PASS information

Title	**A Post-Authorization Safety Study of the Use of Intravenous Telavancin (VIBATIV®) in the Clinical Setting**
Protocol version identifier	CLIN_2014_TLV_001 v2.0
Date of last version of protocol	FINAL 08 July 2014
EU PAS register number	To be confirmed; study will be registered upon approval of the protocol by EMA
Active substance	Telavancin ATC code: J01XA03
Medicinal product	Vibativ 250mg powder for concentrate for solution for infusion Vibativ 750mg powder for concentrate for solution for infusion
Product reference	Antibacterials for systemic use, glycopeptide antibacterials, EU/1/11/705/001 EU/1/11/705/002
Procedure number	EMEA/H/C/1240
Marketing authorisation holder(s)	Clinigen Healthcare Ltd.
Joint PASS	No

Research question and objectives	The objective of this study is to further characterize the adverse drug reaction profile of telavancin when used in the clinical setting.
	Primary objective
	The primary objective of this study is to assess changes in renal function during and after treatment with telavancin. Adverse events will be followed up and all efforts will be made to follow up serious and fatal AEs for at least 6 months.
	Secondary objectives
	Secondary objectives are to assess telavancin in the clinical setting with respect to:
	• Fatal outcomes (assessed for causality)
	• Cardiac disorders
	• Liver and hepatobiliary disorders
	• Tinnitus and hearing loss
	• Monitoring of efficacy of risk minimization measures in place, including
	  • Adherence to the SmPC including:
	  • Use in the recommended indication
	  • Avoidance of use in contraindicated conditions
	  • Correct initial dose and dose adjustment
	  • Renal monitoring, and
	  • Documentation of a negative pregnancy test in Women of child-bearing potential (WCBP)
	  • Use of the pregnancy checklist (sticker).

Country(-ies) of study	European Union. Centres will be selected based upon the first 500 patients treated with telavancin in Europe.
Author	Deborah Roberts MSc Clinical Project Manager Clinigen Group plc Pitcairn House, Crown Square, Centrum 100 Burton-on-Trent, Staffordshire, DE14 2WW **M** +44 7876 871617 **T** +44 1283 495010 **F** +44 1283 494341 **E** deborah.roberts@clinigengroup.com

Marketing authorisation holder(s)

Marketing authorisation holder(s)	Clinigen Healthcare Limited Pitcairn House, Crown Square, Centrum 100 Burton-on-Trent, Staffordshire, DE14 2WW **T** +44 1283 495010
MAH contact person	Deborah Roberts MSc Clinical Project Manager Clinigen Group plc Pitcairn House, Crown Square, Centrum 100 Burton-on-Trent, Staffordshire, DE14 2WW **M** +44 7876 871617 **T** +44 1283 495010 **F** +44 1283 494341 **E** deborah.roberts@clinigengroup.com

1. Table of contents

2. List of abbreviations

Abbreviations	Description of abbreviations
AE	Adverse Event
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase (GPT)
ARF	Acute Renal Failure
AST	Aspartate Aminotransferase (GOT)
AT	All patients treated
BMI	Body Mass Index
CE	Clinically Evaluable
CHMP	Committee for Human Medicinal Products
CrCl	Creatinine clearance
CRF	Electronic Case Report Form
CRO	Contract Research Organization
ECG	Electrocardiogram
EDC	Electronic Data Capture
EMA	European Medicines Agency
hGISA	heteroresistant glycopeptide intermediate *S. aureus*
GPvP	Good Pharmacovigilance Practice
GISA	glycopeptide intermediate *S. aureus*
GRSA	Glycopeptide-resistant *Staphylococcus aureus*
ICH GCP	International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use; Good Clinical Practice
ICU	Intensive Care Unit
ME	Microbiologically Evaluable
MAA	Marketing Authorization Application
MedDRA	Medical Dictionary for Regulatory Activities
MIC	Minimum Inhibitory Concentration
MRSA	Methicillin-resistant *Staphylococcus aureus*
MSSA	Methicillin-susceptible *Staphylococcus aureus*
MV	Mechanical Ventilation
NNIS	National Nosocomial Infections Surveillance
NP	Nosocomial pneumonia
PASS	Post-Authorization Safety Study
PSUR	Periodic Safety Update Report
RIFLE	Risk of renal dysfunction, Injury to the kidney, Failure of kidney function, Loss of kidney function and End-stage kidney disease
RNA	RiboNucleic Acid
SAE	Serious Adverse Event
SDV	Source Data Verification
SmPC	Summary of Product Characteristics
SOC	System Organ Class
SOP	Standard Operating Procedure
TLV	Telavancin
VAN	Vancomycin
VAP	Ventilator Associated Pneumonia
VISA	Vancomycin Intermediate *Staphylococcus aureus*
WCBP	Women of Child Bearing Potential

3. Responsible parties

24 Hour Pharmacovigilance contact	pharmacovigilance@Aptivsolutions.com or Fax +44 (0) 1442 500615
EU Medical Expert:	Professor Alan Boyd BSc MB ChB FFPM Chief Medical Officer Clinigen Group plc Pitcairn House, Crown Square, Centrum 100 Burton-on-Trent, Staffordshire, DE14 2WW Tel: +44 (0)1270 270010 Fax: +44 (0)1270 253832 Mobile: +44 (0)7899 873150 Alan.Boyd@clinigengroup.com
QPPV	Quentin Clarke MSc., BSc (hons) Head of EU Pharmacovigilance Aptiv Solutions 3 Glory Park Avenue, Wooburn Green Buckinghamshire HP10 0DF Tel: +44 1628 643973 Mobile: +44 7903 655076 Fax: +44 1628 643999 quentin.clarke@aptivsolutions.com
Clinical Research Contact:	Deborah Roberts MSc Clinical Project Manager Clinigen Group plc Pitcairn House, Crown Square, Centrum 100 Burton-on-Trent, Staffordshire, DE14 2WW Mobile: +44 7876 871617 Tel: +44 1283 495010 Fax: +44 1283 494341 deborah.roberts@clinigengroup.com

4. Abstract

Title

A Post-Authorization Safety Study of the Use of Intravenous Telavancin (VIBATIV®) in the Clinical Setting;

Version and date of protocol	CLIN_2014_TLV_001 v0.1
Name and affiliation of author	Deborah Roberts, Clinical Project Manager, Clinigen Group plc.

