Event by Outcome[a]			
				Fatal	Resolved/Resolving	Not Resolved	Unknown/No Data
All PTs	**119 (100)**	**79 (66.4)**	**22 (18.5)**	**15 (12.6)**	**46 (38.7)**	**20 (16.8)**	**38 (31.9)**
Hepatic enzyme increased	11 (9.2)	5 (45.5)	3 (27.3)	1 (9.1)	5 (45.5)	0	5 (45.5)
Hepatic failure	10 (8.4)	10 (100)	4 (40)	3 (30)	1 (10)	2 (20)	4 (40)
Liver function test abnormal	9 (7.6)	5 (55.6)	2 (22.2)	1 (11.1)	4 (44.4)	3 (33.3)	1 (11.1)
Transaminases increased	9 (7.6)	4 (44.4)	0	0	6 (66.7)	1 (11.1)	2 (22.2)
Blood bilirubin increased	11 (9.2)	5 (45.5)	1 (9.1)	1 (9.1)	3 (27.3)	3 (27.3)	4 (36.4)
Liver function test increased	10 (8.4)	6 (60)	0	1 (10)	4 (40)	0	5 (50)

Table 44. Hepatobiliary Events Seriousness/Outcomes-Number of Events Preferred Term (Non-Clinical Trial)

PT	No. of Events (% of Total PTs)	No. Serious Events (% of PT)	No. Events with Criterion of Hospitalisation (% of PT)	Distribution of Event by Outcome[a]			
				Fatal	Resolved/Resolving	Not Resolved	Unknown/No Data
All PTs	**119 (100)**	**79 (66.4)**	**22 (18.5)**	**15 (12.6)**	**46 (38.7)**	**20 (16.8)**	**38 (31.9)**
Alanine aminotransferase increased	7 (5.9)	4 (57.1)	2 (28.6)	0	3 (42.9)	0	4 (57.1)
Blood alkaline phosphatase increased	6 (5)	4 (66.7)	2 (33.3)	0	2 (33.3)	2 (33.3)	2 (33.3)
Aspartate aminotransferase increased	4 (3.4)	3 (75)	2 (50)	0	3 (75)	0	1 (25)
Hepatic function abnormal	4 (3.4)	2 (50)	0	1 (25)	1 (25)	1 (25)	1 (25)
Hepatitis	5 (4.2)	4 (80)	2 (40)	1 (20)	3 (60)	0	1 (20)
Acute hepatic failure	4 (3.4)	4 (100)	1 (25)	1 (25)	1 (25)	2 (50)	0
Cholestasis	4 (3.4)	4 (100)	0	1 (25)	2 (50)	1 (25)	0
Hepatotoxicity	3 (2.5)	1 (33.3)	0	1 (33.3)	0	0	2 (66.7)
Liver injury	3 (2.5)	2 (66.7)	0	2 (66.7)	0	1 (33.3)	0
Gamma-glutamyltransferase increased	3 (2.5)	2 (66.7)	1 (33.3)	0	2 (66.7)	0	1 (33.3)
Hepatitis cholestatic	3 (2.5)	3 (100)	0	0	3 (100)	0	0
Drug-induced liver injury	1 (0.8)	1 (100)	0	0	0	0	1 (100)
Hepatic encephalopathy	1 (0.8)	1 (100)	0	1 (100)	0	0	0
Hepatocellular injury	2 (1.7)	2 (100)	0	0	0	1 (50)	1 (50)
Liver disorder	1 (0.8)	1 (100)	1 (100)	0	0	1 (100)	0
Prothrombin time prolonged	2 (1.7)	1 (50)	0	0	1 (50)	0	1 (50)
Aspartate aminotransferase abnormal	1 (0.8)	1 (100)	0	0	0	0	1 (100)
Bilirubin conjugated increased	1 (0.8)	0	0	0	0	0	1 (100)

Table 44. Hepatobiliary Events Seriousness/Outcomes-Number of Events Preferred Term (Non-Clinical Trial)

