2. SYNOPSIS

Name of Sponsor/Company: TEDEC-MEIJI FARMA S.A.	Individual Study Table Referring to part of the Dossier	(for National Authority Use only)
Name of Finished Product: Meiact®, Spectracef®, Telo®	Volume:	
Name of Active Ingredient: Cefditoren pivoxil	Page:	

TITLE OF STUDY

"Multicentre study, prospective, comparative, randomized, double-blind and double-dummy to evaluate the efficacy and safety of cefditoren vs. ciprofloxacin in uncomplicated acute cystitis"

INVESTIGATOR(S) AND STUDY CENTER(S)

No.	SITE	INVESTIGATOR
1	CAP Horta	Dr. Antonio Rivera
2	CAP Cerdanyola del Vallés	Dr. Agustí Guiu Viaplana
3	CAP Florida Nord	Dr. Jose Luis Ballvé Moreno
4	CAP Cornellá	Dr. Josep Ramón Toll Clavero
5	CAP Amadeu Torner	Dr. Rosa Viñas
6	CAP 17 setembre	Dr. Rosaura Figueras Camos
7	Fundación Puigvert	Dr. Joan Palou
8	Centro Salud Legazpi	Dr. Bingen Uriondo San Juan
9	Centro Salud Beasain	Dr. Justo Múgica Campos
10	Centro Salud Billabona	Dr. Pablo Daza
11	Centro Salud Basurto	Dr. Jesús Zorita Valencia
12	Centro Salud Txurdinaga	Dr. Jose Angel del Pozo Iruegas
13	Centro Salud Basurto	Dr. Ander Larrazabal
14	C.S. Torre Ramona	Dr. Natividad González
15	C.S. Torre Ramona	Dr. José Félix Magdalena
16	C.S. Torre Ramona	Dr. Luis Otegui
17	C.S. Canal Imperial	Dr. Mª Antonia Sánchez
18	C.S. Canal Imperial	Dr. Carmen Garcés
19	C.S. Canal Imperial	Dr. José Luis Cañada
20	C.S. Canal Imperial	Dr. José Antonio Galve
21	C.S. Torrero - La Paz	Dr. Fernando Martín
22	C.S. Sagasta - Ruiseñores	Dr. José Porta
23	C.S. Arrabal	Dr. Mª Rosa Magallón
24	C.S. Arrabal	Dr. Mª Sol Reixa
25	C.S. Monzón Urbano	Dr. Isabel Blasco
26	C.S. Lucena	Dr. Antonio Hidalgo
27	C.S. Lucena	Dr. Alicia Álvarez
28	C.S. Lucena	Dr. Gabriel Romera
29	C.S. Rute	Dr. Estrella Castro
30	C. S. Cabra	Dr. Mª Dolores Maestre
31	CAP Bartomeu Fabrés Anglada	Dr. Estíbaliz Redondo
32	CAP Navás-Balsareny	Dr. Gabriel Martín

Name of Sponsor/Company: TEDEC-MEIJI FARMA S.A.	Individual Study Table Referring to part of the Dossier	(for National Authority Use only)
Name of Finished Product: Meiact®, Spectracef®, Telo®	Volume:	
Name of Active Ingredient: Cefditoren pivoxil	Page:	

33	CAP Les Bases-Manresa 3	Dr. Ramón Pons
34	C.S. San Telmo	Dr. Manuel Mª Ortega
35	C.S. Bombarda	Dr. Jesús Torrecilla
36	C.S. San José Norte	Dr. Ana Expósito
37	CAP Remei	Dr. Manel Terns
38	CAP Centelles	Dr. Silvia Narejos
39	ABS La Roca-CAP Dr. Vicens Papaceit	Dr. Josep Lluis Fernández
41	ABS El Castells	Dr. Llüisa Gardeñes
43	CAP El Clot	Dr. Joan Bayó
44	CAP El Maresme	Dr. Pere Torán
45	CAP La Riera	Dr. Pilar Montero
47	C.S. Petrer	Dr. José Vicente Vaquer
48	C.S. Cabo Huertas	Dr. Salvador Pertusa
49	C.S. Rincón de Loix	Dr. Manuel Ramírez
50	C.S. Xixona	Dr. Nicolás Salvador
51	C.S. Orihuela	Dr. José Luis Pardo
52	C.S. El Cristo	Dr. Joaquín Aracil
53	C.S. Paulino Prieto	Dr. Mª Jesús Barreda
54	C.S. Ventanielles	Dr. Artemio Álvarez
55	C.S. Colloto	Dr. Vicente López
56	C.S. Vallobín-La Florida	Dr. Miguel Ángel Prieto
57	C.S. Llanes en Posada	Dr. José Luis Rodríguez
G01	"AHEPA" General Hospital of Athens	Dr. Pavlos Nikolaidis
G02	University Hospital of Rio	Dr. Harris Bassaris
G03	"Sotiria" General Hospital of Chest Diseases of Athens	Dr. Aggelos Pefanis
G04	"G. Genimatas" General Hospital of Athens	Dr. Panagiotis Gargalianos
G05	"Papageorgiou" General Hospital of Thessaloniki	Dr. Chatzimouratidis