Rationale and background

VIBATIV®(telavancin) is an antibiotic which has been approved for the treatment of adults with nosocomial pneumonia (NP) including ventilator-associated pneumonia (VAP), known or suspected to be caused by methicillin resistant *S. aureus* (MRSA). Telavancin should be used only in situations where it is known or suspected that other alternatives are not suitable. The experience with telavancin in Europe is limited to several hundreds of patients in clinical trials. This retrospective chart review is part of the Risk Management Program for telavancin and serves to further characterize the safety profile in the clinical setting, with special emphasis for the renal safety profile.

Research question and objectives

The objective of this study is to further characterize the adverse drug reaction profile of telavancin when used in the clinical setting.

Primary objective

The primary objective of this study is to assess changes in renal function during and after treatment with telavancin. Adverse Events (AEs) received will be followed up and all efforts will be made to follow up Serious Adverse Events (SAEs) for at least 6 months from first administration of telavancin. Any fatal AE/SAEs will be followed up to collect as much information as possible.

Secondary objectives

Secondary objectives are to assess telavancin in the clinical setting with respect to:

- Fatal outcomes (assessed for causality)
- Cardiac disorders
- Liver and hepatobiliary disorders
- Tinnitus and hearing loss
- Monitoring of efficacy of risk minimization measures in place
    - Adherence to the SmPC:
        - Use in the recommended indication
        - Avoidance of use in contraindicated conditions
        - Correct initial dose and dose adjustment
        - Renal monitoring, and
        - Documentation of a negative pregnancy test in women of child-bearing potential (WCBP)
    - Use of the pregnancy checklist (sticker)

Study design

This is a multi-centre, multi-national, post-marketing, retrospective chart review.

Population

The patient population will be from countries within the European Economic Area (i.e. those countries covered by the centralized Marketing Authorisation). Centres will be selected based upon sequential patients treated with telavancin in Europe, where the prescriber agrees to provide the information and data collection/validation is logistically feasible, until the data for 500 patients is collected.

Variables

SAFETY ASSESSMENTS

To investigate the risks of the following endpoints in order to further characterize the safety of telavancin with respect to:

- Renal disorders (e.g., increased serum-creatinine, nephrotoxic co- medications, serum creatinine greater than 50% above baseline, serum creatinine greater than 100% above baseline, urine output, need for renal replacement therapy, classification according to RIFLE criteria, time course, outcome (resolution or not), risk factors for the development of renal impairment and renal function before start of telavancin therapy. Cofactors for renal impairment for which the medical history will be checked are:
    - Hypertension
    - Cardiac disease
    - Diabetes type I or type II
    - Renal disorders.

- Fatal outcomes (all-cause mortality), including cause of death
- Cardiac disorders (e.g., ECG changes)
- Liver and hepatobiliary disorders (e.g., liver function [ALT, AST, ALP and total bilirubin])
- Hearing losses and tinnitus
- Adherence to the SmPC:
    - Indication
    - All contra-indications
    - Initial dosage
    - Dose adjustments
    - Renal monitoring
    - Infusion duration at least 1 hour
    - Caution in case of QT-prolonging concomitant medication
    - patients developing signs or symptoms of impaired hearing
    - Detection and treatment of superinfection
    - antibiotic-associated colitis and pseudomembranous colitis
    - Appropriate additional antibacterial coverage in case of mixed infections
    - Documentation of negative pregnancy test in WCBP

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- Dosage and duration of treatment
- Microbiological outcome (eradication) for patients with a positive baseline isolate

Charts will be reviewed for any follow-up visits up to 6 months after the end of treatment in order to determine the reversibility of the outcomes. This does not preclude further data collection after 6 months in accordance with the standard procedures for Serious Adverse Event (SAE) handling.

Data sources

Patient hospital charts and pharmacy records.

Study size

The planned number of patients is 500.

Data analysis

Data collected during the study will be summarized using descriptive statistics. Stratified analyses will be performed for the following sub-populations: Diabetes type I or type II, obese (BMI categories), age groups, indications (NP, off-label use)

Milestones (planned)

Start of data collection	December 2014
End of data collection	December 2016
Study progress report 1	May 2015
Study progress report 2	May 2016
Registration in the EU PASS register	study will be registered upon approval of the protocol by EMA
Final report of study results	December 2017

5. Amendments and updates

None

6. Milestones

Milestone	Planned date
Start of data collection	December 2014*
End of data collection	December 2016
Study progress report 1	May 2015^
Study progress report 2	May 2016^
<Registration in the EU PAS register>	study will be registered upon approval of the protocol by EMA
Final report of study results	December 2017

*6 months after the end of treatment of the first patient to receive telavancin.

^in line with PSUR submissions.

7. Rationale and background

Nosocomial pneumonia (NP) is a frequent complication in hospitalized patients. Available data suggest that NP occurs at a rate of between 5 to 10 cases per 1,000 hospital admissions. In one study, 2,402 Eurasian patients were prospectively enrolled in a study at a hospital ICU over a one year period [Alp et al, 2004]. 6.8% of patients developed NP. Of these individuals, 75.5% of cases

were ventilator-associated pneumonia (VAP), a condition defined as pneumonia occurring 48 to 72 hours after endotracheal intubation [Alp et al, 2004].
Studies have suggested that the incidence of NP increases as much as 6 to 21 times in patients who are mechanically ventilated. It is commonly reported that up to 25% of all ICU patients who receive mechanical ventilation (MV) develop clinical evidence of pneumonia [Masterton et al, 2008; Torres et al, 2009; CDC VAP guidance 2014].
A meta-analysis estimates that 10% to 20% of patients receiving more than 48 hours of mechanical ventilation (MV) will develop VAP [Chlebicki & Safdar, 2007]. A retrospective study conducted on a large US database reported an incidence of VAP of 9.3% in ICU patients requiring MV for more than 24 hours [Rello et al, 2002].
The median reported rate of pneumonia occurring among MV patients is over ten times higher than in non-ventilated patients in ICUs (34.4 cases versus 3.2 cases per 1,000 ICU days) [McEachern, 1998]. More than 50% of antibiotics prescribed are due to NP. Within the US, the National Nosocomial Infections Surveillance (NNIS) reported in 2008 that the median rate of VAP per 1,000 ventilator-days in NNIS hospitals ranged from 0.7 in paediatric medical-surgical ICUs to 8.3 in trauma ICUs. Median rates in cardiothoracic, neurosurgical, and surgical ICUs were 4.5, 4.5, and 3.4 respectively. Lower rates were reported for other units including coronary (1.2), medical (1.0), medical/surgical major teaching (2.3), and medical-surgical-all others (1.5). The highest pooled mean reported rate was for burn units (10.7) (median rate was not reported). In Canada, NP has recently been estimated to account for 2% of all ICU days at a rate of 10.6 cases per 1,000 ventilator days (95% CI, 5.1-16.1) [Muscedere et al, 2008].