PT	No. of Events (% of Total PTs)	No. Serious Events (% of PT)	No. Events with Criterion of Hospitalisation (% of PT)	Distribution of Event by Outcome[a]			
				Fatal	Resolved/Resolving	Not Resolved	Unknown/No Data
All PTs	**119 (100)**	**79 (66.4)**	**22 (18.5)**	**15 (12.6)**	**46 (38.7)**	**20 (16.8)**	**38 (31.9)**
Coma hepatic	1 (0.8)	1 (100)	0	0	0	1 (100)	0
Hepatobiliary disease	1 (0.8)	1 (100)	1 (100)	0	1 (100)	0	0
Hypofibrinogenaemia	1 (0.8)	1 (100)	0	0	1 (100)	0	0
Jaundice	1 (0.8)	1 (100)	0	0	0	1 (100)	0

a. For the event count, the multiple Lowest Level Terms (LLTs) that code to the same MedDRA PTs within a case, or the PTs duplicated during migration from legacy databases for matching the original assessment are counted once. For the outcome count, the multiple LLTs that code to the same PT within a case or the PTs duplicated during migration from legacy databases (possibly with different outcome), are counted and presented individually. Therefore, for selected PTs the total count of event outcomes may exceed from the total number of events.

PT = Preferred Term.

Table 45. Hepatobiliary Events Outcomes - Number of Events Preferred Term (Clinical Trial)

PT	No. Serious Events (% of PT)	No. Events with Criterion of Hospitalisation (% of PT)	Distribution of Event by Outcome[a]				
			Fatal	Resolved/Resolving	Resolved with Sequelae	Not Resolved	Unknown/No Data
All PTs	**44 (100)**	**23 (52.3)**	**10 (22.7)**	**3 (6.8)**	**4 (9.1)**	**17 (38.6)**	**10 (22.7)**
Hepatic enzyme increased	5 (100)	3 (60)	1 (20)	1 (20)	1 (20)	0	2 (40)
Hepatic failure	5 (100)	1 (20)	2 (40)	0	0	2 (40)	1 (20)
Transaminase increased	3 (100)	3 (100)				2 (66.7)	1 (33.3)
Liver function test abnormal	3 (100)	1 (33.3)	0	0	0	2 (66.7)	1 (33.3)
Liver function test increased	1 (100)	0	0	0	1 (100)	0	0

Table 45. Hepatobiliary Events Outcomes - Number of Events Preferred Term (Clinical Trial)

PT	No. Serious Events (% of PT)	No. Events with Criterion of Hospitalisation (% of PT)	Distribution of Event by Outcome[a]				
			Fatal	Resolved/Resolving	Resolved with Sequelae	Not Resolved	Unknown/No Data
Alanine aminotransferase increased	1 (100)	0	0	0	0	1 (100)	0
Blood alkaline phosphatase increased	1 (100)	1 (100)	0	0	0	0	1 (100)
Aspartate aminotransferase increased	2 (100)	1 (50)	0	0	0	1 (50)	1 (50)
Hepatic function abnormal	2 (100)	2 (100)	0	0	0	2 (100)	0
Hepatitis	1 (100)	0	0	0	0	0	1 (100)
Hepatotoxicity	1 (100)	0	0	0	0	1 (100)	0
Liver injury	1 (100)	0	0	0	0	1 (100)	0
Ascites	3 (100)	3 (100)	1 (33.3)	0	1 (33.3)	1 (33.3)	0
Chronic hepatic failure	2 (100)	0	2 (100)	0	0	0	0
Hepatic encephalopathy	1 (100)	0	0	0	0	1 (100)	0
Liver disorder	1 (100)	1 (100)	0	1 (100)	0	0	0
Drug-induced liver injury	1 (100)	0	1 (100)	0	0	0	0
Gamma-glutamyltransferase abnormal	1 (100)	1 (100)	0	0	0	0	1 (100)
Hepatic amoebiasis	1 (100)	1 (100)	0	0	1 (100)	0	0
Hepatic cirrhosis	1 (100)	0	1 (100)	0	0	0	0
Hepatic infection fungal	1 (100)	1 (100)	0	0	0	0	1 (100)
Hepatic necrosis	1 (100)	0	1 (100)	0	0	0	0
Hepatomegaly	1 (100)	0	1 (100)	0	0	0	0
Hyperbilirubinaemia	1 (100)	1 (100)	0	0	0	1 (100)	0
Hypoalbuminaemia	1 (100)	1 (100)	0	1 (100)	0	0	0

