NON-INTERVENTIONAL POST AUTHORIZATION SAFETY STUDY (PASS) PROTOCOL

TITLE: Prospective, observational cohort, evaluating the incidence of nephrotoxicity, and other adverse events of interest, in patients treated with the higher recommended teicoplanin loading dose (12mg/kg twice a day), and comparison with external historical comparator data

COMPOUND: teicoplanin (TARGOCID® and associated names)

STUDY NUMBER: OBS13842

STUDY NAME: POSY-TEICO

The Study is conducted by Sanofi hereinafter referred also as the "MAH/MAH representative".

Version Number:	6		
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PASS Information

Title	*Prospective, observational cohort, evaluating the incidence of nephrotoxicity and other adverse events of interest in patients treated with the higher recommended teicoplanin loading dose (12 mg/kg twice a day), and comparison with external historical comparator data.*
Protocol version identifier	*6*
Date of last version of protocol	*11-Jun-2015*
EU PAS register number	*Study not registered*
Active substance	*teicoplanin* *Pharmacotherapeutic group: J01XA Glycopeptide antibacterials*
Medicinal product	*Targocid® and associated names*
Product reference	*to be completed at local level*
Procedure number	*DE/H/3916/001-003/MR ; DE/H/3918/001-003/MR ; DE/H/3917/001-003/MR*
Marketing authorization holder(s)	*sanofi-aventis* *to be completed at local level*
Joint PASS	*No*
Research question and objectives	*The safety data for the loading dose of 12 mg/kg bid is limited. The MAH has agreed to the request, made by the CHMP, to perform a post-authorization safety study (PASS) to evaluate the safety of teicoplanin in adult patients who are exposed to the higher loading dose of 12 mg/kg twice a day (24 mg/kg/day).* *The primary objective is to determine the incidence of nephrotoxicity reported in association with teicoplanin higher loading doses of 12 mg/kg twice a day, over the loading dose period (up to day -10). In addition, external historical comparison of nephrotoxicity incidence rates using teicoplanin lower loading dose and vancomycin literature data will be provided.*
Countries of study	*France, Italy, Germany, Austria*
Author	*Anca Rugina* *Clinical Study Director* *Sanofi R&D* *1, avenue Pierre Brossolette* *91385 CHILLY-MAZARIN*

Marketing authorization holder(s)

Marketing authorization holder(s)	*sanofi-aventis* *to be completed at local level*
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2 LIST OF ABBREVIATIONS

AE:	adverse event
ALT:	alanine aminotransferase
ARF:	acute renal failure
AST:	aspartate aminotransferase
bid:	twice a day
CAPD:	continuous ambulatory peritoneal dialysis
CHMP:	Committee on Human Medicinal Products
CI:	confidence interval
eCRF:	electronic case report form
EMA:	European Medicines Agency
EOS:	end of study
EOT:	end of treatment
FPIA:	fluorescence polarization immunoassay
HLGT:	high level group term
HLT:	high level term
HPLC:	high performance liquid chromatography
ICAC:	Independent Clinical Adjudication Committee
ICF:	informed consent form
ICH:	International Conference on Harmonisation
ICU:	intensive care unit
IEC:	Independent Ethics Committee
MAH:	Marketing Authorization Holder
MedDRA:	Medical Dictionary for Regulatory Activities
NA:	not applicable
PCSA:	potentially clinically significant abnormality
PRAC:	Pharmacovigilance Risk Assessment Committee
PT:	preferred term
SAE:	serious adverse event
SmPC:	Summary of Product Characteristics
SOC:	system organ class

3 RESPONSIBLE PARTIES

The **Scientific Expert** is responsible for coordinating the conduct of this multinational post-authorization safety study. He will be involved in the preparation and approval of the protocol and its amendment(s), will assess the progress of the study at both global and site level and is given full authority for presentation/publication of the results. The detailed responsibilities of the Scientific Expert, including his relationship with the other actors responsible for the management and conduct of the study, will be described in the Scientific Charter. This Charter will also describe details about the role of the scientific expert, the purpose and timing of meetings, and all other pertinent details.

The **Independent Clinical Adjudication Committee** (ICAC) is comprised of external clinicians with expertise in relevant clinical specialties who will assess all the study outcomes related to nephrotoxicity and the main safety concerns, as appropriate. Safety reports and relevant clinical documentation will be sent to the ICAC. The detailed responsibilities of the ICAC, its relationship with the other actors responsible for the management and conduct of the study, its membership, and the purpose and timing of meetings will be described in the Adjudication Charter and the Study Manual.

4 ABSTRACT

Title

Prospective, observational cohort, evaluating the incidence of nephrotoxicity and other adverse events of interest in patients treated with the higher recommended teicoplanin loading dose (12 mg/kg twice a day), and comparison with external historical comparator data.

Background

Teicoplanin is a glycopeptide antibiotic, marketed in Europe since 1988 (first approved for marketing in Italy as Targocid® on 30 July 1987), commonly used for the parenteral treatment of the following infections: complicated skin and soft tissue infections, bone and joint infections, hospital acquired pneumonia, community acquired pneumonia, complicated urinary tract infections, infective endocarditis, peritonitis associated with continuous ambulatory peritoneal dialysis (CAPD), bacteremia that occurs in association with any of the above indications. Teicoplanin is also indicated as an alternative oral treatment for *Clostridium difficile* infection-associated diarrhea and colitis (1).

An Article 30 referral procedure EMEA/H/A-30/1301 has been initiated in November 2011 in order to resolve divergences amongst the nationally authorized Summary of Product Characteristics (SmPC) for Targocid and associated names and thus to harmonize its divergent SmPCs across the EU. During the referral Article 30 procedure, the MAH proposed the loading dose of 12 mg/kg bid for severe infections based on Monte-Carlo simulations conducted by Yamada et al (2) suggesting that loading doses of 6 mg/kg bid for 3 administrations for most infections, and 12 mg/kg bid for 3 to 5 administrations should be considered for severe infections such as endocarditis, bone and joint infections. This loading dose of 12 mg/kg bid is currently recommended in the European harmonized SmPCs adopted by the Committee for Medicinal Products for Human Use (CHMP) within the Article 30 referral. A warning is included in sections 4.4 and 4.8 of the SmPC that patients should be especially monitored for adverse reactions when the higher dosage of 12 mg/kg bid is administered.

During this referral Article 30 procedure, a Post Authorization Safety Study (PASS) has been requested by the CHMP, endorsed by the European Commission (EC) on 12 September 2013, in order to evaluate the safety of the higher loading dose of Targocid 12 mg/kg bid (24 mg/kg/day), considering that the safety data available for this loading dose is limited. As a consequence of the referral evaluation, the agreed PASS is mentioned in the Annex IV of the European Commission decision (dated 12 September 2013) as a condition to the Marketing Authorization.

Subsequent to the EC Decision and according to the European regulatory procedure, in line with the conclusion of this referral procedure, the PASS protocol *"Prospective, observational cohort, non-comparative study describing the safety profile of the higher recommended teicoplanin loading dose of 12 mg/kg twice a day"* was submitted to the Pharmacovigilance Risk Assessment Committee (PRAC) on 21 October 2013.

The current version of the protocol provides updated information following the PRAC PASS protocol assessment report adopted on 19 May 2015.

Research question and objectives

The main objective of this study is to estimate the nephrotoxicity potential of the higher loading dose of teicoplanin, utilizing real world clinical practice data. The estimated incidence rates from this study will be further compared to external historical incidence rates for nephrotoxicity associated with vancomycin high dose and with teicoplanin lower loading doses from literature data, as requested by the PRAC.

Teicoplanin is characterized by a long elimination half-life (100 to 170 hours), therefore an initial loading procedure has been recommended to promptly achieve optimal plasma concentration (1). Different doses and intervals of administrations have been proposed to reach predefined targeted trough levels depending on the type of infection, the nature and the susceptibility of the pathogen and on the patient status. The higher loading dose of 12 mg/kg bid for 3 to 5 administrations, followed by 12 mg/kg once a day, is recommended to achieve targeted trough concentrations >20 mg/L (FPIA) in bone and joint infections and 30-40 mg/L (FPIA) in infective endocarditis and other severe infections (1) (2).

Teicoplanin exhibits tri-phasic plasma disposition profile (3) (4), with the first distribution phase, with $t_{1/2}$ of around 0.4-1 hours, occurring immediately after C_{max} and of short duration, the second distribution/elimination phase with $t_{1/2}$ of 5-15 hours occurring roughly up around 24 hours after dosing and the terminal elimination phase ($t_{1/2}$ of 80-170 hours) occurring roughly from 24 hours post-dose. Accordingly, for the BID or OD regimen, for the trough samples taken within a few hours before the next dose, limited variations in teicoplanin concentrations are expected given the predominant 2nd disposition phase, with $t_{1/2}$ of 5-15 hours, occurring over this period of time. Considerable variation in teicoplanin pharmacokinetic parameters has been reported, hence the lack of correlation between doses administered and the corresponding plasma concentrations (5) (6) (7).

The overall duration of treatment with teicoplanin has not been given precisely since it should be adjusted individually, according to the underlying type and severity of infection, the clinical response of the patient and patient factors such as age and renal function. For infective endocarditis, the CHMP considered that 21 days would be the minimum period of use, and that treatment beyond 4 months should be avoided. Duration of teicoplanin treatment in bone and joint infections from epidemiological data varies from 37.7 days (mean duration) to 4 months (in patients with osteo-synthesis devices) (8) (9).

The higher loading dose of 12 mg/kg bid has been proposed based on Monte-Carlo simulations conducted by Yamada et al (2) suggesting that loading doses of 6 mg/kg bid for 3 administrations for most infections, and 12 mg/kg bid for 3 to 5 administrations should be considered for severe infections such as endocarditis, bone and joint infections. This loading dose of 12 mg/kg bid is currently recommended in the European harmonized SmPCs. A warning is included in Sections 4.4 and 4.8 of the SmPC that patients should be especially monitored for adverse reactions when the higher dosage of 12 mg/kg bid is administered.

Since safety data for the loading dose of 12 mg/kg bid (24 mg/kg/day) is limited, the MAH has agreed to the request made by the CHMP, and endorsed by the European Commission on 12 September 2013, to perform a non-interventional post authorization safety study (PASS) to evaluate the safety of Targocid in adults with Gram-positive infections who are exposed to the higher loading dose of 12 mg/kg twice a day (24 mg/kg/day). Prospective collection of adverse events will allow a thorough evaluation of the safety profile of teicoplanin regimens. The data will be prospectively collected until teicoplanin treatment discontinuation and for 60 days after teicoplanin discontinuation.

Targocid and associated names will be referred to as teicoplanin across this document.

Study design

This study is a non-interventional prospective study, involving primary data collection, in which the data collected originate from routine clinical care.

This non-interventional study protocol fulfills the following requirements (10):

- the medicinal product is prescribed in the usual manner in accordance with the terms of the marketing authorization;
- the assignment of the patient to a particular therapeutic strategy is not decided in advance by a trial protocol, but falls within current practice and the prescription of the medicine is clearly separated from the decision to include the patient in the study; and
- no additional diagnostic or monitoring procedures are applied to the patients and epidemiological methods are used for the analysis of collected data.

Population

The study population consists of adults patients (≥18 years old) with infection types for which the higher loading dose of teicoplanin is approved, who are receiving a teicoplanin loading dose of 12 mg/kg twice a day (24 mg/kg/day), as prescribed by the treating physician.

Endpoints

The primary endpoint: incidence of nephrotoxicity reported in patients treated with teicoplanin over the loading dose period (up to Day -10 after treatment initiation).

All nephrotoxic events are evaluated as part of the primary endpoint.

Nephrotoxicity is defined as serum creatinine increase of more than 0.5 mg/dL if the baseline serum creatinine was ≤3 mg/dL or a rise of >1 mg/dL if the initial serum creatinine was >3 mg/dL, or 50% increase from baseline, or a drop in calculated creatinine clearance using Cockroft-Gault formula of ≥50% from baseline.

The secondary endpoints: the following safety endpoints will be evaluated:

- Nephrotoxicity (during the maintenance period and the entire study period)

- Hepatotoxicity defined as: AST or ALT times upper limit of normal or if AST or ALT baseline is abnormal, AST or ALT increase of ≥ 3 times the baseline and adverse events/reactions using the MedDRA SMQ "Hepatic Disorders"
- Thrombocytopenia, defined as: platelets <100 000/mm3 or <100 Giga/L
- Hearing and balance/vestibular disorders: identified via PT terms using MedDRA SMQ for "hearing and vestibular disorders" (narrow) and additionally the PT "balance disorder".
- Additional renal endpoints such as renal failure, dialysis and renal replacement therapy
- Adverse events/reactions

Data sources

Patient's original hospital records (eg, diagnostic tests results, discharge summaries, relevant hospital or clinic notes, autopsy reports) are the source documents for the data collected in this study. Information reported in the eCRF is compared with the original data from source documents in accordance with the study manual to ensure that the information collected is complete, accurate and valid.

The eCRF will allow for targeted data collection on the chosen endpoints, eg, the eCRF will ask for occurrence of hearing and balance/vestibular disorders at each visit, in addition to the other adverse events of interest.

Data collection and validation procedures are detailed in Data Management section.

Study size and duration

The sample size was calculated based on the primary evaluation criteria, the incidence of nephrotoxicity. According to previous studies (presented in Table 1, Annex 3), the incidence of nephrotoxicity associated with a high dose of vancomycin (through ≥15 mg/L) varied between 6.90% and 55.1%. Meta-analysis using random effects models estimated the incidence of nephrotoxicity associated with a high dose of vancomycin to be about 22%.

The sample size was determined based on a non-inferiority objective aimed at demonstrating that the incidence of nephrotoxicity with teicoplanin does not exceed vancomycin's by more than 5% (non-inferiority margin NI). The following assumption was made:

- Null hypothesis: H0: $p \leq p0 + NI$ (p0: historical reference incidence)
- Alternative hypothesis: H1: $p > p0 + NI$

If the upper boundary associated with the 95% two-sided confidence interval of the observed incidence is found to be <27% (ie, historical reference incidence + NI margin: 22+5), non-inferiority versus vancomycin will be claimed. Assuming a slightly better true incidence of 20% under teicoplanin, a sample size of 300 patients will provide 80% power to conclude to the non-inferiority.

The study consists of a loading dose period (up to 3 days), followed by a maintenance dose period (until teicoplanin discontinuation) plus the teicoplanin-free follow-up period (60 days).

The duration of the loading dose period was defined based on Targocid SmPC recommendation for the 12 mg/kg bid, ie, 3 to 5 administrations for severe infections such as endocarditis, bone and joint infections. The duration of the maintenance dose period will depend upon completion of the planned teicoplanin regimen duration for each individual patient. The duration of the follow-up period is defined as 60 days after the last administration of teicoplanin.

The study will be conducted in 4 European countries (France, Italy, Germany, and Austria). The estimated enrollment period is 2 years, which will allow for recruitment of 300 patients. The enrollment period may vary in different countries depending on the Independent Ethics Committee (IEC) process in each country.

Data analyses

The safety analyses will be performed on all patients who have been exposed to at least one dose of teicoplanin during the study.

Primary analysis

Incidence of nephrotoxicity over the loading dose period (up to day -10) will be computed with exact binomial 95% confidence interval. Multiple occurrences of nephrotoxicity in the same patient will be counted only once.

Comparison with external historical data for nephrotoxicity associated with high dose of vancomycin: Non-inferiority versus historical reference incidence of 22% (incidence associated with the high dose of vancomycin) will be claimed if the upper boundary associated with confidence interval of the observed incidence is found to be <27% (ie, historical reference incidence + NI margin: 22+5).

Comparison with external historical data for nephrotoxicity associated with lower loading dose of teicoplanin: The odds ratio for nephrotoxicity associated with a high dose versus a low dose of teicoplanin will be provided.

Secondary analysis

Incidence tables for secondary endpoints by study period (loading dose period, maintenance period and the entire study period) will be provided with 95% confidence intervals, if relevant.

An overall summary of events will be provided including the number and percentage of patients with any AE, any serious AE, any AE leading to death (death as an outcome on the AE CRF page as reported by the Investigator), and any AE leading to permanent teicoplanin discontinuation. Selected events will be analyzed using “time to first event” approach (Kaplan-Meier methodology). Time from the first administration to the first occurrence of the event will be calculated (only the first event will be counted). Kaplan-Meier curves will be provided.

Analysis of clinical laboratory data: Abnormalities in clinical laboratories will be summarized based on potentially clinically significant abnormality (PCSA) criteria and laboratory normal ranges. The following definitions will be applied to laboratory parameters (see Annex 3):

- PCSA values are defined as abnormal values considered medically important by the Sponsor according to predefined criteria/thresholds based on literature review and defined by the Sponsor for clinical laboratory tests.
- PCSA criteria will determine which patients had at least one treatment-emergent PCSA, taking into account all available evaluations.

Other analysis: Statistical analyses will be performed to evaluate the influence of baseline characteristics (age, gender, body mass index (BMI), creatinine clearance, concomitant medications, site of infection, severity of infection and type of center), number of teicoplanin loading doses, and trough serum concentration and treatment duration on the occurrence of adverse events/reactions through univariate subgroup analyses.

A logistic regression will be performed to evaluate covariates associated with the development of selected events.

An additional sensitivity analysis will be performed to evaluate the influence of covariates on the occurrence of nephrotoxicity, with known risk factors of nephrotoxicity forced in the model. Numerous epidemiologic studies have identified a number of baseline risk factors, acute clinical conditions, and diagnostic/therapeutic agents associated with the development of acute renal failure (ARF) in hospitalized patients. The established risk factors in the development of ARF, in-hospital patients, identified in recent scientific published literature (11) (12) (13) are presented in Annex 3. Details of this model are presented in Section 10.7.8.

Sensitivity analysis will be provided on population of patients receiving “at least one high loading dose” and on population of patients receiving “high loading dose duration of 3-5 administrations”. Sensitivity analysis will be conducted for the primary endpoint related to missing data.

To allow for an assessment of the severity of disease, the Simplified Acute Physiology Score SAPS II scoring (14) (15) will be calculated based on data available within the first 24 hours after hospital admission (see Section 10.7.8).

In addition, to describe the relationship of teicoplanin serum concentration (trough) and occurrence of selected events, descriptive statistics and box plot of C_{trough} in patients meeting primary safety endpoints or secondary endpoints versus those not meeting these criteria will be provided.

External historical comparator

Incidence rates which will be used as external historical comparison data for the primary endpoint of nephrotoxicity associated with vancomycin high dose (>15 mg/L), and with teicoplanin lower loading dose of 6 mg/kg every 12 hours for 3 administrations- are provided in Table 1 and Table 2, respectively (Annex 3).

The systemic literature review identified 12 studies for nephrotoxicity associated with vancomycin high dose and 5 studies for nephrotoxicity associated with teicoplanin lower loading dose (16) (17) (18) (19) (20) (21) (22) (23) (24) (25) (26) (27) (28) (29) (30) (31) (32) (33) (34) (35) (36).

A meta-analysis was performed and the incidence of nephrotoxicity was estimated to be about 22% and 2% associated with high dose of vancomycin and with teicoplanin lower loading dose, respectively. Details of calculation of the historical reference incidence were detailed in Section 10.7.10.2.