VIBATIV®, containing telavancin, is an antibiotic which has been approved for the treatment of adults with NP including VAP, known or suspected to be caused by methicillin resistant *S. aureus* (MRSA). Telavancin should be used only in situations where it is known or suspected that other alternatives are not suitable.

Mechanism of action
Telavancin exerts concentration-dependent bactericidal activity against susceptible Gram-positive bacteria. Telavancin inhibits cell wall biosynthesis by binding to late-stage peptidoglycan precursors, including lipid II, which prevents polymerization of the precursor into peptidoglycan and subsequent cross-linking events. Telavancin also binds to bacterial membranes and causes depolarization of membrane potential and an increase in membrane permeability that results in inhibition of protein, RNA, and lipid synthesis.

S. aureus that exhibit high level resistance to glycopeptide antibacterial agents (i.e., GRSA) are not susceptible to telavancin. There is no known cross-resistance between telavancin and other non-glycopeptide classes of antibiotics.

Breakpoints
The minimum inhibitory concentration (MIC) breakpoints are as follows:

Pathogen	**MIC (µg/ml)**
S. aureus (including methicillin-resistant strains)	≤1*

*this is the current approved breakpoint. A change in methodology and consequential change in breakpoint was proposed to EUCAST in November 2013, therefore this is subject to change.

Microbiological susceptibility
The prevalence of acquired resistance may vary geographically and with time for selected species and local information on resistance is desirable, particularly when treating severe infections. In

general, expert advice should be sought when the local prevalence of resistance is such that the utility of the agent in at least some types of infections is questionable.

Clinical efficacy and safety
Telavancin demonstrated efficacy against methicillin-susceptible *S. aureus* (MSSA) and MRSA in two randomized controlled studies in patients with NP, including VAP, involving 751 patients who received telavancin. Despite *in vitro* susceptibility, there are insufficient clinical data to assess the potential for efficacy of telavancin in infections due to heteroresistant glycopeptide intermediate *S. aureus* / glycopeptide intermediate *S. aureus* (hGISA/GISA).

Paediatric population
Telavancin has not yet been studied in paediatric patients. The European Medicines Agency (EMA) has deferred the obligation to submit the results of studies with telavancin in one or more subsets of the paediatric population in NP. There are no data on file regarding paediatric use of telavancin.

Clinical Studies of Telavancin in Nosocomial Pneumonia
Telavancin demonstrated clinical efficacy comparable to vancomycin in two large clinical trials (0015 and 0019) of NP infections caused by Gram-positive pathogens of which more than 40% were MRSA and more than 25% were MSSA.
Telavancin also showed efficacy advantages compared with vancomycin in various subgroups of NP patients, including single Gram-positive pathogens, *S. aureus*, VAP, Vancomycin Intermediate *S. aureus* (VISA) and these are summarised in Table 1.

Table 1: Cure Rates of Telavancin (TLV) and Vancomycin (VAN) in Subgroups of Patients with NP and VAP in Studies 0015 and 0019

Subgroup	Population	Cure Rate		95% CI
		TLV	VAN	
All Patients[1]	AT	441/749 59%	449/754 60%	-0.7% -5.6%, 4.3%
Single Gram-positive pathogen at baseline[2]	ME	139/164 85%	125/165 76%	8.9% 0.3% – 17.5%
***S. aureus* (either MRSA or MSSA)**[3]	ME	123/146 84%	113/152 74%	10.0% 0.7% – 19.2%
MRSA[2]	ME	72/88 82%	86/116 74%	7.9% -3.5% – 19.3%
MSSA[2]	ME	51/58 88%	27/36 75%	12.2% -4.2% – 28.8%
***S. aureus* with VAN MIC ≥ 1 mg/L**[4]	ME	74/85 87%	78/105 74%	12.8% 1.8% – 23.8%
VAP[5]	ME	50/64 78%	33/54 61%	17.5% 0.3% – 32.7%
Late-onset VAP[6]	ME	46/58 79%	27/46 59%	21.1% 2.5% – 37.2%

1. Section 2.7.3 of MAA, Table 48; 2. Section 2.7.3 of MAA, Table 54; 3; Rubenstein 2008 ; 4. Section 2.7.3 of MAA, Table 3.2.1, Table 63; 5. Section 2.7.3 of MAA, Table 85; 6. Table 1.2 for the Target Population; 6. Section 2.7.3 of MAA, Table 48
AT: all patients treated; ME: patients in the clinically evaluable population who have a confirmed Gram- positive pathogen recovered from respiratory specimens or blood cultures at baseline that was not resistant to either study medication. Table reproduced from registration dossier.

Table 2 depicts clinical response for patients in the Target Population who had an MRSA infection. Telavancin and vancomycin had similar cure rates in both the AT and microbiologically evaluable Target Populations when the studies are combined as well in study 0015 and in study 0019. In Study 0015, telavancin had a numerically greater efficacy than vancomycin in the Clinically Evaluable

(microbiologically evaluable) Target Population (Cure rates: 82% telavancin versus 76% vancomycin).

Table 2: Clinical Response at Test-of-Cure – Studies 0015 and 0019, Target Populations for NP with MRSA Infection

	Number of Patients					
	0015		0019		Total	
	TLV n/N (%)	VAN n/N (%)	TLV n/N (%)	VAN n/N (%)	TLV n/N (%)	VAN n/N (%)
AT Target Population						
Cure	58/ 96 (60)	55/ 92 (60)	56/ 101 (55)	53/ 98 (54)	114/ 197 (58)	108/ 190 (57)
Difference (95% CI)	0.6% (-13.4%, 14.7%)		1.4% (-12.5%, 15.3%)		1.0% (-8.9%, 10.9%)	
CE Target Population*						
Cure	51/ 62 (82)	53/ 70 (76)	44/ 63 (70)	43/ 60 (72)	95/ 125 (76)	96/ 130 (74)
Difference (95% CI)	6.5% (-7.4%, 20.5%)		-1.8% (-18.0%, 14.4%)		2.5% (-8.1%, 13.1%)	

* CE and ME Target Populations are the same for patients with Gram-positive only at baseline
Note: clinically evaluable (CE) patients in the registration studies were patients who could be analyzed for efficacy based on clinical parameters. Microbiologically evaluable (ME) patients in addition had a baseline pathogen identified from respiratory specimens or blood cultures that was not resistant for the study drug.
Table reproduced from registration dossier.

