NON-INTERVENTIONAL (NI) STUDY REPORT

PASS information

Title	Non-Interventional Post-Authorization Safety Study to Describe Use by Indication and Clinical Outcomes Among Patients With Complicated Intra-Abdominal Infection or Complicated Skin and Soft Tissue Infection Treated With Tigecycline (Tygacil®) in The European Union
Protocol number	B1811184
Version identifier of the final study report	v1.0 FINAL
Date of last version of the final study report	16 September 2014
EU Post Authorisation Study (PAS) register number	ENCEPP/SDPP/3674
Active substance	Tigecycline, ATC code J01AA12
Medicinal product	Tygacil
Product reference	EU/1/06/336/001
Procedure number	EMEA/H/C/644/ANX 58
Marketing Authorisation Holder (MAH)	Pfizer Limited
Joint PASS	No
Research question and objectives	Tigecycline is an intravenously administered antibiotic indicated in the European Union (EU) for treatment of complicated intra-abdominal infection (cIAI) and complicated skin or soft tissue infection (cSSTI) excluding diabetic foot infection. This retrospective medical record review study is

	evaluating the effectiveness of 2011 Risk Minimization Measures (RMM) aimed at reducing off-label use of tigecycline in the EU by assessing the proportion of off-label use before and after RMM implementation. Primary objectives: 1) Evaluate the effectiveness of tigecycline RMM by describing prescription patterns among patients treated with any dose of tigecycline for any indication (ie, on- or off-label) in the EU prior to implementation of the RMM (ie, 01 February 2010 to 01 February 2011) and following implementation of these measures (ie, 01 February 2012 to 01 February 2013); 2) Determine the incidence of superinfection and lack of efficacy among adult patients treated with approved doses of tigecycline for cIAI and cSSTI in the EU prior to implementation of the RMM (ie, 01 February 2010 to 01 February 2011) and following implementation of these measures (ie, 01 February 2012 to 01 February 2013).
Countries of study	Austria, Greece, Germany, Italy, United Kingdom
Author	Veronica Frajzyngier

Marketing Authorisation Holder(s)

Marketing Authorisation Holder(s)	Pfizer Limited Ramsgate Road, Sandwich, Kent CT130NJ United Kingdom
MAH contact person	Veronica Frajzyngier

TABLE OF CONTENTS

LIST OF IN-TEXT TABLES AND FIGURES

Annex 1. List of stand-alone documents

1. ABSTRACT (STAND-ALONE DOCUMENT)

2. LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	Adverse event
CI	Confidence interval
cIAI	Complicated intra-abdominal infection
CPO	Carbapenamase-producing organism
CRA	Clinical research associate
CRO	Contract research organization
cSSTI	Complicated skin and soft tissue infection
DHPC	Direct to healthcare professional communication
DPA	Data Protection Agency
EC	Ethics Committee
eCRF	Electronic case report form
EMA	European Medicines Agency
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
ESBL(PO)	Extended-spectrum β-lactamase (producing organism)
EU	European Union
FAS	Full analysis set
GCP	Good Clinical Practice
GPP	Good Pharmacoepidemiology Practices
HCP	Healthcare professional
ICF	Informed consent form
ICH	International Conference on Harmonization
ICU	Intensive care unit
IEC	Independent ethics committee
ISPE	International Society for Pharmacoepidemiology
ISPOR	International Society for Pharmacoeconomics and Outcomes Research
MAH	Marketing authorisation holder
MedDRA	Medical Dictionary for Regulatory Activities
mFAS	Modified full analysis set
mPAS	Modified primary analysis set
MRCNS	Methicillin-resistant coagulase-negative *Staphylococcus*
MRSA	Methicillin-resistant *Staphylococcus aureus*
NI	Non-interventional
OR	Odds ratio
PAS	Primary analysis set
PASS	Post-authorization safety study
PhRMA	Pharmaceutical Research and Manufacturers Association
PT	Preferred term
RDMV	Remote data monitoring visit
RMM	Risk minimization measures
RSIV	Remote site initiation visit
SAE	Serious adverse event
SAP	Statistical analysis plan
SD	Standard deviation
SIRS	Systemic inflammatory response syndrome
SmPC	Summary of Product Characteristics

SOC	System organ class
SOP	Standard operating procedure
SQQ	Site qualification questionnaire
TC	Telephone contact
UK	United Kingdom
VRE	Vancomycin-resistant enterococci

3. INVESTIGATORS

The names, affiliations, and contact information of the investigators at each study site are listed in Appendix 3.1.

Principal Investigator(s) of the Protocol

Name, degree(s)	Title	Affiliation
Veronica Frajzyngier, PhD MPH	Non-Interventional Study Lead, Epidemiologist	WSR Epidemiology, Pfizer Inc.
Michele Wible, MS	Statistics Lead	Clinical Statistics, Pfizer Inc.
Scott Rottinghaus, MD, MSc	Clinical Lead	Clinical Affairs, Pfizer Inc
Alvaro Quintana, MD	Medical Lead	Medical Affairs, Pfizer Inc

Lead Country Investigator(s) of the Protocol

Name, degree(s)	Title	Affiliation
Florian Thalhammer, MD	National Coordinator, Austria	Medical University of Vienna Vienna, Austria
Christian Lojewski, MD	National Coordinator, Germany	CHARITE - Universitätsmedizin Berlin, Germany
Andrew Kirby, MD	National Coordinator, UK	Leeds Teaching Hospitals National Health Service Trust Leeds, UK
Panagiotis Kakolyris Gargalianos, MD	National Coordinator, Greece	General Hospital of Athens "G. Gennimatas" Athens, Greece
Pierluigi Viale, MD	National Coordinator, Italy	Azienda Ospedaliero-Universitaria doi Bologna Policlinico S. Orsola Malpighi, Bologna, Italy

4. OTHER RESPONSIBLE PARTIES

External Adjudication Committee Members

Responsible Party Name and Affiliation	Role in the study
Matteo Bassetti Santa Maria della Misericordia University Hospital Piazzale Santa Maria della Misericordia 15 Udine, Italy	Adjudication Committee Chair
Christian Eckmann Klinikum Peine Academic Hospital, Academic Hospital of Medical University Hannover Virchowstr. 8h Peine, Germany	Adjudication Committee Member
Philippe Montravers Bichat-Claude Bernard, APHP 46 rue Henri Huchard Paris Cedex 18,France	Adjudication Committee Member

CRO Responsible Parties

Responsible Party Name and Affiliation	Role in the study
Elisa Baelen Quintiles Europe SARL Ch. du Glapin 6 1162 St Prex, Switzerland	Clinical Project Manager
Leslie Hansen Quintiles Europe SARL Ch. du Glapin 6 1162 St Prex, Switzerland	Clinical Project Director
Ankit Shah Quintiles 201 Broadway Cambridge, MA 02139 USA	Study Statistician
Kathryn Starzyk Quintiles 201 Broadway Cambridge, MA 02139 USA	Epidemiologist

5. MILESTONES

Milestone	Planned date	Actual date	Comments
Dates of Ethics Committee (EC) approvals	All EC approvals expected before the start of data collection date in the respective country / site	First EC approval (Austria): 25 February 2013 Last EC approval (Germany): 14 October 2013	The dates for all EC approvals are provided in Appendix 3
Start of data collection (first patient chart abstraction)	10 May 2013	23 May 2013	
End of data collection (last patient chart abstraction)	31 December 2013	31 January 2014	
Registration in the EU PAS register	Before the start of data collection date	19 March 2013	
Study progress report	30 September 2013	24 September 2013	
Interim report	31 January 2014	24 February 2014	At request of EMA, submission deadline postponed to allow for inclusion of additional information requested by the agency
Final report of study results	30 September 2014	16 September 2014	

6. RATIONALE AND BACKGROUND

Tygacil® (tigecycline) is an intravenously administered antibiotic indicated in the European Union (EU) for treatment of complicated intra-abdominal infection (cIAI) and complicated skin and soft tissue infection (cSSTI) excluding diabetic foot infection. In clinical trials and post-marketing studies, a consistent all-cause mortality differential has been seen between tigecycline and comparator antibiotics, with patients treated with tigecycline for both approved and non-approved indications experiencing a higher mortality rate. It is not known whether this mortality imbalance is related to the newly identified risk of superinfection, defined as an overgrowth of non-susceptible organisms, lack of efficacy, the potential risks of off-label use among tigecycline users, or other factors. In order to address these identified and potential risks, the European Medicines Agency (EMA) required Pfizer to develop and disseminate Risk Minimization Measures (RMM) for tigecycline. These included changes to the Summary of Product Characteristics (SmPC), a Direct to Healthcare Professional Communication (DHPC), and a healthcare provider educational program emphasizing the newly identified risk of superinfection and potential risks of off-label use and lack of efficacy. After development and implementation of these RMM in the EU, the EMA requested that Pfizer initiate an observational, retrospective post-authorization safety study (PASS) to evaluate the effectiveness of the RMM. The goal of this descriptive cohort study was to assess the effectiveness of the RMM by describing indications for tigecycline use and clinical outcomes among adult patients with cIAI or cSSTI treated with approved doses of tigecycline in the EU before and after implementation of the RMM in February 2011.

This non-interventional study was designated as a PASS and is a commitment to EMA.

7. RESEARCH QUESTION AND OBJECTIVES

Primary Objective 1

Evaluate the effectiveness of tigecycline RMM by describing prescription patterns among patients treated with any dose of tigecycline for any indication (ie, on- or off-label) in the EU prior to implementation of the RMM (ie, 01 February 2010 to 01 February 2011) and following implementation of these measures (ie, 01 February 2012 to 01 February 2013).

Primary Objective 2

Determine the incidence of superinfection and lack of efficacy among adult patients treated with approved doses of tigecycline for cIAI and cSSTI in the EU prior to implementation of the RMM (ie, 01 February 2010 to 01 February 2011) and following implementation of these measures (ie, 01 February 2012 to 01 February 2013).

Secondary Objective

Qualitatively describe pathogens associated with infection for which tigecycline use was indicated among patients treated with any dose of tigecycline for any indication in the EU prior to implementation of the RMM (ie, 01 February 2010 to 01 February 2011) and following implementation of these measures (ie, 01 February 2012 to 01 February 2013) using all available microbiology data contained in patient medical records.

Exploratory Objective 1

As microbiology data allow, quantitatively describe the distribution of pathogens associated with infection for which tigecycline use was indicated among patients treated with any dose of tigecycline for any indication in the EU prior to implementation of the RMM (ie, February 2010 to February 2011) and following implementation of these measures (ie, February 2012 to February 2013), stratified by indication for tigecycline use.

Exploratory Objective 2

As availability of covariate data allows, perform exploratory multivariate comparative analysis of:

- Superinfection and lack of efficacy in the pre-RMM implementation period (ie, February 2010 to February 2011) versus the post-RMM implementation period (ie, February 2012 to February 2013) among patients treated with approved doses of tigecycline for approved indications;

- Off-label tigecycline use in the pre-RMM (February 2010 to February 2011) versus the post-RMM implementation period (February 2012 to February 2013).

8. AMENDMENTS AND UPDATES

Table 8.1 Amendments to the Protocol

Amendment number	Date	Substantial or administrative amendment	Protocol section(s) changed	Summary of amendment	Reason
1	31 Jul 2012	S	Section 13	Section 13 revised at EMA's request to reflect that waivers of informed consent will be pursued in all countries according to local legislation with the primary reason being that it would prevent the potential selection bias introduced by requiring consent from tigecycline-treated patients.	Address EMA request to amend the protocol
2	08 Nov 2012	A	Section 8, Section 14.1	Section 8 revised to include the updated mandatory AE reporting language per revised Pfizer SOPs and new EU legislation Section 14.1 revised to indicate that this non-interventional PASS will be publically disclosed in the EU Post-Authorisation Study register	Reflect changing EU requirements for AE reporting and PASS disclosure
3	26 Mar 2013	A	Title Page	ENCePP registration number added	Reflect ENCePP registration number in the protocol
4	11 Nov 2013	S	Substantial amendment : section 10, 11.1; admin-istrative amendments: sections 2.1.1 2.1.2 2.2 2.3.1 2.3.2 2.4.4 3 4 4.1	Substantial amendment entailed clarification that monitoring visits would be done remotely rather than in person (sections 10, 11.1). Administrative changes included clarifications regarding dates of each of the included enrollment time periods (sections 2.1, 2.1.2, 2.2, 2.3.1, 2.3.2, 3, 4, 4.1 and 6.2); the remote nature of the site initiation visit (section	Specifications were made to help clarify details for participating sites. Safety reporting language was updated according to Pfizer SOPs.

			6.1 6.2 8.11 9.1 9.1.3 11.1	6.1); and inclusion of pilot adjudication cases in the analysis (section 2.4.4). The amendment also provided clarification of the data abstraction process (section 4), and addition of new safety reporting language (section 8.1.1)	

*Type: S=Substantial, A=Administrative

9. RESEARCH METHODS

9.1. Study design

This observational non-interventional cohort study involved retrospective medical record review and descriptive analyses. All patients treated with tigecycline for any indication during the study period were retrospectively identified at 13 participating centers in 5 EU countries (Austria, Greece, Germany, Italy and the United Kingdom [UK]) through review of electronic medication databases or paper registries. Patient medical records were reviewed to 1) determine indication for tigecycline use and to 2) identify potential superinfection and lack of efficacy cases among those treated for approved indications. For purposes of identifying potential cases of superinfection and lack of efficacy, use of dosing regimens consistent with tigecycline local labeling (eg, 100 mg loading dose and 25 or 50 mg BID maintenance dosing), patient age (ie, greater than 18 years) and duration of tigecycline treatment (ie, at least 48 hours) was also considered in identifying on-label use. A committee of external adjudicators reviewed all relevant medical record data from potential superinfection and lack of efficacy cases (among on-label users) to determine their actual status with regard to study endpoints.

Frequencies of indications and the proportion of off-label use of tigecycline were calculated before and after RMM implementation. Incidence proportions of superinfection and lack of efficacy among adult patients treated for cIAI and cSSTI were calculated in periods defined as being before and after RMM implementation. A descriptive analysis of pathogens associated with infection treated with tigecycline was performed where microbiology data were available. Assignment of patient therapeutic strategy by the treating physician was not influenced or determined in advance following a study protocol, but rather fell within current practice. As this was an observational descriptive study of patients treated with tigecycline, there were no comparator groups selected.

This observational study adds to the body of knowledge on patterns of tigecycline use in the EU, and allows a descriptive comparison of off-label use of tigecycline, and the incidence proportions of superinfection and potential lack of efficacy among on-label users, pre- and post- implementation of RMM. Collecting data at the site level (as opposed to via administrative electronic health databases) allows linkage among inpatient diagnosis, procedure, medication, and microbiology (when available) data for EU patients; such linkage is not accommodated by currently available databases in these countries. Further,

adjudication of potential cases of superinfection and lack of efficacy allows for objective assessments of these endpoints in this observational setting.

The full study protocol is provided in Appendix 2.

9.2. Setting

The top tigecycline-prescribing EU countries were identified. Hospitals or wards in these countries (Austria, Germany, Greece, the UK, Italy and Spain) with medication records that could be queried to identify tigecycline-treated patients (or paper registries of tigecycline-treated patients) during the periods of interest were identified for potential enrollment in the tigecycline PASS. In order to ensure a sample of 300 patients both before and after implementation of RMM, a total of 127 healthcare professionals (HCPs) at 121 hospitals and medical centers were contacted and asked to participate during the site recruitment phase (October 2012 through April 2013). Local sponsor affiliates identified prescribing sites and provided a list of potential investigators to Quintiles. Site lists per country were sent to the Sponsor Study Lead for review and approval prior to the planned site recruitment start date. Each HCP was asked to complete a site qualification questionnaire (SQQ). The SQQ included questions about the number of patients administered tigecycline between 01 February 2010 and 01 February 2011, and between 01 February 2012 and 01 February 2013, and the availability of human resources at the hospital or ward for conducting such a study. Some HCPs (54/127, 42.5%) replied that they were not interested in participating in the study. Despite the fact that several reminders were sent, some HCPs (38/127, 29.9%) never replied to the invitation and were therefore considered non-responders. Thirty-five HCPs (27.6%) expressed interest in the study and sent back a completed SQQ, Following review of the received SQQ, some interested sites were put on a reserve list (and ultimately excluded), because there were enough qualified sites from the same country with a sufficient number of patients (1 site in Italy and 3 sites in Greece) or the sites had a low number of estimated eligible patients in the 2 study periods (1 site in Austria, 1 site in Germany with only 12-40 eligible patients) or an unbalanced distribution of patients before and after the RMM (2 sites in Greece, with a difference of 70 to 100% in the distribution of their patients population between the 2 study periods).

Twenty-two sites were initially selected for participation, of which 9 were not initiated. For most of the sites selected but not initiated, failure to initiate was due to study timelines (eg, delays observed in local ethics committee [EC] submission or contract negotiations). A total of 7 physicians declined to participate after having been selected because of the informed consent form (ICF) requirements (3 sites in Italy) or because they did not have time to oversee the study or lacked sufficient staff resources (1 site in Austria, 1 site in Italy, 2 in the UK). Finally, the 2 sites selected in Spain were not initiated. Since informed consent is required from all patients (deceased and living) in Spain, and due to the strong likelihood of introducing bias into the study results through inclusion of only consenting patients, start-up activities in this country ceased. It is unknown if participating sites are comparable to contacted sites in term of type (academic versus non academic, characteristics of tigecycline prescribers or location). Five countries (Austria, Germany, Greece, Italy and United Kingdom) with a total of 13 sites ultimately participated in the study. A summary of the site recruitment by country is provided in Table 9.1.

Table 9.1 Site Selection Summary

Country	No. of HCPs contacted	No. of HCPs interested in participating (= SQQ received)	No. of HCPs not interested (prior to selection)	No. of selected sites	No. of participating sites
Austria	35	5 - 1 (20%) Infectious Disease and Internal Medicine - 1 (20%) Medical Department - 1 (20%) Anesthesiology - 1 (20%) Neurosurgery / Neurology - 1 (20%) Intensive Care Unit (ICU)	30 - 19 (63%) ICU - 3 (10%) Internal Medicine - 1 (3%) Internal Medicine / Pulmonology - 1 (3%) Microbiology/Tropical Medicine - 1 (3%) Vascular/chest surgery - 1 (3%) Infectious Disease - 1 (3%) Hygiene/microbiology - 1 (3%) Anesthesiology and ICU - 1 (3%) Tropical medicine, hygiene and microbiology - 1 (3%) Not specified	4	2 - 1 (50%) Neurosurgery / Neurology - 1 (50%) Anesthesiology
Germany	21	7 - 3 (30%) ICU - 2 (29%) General Visceral Transplant Surgery - 1 (14%) Neurosurgery / Neurology - 1 (14%) Anesthesiology	14 - 5 (36%) Not specified - 4 (29%) Surgery - 2 (14 %) ICU - 1 (7%) Internal Medicine - 1 (7%) Anesthesiology and ICU - 1 (7%) Infectious Disease and surgery	5	4 - 1 (25%) ICU - 1 (25%) General Visceral Transplant Surgery - 1 (25%) Neurosurgery / Neurology - 1 (25%) Anesthesiology
Greece	17	8 - 8 (100%) Internal Medicine	9 - 9 (100%) Internal Medicine	3	2 - 2 (100%) Internal Medicine

Country	No. of HCPs contacted	No. of HCPs interested in participating (= SQQ received)	No. of HCPs not interested (prior to selection)	No. of selected sites	No. of participating sites
Italy	16	8 - 5 (63%) Infectious Disease - 1 (13%) ICU - 1 (13%) Surgery - 1 (13%) Medical Sciences	8 - 2 (25%) Infectious Disease - 2 (25%) ICU - 2 (25%) Surgery - 1 (13%) Microbiology unit - 1 (13%) Pharmacy	6	3 -3 (100%) Infectious Disease
UK	32	4 - 1 (25%) ICU - 1 (25%) Surgery - 1 (25%) Pharmacy - 1 (25%) Microbiology	28 - 21 (75%) Microbiology - 3 (11%) Pharmacy - 1 (4%) Infectious Disease - 1 (4%) Medical Biology - 2 (7%) Not specified	2	2 - 1 (50%) ICU - 1 (50%) Infectious Disease
Spain	6	3 - 2 (75%) Infectious Disease - 1 (25%) ICU	3 - 3 (100%) Infectious Disease	2	0

Country	No. of HCPs contacted	No. of HCPs interested in participating (= SQQ received)	No. of HCPs not interested (prior to selection)	No. of selected sites	No. of participating sites
TOTAL	**127**	35 - 8 (23%) Internal medicine - 7 (20%) Infectious disease - 7 (20%) ICU - 2 (6%) Neurosurgery / Neurology - 2 (6%) Surgery - 2 (6%) General Visceral Transplant Surgery - 1 (3%) Pharmacy - 1 (3%) Microbiology - 1 (3%) Infectious Disease and Internal Medicine - 1 (3%) Medical Department - 1 (3%) Anesthesiology - 1 (3%) Anesthesiology - 1 (3%) Medical Sciences	92 - 23 (25%) ICU - 22 (24 %) Microbiology - 13 (14%) Internal Medicine - 7 (8%) Infectious Disease - 6 (7%) Surgery - 4 (4%) Pharmacy - 2 (2%) Anesthesiology and ICU - 1 (1%) Medical Biology - 1 (1%) Internal Medicine / Pulmonology - 1 (1%) Microbiology/Tropical Medicine - 1 (1%) Vascular/chest surgery - 1 (1%) Hygiene/microbiology - 1 (1%) Tropical medicine, hygiene and microbiology - 1 (1%) Infectious Disease and surgery - 8 (9%) Not specified	22	13 - 4 (31%) Infectious Disease - 2 (15%) Internal medicine - 2 (15%) ICUs - 2 (15%) Neurosurgery / Neurology - 2 (15%) Anesthesiology - 1 (8%) General Visceral Transplant Surgery

9.3. Patients

All patients treated with at least one dose of tigecycline and for any indication within selected hospitals or wards between 01 February 2010 and 01 February 2011 and between 01 February 2012 and 01 February 2013 were eligible for inclusion in this PASS. Patients had to have either commenced or completed treatment with tigecycline within the above-specified periods to be considered eligible. Each site was instructed to abstract patient charts in a random order, in order to ensure that if full enrollment at a given site was not completed (for instance, due to competitive enrollment), bias would not be introduced.