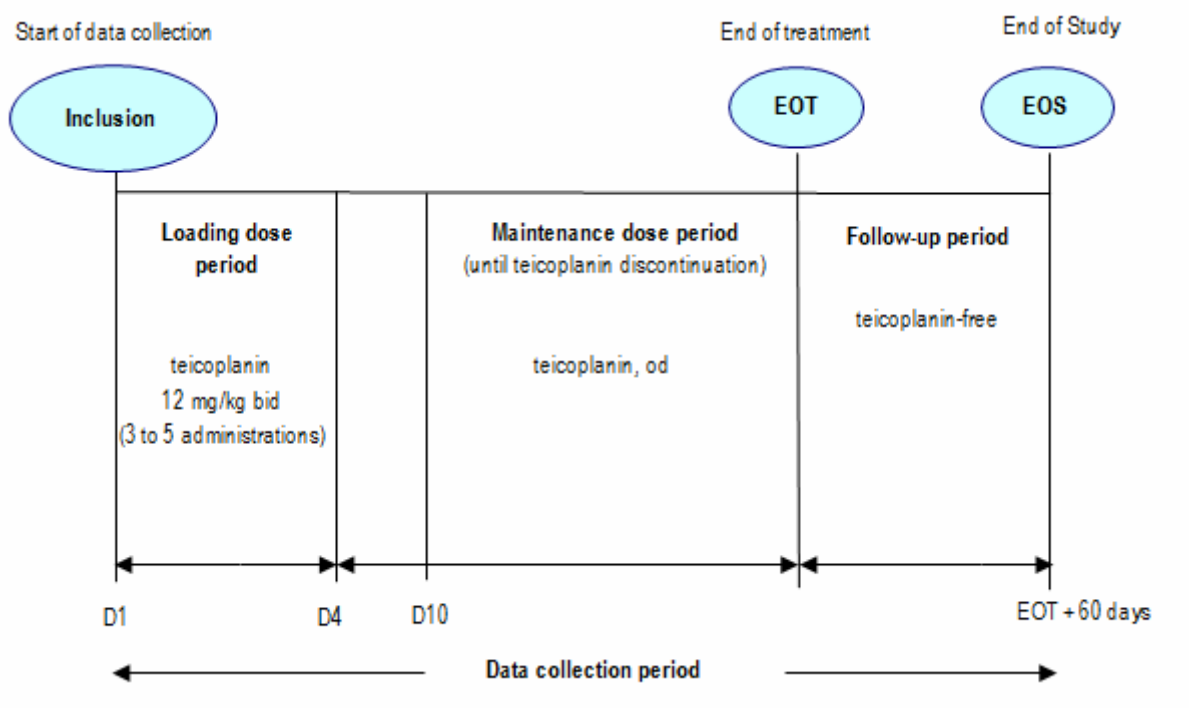
Milestones

The planned study timelines are as follows: Protocol Q3 2015; IEC approval Q4 2015; start of data collection Q1 2016; End of data collection Q3 2018; Final report of study results Q3 2019.

An interim analysis of the safety data, including an analysis of the progress of recruitment, will be performed when recruitment of 50% of the planned sample size population is achieved. The results of the interim analysis, including an analysis of the progress of recruitment, performed when recruitment of 50% of the planned sample size population is achieved, will be submitted to regular authorities as per requested timelines. Annual progress reports will be submitted.

5 STUDY FLOWCHARTS

5.1 GRAPHICAL CLINICAL TRIAL DESIGN



od = once daily

5.2 STUDY FLOWCHART FOR DATA COLLECTION

	Inclusion*	Loading dose period			Maintenance dose period		Follow-up period
	teicoplanin 12 mg/kg bid				teicoplanin, od		Post-treatment period 60 days
Day	1	2	3	4	10	EOT	EOS
Visit	1[a]	2[b]			3	4	5
Informed consent*	X						
Inclusion / Exclusion criteria	X						
Patient demography	X						
Previous medical / Surgical / Medical history	X						
Infection diagnosis / teicoplanin indication	X						
Date of hospitalization	X						
Adverse event recording	X----------						----------X
Physical examination: heart rate, temperature, systolic/diastolic blood pressure	X						
Clinical laboratories[c]	X	X			X	X	X
Prior/Concomitant medication	X	X			X	X	X
teicoplanin serum trough concentration		X			X	X	
teicoplanin prescription/administration: start date, end date, route, dose	X	X			X	X[d]	X
Patient status							X

* prior to patient data collection and to teicoplanin administration

a Visit 1 is defined as the baseline visit (D1), corresponding to patient's enrollment in the study; a window of +24h is allowed for the initiation of teicoplanin

b Visit 2 will take place at the end of the loading dose period (after completion of the loading dose regimen) and will collect data corresponding to the loading dosing. Depending on the number of loading doses administered, the loading dose period could vary from 1 to 3 days.

c Clinical laboratories: Biochemistry: creatinine, creatinine clearance, aspartate aminotransferase (AST), alanine aminotransferase (ALT), total bilirubin, albumin, urea, ; Hematology: WBC, platelet count, neutrophils, lymphocytes, monocytes, eosinophils, basophils; Other: urinary output 24 hours, PaO2, FIO2, Serum potassium and sodium, Serum bicarbonate

d The date of the end of teicoplanin treatment (last administration) will be collected at the end of the treatment period corresponding to the End of treatment visit (EOT) Visit 4. The End of Treatment (EOT, Visit 4) page will be completed at the last administration or/and in case of early discontinuation of teicoplanin.

NOTE: observational study: ie, only available data are collected

6 AMENDMENTS AND UPDATES

This protocol has been updated following PRAC PASS protocol assessment report of 19 May 2015.

7 MILESTONES

Milestone	Planned date
Final protocol	**Q3 2015**
Start of data collection	**Q1 2016**
End of data collection	**Q3 2018**
IEC approval	**Q4 2015**
Registration in the EU PAS register	DD Month YYYY
Final report of study results	**Q3 2019**

An interim analysis of the safety data, including an analysis of the progress of recruitment, will be performed when recruitment of 50% of the planned sample size population is achieved.

Annual progress report will be submitted.

8 RATIONALE AND BACKGROUND

8.1 BACKGROUND

Teicoplanin is a glycopeptide antibiotic, marketed in Europe since 1988 (first approved for marketing in Italy as Targocid on 30 July 1987), commonly used for the parenteral treatment of the following infections: complicated skin and soft tissue infections, bone and joint infections, hospital acquired pneumonia, community acquired pneumonia, complicated urinary tract infections, infective endocarditis, peritonitis associated with continuous ambulatory peritoneal dialysis (CAPD), and bacteremia that occurs in association with any of the above indications. Teicoplanin is also indicated as an alternative oral treatment for *Clostridium difficile* infection-associated diarrhea and colitis (1).

An Article 30 referral procedure EMEA/H/A-30/1301 has been initiated in November 2011 in order to resolve divergences amongst the nationally authorized Summary of Product Characteristics (SmPCs) for Targocid and associated names and thus to harmonize its divergent SmPCs across the EU. During the referral Article 30 procedure, the MAH proposed the higher loading dose of 12 mg/kg bid based on Monte-Carlo simulations conducted by Yamada et al (2), suggesting that loading doses of 6 mg/kg bid for 3 administrations is recommended for most infections, and 12 mg/kg bid for 3 to 5 administrations should be considered for severe infections such as endocarditis, bone and joint infections. This loading dose of 12 mg/kg bid is currently recommended in the European harmonized SmPCs adopted by the CHMP within the Article 30 referral. A warning is included in sections 4.4 and 4.8 of the SmPC that patients should be especially monitored for adverse reactions when the higher dosage of 12 mg/kg bid is administered.

During this referral Article 30 procedure, a Post Approval Safety Study (PASS) has been requested by the CHMP, endorsed by the European Commission (EC) on 12 September 2013, in order to evaluate the safety of the higher loading dose of Targocid 12 mg/kg bid (24 mg/kg/day), considering that the safety data available for this loading dose is limited. As a consequence of the referral evaluation, the agreed PASS is mentioned in the Annex IV of the European Commission decision (dated 12 September 2013) as a condition to the marketing authorization.

Subsequent to the EC Decision and according to the European regulatory procedure, in line with the conclusion of this referral procedure, the PASS protocol *"Prospective, observational cohort, non-comparative study describing the safety profile of the higher recommended teicoplanin loading dose of 12mg/kg twice a day"* was submitted to the Pharmacovigilance Risk Assessment Committee (PRAC) on 21 October 2013.

Further to the review of the updated PASS protocol, submitted on 26 June 2014 following to the first PRAC feedback in April 2014, the PRAC PASS protocol assessment report has been adopted on 11 September 2014.

The current version of the protocol provides updated information following the "PRAC PASS protocol assessment report" adopted on 19 May 2015. Considering the conditions to the marketing authorization, the proposed PASS is designed as an prospective observational study, to collect and evaluate the incidence of nephrotoxicity and other serious adverse events reported in association with the higher recommended Targocid and associated brand names loading dose (12 mg/kg twice a day), in real-world clinical practice conditions, as requested by the CHMP. In addition, external historical comparison data for nephrotoxicity will be provided, as requested.

8.2 RATIONALE

Teicoplanin is characterized by a long elimination half-life (100 to 170 hours), therefore an initial loading procedure has been recommended to promptly achieve optimal plasma concentration (1). Different doses and intervals of administrations have been proposed to reach predefined targeted trough levels depending on the type of infection, the nature and the susceptibility of the pathogen and on the patient status (1) (2). The higher loading dose of 12 mg/kg bid for 3 to 5 administrations, followed by 12 mg/kg once a day, is recommended to achieve targeted trough concentrations >20 mg/L (FPIA) in bone and joint infections and 30-40 mg/L (FPIA) in infective endocarditis and other severe infections (1).

Teicoplanin exhibits tri-phasic plasma disposition profile (3) (4), with the first distribution phase, with $t_{1/2}$ of around 0.4-1 hours, occurring immediately after C_{max} and of short duration, the second distribution/elimination phase with $t_{1/2}$ of 5-15 hours occurring roughly up around 24 hours after dosing and the terminal elimination phase ($t_{1/2}$ of 80-170 hours) occurring roughly from 24 hours post-dose. Accordingly, for the BID or OD regimen, for the trough samples taken within a few hours before the next dose, limited variations in teicoplanin concentrations are expected given the predominant second disposition phase, with $t_{1/2}$ of 5-15 hours, occurring over this period of time. Considerable variation in teicoplanin pharmacokinetic parameters has been reported, hence the lack of correlation between doses administered and the corresponding plasma concentrations (5) (6) (7).

The overall duration of treatment with teicoplanin has not been given precisely since it should be adjusted individually, according to the underlying type and severity of infection, the clinical response of the patient and patient factors such as age and renal function. For infective endocarditis, the CHMP considered that 21 days would be the minimum period of use, and that treatment beyond 4 months should be avoided. Duration of teicoplanin treatment in bone and joint infections from epidemiological data varies from 37.7 days (mean duration) to 4 months (in patients with osteo-synthesis devices) (8) (9).

The higher loading dose of 12 mg/kg bid has been proposed based on Monte-Carlo simulations conducted by Yamada et al (2) suggesting that loading doses of 6 mg/kg bid for 3 administrations for most infections, and 12 mg/kg bid for 3 to 5 administrations should be considered for severe infections such as endocarditis, bone and joint infections. This loading dose of 12 mg/kg bid is currently recommended in the European harmonized SmPCs. A warning is included in Sections 4.4 and 4.8 of the SmPC that patients should be especially monitored for adverse reactions when the higher dosage of 12 mg/kg bid is administered.

The safety data for the loading dose of 12 mg/kg bid (24 mg/kg/day) is limited; the MAH has agreed to the request made by the CHMP, and endorsed by the European Commission on 12 September 2013, to perform a non-interventional post authorization safety study (PASS) to evaluate the safety of Targocid in adults with Gram-positive infections who are exposed to the higher loading dose of 12 mg/kg twice a day (24 mg/kg/day).

The primary objective of this study is to estimate the nephrotoxicity potential of the higher loading dose of teicoplanin, based on real world clinical practice data. The estimated incidence rates from this study will be further compared to external historical incidence rates for nephrotoxicity associated with vancomycin high dose and with teicoplanin lower loading doses from literature data, as requested by the PRAC. The patient data will be prospectively collected until teicoplanin treatment discontinuation plus 60 days thereafter.

9 RESEARCH QUESTION AND OBJECTIVES

9.1 PRIMARY OBJECTIVE

The primary objective is to determine the incidence of nephrotoxicity reported in association with teicoplanin higher loading doses of 12 mg/kg twice a day, over the loading dose period (up to Day -10). All nephrotoxic events are evaluated as part of the primary endpoint.

9.2 SECONDARY OBJECTIVE

The secondary objective is to further evaluate the safety profile of teicoplanin in patients administered loading doses of 12 mg/kg bid, on the following endpoints:

- Incidence of nephrotoxicity (during the maintenance period and the entire study period)
- Incidence of hepatotoxicity (during the loading dose period, the maintenance period and during the entire study period)
- Incidence of thrombocytopenia (during the loading dose period, the maintenance period and during the entire study period)
- Incidence of hearing and balance/vestibular disorders (during the loading dose period, the maintenance period and during the entire study period)
- Additional renal endpoints such as renal failure, dialysis and renal replacement therapy (during the loading dose period, the maintenance period and during the entire study period)
- Incidence of adverse events/reactions (during the loading dose period, the maintenance period and during the entire study period).

10 RESEARCH METHODS

10.1 STUDY DESIGN

This study is a non-interventional, prospective cohort, study involving primary data collection, in which the data collected derive from routine clinical care.

The study operates under real-world clinical practice conditions ie, there are no imposed visits or procedures for the patients participating in the study and only the available data are collected. The decision regarding the teicoplanin treatment administered to the patients included in this study is taken prior to patient's enrollment and irrespective to his/her participation in the study. The study is meeting the following conditions (11):

- the medicinal product is prescribed in the usual manner in accordance with the terms of the marketing authorization
- the assignment of the patient to a particular therapeutic strategy is not decided in advance by a protocol but falls within current practice and the prescription of the medicine is clearly separated from the decision to include the patient in the study; and
- no additional diagnostic or monitoring procedures are applied to the patients and epidemiological methods are used for the analysis of collected data.

10.2 SETTING

10.2.1 Duration of the study

The estimated enrollment period is 2 years which will enable recruitment of the 300 patients. The enrollment period may vary in different countries depending on the IEC approval process in each country.

The study duration includes the loading dose period (up to 3 days), followed by a maintenance dose period until teicoplanin discontinuation and a follow-up period (60 days).

The duration of the loading dose period was defined based on Targocid' SmPC recommendation for the 12 mg/kg bid, ie, 3 to 5 administrations for severe infections such as endocarditis, bone and joint infections. The duration of the maintenance dose period will depend upon completion of the planned teicoplanin regimen duration for each individual patient. The duration of the follow-up period was defined as 60 days after the last administration of teicoplanin.

10.2.2 Eligibility criteria

The study population: adults, aged 18 years or older, with infection types for which the higher loading dose of teicoplanin is approved (as per SmPC) and for whom the treating physician intends to prescribe teicoplanin loading dosage 12 mg/kg twice a day .

Note: The severity of the infection is evaluated by the treating physician prescribing the appropriate teicoplanin regimen with reference to the drug SmPC.

10.2.2.1 Inclusion criteria

- Adult patients (aged 18 years or older), with infection types for which the higher loading dose of teicoplanin is approved (as per SmPC), who are prescribed teicoplanin loading doses of 12 mg/kg twice a day by the treating physician
- Agree to participate and sign the ICF (signed by the patient or by the patient's representative)

10.2.2.2 Exclusion criteria

- Age less than 18 years on the date of inclusion
- Patients with a history of hypersensitivity to teicoplanin (or to any of the excipients listed in SmPC or to vancomycin.

10.2.3 Analysis population(s)

The following population categories are defined:

- The *enrolled* population will consist of all patients who met the eligibility criteria and have a tracking number
- The *safety* population will consist of eligible patients who have signed the ICF and have been exposed to at least one dose of teicoplanin
- The *high dose treated* population will consist of eligible patients who have signed the ICF and have been exposed to at least one high loading dose of teicoplanin
- The *modified high dose* treated population will consist of eligible patients who have signed the ICF and have been exposed to ≥3 administrations of the high loading dose of teicoplanin.

10.2.4 Modalities of recruitment

10.2.4.1 Countries and Investigators selection

The Investigators will be selected by each country affiliate participating in this study.
The centers have been identified based on data issued from prescription records: centers with high usage of the higher loading dose of teicoplanin were contacted for selection. Investigators from 9 European countries were initially contacted. Only countries prescribing the higher dose of teicoplanin have been selected for participation in this study: Germany, Austria, Italy, and France.
The following wards have been identified as participating sites: Intensive care units, Infectious disease units and Septic surgery units.

The Investigators must be qualified by education, training, and experience to assume responsibility for the proper conduct of the study, will meet all the qualifications specified by the applicable regulatory requirements, and will provide evidence of such qualifications through up-to-date curriculum vitae and/or other relevant documentation requested by the sponsor, the IEC, and/or the regulatory authorities.

The Investigators should have available an adequate number of qualified staff and adequate facilities for the foreseen duration of the study. The Investigators will be selected among specialists that treat patients complying with inclusion and exclusion criteria within the selected hospitals.

10.2.4.2 Patient selection

All patients fulfilling the "inclusion / exclusion" criteria and willing to participate are eligible for the study. The enrollment will be done consecutively without any potential for selection bias. No additional selection criteria will be applied. (See Section 10.6.2.2 - Tracking log).

10.3 VARIABLES

10.3.1 Demographic and baseline characteristics

The baseline value is defined as the last available value before the first administration of teicoplanin.

Demographic characteristics

Demographic characteristics are age in years, gender (Male / Female), weight, height and body mass index (BMI) in kg/m², defined as weight (kg)/height2 (m) (quantitative and qualitative variable: <30, ≥30).

Physical examination

Physical examination includes heart rate, temperature and systolic blood pressure.

Current disease characteristics at baseline

Current disease characteristics include: the date of hospitalization and the indication having justified the administration of teicoplanin (infective endocarditis, bone and joint infections, other). The indications will be coded using the MedDRA dictionary (Medical Dictionary for Regulatory Activities) effective at the time of the database lock.

Relevant medical and surgical history

Medical and surgical history will be coded using the MedDRA dictionary.

Medical history includes:

- Underlying renal impairment (eg, chronic kidney insufficiency)

- Heart failure, hypotension, shock volume depletion, absolute or relative hypovolemia
- Chronic liver disease (eg, according to The Child-Pugh classification (36)
- General health status: arterial vascular disease, diabetes, rhabdomyolysis, sepsis, cardiac/vascular surgery, non-renal solid organ transplantation, abdominal compartment syndrome, mechanical ventilation, liver failure
- Hypoalbuminemia
- Glasgow coma score
- Metastasis cancer
- Hematologic malignancy
- AIDS
- Diabetes mellitus

Prior and concomitant medications

All medications taken within 1 month prior to the enrollment and until the end of the study (EOS) will be collected in the eCRF. All medications will be coded using the World Health Organization-Drug Dictionary (WHO-DD) using the version in effect at the time of the database lock.

Prior medications are those medications taken by the patient within 1 month prior to the first teicoplanin administration.

Concomitant medications are any treatments received by the patient from the first teicoplanin administration up to the end of study.

A given medication can be classified both as prior medication and concomitant medication.

Prior and concomitant medications of specific interest include:

- nephrotoxic agent intravenous contrast media, antimicrobial agents (eg, aminoglycosides, amphotericin B, and cyclosporine), antipyretic analgesics (NSAIDs)
- vasopressors
- loop diuretics
- chemotherapeutic agents

Site questionnaire

The site questionnaire will collect descriptive data about the type of investigative center. This includes type of center (eg, intensive care unit, general ward, etc), specialty, number of patients treated with teicoplanin per year, the type of admission (scheduled surgical/medical/unscheduled surgical), see Section 10.6.2.1.

