European Medicines Agency

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Product name: **INVANZ**
Procedure No: **EMEA/H/C/389/II/13**

SCIENTIFIC DISCUSSION

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1. Introduction

Ertapenem sodium is a sterile, synthetic, long-acting, parental, 1β-methylcarbapenem that is structurally related to β-lactam antibiotics with activity against a wide range of gram-positive and gram-negative aerobic and anaerobic bacteria.

The bactericidal activity of ertapenem results from the inhibition of cell wall synthesis and is mediated through ertapenem binding to penicillin binding proteins.
Ertapenem sodium is a white to off-white hygroscopic, crystalline solid. It is soluble in water and 0.9% sodium chloride solution, practically insoluble in ethanol, and insoluble in isopropyl acetate and tetrahydrofuran.

Invanz is supplied as sterile lyophilised powder for intravenous infusion after reconstitution with appropriate diluent and transfer to 50 ml 0.9% Sodium Chloride Injection; or for intramuscular injection following reconstitution with 3.2 ml of 1% lidocaine hydrochloride. Each vial contains 1.046 grams (g) ertapenem sodium, equivalent to 1 g ertapenem.

The initial Marketing Authorisation was granted on 18 April 2002 by the European Commission.

In November 2004 the MAH submitted the present type II variation to include "Complicated skin and soft tissue infection, including diabetic foot infections" for the current approved indications:
"Treatment of the following infections in adults when caused by bacteria known or very likely to be susceptible to ertapenem and when parenteral therapy is required:

- Intra-abdominal infections
- Community acquired pneumonia
- Acute gynaecological infections"

On the basis of the results of a clinical study named "Protocol 034", *a prospective, randomised, multicenter, double-blind, active-treatment-controlled, non-inferiority study to evaluate the safety, tolerability, and efficacy of ertapenem versus piperacillin/tazobactam (P/T) in the treatment of diabetic foot infections (DFI) in adults*, the MAH submitted an application for an extension of indication of the use of Invanz to "Complicated skin and soft tissue infection, including diabetic foot infections". Further to the assessment of the data submitted, **the extension of indication has been restricted to "diabetic foot infections of skin and soft tissue".**

2. Clinical aspects

2.1 Clinical efficacy

- **<u>Description of the main study: Protocole 034.</u>**

Protocol 034 was a prospective, randomised, multicentre, double-blind, active-treatment-controlled, non-inferiority study conducted in 89 centres in the USA to evaluate the safety, tolerability, and efficacy of ertapenem versus piperacillin/tazobactam (P/T) in the treatment of diabetic foot infections (DFI) in adults. This study, which began on 27 April 2001 (FPI) and ended 21 April 2004, was anticipated to enrol 600 patients (300 on ertapenem) from 89 study sites in the United States, in order to achieve 200 clinically evaluable patients in each treatment group. Each patient was expected to complete the study, including follow-up, within 6 weeks. Last Patient Out (LPO) was on 21 April 2004 and all data was received in-house by 24 June 2004.

- **Methods and results from the main study: Protocole 034.**

  - **Methods**

The newly submitted study (P034) was initiated in 27 April 2001 and finished in 21 April 2004, and conducted at 89 centres in the United States.

The study was conducted in conformance with applicable country or local requirements regarding ethical committee review, informed consent, and other statutes or regulations regarding the protection of the rights and welfare of human subjects participating in biomedical research.

Study objectives

- The **primary objective** of the study was to compare the efficacy of ertapenem and piperacillin/tazobactam with respect to the clinical response in patients evaluable for clinical efficacy at the Discontinuation of IV Therapy Assessment.

- **Secondary objectives** were to compare the efficacy of ertapenem and piperacillin /tazobactam in patients evaluable at the Follow-Up Assessment, 10 days post antibiotic therapy with respect to:
a. Clinical response in patients at the Follow-Up Assessment.
b. Clinical and microbiological response at the Follow-Up Assessment in patients with a confirmed microbiologic pathogen.
c. Clinical response in patients at DCIV therapy.
2. To compare the safety and tolerability of ertapenem and piperacillin/tazobactam with respect to drug-related adverse experiences (AEs), drug-related serious adverse events (SAEs), and drug-related adverse events (AEs) leading to study drug discontinuation.

As an additional exploratory objective, the study also aimed at the evaluation of the relationship between the Diabetic Foot Infection (DFI) Wound Score of the primary wound site and clinical response.

Enrolment - Inclusion and exclusion criteria

Inclusion and exclusion criteria were applied in order to enroll patients with appropriate diabetic foot infections that were likely to require 5 to 28 days of parenteral therapy and were not complicated by preexisting conditions which could confound the evaluation of the efficacy or safety profiles of the study drugs.

Particularly, the following **inclusion and exclusion criteria** were considered:
- For a clinical diagnosis of diabetic foot infection, patients must have had well-documented signs and symptoms of acute infection located on or above the foot, but not extending past the knee.
- For patients who had received a >7 day course of prior antibiotic therapy or in whom pseudomonas infection was suspected, wound cultures were to be taken to rule out pathogens resistant to either study drug. If culture results identified pathogen(s) resistant to either study drug after initiating treatment but the patient showed clinical improvement the patient could remain in the study at the discretion of the investigator (upon ammendment of the initial protocol, which required that patients with resistant pathogens at screening would not be enrolled).
- In cases in which patients had prior surgery, at least 7 days must have elapsed before entry into the study.
- Infection had to be without the presence of unremovable indwelling foreign material (such as prosthetic or surgical hardware) or evidence of gangrene that could not be removed with debridement. In cases in which surgical debridement and wound approximation was performed, and, in the opinion of the physician, there was a need to maintain sutures in the wound, the patient was considered eligible if all other criteria were met.
- Patients who receive empiric vancomycin therapy for treatment of enterococcal or MRSA infection or a history of MRSA infection would be considered clinically and microbiologically

unevaluable if entry cultures are only positive for methicillin resistant S. aureus or other organisms susceptible to vancomycin. Patients treated with vancomycin who have mixed infections will be considered clinically evaluable. Gram-positive pathogens will be non-evaluable and gram-negative pathogens and anaerobes will be evaluable.

- Patients who received more than 24 hours of systemic antibiotic therapy known to be effective against the presumed or documented etiologic pathogen(s) within the 3 days prior to receipt of the first dose of study drug, except for those patients entered as clinical failures on prior antibiotic therapy with a positive baseline wound culture, would be considered non-evaluable. In addition, any non-study antibiotic therapy administered between the time of the first dose of study drug and the follow-up assessment would make the patient nonevaluable**.**

Patients with known or suspected osteomyelitis underwent an additional review. The roentgenographic changes characteristic of osteomyelitis can take several weeks to appear on plain films, resulting in falsely negative x-ray findings early in infection. Before the assessment of evaluability was made, a determination of whether osteomyelitis was present at eligibility screening was made based on the date of diagnosis. A window of 7 days from eligibility screening was selected as a conservative estimate for detection of pre-existing osteomyelitis. Patients with osteomyelitis diagnosed within 48 hours of initiation of study therapy were considered clinically non-evaluable due to baseline medical condition unless all infected bone was removed as described in the DAP. For patients with osteomyelitis detected between 48 hours and Study Day 7, the investigator was queried to confirm whether osteomyelitis was present at study entry. If, in the investigator's clinical judgment, osteomyelitis was present at study entry, the patient was clinically non-evaluable. If osteomyelitis was diagnosed after Study Day 7, the patient was considered a clinically evaluable failure, unless, in the opinion of the investigator, extenuating circumstances precluded classification as a failure, in which case the clinical response could be indeterminate.

The studied population cannot be considered representative for the major group of patients with diabetic foot infections, which generally includes osteomyelitis and severely impaired perfusion. Therefore as patients with osteomyelitis have not been included in this study, the CHMP decided that a statement should be included in section 4.4 of the SPC to reflect that **the efficacy of ertapenem in the treatment of diabetic foot infections with concurrent osteomyelitis has not been established**.

Adult patients with diabetes mellitus who met all of the entry criteria and had a clinically or bacteriologically documented diabetic foot infection (defined as at least the presence of cellulitis with or without ulceration, or purulent discharge) judged by the investigator to require parenteral antibiotic therapy for a minimum of 5 days and a maximum of 28 days were enrolled. For a clinical diagnosis of diabetic foot infection, the primary site of infection was required to have either purulent drainage from the wound and/or at least 3 established signs and symptoms of acute infection located on or above the foot, but not extending past the knee.

Patients had an initial eligibility screening assessment within 48 hours prior to initiation of study therapy that included a complete physical examination, detailed clinical wound assessment of the primary and any secondary wounds, a baseline wound culture, and an x-ray examination of the involved lower extremity. Investigators were instructed to make every attempt to obtain a deep tissue culture, however if no culture was obtained or if no baseline pathogen was isolated, the patient remained in the study for clinical evaluation. If culture results from an appropriately obtained wound specimen were not available at the time of the eligibility screening, a patient could have been entered into the study pending the culture results. If the culture results were negative, then the patient was considered to be nonevaluable and must have been withdrawn from the study. (Subsequently, in Protocol Amendment 02, this was further elaborated to include: If the culture results were negative, but the patient showed clinical improvement, they could be continued in the study at the investigator's discretion.) If the baseline culture was known prior to enrolment to contain a pathogen resistant to either study drug, the patient should not have been enrolled in the study. If the baseline culture was found during the study to be resistant to either of the study drugs and there was no clinical improvement, the patient should have been discontinued as a failure; if the patient was improving, he/she was allowed to remain in the study at the discretion of the investigator. (Subsequently, in Protocol Amendment 02, this was further elaborated to include : Patients with pathogens identified as

resistant to either study drug after initiating study therapy but who showed clinical improvement could be continued in the study at the discretion of the investigator.)

Randomisation

Diabetic patients who met all of the entry criteria were randomised to 1 of the 2 study regimens in a 1:1 ratio. Allocations were stratified for severity of disease based on the baseline classification of the primary wound according to the University of Texas Wound Classification Scale. Infections classified as Grade 0 Stage B, Grade 0 Stage D, Grade 1 Stage B, and Grade 1 Stage D were considered moderate diabetic foot infections (Stratum I), while infections classified as Grade 2 Stage B, Grade 2 Stage D, Grade 3 Stage B, and Grade 3 Stage D were considered severe (but not life-threatening) infections (Stratum II).

Changes in the Conduct of the Study or Planned Analyses

Five (5) amendments to the original protocol (34-01, 034-02, 034-04, 034-05, and 034-06) were implemented prior to unblinding the study. One amendment (034-03) incorporating an exploratory health economics objective was not released to investigators and was never implemented.

Two amendments were medically significant, both contained in amendment 02 which was the single protocol amendment that clarified multiple parameters for the study. Also in this protocol, was the clarification for evaluability of : "The evaluability criteria were revised to indicate that patients who received more than 24 hours of systemic antibiotic therapy known to be effective against the presumed or documented etiologic pathogen(s) within the 3 days prior to the first dose of study therapy would be non-evaluable, except for those patients entered as clinical failures on prior antibiotic therapy." These and other details of the amendments appear to increase/clarify the details of study parameters without changing their material nature, including clarifications of primary wound site in patients with multiple sites of infection in the lower extremity so that the tertiary objective evaluating the Diabetic Foot Infection Wound Score and clinical response was clarified to apply only to the primary wound.