STUDY PERIOD

Date of first enrollment: 27-nov-2007

Date of last completed: 21-dec-2009

PHASE OF DEVELOPMENT:
III

Name of Sponsor/Company: TEDEC-MEIJI FARMA S.A.	Individual Study Table Referring to part of the Dossier	(for National Authority Use only)
Name of Finished Product: Meiact®, Spectracef®, Telo®	Volume:	
Name of Active Ingredient: Cefditoren pivoxil	Page:	

OBJECTIVES

To comparatively assess the efficacy and tolerability of the drugs under study in the treatment of acute uncomplicated cystitis

- Main objective

  Efficacy:

  - Microbiological efficacy (primary efficacy endpoint)
  - Clinical efficacy

- Secondary objective

  Safety

METHODOLOGY

Multicentre, prospective, randomised, active drug controlled, two parallel arms, double-blind, double-dummy study.

NUMBER OF PATIENTS (planned and analysed)

A total of 580 patients, 500 patients in Spain and 80 patients in Greece were planned to be included. Finally only 12 patients were included in Greece.

	Cefditoren	Ciprofloxacin
Number of patients planned	290	290
Number of patients randomized (Spain/Greece)	310 (302/8)	301 (297/4)
Number of patients treated (Spain/Greece)	310 (302/8)	298 (294/4)
Number of patients analyzed (Spain/Greece)	288 (281/7)	282 (279/3)

Name of Sponsor/Company: TEDEC-MEIJI FARMA S.A.	Individual Study Table Referring to part of the Dossier	(for National Authority Use only)
Name of Finished Product: Meiact®, Spectracef®, Telo®	Volume:	
Name of Active Ingredient: Cefditoren pivoxil	Page:	

DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION

Inclusion Criteria

- Non-pregnant adult females (≥ 18)
- Clinical signs and symptoms of uncomplicated acute cystitis (dysuria, urgency, frequency, suprapubic pain) with symptoms starting ≤72 hours prior the study entry.
- Positive pre-treatment clean-catch midstream urine culture (≥ 10^3 CFU/ml) and pyuria (10 leukocytes/mm^3 or more than 5 leukocytes/field 40x magnification) within the 48 hours prior to inclusion in the study*.
- *In vitro* susceptibility testing of the isolated uropathogen to the drugs under study*
- Written informed consent.

*Considering cystitis is an acute pathology and the short treatment duration, the patients can be enrolled and can start the treatment before these results are available. Positive culture and pyuria will be mandatory for the confirmation of the diagnosis.

Exclusion criteria

- Males.
- Women who are pregnant, nursing or not using a medically accepted, effective method of birth control.
- Three or more episodes of uncomplicated acute infections of the urinary tract during the past 12 months.
- Symptoms starting >4 days prior to admission

Name of Sponsor/Company: TEDEC-MEIJI FARMA S.A.	Individual Study Table Referring to part of the Dossier	(for National Authority Use only)
Name of Finished Product: Meiact®, Spectracef®, Telo®	Volume:	
Name of Active Ingredient: Cefditoren pivoxil	Page:	

- Body temperature ≥ 38ºC, back pain, chills or other manifestations suggestive of upper urinary infection.
- Evidence of structural or functional alterations of the urinary tract, such as calculi, stenosis, primary renal disease (eg. polycystic renal disease) or neurogenic bladder.
- Underlying disease predisposing to complicated urinary tract infections such as diabetes mellitus, immunosuppresion, leucopenia, heart insufficiency, liver impairment and neoplasic processes.
- Known or suspected hipersensitivity to the drugs under study.
- Patients having received other antibiotics within the 48 hour period prior to study entry.
- Incapable of following instructions and collaborating during the development of the study, according to the investigator´s judgement.