10.3.2 Primary evaluation criteria

The primary evaluation criteria consist of nephrotoxicity defined as increase in serum creatinine more than 0.5 mg/dL if the baseline serum creatinine was ≤3 mg/dL or a rise of >1 mg/dL if the initial serum creatinine was >3 mg/dL, or 50% increase from baseline, or a drop in calculated creatinine clearance using Cockroft-Gault formula of ≥50% from baseline, reported in association with teicoplanin over the loading dose period (up to Day 10).

10.3.3 Secondary evaluation criteria

The secondary evaluation criteria are:

- Incidence of nephrotoxicity during the maintenance period and the entire study period
- Incidence of hepatotoxicity (AST or ALT ≥3 times upper limit of normal or if AST or ALT baseline is abnormal, AST or ALT increase of ≥ 3 times the baseline) during the loading dose period, the maintenance period and during the entire study period and adverse events/reactions recorded using the MedDRA SMQ "Hepatic Disorders"
- Incidence of thrombocytopenia (platelets <100 000/mm^3 or <100 Giga/L) during the loading dose period, the maintenance period and during the entire study period
- Incidence of Hearing and balance/vestibular disorders (identified via PT terms using MedDRA SMQ for "hearing and vestibular disorders" (narrow) and additionally the PT "balance disorder" during the loading dose period, the maintenance period and during the entire study period
- Additional renal endpoints such as renal failure, dialysis and renal replacement therapy will be included during the loading dose period, the maintenance period and during the entire study period
- Incidence of adverse events/reactions during the loading dose period, the maintenance period and during the entire study period.

All adverse events/reactions diagnosed by the investigator will be reported and described. Each AE will be coded to a "preferred term" (PT) and associated "high level group term" (HLGT), "high level term" (HLT) and single primary "system-organ class" (SOC) according to the MedDRA dictionary effective at the time of the database lock.

10.3.4 Other endpoints

The clinical laboratory safety data consist of blood analysis including:

- Hematology: hemoglobin, red blood cells, white blood cells, neutrophils, lymphocytes, monocytes, eosinophils, basophils, platelet count
- Chemistry: creatinine, creatinine clearance, aspartate aminotransferase (AST), alanine aminotransferase (ALT), total bilirubin, albumin, urea
- C_{trough} teicoplanin

Clinical laboratory values (local laboratory) from blood analysis will be analyzed after conversion into standard international units. International units will be used in all tables.

To allow for an assessment of the severity of disease, the Simplified Acute Physiology Score SAPS II scoring (see Annex 3) will be calculated based on data available within the first 24 hours after hospital admission. Description of this score is presented in Section 10.7.8.

10.4 DATA SOURCES

Patient's original hospital records (diagnostic tests results, discharge summaries, relevant hospital or clinic notes, autopsy reports) are the source documents for the data collected in this study. Information reported in the eCRF is compared with the original source documents in accordance with the study manual to ensure that the information collected is complete, accurate and valid.

Data collection and validation procedures will be detailed in the study manuals.

10.5 STUDY SIZE

10.5.1 Determination of sample size

The sample size was calculated based on the primary evaluation criteria, the incidence of nephrotoxicity. According to previous studies (presented in Table 1, Annex 3), the incidence of nephrotoxicity associated with a high dose of vancomycin (through ≥15 mg/L) varied between 6.90% and 55.1%. Meta-analysis using random effects models estimated the incidence of nephrotoxicity associated with a high dose of vancomycin to be about 22%.

The sample size was determined based on a non-inferiority objective aimed at demonstrating that the incidence of nephrotoxicity with teicoplanin does not exceed vancomycin one's by more than 5% (non-inferiority margin NI). The following assumption was made:

- Null hypothesis: H0: $p \leq p0 + NI$ (p0: historical reference incidence)
- Alternative hypothesis: H1: $p > p0 + NI$

If the upper boundary associated with the 95% two-sided confidence interval of the observed incidence is found to be <27% (i.e. historical reference incidence + NI margin: 22+5), non-inferiority versus vancomycin will be claimed. Assuming a slightly better true incidence of 20% under teicoplanin, a sample size of 300 patients will provide 80% power to conclude to the non-inferiority.

10.5.2 Sample size

It is planned to recruit 300 patients, in 4 European countries: France, Italy, Germany and Austria.

10.6 DATA MANAGEMENT

The patient data will be collected primarily from patient's hospital source dossiers by the Investigators or site personnel via eCRF. Information for additional consultations/explorations, laboratory results or hospital readmission during the study follow-up period will also be collected. If the Investigators delegate their responsibility for the eCRF completion to another person, the name, position of this person must be supplied to the sponsor to request a specific access with code for this person. A log-in and a password will be provided to all authorized eCRF users.

Data entry will be performed within 5 days after information is available. Completion guidelines will be released to provide instructions on how to report information in the eCRF.

Regarding the data validation, the specifications of the checks applied on the data are defined in the Data Validation Plan (DVP) including validation listings used for manual review.

Following the validation listings review, DRFs might be edited manually.

The validation plan follows Sanofi's standards and it contains not only the validation listings but all the checks that were deemed necessary for the project, by using either a traffic light code (to ensure the completion of requested fields) and edit checks that will trigger a query to the site if conditions are not met. These edit checks are validated by the programmer and the data manager by creating test cases: clean cases are created to ensure no queries are raised.

Data collection and validation procedures will be detailed in separate operational documents.

The study data will be stored on a specific server including the following specificities:

Dedicated Server and dedicated firewall hosted

- Redundant Internet Access (2 different operators)
- Uninterrupted power supply and generator
- Fire detection and protection by gas
- Zones with hierarchical access and access by badge, camera and record of images
- Same server as in CRO's office and dedicated physical firewall
- Antivirus updated every day
- VPN crypt 128 bits
- Remote crypt daily Safeguard, with data kept at a remote place
- Local daily safeguard. Complete restore if needed at state day -1

Note: This study operates under real-world clinical practice conditions, that is, only the available data are collected.

10.6.1 Data collection schedule

The Investigators will be asked to enter patient's data into the eCRF: at Inclusion Visit 1, Visit 2, Visit 3, Visit 4 end of treatment (EOT) and Visit 5 end of study visit (EOS). In case of early discontinuation and/or at the end of teicoplanin treatment, the End of Treatment page will be completed.

In line with clinical practice and to allow a more timely ascertainment of delayed effects of nephrotoxicity study Visit 3, on Day 10, has been included as well as, a post-treatment follow-up duration of 60 days after teicoplanin discontinuation.

Monitoring of serum concentrations: As per drug's labelling recommendations, teicoplanin trough serum concentrations should be monitored during the loading dose period and at steady state during the maintenance dose period (up to Day 10) in order to ensure that a minimum trough serum concentration has been reached: for endocarditis and other severe infections, teicoplanin trough levels of 15-30 mg/L when measured by HPLC, or 30-40 mg/L when measured by FPIA method.
Note: it is recommended that the same measurement method should be used for all time points for the same patient.

A particular attention should be given to the risk of nephrotoxicity during the study. Decision trees for the management of certain laboratory abnormalities are provided in Annex 3 - General Guidance for the follow-up of laboratory abnormalities.

The data to be collected at each visit is presented in the study flowchart for data collection, Section 5.2. The data will be collected by the Investigator or site personnel via electronic case report forms (eCRFs). The eCRFs will specify data elements of interest to be collected at baseline, during teicoplanin treatment, and during the follow-up period (60 days after the last dose). Patient data, including demographic characteristics, characteristics of infection, medical history and concomitant medication used at study entry, will be recorded on eCRFs. Teicoplanin use during the study will also be recorded on eCRFs. Adverse events/reactions will be collected on eCRFs throughout the entire study duration. Information for additional patient consultations or hospital readmission during the study follow-up period will also be collected.

No patient visits and/or laboratory tests other than the real clinical practice are required.

10.6.2 Data collected

10.6.2.1 Site/Investigator's questionnaire

Prior to the start of recruitment, a 1-page questionnaire will be completed by the main Investigator of each center, to collect the following information about the ward practice: type of center (eg, intensive care unit, general ward, etc); specialty; number of patients treated with teicoplanin per year, the type of admission (scheduled surgical/medical/unscheduled surgical).

10.6.2.2 *Tracking log*

A patient tracking log form will be implemented at each site to document the consecutive enrollment. The tracking log will be completed by the investigators (or designee) for any patient admitted to the ward for whom teicoplanin loading dose of 12 mg/kg twice a day has been prescribed. The following information will also be collected: date of the visit, reason for non-enrollment.

10.6.3 Patient data

The patient data are collected prospectively (a 5-day delay is accepted to enter the data in the eCRF) at Inclusion Visit 1, Visit 2, 3, 4 and at Visit 5. The data to be collected at each visit is presented in the study flowchart for data collection, Section 5.2.

Note: Written informed consent (ICF) from the patient or by his/her legal representative will be obtained prior to data collection. Patient's legally representative has to sign and the patient should also sign as soon as he/she is capable to do so.

10.6.4 Procedure for withdrawal of patients from study follow-up schedule

The Investigators will make every effort to re-contact the patient to determine his/her health status, including at least his/her vital status. Withdrawal from the study does not prevent the use of the data collected up to the date of withdrawal of the consent.

Withdrawal of consent must be understood as the request from the patient or his/her legally acceptable representative to withdraw from the study, with the possibility, based on local requirements, to exercise his right of opposition to transmission of the data to the sponsor or removal of data from the database. In such an occurrence, the investigator will inform, in writing, the study sponsor, and the sponsor will decide how to handle the subject data and samples based on local regulations and data privacy requirements.

Measures envisaged within the study to minimize lost-to-follow-up in the study follow-up period: For patients who do not return to the site during the study follow-up period, the Investigator should make all efforts to recontact the patient (eg, contacting patient's family or private physician, reviewing available registries or health care databases) and to determine his/her health status and outcome. Attempts to contact those patients will be documented in the patient's records (eg, times and dates of attempted telephone contact, receipt for sending a registered letter, etc). The following measures are proposed and will be applied depending on each country regulations: "thank you card" for patient acknowledging how important it is that they have allowed collection of their safety data; reminder messages, texts/SMS, sent by the investigator; letter explaining the importance of follow-up on specific parameters; collection of patient contact details such as phone number, email address, family contact; patient card with information on teicoplanin treatment and sponsor contact details in case of safety issues; appointment card with sections for notes the patient may want to use; support the site for identification of patients at risk for lost-to-follow-up, eg, patients living far, alone, lacking transportation, financial constraints, busy agenda, to enable retention strategy for each situation and maintain frequent contact with these patients.

10.6.5 Logistic aspects

NA.

10.7 DATA ANALYSIS

The safety analyses will be performed on all patients who have been exposed to at least one dose of teicoplanin during the study.
The safety analyses will be based on the reported adverse events/reactions (AEs) and clinical laboratory data.

Standard descriptive statistics will be used to summarize the data.

For continuous variables, the number of available data, mean, standard deviation, median and range (minimum, maximum) will be provided. Categorical variables will be summarized using number and percentage of patients. Patients with missing data will not be included in the calculation of percentages.

The descriptive analysis will be performed globally and by country. The logistic regression will be performed only globally due to limited sample size per country.

10.7.1 Disposition of patient

Disposition of patients will be depicted for patient status and patient analysis populations. The total number of patients for each of the following categories will be described:

- Enrolled patients
- Patients failed to be enrolled and the reason for non-enrollment
- Safety population
- High dose treated population
- Modified high dose treated population

The total number of patients enrolled, treated will be summarized by count and percentage using the number of screened patients as denominator.

The number of patients exposed, who have completed or prematurely discontinued the teicoplanin and the reasons for discontinuation will be summarized using the number of treated patients as denominator.

The incidence of premature treatment discontinuation (irrespective of the reason) and premature treatment discontinuation due to AEs will be presented graphically for the safety population, using Kaplan-Meier method.

10.7.2 Demographic and baseline characteristics

All demographic and baseline characteristics will be summarized for the safety population using descriptive statistics.

Medical history (see Section 10.3.1) will be summarized using counts and percentages.

10.7.3 Prior and concomitant treatment

The prior and concomitant medications will be presented for the Safety population.

Medications will be summarized according to the WHO-DD dictionary, considering the first digit of the ATC class (anatomic category) and the first three digits of the ATC class (therapeutic category). All ATC codes corresponding to a medication will be summarized, patients will be counted once in each ATC categories (anatomic or therapeutic) linked to the medication, therefore patients may be counted several time for the same medication.

The table for prior and concomitant medications will be sorted by decreasing frequency of anatomic category followed by all other therapeutic classes. In case of equal frequency regarding anatomic categories, alphabetical order will be used.

In addition, concomitant known nephrotoxic agents based on WHO-DD will be summarized.

10.7.4 Extent of study treatment exposure

The extent of exposure to teicoplanin will be assessed within the safety population for:

- Duration of teicoplanin exposure in days defined as the difference between the date of last administration and the date of first administration day, plus one day
- The total number of administration by patient during the loading dose period.

Descriptive statistics will be provided for C_{trough} of teicoplanin at the end of loading dose administration and during the maintenance dose.

10.7.5 Primary analysis

Nephrotoxicity incidence over the loading dose period up to day-10 after the first administration will be presented with exact binomial 95% confidence interval. Multiple occurrences of nephrotoxicity over loading dose period (up to Day 10) in the same patient will be counted only once.

Comparison with external historical data for nephrotoxicity associated with a high dose of vancomycin:

Non-inferiority versus historical reference incidence of 22% (incidence associated with the high dose vancomycin) will be claimed if the upper boundary associated with confidence interval of the observed incidence is found to be <27% (ie, historical reference incidence + NI margin: 22+5).

Comparison with external historical data for nephrotoxicity associated with a lower loading dose of teicoplanin:

The odds ratio associated with nephrotoxicity high dose versus low dose of teicoplanin will be provided.

The analysis will be performed on the safety population.

Sensitivity analysis will be conducted in reproducing the same analysis using the "high dose treated population" and the "modified high dose treated population".

10.7.6 Secondary analysis

Incidence and 95% confidence intervals will be provided for:

- Nephrotoxicity during the maintenance period and the entire study period
- Hepatotoxicity during the loading dose period, the maintenance period and during the entire study period
- Thrombocytopenia during the loading dose period, the maintenance period and during the entire study period
- Hearing and balance/vestibular disorders during the loading dose period and, the maintenance period during the entire study period
- Additional renal endpoints: renal failure, dialysis and renal replacement therapy during the loading dose period, the maintenance period and during the entire study period

Incidence tables will be presented for:

- Adverse events/reactions during the loading dose period, the maintenance period and during the entire study period

Adverse events/reactions incidence tables will be presented by system organ class (SOC) (sorted by internationally agreed order), high level term (HLT), and preferred term (PT) sorted in alphabetical order, the number (n) and percentage (%) of patients experiencing an AE. Multiple occurrences of the same event in the same patient will be counted only once in the tables within a study period.

An overall summary of events will be provided including the number and percentage of patients with any AE, any serious AE, any AE leading to death (death as an outcome on the AE CRF page as reported by the Investigator), and any AE leading to permanent teicoplanin discontinuation.

Selected events will be analyzed using "time to first event" approach (Kaplan-Meier methodology). Time from the first administration to the first occurrence of the event will be calculated (only the first event will be counted). Patients without any event will be censored at the end of the study period. Incidence rates at Day 10 and Day 60 of exposure will be presented and Kaplan-Meier curves will be provided.

Rates of each selected event (ie, nephrotoxicity, hepatotoxicity, thrombocytopenia, and hearing and balance/vestibular disorders) will be also presented graphically according to the study period, using bar chart. The analysis of secondary endpoints will be performed on the safety population.

10.7.7 Analysis of other safety endpoints

Scatter plots for creatinine clearance and creatinine, study period versus baseline will be provided. These scatter plots will be also provided by indication.

Abnormalities in clinical laboratories will be summarized based on PCSA criteria and laboratory normal ranges. The following definitions will be applied to laboratory parameters:

- PCSA values are defined as abnormal values considered medically important by the Sponsor according to predefined criteria/thresholds based on literature review and defined by the Sponsor for clinical laboratory tests.
- PCSA criteria will determine which patients had at least one treatment-emergent PCSA, taking into account all available evaluations.

The baseline value for a given parameter is defined as the last available value prior to the exposition to teicoplanin. The analysis of secondary endpoints will be performed on the safety population.

10.7.8 Other analysis

Simplified Acute Physiology Score SAPS II

To allow for an assessment of the severity of disease, the Simplified Acute Physiology Score SAPS II (see Annex 3).scoring will be calculated based on data available within the first 24 hours after hospital admission. The SAPS II score is also included as covariate in the logistic regression model.

Influence of covariates on occurrence of adverse event

Statistical analyses will be performed to evaluate the influence of baseline covariates (age, gender, body mass index, creatinine clearance, concomitant medications, comorbidities, site of infection, severity of infection, teicoplanin number of loading doses, trough serum concentration and treatment duration, when available) on the development of nephrotoxicity, hepatotoxicity, thrombocytopenia, hearing and balance/vestibular disorders as detailed below.

An univariate statistics will be performed first, using analysis of variance or Wilcoxon Mann-Whitney test for quantitative variables, Chi square or Fisher exact test for qualitative variable.

Then a model will be built by the technique of multivariate logistic regression, with a stepwise procedure. Stepping will be stopped when there will be no further candidate variables that will enter in the model at the 5% significance level. The final model will be constructed with the selected variables. The adjusted odds ratio and their 95% confidence interval will be provided for the variables finally selected in the model.

The events to explain will be:

- Nephrotoxicity: Yes / No
- Hepatotoxicity: Yes / No
- Thrombocytopenia: Yes / No
- Hearing and balance/vestibular disorders: Yes / No

Possible explicative variables are listed below:

- Demographic variables:
  - Age (continuous variable)
  - Gender: (Male / Female)
  - BMI: (≤ Median / >Median)
- Prior and concomitant medications of specific interest separately (see Section 10.3.1):
  - Nephrotoxic agent intravenous contrast media, antimicrobial agents , antipyretic analgesics: Yes (if any) / No
  - Vasopressors: Yes (if any) / No
  - Loop diuretics: Yes (if any) / No
  - Chemotherapeutic agents: Yes (if any) / No
- Comorbidities: for each medical history of interest separately at baseline and/or developed during the study (see Section 10.3.1):
  - Underlying renal impairment: Yes (if any renal impairment) / No
  - Heart failure: Yes (if any heart failure) / No
  - Hepatic impairment: Yes / No
  - General health status: Yes (if any) / No

  And other medical history:
  - Diabetes mellitus: Yes / No
  - Chronic kidney insufficiency: Yes / No
  - Liver failure: Yes / No
  - Hypoalbuminemia: Yes / No
  - Arterial vascular disease: Yes / No
  - Volume depletion: Yes / No
  - Sepsis: Yes / No
  - Hypotension/shock: Yes / No
  - Abdominal compartment syndrome: Yes / No

  - Mechanical ventilation: Yes / No
  - Nonrenal solid organ transplantation: Yes / No
  - Rhabdomyolysis: Yes / No
- SAPS II score
- Type of center/medical care separately:
  - Intensive care unit (ICU): Yes / No
  - Infectious disease unit: Yes / No
  - Septic surgery unit: Yes / No
- Renal function at baseline using creatinine clearance (Cockroft-Gault formula)
- Characteristics of infection: site, severity
- Teicoplanin: loading dose, number of loading doses, trough serum concentration
- Treatment duration

Influence of covariates on occurrence of nephrotoxicity: additional sensitivity analysis

This analysis will be conducted in nearly the same manner as the evaluation of influence of covariates on occurrence of adverse events, except that known risk factors of nephrotoxicity will be forced in the model. These risk factors of nephrotoxicity are listed below:

- Advanced age (> 65 years)
- Diabetes mellitus
- Chronic kidney insufficiency
- Heart failure
- Liver failure
- Hypoalbuminemia
- Arterial vascular disease
- Acute clinical conditions (separately):
  - Volume depletion
  - Sepsis
  - Hypotension/shock
  - Abdominal compartment syndrome
  - Mechanical ventilation
  - Non-renal solid organ transplantation
  - Rhabdomyolysis

- Nephrotoxic agents, any among: contrast media, antimicrobial agents, chemotherapeutic agents, NSAIDs

Analysis of C_{trough} of teicoplanin

Descriptive statistics and box plot (mean median Q1 Q3 outliers) of C_{trough} during the loading dose period and the maintenance dose period (one average C_{trough} by patient), in patients meeting the primary or secondary endpoints versus those not meeting these criteria will be provided.