Study medication and Dosage

Ertapenem was given as a single daily dose of 1 g IV. P/T was given at 3.375 g per dose IV every 6 hours. To maintain blinding, a matching IV placebo was administered at hours 6, 12, and 18 to patients randomised to receive ertapenem. The recommended duration of therapy was 5 to 28 days. Consistent with common clinical practice for the management of patients with DFI, investigators had an option to switch patients after at least 5 days of IV study therapy to a protocol specified oral follow-up antibiotic, amoxicillin/clavulanate (875 mg Q12 hours), if they had responded sufficiently and had met protocol-specified criteria for clinical improvement. Patients were to receive at least 5 days of parenteral therapy and to receive no less than 80% of the minimum and no greater than 120% of the maximum recommended antibiotic (IV alone or IV plus optional oral) study therapy. With the exception of open-label vancomycin for resistant Gram-positive infections, use of non-study systemic or topical antimicrobials was not permitted. Open label vancomycin was permitted in this study for treatment of *Enterococcus* or methicillin-resistant *Staphylococcus aureus* (MRSA) according to the usual practice of the investigator.

The comparator in the study, P/T, has a broad spectrum of *in vitro* activity encompassing relevant pathogens in this condition and is licensed for the treatment of skin and skin structure infections, (including ischemic/diabetic foot infections in the US).
After a period of parenteral study therapy, the patients could have been switched to an oral antimicrobial if they had improved sufficiently. Patients were required to meet criteria specified in the protocol before the investigator could have elected to change to oral therapy. The oral switch agent was amoxicillin/clavulanate, 875/125 mg twice daily. The investigator could have utilised another oral switch agent if baseline pathogens demonstrated resistance to the protocol-specified oral switch agent or if the patient was intolerant of the protocol-specified oral switch agent.
Open label vancomycin was permitted in this study for treatment of *Enterococcus* or methicillin-resistant *Staphylococcus aureus* (MRSA) according to the usual practice of the investigator. However,

these patients were considered clinically and microbiologically non-evaluable if entry cultures were only positive for Gram-positive organisms. Patients who received vancomycin may have been considered evaluable if they had mixed Gram-positive and Gram-negative or anaerobic infections; in the per pathogen analyses for these patients, only the Gram-negative pathogens and anaerobes were considered and the outcomes for vancomycin susceptible Gram-positives were considered indeterminate.

The ertapenem dose for this study was based on the results of the Clinical Pharmacology multiple-dose study, and upon the susceptibility of the organisms presumed to be the infecting bacteria, and/or Phase III data. Piperacillin/tazobactam was chosen as the comparator because it is used commonly to treat diabetic foot infections and has been previously shown to be safe and effective in treating these infections. The dosage selected was the usually recommended dose for this indication. It should be noted that the US dose regimen for piptazobactam (3 g piperacillin/375 mg tazobactam) delivers the same total daily dose of each component as 4 g/500 mg t.i.d. but the plasma profiles are inevitably different. There are currently no oral antibiotics indicated for the treatment of diabetic foot infections. Amoxicillin/clavulanate was chosen as the oral switch agent because it is commonly used to treat skin and skin structure infections and has activity both *in vitro* and in clinical studies against the aerobic and anaerobic pathogens commonly associated with diabetic foot infections, such as *Staphylococcus aureus(methicillin-sensitive)*. The usual adult dose for amoxicillin/clavulanate is 500 mg every 12 hours. For more severe infections the dose should be 875 mg every 12 hours or 500 mg every 8 hours. For this study a dose of 875 mg every 12 hours was chosen.

Efficacy evaluation

Clinical assessment of the infectious process was performed at eligibility screening, Day 5 of IV therapy, at the discontinuation of IV therapy (DCIV), at the discontinuation of oral therapy (DCOral) and at the Follow-up Assessment 10-day post antibiotic therapy (FUA). Overall clinical response was evaluated by the investigator at the DCIV and FUA visits. Microbiological response assessments were made separately for each pathogen identified at eligibility screening. Patients were monitored daily for adverse experiences and tolerability at the site of study drug infusion.

The **primary efficacy parameter** was the proportion of DCIV clinically evaluable patients who had a favorable clinical response assessment at the DCIV visit. Clinical response assessments were made by the investigator for all patients at Day 5 of IV Therapy, DCIV Visit, DCOral Visit and FUA Visit. For the efficacy analysis, only the clinical responses at DCIV and the FUA were considered.

The **secondary endpoints** were: (1) The proportion of FUA clinically evaluable patients who had a favorable clinical response assessment (“cure” or “improvement”) at the Follow-Up Assessment, 10 days post antibiotic therapy. (2) The proportion of FUA clinically and microbiologically evaluable patients who had both a favorable clinical (“cure” or “improvement”) and favorable microbiological (“eradication” or “presumptive eradication”) response to baseline pathogens at the Follow-Up Assessment 10 days post antibiotic therapy. (3) The proportion of FUA clinically evaluable patients who had a favorable clinical response assessment (“cure” or “improvement”) at Discontinuation of IV therapy.

The **exploratory endpoints** were: (1) The DFI Wound Score of the primary wound at all scheduled time points. (2) The proportion of FUA microbiologically evaluable patients who had a favorable microbiological response assessment (“eradication” or “presumptive eradication”) at Discontinuation of IV Therapy Assessment. (3) The proportion of FUA microbiologically evaluable patients who had a favorable microbiological response assessment (“eradication” or “presumptive eradication”) at the Follow-Up Assessment, 10 days post antibiotic therapy.

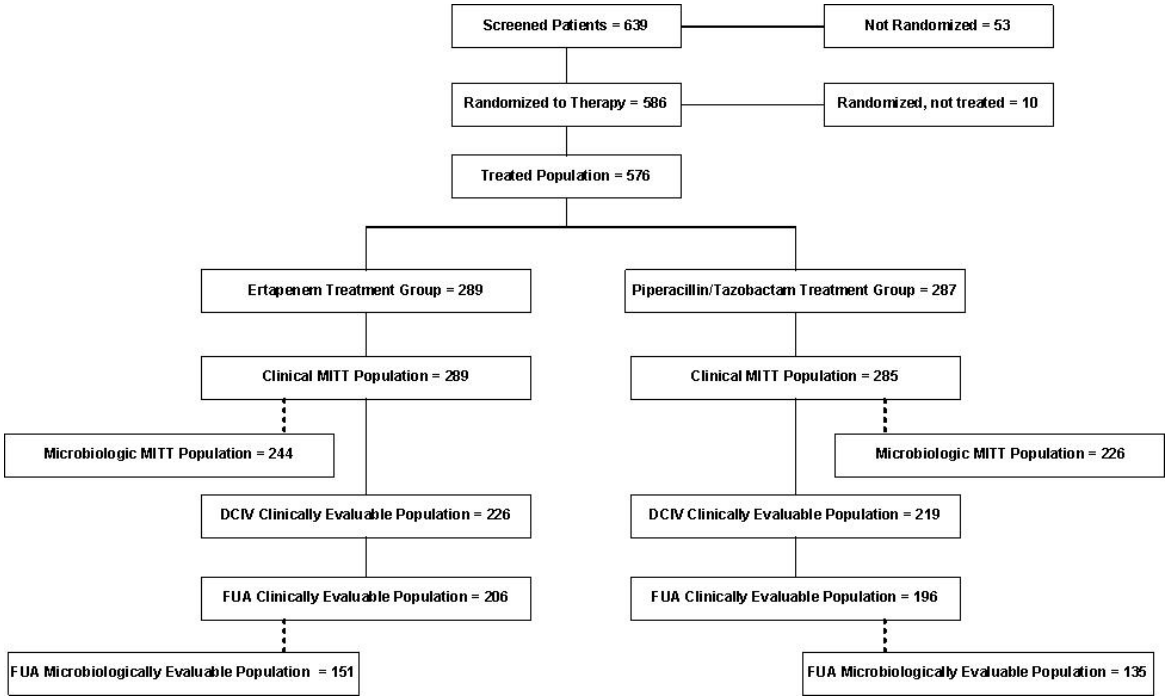
A **microbiological response** was assessed separately for each pathogen identified in the prestudy wound and blood cultures at the DCIV, DCOral, and FUA visits.

Definitions of populations

The following terms are used to describe the study populations analysed in this study:

• **Screened population:** all patients who signed a consent form for the study. This population includes those patients who were not randomised to therapy and those patients who were randomised to therapy.
• **Randomised population:** a subset of the screened population comprised of patients who were randomised to a study regimen, irrespective of whether the patient actually received study therapy. Patients randomised to one treatment group who, due to dispensing errors, mistakenly received study therapy with the other study treatment for the entire parenteral study period were analysed and displayed throughout the report based on the study therapy actually received. No patients received both parenteral study medication at any time during the study.
• **Treated Population:** a subset of the randomised population comprised of patients who received at least one dose of study therapy. Only treated patients are included in the safety analysis.
• **Clinical Modified Intent-to-Treat (MITT) population:** a subset of the treated population that met the minimal disease definition. The **Microbiologic MITT population**, a subset of the clinical MITT population, was comprised of those clinical MITT patients who had a baseline pathogen identified, regardless of susceptibility to study agents, and a microbiological response assessed. Determination of the clinical and microbiologic MITT populations was made prior to unblinding using prespecified criteria as indicated in the DAP .
• **DCIV Clinically Evaluable population:** a subset of the clinical MITT population comprised of patients who met the evaluability criteria specified in the DAP up to and including their discontinuation of IV therapy assessment. This population comprises patients in whom sufficient information was available to determine their outcome at discontinuation of IV therapy and for whom no confounding factors were present that interfered with the assessment of that outcome.
• **FUA Clinically Evaluable population:** A subset of the DCIV Clinically Evaluable population comprised of patients who met the evaluability criteria specified in the DAP up to and including their 10 day post-antibiotic follow-up assessment. This population comprises patients in whom sufficient information was available to determine their outcome at the follow-up assessment, 10 days post-antibiotic therapy, and for whom no confounding factors were present that interfered with the assessment of that outcome.
• **The FUA Microbiologically Evaluable population**, a subset of the FUA clinically evaluable population, is comprised of those clinically evaluable patients who had a baseline pathogen identified and a microbiological response assessed at FUA. Furthermore, it was required that one or more of these baseline pathogens were susceptible to both parenteral study therapies. As all microbiologically evaluable patients were required to be clinically evaluable, the population of clinically and microbiologically evaluable patients is identical to the microbiologically evaluable population; for all data presented hereafter, this group will be referred to as the FUA microbiologically evaluable population.
(Determinations of evaluability were made prior to unblinding using prespecified criteria as indicated in the DAP.)