A projected sample size of at least 300 patients in each period (ie, one year before and after the RMM implementation) was agreed upon with the Agency. The final study sample size is reported in Section 9.7.

9.4. Variables

Indication for Use – Primary Endpoint, Primary Objective 1

Indication for use was defined as the infection type for which tigecycline was prescribed, determined using available medical record data on primary and secondary diagnoses made in the inpatient setting linked to inpatient medication data. All indications among patients treated with tigecycline included in the study are described.

Use of tigecycline for approved indications (cIAI and cSSTI excluding diabetic foot infection) in adult patients (18 years of age or older) was considered to be use for on-label indications, as per the SmPC. Use for any other indication or pediatric use (patients younger than 18 years of age) was considered to be use for off-label indications. When documented in the medical record, reasons for off-label and on-label use were described (eg, no suitable alternative therapies).

Superinfection – Primary Endpoint, Primary Objective 2

Superinfection was defined as emergence of a new isolate at the site of the infection with emergence or worsening of signs and symptoms of infection (ie, deemed a clinical failure), or the development of an infection distant to the site of primary infection, not present at baseline >2 days following initiation of tigecycline therapy. The "2 days" was operationalized as a 48-hour period for the purposes of the study. If the time of dose was unavailable for determining the 48-hour period, then 2 calendar days were used.

Potential cases of this endpoint were identified using medical record data based on the following definition:

- On-label use of tigecycline
  - Indication either cIAI or cSSTI
  - Loading dose of 100 mg
  - Maintenance dose of either 25 mg or 50 mg
- Tigecycline administered for ≥48 hours
- Responses of "Yes" or "Insufficient Information" to the following question in the case report form (CRF) by the abstractor:
  - Was there an emergence of a new infection (evidence of clinical diagnosis or microbiological results) not present at baseline at least 48 hours after initiation of tigecycline therapy?

After identification of potential cases of superinfection a team of three external adjudicators made actual determinations of case status by majority rule or consensus, following review of the CRF and the medical record. The endpoint decision rules were defined in collaboration with the Pfizer and Quintiles study team and approved by the adjudicators. They were documented in the "Endpoint Committee Adjudication Charter" document and were defined using the following decision rules:

- *Definite superinfection:* clinically significant positive culture of microorganism >48 hours after tigecycline therapy initiation in addition to clinical signs and symptoms of infection

  - If the culture is from the same site, microorganism should be different than isolated within the first 48 hours
  - If the culture is from different site, microorganism can be any clinically significant one
  - Cases with inadequate surgical control will not be considered to be definite superinfection

- *Probable superinfection:* same as definite, but lacking culture evidence for definite
- *Non-case of superinfection:* lacking clinical signs or symptoms of superinfection
- *Insufficient information for superinfection case status:* microbiological or clinical data insufficient for the above definitions

For any potential cases determined not to be superinfection, the adjudicators' justification for the assessment was collected, as a single reason or combination of the following reasons:

- Lacking clinical signs and symptoms of superinfection;
- Same organism is cultured from the same site as initial infection;
- Inadequate surgical control; and
- Other (specify)

Lack of Efficacy – Primary Endpoint, Primary Objective 2

Lack of efficacy was defined as the need for additional intervention and/or antibiotic therapy in the absence of clinical improvement to treat the infection, or death due to the infection, >2 days following initiation of tigecycline therapy. The "2 days" was defined as a 48-hour period for the purposes of the study.

Potential cases of this endpoint are identified using medical record data based on the following definition:

- On-label use of tigecycline
  - Indication either cIAI or cSSTI
  - Loading dose of 100 mg
  - Maintenance dose of either 25 mg or 50 mg
- Tigecycline administered for ≥ 48 hours
- Responses of "Yes" or "Insufficient Information" to the following questions in the CRF, by the abstractor:
  - Was there receipt of additional intervention(s) and/or antibacterial therapy that are required to cure infection treated with tigecycline at least 48 hours after initiation of tigecycline therapy?
  - Did death occur at least 48 hours after tigecycline therapy initiation during the hospitalization?

As with superinfection, after identification of potential cases of lack of efficacy, the team of three external adjudicators made actual determinations of case status by majority rule or consensus, using the following decision rules:

- *Definite lack of efficacy:* clinically significant positive culture of a tigecycline-susceptible organism both before Tygacil therapy and after >48 hours of tigecycline therapy in addition to information on progression of infection (absence of clinical improvement); breakthrough infections with this level of evidence should be considered definite cases of lack of efficacy; in the case of death, the event must be due to infection treated with tigecycline to be considered a definite case of lack of efficacy;
    - Cases with inadequate surgical control will not be considered definite lack of efficacy

- *Probable lack of efficacy:* same as definite, but lacking culture evidence for definite;

- *Non-case of lack of efficacy:* clinical improvement after tigecycline therapy or a clinically significant positive culture of an organism not susceptible to tigecycline at baseline; in the case of death, must be not due to the infection treated with tigecycline;

- *Insufficient information for lack of efficacy case status:* microbiological or clinical data insufficient for the above definitions

For any potential cases determined not to be lack of efficacy, the adjudicators' justification for the assessment was collected, as a single reason or combination of the following reasons:

- Evidence of clinical improvement after tigecycline therapy;
- Clinically significant positive culture of an organism not susceptible to tigecycline at baseline;
- Death not due to the infection treated with tigecycline;
- Inadequate surgical control; and
- Other (specify)

Pathogen Associated with Infection – Secondary Endpoint

Data on the pathogen associated with the infection for which tigecycline was prescribed were obtained from microbiology results as available in the patient medical record.

Variables

Variables, their role, data sources and operational definitions are provided in Table 9.2. Subsets of these variables are used in the analysis of the incidence proportions of superinfection and lack of efficacy endpoints as well as in an exploratory analysis of potential predictors of off-label use.

Table 9.2 Variables

Variable	Role	Data source(s)	Operational definition
Country	Baseline characteristic, potential confounder, sub-group identifier	Site	Austria, Germany, Greece, Italy, UK
Age	Baseline characteristic, potential confounder, sub-group identifier	Medical record	Age in years by age groups (ie, <18, 18-44, 45-64, 65+)
Gender	Baseline characteristic, potential confounder, sub-group identifier	Medical record	Gender as recorded in the medical record
Height	Baseline characteristic	Medical record	Height as reported in the medical record (meters)
Weight	Baseline characteristic	Medical record	Weight as reported in the medical record (kilograms)
Tigecycline mono- or combination therapy	Potential confounder, sub-group identifier	Medical record	Concomitant use of other antibiotics
Tigecycline treatment duration	Potential confounder, sub-group identifier	Medical record	Tigecycline treatment duration, in days; defined as difference between the dates of first and last tigecycline doses + 1; grouped into <2, 2-5, 6-14 and 15 + days
Underlying disease severity	Baseline characteristic, potential confounder, sub-group identifier	Medical record	Worst score for each available disease severity scale in the medical record (APACHE, SOFA, etc.)
Tigecycline dose	Potential confounder, sub-group identifier	Medical record	Loading dose categorized into <100, 100, and >100 mg Maintenance dose categorized into >50, 50, 25, and <25 mg
Comorbidities	Baseline characteristic, potential confounder, sub-group identifier	Medical record	History of a comorbidity mentioned in patient's medical chart; Charlson comorbidity index[1]
Prior other antibiotic use	Baseline characteristic, potential confounder, sub-	Medical record	Other antibiotics in use within 7 days prior to tigecycline (yes, no)

	group identifier		
Prior surgery or intervention	Baseline characteristic, potential confounder, sub-group identifier	Medical record	Surgical Procedure or Other Therapeutic Interventions prior to tigecycline during hospitalization (yes, no)

9.5. Data sources and measurement

As this was a retrospective medical chart abstraction study, the medical charts of eligible patients from participating hospitals or wards were the data source for the study. For each enrolled tigecycline-treated patient, a single electronic case report form (eCRF) was completed by the site. This eCRF contained data on diagnoses, medications, procedures and microbiology data, where available, as well as relevant demographic information (eg, gender, age). Each eCRF was authenticated via electronic signature of the signature user (ie, principal investigator) to attest verity of eCRF contents.

The CRF is provided in Appendix 5.

9.6. Bias

To minimize the potential misclassification of the superinfection and lack of efficacy case status based on available data from medical records, a team of three external adjudicators made actual case status determinations by majority rule or consensus. Initial assessments were made blinded to the other adjudicators' assessments. Only at the consensus stage could the adjudicators discuss together individual cases in order to find an agreement. The adjudicators used pre-determined decision rules (section 9.4) in addition to their clinical knowledge and expertise when making case status determinations.

In observational studies requiring consent for use of data from medical records, significant differences in the frequency of outcomes between participants granting consent and non-participants may affect the accuracy of study results. In this study specifically, under-ascertainment of cases of the outcomes of interest could have resulted from differential likelihood of obtaining consent from: 1) tigecycline treated patients who experienced adverse outcomes; 2) next-of-kin of deceased patients; and 3) patients treated during the before RMM period (eg, patients treated more recently may have been more likely to be successfully contacted). These potential differences of tigecycline treated patients granting versus not granting consent would have potentially affected the study's ability to achieve its primary objective of evaluating the effectiveness of the tigecycline RMM. To avoid missing cases by requiring consent from tigecycline-treated patients, waivers of informed consent were pursued according to local legislation in all participating countries where informed consent was required for access to medical records.

In accordance with local regulations, applications for waivers of informed consent were not required in Austria, Germany or the UK. In Greece, waivers of informed consent were granted on a site-by-site basis. A waiver of consent was not granted by the data protection agency in Italy, and all patients who were both *eligible and living* were required to give their

written consent to participate in the study. Eligible patients who were deceased could be enrolled in the study without the consent of next of kin. Because of the potential for missing information on the outcomes of interest due to the inability to enroll living patients in Italy, data from the 3 Italian sites are included in sensitivity analyses only (see section 9.9.5 Sensitivity Analyses).

9.7. Study Size

A projected sample size of at least 300 patients in each period (ie, one year before and after RMM implementation) was agreed upon with the Agency.

As this is a descriptive study with no a priori hypothesis specified for the primary and secondary objectives, power calculations are not relevant. However, the level of precision expected for the assessment of the key endpoint of the proportion of off-label use (Primary Objective 1) was estimated.

The Clopper-Pearson method[2] was used to calculate 95% confidence intervals (CI) for samples of varying size given a proportion of off-label tigecycline use ranging from 25% to 55% (Table 9.3). Hypothetical sample sizes used in Table 9.3 are for a single arm of the study (ie, either before RMM implementation or after RMM implementation), such that the full study sample would be double each single arm sample size. Regardless of assumed proportion of off-label tigecycline use, CIs have a range of approximately 10 for single arm sample sizes ranging from 300 to 500 patients (corresponding to full study sample sizes of 600 to 1000). This indicates that the precision of estimates of the proportion of off-label tigecycline use is not highly sensitive to study sample size.

Table 9.3 Precision around Estimates of Proportion of Off Label Tigecycline Use (95% CI) Ranging from 25% to 55% Given Single Arm Sample Sizes Ranging from 300 to 500

Proportion of Off-label Tigecycline Use	Single Arm Sample Size and Corresponding 95% CI				
	n=300	n=350	n=400	n=450	n=500
25%	20.20, 30.30	20.55, 29.88	20.83, 29.54	21.06, 29.27	21.26, 29.04
35%	29.61, 40.69	30.01, 40.25	30.33, 39.90	30.59, 39.61	30.82, 39.36
45%	39.28, 50.82	39.71, 50.38	40.05, 50.02	40.34, 49.73	40.58, 49.48
55%	49.18, 60.72	49.62, 60.29	49.98, 59.95	50.27, 59.66	50.52, 59.42

9.8. Data transformation

There are no complex data transformations in this descriptive study. Any derived variables are documented in the final Statistical Analysis Plan (SAP), which is provided in Appendix 4.

9.9. Statistical methods

9.9.1. Analysis datasets

The primary analysis dataset (PAS) includes all enrolled patients treated with tigecycline at any dose and for any indication (ie, on- or off-label) from 01 February 2010 to 01 February 2011 or between 01 February 2012 and 01 February 2013 at eligible hospitals or wards in participating EU countries where informed consent from patients was not required. The PAS is used to assess the first primary objective of describing indications for tigecycline use.

The modified primary analysis set (mPAS) is defined as any patient who:

- Received tigecycline for treatment of cIAI and cSSTI (excluding diabetic foot infection)
- Received the approved dosage of tigecycline (100 mg loading dose followed by a 50 mg twice daily or 25mg twice daily maintenance dose in patients with severe hepatic impairment).

The mPAS population was used to evaluate the second primary study objective of determining the incidence of superinfection and lack of efficacy.

The full analysis dataset (FAS) includes all patients who were enrolled and treated with tigecycline at any dose and for any indication (ie, on- or off-label) from 01 February 2010 to 01 February 2011 or between 01 February 2012 and 01 February 2013 at eligible hospitals or wards in participating EU countries. This dataset includes data from countries where informed consent was required and therefore data from patients who provided informed consent (if applicable and required at the country or local level). The FAS was used in sensitivity analyses of the first primary objective of describing indications for Tygacil use.

The modified full analysis set (mFAS) includes any patient who:

- Received tigecycline for treatment of cIAI and cSSTI (excluding diabetic foot infection)
- Received the approved dosage of tigecycline (100 mg loading dose followed by 50mg BID, or 25mg BID in patients with severe hepatic impairment).

The mFAS population was used to for sensitivity analyses of the second primary study objective of determining the incidence of superinfection and lack of efficacy.

9.9.2. Main summary measures

This study used descriptive analyses to describe results for the primary and secondary objectives. Inferential statistics were used as part of the exploratory analyses.

9.9.3. Main statistical methods

Analyses of Indication for Use (Primary Objective 1)

To address the first primary objective of this study, the distribution of indications for tigecycline was analyzed overall and stratified by study period (ie, before vs. after RMM implementation). The primary analysis of this endpoint includes summary statistics (number and percent) only.

Off-label and on-label users of tigecycline are described in terms of the patient characteristics (demographics, co-morbid conditions, severity of illness scores, prior antibiotic therapy and surgical procedures) and treatment characteristics (tigecycline monotherapy vs. combination therapy, dose, duration of treatment, treatment discontinuations, etc.). Number and proportions of patients with on-label and off-label use are presented with corresponding 95% confidence intervals (95% CI). All confidence intervals are exact 95% confidence intervals for binomial probabilities.

Analyses of Superinfection (Primary Objective 2)

Numbers and incidence proportions of potential superinfection cases, as well as adjudicated definite cases, probable cases, non-cases and cases with insufficient information to determine superinfection status were calculated for all patients treated with tigecycline for approved indications overall, as well as within each of the two study periods (before and after RMM implementation). For definite and probable cases, the pathogens associated with superinfection were described and the average time to onset of superinfection was estimated. The time to onset of superinfection was calculated as the number of days between the tigecycline therapy initiation (as recorded in the medical record) and the onset of superinfection (as estimated during adjudication). Number and proportions of patients experiencing superinfection are presented with corresponding 95% confidence intervals (95% CI). All confidence intervals are exact 95% confidence intervals for binomial probabilities.

Analyses of Lack of Efficacy (Primary Objective 2)

Numbers and proportions of potential lack of efficacy cases, as well as adjudicated definite cases, probable cases, non-cases and cases with insufficient information to determine lack of efficacy status were estimated for all patients treated with tigecycline for approved indications, and within each of the two study periods (before and after RMM implementation). Number and proportions of patients experiencing lack of efficacy are presented with corresponding 95% confidence intervals (95% CI). All confidence intervals are exact 95% confidence intervals for binomial probabilities.

Qualitative Analyses of Pathogens Associated with Infection (Secondary Objective)

The distribution of all bacterial pathogens associated with infections treated with tigecycline during the two study periods is provided as a secondary analysis. The resistance phenotype of the organisms is summarized where available. For each microorganism, the count of patients

with that organism is presented by study period and the proportion of the patients with resistant pathogens is presented.

Exploratory analyses

As microbiology data allowed, the distribution of pathogens associated with infection for which tigecycline use was prescribed among patients treated with any dose of tigecycline for any indication prior to implementation of the RMM and following implementation of these measures stratified by indication for tigecycline use was quantitatively described.

An exploratory logistic regression analysis was conducted to evaluate factors associated with off-label use. The analysis was performed using backward elimination and a p-value criterion of 0.05. Study period (before RMM or after RMM), age (<65 or ≥65 years), gender, previous antibiotic therapy (yes vs. no), country, previous surgical procedures (yes vs. no), and number of co-morbidities (0, 1-3, ≥4) were included as covariates. Covariates of interest were not included in the analysis, such as APACHE score, if it was determined that a substantial proportion of values (eg, more than 15-20%) were missing. Due to a small number of events of superinfection and lack of efficacy, exploratory analyses evaluating predictors of these endpoints were not conducted.

9.9.4. Missing values

When missing data occurred, no imputation was made and all statistics were calculated with non-missing values. Count and percentage of missing values are presented in the tables.

9.9.5. Sensitivity analyses

Two sets of sensitivity analyses were conducted. First, to evaluate the potential impact of "insufficient information" for superinfection and lack of efficacy cases on study results, incidence proportions and associated 95% CIs were estimated for "definite" plus "probable" plus "insufficient information" superinfection patients and "definite" plus "probable" plus "insufficient information" lack of efficacy patients treated with approved doses of tigecycline for cIAI and cSSTI.

Secondly, and as described previously, due to the potential for bias due to the limited enrollment of living patients in Italy, data from Italian sites were excluded from primary analyses, and included in sensitivity analyses of the primary study objectives only (See Section 10.1 for more information).

The following data are presented as part of the sensitivity analyses:

- Indications for tigecycline use, including summaries of on- and off-label use (FAS Table 15.1.0a, FAS Table 15.1.1a)
- Patient demographics (FAS Table 15.2.0a)
- Superinfection endpoints (modified full analysis set [mFAS] Table 15.9.0a)
- Incidence of definite superinfection (mFAS Table 15.9.1a)
- Incidence of definite and probable superinfection (mFAS Table 15.9.2a)

- Incidence of superinfection (definite + probable + insufficient information cases) (mPAS Table 15.9.3, mFAS Table 15.9.3a)
- Lack of efficacy endpoints (mFAS Table 15.10.0a)
- Incidence of definite lack of efficacy (mFAS Table 15.10.1a)
- Incidence of definite and probable lack of efficacy (mFAS Table 15.10.2a
- Incidence of lack of efficacy (definite + probable + insufficient information cases) (mPAS Table 15.10.3, mFAS Table 15.10.3a)
- Hospital characteristics (FAS Table 15.13.0a)
- Adverse Events by MedDRA system organ class (SOC) and preferred term (PT) (FAS Table 15.14.0a)
- Adverse Events by Severity (FAS Table 15.14.1a)
- Adverse Events by Action Taken (FAS Table 15.14.2a)
- Adverse Events by Outcome (FAS Table 15.14.3a)
- Serious Adverse Events by SOC and PT (FAS Table 15.15.0a)
- Serious Adverse Events by Seriousness Criteria (FAS Table 15.15.1a)

9.9.6. Amendments to the statistical analysis plan

The Statistical Analysis Plan (SAP) was amended (Amendment 1) to specify that sites in Italy will be excluded from primary analyses and included in sensitivity analyses only. The SAP amendment also included additional detail on patient / chart enrollment procedures.

9.10. Quality control

Throughout the duration of the study, contract research organization (CRO) staff periodically contacted site staff at all participating sites by phone to ensure that the study was being conducted according to protocol, and to provide motivation and support for accurate and timely data abstraction.

To ensure the study quality on an ongoing basis, Clinical Research Associates (CRA) conducted the following activities for each assigned site:

- **Remote Site Initiation Visit (RSIV):** One RSIV was conducted per site. The CRA reviewed study materials with the site including the protocol, RSIV slide-deck, eCRF completion guidelines, safety reporting procedure and study specific logs and worksheets.

- **Telephone Contact (TC) / Routine Phone Monitoring:** Telephone contact was made at least once per month following the RSIV. The primary goal of this activity was to ensure the progress of patient enrollment, ICF process compliance (if applicable), resolution of queries, identification of potential issues, assistance on adjudication packets compilation and answering site questions.

- **Remote Data Monitoring Visit (RDMV):** One remote data monitoring call was performed for each site. The purpose of the RDMV was to verify that the site was conducting the study in compliance with the protocol and any applicable regulations.

- **Remote For-Cause Data Monitoring Visit:** A Remote For-Cause Data Monitoring Visit was conducted on an as-needed basis. Criteria for conducting these visits included high or low patient enrollment rate, low eCRF entry volume, grossly inaccurate or incomplete eCRF or adjudication packets, etc.

9.11. Protection of human subjects

Patient information and consent

Where required (ie, for patients in Italy alive at the time of study initiation), informed consent was pursued from eligible subjects according to the following principles:

- The informed consent form was in compliance with International Conference on Harmonization (ICH) Good Clinical Practice (GCP)[3], local regulatory requirements, and legal requirements.

- The ICF used in this study was approved by the Ethics Committee (EC) before use.

- The investigator ensured that each study patient, or his/her legally acceptable representative, was fully informed about the nature and objectives of the study and possible risks associated with participation. The investigator, or a person designated by the investigator, obtained written informed consent from each patient or the patient's legally acceptable representative before any study-specific activity was performed. The investigator was required to retain the original of each patient's signed consent form.

Independent Ethics Committee (IEC)

The approval of the study protocol, protocol amendments and informed consent waiver applications (or ICFs, if applicable) was sought from central and /or local ECs per local requirements. Required EC and data protection agency (DPA) approvals were received for all sites selected to participate in the study. A complete summary of the central and local EC approval status for these sites is provided in Appendix 3.