TEST PRODUCT, DOSE, MODE OF ADMINISTRATION, AND BATCH NUMBER

Active drug

- Cefditoren pivoxil (Meiact®, Spectracef®, Telo®) supplied in tablets which contain Cefditoren (I.N.N.) (pivoxil) 400 mg, mannitol, propylen glycol and other excipients q.s.
- Dose: one tablet per day for 3 days.
- Oral administration

Placebo

-Tedec Meiji FARMA S.A manufactured cefditoren pivoxil placebo tablets mimicking the active drug tablets.

Note: Batch numbers are provided in appendix 16.1.6.

DURATION OF TREATMENT

3 days in both treatment arms

REFERENCE THERAPY, DOSE, MODE OF ADMINISTRATION, AND BATCH NUMBER

Control drug

- Ciprofloxacin MABO 250 mg EFG supplied in tablets wich contain Ciprofloxacin (I.N.N.) (hydrochloride) 250mg, sodium croscarmellose, anhydrous colloidal silica, cornstarch and other excipients q.s.
- Dose: two tablets per day for 3 days.
- Oral administration

Placebo

Tedec Meiji FARMA S.A manufactured ciprofloxacin placebo tablets mimicking the

active drug tablets.

Ciprofloxacin MABO 250 EFG manufactured by Tedec Meiji Farma S.A. demonstrated to be bioequivalent to the innovator ciprofloxacin (Baycip®, Bayer).

Note: Batch numbers are provided in appendix 16.1.6.

CRITERIA FOR EVALUATION

Efficacy evaluation

Primary endpoint

The primary endpoint was the percentage of subjects from the PP population, who achieved successful microbiological efficacy; defined as bacteriological eradication at 5–9 days post- therapy.

Secondary endpoints

The following variables were analysed on both ITT and PP populations:

- Clinical efficacy at V2
- Microbiological efficacy at V3
- Clinical efficacy at V3

The following definitions were considered in order to assess efficacy:

Clinical and microbiological outcome at Visit 2 (5-9 days post-therapy)

- Microbiological Response:

For the patient to be microbiologically evaluable, a bacterial uropathogen with significant count ($\geq 10^3$ CFU/ml) had to be isolated in the urine culture at the baseline visit.

- *Eradication*: A urine culture, taken at 5-9 days post-therapy showed that all uropathogens isolated at inclusion had been reduced to $<10^2$ CFU/ml.
- *Persistence*: A urine culture, taken at any time after the completion of treatment showed a $\geq 10^2$ CFU/ml of the original uropathogen.
- *Superinfection*: The urine culture showed a $\geq 10^3$ CFU/ml of a uropathogen other than the baseline pathogen, during the course of active therapy.
- *New Infection*: A pathogen, other than the original microorganism found at baseline a level of $\geq 10^3$ CFU/ml, appeared at a level of $\geq 10^3$ CFU/ml, at any time after the treatment was finished.

- Clinical Response:

- *Clinical Cure*: Resolution of signs and symptoms at the 5-9 days post-therapy visit, and with no need of additional antimicrobial therapy.
- *Clinical Failure*: No apparent response to treatment. Persistent signs and symptoms of infection, or reappearance of signs and symptoms before or at the test of cure visit (5-9 days post-therapy), or use of additional antibiotic treatment for the infection.

Clinical and microbiological outcome at Visit 3 (4-6 weeks post-therapy)

The purpose of this visit was to assess the relapses. The definitions of clinical and microbiological response were as follows:

- Microbiological Response:

- *Long-term Sustained Eradication*: A culture taken at 4-6 weeks post-therapy showed that

all the uropathogens isolated initially remained reduced at $<10^2$ CFU/ml.