Profile of Patient Enrolment



Analysis populations

Efficacy results were determined using an "evaluable-patients-only" approach and a "modified intent-to-treat" (MITT) approach. The "evaluable-patients-only" approach was the primary efficacy analysis. Two "evaluable-patients-only" populations were identified. The first contained all patients who were deemed clinically evaluable up to and including the discontinuation of their IV therapy assessment. The second contained all patients who were deemed clinically evaluable up to and including the 10-day post antibiotic therapy follow-up assessment. The population evaluable at DCIV will be used to address the primary hypothesis. All other analyses will be considered in those clinically evaluable at the follow-up assessment.

To address the primary efficacy hypothesis, the proportion of patients within each treatment group who had a favorable clinical response assessment at the discontinuation of IV therapy among those who were clinically evaluable at the discontinuation of IV therapy was calculated. All secondary hypotheses were considered in the population of patients evaluable at the FUA visit. The endpoints are displayed by stratum and combined over strata within each treatment group. The endpoints are displayed by treatment group for each analysis at DCIV and FUA.

Statistical Methods

The **primary objective** of this study was to compare ertapenem with piperacillin / tazobactam in terms of the proportion of patients who had a "favourable" (defined as cure or improved) clinical response. The **primary timepoint** was the DCIV visit and the primary analysis population comprised those patients who were clinically evaluable at that visit. Supportive statistical analyses for efficacy were performed using a number of different patient populations (described above). A number of secondary endpoints, including microbiological response, and timepoints were assessed (also described above).

For the efficacy analysis, only the clinical responses at DCIV and the FUA were considered. For a "favourable" clinical response rating, each primary wound and secondary wound clinically assessed at the eligibility screening must have received a "favourable" clinical response rating. An "unfavourable" clinical response included "failure" and "relapse". For missing data, all assessments of "failure" or "relapse" were carried forward to subsequent timepoints. This included patients discontinuing before their Day 5 visit, if the patient had received at least 48 hours of treatment. All assessments of "cure or improvement" were carried back to previously missing timepoints provided that no prior assessment was available. If a patient was a "cure or improvement" or "indeterminate" at DCIV and was missing subsequent timepoints, information available up to 90 days after the discontinuation of drug could be used to assess clinical response.

The response rates, adjusted for baseline severity of infection, were compared using Cochran-Mantel-Haenszel. Associated 95% confidence intervals were computed. Ertapenem was to be considered at least as effective as piperacillin / tazobactam if the 95% confidence interval for the difference in proportions (ertapenem minus piperacillin/tazobactam) contained zero and the lower limit of the confidence interval was greater than -15 percentage points. A test of the treatment by baseline severity interaction was also performed.

The statistical analysis is generally appropriate. In particular, the analysis populations are sensibly defined and sufficiently wide-ranging. Patient withdrawals and missing data are not considered problematic.

One major concern related to the criteria for success, i.e. the **definition of a "favourable" clinical response**. This concern was raised by the CHMP in the Request for Supplementary Information (RSI) adopted by the CHMP in June 2005. The MAH answered that determining when a complex process like a diabetic foot infection is "cured" can be difficult. Most of these infections resolve slowly with treatment, usually over a period of weeks. The clinical assessment of "cure/improvement" as the favorable clinical response at the discontinuation of IV therapy (DCIV) and at the 10 day posttreatment follow-up (FUA) in Protocol 034 required complete resolution of cardinal signs of infection (i.e., fever, purulence, and lymphangitis) and improvement in most of the remaining signs and symptoms of infection (e.g., chills, fluctuance, non-purulent discharge, erythema, induration, tenderness, pain, skin warmth), since the inflammatory component of these latter signs and symptoms may persist to some degree for days, sometimes weeks, after the active infection has resolved.
As defined in the Protocol, by assigning an outcome of "cure/improvement" at FUA, the investigator had declared that, based on the assessment of signs and symptoms, the patient had been essentially cured of their infection and no longer required antibacterial therapy. At DCIV, an outcome of "cure/improvement" was a determination by the investigator that the infected wound(s) had responded sufficiently to parenteral study therapy so that either (1) the patient was essentially cured and all antibiotic therapy could be discontinued, or (2) the patient had met all required clinical response criteria as defined in the protocol for oral switch and could be transitioned to oral follow-up therapy as per protocol. Patients were required to have received at least 5 days of parenteral study therapy before being switched to oral follow-up study therapy (ampicillin/clavulanate). The following protocol-defined oral switch criteria indicative of a substantial response to the parenteral study therapy needed to be considered by the investigator:

1. Patient received at least 5 full days of IV study therapy;
2. For at least 24 hours, the patient's maximum temperature was <38°C (100.4°F) orally, <38.5°C (101.2°F) by tympanic measurement, or <39°C (102.2°F) by rectal measurement, without the influence of aspirin, acetaminophen, or NSAIDS;
3. WBC was <10,000/mm^3, with ≤5% immature neutrophils (bands) on differential;
4. Patient was able to tolerate oral (or resume enteral) feeding and had no suspected impediment to absorption, (e.g., gastroparesis, vomiting, bowel edema, right-sided heart failure, etc.);
5. Improvement was demonstrated in most (without worsening of any) of the signs and symptoms of diabetic foot infection (primary and secondary wound sites) including a marked and sustained reduction in the following, if present at enrollment:
    - Localised periwound erythema
    - Localised periwound edema (swelling)

- Localised tenderness or pain
- Localised fluctuance
- Localised warmth
- Induration of wound (limb brawny edema)

6. Any purulence associated with wound was completely resolved;
7. Lymphangitis associated with wound was completely resolved;
8. Patient's metabolic status, with regard to hyperglycemia, was resolved to the patient's baseline.

Clinical response analyses are discussed below for patients who received parenteral study therapy only and for patients who received parenteral followed by oral study therapy. The clinical response analyses for patients who received parenteral study therapy only and for patients who received parenteral followed by oral study therapy were done at both the DCIV and FUA time points.
For evaluable patients who received only parenteral study therapy, a clinical response of "cure/improvement" at the DCIV visit is ostensibly an assessment of "cure," since these patients were discontinued from IV study therapy to receive no further antibacterial treatment. For evaluable patients who received parenteral and then switched to oral follow-up study therapy, a clinical response of "cure/improvement" at the DCIV visit represents "improvement," since these patients went on to receive oral follow-up as per Protocol. All assessments of "cure/improvement" at the FUA visit are ostensibly investigator assessments of "cure," since by Protocol definition these patients did not require any additional antibacterial therapy for their infected wounds at the time of the FUA.

Efficacy analyses in the population of patients who received parenteral therapy alone show that the observed "cure" rate for ertapenem was numerically superior and statistically non-inferior to piperacillin/tazobactam at both the DCIV and FUA time points. Additionally the observed "cure" rates for the most severe baseline diabetic foot infections was numerically higher for ertapenem at both DCIV and FUA time points.
The population of patients who had responded sufficiently to parenteral therapy and were then switched to oral study therapy, were by definition considered "improved" at the DCIV assessment. Followed out to the posttreatment visit, a favorable assessment at FUA was indicative of a "cure" since the investigator considered no further anti-infective treatment to be required. Cure rates in these patients at the FUA time point again showed again that the ertapenem regimen was statistically non-inferior to piperacillin/tazobactam. Additionally, the cure rate observed for ertapenem in the most severe baseline infections was numerically higher than that observed for piperacillin/tazobactam.
These results, in conjunction with the overall study results and analyses of improvement and resolution in the signs and symptoms of infection over the course of treatment and follow-up, attest to the efficacy of ertapenem in resolving the infectious process. They further support the conclusion that ertapenem is non-inferior to piperacillin/tazobactam in the treatment of diabetic foot infections.
The CHMP concluded that the MAH has provided a reasoned response based on a clinical/practical point of view. It may be considered sufficiently robust to accept the reasoned assumptions elaborated by the MAH above i.e. that results from the subgroups treated only by parenteral therapy realistically reflect the "cured" category and the subgroups treated by parenteral and oral therapy realistically reflect the "improved" category. The individual results presented under the above assumptions show consistency at both DCIV and FUA and may be sufficiently convincing in support of non-inferiority between Invanz and the comparator.

- **Results of study 034**

Subject/patient disposition :

	Ertapenem	Piperacillin/Tazobactam	Total
Number of patients screened			639
Number of patients not randomised			53
Number of patients randomised	295	291	586
Number of patients randomised but not treated	6	4	10
NUMBER OF PATIENTS TREATED	289	287	576

	COMPLETED THERAPY			COMPLETED STUDY		
	Ertapenem	Piperacillin/ Tazobactam	Total	Ertapenem	Piperacillin/ Tazobactam	Total
COMPLETED:	244	225	469	243	229	472
DISCONTINUED: Total	45	62	107	46	58	104
Clinical adverse experience	17	16	33	11	11	22
Laboratory adverse experience	0	2	2	0	1	1
Lack of efficacy	4	9	13	3	9	12
Lost to follow-up	0	1	1	8	4	12
Patient discontinued for other reason	1	1	2	1	0	1
Patient discontinued with exclusionary medical condition	10	11	21	7	9	16
Patient moved	2	4	6	2	4	6
Patient uncooperative	1	1	2	0	0	0
Patient withdrew consent	4	8	12	5	9	14
Protocol deviation	6	9	15	9	11	20

Table 11-6

Patient Accounting of Evaluability
Randomized Population

Population and Reasons Not Evaluable	Ertapenem (N=295) n	(%)	Piperacillin/ Tazobactam (N=291) n	(%)
Clinical Evaluable Population				
Clinical evaluable at DCIV	226	(76.6)	219	(75.3)
Clinical non-evaluable at DCIV	69	(23.4)	72	(24.7)
Baseline microbiology - no pathogen†	2	(0.7)	4	(1.4)
Baseline microbiology - resistance‡	2	(0.7)	2	(0.7)
Baseline/intercurrent medical events	28	(9.5)	24	(8.2)
Concomitant antibiotics violation	13	(4.4)	13	(4.5)
Disease definition not met	0	(0.0)	2	(0.7)
Inadequate/inappropriate study therapy	25	(8.5)	29	(10.0)
No Visit	1	(0.3)	1	(0.3)
Other	2	(0.7)	2	(0.7)
Prior antibiotics violation	5	(1.7)	9	(3.1)
Clinical evaluable at FUA	206	(69.8)	196	(67.4)
Clinical non-evaluable at FUA	89	(30.2)	95	(32.6)
10-Day Follow-up window violation§	4	(1.4)	8	(2.7)
Baseline microbiology - no pathogen†	2	(0.7)	4	(1.4)
Baseline microbiology - resistance‡	2	(0.7)	2	(0.7)
Baseline/intercurrent medical events	28	(9.5)	24	(8.2)
Concomitant antibiotic violation	16	(5.4)	21	(7.2)
Disease definition not met	0	(0.0)	2	(0.7)
Inadequate/inappropriate study therapy	34	(11.5)	33	(11.3)
No Visit	36	(12.2)	45	(15.5)
Other	0	(0.0)	1	(0.3)
Prior antibiotics violation	5	(1.7)	9	(3.1)
Clinical evaluable at MITT	289	(98.0)	285	(97.9)
Clinical non-evaluable at MITT	6	(2.0)	6	(2.1)
Minimal disease definition not met	0	(0.0)	2	(0.7)
Patient did not receive at least one dose of study therapy	6	(2.0)	4	(1.4)
Microbiologic Evaluable Population				
Microbiologic evaluable at DCIV	168	(56.9)	153	(52.6)
Microbiologic non-evaluable at DCIV	127	(43.1)	138	(47.4)
Baseline microbiology - no pathogen isolated	34	(11.5)	53	(18.2)
Baseline microbiology not performed/inadequate	11	(3.7)	8	(2.7)
No Visit	1	(0.3)	1	(0.3)
Not clinically evaluable	69	(23.4)	72	(24.7)
Baseline microbiology-resistant pathogen‖	30	(10.2)	27	(9.3)
Other	1	(0.3)	0	(0.0)
Microbiologic evaluable at FUA	151	(51.2)	135	(46.4)
Microbiologic non-evaluable at FUA	144	(48.8)	156	(53.6)
Baseline microbiology - no pathogen isolated	34	(11.5)	53	(18.2)
Baseline microbiology not performed/inadequate	11	(3.7)	8	(2.7)
No Visit	36	(12.2)	45	(15.5)
Not clinically evaluable	89	(30.2)	95	(32.6)
Baseline microbiology-resistant pathogen‖	30	(10.2)	27	(9.3)
Microbiologic evaluable at MITT	244	(82.7)	226	(77.7)
Microbiologic non-evaluable at MITT	51	(17.3)	65	(22.3)
Baseline microbiology - no pathogen isolated	34	(11.5)	53	(18.2)
Baseline microbiology not performed or inadequate	11	(3.7)	8	(2.7)
Not clinically MITT evaluable	6	(2.0)	6	(2.1)