Sensitivity analysis relating to the timing of blood samples and next subsequent dosing

Descriptive statistics will be provided for C_{trough} of teicoplanin according to time of sampling prior to the next dosing during the loading dose period, if needed.

Sensitivity analysis related to missing data

For the primary evaluation criteria a sensitivity analysis related to missing data will be performed. We will make the assumption that for the missing data the incidence of nephrotoxicity will vary between half and twice the incidence observed.

Subgroups analyses according to targeted trough concentration

Incidence tables according to targeted trough concentration separated into categories (< 20 mg/L, [20 – 30[mg/L, [30 – 40[mg/L) will be presented for: nephrotoxicity, hepatotoxicity, thrombocytopenia and hearing and balance/vestibular disorders.

10.7.9 Data handling conventions

For time to event analysis, missing data will be handled based on censoring rules. For categorical data, missing data will be reported as missing in the tables. Patients who are lost to follow up for survival data will be considered censored at the last observation.

Patients with missing data for the primary endpoint will be summarized. A sensitivity analysis related to missing data will be performed. All efforts will be made to minimize collect the data for patients lost-to-follow-up. In case, loss-to follow-up occurs despite the measures taken, missing data could appear. In case the missing data concern the assessment of the primary endpoint, the patient could be considered having an insufficient post-administration follow-up (eg, missing laboratory data: serum creatinine, creatinine clearance). It is planned to summarize the number of patients with insufficient post-administration follow-up and to perform a sensitivity analysis related to missing data.

If the date of first dose is unknown, the date of patient's inclusion (V1) will be used. If the date of last dose administration is unknown, no imputation will be done and no treatment duration will be computed.

By convention, the reference period (expressed in days) for the calculation of extent of exposure and time to onset of events is calculated as the difference between the targeted event date and the date of this reference day, plus one day.

10.7.10 External historical comparator

10.7.10.1 Search strategy and selection criteria

Five systematic literature searches were conducted to identify studies that will be used as an external historical comparison as follows: (A) Studies that reported an incidence of nephrotoxicity associated with a high dose of vancomycin, (B) Studies that reported an incidence of nephrotoxicity associated with a lower loading dose of teicoplanin, (C) Studies that reported an incidence of hepatotoxicity associated with a lower loading dose of teicoplanin, and (D) Studies that reported an incidence of hearing and balance disorders associated with a lower loading dose of teicoplanin, (E) Studies that reported an incidence of thrombocytopenia associated with a lower loading dose of teicoplanin. The methodology (databases, search terms and selection criteria) used in each of the literature searches (A-E) has been described below (16) (17) (18) (19) (20) (21) (22) (23) (24) (25) (26) (27) (28) (29) (30) (31) (32) (33) (34) (35) (36).

A. Methodology of systematic literature search for studies reporting an incidence of nephrotoxicity associated with a high dose vancomycin to be used as external historical comparison data

A systematic literature search was conducted to identify studies from Embase and Medline databases published during a period of January 1995 till December 2014. Search terms included "vancomycin" in combination with "nephrotoxicity" or "renal toxicity" or "renal injury." Studies written in languages other than English and those presented solely as abstracts or posters at scientific conferences were not considered in this literature review. High dose of vancomycin was defined as the dosage regimens that achieved serum trough concentrations of 15–20 mg/L. The following was used to define nephrotoxicity in the studies reviewed unless noted otherwise: Increase in serum creatinine of 0.5 mg/dl or a 50% increase from the baseline serum creatinine level for two consecutive laboratory determinations.

Study selection: The initial broad search identified 2,179 articles with search terms vancomycin and nephrotoxicity or renal injury or renal toxicity. The search was further refined by selecting the source as Embase, or Medline or Embase and Medline and publication years from 1995-2014. This broad search yielded 1,795 articles (*Figure 3: Flow diagram of the selection process of the included studies providing incidence of nephrotoxicity associated with vancomycin trough concentration of ≥ 15 mg/L*). Upon review of abstracts, 1,721 studies were excluded due to the following reasons: (1) Abstract or poster presented at a scientific conference or letter to the editor, (2) Aminoglycoside agent or other nephrotoxic agents other than vancomycin, (3) Study population involving children, (4) Standard dose of vancomycin with trough concentration <15 mg/L, (5) Continuous infusion of vancomycin, (6) Full text not available, (7) Studies conducted in non-human subjects, (8) Case reports. Of the 74 abstracts that were found to be potentially relevant, 27 full-text articles were retrieved for more detailed assessment for eligibility based on the following specific selection criteria: (a) high dose of vancomycin achieving trough

concentrations ≥15 mg/L was administered and the observed nephrotoxicity rates could be extracted for vancomycin trough of ≥15 mg/L; (b) the following definition of nephrotoxicity was used: increase of 0.5 mg/dL or 50% or more of baseline serum creatinine level in 2 consecutive laboratory tests; and (c) studies were conducted in adult population aged 18 years or older. Only 12 studies met the criteria and were included in the literature review (Table 1). Fifteen studies were excluded for 2 reasons: (1) Non-consistent definition of nephrotoxicity such as RIFLE criteria or Acute Kidney Injury Network (AKIN) definition (n=5), (2) observed nephrotoxicity rates could not be extracted for vancomycin trough of ≥15 mg/L (n=10). Based on this review, the range of incidence rates for nephrotoxicity associated with vancomycin's high dose is 6.9%-55.1%.

B. Methodology of systematic literature search for studies reporting an incidence of nephrotoxicity associated with a lower loading dose of teicoplanin to be used as external historical comparison data

A systematic literature search was conducted to identify studies reporting incidence of nephrotoxicity associated with a lower loading dose of teicoplanin from Embase and Medline databases published during a period of January 1990 till December 2014. Search terms included "Teicoplanin" in combination with "nephrotoxicity" or "renal toxicity" or "renal injury." Studies written in languages other than English and those presented solely as abstracts or posters at scientific conferences were not considered in this literature review. Lower loading dose of teicoplanin was defined as 6mg/kg or 400 mg. The following was used to define nephrotoxicity in the studies reviewed unless noted otherwise: Increase in serum creatinine of 0.5 mg/dl or a 50% increase from the baseline serum creatinine level for two consecutive laboratory determinations.

Study selection: The initial broad search identified 447 articles with search terms teicoplanin and nephrotoxicity or renal injury or renal toxicity. The search was further refined by selecting the source as Embase, or Medline or Embase and Medline and publication years from 1990-2014. This search yielded 437 articles (*Figure 4: Selection of studies providing incidence of nephrotoxicity associated with lower loading dose of teicoplanin)*. Upon review of abstracts, 35 abstracts were found to be potentially relevant and 402 studies were excluded due to the following reasons: (1) Abstract or poster presented at a scientific conference or letter to the editor, (2) nephrotoxic agents other than teicoplanin or high loading dose of teicoplanin >6 mg/kg, (3) Study population involving children, (4) Full text not available, (5) Studies conducted in non-human subjects, (6) Case reports. Of the 35 abstracts that were found to be relevant, 19 full-text articles were assessed for eligibility based on the following specific selection criteria: (a) Lower loading dose of teicoplanin administered (6 mg/kg or 400 mg) and the observed nephrotoxicity rates could be extracted; (b) the following definition of nephrotoxicity was used: increase of 0.5 mg/dL or 50% or more of baseline serum creatinine level in 2 consecutive laboratory tests; and (c) studies were conducted in adult population aged 18 years or older. Only 5 studies met the criteria and were included in the literature review (Table 2). Fourteen studies were excluded for the following reasons: (1) Non-consistent definition of nephrotoxicity (RIFLE or AKIN criteria) or definition not clearly stated, n=5, (2) Combination therapy of teicoplanin with other antibiotics, n=3 (3) Higher loading dose of >6 mg/kg, n=2, (4) Published meta-analyses from which individual studies were reviewed for inclusion in Table 2, n=3, and (5) No information on number of patients receiving teicoplanin, n=1. Based on this review, the range of incidence rates for nephrotoxicity associated with teicoplanin's lower loading dose is 0.0%-8.0%.

C. Methodology of systematic literature search for studies reporting an incidence of hepatotoxicity associated with a lower loading dose of teicoplanin to be used as external historical comparison data

A systematic literature search was conducted to identify studies reporting incidence of hepatotoxicity associated with a lower loading dose of teicoplanin from Embase and Medline databases published during a period of January 1990 till December 2014. Search terms included "Teicoplanin" in combination with "hepatotoxicity" or "liver injury". Studies written in languages other than English and those presented solely as abstracts or posters at scientific conferences were not considered in this literature review. Lower loading dose of teicoplanin was defined as 6mg/kg or 400 mg. The following was used to define hepatotoxicity in the studies reviewed unless noted otherwise: Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) 3 times the upper limit of normal (AST: 13-33 IU/L, ALT: 8-42 IU/L).

Study selection: The search identified 30 articles with search terms teicoplanin and hepatotoxicity or liver injury (*Figure 5: Selection of studies providing incidence of hepatotoxicity associated with lower loading dose of teicoplanin*). Upon review, 6 abstracts were found to be potentially relevant and 24 studies were excluded due to the following reasons: (1) Abstract or poster presented at a scientific conference or letter to the editor, (2) antibacterial agents other than teicoplanin, (3) Study population involving children, (4) Case reports. Of the 6 abstracts that were found to be relevant, 4 full-text articles were assessed for eligibility based on the following specific selection criteria: (a) Lower loading dose of teicoplanin administered (6 mg/kg or 400 mg) and the observed hepatotoxicity rates could be extracted; (b) the following definition of hepatotoxicity was used: Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) 3 times the upper limit of normal (AST: 13-33 IU/L, ALT: 8-42 IU/L); and (c) studies were conducted in adult population aged 18 years or older. Only 1 study met the criteria and was included in the literature review (Table 2). Three studies were excluded for the following reasons: (1) definition of hepatotoxicity not clearly stated, n=1, (2) Higher loading dose of >6 mg/kg, n=1, (3) a study with suspected overlapping patient population from another study by the same group of authors which was included in our review, n=1. Based on this review, the range of incidence rates for hepatotoxicity associated with teicoplanin's lower loading dose is 0%-5.1%.

D. Methodology of systematic literature search for studies reporting an incidence of hearing and balance disorders associated with a lower loading dose of teicoplanin to be used as external historical comparison data

A systematic literature search was conducted to identify studies reporting incidence of hearing and balance disorders associated with a lower loading dose of teicoplanin from Embase and Medline databases published during a period of January 1990 till December 2014. Search terms included "Teicoplanin" in combination with "ototoxicity" or "hearing impairment" or "balance disorder". Studies written in languages other than English and those presented solely as abstracts or posters at scientific conferences were not considered in this literature review. Lower loading dose of teicoplanin was defined as 6 mg/kg or 400 mg. No specific definition of ototoxicity was used other than findings based on an audiometric evaluation.

Study selection: The initial broad search identified 222 articles with search terms teicoplanin and ototoxicity or hearing impairment or balance disorder. The search was further refined by selecting the source as Embase, or Medline or Embase and Medline and publication years from 1990-2014. This search yielded 210 articles (*Figure 6: Selection of studies providing incidence of hearing and balance disorders associated with lower loading dose of teicoplanin*). Upon review of abstracts, 11 abstracts were found to be potentially relevant and 199 studies were excluded due to the following reasons: (1) Abstract or poster presented at a scientific conference or letter to the editor, (2) antibacterial agents other than teicoplanin or high loading dose of teicoplanin >6 mg/kg, (3) Study population involving children, and (4) Case reports. Of the 11 abstracts that were found to be relevant, 7 full-text articles were assessed for eligibility based on the following specific selection criteria: (a) Lower loading dose of teicoplanin administered (6 mg/kg or 400 mg) and the observed ototoxicity rates could be extracted; (b) studies were conducted in adult population aged 18 years or older. Only 2 studies met the criteria and were included in the literature review (Table 2). Five studies were excluded for the following reasons: (1) Definition of ototoxicity not clearly stated, n=3, (2) Higher loading dose of >6 mg/kg, n=1, (3) Published meta-analyses where no specific information on ototoxicity was available and adverse events were combined, n=1. Based on this review, the range of incidence rates for hearing and balance disorders associated with teicoplanin's lower loading dose is 0.36%-1.71%.

E. Methodology of systematic literature search for studies reporting an incidence of thrombocytopenia associated with a lower loading dose of teicoplanin to be used as external historical comparison data

A systematic literature search was conducted to identify studies reporting incidence of thrombocytopenia associated with a lower loading dose of teicoplanin from Embase and Medline databases published during a period of January 1990 till December 2014. Search terms included "Teicoplanin" in combination with "thrombocytopenia" or "platelet". Studies written in languages other than English and those presented solely as abstracts or posters at scientific conferences were not considered in this literature review. Lower loading dose of teicoplanin was defined as 6mg/kg or 400 mg. Since none of the articles reviewed precisely matched the definition of thrombocytopenia cited in the protocol (i.e. platelet count <100,000/mm3) and since literature on this topic was very limited, we included all articles that defined thrombocytopenia as platelet count <150,000/mm3.

Study selection*:* The initial broad search identified 52 articles with search terms teicoplanin and thrombocytopenia or platelet. The search was further refined by selecting the source as Embase, or Medline or Embase and Medline and publication years from 1990-2014. This search yielded 50 articles (*Figure 7: Selection of studies providing incidence of thrombocytopenia associated with lower loading dose of teicoplanin*). Upon review, 8 abstracts were found to be potentially relevant and 42 studies were excluded due to the following reasons: (1) Abstract or poster presented at a scientific conference or letter to the editor, (2) antibacterial agents other than teicoplanin or high loading dose of teicoplanin >6 mg/kg, (3) Study population involving children, and (4) Case reports. Of the 8 abstracts that were found to be relevant, 5 full-text articles were assessed for eligibility based on the following specific selection criteria: (a) Lower loading dose of teicoplanin administered (6 mg/kg or 400 mg) and the observed thrombocytopenia rates could be extracted; (b) the following definition of thrombocytopenia was used: platelet count <150,000/mm3; and (c) studies were conducted in adult population aged 18 years or older. Only 1 study met the criteria

and was included in the literature review (Table 2). Four studies were excluded for the following reasons: (1) Combination therapy of teicoplanin with other antibiotics (either vancomycin or linezolid or glycopeptide treatment), n=3, (2) No information on number of patients receiving teicoplanin, n=1. Based on this review, the incidence rate for thrombocytopenia associated with teicoplanin's lower loading dose is 1.11%.

10.7.10.2 Determination of historical reference

Incidence of nephrotoxicity with high dose of vancomycin: Pooled estimate

The systemic literature review identified 12 studies that met the criteria (presented in Table 1, Annex 3). These 12 studies were included in the meta-analysis for the calculation of the reference incidence. The meta-analysis was performed along with a test of homogeneity. The test of homogeneity, using Q, is test the null hypothesis: $\tau^2 = 0$. Based on the value of τ^2 the more appropriate analysis was chosen. The value τ^2 was found > 0 and a meta-analysis using random effects models was performed as described in the article of Anne Whitehead and John Whitehead (A general parametric approach to the meta-analysis of randomized clinical trials) (37). For this meta-analysis the inverse variance method was used.

The detail of calculation is presented below:

For each I^{th} study among K studies following data are calculated:

	Vancomycin
Nephrotoxicity incidence	$\hat{p}_{i=\frac{T_i}{N_i}}$
Nephrotoxicity	T_i
Sample size	N_i

The inverse of the asymptotic variance: $w_i = 1 \Big/ \frac{\hat{p}_i * (1-\hat{p}_i)}{N_i}$

Test for homogeneity of the nephrotoxicity incidence across all studies: $Q = \sum w_i (\hat{p}_i - \hat{p})^2$

Q follows a x^2 distribution with (K-1) degree of freedom.

If the hypothesis of homogeneity could be accepted:

The overall estimate: $\hat{p} = \frac{\sum P_i W_i}{\sum W_i}$

With approximate 95% confidence interval: $\hat{p} \pm 1.96\sqrt{\frac{1}{\sum w_i}}$

When homogeneity of nephrotoxicity incidence is rejected a random approach is used and the overall estimate is: $\hat{P}^* = \frac{\sum P_i W_i^*}{\sum W_i^*}$

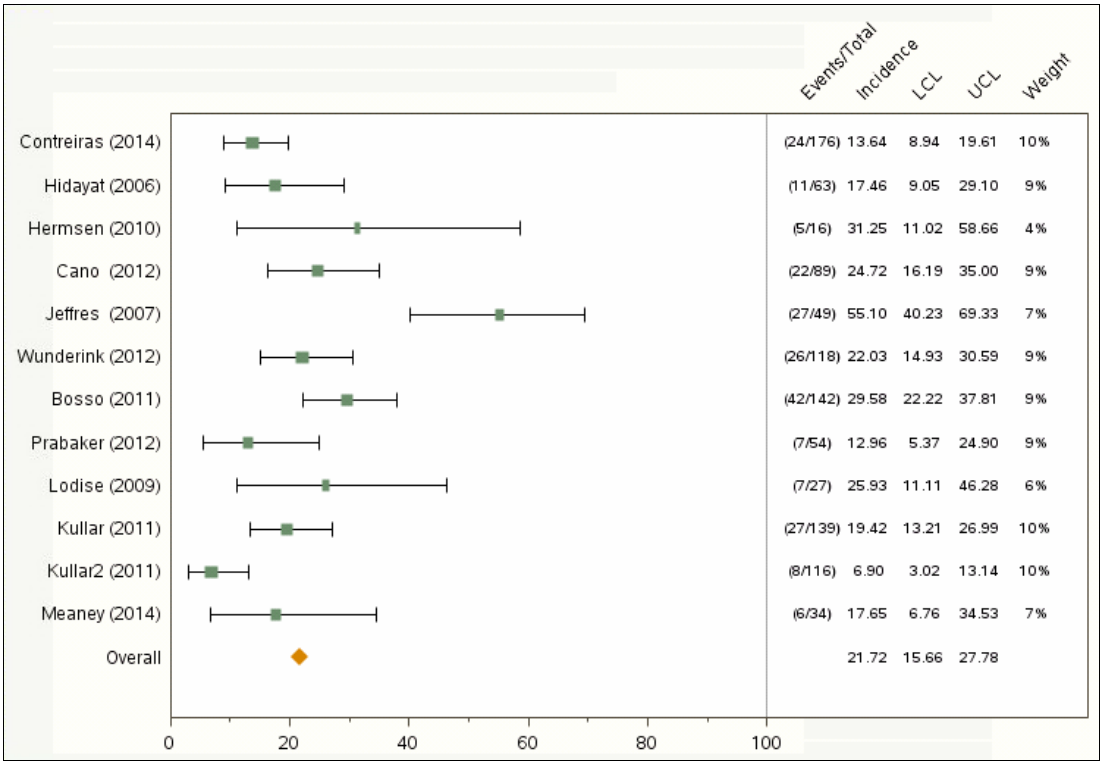
With $W_i^* = (w_i^{-1} + \hat{t}^2)^{-1}$ and $\hat{t}^2 = \frac{Q-(k-1)}{\sum w_i - (\sum w_i^2)/\sum w_i}$

The corresponding approximate 95% confidence interval is: $\hat{P}^* \pm 1.96\sqrt{\frac{1}{\sum w_i^*}}$

The incidence of nephrotoxicity varied between studies from 6.9% to 55.1%. The incidence of nephrotoxicity associated with high dose of vancomycin was estimated to be about 22%.

