This report may include approved and non-approved uses, formulations, or treatment regimens. The results reported may not reflect the overall profile of a product. Before prescribing any product mentioned in this report, healthcare professionals should consult local prescribing information for the product approved in their country.

Name of Sponsor company: Merck & Co., Inc.	Name of Finished Product: INVANZ	
Name of Active Ingredient: ERTAPENEM	Therapeutic area/Indication: Community-Acquired Pneumonia	

Title of Study:
A PROSPECTIVE, MULTICENTER, RANDOMIZED, DOUBLE-BLIND, PILOT STUDY TO EVALUATE THE SAFETY, THE EFFICACY, THE TOLERABILITY, AND THE EMERGENCE OF RESISTANT GRAM-NEGATIVE MICROORGANISMS IN THE BOWEL IN ELDERLY PATIENTS WITH SERIOUS COMMUNITY-ACQUIRED BACTERIAL PNEUMONIA TREATED WITH A SHORT REGIMEN OF ERTAPENEM VERSUS HIGH-DOSE LEVOFLOXACIN P047

Investigators/Study Centers: Multicenter (6 centers in Spain)

Study period (years): Date of first patient enrolment: February, 23rd 2005 Date of last patient completed: May, 18th 2007	Phase of development: IIb

Hypothesis/Objectives:

No formal test of hypothesis was planned for this study.

The objectives of the study were to:

1) Explore whether a short course of ertapenem (1,000 mg intravenous once a day for 5 to 7 days) is at least as effective as a short course of high-dose levofloxacin (750 mg intravenous once a day for 5 to 7 days) for the treatment of serious community-acquired pneumonia (CAP) in elderly patients (≥ 65 years of age) with great likelihood of polymicrobial or Gram-negative microbial etiology.
2) Estimate the impact of the two study therapies on the emergence of resistant Gram-negative microorganisms in the bowel flora of elderly patients treated for CAP.

Study design/Methodology:

Prospective, randomized, controlled, double-blind clinical trial. All patients were randomized in a 1:1 ratio to receive either: (1) ertapenem, 1,000 mg intravenous once a day, and placebo to levofloxacin or (2) levofloxacin, 750 mg intravenous once a day, and placebo to ertapenem. Study therapy was double-blinded. Patients were assessed at baseline, at the discontinuation of study therapy (DOT) and 14 days after the end of study therapy (test-of cure [TOC] visit). The modified intention-to-treat (MITT) population included all patients with a confirmed diagnosis of CAP who received at least 1 dose of study therapy.

Number of patients (planned and analysed):

Planned enrollment was approximately 70 male or female patients, 65 years of age or older.
Due to low accrual rate, this study was stopped when 46 patients had been screened and 43 randomized.

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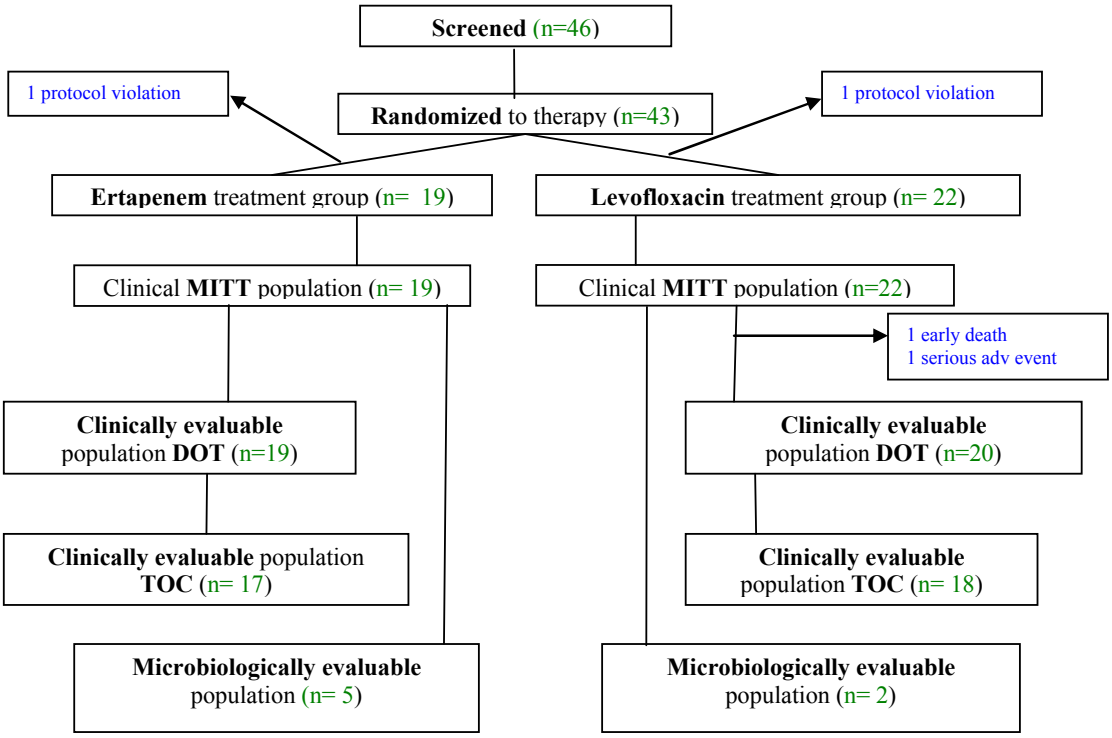