This table contains counts of patient evaluability. Therefore, although a patient may have one or more reasons for being non-evaluable, the patient will be counted only once in the non-evaluable category.
DCIV = Discontinuation of IV Therapy. FUA = Follow-up Assessment.

† Patients entered as clinical failures with >24 hours prior antibiotic therapy in prior 72 hours, but who did not culture a baseline pathogen.

‡ Patients entered with pathogens known at baseline to be resistant to either study drug.

§ Patient was outside FUA visit window specified in DAP (<6 days for Favorable clinical responses or >14 days for Unfavorable clinical responses).

‖ Patients with all baseline pathogens resistant to either study drug.

Data Source: [4.3]

There appeared to be very similar proportions of subjects in each treatment group found not evaluable by each of the criteria listed in the above table for Clinical Evaluable Population. In the Microbiologic Evaluable Population however, there are higher proportions in the comparator group found not evaluable and on more detailed assessment, the principal cause of this can be identified i.e. baseline microbiology – no pathogen isolated.

Baseline Patient Characteristics by Treatment Group
(FUA Clinically Evaluable Population)

	Ertapenem (N=206)		Piperacillin/Tazobactam (N=196)		TOTAL (N=402)	
	n	(%)	n	(%)	n	(%)
Gender						
Female	89	(43.2)	69	(35.2)	158	(39.3)
Male	117	(56.8)	127	(64.8)	244	(60.7)
Race						
Asian	1	(0.5)	1	(0.5)	2	(0.5)
Black	11	(5.3)	16	(8.2)	27	(6.7)
Hispanic	56	(27.2)	45	(23.0)	101	(25.1)
White	137	(66.5)	132	(67.3)	269	(66.9)
Multi-racial	1	(0.5)	2	(1.0)	3	(0.7)
Age (Years)						
18 to 40	18	(8.7)	23	(11.7)	41	(10.2)
41 to 64	124	(60.2)	108	(55.1)	232	(57.7)
65 to 74	39	(18.9)	34	(17.3)	73	(18.2)
≥75	25	(12.1)	31	(15.8)	56	(13.9)
n		206		196		402
Mean		59.3		58.3		58.8
SD		12.7		14.3		13.5
Median		59.0		57.0		58.0
Range		25.0 to 90.0		22.0 to 88.0		22.0 to 90.0
Diabetic Foot Infection Wound Score						
n[†]		187		186		373
Mean		16.1		15.6		15.8
SD		5.6		5.7		5.6
Median		15.0		14.0		15.0
Range		6.0 to 44.0		6.0 to 32.0		6.0 to 44.0
Stratum and Wound Classification						
Moderate diabetic foot infection	142[‡]	(68.9)	135	(68.9)	277	(68.9)
Grade 0 Stage B	2	(1.0)	5	(2.6)	7	(1.7)
Grade 0 Stage D	0	(0.0)	0	(0.0)	0	(0.0)
Grade 1 Stage B	132	(64.1)	125	(63.8)	257	(63.9)
Grade 1 Stage D	8	(3.9)	5	(2.6)	13	(3.2)
Severe (but not life threatening) foot infection	64[§]	(31.1)	61	(31.1)	125	(31.1)
Grade 2 Stage B	49	(23.8)	46	(23.5)	95	(23.6)
Grade 2 Stage D	2	(1.0)	2	(1.0)	4	(1.0)
Grade 3 Stage B	12	(5.8)	11	(5.6)	23	(5.7)
Grade 3 Stage D	1	(0.5)	2	(1.0)	3	(0.7)

SD=Standard deviation.
[†] n = number of patients with a wound score.
[‡] Includes one patient (AN0353) who was misclassified into the moderate stratum when their wound grade and stage indicated a severe infection.
[§] Includes one patient (AN0800) who were misclassified into the severe stratum when their wound grade and stage indicated a moderate infection.

Data Source: [4.1.1; 4.3.5; 4.3.12; 4.3.13]

There were over twice the number of moderate wound infections than severe wound infections in both treatment groups. The wound scores appear very similar in the 2 groups.

Extent of Exposure (Duration of Therapy) by Treatment Group
(FUA Clinically Evaluable Population)

	Ertapenem (N=206)	Piperacillin/Tazobactam (N=196)	TOTAL (N=402)
Days on Study Therapy			
n	206	196	402
Mean	17.2	17.6	17.4
SD	6.95	7.18	7.06
Median	15.5	16.0	16.0
Range	4.0 to 37.0	3.0 to 33.0	3.0 to 37.0
Days on IV Therapy			
n	206	196	402
Mean	11.1	11.3	11.2
SD	7.58	7.26	7.42
Median	8.0	7.0	7.5
Range	4.0 to 32.0	3.0 to 29.0	3.0 to 32.0
Days on Oral Therapy			
n	137	134	271
Mean	9.4	10.0	9.7
SD	3.53	3.99	3.77
Median	8.0	9.0	8.0
Range	4.0 to 23.0	4.0 to 23.0	4.0 to 23.0
Days Missed Therapy[†]			
n[‡]	8	5	13
Mean	1.8	3.2	2.3
SD	0.71	3.9	2.43
Median	2.0	1.0	2.0
Range	1.0 to 3.0	1.0 to 10.0	1.0 to 10.0

[†] Total number of days a patient missed 24 hours of study therapy.
[‡] Excludes 5 patients (3 in the ertapenem group and 2 in the piperacillin/tazobactam group) with no pharmacy record of reconstituted active parenteral study therapy for 1 or more days, but for whom the investigator has documentation of infusion of active parenteral study therapy.
N = Number of patients in each treatment group.
n = Number of patients in category.

Data Source: [4.3.5; 4.3.11]

The 2 treatment groups appeared to be similar with respect to the extent of exposure to overall study therapy, parenteral therapy, and oral therapy. Overall 131 (33%) of these patients (69/206 and 62/196 patients in the ertapenem and P/T groups, respectively) did not receive any oral therapy and were treated entirely with parenteral study therapy. i.e. sixty-seven percent (66.5%) of the clinically evaluable patients in the ertapenem group and 68.4% of the clinically evaluable patients in the comparator group completed therapy with an oral agent. Most patients in both groups received amoxicillin/clavulanate 875/125 mg every 12 hours for a mean duration of approximately 9.4 days in the ertapenem group and 10.0 days in the piperacillin/tazobactam group.

Extent of Exposure (Duration of Therapy) by Treatment Group
(Patients who Received Only Parenteral Study Therapy)
(FUA Clinically Evaluable Population)

	Ertapenem (N=206)	Piperacillin/Tazobactam (N=196)	TOTAL (N=402)
Days on Study Therapy			
Days on IV Therapy			
n	69	62	131
Mean	16.6	15.8	16.2
SD	9.12	9.36	9.21
Median	14.0	14.0	14.0
Range	4.0 to 32.0	3.0 to 29.0	3.0 to 32.0
Days Missed Therapy[†]			
n[‡]	1	-	1
Mean	2.0	-	2.0
SD	-	-	-
Median	2.0	-	2.0
Range	2.0 to 2.0	-	2.0 to 2.0

[†] Total number of days a patient missed 24 hours of study therapy
[‡] Excludes 2 patients (1 in the ertapenem group and 1 in the piperacillin/tazobactam group) with no pharmacy record of reconstituted active parenteral study therapy for 1 or more days, but for whom the investigator has documentation of infusion of active parenteral study therapy.
N = Number of patients in each treatment group.
n = Number of patients in category.

Data Source: [4.3.5; 4.3.11]

As might be expected, the mean duration of parenteral therapy was longer in this subset for both treatment groups (16.6 and 15.8 days, respectively, for the ertapenem and P/T groups). Approximately two thirds of the patients in both treatment groups received oral switch therapy; 93% and 100% of these patients in the ertapenem and P/T groups, respectively, received the protocol specified oral agent, amoxicillin/clavulanate.

Oral Switch Agents by Treatment Group
(FUA Clinically Evaluable Population)

	Ertapenem (N=206)		Piperacillin/Tazobactam (N=196)		TOTAL (N=402)	
	n	(%)	n	(%)	n	(%)
Without Oral Therapy	69	33.5	62	31.6	131	32.6
With Oral Therapy	137	66.5	134	68.4	271	67.4
Amoxicillin (+) clavulanate potassium	127	61.7	134	68.4	261	64.9
Cefoxitin sodium	1	0.5	0	0.0	1	0.2
Cephalexin	3	1.5	0	0.0	3	0.7
Ciprofloxacin	3	1.5	0	0.0	3	0.7
Clindamycin	2	1.0	0	0.0	2	0.5
Dicloxacillin	1	0.5	0	0.0	1	0.2
Levofloxacin	4	1.9	1	0.5	5	1.2

This table counts patients. Although a patient may have more than one oral therapy, the patient is counted only once in the total for patients with oral therapy.
N = The number of patients per treatment group.
n = The total number of patients with the therapy.

Data Source: [4.3.5; 4.3.11]

Baseline Pathogens

The most commonly isolated pathogens in both treatment groups were aerobic gram-positive cocci including S. aureus, enterococci, and Streptococcus agalactiae, gram positive anaerobic cocci, primarily Peptostreptococcus species, and gram-negative bacilli, including E. coli and Pseudomonas aeruginosa.