Figure 1 below presents a forest plot of events denoting nephrotoxicity associated with high dose of vancomycin (through ≥15 mg/L).

Figure 1 - Forest plot of events denoting nephrotoxicity associated with vancomycin high dose (≥15 mg/l)



Squares indicate point estimates, and the size of square indicates the weight of each study. Events: Number of patients with nephrotoxicity, Total: Total number of patients receiving vancomycin high dose, LCL: Lower confidence limit, UCL: Upper confidence limit.

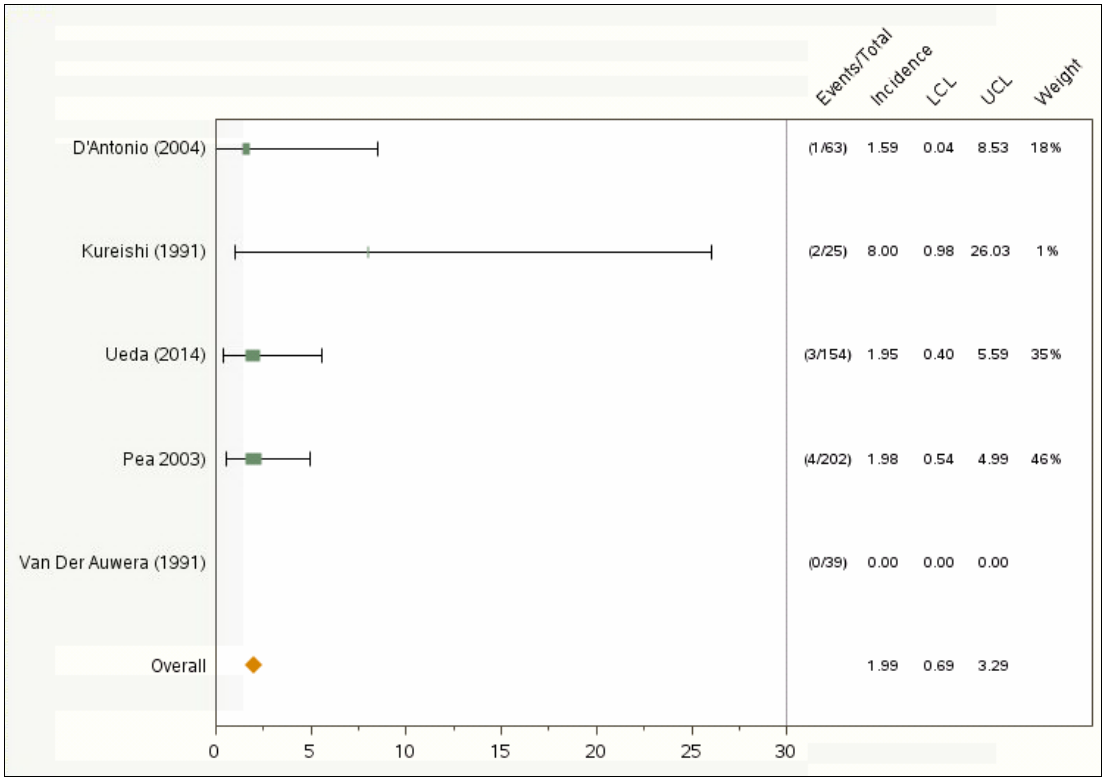
Incidence of nephrotoxicity with lower loading dose of teicoplanin: Pooled estimate

Five studies were identified after the systemic literature review (Table 2, Annex 3). These 5 studies were included in the meta-analysis and a test of homogeneity was performed. The value $\tau 2$ was found <0 and a meta-analysis using fixed effects models were performed.

The range of incidence of nephrotoxicity between studies was 0% to 8%. The incidence of nephrotoxicity associated with lower loading dose of teicoplanin was estimated to be about 2%.

Figure 2 below presents a forest plot of events denoting nephrotoxicity associated with lower loading dose of teicoplanin.

Figure 2 - Forest plot of events denoting nephrotoxicity associated with lower loading dose of teicoplanin



Squares indicate point estimates, and the size of square indicates the weight of each study. Events: Number of patients with nephrotoxicity, Total: Total number of patients receiving lower loading dose of teicoplanin, LCL: Lower confidence limit, UCL: Upper confidence limit.

As described under section 10.7.5, primary analysis will include a comparison of the observed data of nephrotoxicity associated with teicoplanin's higher loading doses of 12 mg/kg twice a day with (1) external historical data for nephrotoxicity associated with a high dose of vancomycin and (2) external historical data for nephrotoxicity associated with a lower loading dose of teicoplanin.

10.7.11 Interim analysis

An interim analysis of the safety data, including an analysis of the progress of recruitment, will be performed when recruitment of 50% of the planned sample size population is achieved.

10.8 QUALITY CONTROL

10.8.1 Data collection, validation and data quality control at MAH/MAH REPRESENTATIVE level

Data will be collected via eCRF. The computerized handling of the data by the MAH/MAH representative after receipt of the information may generate additional requests to which the participating investigators are obliged to respond by confirming or modifying the data questioned. The requests with their responses will be appended to the CRFs held by the Investigator and the MAH/MAH representative.

Data collection and validation procedures will be detailed in the Study manual.

10.8.2 Data quality control at site level

Quality Control will be performed by qualified designated personnel in each country. Taking into account the number of patients included at a particular site. i.e. it will be ensured that sites with higher number of patients recruited will be selected for quality control.

Data quality control will be performed on 100% of participating active sites which have enrolled at least one patient. The monitoring will consist of two parts: the centralized/remote monitoring which will allow checking the recruitment and eligibility reports, and the eCRF data, on a routine base. The other part will be the monitoring on-site which will be achieved according to the centralized/remote monitoring, twice a year. Moreover, contacts by phone will be performed in between site monitoring visits, based on the remote monitoring findings/required corrections. Quality Control will be performed by qualified designated personnel in each country. The methodology of data Quality Control and appropriate consecutive corrective actions will be detailed in the study manual. The following recommendations will be included in the study manual.

- Site selection will be performed either on site-visit or by phone
- Site initiation visit will be carried out on site-visit or web-conference (assuming that the first monitoring visit will be performed on site)
- Site closure will be performed either by phone (at least for non-active sites) or on-site closure visit.

- Monitoring visit: the first visit could be planned no later than 1 month after the first patients inclusion. This visit could be either a monitoring visit at site or performed by phone.
- The other on-site monitoring visits will be performed twice a year when deemed necessary according to the site enrollment and data collection.
- Finally, 100% of core data have to be checked versus source document for all patients. The considered core data are Informed Consent, Inclusion/Exclusion criteria, Teicoplanin administration, and all AE/SAE.

If specific issues are identified in some sites or countries, the percentage of Quality Control in the concerned site/country or in all sites/countries will be appropriately increased and corrective actions will be set up. Quality Control will be performed by qualified designated personnel in each country.

Detailed information will be presented in the study manual.

10.9 LIMITATIONS OF THE RESEARCH METHODS

This study has a number of strengths, such as:

- All the data specific to the study research question and objectives are prospectively collected and recorded in a consistent way for each subject;
- The participating physicians assess the treatment with teicoplanin as per routine clinical practice;
- This study will provide with data on use and safety of teicoplanin maximal recommended loading dose in a “real-world” setting;
- The data collected will be monitored while the study is being conducted enabling a continuous risk-benefice evaluation of the product.

Some limitations of the study need to be noted:

- Subject recruitment may be slow as the higher recommended teicoplanin dosage is used for severe infections only, which are rare and cases are scattered across hospitals;
- The findings of the study may be limited to the selected European countries, and may not be representative to other countries/populations;

- Limitations due to the methodology of using external historical comparison data should be noted: (1) the precise person-days exposure to teicoplanin and/or vancomycin is not available from the published literature listed in tables 1 and 2; therefore, the incidence rates per 100 person-days of teicoplanin and vancomycin treatment have been calculated using the mean or median duration of treatment on which information is available and thus, they provide an approximate estimate of incidence rate; (2) the study populations from the published literature differ from one to another with respect to indication of receiving teicoplanin and vancomycin and patient profile; therefore, keeping in mind the presence of heterogeneity across the studies, a meta-analysis using a random-effects model along with a test of homogeneity was conducted to pool the estimates from external historical comparison data.

10.10 OTHER ASPECTS

NA.

11 PROTECTION OF HUMAN SUBJECTS

11.1 RESPONSIBILITIES OF THE INVESTIGATORS

The Investigators will perform the study in accordance with this protocol, applicable local regulations and international guidelines.

It is the Investigator's responsibility to obtain written informed consent from the patient or from his/her legal representative prior to inclusion in the study, to fill in the eCRF and to record all data pertinent to the investigation. She/he will ensure that the information reported in the eCRF is precise and accurate.

Investigators, under the health care provider's responsibility, should fully inform the patient of all pertinent aspects of the study including the written subject's information. All patients should be informed to the fullest extent possible about the study, in language and terms they are able to understand.

The written ICF will be signed prior to patient's data collection/entry in the study; name filled in and personally dated and signed by the patient or by the patient's legally acceptable representative, and by the person who conducted the informed consent discussion. Patient's legally representative has to sign and the patient should also sign as soon as he/she is capable to do so. The Investigators will retain the original signed consent document and a copy of the signed ICF will be given to the patient or to his/her legal representative.

The ICF and the information sheet used by the Investigator for obtaining the patient's written informed consent must be reviewed and approved by the MAH/MAH REPRESENTATIVE prior to submission to the appropriate IEC for approval / favorable opinion.

In addition, patients or their legal representative will sign the ICF as detailed below or will follow the IEC approved standard practice:

- patients who can read the consent form will do so before writing their name on the form.
- patients who cannot read will have the consent form read to them before writing their name on the form.

11.2 RESPONSIBILITIES OF MAH/MAH REPRESENTATIVE

The MAH/MAH REPRESENTATIVE is responsible for taking all reasonable steps and providing adequate resources to ensure the proper conduct of the study.

The MAH/MAH REPRESENTATIVE is responsible for:

- Local submission(s) complying with data protection rules,
- Any other local submission(s).

11.3 ETHICAL, REGULATORY AND ADMINISTRATIVE RULES

11.3.1 Ethical principles

This study will be conducted in accordance with the principles laid by the 18th World Medical Assembly (Helsinki, 1964) and all subsequent amendments.

11.3.2 Laws and regulations

This study will be conducted in accordance with the "Guideline on good pharmacovigilance practices (GVP), EMA/813938/2011".

Each participating country will locally ensure all necessary regulatory submissions (eg, IEC) are performed in accordance with local regulations including local data protection regulations.

11.3.3 Data protection

The patient's personal data and Investigators' personal data which may be included in the MAH/MAH REPRESENTATIVE database shall be treated in compliance with all local applicable laws and regulations.

When archiving or processing personal data pertaining to the Investigator and/or to the patients, the MAH/MAH REPRESENTATIVE shall take all appropriate measures to safeguard and prevent access to this data by any unauthorized third party.

11.3.4 Insurance

Insurance certificate is not needed for observational studies with non-interventional procedures, except if required by local law. Participating countries may contract insurance according to local specific requirements. The process for obtaining insurance will be detailed in the study manual, if appropriate.

11.3.5 Secrecy agreement

All material, information (oral or written) and unpublished documentation provided to Investigators (or any action carried out by the MAH/MAH REPRESENTATIVE on their behalf), including the present protocol and the CRF, are exclusive property of the MAH/MAH REPRESENTATIVE.

These materials or information (both global and partial) cannot be given or disclosed by the Investigators or by any person of her/his group to unauthorized persons without the prior formal written consent of the MAH/MAH REPRESENTATIVE.

The Investigators shall consider as confidential all the information received, acquired or deduced during the study and will take all necessary steps to ensure that there is no break of confidentiality, other than for information to be disclosed by law.

11.3.6 Record retention

The Investigators shall arrange for the retention of study documentation until the end of the study. In addition the physician will comply with specific local regulations/ recommendations with regards to patient record retention.

It is recommended that the Investigators retains the study documents at least five years after the completion or discontinuation of the study, unless otherwise specified in the Investigator's Agreement in line with additional standards and/or local laws.

However, applicable regulatory requirements will be taken into account in the event that a longer period is required.

11.3.7 Discontinuation of the study

The MAH/MAH REPRESENTATIVE can decide at any time and for any reason to discontinue the study; the decision will be communicated in writing to the participating Investigators. Similarly, should the Investigators decide to withdraw from the study, she/he will have to inform the MAH/MAH REPRESENTATIVE in writing. If appropriate, according to local regulations, IEC and Competent Authorities will be informed. The MAH will ensure that the study is not discontinued without prior enrollment of EMA/CHMP/PRAC as this is an imposed study and a condition of the marketing authorization.

11.3.8 MAH/MAH REPRESENTATIVE audits and inspections by competent authorities

The Investigator agrees to allow the MAH/MAH REPRESENTATIVE auditors/Competent Authorities inspectors to have direct access to his/her study records for review, being understood that this personnel is bound by professional secrecy, and as such will not disclose any personal identity or personal medical information. If ICF is not signed, the access to the source documents is not allowed.

The Investigator will make every effort to help with the performance of the audits and inspections, giving access to all necessary facilities, data, and documents. The confidentiality of the data verified and the protection of the patients will be respected during these inspections.

Any result and information arising from the inspections by the competent authorities will be communicated by the Investigator to the MAH/MAH REPRESENTATIVE.

The Investigator shall take appropriate measures required by the MAH/MAH REPRESENTATIVE to take corrective actions for all problems found during the audit or inspections.

12 MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

This non-interventional PASS study falls under the provisions set out in Directive 2001/83/EC and Regulation (EC) No 726/2004 applicable for any non-interventional study.

All adverse events regardless of seriousness or relationship to teicoplanin, spanning from the first administration of teicoplanin until the end of the data collection as defined by the protocol for each patient are to be collected by the Investigator and reported to the MAH/MAH representative within expedited time frame. An appropriate causality assessment by the Investigator should be performed for these reports. In this situation, the levels of causality, which correspond to a reasonable possibility of causal relationship, should be established in advance in order to determine when an adverse event is considered as an adverse reaction (38). Different methods may be applied for assessing the causal role of a medicinal product on the reported adverse event (eg, WHO-UMC system for standardized case causality assessment).

12.1 SAFETY INSTRUCTIONS

All events will be managed and reported in compliance with all applicable regulations.

As adverse events may be attributed to underlining medical illness or other concomitant medication use, additional information related to the events, eg, relevant medical history, or other concomitant medication use will be provided. Additional follow-up information for any events of interest may be requested from the Investigator if needed.

12.1.1 Definition of adverse event (AE) and serious adverse event (SAE)

An **adverse event** is any untoward medical occurrence in a patient or clinical investigation patient administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment.

A **serious adverse event** is any untoward medical occurrence that at any dose:

- Results in death or;
- Is life-threatening or;
  Note: The term "life-threatening" in the definition of "serious" refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.
- Requires inpatient hospitalization or prolongation of existing hospitalization or;
- Results in persistent or significant disability/incapacity or;
- Is a congenital anomaly/birth defect;
- Is a medically important event.

- Suspected transmission of infectious agent ; is any suspected transmission of an infectious agent via a medicinal product (eg, product contamination)

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.

12.1.2 Collection of overdose and pregnancy

Overdose:

Any case of accidental or intentional overdose, even in the absence of an AE (asymptomatic), is to be reported to the representative of Sanofi (within 30 days) and recorded accordingly on the corresponding page(s) of in the CRF as explained below. In case of overdose the patient should remain under observation for as long as it is considered appropriate by the Investigator. Appropriate symptomatic measures should be taken.

Pregnancy:

Pregnancy occurring in the patient or the female partner of a male patient exposed to a Sanofi medicinal product will be reported to the representative of Sanofi (within 24 hours) and recorded immediately on the corresponding page(s) of in the CRF as explained below.

12.1.3 Obligations of the Investigator regarding safety reporting

12.1.3.1 Adverse events collection

In the case of a serious adverse event the Investigator must immediately:

- SEND (within 24 hours, preferably by fax) the signed and dated corresponding page(s) in the CRF to the representative of MAH whose name, address and fax number appear on the first page of this Protocol;
- ATTACH the photocopy of all examinations carried out and the dates on which these examinations were performed. Care should be taken to ensure that the patient's identity is protected and the patient's identifiers in the study are properly mentioned on any copy of source document provided to MAH/MAH representative. For laboratory results, include the laboratory normal ranges;

All further documentation should be sent to the representative of MAH within 24 hours of knowledge. In addition, any effort should be made to further document each SAE that is fatal or life threatening within the week (7 days) following initial notification.

- ENTER (within 24 hours) the information related to the SAE in the appropriate screens of the e-CRF; the system will automatically send the notification to the representative of MAH after approval of the Investigator within the e-CRF or automatically after a pre-set delay.
- SEND (preferably by fax or e-mail) the photocopy of all examinations carried out and the dates on which these examinations were performed, to the representative of the MAH whose name, fax number and email address appear on the first page of this protocol. Care should be taken to ensure that the patient's identity is protected and the patient's identifiers in the study are properly mentioned on any copy of source document provided to MAH/MAH representative. For laboratory results, include the laboratory normal ranges

All further data updates should be recorded in the e-CRF as appropriate, and further documentation as well as additional information (for Lab data, concomitant Medication, patient status ...) should be sent (by fax or e-mail) to MAH/MAH representative within 24 hours of knowledge. In addition, any effort should be made to further document each serious AE that is fatal or life threatening within the week (7 days) following initial notification

A back-up plan is used (using paper flow) in case the e-CRF system does not work.

In case of any serious event brought to the attention of the Investigator at any time after the end of the study for the patient and considered by him/her to be caused by teicoplanin with a reasonable possibility, this will be reported to the Sponsor.

In case of non-serious adverse events:

- ENTER (within 30 days) the information related to the AE in the appropriate screens of the e-CRF; the system will automatically send the notification to MAH/MAH representative after approval of the Investigator within the e-CRF or automatically after a pre-set delay.

All adverse event pages should be reported to MAH/MAH representative **within 30 days of awareness.**

Abnormalities in clinical laboratories results will be reported as adverse events, if they are:

- symptomatic, or
- requiring either corrective treatment or consultation, or
- leading to teicoplanin discontinuation or modification of dosing, or
- fulfilling a seriousness criterion.