8. Research question and objectives

Telavancin is related to vancomycin and teicoplanin but belongs to a new (sub) class the lipoglycopeptides. Nephrotoxicity, ototoxicity, overgrowth of non-susceptible microorganisms and leucopenia/thrombocytopenia which are known to be associated with vancomycin and teicoplanin are also considered identified or potential risks with telavancin.
The experience with telavancin in Europe is limited to several hundred patients in clinical trials. This retrospective chart review is part of the Risk Management Plan for telavancin and will serve to further characterize the safety profile in the clinical setting, with special emphasis on the renal safety profile.

Other potential risks that are investigated in this review programme are:

- Fatal outcomes
- Cardiac disorders, including prolongation of cardiac repolarization
- Liver and biliary disorders
- Tinnitus and hearing loss
- Adherence to the SmPC, including use in the recommended indication, avoiding use in contraindicated conditions, initial dose and dose adjustment, renal monitoring and documenting of a negative pregnancy test in women of childbearing potential (WCBP).

In order to avoid drug exposure during pregnancy, all WCBP need to have a negative pregnancy test before administration of telavancin. The negative pregnancy test result will be recorded in the patient's medical dossier.

For any pregnancy that nevertheless occurs during treatment with telavancin, a 'VIBATIV® Pregnancy Exposure Registry in the European Union' is in place.
In order to avoid or minimize nephrotoxicity, adequate fluid control and minimization of the use of concomitant nephrotoxic drugs play an important role. Close monitoring of serum creatinine as directed in the SmPC from start of telavancin treatment is important to be able to adjust the dose to the CrCl.
For an overview of all risk minimization measures and expected adverse reactions with telavancin, see sections 4.4 and 4.8 of the telavancin product information (see reference list).

Study Objectives
The objective of this study is to further characterize the adverse drug reaction profile of telavancin when used in the clinical setting.

Primary objective
The primary objective of this study is to assess changes in renal function during and after treatment with telavancin. Adverse Events (AEs) received will be followed up and all efforts will be made to follow up Serious Adverse Events (SAEs) for at least 6 months from first administration of telavancin. Any fatal AE/SAEs will be followed up to collect as much information as possible.
Secondary objectives
Secondary objectives are to assess telavancin in the clinical setting with respect to:

- Fatal outcomes (assessed for causality)
- Cardiac disorders
- Liver and hepatobiliary disorders
- Tinnitus and hearing loss
- Monitoring of efficacy of risk minimization measures in place, including
- Adherence to the SmPC including:
    - Use in the recommended indication
    - Avoidance of use in contraindicated conditions
    - Correct initial dose and dose adjustment
    - Renal monitoring, and
    - Documentation of a negative pregnancy test in WCBP
- Use of the pregnancy checklist (sticker).

9. Research methods

9.1. Study design

This is a multi-centre, multi-national, post-marketing, retrospective chart review. This design was selected because it is not possible to perform a comparator-controlled study, as the current license is restricted to use when 'other alternatives are not suitable'.
This design has been chosen in collaboration with the Committee for Human Medicinal Products (CHMP). Charts of 500 patients will be reviewed after the end of their treatment course with telavancin, irrespective of indication, dose, treatment duration or any patient characteristic.
As this is a non-interventional, retrospective chart review there will be no impact on hospital admission time or clinical procedures. Charts will be reviewed for the period of the patient's hospital admission through 6 months follow up. This will facilitate follow up of outcomes of interest, such as renal impairment, which may not be resolved at the time of patient discharge; any follow-up visits up to at least 6 months after the end of treatment or until resolution is observed will be included in the review. Charts for patients who do not show ongoing adverse effects will

also be reviewed for 6 months post-treatment to identify any latent effects.
Participating centres will be identified by orders placed for telavancin with Clinigen and will be approached using the contact details from the order. The centre will be invited to participate within one month of the order for telavancin. However, data collection will not commence until the patient is 6 months post-treatment, this ensuring that the review is retrospective.
AE reports which occur during or after telavancin treatment should be captured and reported directly to the relevant local authorities at the time of the event, or to the MAH, in line with the prescribing information in the pack. The reporting responsibility of the Sponsor in this retrospective study will only be to report to the relevant Competent Authorities any unreported AEs or SAEs which are found during the review.

9.2. Setting

The study population will consist of patients who have been treated with at least one dose of telavancin based upon a decision by their treating physician. The patients will be selected by follow-up of orders placed for telavancin with an invitation to the clinician to provide data for this PASS. This will continue until data for 500 subjects can be collected. Any refusals to provide data will be documented and assessed for potential of bias. The charts of patients treated with telavancin will be reviewed where the clinician is in agreement and where possible, irrespective of indication, dose or treatment duration. No patients will be excluded.
A patient chart is considered to be the complete patient file including all medical records of the patient concerning the hospitalization during which he or she was treated with telavancin, as well as the out-patient post-hospitalization follow-up notes. The chart includes physician's notes as well as ICU schemes, lab results and imaging study results and results of any other investigation performed during treatment with telavancin or in the follow-up period.

Inclusion Criteria
For this retrospective chart review, the only inclusion criterion is past treatment with telavancin.

Exclusion Criteria
For this study, there are no exclusion criteria. All patients receiving telavancin will be included, where the physician and/or the institution consents to providing data.
Note: Centres participating in this PASS cannot include any patients in other telavancin studies until the total number of 500 charts reviewed is reached. The design of the PASS (especially the assessment of use of telavancin according to the SmPC) is not compatible with treatment of a patient according to a clinical study protocol.

9.3. Variables

Primary Variable
To investigate the risks of the following endpoints in order to further characterize the safety of telavancin with respect to:

- Renal disorders (e.g., increased serum-creatinine, presence of potentially nephrotoxic co-medications as cofactors for renal impairment).

The frequency of renal impairment will be investigated, serum creatinine greater than 50% above baseline, serum creatinine greater than 100% above baseline, urine output, need for renal replacement therapy, classification according to RIFLE criteria [see Appendix 2]).
Other characteristics of renal impairment that are investigated are time course, outcome

(resolution or not), risk factors for the development of renal impairment and renal function before start of telavancin therapy.
Cofactors for renal impairment for which the medical history will be checked are:

- Hypertension
- Cardiac disease
- Diabetes type I or type II
- Renal disorders.