Patients with monomicrobial or polymicrobial infections with pathogens that were only non-susceptible (intermediate or resistant) to parenteral study therapy isolated from either the primary infection site or blood were clinically but not microbiologically evaluable in cases where there was clinical improvement and the investigator elected to continue the patient on blinded parenteral therapy. In cases where *in vitro* susceptibility results to study agents were not reported, all organisms except for methicillin-resistant staphylococci were assumed to be susceptible to both ertapenem and piperacillin/tazobactam for the purpose of evaluability determination. All methicillin-resistant staphylococci were assumed to be resistant to both ertapenem and piperacillin/tazobactam regardless of *in vitro* susceptibility results. All of the pathogens from a patient with a polymicrobial infection were included in the per-pathogen analyses regardless of baseline susceptibility of each individual pathogen. If the patient was also microbiologically evaluable, then microbiologic outcomes were assessed for all baseline pathogens regardless of baseline susceptibility of each individual pathogen.

Polymicrobial infection was defined as an infection in a microbiologically evaluable patient with 2 or more different baseline bacterial pathogens. Non-polymicrobial infection included microbiologically evaluable patients with a single baseline pathogen and also patients who were clinically evaluable but not microbiologically evaluable. If vancomycin was used to treat resistant gram-positive infections, all gram-positive aerobic organisms were assigned an indeterminate microbiological outcome.

Of the 206 FUA clinically evaluable patients in the ertapenem group 172 (83.5%) had at least 1 baseline wound or blood pathogen identified at study entry. Ninety-nine (99) of these (48.1% of FUA clinically evaluable patients) had polymicrobial infections.
Of the 196 FUA clinically evaluable patients in the piperacillin/tazobactam group 149 (76.0%) had at least 1 baseline wound or blood pathogen identified at study entry. Eighty-eight (88) of these (44.9% of FUA clinically evaluable patients) had polymicrobial infections.

The most commonly isolated pathogens in the FUA clinically evaluable population were similar to those seen in the treated population. *Staphylococcus aureus* was the single most commonly isolated pathogen (90 isolates in the ertapenem group and 79 isolates in the piperacillin/tazobactam group) in the FUA clinically evaluable population. Seventy-one (71) (78.9%) isolates in the ertapenem group and 64 (81.0%) isolates in the piperacillin/tazobactam group were methicillin-sensitive *S. aureus* (MSSA).

Overall, the distribution and susceptibility patterns of baseline pathogens in the 2 treatment groups were similar with the exception of enterococci and *Pseudomonas aeruginosa*. In the ertapenem treatment group, 16.7% (6 of 36) of enterococcal isolates tested were susceptible to ertapenem while 94.4% (34 of 36) of enterococcal isolates were susceptible to piperacillin/tazobactam. Similarly, in the piperacillin/tazobactam treatment group, 13.6% (3 of 22) of enterococcal isolates were susceptible to ertapenem while 90.9% (20 of 22) of enterococcal isolates were susceptible to piperacillin/tazobactam. Vancomycin susceptibility was reported for 32 enterococcal isolates (18 in the ertapenem group and 14 in the piperacillin/tazobactam group) and all were vancomycin sensitive.
In the ertapenem treatment group, for *Pseudomonas aeruginosa*, 33.3% (6 of 18) of isolates were susceptible to ertapenem while 100% (18 of 18) of isolates were susceptible to piperacillin/tazobactam. In the piperacillin/tazobactam treatment group, 70% (7 of 10) *Pseudomonas aeruginosa* isolates were susceptible to ertapenem while 80% (8 of 10) isolates were susceptible to piperacillin/tazobactam.

The only pathogens isolated from blood in the piperacillin/tazobactam group were gram-positive aerobic cocci, methicillin-sensitive *Staphylococcus aureus*, *Streptococcus agalactiae, Streptococcus pyogenes,* and *Streptococcus viridans*. All bacteremic patients had blood isolates which were susceptible *in vitro* to the study drug received with the exception of AN594 which grew out *Streptococcus viridans* which was not tested, but was presumed to be sensitive to both study drugs. One FUA clinically evaluable patient in the ertapenem group(MRSA) and 2 FUA clinically evaluable patients in the piperacillin/tazobactam group (S. pyogenes, S. agalactiae) were bacteremic at baseline.

Clinical efficacy per patient

To address the primary hypothesis, the estimated proportion, adjusting for baseline severity, of DCIV clinically evaluable patients with a favorable clinical response assessment at the DCIV time point was evaluated in both treatment groups.
To address another important secondary efficacy hypothesis, the proportion of FUA clinically evaluable patients with a favorable clinical response assessment was also evaluated in both treatment groups at the 10-day follow-up assessment visit.

Subgroup Analyses

Clinical response rates decreased in both treatment groups with increasing depth of the wound (Grades 0 through 3 according to the University of Texas Diabetic Wound Classification). Most of the FUA clinically evaluable patients in both treatment groups (68% in the ertapenem group; 66% in the P/T group) had wounds extending through the epidermis or dermis without penetration to the tendon, capsule or bone (Grade 1). A third of all FUA clinically evaluable of patients in both treatment groups (31%) had wounds extending to either the tendon or capsule (Grade 2) or to the bone or joint (Grade 3) and these infections were appropriately considered severe.

Proportion of Patients With Favorable Clinical Response Assessment at DCIV and FUA Displayed by Gender, Age Category and Race (FUA Clinically Evaluable Population) (Observed† Data)

	Treatment Group						Observed† Differences (A - B)
	Ertapenem (A) (N=206)			Piperacillin/Tazobactam (B) (N=196)			
		Observed† Response			Observed† Response		
	n/m	%	(95% CI)	n/m	%	(95% CI)	%
DCIV							
Female	84/88‡	95.5	(88.8, 98.7)	65/69	94.2	(85.8, 98.4)	1.3
Male	108/117	92.3	(85.9, 96.4)	113/126§	89.7	(83.0, 94.4)	2.6
Age <65	133/141‡	94.3	(89.1, 97.5)	117/131	89.3	(82.7, 94.0)	5.0
Age ≥65	59/64	92.2	(82.7, 97.4)	61/64§	95.3	(86.9, 99.0)	-3.1
Age <75	171/180‡	95.0	(90.7, 97.7)	148/164§	90.2	(84.6, 94.3)	4.8
Age ≥75	21/25	84.0	(63.9, 95.5)	30/31	96.8	(83.3, 99.9)	-12.8
Asian	1/1	100.0	-	0/1	0.0	-	100.0
Black	8/10‡	80.0	(44.4, 97.5)	14/16	87.5	(61.7, 98.4)	-7.5
Multi-racial	1/1	100.0	-	2/2	100.0	-	0.0
White	128/137	93.4	(87.9, 97.0)	119/131§	90.8	(84.5, 95.2)	2.6
Hispanic	54/56	96.4	(87.7, 99.6)	43/45	95.6	(84.9, 99.5)	0.9
FUA							
Female	81/89	91.0	(83.1, 96.0)	61/69	88.4	(78.4, 94.9)	2.6
Male	99/117	84.6	(76.8, 90.6)	101/127	79.5	(71.5, 86.2)	5.1
Age <65	128/142	90.1	(84.0, 94.5)	105/131	80.2	(72.3, 86.6)	10.0
Age ≥65	52/64	81.3	(69.5, 89.9)	57/65	87.7	(77.2, 94.5)	-6.4
Age <75	161/181	89.0	(83.5, 93.1)	134/165	81.2	(74.4, 86.9)	7.7
Age ≥75	19/25	76.0	(54.9, 90.6)	28/31	90.3	(74.2, 98.0)	-14.3
Asian	1/1	100.0	-	0/1	0.0	-	100.0
Black	9/11	81.8	(48.2, 97.7)	13/16	81.3	(54.4, 96.0)	0.6
Multi-racial	1/1	100.0	-	1/2	50.0	-	50.0
White	118/137	86.1	(79.2, 91.4)	107/132	81.1	(73.3, 87.4)	5.1
Hispanic	51/56	91.1	(80.4, 97.0)	41/45	91.1	(78.8, 97.5)	-0.0

† Computed from a model pooling across baseline severity.
‡ One patient in the ertapenem group (AN 755) was clinically evaluable at FUA but had indeterminate clinical response at DCIV and was excluded from this analysis.
§ One patient in the piperacillin/tazobactam group (AN 372) was clinically evaluable at FUA but had an indeterminate clinical responses at DCIV and was excluded from this analysis
N = Number of FUA clinically evaluable patients in each treatment group.
n/m = Number of FUA clinically evaluable patients with favorable assessment / number of FUA clinically evaluable patients with assessment.
CI = Confidence interval. DCIV = Discontinuation of IV therapy. FUA = Follow-Up Assessment.

Data Source: [4.1.1; 4.3.3; 4.3.5; 4.3.13]

The clinical response with ertapenem seems to be worse with increasing age (90.1% for < 65 years vs. 81.3% for > 65 years and 89.0% for < 75 years vs. 76.0% for > 75 years), whilst the reverse was observed for piperacillin-tazobactam (80.2% for < 65 years vs. 87.7% for > 65 years and 81.2% for < 75 years against 90.3% for > 75 years). In patients above 75 years (25 for the ertapenem arm and 31 for the piperacillin-tazobactam arm) the observed difference between treatments was –14.3, while the difference between the lower CI95 was around 20%. These differences also affect the generalisation of the results from the presented study to the general population. In the RSI adopted in June 2005, the MAH was requested to comment upon this issue.

In his answer, the MAH explained that while the favorable clinical response rates at DCIV and FUA were numerically greater for piperacillin/tazobactam in the oldest decades (70 to 79 and 80 to 89 years of age) this was not true for patients 50 to 59 or 60 to 69 years age, the age groups with the largest proportion of patients studied and where the ertapenem response rates were higher. Upon careful statistical analysis, the data do not appear to support a clear age trend with regard to treatment effect.

The MAH presented the data in groups of 10-years, rather than the dichotomies described in the question. This has the potential to mask differences of potential importance. However, the MAH's

position, that the data do not appear to support a clear trend for age, is supported by the CHMP, but a decreased effect in elderly patients cannot be ruled out based on the data.

Clinical efficacy per pathogen

The most common baseline species identified in the FUA clinically evaluable population with Diabetic Foot Infections at the DCIV visit were gram positive aerobic cocci including *S. aureus*, enterococci, *and S. agalactiae*; gram-negative aerobic rods including *E, coli* and *P. aeruginosa*; gram-positive anaerobic cocci, primarily *Peptostreptococcus* species, and gram-negative anaerobic rods, including *Porphyromonas* and *Prevotella* species.

S. pyogenes, a well-recognised pathogen in skin/soft tissue infection, was only very rarely observed. Despite the study 034 was conducted in US, the epidemiology of the pathogens isolated in Protocol 034 was generally similar to other studies, which were conducted in the EU. The evidence that *S. pyogenes* is uncommon in DFI studies justifies the lack of infections with *S. pyogenes* in this study. The epidemiology of pathogens is shown to be broadly similar to those in other EU studies, which satisfies concerns over external validity.