Ethical conduct of the study

The study was conducted in accordance with legal and regulatory requirements, as well as with scientific purpose, value and rigor and followed generally accepted research practices such as *Good Pharmacoepidemiology Practices* issued by the International Society for Pharmacoepidemiology (ISPE)[4] and similar documents.

10. RESULTS

10.1. Participants

Site and patient enrollment through end of study

Thirteen sites with a projected eligible patient pool of at least 850 patients in each of the before and after RMM periods (ie, over 1700 patients in total) participated in the study. The first site was initiated on 22 March 2013 and the last site was initiated on 23 January 2014.

The first patient was enrolled (where enrollment is defined as abstraction of the patient's medical record) on 23 May 2013. A total of 777 patients (399 before RMM, 378 after RMM) were enrolled in the study at the 13 initiated sites in 5 countries (Austria, Germany, Italy, Greece and the UK).

Significant delays were observed in study start-up activities in Greece due to the pursuit of a waiver of informed consent requirements and the changes to relevant legislation impacting the EC approval and site contracting processes. Submissions to the DPA were complete by mid-October 2013, and the approval letter was received 12 December 2013. Site 1006 was initiated on 7 January 2014 and Site 1004 was initiated on 23 January 2014. As a result, enrollment was extended by one month (to 31 January 2014) to allow the newly initiated sites in Greece and several sites with remaining after-RMM patients to achieve the targeted number of enrolled patients in the 'after RMM' cohort. Patient enrollment was complete by 31 January 2014, with a total of 777 patients enrolled in the study by the end of the abstraction period. Fewer patients than originally projected (based on responses from the SQQ) were enrolled in some sites, as shown in Table 10.1.

Table 10.1 Summary of Number of Patients Expected (based on SQQ) vs. Number of Patients Enrolled

Site Number	Country	Before RMM		After RMM		Total		Reasons for not meeting expected patient enrollment
		# of patients expected	# of patients enrolled	# of patients expected	# of patients enrolled	# of patients expected	# of patients enrolled	
1016	Austria	213	38 (18%)	86	51 (59%)	299	89 (33%)	- 42 (14%) incomplete medical charts - 3 (1%) did not meet inclusion criteria - 165 (55%) not included because site did not have resources available to enter more data
1020	Austria	20	5 (25%)	20	7 (35%)	40	12 (30%)	- 20 (50%) did not receive tigecycline - 8 (20%) did not meet inclusion criteria
1023	UK	271	167 (62%)	93	67 (72%)	364	234 (64%)	- 26 (7%) incomplete medical charts - 104 (29%) not included because site was asked to stop entering patients from the 'before RMM' period when all patients from the 'after RMM' period were entered
1030	UK	57	2 (4%)	88	8 (9%)	145	10 (7%)	- 135 (93%) not included because site did not have resources available to enter more data

Site Number	Country	Before RMM		After RMM		Total		Reasons for not meeting expected patient enrollment
		# of patients expected	# of patients enrolled	# of patients expected	# of patients enrolled	# of patients expected	# of patients enrolled	
1015	Germany	69	62 (90%)	45	36 (80%)	114	98 (86%)	- 6 (6%) did not meet inclusion criteria - 8 (8%) Incomplete medical charts - 1 (1%) not included because site was asked to stop entering patients from the before RMM period when all patients from the after RMM period were entered
1024	Germany	39	39 (100%)	43	43 (100%)	82	82 (100%)	- All eligible patients were enrolled
1027	Germany	33	26 (79%)	64	57 (89%)	97	83 (86%)	- 12 (12%) did not meet inclusion criteria - 2 (2%) not included because abstraction period ended
1001	Germany	27	19 (70%)	37	33 (89%)	64	52 (81%)	- 12 (19%) did not meet inclusion criteria
1004	Greece	41	1(2%)	40	0 (0%)	81	1 (1%)	- 80 (99%) not included because delayed site activation left little time remaining in the abstraction period and the site did not have resource availability to enter more data

Site Number	Country	Before RMM		After RMM		Total		Reasons for not meeting expected patient enrollment
		# of patients expected	# of patients enrolled	# of patients expected	# of patients enrolled	# of patients expected	# of patients enrolled	
1006	Greece	15	14 (93%)	16	12 (75%)	31	26 (84%)	- 4 (13%) incomplete medical charts - 1 (3%) did not meet inclusion criteria
1002	Italy	65 (breakdown of living and deceased patients not available)	12 (18%) (12 deceased patients)	174 (breakdown of living and deceased patients not available)	0 (0%)	239 (breakdown of living and deceased patients not available)	12 (5%) (12 deceased patients)	- Site did not have resources available to enter more data - No signed ICFs were received from living patients
1017	Italy	30 (19 living and 11 deceased patients)	11 (36%) (7 living and 4 deceased patients)	66 (37 living and 29 deceased patients)	19 (29%) (18 living and 1 deceased patients)	96 (56 living and 40 deceased patients)	30 (31%) (25 living and 5 deceased patients)	- 9 (9%) did not meet inclusion criteria - 29 (30%) Incomplete medical charts - 9 (9%) ICFs not signed - 19 (20%) Abstraction period ended
1018	Italy	9 (breakdown of living and deceased patients not available)	3 (33%) (3 deceased patients)	196 (breakdown of living and deceased patients not available)	45 (22%) (45 deceased patients)	205 (breakdown of living and deceased patients not available)	48 (23%) (47 deceased patients)	- Abstraction period ended - No signed ICFs were received from living patients
Total number of patients:		889	399 (44%)	968	378 (39%)	1857	777 (42%)	

Composition of the final analysis datasets

A total of 777 patients were enrolled in the study (399 before RMM, 378 after RMM) at 13 initiated sites in 5 countries (Austria, Germany, Italy, Greece and the UK) (Table 10.2). The PAS population for the first primary objective (analyses of indications for tigecycline use) and the secondary objective (qualitative analysis of pathogens associated with infection) excludes the 90 patients enrolled in Italy for a total patient number of 687. The FAS population, used for sensitivity analyses, includes all 777 patients (Table 10.2).

The second primary objective (analyses of superinfection and lack of efficacy) was analyzed using a subset of the PAS, which excludes patients administered tigecycline for off-label indications or with off-label dosages. This mPAS population for these endpoints includes 199 patients overall, 105 before RMM and 94 after RMM. These datasets were used to generate the results discussed in Section 10.4.

Figure 10-1 Enrollment and Analysis Dataset Flowchart

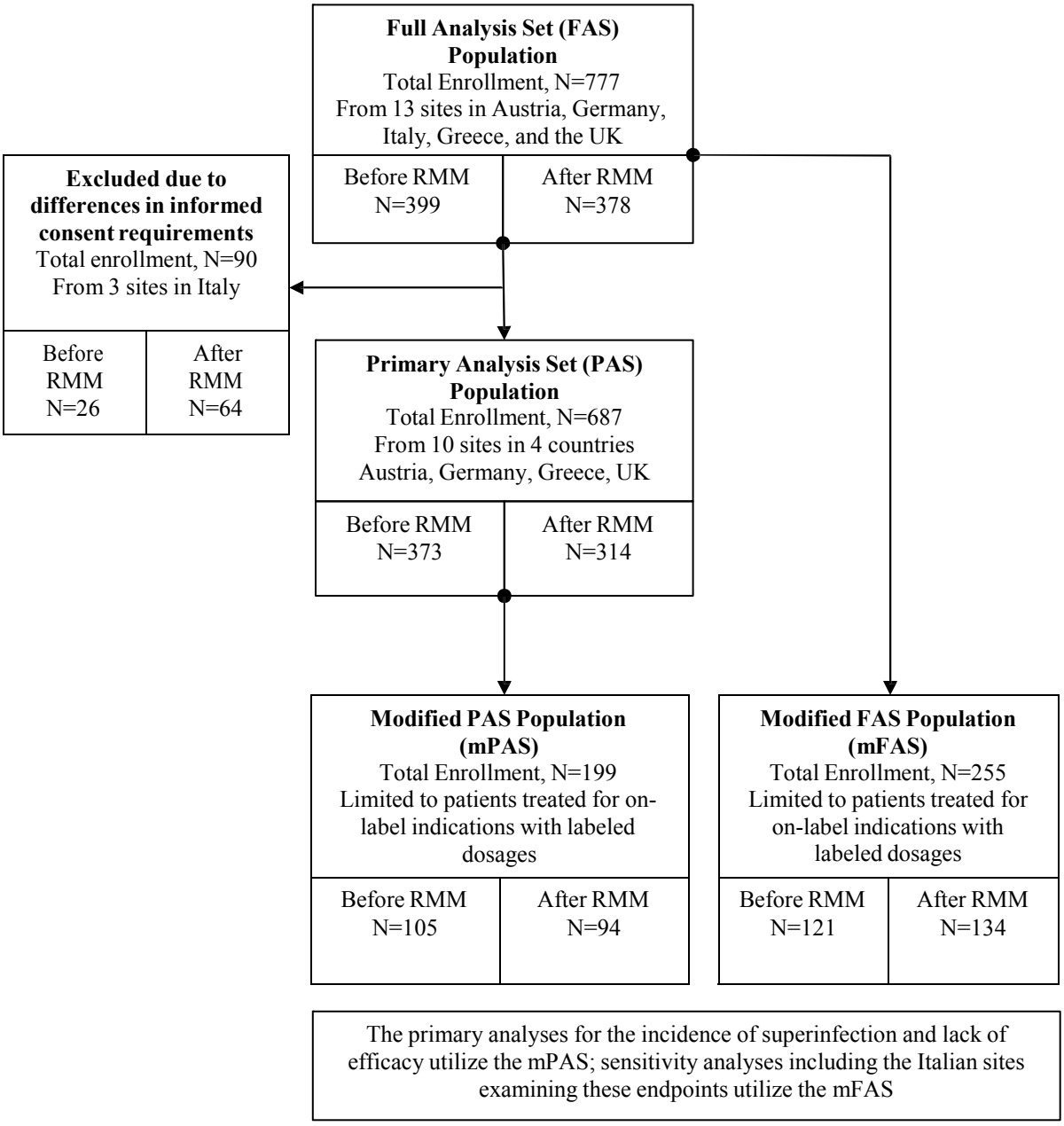

Table 10.2 Site and Patient Enrollment Summary by Country

Site Number	Country	Number of Patients Enrolled		
		Before RMM	After RMM	Total
1016	Austria	38	51	89
1020	Austria	5	7	12
1023	UK	167	67	234
1030	UK	2	8	10
1015	Germany	62	36	98
1024	Germany	39	43	82
1027	Germany	26	57	83
1001	Germany	19	33	52
1004	Greece	1	0	1
1006	Greece	14	12	26
1002	Italy	12	0	12
1017	Italy	11	19	30
1018	Italy	3	45	48
Total number of patients:		399	378	777
Total number of patients excluding Italy:		373	314	687

10.2. Descriptive data

Since the primary and secondary objectives of this study are descriptive, all results are presented as part of the main results in Section 10.4.

10.3. Outcome data

Since the primary and secondary objectives of this study are descriptive, all results are presented as part of the main results in Section 10.4.

10.4. Main results

Patient background characteristics

Overall, the mean age on admission for enrolled patients (regardless of indication or study period) was 61.4 years (SD 16.40, range 12 to 97 years), with the majority of patients between 45 and 64 (n=271, 39.4%) or over 65 years of age (n=310, 45.1%) (Table 15.2.0). There was a slightly higher proportion of males enrolled (n=357; 52.0%). Patients treated with tigecycline before the RMM (for any indication) were slightly older compared with those treated after the RMM (mean 63.2, SD 15.98 versus mean 59.2, SD 16.66). Body weight was wide ranging, but consistent across indications and time periods; results for body weight and body mass index are shown in (Table 15.2.0).

Relevant medical history across indications included a history of malignancy of any type (n=208, 30.3%), chemotherapy within the last six months (n=51, 7.4%) and radiation or steroid treatment (n=36, 5.2%) (Table 15.3.0). An immunocompromised state of any type

was reported for 137 patients (19.9%). Diabetes with (n=51, 7.4%) or without (n=121, 17.6%) end organ damage and moderate/severe renal disease (n=169, 24.6%) were also commonly reported. Over a third of patients (36.7%) had one or more forms of cardiovascular or cerebrovascular disease (eg, history of myocardial infarction, unspecified cerebrovascular disease, peripheral vascular disease, congestive heart failure). Liver disease was reported in 128 patients (18.6%), with 89 (13.0%) characterized as moderate to severe, and 84 (12.2%) had chronic pulmonary disease. Recorded neutropenia within six months of admission was reported in 21 patients (3.1%) (Table 15.3.0).

Overall, the burden of co-morbidities as assessed by the presence of relevant medical history appeared to be higher for patients treated after the RMM compared to patients treated before the RMM. A higher proportion of patients treated after the RMM had a history of malignancy (33.1% vs. 27.9% before RMM), were in an immunocompromised state (21.7% vs. 18.5% before RMM), and had liver disease (22.9% vs. 15.0% before RMM) or moderate to severe renal disease (28.0% vs. 21.7% before RMM) (Table 15.3.0).

Overall, most patients were initially admitted to the surgical (327/687, 47.6%) or medical (138/687, 20.1%) wards or directly to the ICU (107/687, 15.6%). Standard measures of the patient's disease status prior to initiating tigecycline were available in the medical record for 405 of the 687 patients (59.0%). Patients appeared to have similar overall condition in the before-RMM period as compared with the after-RMM period, as evidenced by scores on ICU predictive scoring systems, as shown in Table 15.6.0.

Overall, 68.3% of patients were discharged alive. The mortality rate was lower before the RMM (36.0% after versus 28.2% before the RMM) (Table 15.8.0). Reported primary causes of death for individual patients are presented in Listing 6.

Hospital characteristics

Of the 10 sites with patients included in the PAS, 9 (90%) were university centers and 1 was a public hospital. The range of number of beds in the hospitals was 344 to 3222, and the hospitals had a range of 1 to 26 ICUs. A specific definition of ICU was not provided to the sites as part of the data collection; as a result, the reported number of ICUs may represent a spectrum of critical care unit types (eg, including sub-ICUs). At 6 hospitals, the enrolled patients came from a specific ward or department, and at the remaining 4 institutions, eligible patients were enrolled from the hospital as a whole (Table 15.13.0).

Primary Objective 1: Prescription Patterns

Indications for tigecycline treatment

Overall, less than half of the patients treated with tigecycline (314/687, 45.7%, 95% CI 41.9% - 49.5%) were treated for an off-label indication, including 7 patients (1.0%) who were less than 18 years of age on admission (Table 15.1.1 and Table 15.2.0). Prior to implementation of the RMM, 54.2% of the indications were off-label (202/373, 95% CI 49.0% - 59.3%), whereas after the RMM, the proportion of patients treated for an off-label indication decreased to 35.7% (112/314, 95% CI 30.4% - 41.2%). Proportion of patients treated for on-label and off-label use are presented by country overall (Table 15.1.1a.1) and

by country and site (Table 15.1.1a.1.1, Table 15.1.1a.1.2, Table 15.1.1a.1.3, Table 15.1.1a.1.4 and Table 15.1.1a.1.5). The lowest proportion of off label use was observed in Italy (22/90, 25.4%) and the highest was observed in Austria (61/101, 60.4%). In the remaining 3 countries, the proportion of off label use was 107/315 (34.0%) in Germany, 9/27 (33.3%) in Greece and 137/244 (56.1%) in the UK. A decrease in off-label use after RMM was seen across all countries.

On-label cIAI indications were reported for 271 of the 679 adult patients (39.9%). Overall, the most commonly reported on-label cIAI indications were secondary peritonitis (n=99, 14.6%), intra-abdominal abscess (n=67, 9.9%), and intestinal perforation (n=50, 7.4%) (Table 15.1.0). On-label cSSTI indications were reported for 102 of the 679 adult patients (15.0%), and the most commonly reported cSSTIs were wound infections (n=58, 8.5%), cellulitis (n=11, 1.6%), major abscess (n=9, 1.3%) and cutaneous ulcer (n=8, 1.2%). The proportions of cIAI and cSSTI indications were both higher in the after RMM period (46.0% and 19.4%, respectively) compared to the before RMM period (34.9% and 11.4%, respectively). The most marked increases in the proportion of cIAI type were secondary peritonitis (9.5% before RMM, 20.7% after RMM), intestinal perforation (4.9% before RMM, 10.4% after RMM) and intra-abdominal abscess (7.8% before RMM, 12.3% after RMM). For cSSTI, the largest increase was in wound infections (6.5% before RMM, 11.0% after RMM).

A total of 306 indications (45.1% of all reported indications) were reported as something other than cIAI or cSSTI. The most commonly reported off-label indications were characterized as “other” (n=173, 25.5%), hospital acquired pneumonia (n=56, 8.2%), pneumonia other (n=43, 6.3%), bacteremia (n=35, 5.2%) and diabetic foot infection (n=10, 1.5%) (Table 15.1.0). For 9 patients, more than one indication described as an “other” off-label indication was reported. The most commonly cited “other” off-label indications are shown in Listing 1.

Prior to implementation of the RMM, a total of 125 of the 199 patients (62.8%) with off-label indications were treated for “other” off-label indications (ie, off-label indications other than hospital acquired pneumonia, other pneumonia, diabetic foot infection or bacteremia) (Table 15.1.0). Of the 130 “other” indications for use reported for the 125 patients, the most commonly reported were cholecystitis/cholecystitis acute (n=24), cholangitis (n=19) and diverticulitis (n=14) (Listing 1). After implementation of the RMM, a total of 48 of the 107 patients who were treated off-label (44.9%) were treated for “other” off-label indications (Table 15.1.0). Of the 56 “other” indications for use reported for the 48 patients, the most commonly reported were infectious pleural effusion (n=4), staphyloccocal infection/staphylococcus test positive (n=4) and pyrexia/post-operative fever (n=4) (Listing 1). The distribution of indications for tigecycline use is presented by country (Table 15.1.0a.1) and by country and site (Table 15.1.0a.1.1, Table 15.1.0a.1.2, Table 15.1.0a.1.3, Table 15.1.0a.1.4 and Table 15.1.0a.1.5). No substantial differences in specific indication patterns for on-label use were noted.

There were 16 total reports of prophylactic use (2.4%), explicitly described as such in the medical record, 9 prior to implementation of the RMM and 7 after RMM (Table 15.1.0). Overall, the indicated infection was reported as present at the time of admission in

approximately half of cases (n=350, 51.5%); however, the proportion was higher before (n=216, 58.4%) compared to after RMM implementation (n=134, 43.4%) (Table 15.1.0).

The most commonly reported admission diagnoses across the two periods were arterial hypertension, hypertension, diabetes mellitus, atrial fibrillation, cholangitis and pneumonia; admissions for cholecystis and cholangitis were more common in the before RMM period compared to after RMM (Table 15.6.1).

Of the 7 patients younger than 18 years of age at hospital admission, 2 were treated before the RMM and 5 after the RMM (Table 15.2.0). The pediatric patients ranged in age from 12 to 17 years. Indications for tigecycline use in the pediatric patients included one cIAI (intestinal perforation) two cSSTI (wound infection, abscess infection) and 5 other indications (bacteremia, chronic mycobacterium, exacerbation of cystic fibrosis, cystic fibrosis with pseudomonas and stenotrophomonas colonization and bronchectasis infective exacerbation). All 7 patients were discharged alive (Listing 11).

Patient characteristics, by treatment indication

A slightly higher proportion of patients treated for off label indications were over the age of 65 (49.7%) when compared with cIAI (40.6%) and cSSTI patients (43.1%) (Table 15.2.0). A higher proportion of cSSTI and off-label patients were admitted directly to the ICU (cSSTI 20.6%, off-label 17.8%) compared with cIAI patients (11.1%) (Table 15.6.0). A greater proportion of patients treated for cIAI as compared with cSSTI and off-label patients had a history of malignancy (40.6 % vs. 19.6% in cSSTI and 24.8% in off label) and organ transplantation (16.2% vs. 2.0% in cSSTI and 6.7% in off-label). Compared with patients treated for on-label indications, a higher proportion of patients treated for off-label indications had severe renal disease, diabetes with end organ damage and chronic pulmonary disease (Table 15.3.0). Patients treated for cIAIs and off-label indications had the highest mortality rates (34.7% and 32.5%, respectively), compared to patients treated for cSSTI (20.6%). While the mortality rate across all indications was higher after the RMM, this was particularly true in the cIAI population (30.2% before versus 38.7% after) and the off-label population (27.7% before versus 42.0% after) (Table 15.8.0).

Other treatment patterns

Overall, tigecycline was used as monotherapy in 46.6% of patients, and the ratio of monotherapy to combination therapy was generally consistent across on- and off-label indications (Table 15.7.0). The most commonly prescribed antibiotics used in combination with tigecycline were meropenem (88/687, 12.8%), ciprofloxacin (67/687, 9.8%), vancomycin (66/687, 9.6%) and ceftazidime (59/687, 8.6%) (Table 15.7.0), with 136 (19.8%) reported as “other” antibiotics, shown in Listing 4. Across indications, tigecycline was used in combination therapy less often in the before RMM period as compared with the after RMM period (46.9% versus 61.1%). Combination therapy was more commonly used for off-label indications in the after RMM period (69.6%) as compared to the before RMM period (44.1%) (Table 15.7.0)

Tigecycline treatment was most commonly initiated in the intensive care unit (ICU, n=373, 54.3%), on the surgical ward (n=155, 22.6%) or on the medical ward (n=85, 12.4%). In the cIAI indication, the proportion of patients treated in the ICU increased from 54.6% before

RMM to 78.9% after RMM. Similarly, the proportion of patients treated for off-label indications who initiated treatment in the ICU also was greater in the after RMM period, with 33.8% treated in the ICU before RMM and 60.2% after. The proportion of cSSTIs initially treated in the ICU was consistent in the two periods (Table 15.7.0).