Secondary Variables
The following information will be collected:

- Fatal outcomes (all-cause mortality), including cause of death
  Twenty-eight day all-cause mortality and all mortality during treatment if treatment duration exceeds 28 days. Any autopsy reports will be collected if available
- Cardiac disorders (e.g., ECG changes)
  Prolongation of cardiac repolarization is an identified risk for telavancin and QT prolongation will be checked as well as any case of torsade de pointes.
- Liver and hepatobiliary disorders (e.g., liver function [ALT, AST, ALP and total bilirubin].
  Hepatotoxicity is a potential risk for telavancin. Increases in hepatic enzymes along with signs and symptoms of liver impairment will be recorded, in order to recognize any cases of drug-induced liver disorder.
- Hearing losses and tinnitus
  Ototoxicity is an identified risk for telavancin, although very few cases have been reported. Information to be collected will include a detailed overview of all medication administered to exclude contribution of other ototoxic drugs.
- Adherence to the SmPC is measured as follows: use in the recommended indication, avoiding use in contraindicated conditions, initial dose and dose adjustment, renal monitoring, and documenting a negative pregnancy test in women of childbearing potential (including a check of the efficacy of the prescriber checklist and use of the sticker).
  Adherence will be checked to:
  - Indication
  - All contra-indications
  - Initial dosage
  - Dose adjustments
  - Renal monitoring
    Available serum creatinine values will be recorded, especially values expected based on SmPC recommendations (prior to dosing, daily for days 1-5 and every 48-72 hours thereafter).
  - Other precautions
    - Infusion duration at least 1 hour
    - Caution in case of QT-prolonging concomitant medication, congenital long QT syndrome, known prolongation of the QTc interval, uncompensated heart failure or severe ventricular hypertrophy
    - Ear-nose-throat evaluation of patients developing signs or symptoms of impaired hearing
    - Detection and treatment of superinfection
    - Consideration of antibiotic-associated colitis and pseudomembranous colitis in patients presenting with diarrhoea during or shortly following treatment
    - Treatment with antibiotics assuring Gram negative coverage in case of (suspicion of) mixed infections.
  - Documentation of negative pregnancy test in WCBP.

OTHER ASSESSMENTS OF VARIABLES

- Dosage and duration of treatment
- Microbiological outcome (eradication) for patients with a positive baseline isolate (ME population), with overview of pathogens isolated.
- Demographics:
  - Age (on date of first dose of telavancin)
  - Sex
  - Race
  - Height and body weight (to calculate the BMI)
- Medical History – all relevant past and present conditions and surgical procedures will be recorded with the following conditions (if present) always recorded:
  - Diabetes Type I or Type II
  - Renal disorders
  - Cardiac disorders
  - Hepatic disorders
  - Hearing problems
  - Past history of related infectious disease
  - Immune suppression
- Diagnosis of the target disease, severity and duration of disease
  - Condition
  - Diagnosis date
  - Bacteria isolated (species name(s), MIC value(s)
  - Severity where possible APACHE II score [Knaus et al, 1987.] (See Appendix 3) or modified clinical pulmonary infection score [Fartoukh et al, 2003.] (See Appendix 4)
- In case of discontinuation of telavancin before the planned end of treatment: need for treatment with another antibiotic, generic name of that other antibiotic
- Has the patient received telavancin previously

Charts will be reviewed for any follow-up visits up to 6 months after the end of treatment in order to determine the reversibility of the outcomes. For example, to see if the renal function recovered of a patient who experienced ARF during treatment or if hearing recovered after discontinuation in a patient with hearing loss during telavancin treatment. This does not preclude further data collection after 6 months in accordance with the standard procedures for SAE handling.

9.4. Data sources

Data will be collected from patients' medical records and captured in an electronic database.

9.5. Study size

The planned number of patients is 500, based on the sample size calculation for the primary outcome of renal events. With the assumption, based on data from the phase 3 clinical trials, that 22% of patients will develop an increase in serum creatinine greater than 50% above baseline (SC50B), it can be said with 95% confidence, that a sample of 500 patients will provide at least 92 patients with SC50B events: that is, 83% or more patients from the expected 110 individuals (500

patients * 22% incidence) with SC50B will develop the event. The figure of 22% is based on the observed renal AE frequency in the clinical trial data for NP.

9.6. Data management

The physician or designee is responsible to ensure that all data in the CRFs and queries are accurate and complete and that all entries are verifiable with source documents. These documents should be appropriately maintained by the site. A patient chart is considered to be the complete patient file including all medical records of the patient concerning the hospitalization during which he or she was treated with telavancin, as well as the out-patient post-hospitalization follow-up notes. The chart includes physician's notes as well as ICU schemes, lab results and imaging study results and results of any other investigation performed during treatment with telavancin or in the follow-up period.
The physician or designee will enter data collected using a case report form (CRF). CRFs and any supporting documents should be available for review or retrieval at any given time.
The monitor should verify the data in the CRFs with source documents according to the Source Data Verification (SDV) plan and confirm that there are no inconsistencies between them.
Source data must be available at the site documenting the existence of study patients and to substantiate the integrity of the study data collected to be able to perform the retrospective chart review. All elements pertaining to the charts should be filed at the moment of review, e.g., all lab and imaging results, the discharge letter, etc. should be available.
Data management will be coordinated by the designated CRO on behalf of the sponsor in accordance with standard operating procedures (SOPs) for data management. All study specific processes and definitions will be documented by Data Management. CRF completion will be described in the CRF completion guidelines. Coding of medical terms and medications will be performed using MedDRA and World Health Organization Drug Reference List respectively.

9.7. Data analysis

In general, all demographic, efficacy and safety variables will be summarised using descriptive statistics and graphs as appropriate. Continuous variables will be summarised by mean, SD, median, minimum, maximum and number of patients. Categorical variables will be summarized using frequency tabulations. Individual data will be presented in patient listings. Medical history and prior and concurrent medications will be summarised and listed.

AEs will be classified using the MedDRA classification system. The simple frequency and rate per patient-unit time of AEs will be tabulated by System Organ Class (SOC) and MedDRA Preferred Term. SAEs (including those defined in Section 5.5 of the protocol), AEs leading to discontinuation of telavancin and AEs leading to death will be listed and summarised separately, again by SOC and Preferred Term.

Time to first occurrence of a given AE, time to discontinuation due to AE and time to death will be summarised graphically by Kaplan-Meier curves.

Any statistical tests performed (for example in multivariate regression analyses) will be assessed at a 2-sided significance level of 5% unless otherwise specified.

Details of analysis are documented in the Statistical Analysis Plan.

9.8. Quality control

The physician and the institution must accept monitoring and auditing by the sponsor or delegated CRO as well as inspections from relevant regulatory authorities. In these instances, they must provide all study-related records, such as source documents when they are requested by the sponsor monitors and auditors or regulatory authorities. The confidentiality of the patient's identities shall be well protected consistent with local and national regulations.