There were 4 ertapenem-targeted pathogens for which sufficient numbers of isolates were available (10 per group, as outlined in the Data Analysis Plan [DAP]) to determine a 95% CI around the difference in clinical response rates between the 2 treatment groups. Among these pathogens, the only pathogen for which piperacillin/tazobactam had a higher clinical response rate than ertapenem was *Streptococcus agalactiae* (between treatment difference -13.2; 95% CI: -38.3, 10.9). The inclusion of zero in the 95% CI around the difference in response rates indicates that this difference was not statistically significant. A previous study in skin and skin structure infections demonstrated ertapenem had a similar response as piperacillin/tazobactam in the treatment of *S. agalactiae* infections.
The favorable clinical response rates for MRSA in both treatment groups also appear to be similar. The MRSA favorable clinical response rates were 14/18 isolates (77.8%) in the ertapenem group and 10/15 isolates (66.7%) in the piperacillin/tazobactam group.

The population of FUA clinically evaluable patients with MRSA was further analysed. In the ertapenem group, 6 of the 18 (33.3%) FUA clinically evaluable patients were monomicrobial infections. In the piperacillin/tazobactam group, 5 out of 15 (33.3%) of MRSA infections were monomicrobial infections. The clinical response rates for MRSA in both treatment groups appear to be similar irrespective of the use of concomitant vancomycin. In the ertapenem group, 7 of 18 (38.8%) patients with MRSA had received concomitant vancomycin; of the 7 patients who had received vancomycin, 5 (71.4%) had a favorable clinical response. Eleven (11) patients did not receive vancomycin, of which 9 patients (81.8%) had a favorable clinical response. In the piperacillin/tazobactam group, 5 of 15 (33.3%) patients with MRSA had received concomitant vancomycin; of the 5 patients who had received vancomycin, 3 (60.0%) had a favorable clinical response. Ten (10) patients did not receive vancomycin, of which 7 patients (70.0%) had a favorable clinical response.

Upon further sub-analysis, the clinical response rates for MRSA in both treatment groups appear to be similar irrespective of the use of concomitant vancomycin among monomicrobial or polymicrobial groups. In the ertapenem group, 5 of 5 (100%) patients with polymicrobial MRSA infection who had not received concomitant vancomycin had a favorable clinical response; of the 7 patients who had received vancomycin, 5 (71.4%) had a favorable clinical response. In the piperacillin/tazobactam group, 4 of 5 (80.0%) patients with polymicrobial MRSA infection who had not received concomitant vancomycin had a favorable clinical response; of the 5 patients with polymicrobial infections who had received vancomycin, 3 (60.0%) had a favorable clinical response.

All 11 patients in the clinical EPP population (6 in the ertapenem group and 5 in the piperacillin/tazobactam group) with MRSA isolated as a sole baseline pathogen had not received vancomycin. In the ertapenem group, 4 of 6 (66.7%) patients with monomicrobial MRSA infection who had not received concomitant vancomycin had a favorable clinical response. In the

piperacillin/tazobactam group, 3 of 5 (60.0%) patients with monomicrobial MRSA infection who had not received concomitant vancomycin had a favorable clinical response.

For Pseudomonas aeruginosa, the favorable clinical response rates were 15/18 isolates (83.3%) in the ertapenem group and 7/10 isolates (70.0%) in the piperacillin/tazobactam group. The difference in the clinical response rates between the 2 treatment groups was 13.3% (95% CI: -18.2, 48.7). In patients whose culture results demonstrated organisms for which resistance to the protocol-specified switch agent amoxicillin/clavulanate was a concern, alternative oral antibacterial therapy was permitted. Six (6) out of 18 patients (33.3%) in the ertapenem group and 1 out of 10 patients (10%) in the piperacillin/tazobactam group were switched to oral study therapy consisting of amoxicillin/clavulanate and an antipseudomonal oral agent (ciprofloxacin or levofloxacin) following parenteral therapy. In patients who did not receive an antipseudomonal oral agent, 9 out of 12 patients (75.0%) in the ertapenem group had a favorable clinical response while 6 out of 9 patients (66.7%) in the piperacillin/tazobactam group had a favorable clinical response. The clinical response rates for P. aeruginosa appeared to be similar in both treatment groups irrespective of the use of an oral antipseudomonal agent following parenteral therapy.

Clinical response rates for *MRSA, enterococci* and *Pseudomonas aeruginosa* were remarkably high, completely independently of the addition or not of vancomycin for *MRSA* or *enterococci,* or the use of an antipseudomonal agent during the switch to oral therapy, respectively. Several explanations may account for the higher than expected favorable clinical response rates for MRSA, enterococci and *Pseudomonas aeruginosa* in this study. First, factors other than antibiotic susceptibility may have influenced the clinical response. The study investigators took a multi-disciplinary approach incorporating off-loading, local wound care, optimisation of glycemic control, and surgical intervention (when necessary) in addition to antimicrobial therapy. These factors were applied equally across treatment groups and without knowledge of treatment group by the investigators. Second, although MRSA, enterococci, and *P. aeruginosa* have all been implicated as pathogens in diabetic foot infections, their contribution to the infectious process remains a topic of some controversy. Finally, another contributing factor, particularly in patients with MRSA, is the frequency of polymicrobial infections. It is acknowledged that the adequacy of the chosen primary endpoint for DFI may still be open to discussion and that improvement may be eventually possible, particularly with regard to clinical variables and staging, since the relevance of microbiologic findings may be more open to dispute. Under these circumstances, a more careful choice of the analyses that should figure in the main dossier is warranted.

Clinical efficacy Per pathogen (blood isolates only)

To be included in this analysis, a clinically evaluable patient had to have a baseline pathogen isolated from blood. Bacteremia was uncommon in both treatment groups. One patient in the ertapenem group and 3 patients in the piperacillin/tazobactam group were bacteremic at baseline. One baseline blood isolate was identified from each patient. All of the isolates identified from blood were gram-positive aerobic cocci. None of the patients with baseline pathogens isolated from blood had persistent bacteremia. In each of the 3 patients with positive blood cultures at baseline, no follow-up cultures were considered necessary and the pathogens were presumed eradicated. The small number of isolates precluded meaningful comparison between the 2 treatment groups.

Microbiological efficacy per patient

For this analysis, 151 out of 289 treated patients (52.2%) in the ertapenem group were FUA microbiologically evaluable and 135 out of 287 treated patients (47.0%) in the piperacillin/tazobactam group were FUA microbiologically evaluable.
If no specimen was obtained for culture at a follow-up visit, the microbiological outcome was presumed based on the clinical outcome; eradication was presumed for favorable clinical outcomes and persistence was presumed for unfavorable clinical outcomes. For a favorable overall per patient microbiological response, all pathogens identified at baseline should have been eradicated or presumed to be eradicated.

The lower proportion of comparator group subjects qualifying as microbiologically evaluable implies fewer had specimen taken for culture than in the ertepenem group.

Combined Clinical and Microbiological Efficacy

The proportion of FUA microbiologically evaluable patients with both a favorable clinical and a favorable microbiological response assessment was evaluated in both treatment groups at the FUA visit.
If both the clinical assessment and the overall microbiological assessment were "favourable," the patient was counted as "favourable" for this analysis. If either or both the clinical and the microbiological assessments were classified as "unfavourable," then the patient was counted as "unfavourable" in the analysis.

MITT population

Analysis of the clinical response rates in the clinical MITT population was performed to support the primary analyses of the evaluable population. The results for the MITT clinical efficacy were consistent with the clinical response rates in the clinically evaluable population and supported the primary and secondary efficacy hypotheses and the results for the MITT microbiological efficacy were consistent with the microbiological response rates in the microbiologically evaluable population.

Emergent Infections

Emergent pathogens were pathogens that were not present at baseline, but were isolated from patients with clinical evidence of infection after study therapy had been initiated. Emergent pathogens isolated during study therapy were termed "superinfections." Emergent pathogens isolated after study therapy was completed were termed "new infections."
One patient in the ertapenem group (AN 229) and one patient in the piperacillin/tazobactam group (AN 807) developed bacteremia following discontinuation of study therapy. Both patients grew out methicillin-sensitive *S. aureus*. No FUA clinically evaluable patients in either treatment group had persistence of baseline pathogens at the FUA visit due to the development of resistance to study therapy.

Overall, the most common emergent pathogens in the ertapenem treatment group were *Enterococcus* species and *Pseudomonas aeruginosa*. In the piperacillin/tazobactam treatment group, the most common emergent pathogen was *S. aureus*. The incidence of new and superinfections was low and appeared to be similar between the 2 treatment groups.

Exploratory Analyses—Diabetic Foot Wound Score

The clinical response assessment at DCIV and FUA was also analysed within each treatment group by baseline diabetic foot wound score, a composite score based on general wound parameters (signs and symptoms of infection) and wound measurements. Clinical response rates were similar in both treatment groups across baseline wound scores at DCIV and FUA and the response rates generally decreased with an increase in baseline wound score.

- **Conclusion on efficacy**

The data from the single pivotal study 034 does **not support the claimed proposed indication *Complicated skin and soft tissue infection (cSSTI), including diabetic foot infections.*** It may only **support the indication restricted to *diabetic foot infections (DFI).***
To support its request for cSSTI, the MAH mentioned again an earlier study (protocol 016), where the efficacy of ertapenem, 1.0 g IV once daily was compared with piperacillin/tazobactam, 3.375 g every 6 hours, in the treatment of complicated skin and skin structure infections, defined as lower limb infections in diabetics, infected pressure sores, deep tissue infections in which enterobacteria or anaerobes were likely or which required surgical drainage, extensive cellulititis, wound infections and perineal abscesses. In study 016, patients were stratified at baseline according to the presence or absence of complicating underlying disease. Stratum I consisted of those with decubitus ulcers, diabetes mellitus or other neuropathic conditions whereas Stratum II contained all other patients.

Overall 60 % of patients had received an antimicrobial agent within 14 days of study entry, predominantly beta-lactam compound. Further to its evaluation, study 016 had been deemed unsuitable for granting the same proposed indication in the original Marketing Authorisation Application (MAA). As already assessed in the original MAA, there were too many concerns with the overall efficacy results in Protocol 016 per se, even to grant a restricted indication of cSSTI excluding DFI.
Protocol 034 provided evidence in only one subgroup of infections within the heterogenous clinical condition of cSSTI, namely DFI. Therefore, it can only support an indication of DFI, as satisfactory efficacy evidence in the other conditions within the heterogenous clinical condition of cSSTI is not available. Given the heterogeneity of the two patient populations recruited into the two studies, it is considered that Protocol 034 does not provide the additional evidence required such that, together, the trials support the broad indication of cSSTI.

2.2 Clinical safety

- **Safety data from the main study: Protocole 034.**

Adverse experiences that occurred while the patient was on parenteral study therapy are more likely to be related to the parenteral study therapy than those occurring after the completion of the parenteral therapy (i.e., during oral therapy or the follow-up period). For this reason, separate analyses are presented on adverse experiences that occurred specifically within the parenteral treatment period and on those that occurred during study therapy and the 14-day follow-up period (i.e., parenteral and oral antibiotic therapy and the 14-day follow-up period).