Table 45. Hepatobiliary Events Outcomes - Number of Events Preferred Term (Clinical Trial)

PT	No. Serious Events (% of PT)	No. Events with Criterion of Hospitalisation (% of PT)	Distribution of Event by Outcome[a]				
			Fatal	Resolved/Resolving	Resolved with Sequelae	Not Resolved	Unknown/No Data
International normalised ratio increased	1 (100)	1 (100)	0	0	0	1 (100)	0
Pneumobilia	1 (100)	1 (100)	0	0	0	1 (100)	0

a. For the event count, the multiple Lowest Level Terms (LLTs) that code to the same MedDRA PTs within a case, or the PTs duplicated during migration from legacy databases for matching the original assessment are counted once. For the outcome count, the multiple LLTs that code to the same PT within a case or the PTs duplicated during migration from legacy databases (possibly with different outcome), are counted and presented individually. Therefore, for selected PTs the total count of event outcomes may exceed from the total number of events.
PT = Preferred Term.

Note: Events displayed in the table are those reported in CT cases involving anidulafungin only; all the events are presented regardless they were related or not to anidulafungin therapy.

Table 46. Convulsions Outcome - Number of Events Preferred Term (Non- Clinical Trial)[a]

PT	No. of Events (% of Total PTs)	No. Serious Events (% of PT)	No. Events with Criterion of Hospitalisation (% of PT)	Distribution of Event by Outcome	
				Resolved/Resolving	Unknown/No Data
All PTs	**18 (100)**	**18 (100)**	**1 (5.6)**	**10 (55.6)**	**8 (44.4)**
Seizure	15 (83.3)	15 (100)	1 (6.7)	8(53.3)	7 (46.7)
Myoclonic epilepsy	1 (5.6)	1 (100)	0	1 (100)	0
Status epilepticus	2 (11.1)	2 (100)	0	1 (50)	1 (50)

a.For the event count, the multiple Lowest Level Terms (LLTs) that code to the same MedDRA PTs within a case, or the PTs duplicated during migration from legacy databases for matching the original assessment are counted once. For the outcome count, the multiple LLTs that code to the same PT within a case or the PTs duplicated during migration from legacy databases (possibly with different outcome), are counted and presented individually. Therefore, for selected PTs the total count of event outcomes may exceed from the total number of events.
PT = Preferred Term.

Table 47. Convulsions Outcome - Number of Events Preferred Term (Clinical Trial)[a]

PT	No. Serious Events (% of PT)	No. Events with Criterion of Hospitalisation (% of PT)	Distribution of Event by Outcome				
			Fatal	Resolved / Resolving	Resolved with Sequelae	Not Resolved	Unknown / No Data
All PTs	**23 (100)**	**10 (43.5)**	**2 (8.7)**	**16 (69.6)**	**1 (4.3)**	**1 (4.3)**	**3 (13)**
Seizure	20 (100)	9 (45)	2 (10)	13 (65)	1 (5)	1 (5)	3 (15)
Generalised tonic-clonic seizure	2 (100)	1 (50)	0	2 (100)	0	0	0
Myoclonic epilepsy	1 (100)	0	0	1 (100)	0	0	0

a. For the event count, the multiple Lowest Level Terms (LLTs) that code to the same MedDRA PTs within a case, or the PTs duplicated during migration from legacy databases for matching the original assessment are counted once. For the outcome count, the multiple LLTs that code to the same PT within a case or the PTs duplicated during migration from legacy databases (possibly with different outcome), are counted and presented individually. Therefore, for selected PTs the total count of event outcomes may exceed from the total number of events.
PT = Preferred Term.
Note: Events displayed in the table are those reported in CT cases involving anidulafungin only; all the events are presented regardless they were related or not to anidulafungin therapy.