The sponsor is implementing and maintaining quality assurance and quality control systems with written SOPs to ensure that trials are conducted and data are generated, documented and reported in compliance with the protocol, ICH GCP, GPvP and applicable regulatory requirement(s).

9.9. Limitations of the research methods

Due to the study design, data captured will be those documented during normal clinical practice, therefore it is expected that not all data points detailed in the CRF will be available. Any missing data will not be retrievable. Due to the low incidence of some patient sub-sets, this will affect the statistical significance of the data analyses. Management of this variation is accounted for in the Statistical Analysis Plan.

The study population will consist of patients who have been treated with telavancin based upon a decision by their treating physician. In order to reduce selection bias, the patients will be selected by follow-up of all orders placed for telavancin with an invitation to the clinician to provide data for this PASS, where valid contact details are supplied. This will continue until data for 500 subjects can be collected. Any refusals to provide data will be documented and assessed for potential of bias. The charts of all patients treated with telavancin will be reviewed where the clinician is in agreement, irrespective of indication, dose, treatment duration. No patients will be excluded.

9.10. Other aspects

<u>Administration</u>

The sponsor will provide the physician and/or institution with the following:

- Study protocol (and amendments, as applicable)
- CRFs and SAE Report Worksheet
- Study File
- Study contract
- Approval of regulatory authority and all documents related to submission, if local regulations require.

In order to start the study, the physician and/or institution is required to provide the following documentation to the sponsor:

- Signed confidentiality agreement
- Executed Study Contract
- Notification letter to the Independent Ethics Committee (if required locally)
- Current Curricula Vitae of the physician (signed and dated, brief and in English)
- Laboratory normal reference ranges

At the end of the study, the sponsor is responsible for the collection of CRFs and other study documentation.

The physician will archive all study data (e.g., source data, copies of the CRFs, and the Study File)

and relevant correspondence. These documents are to be kept on file for the appropriate term determined by local regulation. It is recommended, however, that records be retained for at least five years in the event follow-up is necessary. The physician agrees to obtain the sponsor's agreement prior to disposal, moving, or transferring of any study-related records. The sponsor will archive and retain all documents pertaining to the study according to local regulations.
All data will be entered on CRFs supplied for each patient. Copies will be provided at the end of the study.

Protocol Amendment and/or Revision
Any changes to the study that arise after approval of the protocol must be documented as protocol amendments/substantial amendments and/or administrative changes/non-substantial amendments. The changes will become effective only after the approval of the sponsor, the physician, the regulatory authority.

10. Protection of human subjects

For a non-interventional study, like this retrospective chart review, the applicable regulations do not require prior approval by a central or local review board or ethics committee. The sponsor, however, will nevertheless submit the PASS protocol to concerned review boards or ethics committees for notification, if local regulations require.

This study will be performed in accordance with current applicable Good Pharmacovigilance Practice guidelines. This protocol has been approved by the CHMP.

This study is a retrospective chart review of a centrally-authorised product and therefore non-interventional in nature. Only data created during treatment and follow-up of the patient are available for collection in the study. No informed consent is needed according to the applicable regulations (Clinical Trial Directive 2001/20/EC), Data Protection Directive (95/46/EC) and the Guidelines for Good Pharmacoepidemiology Practices (GPP). No informed consent will be asked, since it would not allow the inclusion of all consecutive patients treated with telavancin in a participating centre and therefore risks causing bias to the results of the survey of use in the clinical setting.

The risk for the patient to “participate” in this study is absent. The treatment decision is taken by the physician and there are no investigations prescribed. Only the collected data are reviewed after the patient has completed treatment and has been seen for a visit to verify recovery (in accordance with local practice).
Individual patient medical information collected in the context of this study is considered confidential and disclosure of identifiable patient data to third parties is prohibited.

The sponsor shall not disclose any confidential information on patients obtained during the performance of their duties in the clinical study without justifiable reasons.

The sponsor affirms the patient's right to protection against invasion of privacy. Only a patient identification number will identify patient data retrieved by the sponsor. However, the sponsor requires the physician to permit the sponsor, sponsor's representative(s), the IRB/IEC and when necessary, representatives of the regulatory health authorities to review and/or to copy any charts relevant to the study.
The sponsor will not collect any patient identifiers such as names, initials or birth dates. The patients will be assigned a consecutive patient number, which will be recorded in the patient chart.

11. Management and reporting of adverse events/adverse reactions

Definition of Adverse Events (AEs)

AE Adverse Event

Any untoward medical occurrence in a patient or clinical trial subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment An adverse event can therefore be any unfavourable and unintended sign (e.g. an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to a medicinal product.

This PASS is designed to further characterize specific AEs of interest that require more extensive collection of information, both in the CRF as well as on the AE forms. These events are:

- Renal
- Cardiovascular
- Hepatic
- Hypersensitivity
- Sudden death

SADR Serious Adverse Drug Reaction

Any AE that is considered to be related to a medicinal product that at any dose (even if used outside the terms of the Summary of Product Characteristics)- :

- Results in death;
- Is life-threatening;
- Requires inpatient hospitalization or a prolongation of an existing hospitalization;
- Results in persistent or significant disability/incapacity;
- Is a congenital anomaly/birth defect;
- Is an otherwise significant medical event; that may not have resulted in any of the above outcomes, but based upon appropriate medical judgment, may have jeopardized the patient or subject, and may have required medical or surgical intervention to prevent one of the outcomes listed within this definition; or could be a suspected transmission via a medicinal product of an infectious agent.

Any suspected transmission via a medicinal product of an infectious agent is also considered a serious adverse reaction.

It should be noted that all serious adverse drug reactions considered to be related to telavancin should be reported to the competent authorities at the time of the event and in line with local country regulations. Any serious adverse reactions documented as part of this PASS will be reconciled with the telavancin safety database to ensure that they have been reported appropriately and in a timely manner. Any events that are found to have not been reported at the time of the event will be reported retrospectively.

Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the definition above. These events, including those that may result in disability, should also usually be considered serious. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse.

If a patient becomes pregnant during treatment, this should be collected and followed up as if it were an SAE. Refer to “Procedure in Case of Pregnancy” Section.

Criteria for Causal Relationship to the Study Drug (Telavancin)

AEs that fall under either "Possible" or "Probable" should be defined as "AEs whose relationship to the study drugs could not be ruled out".

Causal relationship to the study drug	Criteria for casual relationship
Not Related	A clinical event, including laboratory test abnormality, with a temporal relationship to drug administration, which makes a causal relationship improbable, and/or in which other drugs, chemicals or underlying disease provide plausible explanations.
Related	A clinical event, including laboratory test abnormality, with a reasonable time sequence to administration of the drug, unlikely to be attributed to concurrent disease or other drugs or chemicals, and which follows a clinically reasonable response on re-administration (rechallenge) or withdrawal (dechallenge).