The patient's systemic condition at initiation of tigecycline was only available for 337 of the 687 patients; of those, 181 (53.7%) were septic, 41 (12.2%) had severe sepsis, 72 (21.4%) were in septic shock and 43 (12.8%) had systemic inflammatory response syndrome (SIRS) (Table 15.7.0). The proportion of patients with sepsis and severe sepsis at the time of initiating tigecycline was higher before the RMM as compared to after the RMM (59.9% vs. 47.3% and 15.1% vs. 9.1%, respectively). The proportion of patients with SIRS at the time of initiating tigecycline was greater after RMM (35/165, 21.2%) as compared to before RMM (8/172, 4.7%) (Table 15.7.0).

The majority of patients were treated with other antibiotics within 7 days prior to initiating tigecycline (519/672, 77.2%). Other antibiotic use within 7 days prior to initiating tigecycline was more common in patients treated for any indication after the RMM as compared to before the RMM (87.1% after versus 69.1% before) (Table 15.4.0). Across time periods, other antibiotic use was reported in similar proportions in cIAI (81.1%) and cSSTI patients (80.8%) but in a lower proportion of off-label patients (72.6%). Overall, the most commonly reported antibiotics used within 7 days prior to initiating tigecycline were meropenem (32.8%), vancomycin (28.5%), ciprofloxacin (21.0%), piperacillin/tazobactam (20.2%) and metronizadole (19.5%) (Table 15.4.0). Use of "other" (ie, not specifically solicited in the eCRF) antibiotics was reported in 39.7% of patients overall (and in 51.3% of cSSTI patients). The most commonly reported "other" antibiotics, all reported in <4% of patients, were cefuroxime, clindamycin, clarithromycin, and erythromycin; fluconazole, while not an antibiotic, was also reported (Table 15.4.1). The distribution of these agents (by individual patient) is provided in Listing 2.

Overall, 58.7% of patients underwent a surgical procedure or therapeutic intervention during the hospitalization and prior to being treated with tigecycline (Table 15.5.0). The most commonly reported interventions were wound closure, drainage, treatment or debridement (11.2% combined), laparotomy (7.3%), peritoneal lavage (5.5%), colectomy (4.7%), liver transplant (4.2%), abscess drainage (3.5%) and hepatectomy (3.2%). Previous surgical procedures or interventions were noted in a higher proportion of cIAI patients (n=212, 78.2%) and cSSTI patients (n=69, 67.6%) as compared with off label patients (n=122, 38.9%). A marked difference was also observed in the proportion of patients who had undergone a surgical procedure or therapeutic intervention in the period before the RMM (170/373, 45.6%) and after the RMM (233/314, 74.2%). Notably, in the after RMM period, 133 of 142 of the cIAI patients (93.7%) had undergone a surgical procedure or therapeutic intervention (Table 15.5.0).

The majority of patients across indications received the recommended loading dose of 100 mg (n=526, 76.6%) and received a maintenance dose of 50 mg twice daily (n=544, 79.4%) (Table 15.7.0). Twenty-five patients (3.6%) reportedly did not receive a loading dose at all. Patients in the before RMM period were more likely to receive the on-label 100 mg loading dose (81.2% before RMM, 71.1% after RMM). There were higher rates of both lower than

100 mg and higher than 100 mg loading doses in the after RMM period. Five patients (1.3%, all in the before RMM period) did not receive a maintenance dose; the possibility that these patients died prior to receiving a maintenance dose cannot be excluded (Table 15.7.0). A higher proportion of patients in the before RMM period (85.5%) received the labeled 50 mg twice daily maintenance dose as compared with the after RMM period (72.3%). In both periods, the highest proportion of use of doses greater than 50 mg was in patients with cSSTIs; the proportion of patients administered higher maintenance doses in off-label indications was similar to that observed in the cIAI patients (Table 15.7.0).

The overall mean duration of tigecycline treatment across indications (approved and unapproved) was 9.4 days [standard deviation (SD) 9.18]. The mean duration of treatment after the RMM was 10.3 days (SD 7.66) and before the RMM was 8.6 days (SD 10.25). The majority of patients were treated either between 2 and 5 days (211/687, 30.7%) or between 6 and 14 days (341/687, 49.6%). Patients treated for cIAI had a mean duration of treatment of 9.0 days (SD 9.94) and patients with cSSTI indications had a mean duration of treatment of 11.6 days (SD 9.03). The median total number of tigecycline doses administered was 11 (range 1 to 138 doses) (Table 15.7.0). Due to the high end of the range of number of doses, this information was queried and confirmed by the investigator. The patient who received 138 doses (Patient ID 1016-1013) suffered multiple cholangitic abscesses (cIAI) with vancomycin-resistant *Enterococcus* (VRE) and extended-spectrum beta-lactamase (ESBL) *Klebsiella pneumonia* post-liver transplantation. These abscesses could not be managed under broad antimicrobial therapy and tigecycline was initiated. Recovery was slow and extended therapy duration was required. Similarly, the patient with the highest duration of therapy for an off-label indication (Patient 1015-1084) was also confirmed. The patient was treated (before the RMM) in the ICU for more than one year for infections with *Staphylococcus epidermidis*, *Enterococcus faecium* and *Citrobacter braakii* and required six treatment periods of tigecycline (Listing 9).

Treatment interruptions, defined as a treatment interruption of tigecycline therapy for more than 24 hours for any reason, were reported in 28 patients (7.5%) before RMM and 18 patients (5.7%) after RMM. Durations of treatment interruptions and distribution of interruptions by indication are shown in Table 15.7.0.

Sites were asked whether anything occurred at their institution that may have influenced tigecycline prescribing practices in either the before RMM or after RMM periods. One hospital (Site # 1023) included in the PAS indicated “yes”, citing that 4 patients were treated with tigecycline due to there being supply problems with aztreonam before the RMM and an outbreak of VRE in the after RMM period that resulted in an increased use of tigecycline. One of the Italian sites (Site # 1002) included only in the FAS also indicated “yes”, citing an increase in carbapenemase- producing *Klebsiella pneumoniae* in both periods including several cases where colistin and tigecycline were the only available active antibiotics. This was queried and determined to be a continuous event rather than 2 separate increases (Listing 10).

Primary Objective 2: Incidence of Superinfection and Lack of Efficacy

Superinfection

The overall incidence proportion of definite and probable superinfection across indications was 4.5% (95% CI 2.1% - 8.4%), with 3.8% before RMM (95% CI: 1.1% - 9.5%) and 5.3% after RMM (1.8% - 12.0%). Incidence proportion of superinfection stratified by selected demographic and treatment characteristics is also presented (Table 15.9.2).

A total of 60 potential superinfection cases were reported amongst the 199 patients included in the mPAS population (Table 15.9.0). Potential superinfection was reported in 49 (32.5%) cIAI cases and 11 (22.9%) cSSTI cases. Amongst the 49 cIAI potential cases, 4 (8.2%) were adjudicated as probable cases and 2 (4.1%) were adjudicated as definite cases (total probable or definite 6 [12.2%]). In the 6 probable or definite cIAI cases, the pathogens associated with superinfection were *Enteroccocus spp.* (n=4, 66.7%), *Klebsiella spp.* (n=3, 50.0%), *Escherichia coli* (n=2, 33.3%), *Proteus spp.* (n=1, 16.7%) and *P. aeruginosa* (n=1, 16.7%) (Table 15.9.0). For 4 cases, the information available was considered insufficient for adjudication. For the remaining 39 cases that were determined not to be a superinfection, the most commonly cited reasons were lacking clinical signs and symptoms of superinfection AND inadequate surgical control (n=9, 23.1%), same organism is cultured from the same site as initial infection AND inadequate surgical control (n=7, 17.9%) and "other" reasons (n=9, 23.1%). In most cases, the "other" designation included a combination of an expected criterion (eg, lack of clinical signs and symptoms) and an additional consideration or explanation (Listing 7).

Amongst the 11 cSSTI potential superinfection cases, 1 (9.1%) was adjudicated as a probable case and 2 (18.2%) were adjudicated as definite cases (total probable or definite n=3 [27.2%]). In the 3 probable or definite cSSTI cases, the pathogens associated with superinfection were one report each of *Enteroccocus spp.*, *Proteus spp.*, *Enterobacter spp.* and *Citrobacter spp* (Table 15.9.0). The mean time to onset of probable or definite superinfection in cIAI patients was 15.2 days (SD 7.05) and in cSSTI patients was 11.7 days (SD 6.43). For 2 cases, the information available was considered insufficient for adjudication. For the remaining 6 cases that were determined not to be a superinfection, the most commonly cited reasons were "other" (n=3, 50%) (Listing 7), lacking clinical signs and symptoms of superinfection AND inadequate surgical control (n=2, 33.3%) and lacking clinical signs and symptoms of superinfection AND same organism cultured from the same site (n=1, 16.7%).

Lack of efficacy

The overall incidence proportion of definite and probable lack of efficacy was 5.5% (95% CI 2.8% - 9.7%), with 2.9% before RMM (95% CI: 0.6% - 8.1%) and 8.5% after (3.8% - 16.1%). Incidence proportion of lack of efficacy stratified by selected demographic and treatment characteristics are also presented (Table 15.10.2).

A total of 107 potential lack of efficacy cases were reported amongst the 199 patients included in the mPAS population (Table 15.10.0). Potential lack of efficacy was reported in 82 (54.3%) cIAI cases and 25 (52.1%) cSSTI cases. Amongst the 82 cIAI potential cases, 8 cases (9.8%) were adjudicated as either probable or definite cases (6 [7.3%] probable, 2 [2.4%] definite). For 7 cases, the information available was considered insufficient for adjudication. For the remaining 67 cases that were determined not to be lack of efficacy, the most commonly cited reasons were inadequate surgical control (n=12, 17.9%), evidence of

clinical improvement after tigecycline therapy (n=11, 16.4%), evidence of clinical improvement after tigecycline therapy AND inadequate surgical control (n=11, 16.4%), clinically significant positive culture of an organism not susceptible to tigecycline at baseline AND inadequate surgical control (n=8, 11.9%) and "other" reasons (n=11, 16.4%). In most cases, the "other" designation included a combination of an expected criterion (eg, inadequate surgical control) and an additional consideration or explanation, such as death due to reasons other than the infection for which tigecycline was used (Listing 8).

Amongst the 25 cSSTI potential cases, 3 cases (12.0%) were adjudicated as probable or definite cases (none were adjudicated as definite). For 3 cases, the information available was considered insufficient for adjudication. For the remaining 19 cases that were determined not to be lack of efficacy, the most commonly cited reasons were evidence of clinical improvement after tigecycline therapy AND inadequate surgical control (n=4, 21.1%) and evidence of clinical improvement after tigecycline therapy (n=3, 15.8%).

Secondary Objective: Pathogens Associated with Tigecycline-treated Infections

Identified pathogens associated with tigecycline-treated infections were analyzed across the complete PAS population (N=687). Overall, the most commonly reported pathogens were *Enterococcus spp.* (n=224), *Staphylococcus spp.* (n=193), *Escherichia coli* (n=111), *Klebsiella spp.* (n=78), *Pseudomonas aeruginosa* (n=57) and *Streptococcus spp.* (n=49) (Table 15.12.0). Gram-positive and gram-negative pathogens were reported in a greater proportion of patients in the after RMM period than the before RMM period across all indications.

Pseudomonas aeruginosa is an inherently resistant organism. Thirty-two of the 57 cases (56.1%) of *Pseudomonas aeruginosa* were after the RMM, of which 13 (40.6%) were reported to have a resistant phenotype (Table 15.12.0). Two common Gram positive pathogens showed the highest proportions of reported pathogens with phenotypic resistance overall, *Staphylococcus spp.* (81/193, 42.0%) and *Enterococcus spp.* (67/224, 29.9%). A higher proportion of phenotypic resistance in *Staphylococcus spp.* cases was reported in the after RMM period (49/106, 46.2%) as compared with the before RMM period (32/87, 36.8%). The proportion of phenotypic resistance in *Enterococcus spp.* was similar (29.1% before RMM; 30.3% after RMM). *Proteus spp.* were reported in 7 patients before the RMM and in 12 patients after the RMM. In general, there was an increase in the proportion of patients with resistant Gram-positive pathogens in the period after RMM compared to the before RMM period, and a decrease in the proportion of resistant Gram-negative pathogens identified (Table 15.12.0). Detection of anaerobes was less common in both periods, with only 49 patients (25 before RMM, 24 after RMM) with identified pathogens. A resistant phenotype was detected in only one patient (*Bacteroides spp.*) (Table 15.12.0).

Exploratory analyses

Exploratory Objective 1: Pathogens Associated with Tigecycline-treated Infections, by indication.

While *Enterococcus spp.* pathogens were the most commonly reported in cIAI patients, *Staphylococcus spp.* were the most commonly reported in cSSTI and off-label patients. By

indication, the most substantial relative increase in reported pathogen was for *Enterococcus spp.,* which were reported in 36.4% of cIAI patients and 21.4% of cSSTI patients before the RMM and in 59.9% of cIAI patients and 33.3% of cSSTI patients after the RMM. Anaerobes were more commonly reported in cIAI and off-label patients as compared to cSSTI patients (Table 15.12.1).

Specific resistant species were solicited in the CRF including methicillin-resistant *Staphylococcus aureus* (MRSA), methicillin-resistant coagulase-negative *Staphylococcus* (MRCNS), vancomycin-resistant *Enterococcus* (VRE), carbapenamase-producing organism (CPO) and extended-spectrum beta-lactamase producing organism (ESBLPO). The proportion of patients with identified multi-drug resistant organisms overall was increased from the before RMM to the after RMM period in all indications, particularly in cIAI patients (n=26 [20.2%] vs. n=44 [31.0%] and off-label cases (n=39 [19.3%] vs. n=46 [41.1%]). The largest relative increase in reports was of VRE in the after RMM period as compared to the before RMM period, across all indications (7.0% vs. 15.5% cIAI; 11.9% vs. 13.3% cSSTI; 2.0% vs. 8.9% off label) (Table 15.12.1).

Exploratory Objective 2: Multivariate analysis of factors associated with off-label use

An exploratory logistic regression analysis was performed to evaluate factors associated with off-label use. Treatment in the after RMM period was associated with significantly decreased odds of off-label use compared to treatment in the before RMM period (adjusted odds ratio (OR) 0.66, 95% CI 0.46 - 0.94) (Table 15.11.0). For country, Germany, as the largest source of data, was used as the reference group. Patients in Austria (OR 2.46, 95% CI 1.48 - 4.11) and the UK (OR 1.59, 95% CI 1.04 - 2.41) were significantly more likely to be treated off-label compared to patients in Germany (Table 15.11.0). A history of previous surgical procedures was associated with increased likelihood of off-label use (OR 4.52, 95% CI 3.10 - 6.59). No other variables (ie, age, gender, previous antibiotic therapy or number of co-morbidities) reached statistical significance.

10.5. Other analyses

Sensitivity analysis including data from Italy

Analyses of the primary objectives (tigecycline treatment patterns and superinfection/lack of efficacy endpoints) as well as patient demographics and site characteristics which included the patients from Italy (ie, the FAS population) were generated in order to maximize sample size and generalizability, while restricting the susceptibility of primary analyses to bias. In the PAS, 218 of the 687 patients (31.7%) died prior to hospital discharge (Table 15.8.0). In contrast, 65 of the 90 patients enrolled from the sites in Italy (72.2%) were deceased at the time of study enrollment (it should be noted that some patients may have died after discharge but prior to study enrollment) (Table 10.1).

Overall, differences between the FAS and PAS populations were negligible. The patient demographics of the FAS were almost identical to the PAS (Table 15.2.0, Table 15.2.0a). With the exception of all of the Italian sites enrolling patients from the hospital as a whole

(rather than a specific ward), hospital characteristics were also similar (Table 15.13.0,Table 15.13.0a).

In regards to the proportion of off-label use, inclusion of the 90 patients from Italy had a small effect (PAS 45.7% off-label use, FAS 43.2%) (Table 15.1.1, Table 15.1.1a). Since it is likely that a higher proportion of the enrolled patients in Italy were deceased at the time of enrollment, the slightly higher rate of off-label use may be associated with the patients' underlying condition.

The proportion of cSSTI across both periods was the same in the PAS and FAS populations (15.0% and 14.8%, respectively) (Table 15.1.0, Table 15.1.0a). There was a slightly higher proportion of cIAI cases in the FAS (42.5% FAS versus 39.9% PAS) and slightly lower proportion of "other" indications (42.7% FAS versus 45.1% PAS). Only one additional patient in the FAS was treated prophylactically. None of the patients from the Italian sites were less than 18 years of age (Table 15.2.0, Table 15.2.0a).

All of the 11 reported AEs with explicit attribution to tigecycline were experienced by patients included in the PAS.

Sensitivity analysis including indeterminate potential cases of superinfection and lack of efficacy

Analyses including indeterminate cases in the mPAS superinfection and lack of efficacy cases are found in Table 15.9.3 and Table 15.10.3, respectively. The overall incidence proportion of definite, probable and indeterminate superinfection across indications in the mPAS was 8.0% (95% CI 4.7% - 12.7%), with 8.6% before RMM (95% CI: 4.0% - 15.7%) and 7.5% after RMM (3.1% - 14.7%). The overall incidence proportion of definite, probable and indeterminate lack of efficacy in the mPAS was 10.6% (95% CI 6.7% - 15.7%), with 9.5% before RMM (95% CI: 4.7% - 16.8%) and 11.7% after (6.0% - 20.0%).

Similar analyses including the mFAS population for definite and probable superinfection and lack of efficacy are found in

Table 15.9.2a and Table 15.10.2a, respectively, and for the mFAS including indeterminate cases in

Table 15.9.3a and Table 15.10.3a, respectively. Overall, findings were similar between the mPAS and mFAS populations.

10.6. Adverse events / adverse reactions

10.6.1. Overview of adverse events

Adverse events (AE) with explicit attribution ('related') to any Pfizer drug that appeared in the defined dataset (defined per the patient population and study period specified in the protocol) were to be reported.

A total of 11 related AEs in 8 patients were reported, including 8 related serious adverse events (SAEs) in 5 patients. AEs are summarized by MedDRA SOC and preferred term (Version 16.1) in Table 15.14.0. Five of the AEs (45.5%) were infections (SOC Infections

and Infestations) with 2 patients each reported with pneumonia and pseudomonas infection and one patient reported with sepsis. Six patients permanently discontinued tigecycline due to AEs, one patient each with pneumonia, pseudomonas infection, nausea, drug hypersensitivity, increased hepatic enzymes and pruritic rash.

AEs are presented by severity in Table 15.14.1, by action taken in Table 15.14.2 and by event outcome in Table 15.14.3.

10.6.2. Deaths and other serious adverse events

A total of 8 related SAEs were reported in 5 patients (Table 15.15.0). Of these patients, 3 had an outcome of death (patients [redacted], [redacted] and [redacted]) and are described in more detail below. Of the two remaining patients, one ([redacted]) had an SAE of pneumonia requiring hospitalization, which resolved, and the other patient ([redacted]) experienced a drug hypersensitivity reaction that was considered an important medical event by the investigator. SAEs are presented by seriousness criteria in Table 15.15.1 .

Deaths

Patient [redacted], an 86 year old female, received tigecycline from 12 November 2012 to 24 November 2012 (loading dose 100 mg, maintenance dose 50 mg BID) for an unspecified infection in combination with fluconazole and piperacillin tazobactam. The patient was admitted with complications following cholecystectomy including hepatic necrosis. Biliary stenting resulted in a perforated biliary line. She developed a pseudomonas infection on 24 November 2012 and tigecycline was discontinued. The patient died on [redacted] February 2013 due to multi-organ failure and liver necrosis. It was unclear if the pseudomonas infection contributed to the patient's multi-organ failure and no autopsy was performed. The investigator considered there to be a reasonable possibility that the pseudomonas infection was related to tigecycline use.

Patient [redacted] was an 88 year old female who received tigecycline from 18 March 2010 to 21 March 2010 (loading dose 100 mg, maintenance dose 50 mg BID) for cholecystitis, until the day of her death (21 March 2010). The patient's relevant medical history included ongoing chronic obstructive pulmonary disease and congestive cardiac failure. On 18 March 2010, the patient developed septicemia and cholecystitis and was admitted with a diagnosis of biliary sepsis secondary to obstructive biliary tract stones. The patient was not operated due to co-morbidities. The patient deteriorated clinically and developed pneumonia on 20 March 2010. The septicemia and cholecystitis progressed, resulting in multi-organ failure and death due to these events and pneumonia on 21 March 2010. No microbiology testing or autopsy was performed. The investigator considered there was a reasonable possibility that the events were related to tigecycline.

Patient [redacted] was a 63 year old female who received tigecycline from 21 August 2010 to 30 August 2010 (loading dose 100 mg, maintenance dose 50 mg BID) for sepsis. The patient's relevant medical history included adenocarcinoma of the gallbladder and laparoscopic cholecystectomy and hemihepatectomy on 11 June 2010. On 27 August 2010 the patient underwent re-laparotomy for an anastomotic leak and on 31 August 2010, the

patient developed a pseudomonal superinfection. Tigecycline was discontinued and the patient received fluconazole, metronidazole, ciprofloxacin, vancomycin, co-trimoxazole, aztreonam, gentamicin and teicoplanin. On [redacted] September 2010, the patient died as a result of multi-organ failure, pneumonia and gallbladder cancer. While the pseudomonas infection reportedly contributed to the patient's morbidity, its association with mortality was unclear due to complications associated with the malignancy, 2 surgical leaks and myocardial infarctions. The investigator considered there was a reasonable possibility that the pseudomonas infection and pneumonia were related to the study drug and unrelated to any concomitant medication.

Other SAEs

Patient [redacted], a 50 year old male, was treated with tigecycline from 14 February 2014 to 20 February 2014 (loading dose 100 mg, maintenance dose 50 mg BID) for peritonitis secondary to diverticulitis. On 21 February 2014, the patient developed pneumonia, possibly a superinfection associated with the use of tigecycline. The pneumonia resulted in a prolonged hospitalization; the patient recovered on 02 March 2012.