Table 48. QT prolongation /Torsade de Pointes Outcomes - Number of Events Preferred Term (Non-Clinical Trial)[a]

PT	No. of Events (% of Total PTs)	No. Serious Events (% of PT)	No. Events with Criterion of Hospitalisation (% of PT)	Distribution of Event by Outcome		
				Fatal	Resolved / Resolving	Unknown / No Data
All PTs	**19 (100)**	**19 (100)**	**4 (21.1)**	**10 (52.6)**	**6 (31.6)**	**3 (15.8)**
Multiple organ dysfunction syndrome	9 (47.4)	9 (100)	3 (33.3)	8 (88.9)	0	1 (11.1)
Cardiac arrest	3 (15.8)	3 (100)	0	2 66.73)	1 (33.3)	0

Table 48. QT prolongation /Torsade de Pointes Outcomes - Number of Events Preferred Term (Non-Clinical Trial)[a]

PT	No. of Events (% of Total PTs)	No. Serious Events (% of PT)	No. Events with Criterion of Hospitalisation (% of PT)	Distribution of Event by Outcome		
				Fatal	Resolved / Resolving	Unknown / No Data
All PTs	**19 (100)**	**19 (100)**	**4 (21.1)**	**10 (52.6)**	**6 (31.6)**	**3 (15.8)**
Ventricular fibrillation	1 (5.3)	1 (100)	0	0	1 (100)	0
Ventricular tachycardia	1 (5.3)	1 (100)				1 (100)
Loss of consciousness	2 (10.5)	2 (100)	0	0	2 (100)	0
Syncope	2 (10.5)	2 (100)	1 (50)	0	2 (100)	0
Torsade de pointes	1 (5.3)	1 (100)	0	0	0	1 (100)

a. For the event count, the multiple Lowest Level Terms (LLTs) that code to the same MedDRA PTs within a case, or the PTs duplicated during migration from legacy databases for matching the original assessment are counted once. For the outcome count, the multiple LLTs that code to the same PT within a case or the PTs duplicated during migration from legacy databases (possibly with different outcome), are counted and presented individually. Therefore, for selected PTs the total count of event outcomes may exceed from the total number of events.
PT = Preferred Term.
Note: The increase of the number of CT and non CT cases is due to a new PT (Multiple organ dysfunction syndrome) added in the SMQ for QT prolongation that was added at the time of MedDRA version 21.0

Table 49. QT prolongation /Torsade de Pointes Outcomes - Number of Events Preferred Term (CT)[a]

PT	No. of Events (% of Total PTs)	No. Serious Events (% of PT)	No. Events with Criterion of Hospitalisation (% of PT)	Distribution of Event by Outcome				
				Fatal	Resolved/Resolving	Resolved with Sequelae	Not Resolved	Unknown/No Data
All PTs	**97 (100)**	**97 (100)**	**11 (11.3)**	**81 (83.5)**	**11 (11.3)**	**2 2.1)**	**2 (2.1)**	**1 (1)**
Multiple organ dysfunction syndrome	42 (43.3)	42 (100)	5 (11.9)	39 (92.9)	1 (2.4)	0	2 (4.8)	0
Cardiac arrest	33 (34)	33 (100)	3 (9.1)	25 (75.8)	5 (15.2)	2 (6.1)		1 (3)
Cardio-respiratory arrest	16 (16.5)	16 (100)	2 (12.5)	15 (93.8)	1 (6.3)	0		0
Ventricular fibrillation	2 (2.1)	2 (100)	1 (50)	0	2 (100)	0		0
Ventricular tachycardia	2 (2.1)	2 (100)	0	1 (50)	1 (50)	0		0
Electrocardiogram QT prolonged	1 (1)	1 (100)	0	0	1 (100)	0		0
Ventricular arrhythmia	1 (1)	1 (100)	0	1 (100)	0	0		0

a. For the event count, the multiple Lowest Level Terms (LLTs) that code to the same MedDRA PTs within a case, or the PTs duplicated during migration from legacy databases for matching the original assessment are counted once. For the outcome count, the multiple LLTs that code to the same PT within a case or the PTs duplicated during migration from legacy databases (possibly with different outcome), are counted and presented individually. Therefore, for selected PTs the total count of event outcomes may exceed from the total number of events.
PT = Preferred Term.
Note: The increase of the number of CT and non CT cases is due to a new PT (Multiple organ dysfunction syndrome) added in the SMQ for QT prolongation that was added at the time of MedDRA version 21.0
Events displayed in the table are those reported in CT cases involving anidulafungin only; all the events are presented regardless they were related or not to anidulafungin therapy.

