SYNOPSIS

Title of Study:
Pharmacoeconomic analyses of first line meropenem versus standard antibiotic treatment in secondary nosocomial sepsis syndrome patients. An open, randomised multi-centre study.

Studied period:
4 years
First subject in: 01-March-2002
Last subject out: 25-May-2006

Phase of development: IV

Objectives:
The ***primary*** objective of the study was to demonstrate the cost-effectiveness of meropenem 1.0g IV. 8-hourly, due to shorter time to recovery from sepsis, compared with standard antibiotics as first line therapy in intensive care unit subjects with secondary nosocomial sepsis syndrome with the following assumption: Inferences about the objectives of this trial will only be valid if a summary of the mortality rates suggests that the mortality rate among patients randomised to receive meropenem as first line therapy appears to be as low, or lower, than for patients randomised to the standard first line therapy before efficacy of meropenem.

The ***secondary*** objective was:

Overall: To demonstrate that because first line meropenem has greater efficacy than standard first line therapy, meropenem patients have shorter stays in ICU and in the hospital, with resulting savings in health care resource utilisation and costs.

Efficacy: To demonstrate that first line meropenem will contribute to reduced length of ICU and hospital stay, in comparison with standard antibiotics

To summarise the reasons for discontinuation of first line therapy for meropenem and standard antibiotics

To demonstrate that first line meropenem will contribute to decreased requirement for second line therapy, in comparison with standard antibiotics

To present data that suggests line meropenem will contribute to decreased mortality, in comparison with standard antibiotics

Health economics: To demonstrate hospital resource savings following first line Meropenem therapy, in comparison with standard antibiotics, after establishing that mortality rate for meropenem arm appears to be no worse than for standard first line therapies.

Methodology: Open, randomised, multi-centre study with a parallel group design.

Number of patients (planned and analysed):	planned for randomisation:	320 in total (160 per group)
	planned for completion:	128 subjects per group
	screened:	131
	screen failure:	23
	randomised:	108
	included in the ITT population:	56
	completed as per protocol:	50

Diagnosis and main criteria for inclusion:
Male and female subjects aged ≥ 18 , requiring intensive care treatment related to secondary nosocomial sepsis, and require potent broad spectrum intravenous antibiotic therapy.

Investigational Product, dosage and mode of administration:
Meronem IV 500 mg vial for IV injection or infusion containing meropenem 500 mg powder in a vial for reconstitution with 10 ml *water for injection* or with 50 – 200 ml compatible infusion fluid in the form of meropenem trihydrate. Dosage is 1 g 8 hourly by intravenous (IV) bolus injection over 5 minutes or by IV infusion over 15 – 30 minutes.

Duration of treatment:
Target duration of the first line antibiotic therapy is 7 – 14 days, where there is a clinical response and microbiological sensitivity to the trial therapy is proven. Some subjects may require longer treatment for clinical reasons.

Reference therapy / comparators, dosage and mode of administration:
Standard antibiotic therapies usually employed by the investigator(s) according to local guidelines and practice. Dosage and administration to be determined by prescribing instructions contained in the relevant product data sheets, and according to local therapeutic practice.

Criteria for evaluation:

Efficacy variables:

Primary efficacy parameter:
Number of days from randomisation to recovery from sepsis among those patients who survived the trial period.
This endpoint was considered in conjunction with the observed mortality rates to determine whether any reduction in time to recovery from sepsis, among patients first treated with meropenem, was meaningful.

Secondary efficacy parameters:

- Number of days from randomisation to ready to discharge from the ICU, for patients who survived the trial
- Number of days from randomisation until patient was discharged from the ICU, for patients who survived the trial
- Number of days on first line antibiotic therapy
- Number of days from randomisation until patient was discharged
- from hospital (measured up to 28 days from cessation of first line therapy), for patients who survived the trial
- Proportion of patients who recovered from sepsis following first line antibiotic treatment only
- Proportional of all patients who were ready to discharge from the ICU following first line antibiotic treatment only
- Proportion of patients who were ready to discharge from the ICU following first line antibiotic treatment at discharge, or at 28th day after ceasing the first line therapy
- Mortality rate due to “all causes” in the meropenem group and the standard antibiotic therapy group
- Mortality rate due to infection in the meropenem group and the standard antibiotic therapy group

Health economy variables:

Resource utilisation for main treatment and diagnostic procedures, tools and materials;
Average number of survived days;
Average cost of therapy;
Number of days spent in ICU

- Time to recovery from sepsis
- Time to recovery from general health problems in the (ICU)

- Duration of stay in the ICU and the hospital, from randomisation up to 28 days after the last dose of trial therapy.
- Following clinical cure, or other outcome, the usage of hospital resources to arrive at the outcome will be assessed and interpreted in conjunction, with observed differences seen in response rates.