In addition, the followings should be reported as adverse events/reactions:

- Nephrotoxicity, defined as serum creatinine increase of more than 0.5 mg/dL if the baseline serum creatinine was ≤3 mg/ dL or a rise of >1 mg/dL if the initial serum creatinine was >3 mg/dL, or 50% increase from baseline, or a drop in calculated creatinine clearance using Cockroft-Gault formula of ≥50% from baseline

- Hepatotoxicity, defined as AST or ALT ≥3 times upper limit of normal or if AST or ALT baseline is abnormal, AST or ALT increase of ≥ 3 times the baseline and adverse events using the MedDRA SMQ "Hepatic Disorder"
- Thrombocytopenia, defined as platelets <100 000/mm^3 or <100 Giga/L
- Hearing and balance/vestibular disorders

All events will be thoroughly followed-up until clinical recovery is complete or laboratory results have returned to normal or to baseline values, or until progression has been stabilized, in order to ensure the safety follow-up of the patients. This may imply that observations will continue beyond the last planned visit per protocol, and that additional investigations may be requested by the monitoring team until the final outcome is available for collection. Patients who experience an ongoing nephrotoxic event at the prespecified study end-date, should be followed until resolution, stabilization, or death and related data will be collected.

12.2 SAFETY OBSERVATIONS

- The Investigator should take all appropriate measures to ensure the safety of the patients as per normal practice.
- In case of any serious adverse event, the patient must be followed up until clinical recovery is complete and laboratory results have returned to normal, or until progression has been stabilized. This may imply that follow-up will continue after the patient has left the study;
- In case of any serious adverse event brought to the attention of the Investigator at any time after cessation of the teicoplanin, and considered by him/her to be caused by teicoplanin with a reasonable possibility, this should be reported to the MAH/MAH representative.

12.3 OBLIGATIONS OF MAH/MAH REPRESENTATIVE

During the course of the study, the MAH/MAH REPRESENTATIVE will report safety data to health authorities according to Directive 2001/83/EC and in accordance with all applicable local and global regulations (eg, all serious adverse reactions within 15 days from the date of receipt of the reports to the health authorities; all non-serious adverse reactions within 90 days from the date of receipt of the reports to the health authorities for some European countries).

The MAH will report all safety observations collected during the conduct of the study in the final study report.

13 PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

The final study report, the annual progress reports as well as the results of the interim analysis, including an analysis of the progress of recruitment, performed when recruitment of 50% of the planned sample size population is achieved, will be submitted to regular authorities as per requested timelines.

13.1 OWNERSHIP AND USE OF DATA AND STUDY RESULTS

No use of the data will be possible without the authorization of the MAH/MAH REPRESENTATIVE conducting the study

The Scientific Expert will have full access to the final data allowing for appropriate academic analysis and reporting of the study results.

13.2 PUBLICATIONS

The Scientific Expert is responsible for presentations and/or publications. The study results must be submitted for review to the Scientific Expert, before publication.

All study Investigators give full authority to the Scientific Expert for primary presentation and/or primary publication of results. No other publication is allowed before the primary publication. Any subsequent presentation or publication by a study participant (including for substudies) must be approved by the Scientific Expert and make reference to the study and the primary publication. The final decision to publish any manuscript/ abstract/ presentation will be made by the Scientific Expert after prior notice to the MAH/MAH REPRESENTATIVE allowing for its internal review and comments. All manuscript/ abstract/ presentation must be submitted for internal review to the MAH/MAH REPRESENTATIVE at least forty-five (45) calendar days in advance. The MAH/MAH REPRESENTATIVE may request that the MAH/MAH REPRESENTATIVE's name and/or names of one or several of its employees appear or do not appear in such publication.

The MAH/MAH REPRESENTATIVE can delay publication or communication for a limited time in order to protect the confidentiality or proprietary nature of any information contained therein.

A Publication Committee responsible for the overall publication plan can be set up upon needs. Its main mission could be:

- To define the overall publication plan including the primary publications reporting new scientific findings/data from the study
- To review and approve (or abstain) all other publications proposals and draft manuscripts regarding subsequent publications including local publications.

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ANNEXES

Annex 1 List of stand-alone documents

Number	Document reference number	Date	Title
1	Number	DD Month YYYY	Text
2	Number	DD Month YYYY	Text
3	Number	DD Month YYYY	Text

Eg list of all participating Investigators

Annex 2 ENCePP checklist for study protocols

A copy of the ENCePP Checklist for Study protocols available at http://www.encepp.eu/standards_and_guidances/index.html completed and signed by the main author of the study protocol should be included in Annex 2.

The checklist will facilitate the review of the protocol and evaluation of whether investigators have considered important methodological aspects.

In question 9.5 of the Checklist, Revision 1:

“Study start” means “Start of data collection”

“Study progress” means “Progress report(s)”

“Study completion” means “End of data collection”

“Reporting” means “Final report of the study results”

Annex 3 Additional information

Table 1 - External Historical Comparison Data on the Incidence of Nephrotoxicity Associated with a High Dose of Vancomycin (>15 mg/L) from Published Literature

Reference	Study population	Dose of Vancomycin	Definition of Nephrotoxicity	Number of patients with Nephrotoxicity	Total N in Vancomycin	Vancomycin Mean/Median Treatment Duration (Days)	Incidence Rate reported as % (95% CI)[†]	Incidence Rate per 100 Persons-days of treatment (95% CI)[‡]
Contreiras et al (2014)	Patients with septic arthritis or pneumonia who had received IV vancomycin therapy for more than 7 days, had achieved at least one steady-state vancomycin trough level of 15–20 mg/L	Trough concentration of 15–20 mg/L, Median daily dose of 2g.	Increase in SCr of ≥ 44.2µmol/L or an increase in SCr ≥ 50% from baseline on 2 consecutive days.	24	176	15	13.64 (8.94, 19.61)	0.91 (0.55-1.27)
Hidayat et al (2006)	Adult patients infected with MRSA	High trough concentration of 15-20 µg/mL	Increase of 0.5mg/dL (44.2 µmol/L) or 50% or more of baseline SCr level in 2 consecutive laboratory tests	11	63	12	17.46 (9.05, 29.10)	1.46 (0.60-2.31)
Hermsen et al (2010)	Adults with MRSA pneumonia, endocarditis or osteomyelitis who received vancomycin for ≥ 5 days.	Mean vancomycin trough level high (≥ 15 mg/L)	Rise in SCr ≥ 0.5 mg/dl or 50% increase in SCr	5	16	11	31.25 (11.02, 58.66)	2.84 (0.35-5.33)
Cano et al (2012)	ICU patients with a diagnosis of HAP, VAP, or HCAP treated at 4 academic medical centers in the United States.	Mean vancomycin trough level high (> 15 mg/L)	Increase in SCr 0.5 mg/dl or 50%above baseline, whichever was greater, in at least 2 consecutive measurements	22	89	8	24.71 (16.19, 35.00)	4.26 (2.17-6.34)
Jeffres et al (2007)	All hospitalized patients with MRSA HCAP who were treated with vancomycin.	Patients with high trough concentration of ≥15 µg/mL (N=49)	Either a 0.5-mg/dL increase from baseline in SCr or a ≥50% increase from baseline in SCr based on serial SCr measurements	27	49	Not Stated	55.10 (40.23, 69.33)	Cannot be estimated*

Reference	Study population	Dose of Vancomycin	Definition of Nephrotoxicity	Number of patients with Nephrotoxicity	Total N in Vancomycin	Vancomycin Mean/Median Treatment Duration (Days)	Incidence Rate reported as % (95% CI)†	Incidence Rate per 100 Persons-days of treatment (95% CI)‡
Wunderink et al (2012)	Hospitalized patients aged >18 years with radiographically documented HAP or HCAP	Patients with high trough concentration of ≥15 µg/mL)	0.5-mg/mL increase in SCr level if normal at baseline or 50% increase if abnormal at baseline	26	118	Not Stated	22.03 (14.93, 30.59)	Cannot be estimated*
Bosso et al (2011)	Adult patients with documented MRSA infection receiving vancomycin for at least 72 h with at least one vancomycin trough concentration determined under steady-state conditions	Patients with high trough concentration of ≥15 mg/L	Increase in SCr of 0.5 mg/dl or a 50% increase from the baseline SCr level for two consecutive laboratory determinations.	42	142	10.6	29.58 (22.22, 37.81)	2.79 (1.95, 3.63)
Prabaker et al (2012)	Patients who received high dose vancomycin for various infections such as skin/soft tissue infection, pneumonia, bacteremia	Patients with mean trough 15 mg/L	Increase in SCr by either 0.5 mg/dL or 50% for at least 2 consecutive days after receipt of vancomycin, up to 72 hours after the final dose	7	54	7	12.96 (5.37, 24.90)	1.85 (0.48, 3.22)
Lodise et al (2009)	Patients who received vancomycin for a suspected or proven gram-positive infection during the period from 1 January 2005 through 31 December 2006	Patients with initial trough concentration of >15 mg/L	Increase in the SCr level of 0.5 mg/dL or 50%, whichever was greater, on at least 2 consecutive days during the period from initiation of vancomycin therapy to 72 h after completion of therapy	7	27	Not stated	25.93 (11.11, 46.28)	Cannot be estimated*
Kullar et al (2011)	Patients with documented MRSA bacteremia initially treated with vancomycin	Patients with initial trough concentration of ≥15 mg/L	Increase in Scr of 0.5 mg/dl or > 50% increase from baseline, whichever is greater	27	139	Not stated	19.42 (13.21, 26.99)	Cannot be estimated*

Reference	Study population	Dose of Vancomycin	Definition of Nephrotoxicity	Number of patients with Nephrotoxicity	Total N in Vancomycin	Vancomycin Mean/Median Treatment Duration (Days)	Incidence Rate reported as % (95% CI)†	Incidence Rate per 100 Persons-days of treatment (95% CI)‡
Kullar et al (2011)	Adult patients with gram positive infections requiring trough vancomycin serum concentration of 15-20 mg/L	Patients with initial trough concentration of 15-20 mg/L	Increase in Scr of 0.5 mg/dl or > 50% increase from baseline, whichever is greater	8	116	8	6.90 (3.02, 13.14)	0.86 (0.26, 1.46)
Meaney et al (2014)	Adult internal medicine patients receiving vancomycin treatment for soft tissue and skin infections, bacteremia, endocarditis, pneumonia	Patients with trough concentration of ≥15 mg/L	Increase in Scr of 0.5 mg/dl or > 50% increase from baseline, whichever is greater	6	34	Not stated	17.65 (6.76, 34.53)	Cannot be estimated*

Footnotes:
Abbreviations: SCr, Serum creatinine; CI, Confidence Interval; MRSA, Methicillin-resistant Staphylococcus Aureus, HAP, Hospital-acquired pneumonia, HCAP, Health-care associated pneumonia, VAP, Ventilator-associated pneumonia
† Incidence rate has been calculated as a proportion of patients who experienced nephrotoxicity of all patients who received the treatment and reported as %.
‡ Incidence rate has been calculated per 100 person-days of treatment by taking into account the mean/median duration of treatment.
* Incidence rate per 100 person-days of treatment cannot be estimated as mean or median duration of vancomycin treatment is not available in the article

Table 2 - External historical comparison data on the incidence of all endpoints associated with a lower loading dose of teicoplanin from published literature

Reference	Study population	Dose of Teicoplanin	Endpoint	Definition of the endpoint	Number of patients with endpoint	Total N in Teicoplanin Group	Teicoplanin Mean Treatment Duration (Days)	Incidence Rate reported as % (95% CI)[†]	Incidence Rate per 100 Persons-days of treatment (95% CI)[‡]
D'Antonio et al (2004)	124 febrile patients with hematological malignancies	6 mg/kg in 250 ml of 0.9% normal saline over 60 min twice on the first 2 days and thereafter once a day	Nephrotoxicity	Reversible renal toxicity	1	63	12.20	1.59 (0.04, 8.53)	0.13 (-0.12, 0.39)
Kureishi et al (1991)	Febrile neutropenic patients older than 18 years	Loading dosage of 6 mg/kg q12h i.v. for three doses, followed by a maintenance dosage of 6 mg/kg q24h	Nephrotoxicity	Rise in the SCr concentration from the normal range to 1.1 mg/dl for males and to 1.0 mg/dl for females.	2	25	22.40	8.00 (0.98, 26.03)	0.357 (-0.14, 0.85)

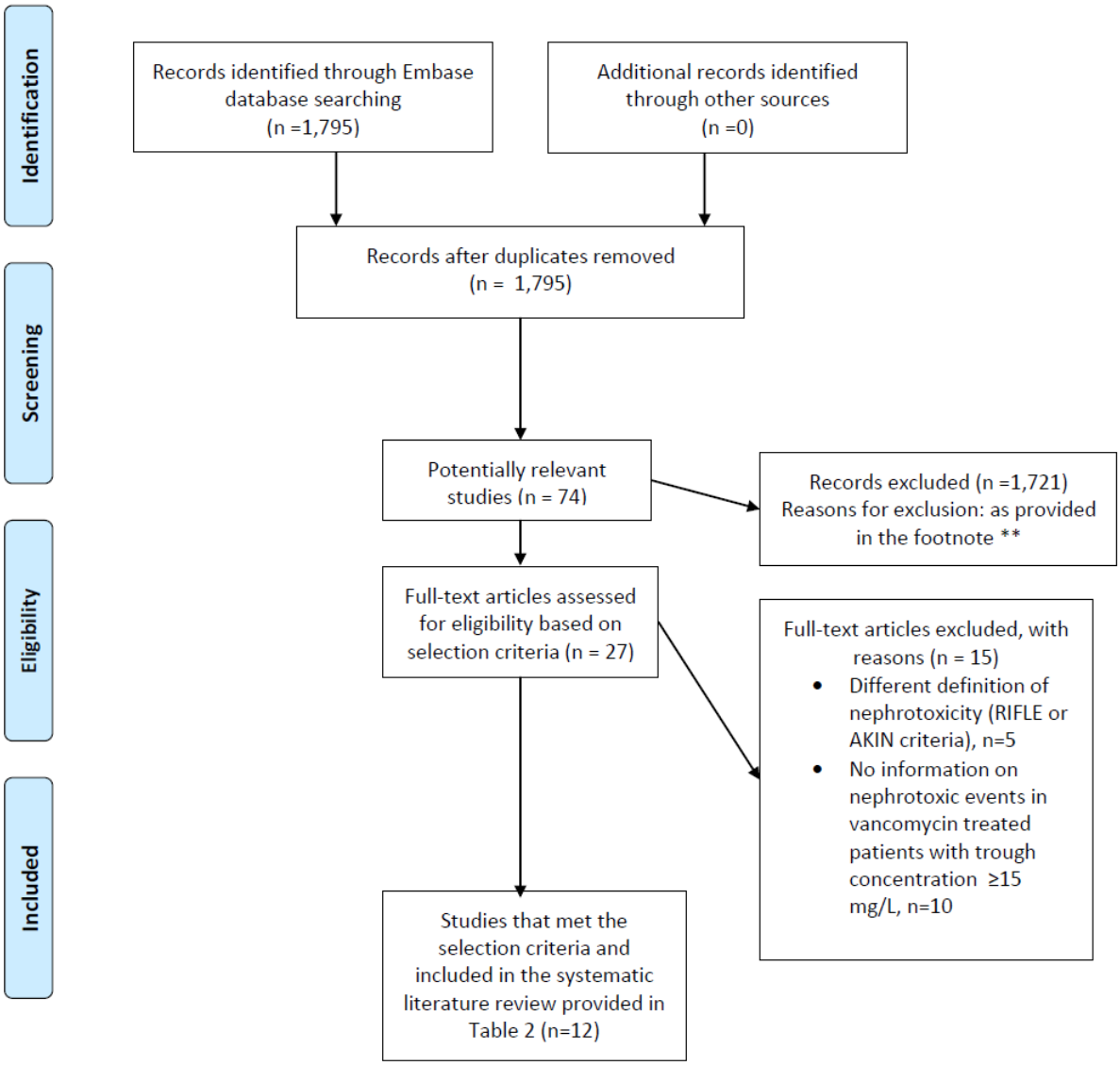
Reference	Study population	Dose of Teicoplanin	Endpoint	Definition of the endpoint	Number of patients with endpoint	Total N in Teicoplanin Group	Teicoplanin Mean Treatment Duration (Days)	Incidence Rate reported as % (95% CI)[†]	Incidence Rate per 100 Persons-days of treatment (95% CI)[‡]
Ueda et al (2014)	154 patients with isolated MRSA or gram-positive infection	Loading dose of 400 mg twice daily on the first day followed by 400 mg once daily (n=16) OR Loading dose of 400 mg twice daily on initial 2 days followed by 400 mg once daily (n=78) OR Loading dose of 600 mg twice daily for the initial 2 days followed by 600 mg daily on the third day followed by 400 mg once daily (n=60)	Nephrotoxicity	SCr increase of more than 0.5 mg/L or 50% increase from baseline	3	154	Not stated	1.95 (0.40, 5.59)	Cannot be estimated
Pea et al (2003)	202 adult critically ill patients being treated for suspected or documented Grampositive multiresistant infections multiresistant infections	Initial loading dose of 6mg/kg every 12 hours for 3 doses followed by a maintainence dose based on patients renal function	Nephrotoxicity	Increase in SCr >0.5 mg/dL	4	202	Not stated	1.98 (0.54, 4.99)	Cannot be estimated
Van Der Auwera et al (1991)	74 immunocompromis-ed patients with severe infection due to gram-positive organisms	400 mg once a day (qd) i.v. (approximately 6 mg/kg) (infused over 30 min) for the first 3 days and then 200 mg qd i.v. until 3 days of apyrexia	Nephrotoxicity	Increase in serum creatinine ≥0.5 mg/dL	0	36	11	0.00 (0.00, 0.00)	Cannot be estimated

Reference	Study population	Dose of Teicoplanin	Endpoint	Definition of the endpoint	Number of patients with endpoint	Total N in Teicoplanin Group	Teicoplanin Mean Treatment Duration (Days)	Incidence Rate reported as % (95% CI)[†]	Incidence Rate per 100 Persons-days of treatment (95% CI)[‡]
Ueda et al (2014)	154 patients with isolated MRSA or gram-positive infection	loading dose of 400 mg twice daily on the first day followed by 400 mg once daily (n=16)	Hepatotoxicity	AST or ALT 3 times the upper limit of normal (AST: 13-33 IU/L, ALT: 8-42 IU/L).	0	16	9.20	0.00 (0.00, 0.00)	0.000 (0.00, 0.00)
Ueda et al (2014)	154 patients with isolated MRSA or gram-positive infection	loading dose of 400 mg twice daily on intital 2 days followed by 400 mg once daily (n=78)	Hepatotoxicity	AST or ALT 3 times the upper limit of normal (AST: 13-33 IU/L, ALT: 8-42 IU/L).	4	78	9.10	5.13 (1.41, 12.61)	0.564 (0.011, 1.116)
Ueda et al (2014)	154 patients with isolated MRSA or gram-positive infection	Loading dose of 600 mg twice daily for the initial 2 days followed by 600 mg daily on the third day followed by 400 mg once daily (n=60)	Hepatotoxicity	AST or ALT 3 times the upper limit of normal (AST: 13-33 IU/L, ALT: 8-42 IU/L).	2	60	9.80	3.33 (0.41, 11.53)	0.340 (-0.131, 0.812)
Menichetti et al (1994)	635 consecutive febrile patients with hematologic malignancies and chemotherapy-induced neutropenia	6 mg/kg/day in a single daily dose dissolved in 10 ml of sterile water and administered intravenously over 3 min, with an initial loading dose of 8 mg/kg	Hearing and balance disorders	Transient hearing loss	1	275	12.00	0.36 (0.01, 2.01)	0.030 (-0.029, 0.090)