Patient [redacted], a 58 year old female, initiated treatment with tigecycline on 14 January 2013 (loading dose 100 mg, maintenance dose 50 mg BID) for uncomplicated diverticulitis. On 14 January 2013, the patient experienced tingling lips and throat and dry throat during her second dose of tigecycline. Tigecycline was discontinued and the events resolved within 24 hours.

10.6.3. Other adverse events

Three non-serious events were reported in 3 patients for which the investigator considered there to be a reasonable possibility that the event was related to tigecycline. The reported events included one patient each with elevated hepatic enzymes, nausea and pruritic rash.

11. DISCUSSION

11.1. Key results

A sample size of at least 300 patients in each period before and after the RMM was projected. Although the proportion of projected eligible patients that actually met enrollment criteria was low at some sites, the minimum enrollment target was met, and the final primary data set used for the analyses included 373 patients in the before RMM period and 314 in the after RMM period in the PAS. Some notable differences in patient medical and treatment history prior to initiating tigecycline therapy were found between the periods. A higher proportion of patients had undergone a surgical procedure or therapeutic intervention in the period after the RMM (74.2%) as compared to before the RMM (45.6%); this was particularly true for cIAI patients, of whom 93.7% had undergone a surgical procedure or therapeutic intervention. Other antibiotic use within 7 days prior to initiating tigecycline was more common in patients treated for any indication after the RMM as compared to before the RMM (87.1% after versus 69.1% before).

Overall, the rate of off-label use was 45.7%. Off-label use decreased from 54.2% before RMM to 35.7% after RMM. For 16 patients, treatment was explicitly described as prophylactic (9 before RMM, 7 after RMM); in addition, 7 adolescent patients (under the age of 18) on hospital admission were treated with tigecycline (2 before RMM, 5 after RMM). As part of an exploratory analysis to better understand the factors associated with off-label use, treatment in the before RMM period, undergoing a prior surgical procedure, and country where treated were the three factors significantly associated with off-label use, controlling for other factors.

A total of 306 indications (45.1% of all reported indications) were reported as something other than cIAI or cSSTI, with the most commonly reported off-label indications being hospital acquired pneumonia/pneumonia other, bacteremia, diabetic foot infections and "other". The distribution of "other" indications in the before and after RMM periods differed, with more reports of cholangitis, cholecystitis and diverticulitis before the RMM, and of infectious pleural effusion, staphyloccocal infection/staphylococcus test positive and pyrexia/post-operative fever after the RMM.

The incidence proportion of definite or probable superinfection across approved indications was 4.5% (95% CI 2.1% - 8.4%), with no substantial differences between the before RMM period [3.8% (95% CI: 1.1% - 9.5%)] and the after RMM period [5.3% (1.8% - 12.0%)]. The incidence proportion of definite or probable lack of efficacy was 5.5% (95% CI 2.8% - 9.7%), with a lower incidence before RMM [2.9% (95% CI: 0.6% - 8.1%)] than after [8.5% (3.8% - 16.1%)], with wide and overlapping confidence intervals. Inclusion of the Italian subset of patients did not alter interpretation of the study results. For both endpoints, restricting analyses to definite cases or inclusion of indeterminate cases, and inclusion of the Italian subset of patients, did not alter interpretation of the results.

Across all patients, the most commonly reported pathogens were *Enterococcus spp.*, *Staphylococcus spp., Escherichia coli, Klebsiella spp.*, *Pseudomonas aeruginosa* and *Streptococcus spp*. In general, there was an increase in the proportion of patients with resistant Gram-positive and Gram-negative pathogens identified in the period after RMM compared to the before RMM period. The most substantial relative increase was seen in *Enterococcus spp.* The proportion of patients with identified multi-drug resistant organisms also increased in cIAI patients. There was an increase in reports of VRE in the after RMM period as compared to the before RMM period, across all indications.

A total of 11 AEs, which were explicitly described as potentially related to treatment with tigecycline in the medical record, were identified, including 8 SAEs. Overall, the nature of the events was expected and no new safety issues were identified through evaluation of the AEs.

11.2. Limitations

It is possible that unmeasured factors influenced the relationship between the RMM and study endpoints. For instance, it is difficult to separate the impact of the RMM on off-label use from the impact of changes in antimicrobial resistance among bacterial isolates causing infections in sites other than approved indications. However, our findings of decreased off-

label use correspond more with a scenario of decreased resistance, an unlikely scenario. While two sites reported local circumstances that may have affected tigecycline utilization in one or both of the periods, the reported circumstances did not provide support for a pattern of decreased off-label use in the post RMM period. Nonetheless, the possibility that other unmeasured factors independent of the RMM (eg, a shift in prescribing practices unrelated to the RMM or increased availability of other treatments) may also have influenced tigecycline prescribing before and after the RMM cannot be excluded.

Further, the study did not examine the role of exposure to individual components of the RMM (e.g. the direct healthcare professional communication or educational program) on study endpoints. It is not possible to determine to which (if any) component of the RMM the treating physicians had been exposed.

Although expert adjudication of potential cases of superinfection and lack of efficacy was intended to provide standardized assessment of the study endpoints, the lack of sufficient data on microbiology and clinical assessments in the medical record data made case classification difficult in some cases. For instance, in the mPAS population, 6 (10%) of potential superinfection cases and 10 (9%) of lack of efficacy cases were deemed to have insufficient information for adjudication.

Microbiology data was only available for 68% of patients in the PAS, inhibiting ability to accurately assess distribution of pathogens, and in particular, the existence of resistant phenotypes among this patient population.

In regards to safety, the retrospective collection of AEs potentially related to treatment with tigecycline (limited here to 11 events) is difficult to interpret as not all potentially relevant events are likely to be identified and explicit attribution to tigecycline in the medical record is assumed to be uncommon. However, the objective of this study was not to report adverse event occurrence from individual study cases. Rather, the primary objectives of this study were to evaluate superinfection, lack of efficacy, and off-label use.

11.3. Interpretation

This PASS sought to evaluate, in select countries in Europe, the effectiveness of RMM aiming to educate the health care community about the newly identified risk of superinfection and potential risks of off-label use and lack of efficacy.

Off label use of tigecycline decreased after implementation of the RMM, and the before RMM period was a significant predictor of off-label use in exploratory multivariate analyses. While this is promising, the ability to directly attribute this change to the RMM is limited, given the study limitations described above. Incidence proportions of definite or probable superinfection or lack of efficacy observed in the before RMM and after RMM periods were low; however, interpretation of differences across before and after RMM periods is difficult due to wide confidence intervals around these estimates.

Overall, the mortality rate observed in patients administered at least one dose of tigecycline for any indication in this study was 31.7%. Patients treated for cIAIs and off label indications

had the highest mortality rate compared to cSSTI. The mortality rate overall appeared to be higher after the RMM, and specifically, in the cIAI and off-label population subgroups. There were important differences noted in the populations before and after the RMM which may have contributed to differences in mortality, such as increased proportions of surgical intervention prior to tigecycline use and an increase in the proportion of patients with resistant Gram-positive pathogens and identified multi-drug resistant organisms after the RMM relative to before the RMM, particularly among cIAI and off-label indication patients.

11.4. Generalisability

Although one of the planned countries (Italy) was excluded from the primary analyses, and Spain was excluded from the study, the geographical distribution of the study still included 4 high-prescribing tigecycline countries in the EU (Austria, Germany, Greece and the UK), and sensitivity analyses including Italy exhibited results consistent with the primary analyses. It should be noted, however, that the majority of patients were enrolled by sites in Germany (315/687, 45.9%) and the UK (244/687, 35.5%), which may limit somewhat the external validity of the results beyond these two major markets. The possibility that sites contributing data to the study are not representative of sites that did not contribute data cannot be excluded.

12. OTHER INFORMATION

Not applicable.

13. CONCLUSIONS

The goal of this descriptive cohort study was to assess the effectiveness of the RMM by describing indications for tigecycline use, and to describe clinical outcomes among adult patients with cIAI or cSSTI treated with approved doses of tigecycline in the EU before and after implementation of the RMM in February 2011. The study found that:

- The proportion of off-label use decreased following the implementation of RMM; and
- Overall proportions of definite and probable superinfection and lack of efficacy were low in both the before and the after RMM periods.

However, while the decrease in off-label use following implementation of RMM is notable, the possibility that factors other than RMM may have contributed to this decrease cannot be excluded.

14. REFERENCES

1. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation." Journal of chronic diseases 1987. 40;5:373-383.

2. Clopper CJ, Pearson ES. The use of confidence or fiducial limits illustrated in the case of the binomial, Biometrika 1934. 26: 404–416.

3. Dixon, JR. The international conference on harmonization good clinical practice guideline. Quality Assurance: Good Practice, Regulation, and Law 1999 6;2: 65-74.

4. International Society for Pharmacoepidemiology. Guidelines for good pharmacoepidemiology practices (GPP). Pharmacoepidemiol Drug Safety 2008;17:200-208.

15. LIST OF SOURCE TABLES AND FIGURES

Table 15.1.0 Indications for Tigecycline Use – Primary Analysis Set (PAS) population

	Before RMM (N=370)#	After RMM (N=309)#	Overall (N=679)#
cIAI	129(34.9%)	142(46.0%)	271(39.9%)
Intra-abdominal abscess	29(7.8%)	38(12.3%)	67(9.9%)
Perforated appendicitis	2(0.5%)	1(0.3%)	3(0.4%)
Perforated diverticulitis complicated by abscess formation or fecal contamination	6(1.6%)	4(1.3%)	10(1.5%)
Cholecystitis with evidence of perforation or empyema	10(2.7%)	8(2.6%)	18(2.7%)
Intestinal perforation (large or small intestine with abscess or fecal contamination)	18(4.9%)	32(10.4%)	50(7.4%)
Purulent or diffuse peritonitis or peritonitis associated with fecal contamination	8(2.2%)	5(1.6%)	13(1.9%)
Gastric ulcer perforation	3(0.8%)	1(0.3%)	4(0.6%)
Duodenal ulcer perforation	3(0.8%)	3(1.0%)	6(0.9%)
Traumatic bowel perforation	3(0.8%)	3(1.0%)	6(0.9%)
Primary peritonitis	6(1.6%)	2(0.6%)	8(1.2%)
Secondary peritonitis	35(9.5%)	64(20.7%)	99(14.6%)
Tertiary peritonitis	2(0.5%)	2(0.6%)	4(0.6%)
Other cIAI	20(5.4%)	22(7.1%)	42(6.2%)
cSSTI	42(11.4%)	60(19.4%)	102(15.0%)
Cutaneous ulcer	3(0.8%)	5(1.6%)	8(1.2%)
Burns	0(0.0%)	1(0.3%)	1(0.1%)
Major abscess	5(1.4%)	4(1.3%)	9(1.3%)
Cellulitis	6(1.6%)	5(1.6%)	11(1.6%)
Infected catheter site	2(0.5%)	4(1.3%)	6(0.9%)
Wound infection	24(6.5%)	34(11.0%)	58(8.5%)
Group A beta-hemolytic streptococcal gangrene	0(0.0%)	0(0.0%)	0(0.0%)
Necrotizing fasciitis	0(0.0%)	1(0.3%)	1(0.1%)
Fournier's gangrene	0(0.0%)	1(0.3%)	1(0.1%)
Ecthyma gangrenosum	0(0.0%)	0(0.0%)	0(0.0%)
Infected human or animal bites	0(0.0%)	1(0.3%)	1(0.1%)
Other cSSTI	4(1.1%)	5(1.6%)	9(1.3%)
Other	199(53.8%)	107(34.6%)	306(45.1%)
Hospital acquired pneumonia	31(8.4%)	25(8.1%)	56(8.2%)
Pneumonia (other)	23(6.2%)	20(6.5%)	43(6.3%)
Diabetic foot infection	7(1.9%)	3(1.0%)	10(1.5%)
Bacteremia	19(5.1%)	16(5.2%)	35(5.2%)

Table 15.1.0 Indications for Tigecycline Use – Primary Analysis Set (PAS) population

	Before RMM (N=370)#	After RMM (N=309)#	Overall (N=679)#
Other*	125(33.8%)	48(15.5%)	173(25.5%)
Prophylactic Use of Tigecycline explicitly mentioned in the chart			
n	370	309	679
Yes	9(2.4%)	7(2.3%)	16(2.4%)
No	361(97.6%)	302(97.7%)	663(97.6%)
Missing	0	0	0
Infection Present at Admission			
n	370	309	679
Yes	216(58.4%)	134(43.4%)	350(51.5%)
No	154(41.6%)	175(56.6%)	329(48.5%)
Missing	0	0	0

cIAI=Complicated Intra-Abdominal Infection, cSSTI=Complicated Skin or Soft Tissue Infection, RMM=Risk Minimization Measure.
*Please refer to Listing 1 for further specification.
#Patients with age less than 18 years are not included. Also, patient [redacted] is not included as this patient is considered to be off-label because of the dosing sequence, despite this patient being prescribed Tigecycline for cIAI indication and is above 18 years of age.
Data cut-off date: 22May2014
Analysis dataset: A_DEMO
Created by Y:\Pfizer\Tygacil\Tables\Table1.0.sas

Table 15.1.0a Sensitivity Analysis: Indications for Tigecycline Use – Full Analysis Set (FAS) population

	Before RMM (N=396)#	After RMM (N=373)#	Overall (N=769)#
cIAI	144(36.4%)	183(49.1%)	327(42.5%)
Intra-abdominal abscess	35(8.8%)	49(13.1%)	84(10.9%)
Perforated appendicitis	2(0.5%)	1(0.3%)	3(0.4%)
Perforated diverticulitis complicated by abscess formation or fecal contamination	6(1.5%)	6(1.6%)	12(1.6%)
Cholecystitis with evidence of perforation or empyema	10(2.5%)	10(2.7%)	20(2.6%)
Intestinal perforation (large or small intestine with abscess or fecal contamination)	19(4.8%)	33(8.8%)	52(6.8%)
Purulent or diffuse peritonitis or peritonitis associated with fecal contamination	9(2.3%)	5(1.3%)	14(1.8%)
Gastric ulcer perforation	3(0.8%)	1(0.3%)	4(0.5%)
Duodenal ulcer perforation	3(0.8%)	3(0.8%)	6(0.8%)
Traumatic bowel perforation	3(0.8%)	3(0.8%)	6(0.8%)
Primary peritonitis	6(1.5%)	5(1.3%)	11(1.4%)
Secondary peritonitis	37(9.3%)	82(22.0%)	119(15.5%)
Tertiary peritonitis	2(0.5%)	3(0.8%)	5(0.7%)
Other cIAI	25(6.3%)	28(7.5%)	53(6.9%)
cSSTI	45(11.4%)	69(18.5%)	114(14.8%)
Cutaneous ulcer	4(1.0%)	7(1.9%)	11(1.4%)
Burns	0(0.0%)	1(0.3%)	1(0.1%)
Major abscess	5(1.3%)	5(1.3%)	10(1.3%)
Cellulitis	6(1.5%)	6(1.6%)	12(1.6%)
Infected catheter site	2(0.5%)	4(1.1%)	6(0.8%)
Wound infection	26(6.6%)	37(9.9%)	63(8.2%)
Group A beta-hemolytic streptococcal gangrene	0(0.0%)	0(0.0%)	0(0.0%)
Necrotizing fasciitis	0(0.0%)	2(0.5%)	2(0.3%)
Fournier's gangrene	0(0.0%)	1(0.3%)	1(0.1%)
Ecthyma gangrenosum	0(0.0%)	0(0.0%)	0(0.0%)
Infected human or animal bites	0(0.0%)	1(0.3%)	1(0.1%)
Other cSSTI	4(1.0%)	6(1.6%)	10(1.3%)
Other	207(52.3%)	121(32.4%)	328(42.7%)
Hospital acquired pneumonia	34(8.6%)	27(7.2%)	61(7.9%)
Pneumonia (other)	24(6.1%)	25(6.7%)	49(6.4%)
Diabetic foot infection	7(1.8%)	3(0.8%)	10(1.3%)
Bacteremia	24(6.1%)	23(6.2%)	47(6.1%)

Table 15.1.0a Sensitivity Analysis: Indications for Tigecycline Use – Full Analysis Set (FAS) population

	Before RMM (N=396)#	After RMM (N=373)#	Overall (N=769)#
Other*	126(31.8%)	48(12.9%)	174(22.6%)
Prophylactic Use of Tigecycline explicitly mentioned in the chart			
n	396	373	769
Yes	9(2.3%)	8(2.1%)	17(2.2%)
No	387(97.7%)	365(97.9%)	752(97.8%)
Missing	0	0	0
Infection Present at Admission			
n	396	373	769
Yes	221(55.8%)	159(42.6%)	380(49.4%)
No	175(44.2%)	214(57.4%)	389(50.6%)
Missing	0	0	0

cIAI=Complicated Intra-Abdominal Infection, cSSTI=Complicated Skin or Soft Tissue Infection, RMM=Risk Minimization Measure.
*Please refer to Listing 1 for further specification.
#Patients with age less than 18 years are not included. Also, patient [redacted] is not included as this patient is considered to be off-label because of the dosing sequence, despite this patient being prescribed Tigecycline for cIAI indication and is above 18 years of age.
Data cut-off date: 22May2014
Analysis dataset: A_DEMO
Created by Y:\Pfizer\Tygacil\Tables\Table1.0a.sas

Table 15.1.0a.1 Indications for Tigecycline Use by Country - Germany

	Before RMM (N=144)#	After RMM (N=168)#	Overall (N=312)#
cIAI	65(45.1%)	102(60.7%)	167(53.5%)
Intra-abdominal abscess	15(10.4%)	22(13.1%)	37(11.9%)
Perforated appendicitis	0(0.0%)	1(0.6%)	1(0.3%)
Perforated diverticulitis complicated by abscess formation or fecal contamination	0(0.0%)	1(0.6%)	1(0.3%)
Cholecystitis with evidence of perforation or empyema	5(3.5%)	8(4.8%)	13(4.2%)
Intestinal perforation (large or small intestine with abscess or fecal contamination)	8(5.6%)	25(14.9%)	33(10.6%)
Purulent or diffuse peritonitis or peritonitis associated with fecal contamination	5(3.5%)	3(1.8%)	8(2.6%)
Gastric ulcer perforation	2(1.4%)	1(0.6%)	3(1.0%)
Duodenal ulcer perforation	2(1.4%)	2(1.2%)	4(1.3%)
Traumatic bowel perforation	0(0.0%)	2(1.2%)	2(0.6%)
Primary peritonitis	4(2.8%)	1(0.6%)	5(1.6%)
Secondary peritonitis	27(18.8%)	56(33.3%)	83(26.6%)
Tertiary peritonitis	2(1.4%)	2(1.2%)	4(1.3%)
Other cIAI	10(6.9%)	15(8.9%)	25(8.0%)
cSSTI	17(11.8%)	24(14.3%)	41(13.1%)
Cutaneous ulcer	0(0.0%)	0(0.0%)	0(0.0%)
Burns	0(0.0%)	0(0.0%)	0(0.0%)
Major abscess	2(1.4%)	2(1.2%)	4(1.3%)
Cellulitis	0(0.0%)	0(0.0%)	0(0.0%)
Infected catheter site	2(1.4%)	1(0.6%)	3(1.0%)
Wound infection	12(8.3%)	19(11.3%)	31(9.9%)
Group A beta-hemolytic streptococcal gangrene	0(0.0%)	0(0.0%)	0(0.0%)
Necrotizing fasciitis	0(0.0%)	1(0.6%)	1(0.3%)
Fournier's gangrene	0(0.0%)	0(0.0%)	0(0.0%)
Ecthyma gangrenosum	0(0.0%)	0(0.0%)	0(0.0%)
Infected human or animal bites	0(0.0%)	0(0.0%)	0(0.0%)
Other cSSTI	1(0.7%)	2(1.2%)	3(1.0%)
Other	62(43.1%)	42(25.0%)	104(33.3%)
Hospital acquired pneumonia	25(17.4%)	17(10.1%)	42(13.5%)
Pneumonia (other)	15(10.4%)	9(5.4%)	24(7.7%)
Diabetic foot infection	0(0.0%)	0(0.0%)	0(0.0%)
Bacteremia	11(7.6%)	10(6.0%)	21(6.7%)
Other*	15(10.4%)	9(5.4%)	24(7.7%)

Table 15.1.0a.1 Indications for Tigecycline Use by Country - Germany

	Before RMM (N=144)#	After RMM (N=168)#	Overall (N=312)#
Prophylactic Use of Tigecycline explicitly mentioned in the chart			
n	144	[redacted]	[redacted]
Yes	4(2.8%)	3(1.8%)	7(2.2%)
No	140(97.2%)	165(98.2%)	305(97.8%)
Missing	0	0	0
Infection Present at Admission			
n	144	168	312
Yes	59(41.0%)	57(33.9%)	116(37.2%)
No	85(59.0%)	111(66.1%)	196(62.8%)
Missing	0	0	0

cIAI=Complicated Intra-Abdominal Infection, cSSTI=Complicated Skin or Soft Tissue Infection, RMM=Risk Minimization Measure.
*Please refer to Listing 1 for further specification.
#Patients with age less than 18 years are not included. Also, patient [redacted] is not included as this patient is considered to be off-label because of the dosing sequence despite this patient being prescribed Tigecycline for cIAI indication and is above 18 years of age.
Data cut-off date: 22May2014
Analysis dataset: A_DEMO
Created by Y:\Pfizer\Tygacil\Tables\Table1.0a.1.sas