Criteria for Defining the Severity of an Adverse Event

The following standard with 3 grades is to be used to measure the severity of AEs, including abnormal clinical laboratory values.

- Mild: No disruption of normal daily activities
- Moderate: Affect normal daily activities
- Severe: Inability to perform daily activities.

Note: The term “severe” is used to describe the intensity of the AE and should not be confused with the term “serious”.

Collection and Reporting of Adverse Events (AEs)

When treating a patient with a licenced medication the physician has a responsibility to report any adverse events in accordance with local requirements for marketed products. If an AE or SAE is documented on the PASS CRF, cross-checking will be carried out to ensure that the AE or SAE has been reported, if required. If there is no corresponding report found on the global pharmacovigilance database for telavancin, then the safety data collected as part of the PASS will be included in the pharmacovigilance database, and if the AE fulfils criteria for expedited reporting, will be reported also.

Should the treating physician become aware of an unreported AE in the process of collecting data for the PASS, then the information should be submitted as soon as possible (as per local regulatory requirements) and also by reporting to Clinigen safety: pharmacovigilance@Aptivsolutions.com or Fax to +44 (0) 1442 500615.

Follow-up to Adverse Events

Serious Adverse Events will be followed up according to standard procedures using specific follow-up questionnaires until resolution or until a stable situation is reached. It is anticipated that follow-up will cover a period of at least 6 months; longer in the case of any unresolved events.

Procedure in Case of Pregnancy

Any information supplied relating to a pregnancy whilst on treatment will also be included in the

'VIBATIV® Pregnancy Exposure Registry in the European Union'.

12. Plans for disseminating and communicating study results

Information concerning the study drug, patent applications, processes, unpublished scientific data and other pertinent information is confidential and remains the property of the sponsor. Details should be disclosed only to the persons involved in the approval or conduct of the study. The physician may use this information for the purpose of the study only. It is understood by the physician that the sponsor will use the information obtained during the retrospective chart review study in connection with the development of the drug and therefore may disclose it as required to other clinical physicians or to regulatory agencies. In order to allow for the use of the information derived from this retrospective chart review study, the physician understands that he/she has an obligation to provide the sponsor with all data obtained during the study.
The study will be considered for publication or presentation at (scientific) symposia and congresses. The physician will be entitled to publish or disclose the data generated at their respective institution only after allowing the sponsor to review all transcripts, texts of presentations, and abstracts related to the study at least 90 days prior to the intended submission for publication. This is necessary to prevent premature disclosure of data and is in no way intended to restrict publication of facts or opinions formulated by the physician. The sponsor will inform the physician in writing of any objection or question arising within 30 days of receipt of the proposed publication material.

13. References

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SIGNATURE PAGE

EU Medical Expert: Signature Print Name Date	Professor Alan Boyd BSc MB ChB FFPM Chief Medical Officer Clinigen Group plc Pitcairn House, Crown Square, Centrum 100 Burton-on-Trent, Staffordshire, DE14 2WW
QPPV Signature Print Name Date	Quentin Clarke_MSc., BSc (hons) Head of EU Pharmacovigilance Aptiv Solutions 3 Glory Park Avenue, Wooburn Green Buckinghamshire HP10 0DF
Clinical Research Contact: Signature Print Name Date	Deborah Roberts MSc Clinical Project Manager Clinigen Group plc Pitcairn House, Crown Square, Centrum 100 Burton-on-Trent, Staffordshire, DE14 2WW
Statistician: Signature Print Name Date	Kevin J Carroll, BSc, MSc, CStat, CSci, Honorary Senior Lecturer Managing Director, KJC Statistics Ltd, 1 Park Street, Macclesfield Cheshire, SK11 6SR, UK

Annex 1. List of stand-alone documents

Number	Document reference number	Date	Title
1	CLIN_2014_TLV_001_SAP v2.0	08July2014	Statistical Analysis Plan

Annex 2. ENCePP checklist for study protocols

See separate document

Annex 3. Additional information

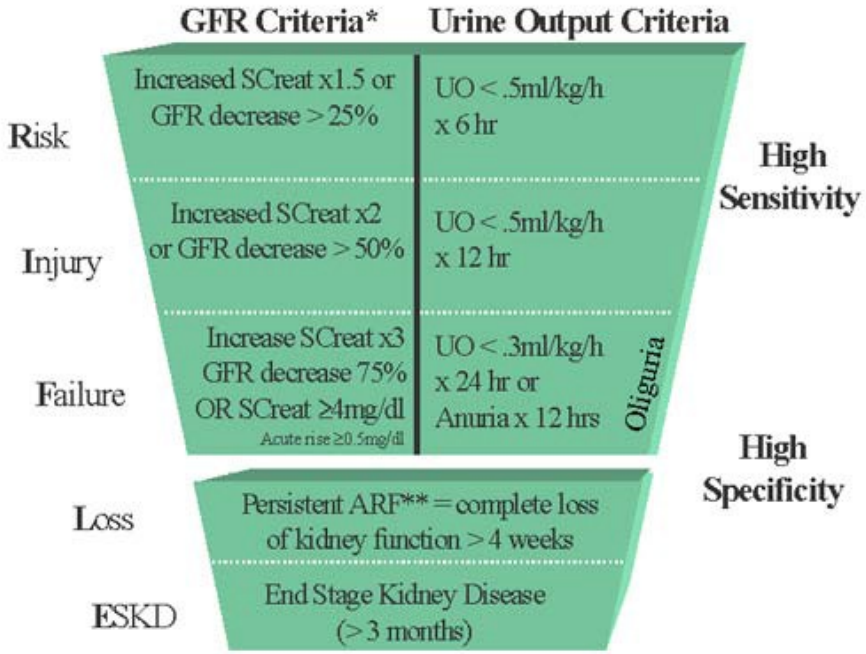
Appendix 1: Events To Be Always Considered Serious

If any of the following AEs occur during the study, they should be considered as serious AEs and reported as described in Section 5.5.

- acute liver failure
- acute renal failure
- acute respiratory failure
- agranulocytosis
- anaphylaxis
- any malignancy
- aplastic anemia
- confirmed or suspected endotoxin shock
- confirmed or suspected transmission of infectious agent by marketed product
- congenital anomalies
- liver necrosis
- malignant hypertension
- pulmonary fibrosis
- pulmonary hypertension
- sclerosing syndromes
- seizure (only central neurological seizure)
- torsades de pointes
- toxic epidermal necrolysis
- ventricular fibrillation

Appendix 2: Rifle Criteria

From Bellomo et al, 2004.