Diagnosis and main criteria for inclusion:

Patients had to meet the following inclusion criteria:

a. At least 65 years old.
b. Clinically suspected and/or bacteriologically documented CAP.
c. Great likelihood of Gram-negative microbial etiology defined as at least 1 of the following criteria: high risk for aspiration, antibiotic treatment within 3 months prior to enrollment, hospitalization within 3 months prior to enrollment, debilitating concomitant disease, institutionalized, significant degree of dependency requiring assistance for dressing and feeding.
d. Patient´s infection characterized as serious (requiring hospitalization or outpatient parenteral antibiotic treatment).
e. Patient´s infection known or suspected, according to the judgment of the attending physician, to be caused by microorganisms susceptible to the study antibiotics.

Test product, dose and mode of administration, batch number:
Ertapenem: 1 gr iv qd for 5 to 7 days. INVANZ® Batch numbers: [redacted]
Levofloxacin: 750 mg iv qd for 5 to 7 days. TAVANIC® Batch numbers: [redacted]

Criteria for evaluation:

Efficacy:

Clinical efficacy. The main efficacy analysis was defined as the proportion of patients with a favorable efficacy response (1) at the time of DOT, and; (2) at 2 weeks post-DOT, also named TOC visit. "Cure" or "improvement" were considered favorable clinical responses at the DOT visit. Only "cure" was considered as a favorable clinical response at the 14 days after DOT visit (TOC visit).

Patients included in the primary efficacy analysis were those in the clinically evaluable population, defined

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as patients who met the criteria for a diagnosis of CAP, met all enrollment criteria, received a proper duration of antimicrobial therapy (≥ 3 days on intravenous therapy), had no major protocol violations that would affect the assessment of efficacy, and had clinical assessment information available.

Additional secondary efficacy analyses: were predefined using an MITT approach. Patients included in the MITT analysis were those who received at least one administered dose of study drug, and had a confirmed diagnosis of CAP.

Microbiological efficacy. Microbiological efficacy was measured among patients who had at least one pathogen isolated from adequate respiratory samples or blood cultures (microbiologically evaluable patients) and was expressed as the proportion of patients who met the criteria for favorable microbiological response (i.e. "eradication" or "presumptive eradication" at DOT and TOC visits).

Safety: All patients entered into the study who received at least one administered dose of study drug were included in the safety analyses (all-patients-treated analysis). The main safety analysis was the proportion of patients treated with ertapenem or levofloxacin who developed a drug-related serious AE.

Assessment of emergence of resistant Gram-negative microorganisms during CAP therapy. Rectal swab specimens collected from patients at baseline, DOT, and the TOC visit were used for microbiologic studies.
Resistance rates at specified time points were expressed as the number of assessable patients with any resistant Enterobacteriaceae recovered from the rectal swab / number of assessable patients (a patient could have ≥ 1 resistant isolate).

Statistical methods:
Proportion of patients with a favorable efficacy response (1) at the time of DOT, and; (2) 2 weeks post-DOT (TOC visit), including their 95% confidence intervals (CI)
Proportion of patients who met the criteria for favorable microbiological response.
Proportion of patients treated with ertapenem or levofloxacin who developed a drug-related serious AE.
Proportion of assessable patients with any resistant *Enterobacteriaceae* recovered from the rectal swab.

SUMMARY

EFFICACY RESULTS:
Clinical Efficacy

A) Primary analysis: Clinically evaluable population.

				Study group	
				Ertapenem	Levofloxacin
				n	n
VISIT	DOT (Discontinuation of treatment)	Clinical response	Cure	18	14
			Improvement	0	3
			Failure	1	3
	TOC (Test of cure)	Clinical response	Cure	17	16
			Failure	1	2

Proportion of patients with favorable response at discontinuation of treatment (DOT) visit.
Ertapenem: 95%; 95% CI (74, 100)
Levofloxacin: 85% 95% CI (62, 97)

Proportion of patients with favorable response at test of cure (TOC) visit.
Ertapenem: 94%; 95% CI (73, 100)
Levofloxacin: 89%; 95% CI (65, 99)