Table 15.1.0a.1 Indications for Tigecycline Use by Country - Austria

	Before RMM (N=43)#	After RMM (N=57)#	Overall (N=100)#
cIAI	8(18.6%)	10(17.5%)	18(18.0%)
Intra-abdominal abscess	1(2.3%)	0(0.0%)	1(1.0%)
Perforated appendicitis	0(0.0%)	0(0.0%)	0(0.0%)
Perforated diverticulitis complicated by abscess formation or fecal contamination	0(0.0%)	3(5.3%)	3(3.0%)
Cholecystitis with evidence of perforation or empyema	1(2.3%)	0(0.0%)	1(1.0%)
Intestinal perforation (large or small intestine with abscess or fecal contamination)	1(2.3%)	3(5.3%)	4(4.0%)
Purulent or diffuse peritonitis or peritonitis associated with fecal contamination	0(0.0%)	1(1.8%)	1(1.0%)
Gastric ulcer perforation	0(0.0%)	0(0.0%)	0(0.0%)
Duodenal ulcer perforation	0(0.0%)	0(0.0%)	0(0.0%)
Traumatic bowel perforation	0(0.0%)	1(1.8%)	1(1.0%)
Primary peritonitis	0(0.0%)	0(0.0%)	0(0.0%)
Secondary peritonitis	3(7.0%)	3(5.3%)	6(6.0%)
Tertiary peritonitis	0(0.0%)	0(0.0%)	0(0.0%)
Other cIAI	3(7.0%)	3(5.3%)	6(6.0%)
cSSTI	7(16.3%)	15(26.3%)	22(22.0%)
Cutaneous ulcer	0(0.0%)	0(0.0%)	0(0.0%)
Burns	0(0.0%)	1(1.8%)	1(1.0%)
Major abscess	1(2.3%)	1(1.8%)	2(2.0%)
Cellulitis	1(2.3%)	1(1.8%)	2(2.0%)
Infected catheter site	0(0.0%)	3(5.3%)	3(3.0%)
Wound infection	5(11.6%)	6(10.5%)	11(11.0%)
Group A beta-hemolytic streptococcal gangrene	0(0.0%)	0(0.0%)	0(0.0%)
Necrotizing fasciitis	0(0.0%)	0(0.0%)	0(0.0%)
Fournier's gangrene	0(0.0%)	1(1.8%)	1(1.0%)
Ecthyma gangrenosum	0(0.0%)	0(0.0%)	0(0.0%)
Infected human or animal bites	0(0.0%)	0(0.0%)	0(0.0%)
Other cSSTI	1(2.3%)	2(3.5%)	3(3.0%)
Other	28(65.1%)	32(56.1%)	60(60.0%)
Hospital acquired pneumonia	5(11.6%)	4(7.0%)	9(9.0%)
Pneumonia (other)	6(14.0%)	10(17.5%)	16(16.0%)
Diabetic foot infection	2(4.7%)	1(1.8%)	3(3.0%)
Bacteremia	2(4.7%)	3(5.3%)	5(5.0%)

Table 15.1.0a.1 Indications for Tigecycline Use by Country - Austria

	Before RMM (N=43)#	After RMM (N=57)#	Overall (N=100)#
Other*	13(30.2%)	15(26.3%)	28(28.0%)
Prophylactic Use of Tigecycline explicitly mentioned in the chart			
n	43	57	100
Yes	0(0.0%)	2(3.5%)	2(2.0%)
No	43(100.0%)	55(96.5%)	98(98.0%)
Missing	0	0	0
Infection Present at Admission			
n	43	57	100
Yes	31(72.1%)	36(63.2%)	67(67.0%)
No	12(27.9%)	21(36.8%)	33(33.0%)
Missing	0	0	0

cIAI=Complicated Intra-Abdominal Infection, cSSTI=Complicated Skin or Soft Tissue Infection, RMM=Risk Minimization Measure.
*Please refer to Listing 1 for further specification.
#Patients with age less than 18 years are not included. Also, patient 1[redacted] is not included as this patient is considered to be off-label because of the dosing sequence despite this patient being prescribed Tigecycline for cIAI indication and is above 18 years of age.
Data cut-off date: 22May2014
Analysis dataset: A_DEMO
Created by Y:\Pfizer\Tygacil\Tables\Table1.0a.1.sas

Table 15.1.0a.1 Indications for Tigecycline Use by Country - Greece

	Before RMM (N=15)#	After RMM (N=11)#	Overall (N=26)#
cIAI	5(33.3%)	2(18.2%)	7(26.9%)
Intra-abdominal abscess	1(6.7%)	0(0.0%)	1(3.8%)
Perforated appendicitis	0(0.0%)	0(0.0%)	0(0.0%)
Perforated diverticulitis complicated by abscess formation or fecal contamination	0(0.0%)	0(0.0%)	0(0.0%)
Cholecystitis with evidence of perforation or empyema	1(6.7%)	0(0.0%)	1(3.8%)
Intestinal perforation (large or small intestine with abscess or fecal contamination)	0(0.0%)	0(0.0%)	0(0.0%)
Purulent or diffuse peritonitis or peritonitis associated with fecal contamination	0(0.0%)	0(0.0%)	0(0.0%)
Gastric ulcer perforation	0(0.0%)	0(0.0%)	0(0.0%)
Duodenal ulcer perforation	0(0.0%)	0(0.0%)	0(0.0%)
Traumatic bowel perforation	0(0.0%)	0(0.0%)	0(0.0%)
Primary peritonitis	0(0.0%)	0(0.0%)	0(0.0%)
Secondary peritonitis	0(0.0%)	0(0.0%)	0(0.0%)
Tertiary peritonitis	0(0.0%)	0(0.0%)	0(0.0%)
Other cIAI	3(20.0%)	2(18.2%)	5(19.2%)
cSSTI	4(26.7%)	7(63.6%)	11(42.3%)
Cutaneous ulcer	3(20.0%)	5(45.5%)	8(30.8%)
Burns	0(0.0%)	0(0.0%)	0(0.0%)
Major abscess	0(0.0%)	0(0.0%)	0(0.0%)
Cellulitis	1(6.7%)	0(0.0%)	1(3.8%)
Infected catheter site	0(0.0%)	0(0.0%)	0(0.0%)
Wound infection	0(0.0%)	1(9.1%)	1(3.8%)
Group A beta-hemolytic streptococcal gangrene	0(0.0%)	0(0.0%)	0(0.0%)
Necrotizing fasciitis	0(0.0%)	0(0.0%)	0(0.0%)
Fournier's gangrene	0(0.0%)	0(0.0%)	0(0.0%)
Ecthyma gangrenosum	0(0.0%)	0(0.0%)	0(0.0%)
Infected human or animal bites	0(0.0%)	0(0.0%)	0(0.0%)
Other cSSTI	1(6.7%)	1(9.1%)	2(7.7%)
Other	6(40.0%)	2(18.2%)	8(30.8%)
Hospital acquired pneumonia	0(0.0%)	0(0.0%)	0(0.0%)
Pneumonia (other)	1(6.7%)	0(0.0%)	1(3.8%)
Diabetic foot infection	0(0.0%)	0(0.0%)	0(0.0%)

Table 15.1.0a.1 Indications for Tigecycline Use by Country - Greece

	Before RMM (N=15)#	After RMM (N=11)#	Overall (N=26)#
Bacteremia	2(13.3%)	2(18.2%)	4(15.4%)
Other*	4(26.7%)	0(0.0%)	4(15.4%)
Prophylactic Use of Tigecycline explicitly mentioned in the chart			
n	15	11	26
Yes	0(0.0%)	0(0.0%)	0(0.0%)
No	15(100.0%)	11(100.0%)	26(100.0%)
Missing	0	0	0
Infection Present at Admission			
n	15	11	26
Yes	10(66.7%)	4(36.4%)	14(53.8%)
No	5(33.3%)	7(63.6%)	12(46.2%)
Missing	0	0	0

cIAI=Complicated Intra-Abdominal Infection, cSSTI=Complicated Skin or Soft Tissue Infection, RMM=Risk Minimization Measure.
*Please refer to Listing 1 for further specification.
#Patients with age less than 18 years are not included. Also, patient [redacted] is not included as this patient is considered to be off-label because of the dosing sequence despite this patient being prescribed Tigecycline for cIAI indication and is above 18 years of age.
Data cut-off date: 22May2014
Analysis dataset: A_DEMO
Created by Y:\Pfizer\Tygacil\Tables\Table1.0a.1.sas

Table 15.1.0a.1 Indications for Tigecycline Use by Country - UK

	Before RMM (N=168)#	After RMM (N=73)#	Overall (N=241)#
cIAI	51(30.4%)	28(38.4%)	79(32.8%)
Intra-abdominal abscess	12(7.1%)	16(21.9%)	28(11.6%)
Perforated appendicitis	2(1.2%)	0(0.0%)	2(0.8%)
Perforated diverticulitis complicated by abscess formation or fecal contamination	6(3.6%)	0(0.0%)	6(2.5%)
Cholecystitis with evidence of perforation or empyema	3(1.8%)	0(0.0%)	3(1.2%)
Intestinal perforation (large or small intestine with abscess or fecal contamination)	9(5.4%)	4(5.5%)	13(5.4%)
Purulent or diffuse peritonitis or peritonitis associated with fecal contamination	3(1.8%)	1(1.4%)	4(1.7%)
Gastric ulcer perforation	1(0.6%)	0(0.0%)	1(0.4%)
Duodenal ulcer perforation	1(0.6%)	1(1.4%)	2(0.8%)
Traumatic bowel perforation	3(1.8%)	0(0.0%)	3(1.2%)
Primary peritonitis	2(1.2%)	1(1.4%)	3(1.2%)
Secondary peritonitis	5(3.0%)	5(6.8%)	10(4.1%)
Tertiary peritonitis	0(0.0%)	0(0.0%)	0(0.0%)
Other cIAI	4(2.4%)	2(2.7%)	6(2.5%)
cSSTI	14(8.3%)	14(19.2%)	28(11.6%)
Cutaneous ulcer	0(0.0%)	0(0.0%)	0(0.0%)
Burns	0(0.0%)	0(0.0%)	0(0.0%)
Major abscess	2(1.2%)	1(1.4%)	3(1.2%)
Cellulitis	4(2.4%)	4(5.5%)	8(3.3%)
Infected catheter site	0(0.0%)	0(0.0%)	0(0.0%)
Wound infection	7(4.2%)	8(11.0%)	15(6.2%)
Group A beta-hemolytic streptococcal gangrene	0(0.0%)	0(0.0%)	0(0.0%)
Necrotizing fasciitis	0(0.0%)	0(0.0%)	0(0.0%)
Fournier's gangrene	0(0.0%)	0(0.0%)	0(0.0%)
Ecthyma gangrenosum	0(0.0%)	0(0.0%)	0(0.0%)
Infected human or animal bites	0(0.0%)	1(1.4%)	1(0.4%)
Other cSSTI	1(0.6%)	0(0.0%)	1(0.4%)
Other	103(61.3%)	31(42.5%)	134(55.6%)
Hospital acquired pneumonia	1(0.6%)	4(5.5%)	5(2.1%)
Pneumonia (other)	1(0.6%)	1(1.4%)	2(0.8%)
Diabetic foot infection	5(3.0%)	2(2.7%)	7(2.9%)

Table 15.1.0a.1 Indications for Tigecycline Use by Country - UK

	Before RMM (N=168)#	After RMM (N=73)#	Overall (N=241)#
Bacteremia	4(2.4%)	1(1.4%)	5(2.1%)
Other*	93(55.4%)	24(32.9%)	117(48.5%)
Prophylactic Use of Tigecycline explicitly mentioned in the chart			
n	168	73	241
Yes	5(3.0%)	2(2.7%)	7(2.9%)
No	163(97.0%)	71(97.3%)	234(97.1%)
Missing	0	0	0
Infection Present at Admission			
n	168	73	241
Yes	116(69.0%)	37(50.7%)	153(63.5%)
No	52(31.0%)	36(49.3%)	88(36.5%)
Missing	0	0	0

cIAI=Complicated Intra-Abdominal Infection, cSSTI=Complicated Skin or Soft Tissue Infection, RMM=Risk Minimization Measure.
*Please refer to Listing 1 for further specification.
#Patients with age less than 18 years are not included. Also, patient [redacted] is not included as this patient is considered to be off-label because of the dosing sequence despite this patient being prescribed Tigecycline for cIAI indication and is above 18 years of age.
Data cut-off date: 22May2014
Analysis dataset: A_DEMO
Created by Y:\Pfizer\Tygacil\Tables\Table1.0a.1.sas

Table 15.1.0a.1 Indications for Tigecycline Use by Country - Italy

	Before RMM (N=26)#	After RMM (N=64)#	Overall (N=90)#
cIAI	15(57.7%)	41(64.1%)	56(62.2%)
Intra-abdominal abscess	6(23.1%)	11(17.2%)	17(18.9%)
Perforated appendicitis	0(0.0%)	0(0.0%)	0(0.0%)
Perforated diverticulitis complicated by abscess formation or fecal contamination	0(0.0%)	2(3.1%)	2(2.2%)
Cholecystitis with evidence of perforation or empyema	0(0.0%)	2(3.1%)	2(2.2%)
Intestinal perforation (large or small intestine with abscess or fecal contamination)	1(3.8%)	1(1.6%)	2(2.2%)
Purulent or diffuse peritonitis or peritonitis associated with fecal contamination	1(3.8%)	0(0.0%)	1(1.1%)
Gastric ulcer perforation	0(0.0%)	0(0.0%)	0(0.0%)
Duodenal ulcer perforation	0(0.0%)	0(0.0%)	0(0.0%)
Traumatic bowel perforation	0(0.0%)	0(0.0%)	0(0.0%)
Primary peritonitis	0(0.0%)	3(4.7%)	3(3.3%)
Secondary peritonitis	2(7.7%)	18(28.1%)	20(22.2%)
Tertiary peritonitis	0(0.0%)	1(1.6%)	1(1.1%)
Other cIAI	5(19.2%)	6(9.4%)	11(12.2%)
cSSTI	3(11.5%)	9(14.1%)	12(13.3%)
Cutaneous ulcer	1(3.8%)	2(3.1%)	3(3.3%)
Burns	0(0.0%)	0(0.0%)	0(0.0%)
Major abscess	0(0.0%)	1(1.6%)	1(1.1%)
Cellulitis	0(0.0%)	1(1.6%)	1(1.1%)
Infected catheter site	0(0.0%)	0(0.0%)	0(0.0%)
Wound infection	2(7.7%)	3(4.7%)	5(5.6%)
Group A beta-hemolytic streptococcal gangrene	0(0.0%)	0(0.0%)	0(0.0%)
Necrotizing fasciitis	0(0.0%)	1(1.6%)	1(1.1%)
Fournier's gangrene	0(0.0%)	0(0.0%)	0(0.0%)
Ecthyma gangrenosum	0(0.0%)	0(0.0%)	0(0.0%)
Infected human or animal bites	0(0.0%)	0(0.0%)	0(0.0%)
Other cSSTI	0(0.0%)	1(1.6%)	1(1.1%)
Other	8(30.8%)	14(21.9%)	22(24.4%)
Hospital acquired pneumonia	3(11.5%)	2(3.1%)	5(5.6%)
Pneumonia (other)	1(3.8%)	5(7.8%)	6(6.7%)
Diabetic foot infection	0(0.0%)	0(0.0%)	0(0.0%)
Bacteremia	5(19.2%)	7(10.9%)	12(13.3%)

Table 15.1.0a.1 Indications for Tigecycline Use by Country - Italy

	Before RMM (N=26)#	After RMM (N=64)#	Overall (N=90)#
Other*	1(3.8%)	0(0.0%)	1(1.1%)
Prophylactic Use of Tigecycline explicitly mentioned in the chart			
n	26	64	90
Yes	0(0.0%)	1(1.6%)	1(1.1%)
No	26(100.0%)	63(98.4%)	89(98.9%)
Missing	0	0	0
Infection Present at Admission			
n	26	64	90
Yes	5(19.2%)	25(39.1%)	30(33.3%)
No	21(80.8%)	39(60.9%)	60(66.7%)
Missing	0	0	0

cIAI=Complicated Intra-Abdominal Infection, cSSTI=Complicated Skin or Soft Tissue Infection, RMM=Risk Minimization Measure.
*Please refer to Listing 1 for further specification.
#Patients with age less than 18 years are not included. Also, patient [redacted] is not included as this patient is considered to be off-label because of the dosing sequence despite this patient being prescribed Tigecycline for cIAI indication and is above 18 years of age.
Data cut-off date: 22May2014
Analysis dataset: A_DEMO
Created by Y:\Pfizer\Tygacil\Tables\Table1.0a.1.sas

Table 15.1.0a.1.1 Indications for Tigecycline Use by Country and Site - Germany

	Before RMM (N=19)#	After RMM (N=32)#	Overall (N=51)#
Site 1001			
cIAI	16(84.2%)	24(75.0%)	40(78.4%)
Intra-abdominal abscess	10(52.6%)	8(25.0%)	18(35.3%)
Perforated appendicitis	0(0.0%)	0(0.0%)	0(0.0%)
Perforated diverticulitis complicated by abscess formation or fecal contamination	0(0.0%)	0(0.0%)	0(0.0%)
Cholecystitis with evidence of perforation or empyema	2(10.5%)	1(3.1%)	3(5.9%)
Intestinal perforation (large or small intestine with abscess or fecal contamination)	4(21.1%)	9(28.1%)	13(25.5%)
Purulent or diffuse peritonitis or peritonitis associated with fecal contamination	2(10.5%)	2(6.3%)	4(7.8%)
Gastric ulcer perforation	0(0.0%)	0(0.0%)	0(0.0%)
Duodenal ulcer perforation	0(0.0%)	1(3.1%)	1(2.0%)
Traumatic bowel perforation	0(0.0%)	1(3.1%)	1(2.0%)
Primary peritonitis	1(5.3%)	1(3.1%)	2(3.9%)
Secondary peritonitis	4(21.1%)	8(25.0%)	12(23.5%)
Tertiary peritonitis	0(0.0%)	0(0.0%)	0(0.0%)
Other cIAI	1(5.3%)	5(15.6%)	6(11.8%)
cSSTI	2(10.5%)	4(12.5%)	6(11.8%)
Cutaneous ulcer	0(0.0%)	0(0.0%)	0(0.0%)
Burns	0(0.0%)	0(0.0%)	0(0.0%)
Major abscess	0(0.0%)	1(3.1%)	1(2.0%)
Cellulitis	0(0.0%)	0(0.0%)	0(0.0%)
Infected catheter site	0(0.0%)	0(0.0%)	0(0.0%)
Wound infection	1(5.3%)	2(6.3%)	3(5.9%)
Group A beta-hemolytic streptococcal gangrene	0(0.0%)	0(0.0%)	0(0.0%)
Necrotizing fasciitis	0(0.0%)	0(0.0%)	0(0.0%)
Fournier's gangrene	0(0.0%)	0(0.0%)	0(0.0%)
Ecthyma gangrenosum	0(0.0%)	0(0.0%)	0(0.0%)
Infected human or animal bites	0(0.0%)	0(0.0%)	0(0.0%)
Other cSSTI	1(5.3%)	1(3.1%)	2(3.9%)
Other	1(5.3%)	4(12.5%)	5(9.8%)
Hospital acquired pneumonia	0(0.0%)	0(0.0%)	0(0.0%)
Pneumonia (other)	1(5.3%)	1(3.1%)	2(3.9%)
Diabetic foot infection	0(0.0%)	0(0.0%)	0(0.0%)

Table 15.1.0a.1.1 Indications for Tigecycline Use by Country and Site - Germany

	Before RMM (N=19)#	After RMM (N=32)#	Overall (N=51)#
Bacteremia	0(0.0%)	3(9.4%)	3(5.9%)
Other*	0(0.0%)	1(3.1%)	1(2.0%)
Prophylactic Use of Tigecycline explicitly mentioned in the chart			
n	19	32	51
Yes	0(0.0%)	1(3.1%)	1(2.0%)
No	19(100.0%)	31(96.9%)	50(98.0%)
Missing	0	0	0
Infection Present at Admission			
n	19	32	51
Yes	12(63.2%)	22(68.8%)	34(66.7%)
No	7(36.8%)	10(31.3%)	17(33.3%)
Missing	0	0	0

cIAI=Complicated Intra-Abdominal Infection, cSSTI=Complicated Skin or Soft Tissue Infection, RMM=Risk Minimization Measure.
*Please refer to Listing 1 for further specification.
#Patients with age less than 18 years are not included.
Data cut-off date: 22May2014
Analysis dataset: A_DEMO
Created by Y:\Pfizer\Tygacil\Tables\Table1.0a.1.1.sas

Table 15.1.0a.1.1 Indications for Tigecycline Use by Country and Site - Germany

	Before RMM (N=60)#	After RMM (N=36)#	Overall (N=96)#
Site 1015			
cIAI	15(25.0%)	9(25.0%)	24(25.0%)
Intra-abdominal abscess	1(1.7%)	3(8.3%)	4(4.2%)
Perforated appendicitis	0(0.0%)	1(2.8%)	1(1.0%)
Perforated diverticulitis complicated by abscess formation or fecal contamination	0(0.0%)	1(2.8%)	1(1.0%)
Cholecystitis with evidence of perforation or empyema	1(1.7%)	0(0.0%)	1(1.0%)
Intestinal perforation (large or small intestine with abscess or fecal contamination)	2(3.3%)	3(8.3%)	5(5.2%)
Purulent or diffuse peritonitis or peritonitis associated with fecal contamination	3(5.0%)	0(0.0%)	3(3.1%)
Gastric ulcer perforation	0(0.0%)	0(0.0%)	0(0.0%)
Duodenal ulcer perforation	1(1.7%)	1(2.8%)	2(2.1%)
Traumatic bowel perforation	0(0.0%)	0(0.0%)	0(0.0%)
Primary peritonitis	2(3.3%)	0(0.0%)	2(2.1%)
Secondary peritonitis	2(3.3%)	2(5.6%)	4(4.2%)
Tertiary peritonitis	1(1.7%)	2(5.6%)	3(3.1%)
Other cIAI	3(5.0%)	1(2.8%)	4(4.2%)
cSSTI	13(21.7%)	14(38.9%)	27(28.1%)
Cutaneous ulcer	0(0.0%)	0(0.0%)	0(0.0%)
Burns	0(0.0%)	0(0.0%)	0(0.0%)
Major abscess	2(3.3%)	0(0.0%)	2(2.1%)
Cellulitis	0(0.0%)	0(0.0%)	0(0.0%)
Infected catheter site	2(3.3%)	1(2.8%)	3(3.1%)
Wound infection	9(15.0%)	13(36.1%)	22(22.9%)
Group A beta-hemolytic streptococcal gangrene	0(0.0%)	0(0.0%)	0(0.0%)
Necrotizing fasciitis	0(0.0%)	0(0.0%)	0(0.0%)
Fournier's gangrene	0(0.0%)	0(0.0%)	0(0.0%)
Ecthyma gangrenosum	0(0.0%)	0(0.0%)	0(0.0%)
Infected human or animal bites	0(0.0%)	0(0.0%)	0(0.0%)
Other cSSTI	0(0.0%)	0(0.0%)	0(0.0%)
Other	32(53.3%)	13(36.1%)	45(46.9%)
Hospital acquired pneumonia	12(20.0%)	6(16.7%)	18(18.8%)
Pneumonia (other)	6(10.0%)	2(5.6%)	8(8.3%)
Diabetic foot infection	0(0.0%)	0(0.0%)	0(0.0%)