Reference	Study population	Dose of Teicoplanin	Endpoint	Definition of the endpoint	Number of patients with endpoint	Total N in Teicoplanin Group	Teicoplanin Mean Treatment Duration (Days)	Incidence Rate reported as % (95% CI)†	Incidence Rate per 100 Persons-days of treatment (95% CI)‡
Rolston et al (1999)	240 patients with suspected bacteremia/septicemia secondary to vascular access-associated gram-positive infection	Three loading doses of teicoplanin, 6 mg/kg, at 12-h intervals, followed by an alternating doseof teicoplanin, 6 mg/kg, every 12 h.	Hearing and balance disorders	Ototoxicity based on Audiometric evaluation	2	117	Not stated	1.71 (0.21, 6.04)	Cannot be estimated
Wang et al (2013)	270 adult patients > 18 years with teicoplanin-treated MRSA BSI in two Taiwan medical centers (years 2006-09)	Loading dose: 6 mg/kg every 12 hours for 3 doses; Maintenance dose: 6 mg/kg every 24 hrs	Thrombocytopenia	Platelet count < 150,000/μL	3	270	19.00	1.11 (0.23, 3.21)	0.058 (-0.008, 0.125)

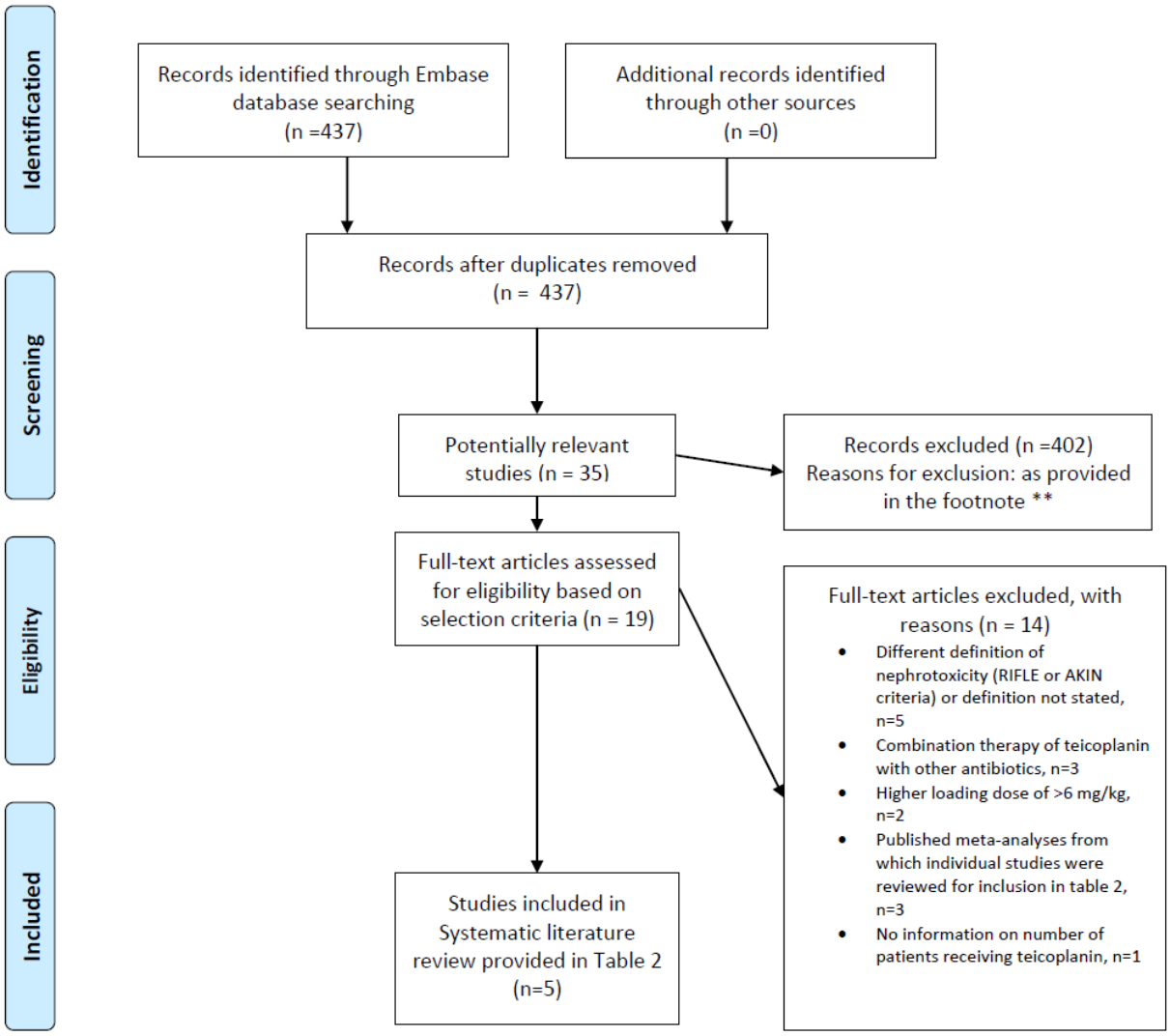
Footnotes:
Abbreviations: SCr, Serum creatinine; CI, Confidence Interval; MRSA, Methicillin-resistant Staphylococcus Aureus; BSI, Blood stream infection, AST, Aspartate aminotransferase; AST, Alanine aminotransferase
† Incidence rate has been calculated as a proportion of patients who experienced nephrotoxicity of all patients who received the treatment and reported as %.
‡ Incidence rate has been calculated per 100 person-days of treatment by taking into account the mean/median duration of treatment.

Figure 3. Flow diagram of the selection process of the included studies providing incidence of nephrotoxicity associated with vancomycin trough concentration of ≥ 15 mg/L



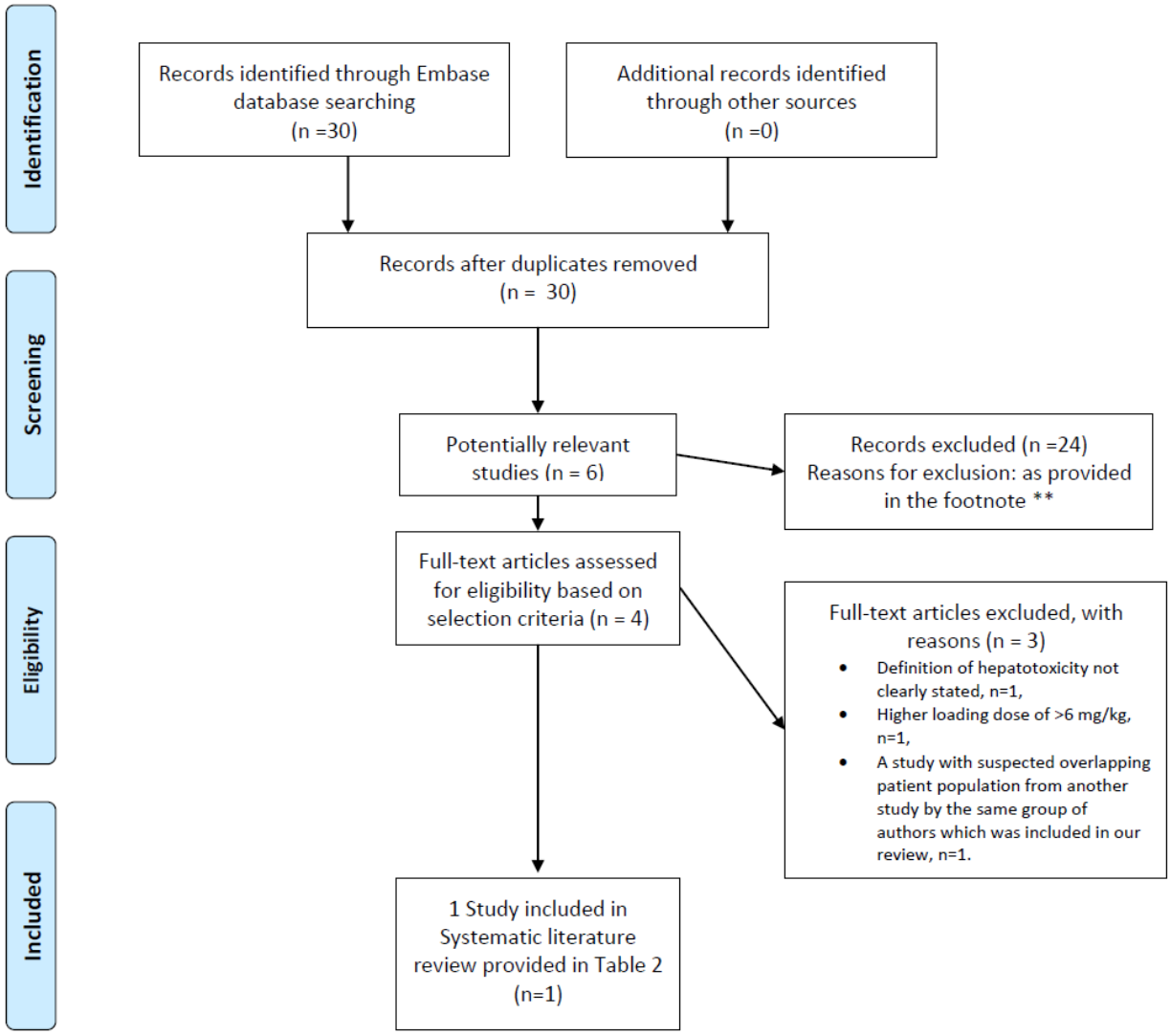
** (1) Abstract or poster presented at a scientific conference or letter to the editor, (2) Aminoglycoside agent or other nephrotoxic agents other than vancomycin, (3) Study population: Children, (4) Standard dose of vancomycin with trough concentration <15 mg/L, (5) Continuous infusion of Vancomycin, (6) Full text not available, (7) Studies conducted in non-human subjects, (8) Case reports

Figure 4. Selection of studies providing incidence of nephrotoxicity associated with lower loading dose of teicoplanin



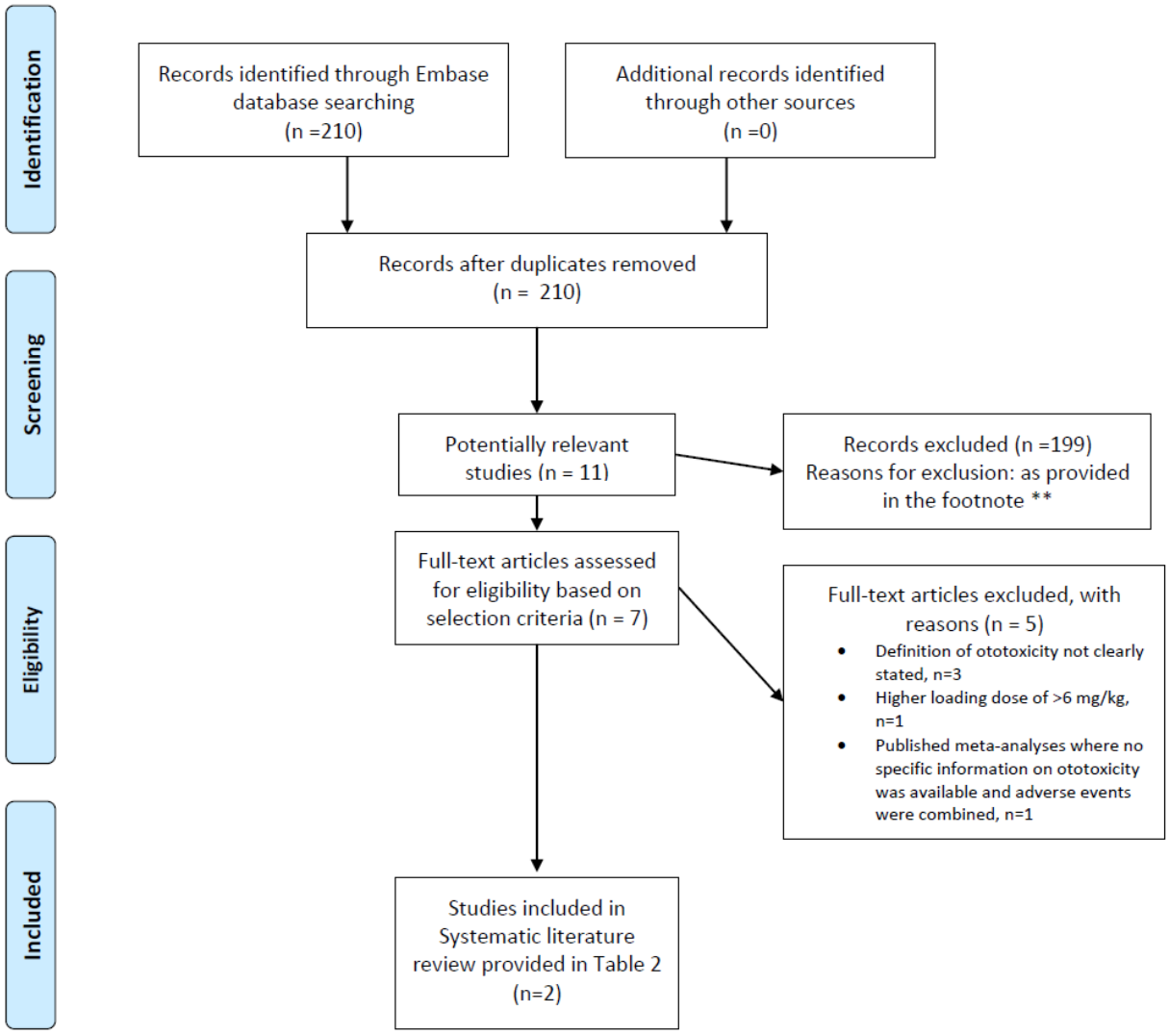
** (1) Abstract or poster presented at a scientific conference or letter to the editor, (2) Other nephrotoxic agents other than teicoplanin or high loading dose of teicoplanin >6 mg/kg, (3) Study population: Children, (4) Full text not available, (5) Studies conducted in non-human subjects, (6) Case report

Figure 5. Selection of studies providing incidence of hepatotoxicity associated with lower loading dose of teicoplanin



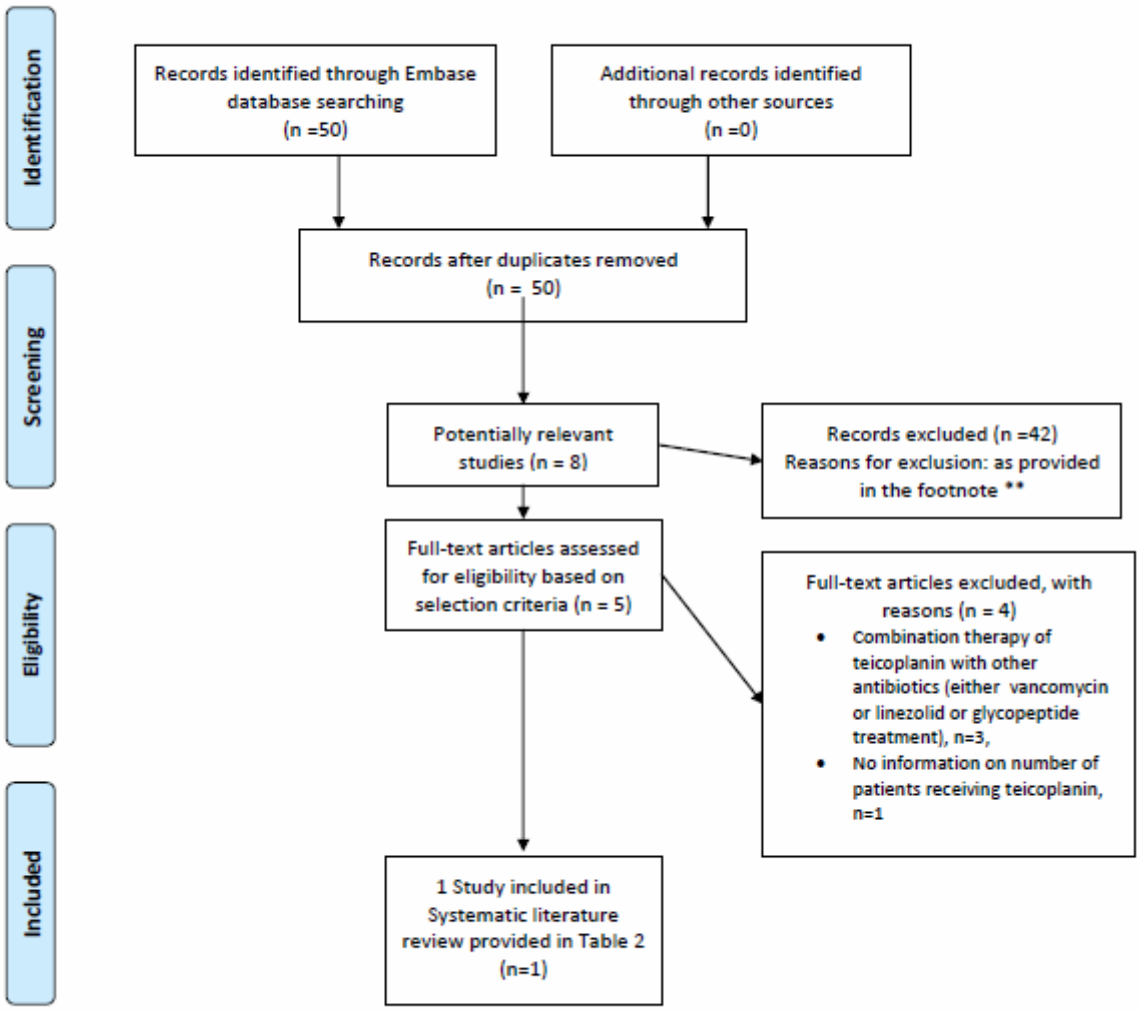
** (1) Abstract or poster presented at a scientific conference or letter to the editor, (2) antibacterial agents other than teicoplanin, (3) Study population involving children, (4) Case reports

Figure 6. Selection of studies providing incidence of hearing and balance disorders associated with lower loading dose of teicoplanin



** (1) Abstract or poster presented at a scientific conference or letter to the editor, (2) antibacterial agents other than teicoplanin or high loading dose of teicoplanin >6 mg/kg, (3) Study population involving children, and (4) Case reports.

Figure 7. Selection of studies providing incidence of thrombocytopenia associated with lower loading dose of teicoplanin



** (1) Abstract or poster presented at a scientific conference or letter to the editor, (2) antibacterial agents other than teicoplanin or high loading dose of teicoplanin >6 mg/kg, (3) Study population involving children, and (4) Case reports.