B) Secondary analysis: MIIT population

				Study group	
				Ertapenem	Levofloxacin
				n	n
VISIT	DOT (Discontinuation of treatment)	Clinical response	Cure	18	14
			Improvement	0	3
			Failure	1	3
	TOC (Test of cure)	Clinical response	Cure	17	16
			Failure	2	6

Proportion of patients with favorable response at discontinuation of treatment (DOT) visit.
Ertapenem: 95%; 95% CI (74, 100)
Levofloxacin: 77% 95% CI (55, 92)

Proportion of patients with favorable response at test of cure (TOC) visit.
Ertapenem: 89%; 95% CI (67, 99)
Levofloxacin: 73%; 95% CI (50, 89)

Microbiological efficacy.
Only 7 (17,1%) of the patients in the MITT population met the criteria for microbiological evaluation: 5 (26,3%) in the ertapenem group and 2 (9,1%) in the levofloxacin group.
All of the microbiologically evaluable patients reached a favorable microbiological response ("presumptive eradication") at both DOT and TOC visits.

Baseline microbiology results
None of the 43 patients were positive for Legionella Ag. None of the 14 patients (6 in the ertapenem group and 8 in the levofloxacin group) whose samples were tested for acid-fast bacilli were positive.
Respiratory samples. In the ertapenem group, samples for direct diagnosis were collected from 11 patients. All were spontaneous sputum, none were aspirates or obtained by invasive methods. In the levofloxacin group, samples for direct diagnosis collected from 14 patients (all provided spontaneous sputum, of which 10 were cultured for routine bacterial pathogens, and 1 also provided pleural fluid).
Blood cultures obtained. Ertapenem group: 2 (with accompanying sputum). Levofloxacin group: 2 (with accompanying sputum) and 2 other with only blood.
Sample culture results. In the ertapenem group, 5 patients had positive sputum cultures (2 with *Haemophilus influenzae*, 1 with both *H. influenzae* and *Streptococcus pneumoniae*, and 2 with *S. pneumoniae*) In the levofloxacin group, 2 patients had positive sputum cultures for *S. pneumoniae*, one of them with positive blood cultures for *S. pneumoniae*.

SAFETY RESULTS:
Safety
Adverse events (AEs) were reported from 10 of 20 patients in the ertapenem group (50%, 95%CI: [26, 74]) and from 14 of 23 patients in the levofloxacin group (61%; 95%CI: [39, 83]).
A total of 39 episodes of AE (38 clinical; 1 laboratory; 10 reported as drug-related) were reported in the ertapenem group; and 30 (24 clinical; 6 laboratory; 7 reported as drug-related).
In the ertapenem group, 1 episode of diarrhea, was considered both drug-related and a serious adverse event. There were no interruptions in the ertapenem treatment due to adverse events.
In the levofloxacin group, 2 patients reported drug-related AEs that were also considered to be serious. One patient presented with a haematoma in the gracilis muscle and another one with an episode of dizziness, shortness of breath, nausea and vomiting at the time of levofloxacin infusion, which stopped after intterrupting the treatment and relapsed after re-initiating the infusion. This latter patient had to have

levofloxacin treatment interrupted.

Tolerability

Episodes of local erythema, induration, pain, heat, swelling, ulceration, phlebitis and itching in relation with the infusion of both ertapenem and levofloxacin were similar in frequency and intensity in both groups.

Assessment of emergence of resistant Gram-negative microorganisms during therapy

The following tables and graphics represent, by treatment group, the evolution over time of *Enterobacteriaceae* and *Pseudomonas aeruginosa* isolates from available rectal swabs from patients, and their resistance to different antibiotics.

Study group	**Ertapenem**			**Levofloxacin**		
Visit	Basal (n=17)	Discontinuation of treatment (DOC) (n=19)	Test of cure (TOC) (n=14)	Basal (n=19)	Discontinuation of treatment (DOC) (n=15)	Test of cure (TOC) (n=14)
Ceftazidime-resistant *Enterobacteriaceae*	2	1	1	1	0	1
Ertapenem-resistant *Enterobacteriaceae*	0	0	0	0	0	0
Ciprofloxacin-resistant *Enterobacteriaceae*	1	2	1	5	2	5

Study group	**Ertapenem**			**Levofloxacin**		
Visit	Basal (n=17)	Discontinuation of treatment (DOC) (n=19)	Test of cure (TOC) (n=14)	Basal (n=19)	Discontinuation of treatment (DOC) (n=15)	Test of cure (TOC) (n=14)
Ceftazidime-resistant *P aeruginosa*	0	0	0	0	0	0
Imipenem-resistant *P aeruginosa*	0	0	1	0	0	0
Ciprofloxacin-resistant *P aeruginosa*	0	0	0	0	0	0

Date of report: May, 7th 2008.

Contact: Merck National Service Center [redacted]