Table 50. Important Potential Risk: Hepatic impairment and other serious toxicities in neonates (< 1 month of age) (Non-Clinical Trial)[a]

PT	No. of Events (% of Total PTs)	No. Serious Events (% of PT)	No. Events with Criterion of Hospitalisation (% of PT)	Distribution of Event by Outcome				
				Fatal	Resolved/ Resolving	Resolved with Sequelae	Not Resolved	Unknown/ No Data
All PTs	3 (100)	3 (100)	0	0	3 (100)	0	0	0
Blood bilirubin increased	1 (33.3)	1 (100)	0	0	1 (100)	0	0	0
Liver function test abnormal	1 (33.3)	1 (100)	0	0	1 (100)	0	0	0
Transaminases increased	1 (33.3)	1 (100)	0	0	1 (100)	0	0	0

b.For the event count, the multiple Lowest Level Terms (LLTs) that code to the same MedDRA PTs within a case, or the PTs duplicated during migration from legacy databases for matching the original assessment are counted once. For the outcome count, the multiple LLTs that code to the same PT within a case or the PTs duplicated during migration from legacy databases (possibly with different outcome), are counted and presented individually. Therefore, for selected PTs the total count of event outcomes may exceed from the total number of events.
PT = Preferred Term.

ANNEX 8. SUMMARY OF CHANGES TO THE RISK MANAGEMENT PLAN OVER TIME

Version	Approval date Procedure	Change
1.2 Versions 1.0 and 1.1 updated during Agency assessment	20 September 2007 EMEA/H/C/000788	Identified Risks Infusion-related reactions Hepatobiliary events Potential Risks Convulsions Anesthetic exacerbation of infusion-associated reactions QT prolongation/Torsade de pointes Missing information Children/adolescents Neutropenic patients Pregnant women Elderly Updated based on interactions with EMA. Version 1.2 represents agreed initial RMP.
2.0	Not applicable EMEA/H/C/788/X/007	No change to safety concerns. Provide updated information up to 31 July 2008 as part of routine review in line with the PSUR submission
2.1	Not applicable EMEA/H/C/788/X/007	No change to safety concerns. Updated to include drug format without solvent for dilution with water for injections (WFI) and included risk management activities during transition to use of WFI for preparation of concentrate
2.2	23 July 2009 EMEA/H/C/788/X/007	No change to safety concerns. Revised per Day 150 Assessment Report Updated Letter to Healthcare Professionals in Annex 7, and SmPC in Annex 2
3.0	25 June 2009 EMEA/H/C/788/RMP/036	No change to safety concerns. Provide updated information to 31 January 2009 as part of routine review in line with the PSUR submission. Also updated in response to Assessment report for PSUR 2.
4.0	17 December 2009 EMEA/H/C/788/PSUR/030	No change to safety concerns. Merge RMP v 2.2 and 3.0 to cover both anidulafungin presentations
5.0	RMP date: 21 March 2011 EMEA/H/C/788/RMP/038	No change to safety concerns. Provided updated information to 31 January 2011 as part of routine review in line with PSUR submission. Also updated in response to Assessment Report for PSUR 6