Table 15.1.0a.1.1 Indications for Tigecycline Use by Country and Site - Germany

	Before RMM (N=60)#	After RMM (N=36)#	Overall (N=96)#
Bacteremia	10(16.7%)	5(13.9%)	15(15.6%)
Other*	6(10.0%)	2(5.6%)	8(8.3%)
Prophylactic Use of Tigecycline explicitly mentioned in the chart			
n	60	36	96
Yes	1(1.7%)	0(0.0%)	1(1.0%)
No	59(98.3%)	36(100.0%)	95(99.0%)
Missing	0	0	0
Infection Present at Admission			
n	60	36	96
Yes	31(51.7%)	20(55.6%)	51(53.1%)
No	29(48.3%)	16(44.4%)	45(46.9%)
Missing	0	0	0

cIAI=Complicated Intra-Abdominal Infection, cSSTI=Complicated Skin or Soft Tissue Infection, RMM=Risk Minimization Measure.
*Please refer to Listing 1 for further specification.
#Patients with age less than 18 years are not included.
Data cut-off date: 22May2014
Analysis dataset: A_DEMO
Created by Y:\Pfizer\Tygacil\Tables\Table1.0a.1.1.sas

Table 15.1.0a.1.1 Indications for Tigecycline Use by Country and Site - Germany

	Before RMM (N=39)#	After RMM (N=43)#	Overall (N=82)#
Site 1024			
cIAI	11(28.2%)	15(34.9%)	26(31.7%)
Intra-abdominal abscess	1(2.6%)	2(4.7%)	3(3.7%)
Perforated appendicitis	0(0.0%)	0(0.0%)	0(0.0%)
Perforated diverticulitis complicated by abscess formation or fecal contamination	0(0.0%)	0(0.0%)	0(0.0%)
Cholecystitis with evidence of perforation or empyema	0(0.0%)	0(0.0%)	0(0.0%)
Intestinal perforation (large or small intestine with abscess or fecal contamination)	0(0.0%)	1(2.3%)	1(1.2%)
Purulent or diffuse peritonitis or peritonitis associated with fecal contamination	0(0.0%)	0(0.0%)	0(0.0%)
Gastric ulcer perforation	1(2.6%)	0(0.0%)	1(1.2%)
Duodenal ulcer perforation	1(2.6%)	0(0.0%)	1(1.2%)
Traumatic bowel perforation	0(0.0%)	0(0.0%)	0(0.0%)
Primary peritonitis	1(2.6%)	0(0.0%)	1(1.2%)
Secondary peritonitis	1(2.6%)	4(9.3%)	5(6.1%)
Tertiary peritonitis	0(0.0%)	0(0.0%)	0(0.0%)
Other cIAI	6(15.4%)	8(18.6%)	14(17.1%)
cSSTI	2(5.1%)	6(14.0%)	8(9.8%)
Cutaneous ulcer	0(0.0%)	0(0.0%)	0(0.0%)
Burns	0(0.0%)	0(0.0%)	0(0.0%)
Major abscess	0(0.0%)	1(2.3%)	1(1.2%)
Cellulitis	0(0.0%)	0(0.0%)	0(0.0%)
Infected catheter site	0(0.0%)	0(0.0%)	0(0.0%)
Wound infection	2(5.1%)	4(9.3%)	6(7.3%)
Group A beta-hemolytic streptococcal gangrene	0(0.0%)	0(0.0%)	0(0.0%)
Necrotizing fasciitis	0(0.0%)	1(2.3%)	1(1.2%)
Fournier's gangrene	0(0.0%)	0(0.0%)	0(0.0%)
Ecthyma gangrenosum	0(0.0%)	0(0.0%)	0(0.0%)
Infected human or animal bites	0(0.0%)	0(0.0%)	0(0.0%)
Other cSSTI	0(0.0%)	1(2.3%)	1(1.2%)
Other	26(66.7%)	22(51.2%)	48(58.5%)
Hospital acquired pneumonia	12(30.8%)	10(23.3%)	22(26.8%)
Pneumonia (other)	6(15.4%)	5(11.6%)	11(13.4%)
Diabetic foot infection	0(0.0%)	0(0.0%)	0(0.0%)
Bacteremia	1(2.6%)	2(4.7%)	3(3.7%)
Other*	9(23.1%)	5(11.6%)	14(17.1%)

Table 15.1.0a.1.1 Indications for Tigecycline Use by Country and Site - Germany

	Before RMM (N=39)#	After RMM (N=43)#	Overall (N=82)#
Prophylactic Use of Tigecycline explicitly mentioned in the chart			
n	39		
Yes	2(5.1%)	1(2.3%)	3(3.7%)
No	37(94.9%)	42(97.7%)	79(96.3%)
Missing	0	0	0
Infection Present at Admission			
n	39	43	82
Yes	13(33.3%)	12(27.9%)	25(30.5%)
No	26(66.7%)	31(72.1%)	57(69.5%)
Missing	0	0	0

cIAI=Complicated Intra-Abdominal Infection, cSSTI=Complicated Skin or Soft Tissue Infection, RMM=Risk Minimization Measure.
*Please refer to Listing 1 for further specification.
#Patients with age less than 18 years are not included.
Data cut-off date: 22May2014
Analysis dataset: A_DEMO
Created by Y:\Pfizer\Tygacil\Tables\Table1.0a.1.1.sas

Table 15.1.0a.1.1 Indications for Tigecycline Use by Country and Site - Germany

	Before RMM (N=26)#	After RMM (N=57)#	Overall (N=83)#
Site 1027			
cIAI	23(88.5%)	54(94.7%)	77(92.8%)
Intra-abdominal abscess	3(11.5%)	9(15.8%)	12(14.5%)
Perforated appendicitis	0(0.0%)	0(0.0%)	0(0.0%)
Perforated diverticulitis complicated by abscess formation or fecal contamination	0(0.0%)	0(0.0%)	0(0.0%)
Cholecystitis with evidence of perforation or empyema	2(7.7%)	7(12.3%)	9(10.8%)
Intestinal perforation (large or small intestine with abscess or fecal contamination)	2(7.7%)	12(21.1%)	14(16.9%)
Purulent or diffuse peritonitis or peritonitis associated with fecal contamination	0(0.0%)	1(1.8%)	1(1.2%)
Gastric ulcer perforation	1(3.8%)	1(1.8%)	2(2.4%)
Duodenal ulcer perforation	0(0.0%)	0(0.0%)	0(0.0%)
Traumatic bowel perforation	0(0.0%)	1(1.8%)	1(1.2%)
Primary peritonitis	0(0.0%)	0(0.0%)	0(0.0%)
Secondary peritonitis	20(76.9%)	42(73.7%)	62(74.7%)
Tertiary peritonitis	1(3.8%)	0(0.0%)	1(1.2%)
Other cIAI	0(0.0%)	1(1.8%)	1(1.2%)
cSSTI	0(0.0%)	0(0.0%)	0(0.0%)
Cutaneous ulcer	0(0.0%)	0(0.0%)	0(0.0%)
Burns	0(0.0%)	0(0.0%)	0(0.0%)
Major abscess	0(0.0%)	0(0.0%)	0(0.0%)
Cellulitis	0(0.0%)	0(0.0%)	0(0.0%)
Infected catheter site	0(0.0%)	0(0.0%)	0(0.0%)
Wound infection	0(0.0%)	0(0.0%)	0(0.0%)
Group A beta-hemolytic streptococcal gangrene	0(0.0%)	0(0.0%)	0(0.0%)
Necrotizing fasciitis	0(0.0%)	0(0.0%)	0(0.0%)
Fournier's gangrene	0(0.0%)	0(0.0%)	0(0.0%)
Ecthyma gangrenosum	0(0.0%)	0(0.0%)	0(0.0%)
Infected human or animal bites	0(0.0%)	0(0.0%)	0(0.0%)
Other cSSTI	0(0.0%)	0(0.0%)	0(0.0%)
Other	3(11.5%)	3(5.3%)	6(7.2%)
Hospital acquired pneumonia	1(3.8%)	1(1.8%)	2(2.4%)
Pneumonia (other)	2(7.7%)	1(1.8%)	3(3.6%)
Diabetic foot infection	0(0.0%)	0(0.0%)	0(0.0%)
Bacteremia	0(0.0%)	0(0.0%)	0(0.0%)
Other*	0(0.0%)	1(1.8%)	1(1.2%)

Table 15.1.0a.1.1 Indications for Tigecycline Use by Country and Site - Germany

	Before RMM (N=26)#	After RMM (N=57)#	Overall (N=83)#
Prophylactic Use of Tigecycline explicitly mentioned in the chart			
n	26		
Yes	1(3.8%)	1(1.8%)	2(2.4%)
No	25(96.2%)	56(98.2%)	81(97.6%)
Missing	0	0	0
Infection Present at Admission			
n	26	57	83
Yes	3(11.5%)	3(5.3%)	6(7.2%)
No	23(88.5%)	54(94.7%)	77(92.8%)
Missing	0	0	0

cIAI=Complicated Intra-Abdominal Infection, cSSTI=Complicated Skin or Soft Tissue Infection, RMM=Risk Minimization Measure.
*Please refer to Listing 1 for further specification.
#Patients with age less than 18 years are not included.
Data cut-off date: 22May2014
Analysis dataset: A_DEMO
Created by Y:\Pfizer\Tygacil\Tables\Table1.0a.1.1.sas

Table 15.1.0a.1.2 Indications for Tigecycline Use by Country and Site - Austria

	Before RMM (N=38)#	After RMM (N=50)#	Overall (N=88)#
Site 1016			
cIAI	8(21.1%)	10(20.0%)	18(20.5%)
Intra-abdominal abscess	1(2.6%)	0(0.0%)	1(1.1%)
Perforated appendicitis	0(0.0%)	0(0.0%)	0(0.0%)
Perforated diverticulitis complicated by abscess formation or fecal contamination	0(0.0%)	3(6.0%)	3(3.4%)
Cholecystitis with evidence of perforation or empyema	1(2.6%)	0(0.0%)	1(1.1%)
Intestinal perforation (large or small intestine with abscess or fecal contamination)	1(2.6%)	3(6.0%)	4(4.5%)
Purulent or diffuse peritonitis or peritonitis associated with fecal contamination	0(0.0%)	1(2.0%)	1(1.1%)
Gastric ulcer perforation	0(0.0%)	0(0.0%)	0(0.0%)
Duodenal ulcer perforation	0(0.0%)	0(0.0%)	0(0.0%)
Traumatic bowel perforation	0(0.0%)	1(2.0%)	1(1.1%)
Primary peritonitis	0(0.0%)	0(0.0%)	0(0.0%)
Secondary peritonitis	3(7.9%)	3(6.0%)	6(6.8%)
Tertiary peritonitis	0(0.0%)	0(0.0%)	0(0.0%)
Other cIAI	3(7.9%)	3(6.0%)	6(6.8%)
cSSTI	7(18.4%)	14(28.0%)	21(23.9%)
Cutaneous ulcer	0(0.0%)	0(0.0%)	0(0.0%)
Burns	0(0.0%)	1(2.0%)	1(1.1%)
Major abscess	1(2.6%)	0(0.0%)	1(1.1%)
Cellulitis	1(2.6%)	1(2.0%)	2(2.3%)
Infected catheter site	0(0.0%)	3(6.0%)	3(3.4%)
Wound infection	5(13.2%)	6(12.0%)	11(12.5%)
Group A beta-hemolytic streptococcal gangrene	0(0.0%)	0(0.0%)	0(0.0%)
Necrotizing fasciitis	0(0.0%)	0(0.0%)	0(0.0%)
Fournier's gangrene	0(0.0%)	1(2.0%)	1(1.1%)
Ecthyma gangrenosum	0(0.0%)	0(0.0%)	0(0.0%)
Infected human or animal bites	0(0.0%)	0(0.0%)	0(0.0%)
Other cSSTI	1(2.6%)	2(4.0%)	3(3.4%)
Other	23(60.5%)	26(52.0%)	49(55.7%)
Hospital acquired pneumonia	3(7.9%)	2(4.0%)	5(5.7%)
Pneumonia (other)	3(7.9%)	8(16.0%)	11(12.5%)

Table 15.1.0a.1.2 Indications for Tigecycline Use by Country and Site - Austria

	Before RMM (N=38)#	After RMM (N=50)#	Overall (N=88)#
Diabetic foot infection	2(5.3%)	1(2.0%)	3(3.4%)
Bacteremia	2(5.3%)	3(6.0%)	5(5.7%)
Other*	13(34.2%)	13(26.0%)	26(29.5%)
Prophylactic Use of Tigecycline explicitly mentioned in the chart			
n	38	50	88
Yes	0(0.0%)	0(0.0%)	0(0.0%)
No	38(100.0%)	50(100.0%)	88(100.0%)
Missing	0	0	0
Infection Present at Admission			
n	38	50	88
Yes	27(71.1%)	29(58.0%)	56(63.6%)
No	11(28.9%)	21(42.0%)	32(36.4%)
Missing	0	0	0

cIAI=Complicated Intra-Abdominal Infection, cSSTI=Complicated Skin or Soft Tissue Infection, RMM=Risk Minimization Measure.
*Please refer to Listing 1 for further specification.
#Patients with age less than 18 years are not included.
Data cut-off date: 22May2014
Analysis dataset: A_DEMO
Created by Y:\Pfizer\Tygacil\Tables\Table1.0a.1.2.sas

Table 15.1.0a.1.2 Indications for Tigecycline Use by Country and Site - Austria

	Before RMM (N=5) #	After RMM (N=7) #	Overall (N=12) #
Site 1020			
cIAI	0(0.0%)	0(0.0%)	0(0.0%)
Intra-abdominal abscess	0(0.0%)	0(0.0%)	0(0.0%)
Perforated appendicitis	0(0.0%)	0(0.0%)	0(0.0%)
Perforated diverticulitis complicated by abscess formation or fecal contamination	0(0.0%)	0(0.0%)	0(0.0%)
Cholecystitis with evidence of perforation or empyema	0(0.0%)	0(0.0%)	0(0.0%)
Intestinal perforation (large or small intestine with abscess or fecal contamination)	0(0.0%)	0(0.0%)	0(0.0%)
Purulent or diffuse peritonitis or peritonitis associated with fecal contamination	0(0.0%)	0(0.0%)	0(0.0%)
Gastric ulcer perforation	0(0.0%)	0(0.0%)	0(0.0%)
Duodenal ulcer perforation	0(0.0%)	0(0.0%)	0(0.0%)
Traumatic bowel perforation	0(0.0%)	0(0.0%)	0(0.0%)
Primary peritonitis	0(0.0%)	0(0.0%)	0(0.0%)
Secondary peritonitis	0(0.0%)	0(0.0%)	0(0.0%)
Tertiary peritonitis	0(0.0%)	0(0.0%)	0(0.0%)
Other cIAI	0(0.0%)	0(0.0%)	0(0.0%)
cSSTI	0(0.0%)	1(14.3%)	1(8.3%)
Cutaneous ulcer	0(0.0%)	0(0.0%)	0(0.0%)
Burns	0(0.0%)	0(0.0%)	0(0.0%)
Major abscess	0(0.0%)	1(14.3%)	1(8.3%)
Cellulitis	0(0.0%)	0(0.0%)	0(0.0%)
Infected catheter site	0(0.0%)	0(0.0%)	0(0.0%)
Wound infection	0(0.0%)	0(0.0%)	0(0.0%)
Group A beta-hemolytic streptococcal gangrene	0(0.0%)	0(0.0%)	0(0.0%)
Necrotizing fasciitis	0(0.0%)	0(0.0%)	0(0.0%)
Fournier's gangrene	0(0.0%)	0(0.0%)	0(0.0%)
Ecthyma gangrenosum	0(0.0%)	0(0.0%)	0(0.0%)
Infected human or animal bites	0(0.0%)	0(0.0%)	0(0.0%)
Other cSSTI	0(0.0%)	0(0.0%)	0(0.0%)
Other	5(100.0%)	6(85.7%)	11(91.7%)
Hospital acquired pneumonia	2(40.0%)	2(28.6%)	4(33.3%)
Pneumonia (other)	3(60.0%)	2(28.6%)	5(41.7%)
Diabetic foot infection	0(0.0%)	0(0.0%)	0(0.0%)
Bacteremia	0(0.0%)	0(0.0%)	0(0.0%)
Other*	0(0.0%)	2(28.6%)	2(16.7%)

Table 15.1.0a.1.2 Indications for Tigecycline Use by Country and Site - Austria

	Before RMM (N=5)#	After RMM (N=7)#	Overall (N=12)#
Prophylactic Use of Tigecycline explicitly mentioned in the chart			
n	5	7	12
Yes	0(0.0%)	2(28.6%)	2(16.7%)
No	5(100.0%)	5(71.4%)	10(83.3%)
Missing	0	0	0
Infection Present at Admission			
n	5	7	12
Yes	4(80.0%)	7(100.0%)	11(91.7%)
No	1(20.0%)	0(0.0%)	1(8.3%)
Missing	0	0	0

cIAI=Complicated Intra-Abdominal Infection, cSSTI=Complicated Skin or Soft Tissue Infection, RMM=Risk Minimization Measure.
*Please refer to Listing 1 for further specification.
#Patients with age less than 18 years are not included.
Data cut-off date: 22May2014
Analysis dataset: A_DEMO
Created by Y:\Pfizer\Tygacil\Tables\Table1.0a.1.2.sas

Table 15.1.0a.1.3 Indications for Tigecycline Use by Country and Site - Greece

	Before RMM (N=1)#	After RMM (N=0)#	Overall (N=1)#
Site 1004			
cIAI	0(0.0%)		0(0.0%)
Intra-abdominal abscess	0(0.0%)		0(0.0%)
Perforated appendicitis	0(0.0%)		0(0.0%)
Perforated diverticulitis complicated by abscess formation or fecal contamination	0(0.0%)		0(0.0%)
Cholecystitis with evidence of perforation or empyema	0(0.0%)		0(0.0%)
Intestinal perforation (large or small intestine with abscess or fecal contamination)	0(0.0%)		0(0.0%)
Purulent or diffuse peritonitis or peritonitis associated with fecal contamination	0(0.0%)		0(0.0%)
Gastric ulcer perforation	0(0.0%)		0(0.0%)
Duodenal ulcer perforation	0(0.0%)		0(0.0%)
Traumatic bowel perforation	0(0.0%)		0(0.0%)
Primary peritonitis	0(0.0%)		0(0.0%)
Secondary peritonitis	0(0.0%)		0(0.0%)
Tertiary peritonitis	0(0.0%)		0(0.0%)
Other cIAI	0(0.0%)		0(0.0%)
cSSTI	0(0.0%)		0(0.0%)
Cutaneous ulcer	0(0.0%)		0(0.0%)
Burns	0(0.0%)		0(0.0%)
Major abscess	0(0.0%)		0(0.0%)
Cellulitis	0(0.0%)		0(0.0%)
Infected catheter site	0(0.0%)		0(0.0%)
Wound infection	0(0.0%)		0(0.0%)
Group A beta-hemolytic streptococcal gangrene	0(0.0%)		0(0.0%)
Necrotizing fasciitis	0(0.0%)		0(0.0%)
Fournier's gangrene	0(0.0%)		0(0.0%)
Ecthyma gangrenosum	0(0.0%)		0(0.0%)
Infected human or animal bites	0(0.0%)		0(0.0%)
Other cSSTI	0(0.0%)		0(0.0%)
Other	1(100.0%)		1(100.0%)
Hospital acquired pneumonia	0(0.0%)		0(0.0%)
Pneumonia (other)	0(0.0%)		0(0.0%)
Diabetic foot infection	0(0.0%)		0(0.0%)

Table 15.1.0a.1.3 Indications for Tigecycline Use by Country and Site - Greece

	Before RMM (N=1)#	After RMM (N=0)#	Overall (N=1)#
Bacteremia	0(0.0%)		0(0.0%)
Other*	1(100.0%)		1(100.0%)
Prophylactic Use of Tigecycline explicitly mentioned in the chart			
n	1		1
Yes	0(0.0%)		0(0.0%)
No	1(100.0%)		1(100.0%)
Missing	0		0
Infection Present at Admission			
n	1		1
Yes	1(100.0%)		1(100.0%)
No	0(0.0%)		0(0.0%)
Missing	0		0

cIAI=Complicated Intra-Abdominal Infection, cSSTI=Complicated Skin or Soft Tissue Infection, RMM=Risk Minimization Measure.
*Please refer to Listing 1 for further specification.
#Patients with age less than 18 years are not included.
Data cut-off date: 22May2014
Analysis dataset: A_DEMO
Created by Y:\Pfizer\Tygacil\Tables\Table1.0a.1.3.sas