Proposed classification scheme for acute renal failure (ARF). The classification system includes separate criteria for creatinine and urine output (UO). A patient can fulfill the criteria through changes in serum creatinine (SCreat) or changes in UO, or both. The criteria that lead to the worst possible classification should be used. Note that the F component of RIFLE is present even if the increase in SCreat is under threefold as long as the new SCreat is greater than 4.0 mg/dl (350 µmol/l) in the setting of an acute increase of at least 0.5 mg/dl (44 µmol/l). The designation RIFLE-FC should be used in this case to denote 'acute-on-chronic' disease. Similarly, when the RIFLE-F classification is achieved by UO criteria, a designation of RIFLE-FO should be used to denote oliguria. The shape of the figure denotes the fact that more patients (high sensitivity) will be included in the mild category, including some without actually having renal failure (less specificity). In contrast, at the bottom of the figure the criteria are strict and therefore specific, but some patients will be missed.

*GFR = Glomerular Filtration Rate; **ARF = Acute Renal Failure

Appendix 3: Apache II Score

From Knaus et al, 1985.

The APACHE II Severity of Disease Classification System§

The APACHE II Severity of Disease Classification System§										
		High Abnormal Range					Low Abnormal Range			
	4	3	2	1	0	1	2	3	4	Points
Physiologic Variable										
Temperature – rectal (°C)	≥41°	39 to 40.9°		38.5 to 38.9°	36 to 38.4°	34 to 35.9°	32 to 33.9°	30 to 31.9°	≤29.9°	
Mean Arterial Pressure – mm Hg	≥160	130 to 159	110 to 129		70 to 109		50 to 69		≤49	
Heart Rate (ventricular response)	≥180	140 to 179	110 to 139		70 to 109		55 to 69	40 to 54	≤39	
Respiratory Rate(non-ventilated or ventilated)	≥50	35 to 49		25 to 34	12 to 24	10 to 11	6 to 9		≤5	
Oxygenation: A-aDO2 or PaO2 (mm Hg) a. FIO2 ³0.5 record A-aDO3	≥500	350 to 499	200 to 349		<200					
b. FIO2 <0.5 record PaO2					PO2>70	PO2 61 to 70		PO2 55 to 60	PO2<55	
Arterial pH (preferred)	≥7.7	7.6 to 7.69		7.5 to 7.59	7.33 to 7.49		7.25 to 7.32	7.15 to 7.24	<7.15	
Serum HCO3 (venous mEq/l) (not preferred, but may use if no ABGs)	≥52	41 to 51.9		32 to 40.9	22 to 31.9		18 to 21.9	15 to 17.9	<15	
Serum Sodium (mEq/l)	≥180	160 to 179	155 to 159	150 to 154	130 to 149		120 to 129	111 to 119	<110	
Serum Potassium (mEq/l)	≥7	6 to 6.9		5.5 to 5.9	3.5 to 5.4	3 to 3.4	2.5 to 2.9		<2.5	
Serum Creatinine (mg/dl) Double point score for acute renal failure	≥3.5	2 to 3.4	1.5 to 1.9		0.6 to 1.4		<0.6			
Hematocrit (%)	≥60		50 to 59.9	46 to 49.9	30 to 45.9		20 to 29.9		<20	
White Blood Count (total/mm3) (in 1000s)	≥40		20 to 39.9	15 to 19.9	3 to 14.9		1 to 2.9		<1	
Glasgow Coma Score (GCS): Score = 15 minus actual GCS										
A -Total Acute Physiology Score (sum of 12 above points)										
B - Age points (years) ≤44 = 0; 45 to 54 = 2; 55 to 64 =3; 65 to 74 = 5; ≥75 = 6										
C - Chronic Health Points (see below)										

Total APACHE II Score (add together the points from +B+C)			
Chronic Health Points: If the patient has a history of severe organ system insufficiency or is immunocompromised as defined below, assign points as follows:			
5 points for non-operative or emergency postoperative patients			
2 points for elective postoperative patients.			
Definitions : organ insufficiency or immunocompromised state must have been evident prior to this hospital admission and conform to the following criteria:			
Liver – biopsy proven cirrhosis and documented portal hypertension; episodes of past upper GI bleeding attributed to portal hypertension; ..			
or prior episodes of hepatic failure/encephalopathy/coma			
Cardiovascular – New York Heart Association Class IV.			
Respiratory – Chronic restrictive, obstructive, or vascular disease resulting in severe exercise restriction (i.e., unable to climb stairs or perform household duties);			
or documented chronic hypoxia, hypercapnia, secondary polycythemia, severe pulmonary hypertension (>40 mmHg), or respirator dependency			
Renal – receiving chronic dialysis.			
Immunocompromised – the patient has received therapy that suppresses resistance to infection			
(e.g., immunosuppression, chemotherapy, radiation, long term or recent high dose steroids,			
or has a disease that is sufficiently advanced to suppress resistance to infection, e.g., leukemia, lymphoma, AIDS).			
Interpretation of Score:			
0 to 4 = ~4% death rate	10 to 14 = ~15% death rate	20 to 24 = ~40% death rate	30 to 34 = ~75% death rate
5 to 9 = ~8% death rate	15 to 19 = ~25% death rate	25 to 29 = ~55% death rate	Over 34 = ~85% death rate

Appendix 4: Modified Pulmonary Infection Score

From Fartoukh et al, 2003.

THE MODIFIED CLINICAL PULMONARY INFECTION SCORE			
CPIS Points	0	1	2
Tracheal secretions	Rare	Abundant	Abundant + purulent
Chest X-ray infiltrates	No infiltrate	Diffused	Localized
Temperature, °C	≥ 36.5 and ≤ 38.4	≥ 38.5 and ≤ 38.9	≥ 39 or ≤ 36
Leukocytes count, per mm3	≥ 4,000 and ≤ 11,000	< 4,000 or >11,000	< 4,000 or >11,000 + band forms ≥ 500
PAO2/FIO2,mmHg	> 240 or ARDS		≤ 240 and no evidence of ARDS
Microbiology	Negative		Positive
Definition of abbreviations : ARDS = acute respiratory distress syndrome; CPIS = clinical pulmonary infection score.			
The modified CPIS at baseline was calculated from the first five variables (2).			
The CPIS gram and CPIS culture were calculated from the CPIS baseline score by adding			
two more points when gram stains or culture were positive.			
A score of more than six at baseline or after incorporating the gram stains (CPIS gram)			
or culture (CPIS culture) results was considered suggestive of pneumonia			