Patient exposure

Adverse experiences were recorded during parenteral and oral study therapy and for 14 days after the last dose of study therapy (safety follow-up period). Of the 639 patients enrolled, 576 received at least 1 dose of parenteral study therapy (289 in the ertapenem group and 287 in the piperacillin/tazobactam group) and are included in the analysis of adverse experiences. Ten (10) patients (ANs 0232, 0235, 0236, 0313, 0773, and 1055 in the ertapenem treatment group and 419, 471, 488, and 683 in the piperacillin/tazobactam group) were randomised but did not receive any study medication. These patients were excluded from the safety analyses.

Patients in the ertapenem group received up to 33 days of therapy with a mean duration for any dose of 10.6 days. Patients in the piperacillin/tazobactam group received up to 30 days of therapy with a mean duration of 11.0 days.

Clinical Adverse events

- **During parental therapy**

The table below displays the number (percent) of all patients who received at least 1 dose of study therapy with clinical adverse events during parenteral therapy by category.

Clinical Adverse Events Summary
During Parenteral Therapy
(Treated Population)

	Ertapenem (N=289)		Piperacillin/Tazobactam (N=287)	
	n	(%)	n	(%)
Number (%) of patients:				
With one or more adverse experiences	137	(47.4)	136	(47.4)
With no adverse experience	152	(52.6)	151	(52.6)
With drug-related adverse experiences[†]	44[‡]	(15.2)	57	(19.9)
With serious adverse experiences	16	(5.5)	20	(7.0)
With serious drug-related adverse experiences	1	(0.3)	1	(0.3)
Who died	1	(0.3)	1	(0.3)
Discontinued due to adverse experiences	16	(5.5)	17[§]	(5.9)
Discontinued due to drug-related adverse experiences	3	(1.0)	6[‖]	(2.1)
Discontinued due to serious adverse experiences	8	(2.8)	10	(3.5)
Discontinued due to serious drug-related adverse experiences	0	(0.0)	0	(0.0)

[†] Determined by the investigator to be possibly, probably or definitely drug related.
[‡] Includes 1 patient (AN482) with an AE of Red Man Syndrome recorded as related to study therapy, but which was documented as being a reaction to vancomycin.
[§] Two patients (AN 0767 and AN 1060) who experienced AEs leading to discontinuation starting on the last day of parenteral therapy but which were related to oral therapy are included in this table. One patient (AN 0605) who's AE leading to discontinuation began the day after parenteral therapy ended, but was considered related to parenteral therapy is excluded.
[‖] Includes one patient (AN 0767) whose clinical adverse events began on the last day of parenteral study therapy (first day of oral study therapy) but which was related to oral therapy.

Data Source: [4.2.1; 4.3.11]

Overall, 273 out of 576 treated patients (47.4%) had clinical adverse experiences reported during parenteral therapy. One patient in the ertapenem group (AN 0715) experienced a serious adverse experience of positive blood culture that began on the first day of study therapy but prior to the first dose. The patient discontinued from parenteral therapy on Study Day 2. The investigator did not consider the positive blood culture related to study therapy. Because the onset of the serious adverse experience occurred prior to initiation of study therapy, this patient is not included in the number of patients with clinical adverse experiences during parenteral therapy, serious clinical adverse experiences, clinical adverse experiences leading to discontinuation, or serious clinical adverse experiences leading to discontinuation during parenteral therapy or during the study therapy and follow-up period. There was 1 patient in the ertapenem group and 1 patient in the piperacillin/tazobactam group with serious drug-related clinical adverse experiences.

Clinical adverse experiences occurring in 5% or more of patients in either treatment group were defined as frequently occurring clinical adverse experiences. The frequently occurring clinical adverse events were: **diarrhoea**, **nausea** and **headache**.

The most common adverse experiences with an incidence ≥3% were **gastrointestinal disorders**, **general disorders and administration site conditions**, and **nervous system disorders**. The incidence of clinical adverse experiences was similar between the 2 treatment groups.

There are no apparent differences between the 2 treatment groups for these adverse experiences with the exception of diarrhea. During parenteral therapy, diarrhea was reported by 24 patients (8.3%) in the ertapenem group and 41 patients (14.3%) in the piperacillin/tazobactam group. The results suggest that ertapenem may have a lower incidence of diarrhea than piperacillin/tazobactam.

The most common drug-related clinical adverse experiences with an incidence ≥1% were **gastrointestinal disorders** (9.7% of patients in the ertapenem group and 13.2% in the piperacillin group) and **general disorders and administration site conditions** (1.7% of patients in the ertapenem

group and 4.5% in the piperacillin/tazobactam group). The incidence of drug-related clinical adverse experiences was similar between the 2 treatment groups.

- **During study therapy and the 14-day follow-up period**

The table below displays the number (percent) of all patients who received at least 1 dose of study therapy with clinical adverse experiences during study therapy and 14 day Follow-up period by category.

Clinical Adverse Events Summary
During Study Therapy and 14-Day Follow-Up Period
(Treated Population)

	Ertapenem (N=289)		Piperacillin/Tazobactam (N=287)	
	n	(%)	n	(%)
Number (%) of patients:				
With one or more adverse experiences	162	(56.1)	169	(58.9)
With no adverse experience	127	(43.9)	118	(41.1)
With drug-related adverse experiences[†]	51[‡]	(17.6)	66	(23.0)
With serious adverse experiences	33	(11.4)	42	(14.6)
With serious drug-related adverse experiences	1	(0.3)	1	(0.3)
Who died	4[§]	(1.4)	2	(0.7)
Discontinued due to adverse experiences	21	(7.3)	19	(6.6)
Discontinued due to drug-related adverse experiences	4	(1.4)	7	(2.4)
Discontinued due to serious adverse experiences	10	(3.5)	10	(3.5)
Discontinued due to serious drug-related adverse experiences	0	(0.0)	0	(0.0)

[†] Determined by the investigator to be possibly, probably or definitely drug related.
[‡] Includes 1 patient (AN482) with an AE of Red Man Syndrome recorded as related to study therapy, but which was documented as being a reaction to vancomycin.
[§] One patient (AN 0446) is omitted from this table. This patient's Clinical AE resulting in death occurred outside the 14-day follow-up period.

Data Source: [4.2.1; 4.3.11]

Overall, 331 out of 576 treated patients (57.5%) had clinical adverse experiences reported during study therapy and 14-day follow-up period. The incidence of clinical adverse experiences, including serious adverse experiences, deaths, drug-related adverse experiences, and discontinuations due to adverse experiences, was similar in the 2 treatment groups. There was 1 patient in the ertapenem group and 1 patient in the piperacillin/tazobactam group who had serious drug-related clinical adverse experiences reported during study therapy and the 14-day follow-up period.

The most common clinical adverse experiences with an incidence ≥3% were **gastrointestinal disorders** (23.5% of patients in the ertapenem group and 30.0% in the piperacillin/tazobactam group), **infections** (16.3% of patients in the ertapenem group and 15.3% in the piperacillin/tazobactam group), and **general disorders and administration site conditions** (11.8% of patients in the ertapenem group and 18.8% .in the piperacillin/tazobactam group). The incidence of clinical adverse experiences was similar between the two treatment groups.

The most common medictation-related clinical adverse experiences with an incidence ≥1% were **gastrointestinal disorders** (11.1% of patients in the ertapenem group and 16.0% in the piperacillin/tazobactam group) and **infections** (3.5% of patients in the ertapenem group and 2.4% in the piperacillin/tazobactam group). The incidence of clinical drug-related adverse experiences was similar between the 2 treatment groups.

Serious adverse events and deaths

One patient in each treatment group died during the parenteral therapy period. One patient (AN 0832 an 84 year old male) in the ertapenem treatment group had an adverse experience of pneumonia during the parenteral therapy period due to lung cancer diagnosed during the follow-up period. The patient died during the follow-up period. The death was not considered to be related to study therapy. One patient (AN 1009 a 73 year old male) in the piperacillin/tazobactam group died due to myocardial infarction during the parenteral therapy period. The death was not considered to be related to study drug.

Four (4) patients in the ertapenem group and one patient in the piperacillin/tazobactam group experienced adverse experiences resulting in death after parenteral therapy but while on oral antibiotic therapy or during the 14 day follow-up period following study therapy. None of these deaths were considered to be drug related.

Laboratory findings

- **During parental therapy**

The table below displays the number (percent) of patients with laboratory adverse experiences during parenteral therapy.

Laboratory Adverse Events Summary During Parenteral Therapy (Treated Population)

	Ertapenem (N=289)		Piperacillin/Tazobactam (N=287)	
	n	(%)	n	(%)
Number (%) of Patients:				
With at least one lab test postbaseline	272		273	
With one or more adverse experiences	32	(11.8)	51	(18.7)
With no adverse experience	240	(88.2)	222	(81.3)
With drug-related adverse experiences†	11	(4.0)	27	(9.9)
With serious adverse experiences	2	(0.7)	0	(0.0)
With serious drug-related adverse experiences	0	(0.0)	0	(0.0)
Who died	0	(0.0)	0	(0.0)
Discontinued due to adverse experiences	0	(0.0)	2	(0.7)
Discontinued due to drug-related adverse experiences	0	(0.0)	2	(0.7)
Discontinued due to serious adverse experiences	0	(0.0)	0	(0.0)
Discontinued due to serious drug-related adverse experiences	0	(0.0)	0	(0.0)

† Determined by the investigator to be possibly, probably or definitely drug related.
The percent = number of patients within the laboratory adverse events category/number of patients with one or more laboratory tests postbaseline

Data Source: [4.2.1; 4.3.11]

Five hundred forty-five (545) of the 576 treated patients had at least 1 laboratory test post baseline. Eighty-three (83) of these had laboratory adverse experiences, 32 (11.8%) in the ertapenem group and 51 (18.7%) in the piperacillin/tazobactam group. There were 2 patients with serious laboratory adverse experiences, both in the ertapenem group. Neither of these serious adverse experiences was considered drug related and neither resulted in discontinuation from study therapy. Two (2) patients in the piperacillin/tazobactam group were discontinued due to drug-related laboratory adverse experiences.

During parenteral therapy the most common laboratory adverse experiences in both treatment groups with an incidence ≥3% were **increases in erythrocyte sedimentation rate and blood glucose**.

Medication-related laboratory adverse experiences with an incidence ≥1% were generally uncommon in both treatment groups. The most common drug-related laboratory adverse experiences during

parenteral therapy were **increases in erythrocyte sedimentation rate and liver transaminases** (ALT and AST).

Two patients (0.7%) in the ertapenem group had serious laboratory adverse experiences during parenteral therapy that were not considered medication-related. No serious laboratory adverse experiences occurred in the piperacillin/tazobactam group. AN 0484 had increased blood glucose and decreased blood potassium reported as serious laboratory adverse experiences. AN 0944 had increased blood potassium reported as a serious laboratory adverse experience.

There was a decreased relative risk of medication-related laboratory adverse experiences in the ertapenem group compared with piperacillin/tazobactam. The 2 treatment groups were not significantly different with respect to discontinuations due to medication-related laboratory adverse experiences. No serious medication-related adverse experiences were observed in either treatment group.