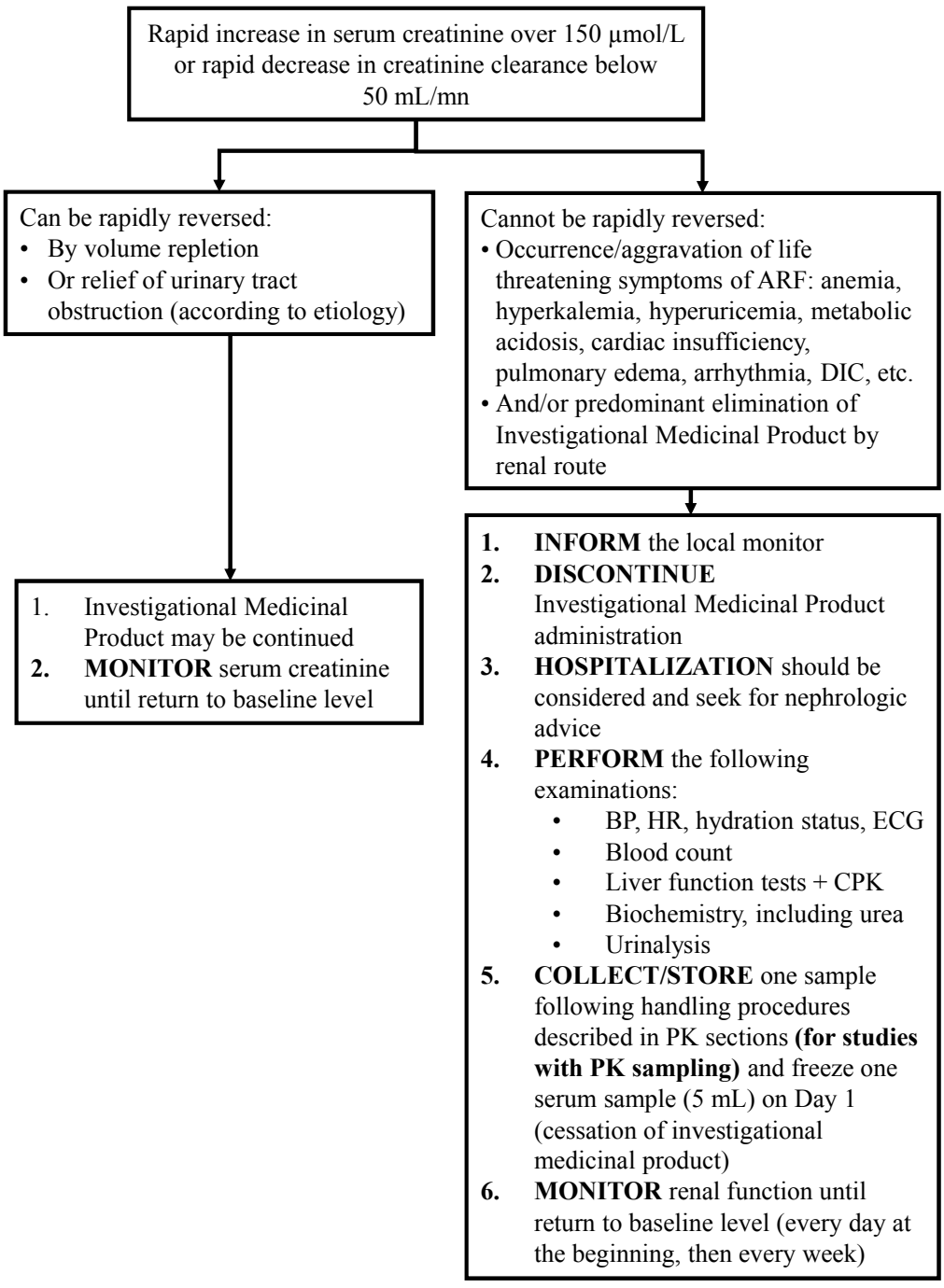
SAPS II scoring sheet

Variable points	26	13	12	11	9	7	6	5	4	3	2	0	1	2	3	4	6	7	8	9	10	12	15	16	17	18
Age, years												< 40						40 – 59				60 – 69	70 – 74	75 – 79		> 80
Heart rate, beats/min				< 40							40 – 69	70 – 119				120 – 159		≥ 160								
Systolic BP (mmHg)		< 70						70 – 99				100 – 199		> 200												
Body Temperature, °C, (°F)												< 39° (102.2°)			>39° (>102.2°)											
Only if ventilation or continuous spontaneous arterial pressure PaO_2, mm Hg/FiO_2				< 100	100 – 199		≥ 200																			
PaO_2, kpa/FiO_2				< 13.3	13.3 – 26.5		≥ 26.6																			
Urinary output, L/D				< 0.500					0.500 – 0.999			≥ 1000														
Serum urea level, mmol/dl												< 10.0 (< 0.60) < 28					10.0 – 29.9 (6.0 – 1.79) 28 – 83				≥ 30.0	(≥ 1.80) ≥ 84			
WBC count (1.0/cu mm)			< 1.0									1.0 – 19.9			≥ 20.0											
Serum potassium mmol/l										< 3.0		3.0 – 4.9			≥ 5.0											
Serum Sodium level, mmol/l								< 125				125 – 144	> 145													
Serum bicarbonate level, mEq/l							< 15			15 – 19		≥ 20														
Bilirubin level, mmol/l (mg/dl)												< 68.4 (< 4.0)				68.4 – 102.5 (4.0 – 5.9)				≥ 102.6 (≥ 6.0)						
Glasgow Coma Score	< 6	6 – 8				9 – 10		11 – 13				14 – 15														
Chronic disease																				Metast. cancer	Hema-tologic malig-nancy				AIDS	
Type of admission												Sched. surgical					Medical		Unsched. surgical							
Sum of points																										

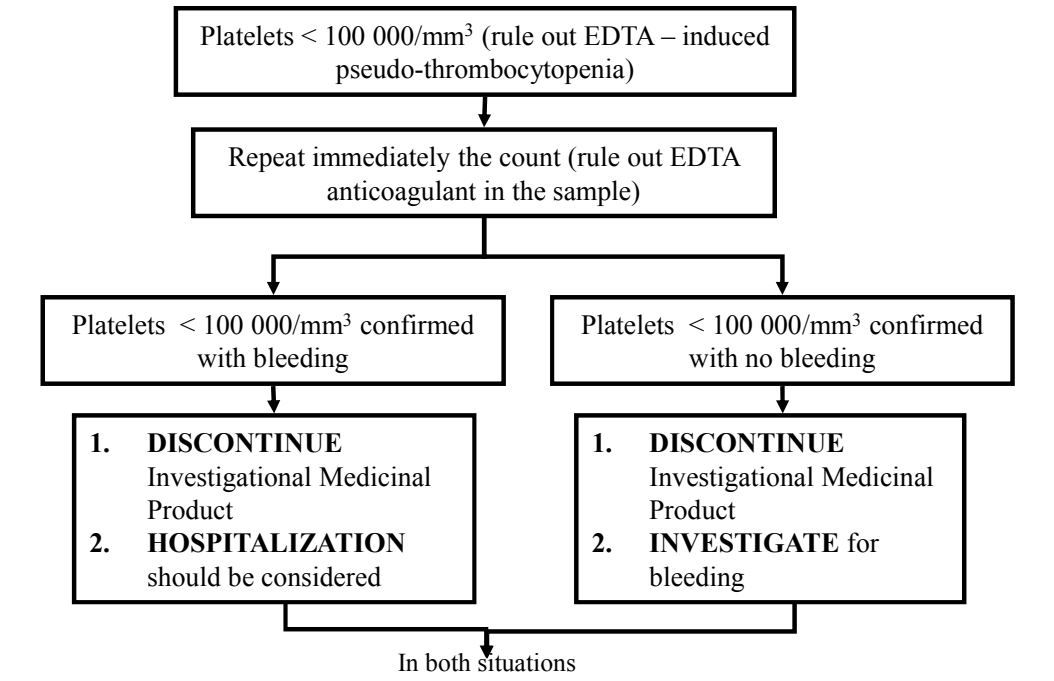
Total SAPS II Score = Points
Risk of Hospital Death =

General guidance for the follow-up of laboratory abnormalities

ACUTE RENAL FAILURE

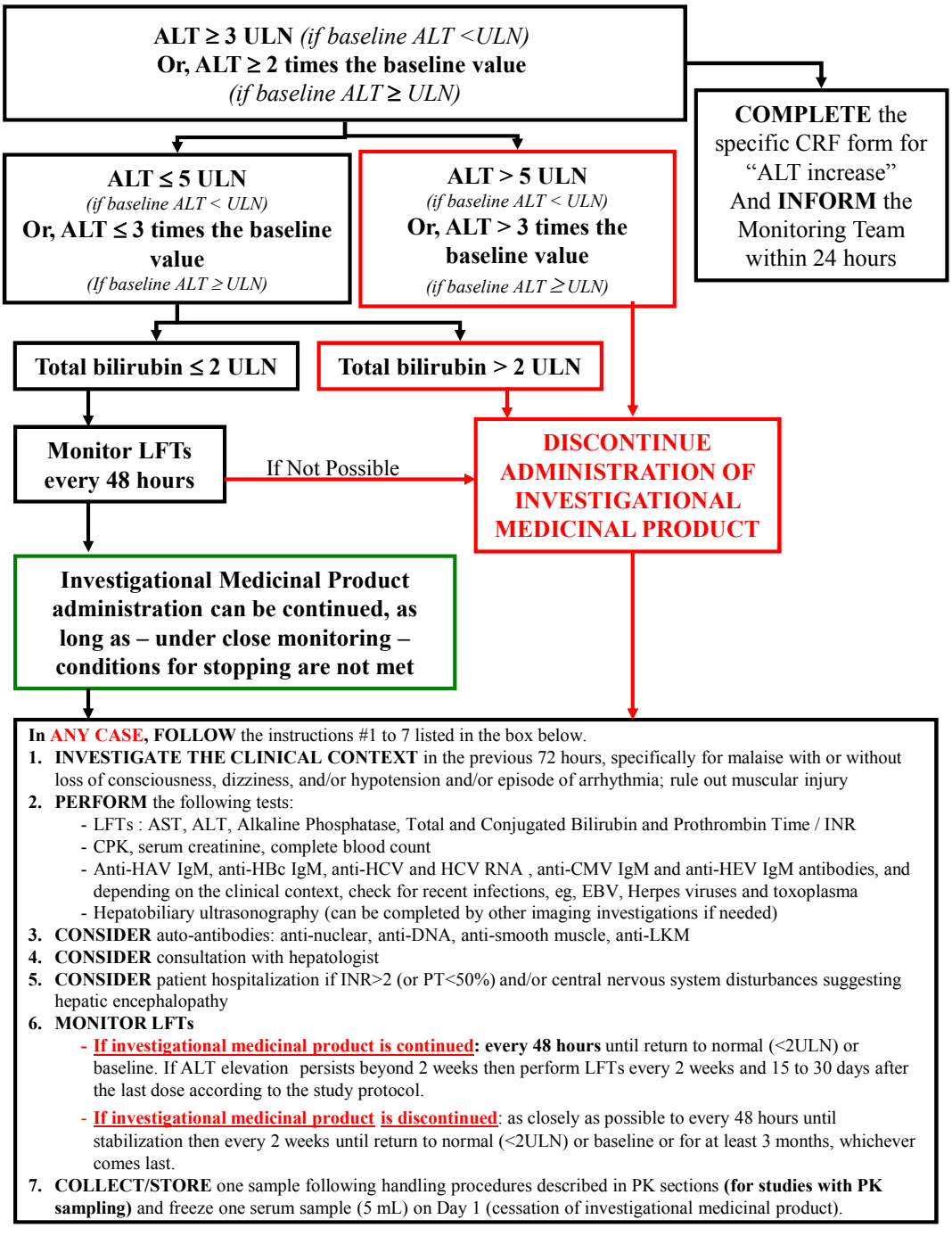


THROMBOCYTOPENIA



Note:
The procedures above flowchart are to be discussed with the patient only in case described in the the event occurs. If applicable (according to local regulations), an additional consent (e.g., for HIV testing) will only be obtained in the case the event actually occurs.

INCREASE IN ALT



CRITERIA for POTENTIALLY CLINICALLY SIGNIFICANT ABNORMALITIES

(From BTD-009536 – 21-MAY-2014)

Parameter	PCSA	Comments
Clinical Chemistry		
ALT	By distribution analysis : >3 ULN >5 ULN >10 ULN >20 ULN	Enzymes activities must be expressed in ULN, not in IU/L. Concept paper on DILI – FDA draft Guidance Oct 2007. Internal DILI WG Oct 2008. Categories are cumulative. First row is mandatory. Rows following one mentioning zero can be deleted.
AST	By distribution analysis : >3 ULN >5 ULN >10 ULN >20 ULN	Enzymes activities must be expressed in ULN, not in IU/L. Concept paper on DILI – FDA draft Guidance Oct 2007. Internal DILI WG Oct 2008. Categories are cumulative. First row is mandatory. Rows following one mentioning zero can be deleted.
Alkaline Phosphatase	>1.5 ULN	Enzymes activities must be expressed in ULN, not in IU/L. Concept paper on DILI – FDA draft Guidance Oct 2007. Internal DILI WG Oct 2008.
Total Bilirubin	>1.5 ULN >2 ULN	Must be expressed in ULN, not in µmol/L or mg/L. Categories are cumulative. Concept paper on DILI – FDA draft Guidance Oct 2007. Internal DILI WG Oct 2008.
Conjugated Bilirubin	>35% Total Bilirubin and TBILI>1.5 ULN	Conjugated bilirubin dosed on a case-by-case basis.
ALT and Total Bilirubin	ALT>3 ULN and TBILI>2 ULN	Concept paper on DILI – FDA draft Guidance Oct 2007. Internal DILI WG Oct 2008. To be counted within a same treatment phase, whatever the interval between measurements.
CPK	>3 ULN >10 ULN	FDA Feb 2005. Am J Cardiol April 2006. Categories are cumulative. First row is mandatory. Rows following one mentioning zero can be deleted.
eGFR (mL/min/1.73m2) (Estimate of GFR based on an MDRD equation)	<15 (end stage renal disease) ≥15 - <30 (severe decrease in GFR) ≥30 - < 60 (moderate decrease in GFR) ≥60 - <90 (mild decrease in GFR) ≥ 90 (normal GFR)	FDA draft Guidance 2010 Pharmacokinetics in patients with impaired renal function-study design, data analysis, and impact on dosing and labeling
CLcr (mL/min) (Estimated creatinine clearance based on the Cokcroft-Gault equation)	<15 (end stage renal disease) ≥15 - <30 (severe decrease in GFR) ≥30 - < 60 (moderate decrease in GFR) ≥60 - <90 (mild decrease in GFR) ≥ 90 (normal GFR)	FDA draft Guidance 2010 Pharmacokinetics in patients with impaired renal function-study design, data analysis, and impact on dosing and labeling

CRITERIA for POTENTIALLY CLINICALLY SIGNIFICANT ABNORMALITIES

(From BTD-009536 – 21-MAY-2014)

Parameter	PCSA	Comments
Creatinine	≥150 µmol/L (Adults) ≥30% change from baseline ≥100% change from baseline	Benichou C., 1994.
Uric Acid Hyperuricemia Hypouricemia	 >408 µmol/L <120 µmol/L	Harrison- Principles of internal Medicine 17th Ed., 2008.
Blood Urea Nitrogen	≥17 mmol/L	
Chloride	<80 mmol/L >115 mmol/L	
Sodium	≤129 mmol/L ≥160 mmol/L	
Potassium	<3 mmol/L ≥5.5 mmol/L	FDA Feb 2005.
Total Cholesterol	≥7.74 mmol/L	Threshold for therapeutic intervention.
Triglycerides	≥4.6 mmol/L	Threshold for therapeutic intervention.
Lipasemia	≥3 ULN	
Amylasemia	≥3 ULN	
Glucose Hypoglycaemia Hyperglycaemia	 ≤3.9 mmol/L and <LLN ≥11.1 mmol/L (unfasted); ≥7 mmol/L (fasted)	 ADA May 2005. ADA Jan 2008.
HbA1c	>8%	
Albumin	≤25 g/L	
CRP	>2 ULN or >10 mg/L (if ULN not provided)	FDA Sept 2005.
Hematology		
WBC	<3.0 Giga/L (Non-Black); <2.0 Giga/L (Black) ≥16.0 Giga/L	Increase in WBC: not relevant. To be interpreted only if no differential count available.
Lymphocytes	>4.0 Giga/L	
Neutrophils	<1.5 Giga/L (Non-Black);<1.0 Giga/L (Black)	International Consensus meeting on drug-induced blood cytopenias, 1991. FDA criteria.
Monocytes	>0.7 Giga/L	
Basophils	>0.1 Giga/L	
Eosinophils	>0.5 Giga/L or >ULN (if ULN≥0.5 Giga/L)	Harrison- Principles of internal Medicine 17th Ed., 2008.
Hemoglobin	≤115 g/L (Male); ≤95 g/L (Female) ≥185 g/L (Male); ≥165 g/L (Female) Decrease from Baseline ≥20 g/L	Criteria based upon decrease from baseline are more relevant than based on absolute value. Other categories for decrease from baseline can be used (≥30 g/L, ≥40 g/L, ≥50 g/L).
Hematocrit	≤0.37 v/v (Male) ; ≤0.32 v/v (Female) ≥0.55 v/v (Male) ; ≥0.5 v/v (Female)	
RBC	≥6 Tera/L	Unless specifically required for particular drug development, the analysis is redundant with that of Hb. Otherwise, consider FDA criteria.

CRITERIA for POTENTIALLY CLINICALLY SIGNIFICANT ABNORMALITIES

(From BTD-009536 – 21-MAY-2014)

Parameter	PCSA	Comments
Platelets	<100 Giga/L ≥700 Giga/L	International Consensus meeting on drug-induced blood cytopenias, 1991.
Urinalysis		
pH	≤4.6 ≥8	
Vital signs		
HR	≤50 bpm and decrease from baseline ≥20 bpm ≥120 bpm and increase from baseline≥20 bpm	To be applied for all positions (including missing) except STANDING.
SBP	≤95 mmHg and decrease from baseline ≥20mmHg ≥160 mmHg and increase from baseline ≥20 mmHg	To be applied for all positions (including missing) except STANDING.
DBP	≤45 mmHg and decrease from baseline ≥10 mmHg ≥110 mmHg and increase from baseline ≥10 mmHg	To be applied for all positions (including missing) except STANDING.
Orthostatic Hypotension Orthostatic SDB Orthostatic DBP	 ≤-20 mmHg ≤-10 mmHg	
Weight	≥5% increase from baseline ≥5% decrease from baseline	FDA Feb 2007.
ECG		Ref.: ICH E14 guidance (2005) and E14 Q&A (2012), and Cardiac Safety Research Consortium White Paper on PR and QRS (Nada et al. Am Heart J. 2013; 165(**16**) : 489-500)
HR	<50 bpm <50 bpm and decrease from baseline ≥20 bpm <40 bpm <40 bpm and decrease from baseline ≥20 bpm <30 bpm <30 bpm and decrease from baseline ≥20 bpm >90 bpm >90 bpm and increase from baseline ≥20bpm >100 bpm >100 bpm and increase from baseline ≥20bpm >120 bpm >120 bpm and increase from baseline ≥20 bpm	Categories are cumulative Categories are cumulative
PR	>200 ms >200 ms and increase from baseline ≥25% > 220 ms >220 ms and increase from baseline ≥25% > 240 ms > 240 ms and increase from baseline ≥25%	Categories are cumulative
QRS	>110 ms >110 msec and increase from baseline ≥25% >120 ms >120 ms and increase from baseline ≥25%	Categories are cumulative
QT	>500 ms	

CRITERIA for POTENTIALLY CLINICALLY SIGNIFICANT ABNORMALITIES

(From BTD-009536 – 21-MAY-2014)

Parameter	PCSA	Comments
QTc	Absolute values (ms) >450 ms >480 ms >500 ms Increase from baseline Increase from baseline]30-60] ms Increase from baseline >60 ms	To be applied to any kind of QT correction formula. Absolute values categories are cumulative QTc >480 ms and ΔQTc>60 ms are the 2 PCSA categories to be identified in individual subjects/patients listings.