Safety variables:

Clinical and laboratory parameters;

Adverse events arising during the course of the study

Statistical methods:

Demographic and other baseline characteristics:

Descriptive statistics

Efficacy parameters:

The primary efficacy analysis was performed on the ITT population. Supportive analysis was performed on the PP population.

The primary efficacy variable (number of days to recovery from sepsis) was compared by the logrank test.

The Cox regression model was applied to explore possible covariates. Age, gender and baseline APACHE II scores were included in the model.

In the supportive analysis, the logrank test was performed on the PP population.

A Cox regression was also performed with age, gender and baseline APACHE II scores as covariates.

The secondary efficacy analysis was performed on the ITT population only.

The time to discharge or to "ready to discharge" from ICU, discharge from hospital and the time on first line treatment for the two study groups were compared by the logrank test.

Possible covariates (Apache II score, age, gender) were also investigated by the Cox regression model.

Logistic regression model was developed to compare the proportional recovery from sepsis following 1st line antibiotic treatment; the proportion of patients who are ready to discharge from the ICU following first line antibiotic treatment only; the proportion of patients who are ready to discharge from the ICU following first line antibiotic treatment at discharge, or at 28th day after ceasing the first line therapy for the two study groups while controlling for the effects of possible covariates.

Health economy:

As quality of life (utility) of patients was not measured, only cost per survival rate could be calculated instead of incremental cost-effectiveness rate.

Survival analysis and cost analysis were performed for both the ITT and the PP population.

Decision on the applied health economic analytical method was made after calculating the difference in patient survival.

Those patients who died due to sepsis in the ICU have been excluded from the ITT population.

Health economic outcomes were calculated for all patient groups.

Safety parameters:

Descriptive statistics

No statistical analysis was performed; data are presented as frequency tables.

Results:

Efficacy:

Primary analysis was performed on the ITT population. Supportive analysis was performed on the PP population.

The low sample size (56 patients in two treatment groups instead of ~ 122 patients/group) resulted a very low power for the hypothesis tests.

For the ITT population, the average number of days to recovery from sepsis was lower in the Meropenem than in the Comparator group (*8.6 [sd=4.97] days* vs. *11.7 [sd=9.53] days,* respectively), but the difference between treatment groups was not statistically significant.

For the PP population, the average number of days to recovery from sepsis was lower in Meropenem group, but the difference between the treatment groups was not statistically significant.

Secondary analysis was performed on the ITT population only.

The time to discharge or to "ready to discharge" from ICU, discharge from hospital and the time on first line treatment for the two study groups were compared by the logrank test. None of the parameters differed significantly between the two groups (p=0.6963, p=0.8731, p=0.4580, p=0.1780, respectively).

Possible covariates (Apache II score, age, gender) were also investigated by the Cox regression model. Results of the Cox regression models are presented in details in the statistical report.

Logistic regression model was developed to compare the proportional recovery from sepsis following 1st line antibiotic treatment; the proportion of patients who are ready to discharge from the ICU following first line antibiotic treatment only; the proportion of patients who are ready to discharge from the ICU following first line antibiotic treatment at discharge, or at 28th day after ceasing the first line therapy for the two study groups while controlling for the effects of possible covariates. None of these proportions differed significantly between the two treatment groups (p=0.1358, p=0.4536, p=0.7844, p=0.8233, respectively).

Health economy:

Summary of cost and survival analysis

The study was not powered to differentiate survival and treatment cost of meropenem therapy from standard antibiotics. The variation of standard antibiotic therapy in the comparator group and the large portion of missing observations have further reduced the ability to draw strong conclusions on the health economic benefits of meropenem.

Safety:

All subjects taking at least one dose of the study drug or control treatment, and for whom post-dose information is available were evaluated for safety.

Altogether 16 AEs occurred during the study. 11 out of them can be regarded as serious.

The outcomes of the adverse events were the following: patient recovered in 6 cases, patient died in 8 cases and 2 adverse events were ongoing at the end of the trial period.

5 AEs were moderate and 11 severe in intensity.

The most frequently occurring AEs was cardiac arrest/asystolia (3 events).