One patient in the piperacillin/tazobactam group (AN 0298) experienced a serious clinical adverse experience of hypoglycemic seizure that was definitely not related to study therapy. Of note, there were no seizures reported in any patient who received ertapenem in the study. There were no adverse experiences of seizure in either treatment group during the 14-day follow-up period.

- **During study therapy and the 14-day follow-up period**

The table below displays the number (percent) of all patients who received at least 1 dose of study therapy with clinical adverse experiences during study therapy and the follow-up period (14 days after discontinuation of parenteral and oral study therapy) by category.

Laboratory Adverse Events Summary During Study Therapy and 14-Day Follow-Up Period (Treated Population)

	Ertapenem (N=289)		Piperacillin/Tazobactam (N=287)	
	n	(%)	n	(%)
Number (%) of Patients:				
With at least one lab test postbaseline	281		276	
With one or more adverse experiences	46	(16.4)	69	(25.0)
With no adverse experience	235	(83.6)	207	(75.0)
With drug-related adverse experiences†	15	(5.3)	31	(11.2)
With serious adverse experiences	3	(1.1)	0	(0.0)
With serious drug-related adverse experiences	0	(0.0)	0	(0.0)
Who died	0	(0.0)	0	(0.0)
Discontinued due to adverse experiences	0	(0.0)	2	(0.7)
Discontinued due to drug-related adverse experiences	0	(0.0)	2	(0.7)
Discontinued due to serious adverse experiences	0	(0.0)	0	(0.0)
Discontinued due to serious drug-related adverse experiences	0	(0.0)	0	(0.0)

† Determined by the investigator to be possibly, probably or definitely drug related.
The percent = number of patients within the laboratory adverse events category/number of patients with one or more laboratory tests postbaseline

Data Source: [4.2.1; 4.3.11]

The most common laboratory adverse experiences during study therapy and 14-day follow-up period with an incidence ≥3 % were **increases in C-reactive protein (CRP), blood glucose, aspartate aminotransferase (AST), and erythrocyte sedimentation rate**.

When the MAH applied for this extension of indication, he proposed to include C-reactive protein and decrease in blood sodium in section 4.8 of the SPC.

As the number of cases of decrease in blood sodium and increase in C-reactive protein reported during study 034 was limited, a detailed cumulative safety review from post-marketing data of cases of decrease in blood sodium and increase in C-reactive protein were requested by the CHMP before concluding on the addition of these 2 events in the SPC.

The review performed by the MAH from 30.03.2001 to 22.06.2005 identified 4 reports of hyponatremia received from inception to 22.06.2005, which did not provide substantial information to infer more than a temporal relationship of ertapenem with hyponatremia and no report with increase of c-protein reactive. Therefore, the CHMP concluded that this cumulative safety review has not detected any signals associated for either of the 2 events. Furthermore the rise in the CRP is often seen *after* onset of antibiotic therapy in patients with bacterial infections (particularly those with chronic disease), the CHMP requested information on the temporal characteristics of the rise and fall of the CRP for study 034. In the answer from the MAH, all reports of medication-related C-reactive protein elevations were from a single clinical site in the study. The assessment of these elevations in C-reactive protein as medication-related non-serious adverse experiences is not representative of the experience of other clinical sites in the study. It is most likely that the CRP increases observed in these patients are attributable to an acute phase reaction in response to infection or ongoing inflammation. Further to the evaluation of the submitted data, **the CHMP concluded that there was no signal requiring the addition of C-reactive protein and decrease in blood sodium in section 4.8 of the SPC.**

The most common medication-related laboratory adverse experiences during study therapy and 14-day follow-up period with an incidence ≥1% were **increases in erythrocyte sedimentation rate and liver transaminases** (ALT and AST). The incidence of medication-related laboratory adverse experiences appeared similar to that seen during the parenteral therapy period.

- **Conclusion on laboratory findings**

Laboratory abnormalities are common in patients with acute bacterial infections. In addition to reviewing investigator-reported laboratory adverse experiences, assessment of the relative laboratory safety of each treatment group was accomplished by predefining clinically significant laboratory abnormalities (CSLAs) for specified tests and then identifying patients whose worst laboratory value represented a worsening from baseline and met the criteria for a CSLA. The combination of these 2 approaches to the analysis of laboratory abnormalities provides a more complete overview of the profile of laboratory safety.

The most common CSLAs in both the parenteral therapy period and the study therapy and 14-day follow-up period were **elevated serum creatinine** and **decreased absolute neutrophil count (ANC)**. As expected in a diabetic population, many patients in the treated population had pre-existing renal disorders such as diabetic nephropathy (5.4%) and renal insufficiency (6.1%). Overall, the proportion of patients with CSLAs was low and generally similar between the 2 treatment groups. The proportion of patients with CSLAs in the study therapy and 14-day follow-up period was similar to that seen in the parenteral therapy period. Very few patients treated with ertapenem had a creatinine clearance (CrCl) level ≤30 ml/min/1.73 m^2. An analysis of the clinical and laboratory AE profile using a CrCl level of 60 ml/min/1.73 m^2 as the cut-off point for renal dysfunction showed no substantive differences between patients with CrCl ≤60 and those with CrCl >60. Given the relatively few patients in the analyses, however, detailed comparison between the 2 populations (CrCl ≤60 and CrCl >60) is limited. Overall, the 2 populations appear generally similar and the adverse event profile in these patients was generally similar to that which appears presently in the EU SPC. Although the fact that the data is scarce does not warrant any specific amendment to the product's literature regarding patients with renal insufficiency.

- **Conclusion on safety**

The frequently occurring clinical adverse events during parental therapy were: **diarrhea**, **nausea** and **headache**.

None of the deaths occurring during the parenteral therapy period or after parenteral therapy but while on oral antibiotic therapy or during the 14 day follow-up period following study therapy, were considered to be medication related.

The most common clinically significant laboratory abnormalities in both the parenteral therapy period and the study therapy and 14-day follow-up period were **elevated serum creatinine** and **decreased absolute neutrophil count (ANC)**.

With respect to the above data revealed in the responses on C-reactive protein and blood sodium, the addition of **elevations in C-reactive protein** and **decreases in blood sodium** was not supported by the CHMP.

Further to the assessment of the data submitted, no major new safety issues have been identified that needed to be added to the SPC.

3. Conclusions and Benefit / Risk Assessment

Protocol 034 provided evidence in only one subgroup of infections within the heterogenous clinical condition of cSSTI, namely DFI. Therefore, it can only support an indication of DFI, as satisfactory efficacy evidence in the other conditions within the heterogenous clinical condition of cSSTI is not available.

Further to the assessment of the data submitted, no major new safety issues have been identified. With respect to the above data revealed in the responses on C-reactive protein and blood sodium, the addition of elevations in C-reactive protein and decreases in blood sodium was not supported by the CHMP.

The overall benefit-risk assessment is then negative for an extension of the therapeutic indication to the use in Invanz to complicated skin and soft tissue infection, including diabetic foot infections, but positive for the restricted indication of diabetic foot infections only.

4. Changes to the Product Information

- **Section 4.1 “Therapeutic indications” of the SPC**

A fourth bullet point has been added to as follows:

- *Diabetic foot infections of the skin and soft tissue (see section 4.4).*

- **Section 4.4 “Special warnings and special precautions for use” of the SPC**

The following statement has been added:
Efficacy of ertapenem in the treatment of diabetic foot infections with concurrent osteomyelitis has not been established.

- **Section 4.8 “Undesirable effects” of the SPC**

This section has been rearranged to allow for a better overview of data belonging to different age groups.

In order to have this section up-to-date with regard to the EME/QRD template and SCP guideline, the post-marketing reported adverse reactions *Very rare = < 1/10,000* has been moved to the table of adverses reactions instead of being in a separate paragraph.
Therefore,
Very rare: anaphylaxis including anaphylactoid reactions has been moved to Immune system disorders,
Very rare: hallucinations has been moved to Nervous system disorders.

- **Section 5.1 "Pharmacodynamic properties" of the SPC**

The full section has been updated to be in accordance with the current Note for Guidance on Evaluation of Medicinal Products indicated for Treatment of Bacterial Infections (CPMP/EWP/558/95 adopted April 2004). This update was the subject of questions in the RSI adopted in June 2005 and the RSI adopted in October 2005. The table presented in this section 5.1 does now follow the ***Section V.4.2. Format for section 5.1*** *(page 20 of 23)* of the above-mentioned Nfg, where it is stated that the relevant pathogens related to the requested indications should be categorised under the 3 headings given in the guideline: "*Commonly susceptible species*", "*Species for which acquired resistance may be a problem*" and "*Inherently resistant organisms*."

Further to assessment of pre-clinical studies, the PK/PD relationship has been added to this section and should now read:

Pharmacokinetic/Pharmacodynamic (PK/PD) relationship
Similar to other beta-lactam antimicrobial agents, the time that the plasma concentration of ertapenem exceeds the MIC of the infecting organism has been shown to best correlate with efficacy in pre-clinical PK/PD studies.

Additionally the description of the mechanisms of resistance has been revised to include more detail further to the request from the CHMP in its RSI adopted in October 2005, and replace the previous 2 paragraphs on *Resistance*. It should be read:

Mechanism of Resistance

For species considered susceptible to ertapenem, resistance was uncommon in surveillance studies in Europe. In resistant isolates, resistance to other antibacterial agents of the carbapenem class was seen in some but not all isolates. Ertapenem is effectively stable to hydrolysis by most classes of beta-lactamases, including penicillinases, cephalosporinases and extended spectrum beta-lactamases, but not metallo-beta-lactamases.
Methicillin-resistant staphylococci and enterococci are resistant to ertapenem, owing to PBP target insensitivity; P. aeruginosa and other non-fermentative bacteria are generally resistant, probably owing to limited penetration and to active efflux.

Resistance is uncommon in Enterobacteriaceae and the drug is generally active against those with extended-spectrum beta-lactamases (ESBLs). Resistance can however be observed when ESBLs or other potent beta-lactamases (e.g. AmpC types) are present in conjunction with reduced permeability, arising by the loss of one or more outer membrane porins, or with up-regulated efflux. Resistance can also arise via the acquisition of betalactamases with significant carbapenem-hydrolysing activity (e.g. IMP and VIM metallo-beta-lactamases or KPC types), though these are rare.

The mechanism of action of ertapenem differs from that of other classes of antibiotics, such as quinolones, aminoglycosides, macrolides and tetracyclines. There is no target-based cross-resistance between ertapenem and these substances. However, micro-organisms may exhibit resistance to more than one class of antibacterial agents when the mechanism is, or includes, impermeability to some compounds and/or an efflux pump.

The MAH commits to implement appropriate studies in the post-marketing period to collect data on the prevalence of resistance, both within Europe and in the rest of the world, to enable the updating of

the SPC whenever the resistance patterns change. These worldwide resistance surveillance studies are currently ongoing. In accordance with CPMP Guidance Document CPMP/EWP/520/96 (18 June, 1997), “Note for guidance on the pharmacodynamic section of the SPC for anti-bacterial medicinal products”, the prevalence of resistance information in the Section 5.1 of the SPC will be updated at the 5-year periodic update. This periodic update coincides with the registration renewal submission, scheduled for October 2006.