Table 15.1.0a.1.3 Indications for Tigecycline Use by Country and Site - Greece

	Before RMM (N=14)#	After RMM (N=11)#	Overall (N=25)#
Site 1006			
cIAI	5(35.7%)	2(18.2%)	7(28.0%)
Intra-abdominal abscess	1(7.1%)	0(0.0%)	1(4.0%)
Perforated appendicitis	0(0.0%)	0(0.0%)	0(0.0%)
Perforated diverticulitis complicated by abscess formation or fecal contamination	0(0.0%)	0(0.0%)	0(0.0%)
Cholecystitis with evidence of perforation or empyema	1(7.1%)	0(0.0%)	1(4.0%)
Intestinal perforation (large or small intestine with abscess or fecal contamination)	0(0.0%)	0(0.0%)	0(0.0%)
Purulent or diffuse peritonitis or peritonitis associated with fecal contamination	0(0.0%)	0(0.0%)	0(0.0%)
Gastric ulcer perforation	0(0.0%)	0(0.0%)	0(0.0%)
Duodenal ulcer perforation	0(0.0%)	0(0.0%)	0(0.0%)
Traumatic bowel perforation	0(0.0%)	0(0.0%)	0(0.0%)
Primary peritonitis	0(0.0%)	0(0.0%)	0(0.0%)
Secondary peritonitis	0(0.0%)	0(0.0%)	0(0.0%)
Tertiary peritonitis	0(0.0%)	0(0.0%)	0(0.0%)
Other cIAI	3(21.4%)	2(18.2%)	5(20.0%)
cSSTI	4(28.6%)	7(63.6%)	11(44.0%)
Cutaneous ulcer	3(21.4%)	5(45.5%)	8(32.0%)
Burns	0(0.0%)	0(0.0%)	0(0.0%)
Major abscess	0(0.0%)	0(0.0%)	0(0.0%)
Cellulitis	1(7.1%)	0(0.0%)	1(4.0%)
Infected catheter site	0(0.0%)	0(0.0%)	0(0.0%)
Wound infection	0(0.0%)	1(9.1%)	1(4.0%)
Group A beta-hemolytic streptococcal gangrene	0(0.0%)	0(0.0%)	0(0.0%)
Necrotizing fasciitis	0(0.0%)	0(0.0%)	0(0.0%)
Fournier's gangrene	0(0.0%)	0(0.0%)	0(0.0%)
Ecthyma gangrenosum	0(0.0%)	0(0.0%)	0(0.0%)
Infected human or animal bites	0(0.0%)	0(0.0%)	0(0.0%)
Other cSSTI	1(7.1%)	1(9.1%)	2(8.0%)
Other	5(35.7%)	2(18.2%)	7(28.0%)
Hospital acquired pneumonia	0(0.0%)	0(0.0%)	0(0.0%)
Pneumonia (other)	1(7.1%)	0(0.0%)	1(4.0%)
Diabetic foot infection	0(0.0%)	0(0.0%)	0(0.0%)
Bacteremia	2(14.3%)	2(18.2%)	4(16.0%)
Other*	3(21.4%)	0(0.0%)	3(12.0%)

Table 15.1.0a.1.3 Indications for Tigecycline Use by Country and Site - Greece

	Before RMM (N=14)#	After RMM (N=11)#	Overall (N=25)#
Prophylactic Use of Tigecycline explicitly mentioned in the chart			
n	14		
Yes	0(0.0%)	0(0.0%)	0(0.0%)
No	14(100.0%)	11(100.0%)	25(100.0%)
Missing	0	0	0
Infection Present at Admission			
n	14	11	25
Yes	9(64.3%)	4(36.4%)	13(52.0%)
No	5(35.7%)	7(63.6%)	12(48.0%)
Missing	0	0	0

cIAI=Complicated Intra-Abdominal Infection, cSSTI=Complicated Skin or Soft Tissue Infection, RMM=Risk Minimization Measure.
*Please refer to Listing 1 for further specification.
#Patients with age less than 18 years are not included.
Data cut-off date: 22May2014
Analysis dataset: A_DEMO
Created by Y:\Pfizer\Tygacil\Tables\Table1.0a.1.3.sas

Table 15.1.0a.1.4 Indications for Tigecycline Use by Country and Site - UK

	Before RMM (N=166)#	After RMM (N=65)#	Overall (N=231)#
Site 1023			
cIAI	51(30.7%)	28(43.1%)	79(34.2%)
Intra-abdominal abscess	12(7.2%)	16(24.6%)	28(12.1%)
Perforated appendicitis	2(1.2%)	0(0.0%)	2(0.9%)
Perforated diverticulitis complicated by abscess formation or fecal contamination	6(3.6%)	0(0.0%)	6(2.6%)
Cholecystitis with evidence of perforation or empyema	3(1.8%)	0(0.0%)	3(1.3%)
Intestinal perforation (large or small intestine with abscess or fecal contamination)	9(5.4%)	4(6.2%)	13(5.6%)
Purulent or diffuse peritonitis or peritonitis associated with fecal contamination	3(1.8%)	1(1.5%)	4(1.7%)
Gastric ulcer perforation	1(0.6%)	0(0.0%)	1(0.4%)
Duodenal ulcer perforation	1(0.6%)	1(1.5%)	2(0.9%)
Traumatic bowel perforation	3(1.8%)	0(0.0%)	3(1.3%)
Primary peritonitis	2(1.2%)	1(1.5%)	3(1.3%)
Secondary peritonitis	5(3.0%)	5(7.7%)	10(4.3%)
Tertiary peritonitis	0(0.0%)	0(0.0%)	0(0.0%)
Other cIAI	4(2.4%)	2(3.1%)	6(2.6%)
cSSTI	13(7.8%)	13(20.0%)	26(11.3%)
Cutaneous ulcer	0(0.0%)	0(0.0%)	0(0.0%)
Burns	0(0.0%)	0(0.0%)	0(0.0%)
Major abscess	2(1.2%)	1(1.5%)	3(1.3%)
Cellulitis	4(2.4%)	4(6.2%)	8(3.5%)
Infected catheter site	0(0.0%)	0(0.0%)	0(0.0%)
Wound infection	6(3.6%)	7(10.8%)	13(5.6%)
Group A beta-hemolytic streptococcal gangrene	0(0.0%)	0(0.0%)	0(0.0%)
Necrotizing fasciitis	0(0.0%)	0(0.0%)	0(0.0%)
Fournier's gangrene	0(0.0%)	0(0.0%)	0(0.0%)
Ecthyma gangrenosum	0(0.0%)	0(0.0%)	0(0.0%)
Infected human or animal bites	0(0.0%)	1(1.5%)	1(0.4%)
Other cSSTI	1(0.6%)	0(0.0%)	1(0.4%)
Other	102(61.4%)	24(36.9%)	126(54.5%)
Hospital acquired pneumonia	1(0.6%)	1(1.5%)	2(0.9%)
Pneumonia (other)	1(0.6%)	1(1.5%)	2(0.9%)
Diabetic foot infection	5(3.0%)	2(3.1%)	7(3.0%)

Table 15.1.0a.1.4 Indications for Tigecycline Use by Country and Site - UK

	Before RMM (N=166)#	After RMM (N=65)#	Overall (N=231)#
Bacteremia	4(2.4%)	1(1.5%)	5(2.2%)
Other*	92(55.4%)	19(29.2%)	111(48.1%)
Prophylactic Use of Tigecycline explicitly mentioned in the chart			
n	166	65	231
Yes	5(3.0%)	1(1.5%)	6(2.6%)
No	161(97.0%)	64(98.5%)	225(97.4%)
Missing	0	0	0
Infection Present at Admission			
n	166	65	231
Yes	115(69.3%)	34(52.3%)	149(64.5%)
No	51(30.7%)	31(47.7%)	82(35.5%)
Missing	0	0	0

cIAI=Complicated Intra-Abdominal Infection, cSSTI=Complicated Skin or Soft Tissue Infection, RMM=Risk Minimization Measure.
*Please refer to Listing 1 for further specification.
#Patients with age less than 18 years are not included.
Data cut-off date: 22May2014
Analysis dataset: A_DEMO
Created by Y:\Pfizer\Tygacil\Tables\Table1.0a.1.4.sas

Table 15.1.0a.1.4 Indications for Tigecycline Use by Country and Site - UK

	Before RMM (N=2)#	After RMM (N=8)#	Overall (N=10)#
Site 1030			
cIAI	0(0.0%)	0(0.0%)	0(0.0%)
Intra-abdominal abscess	0(0.0%)	0(0.0%)	0(0.0%)
Perforated appendicitis	0(0.0%)	0(0.0%)	0(0.0%)
Perforated diverticulitis complicated by abscess formation or fecal contamination	0(0.0%)	0(0.0%)	0(0.0%)
Cholecystitis with evidence of perforation or empyema	0(0.0%)	0(0.0%)	0(0.0%)
Intestinal perforation (large or small intestine with abscess or fecal contamination)	0(0.0%)	0(0.0%)	0(0.0%)
Purulent or diffuse peritonitis or peritonitis associated with fecal contamination	0(0.0%)	0(0.0%)	0(0.0%)
Gastric ulcer perforation	0(0.0%)	0(0.0%)	0(0.0%)
Duodenal ulcer perforation	0(0.0%)	0(0.0%)	0(0.0%)
Traumatic bowel perforation	0(0.0%)	0(0.0%)	0(0.0%)
Primary peritonitis	0(0.0%)	0(0.0%)	0(0.0%)
Secondary peritonitis	0(0.0%)	0(0.0%)	0(0.0%)
Tertiary peritonitis	0(0.0%)	0(0.0%)	0(0.0%)
Other cIAI	0(0.0%)	0(0.0%)	0(0.0%)
cSSTI	1(50.0%)	1(12.5%)	2(20.0%)
Cutaneous ulcer	0(0.0%)	0(0.0%)	0(0.0%)
Burns	0(0.0%)	0(0.0%)	0(0.0%)
Major abscess	0(0.0%)	0(0.0%)	0(0.0%)
Cellulitis	0(0.0%)	0(0.0%)	0(0.0%)
Infected catheter site	0(0.0%)	0(0.0%)	0(0.0%)
Wound infection	1(50.0%)	1(12.5%)	2(20.0%)
Group A beta-hemolytic streptococcal gangrene	0(0.0%)	0(0.0%)	0(0.0%)
Necrotizing fasciitis	0(0.0%)	0(0.0%)	0(0.0%)
Fournier's gangrene	0(0.0%)	0(0.0%)	0(0.0%)
Ecthyma gangrenosum	0(0.0%)	0(0.0%)	0(0.0%)
Infected human or animal bites	0(0.0%)	0(0.0%)	0(0.0%)
Other cSSTI	0(0.0%)	0(0.0%)	0(0.0%)
Other	1(50.0%)	7(87.5%)	8(80.0%)
Hospital acquired pneumonia	0(0.0%)	3(37.5%)	3(30.0%)
Pneumonia (other)	0(0.0%)	0(0.0%)	0(0.0%)
Diabetic foot infection	0(0.0%)	0(0.0%)	0(0.0%)
Bacteremia	0(0.0%)	0(0.0%)	0(0.0%)
Other*	1(50.0%)	5(62.5%)	6(60.0%)

Table 15.1.0a.1.4 Indications for Tigecycline Use by Country and Site - UK

	Before RMM (N=2)#	After RMM (N=8)#	Overall (N=10)#
Prophylactic Use of Tigecycline explicitly mentioned in the chart			
n	2	8	10
Yes	0(0.0%)	1(12.5%)	1(10.0%)
No	2(100.0%)	7(87.5%)	9(90.0%)
Missing	0	0	0
Infection Present at Admission			
n	2	8	10
Yes	1(50.0%)	3(37.5%)	4(40.0%)
No	1(50.0%)	5(62.5%)	6(60.0%)
Missing	0	0	0

cIAI=Complicated Intra-Abdominal Infection, cSSTI=Complicated Skin or Soft Tissue Infection, RMM=Risk Minimization Measure.
*Please refer to Listing 1 for further specification.
#Patients with age less than 18 years are not included.
Data cut-off date: 22May2014
Analysis dataset: A_DEMO
Created by Y:\Pfizer\Tygacil\Tables\Table1.0a.1.4.sas

Table 15.1.0a.1.5 Indications for Tigecycline Use by Country and Site - Italy

	Before RMM (N=12)#	After RMM (N=0)#	Overall (N=12)#
Site 1002			
cIAI	6(50.0%)		6(50.0%)
Intra-abdominal abscess	3(25.0%)		3(25.0%)
Perforated appendicitis	0(0.0%)		0(0.0%)
Perforated diverticulitis complicated by abscess formation or fecal contamination	0(0.0%)		0(0.0%)
Cholecystitis with evidence of perforation or empyema	0(0.0%)		0(0.0%)
Intestinal perforation (large or small intestine with abscess or fecal contamination)	0(0.0%)		0(0.0%)
Purulent or diffuse peritonitis or peritonitis associated with fecal contamination	1(8.3%)		1(8.3%)
Gastric ulcer perforation	0(0.0%)		0(0.0%)
Duodenal ulcer perforation	0(0.0%)		0(0.0%)
Traumatic bowel perforation	0(0.0%)		0(0.0%)
Primary peritonitis	0(0.0%)		0(0.0%)
Secondary peritonitis	0(0.0%)		0(0.0%)
Tertiary peritonitis	0(0.0%)		0(0.0%)
Other cIAI	2(16.7%)		2(16.7%)
cSSTI	0(0.0%)		0(0.0%)
Cutaneous ulcer	0(0.0%)		0(0.0%)
Burns	0(0.0%)		0(0.0%)
Major abscess	0(0.0%)		0(0.0%)
Cellulitis	0(0.0%)		0(0.0%)
Infected catheter site	0(0.0%)		0(0.0%)
Wound infection	0(0.0%)		0(0.0%)
Group A beta-hemolytic streptococcal gangrene	0(0.0%)		0(0.0%)
Necrotizing fasciitis	0(0.0%)		0(0.0%)
Fournier's gangrene	0(0.0%)		0(0.0%)
Ecthyma gangrenosum	0(0.0%)		0(0.0%)
Infected human or animal bites	0(0.0%)		0(0.0%)
Other cSSTI	0(0.0%)		0(0.0%)
Other	6(50.0%)		6(50.0%)
Hospital acquired pneumonia	3(25.0%)		3(25.0%)
Pneumonia (other)	1(8.3%)		1(8.3%)
Diabetic foot infection	0(0.0%)		0(0.0%)

Table 15.1.0a.1.5 Indications for Tigecycline Use by Country and Site - Italy

	Before RMM (N=12)#	After RMM (N=0)#	Overall (N=12)#
Bacteremia	4(33.3%)		4(33.3%)
Other*	0(0.0%)		0(0.0%)
Prophylactic Use of Tigecycline explicitly mentioned in the chart			
n	12		12
Yes	0(0.0%)		0(0.0%)
No	12(100.0%)		12(100.0%)
Missing	0		0
Infection Present at Admission			
n	12		12
Yes	2(16.7%)		2(16.7%)
No	10(83.3%)		10(83.3%)
Missing	0		0

cIAI=Complicated Intra-Abdominal Infection, cSSTI=Complicated Skin or Soft Tissue Infection, RMM=Risk Minimization Measure.
*Please refer to Listing 1 for further specification.
#Patients with age less than 18 years are not included.
Data cut-off date: 22May2014
Analysis dataset: A_DEMO
Created by Y:\Pfizer\Tygacil\Tables\Table1.0a.1.5.sas

Table 15.1.0a.1.5 Indications for Tigecycline Use by Country and Site - Italy

	Before RMM (N=11)#	After RMM (N=19)#	Overall (N=30)#
Site 1017			
cIAI	7(63.6%)	12(63.2%)	19(63.3%)
Intra-abdominal abscess	3(27.3%)	4(21.1%)	7(23.3%)
Perforated appendicitis	0(0.0%)	0(0.0%)	0(0.0%)
Perforated diverticulitis complicated by abscess formation or fecal contamination	0(0.0%)	2(10.5%)	2(6.7%)
Cholecystitis with evidence of perforation or empyema	0(0.0%)	0(0.0%)	0(0.0%)
Intestinal perforation (large or small intestine with abscess or fecal contamination)	0(0.0%)	0(0.0%)	0(0.0%)
Purulent or diffuse peritonitis or peritonitis associated with fecal contamination	0(0.0%)	0(0.0%)	0(0.0%)
Gastric ulcer perforation	0(0.0%)	0(0.0%)	0(0.0%)
Duodenal ulcer perforation	0(0.0%)	0(0.0%)	0(0.0%)
Traumatic bowel perforation	0(0.0%)	0(0.0%)	0(0.0%)
Primary peritonitis	0(0.0%)	0(0.0%)	0(0.0%)
Secondary peritonitis	1(9.1%)	2(10.5%)	3(10.0%)
Tertiary peritonitis	0(0.0%)	0(0.0%)	0(0.0%)
Other cIAI	3(27.3%)	5(26.3%)	8(26.7%)
cSSTI	3(27.3%)	6(31.6%)	9(30.0%)
Cutaneous ulcer	1(9.1%)	2(10.5%)	3(10.0%)
Burns	0(0.0%)	0(0.0%)	0(0.0%)
Major abscess	0(0.0%)	0(0.0%)	0(0.0%)
Cellulitis	0(0.0%)	0(0.0%)	0(0.0%)
Infected catheter site	0(0.0%)	0(0.0%)	0(0.0%)
Wound infection	2(18.2%)	3(15.8%)	5(16.7%)
Group A beta-hemolytic streptococcal gangrene	0(0.0%)	0(0.0%)	0(0.0%)
Necrotizing fasciitis	0(0.0%)	1(5.3%)	1(3.3%)
Fournier's gangrene	0(0.0%)	0(0.0%)	0(0.0%)
Ecthyma gangrenosum	0(0.0%)	0(0.0%)	0(0.0%)
Infected human or animal bites	0(0.0%)	0(0.0%)	0(0.0%)
Other cSSTI	0(0.0%)	0(0.0%)	0(0.0%)
Other	1(9.1%)	1(5.3%)	2(6.7%)
Hospital acquired pneumonia	0(0.0%)	0(0.0%)	0(0.0%)
Pneumonia (other)	0(0.0%)	0(0.0%)	0(0.0%)
Diabetic foot infection	0(0.0%)	0(0.0%)	0(0.0%)
Bacteremia	0(0.0%)	1(5.3%)	1(3.3%)
Other*	1(9.1%)	0(0.0%)	1(3.3%)

Table 15.1.0a.1.5 Indications for Tigecycline Use by Country and Site - Italy

	Before RMM (N=11)#	After RMM (N=19)#	Overall (N=30)#
Prophylactic Use of Tigecycline explicitly mentioned in the chart			
n	11		
Yes	0(0.0%)	0(0.0%)	0(0.0%)
No	11(100.0%)	19(100.0%)	30(100.0%)
Missing	0	0	0
Infection Present at Admission			
n	11	19	30
Yes	2(18.2%)	5(26.3%)	7(23.3%)
No	9(81.8%)	14(73.7%)	23(76.7%)
Missing	0	0	0

cIAI=Complicated Intra-Abdominal Infection, cSSTI=Complicated Skin or Soft Tissue Infection, RMM=Risk Minimization Measure.
*Please refer to Listing 1 for further specification.
#Patients with age less than 18 years are not included.
Data cut-off date: 22May2014
Analysis dataset: A_DEMO
Created by Y:\Pfizer\Tygacil\Tables\Table1.0a.1.5.sas

Table 15.1.1 Indications for Tigecycline Use – On/Off Label Use – Primary Analysis Set (PAS) population

	Before RMM (N=373)	After RMM (N=314)	Overall (N=687)
On-Label Indications (cIAI or cSSTI in adult patients)	171(45.8%)	202(64.3%)	373(54.3%)
Off-Label Indications (other infection or use in pediatric patients)	202(54.2%)	112(35.7%)	314(45.7%)

cIAI=Complicated Intra-Abdominal Infection, cSSTI=Complicated Skin or Soft Tissue Infection, RMM=Risk Minimization Measure.
Data cut-off date: 22May2014
Analysis dataset: A_DEMO
Created by Y:\Pfizer\Tygacil\Tables\Table1.1.sas

Table 15.1.1a Sensitivity Analysis: Indications for Tigecycline Use – On/Off Label Use – Full Analysis Set (FAS) population

	Before RMM (N=399)	After RMM (N=378)	Overall (N=777)
On-Label Indications (cIAI or cSSTI in adult patients)	189(47.4%)	252(66.7%)	441(56.8%)
Off-Label Indications (other infection or use in pediatric patients)	210(52.6%)	126(33.3%)	336(43.2%)

cIAI=Complicated Intra-Abdominal Infection, cSSTI=Complicated Skin or Soft Tissue Infection, RMM=Risk Minimization Measure.
Data cut-off date: 22May2014
Analysis dataset: A_DEMO
Created by Y:\Pfizer\Tygacil\Tables\Table1.1a.sas

Table 15.1.1a.1 Indications for Tigecycline Use – On/Off Label Use by Country - Germany

	Before RMM (N=146)	After RMM (N=169)	Overall (N=315)
On-Label Indications (cIAI or cSSTI in adult patients)	82(56.2%)	126(74.6%)	208(66.0%)
Off-Label Indications (other infection or use in pediatric patients)	64(43.8%)	43(25.4%)	107(34.0%)

cIAI=Complicated Intra-Abdominal Infection, cSSTI=Complicated Skin or Soft Tissue Infection, RMM=Risk Minimization Measure.
Data cut-off date: 22May2014
Analysis dataset: A_DEMO
Created by Y:\Pfizer\Tygacil\Tables\Table1.1a.1.sas

Table 15.1.1a.1 Indications for Tigecycline Use – On/Off Label Use by Country - Austria

	Before RMM (N=43)	After RMM (N=58)	Overall (N=101)
On-Label Indications (cIAI or cSSTI in adult patients)	15(34.9%)	25(43.1%)	40(39.6%)
Off-Label Indications (other infection or use in pediatric patients)	28(65.1%)	33(56.9%)	61(60.4%)

cIAI=Complicated Intra-Abdominal Infection, cSSTI=Complicated Skin or Soft Tissue Infection, RMM=Risk Minimization Measure.
Data cut-off date: 22May2014
Analysis dataset: A_DEMO
Created by Y:\Pfizer\Tygacil\Tables\Table1.1a.1.sas