Version	Approval date Procedure	Change
6.0	RMP date: 27 January 2012	Included the ongoing FUMs to the body of the RMP.
7.0	Not applicable EMEA/H/C/000788/PSUR 034 RMP 039	No change to safety concerns. Provided updated information to 31 January 2012 as part of routine review in line with PSUR submission.
8.0	23 August 2012 EMEA/H/C/000788/R/0020	No change to safety concerns. Provided updated information in response to CHMP LoOI, dated 24 May 2012
9.0	RMP date: 31 August 2012 EMEA/H/C/000788/RMP 041	Added patients with deep tissue infections to table containing Important limited/missing information. Provided updated information in response to EMA/439075/2012, dated 29 June 2012
10.0	PRAC Recommendation: 5 September 2013 EMEA/H/C/000788/PSU/0040	No change to safety concerns. Updated to new EMA template and provided updated information to 31 January 2013 as part of routine review in line with PSUR submission.
11.0	26 August 2014 EMEA/H/000788/II/0026	Removed neutropenic patients and patients with deep tissue infection from Missing Information. Updated with data from studies in subjects with neutropenia and deep tissue infection.
12.0	Not applicable EMEA/H/C/PSUSA/00000215/201701	Module SI: Epidemiology revised. Module SIII: Clinical trials exposure data updated aligned with new cut-off date and updates on Study A8851008. Module SV: Updates aligned with new cut-off date Module SVI: Updates on potential for overdose, medication errors, resistance aligned with new cut-off date. Module SVII: Safety data tables for all important risks have been updated. Module SVIII: Convulsion moved from important potential risk to important identified risk Part III: Updated planned Pharmacovigilance actions (1008 and 1030, SENTRY) Part V and Part VI: tables and milestones updates Annexes: 2-3-4-5-7-9 The RMP is presented in a consolidated format

Version	Approval date Procedure	Change
12.1	08 March 2018 EMEA/H/C/000788/II/0036	Module SIII: Clinical trials exposure data updated aligned with new cut-off date. Module SV: Updates aligned with new cut-off date Module SVI: Updates on potential for overdose, medication errors, aligned with new cut-off date. Module SVII: Post marketing Data tables for all important risks have been updated Module V.1. Risk Minimisation Measures by Safety Concerns: updates on Anaphylaxis and infusion-associated adverse reactions, Children and Pregnancy Annexes: 2-3 updated based on new cut-off The changes submitted in RMP version 12 by the MAH were extensive and were not a direct result of data presented in the latest PSUR (2017). Therefore, the version 12 of the RMP was not accepted in previous procedure. The MAH was requested to submit a separate variation to update the RMP to version 12.1.

Version	Approval date Procedure	Change
13.0-13.1	Not applicable	PART I: Indication and posology updated to reflect the proposed extension for use in individuals from the age of 1 month. PART II Module SI Updated to include paediatric epidemiological data. PART II Module SII Revised and aligned with the GVP Module V Rev 2 requirements. PART II Module SIII Updated to data lock point 15 October 2018. Presentation of paediatric exposure data (studies A8851008 and VER002-12). PART II Module SIV Updated based on new data available following completion of study A8851008 and aligned with the GVP Module V Rev 2 requirements. PART II Module SV Alignment with the GVP Module V Rev 2 requirements. The post-authorisation exposure was updated. PART II Module SVI Alignment with the GVP Module V Rev 2 requirements. PART II Module SVII Reclassification of the safety concerns in line with the GVP Module V Rev 2 and following completion of study A8851008. The MAH proposes to reclassify all current potential and identified risks to risks 'not important' and to add a new important potential risk i.e. *Hepatic impairment and other serious toxicities in neonates < 1 month of age*. In addition the MAH proposes to reclassify the safety concerns *Children/adolescents* and *Elderly* in Missing information for removal. *Pregnant women* and *Resistance* are removed based on the Request for Supplementary Information (RSI) received on 20 November 2019. PART II Module SVIII The list of safety concerns has been updated based on the reclassification presented in Module SVII. PART III No major changes. Aligned to the current GVP Module V Rev. 2 and on the RSI request. PART IV Alignment with the GVP Module V Rev 2 requirements and on RSI request. PART V Updated according to the changes made to the safety concerns in Module VII. PART VI The text has been updated as per current template accompanying GVP Module V Rev 2 and RSI request. PART VII The annexes have been revised to match the current template accompanying GVP Module V Rev 2.