- *Persistence*: A urine culture taken at any time after the completion of therapy, grew $\geq 10^2$ CFU/ml of the original uropathogen. These patients were carried forward from the previous visit (5-9 days post-therapy).
- *Superinfection*: A urine culture grew $\geq 10^3$ CFU/ml of a uropathogen other than the baseline pathogen during the course of the active therapy, with symptoms of infection as previously stated.
- *Recurrence*: A urine culture grew $\geq 10^2$ CFU/ml of the original uropathogen taken anytime after documented eradication at the 5-9 day post-therapy visit, up to and including the 4-6 weeks post-therapy visit,
- *New Infection*: A pathogen other than the original microorganism found at baseline at a level $\geq 10^3$ CFU/ml, appears at a concentration of $\geq 10^3$ CFU/ml at any moment once treatment was finished.

- Clinical Response:

- *Sustained Cure*: All the signs and symptoms at the baseline visit showed no evidence of re-emerging at the follow-up visit at 4-6 weeks post-therapy.
- *Failure*: patients carried forward from the 5-9 days post-therapy visit.
- *Relapse*: The signs and symptoms, absent at the visit at 5-9 days post-therapy, reappeared at 4-6 weeks post-therapy visit.

Safety evaluation

All patients having received at least one dose of the drugs under study were included in the safety analysis.

The safety assesment included adverse events, physical examination and analytical parameters.

STATISTICAL METHODS:

A bilateral risk of $\alpha = 5\%$, should be fixed for all analyses expected in the protocol.

The quantitative variables should be described by size, mean, standard deviation, 95% bilateral confidence interval, median, interquartilic range, minimum and maximum.

The qualitative variables should be summarised in a table that will include the absolute and relative frequencies per treatment group and in the population as a whole. Regarding the variable, a 95% bilateral confidence level should be presented.

Population at Inclusion

The description and comparison of the population groups mITT and PP should be based on demographic characteristics, medical history and associated treatment.

The quantitative variables of normal distribution should be compared by means of the Student t test, with Sattherwhaite correction in the case of variance imbalance. The distribution of quantitative parameters should be analysed by using the Shapiro-Wilk test. The quantitative parameters without normal distribution and ordinal parameters should be compared by means of the Wilkinson-Mann-Whitney non-parametric test.

The qualitative parameters should be analyzed by means of the χ^2 test or, if not applicable, the Fisher exact test.

Programmes were created using SAS® version 9.2

SUMMARY OF RESULTS AND CONCLUSIONS

Efficacy

Per protocol population analysis (main population)

Results showed that microbiological eradication was higher than 80% in both treatment groups at V2 and V3. The microbiological eradication rates at V2 were 82.20% in the cefditoren group and 91.91% in the ciprofloxacin group (p=0.020); these differences precluded to demonstrate the non-inferiority between cefditoren and ciprofloxacin (difference -9.71%; CI:-17.99,-1.42). On the opposite, at V3 the differences were very small with eradication rates of 91.03% in the cefditoren group and 90.83% in the ciprofloxacin one (p=0.963).

Clinical response did not show statistically significant differences at V2 between cefditoren

(86.44%) and ciprofloxacin (96.39%) (p= 0.104) nor at V3 (96.39% for cefditoren and 94.64% for ciprofloxacin) (p= 0.735).

Eradication rates of *E. coli* were analyzed in the PP population showing at V2 eradication rates of 80.00% in the cefditoren group and 91.89% in the ciprofloxacin with statistically significant differences between them (p=0.014). Among patients where *E. coli* was isolated, clinical response rates were 83.33% in the cefditoren group and 92.79% in the ciprofloxacin one (p= 0.036). At V3, 96.55% of the patients in cefditoren group and 93.41% in the ciprofloxacin group were assessed as sustained eradication (p=0.484). Very similar values were obtained when the clinical response at V3 was analyzed: 98.39% in the cefditoren group and 94.68% in the ciprofloxacin group, not being the differences statistically significant (p= 0.403).

Efficacy was also assessed separately in those patients with colony counts $\geq 10^5$ cfu/ml. At baseline, 68.64% and 72.06% of the patients from cefditoren and ciprofloxacin groups respectively had bacterial counts in the urine culture of CFU$\geq 10^5$/ml. At V2, 81.48% in the cefditoren group and 89.80% in the ciprofloxacin had the microorganism eradicated (p= 0.110). Similar results were obtained at V3.

The age as a factor of influence was also tested. Overall, the efficacy results from any of the resulting groups at both V2 and V3 were in the same direction than the results from the global PP population.

Modified intent to treat population analysis

The results of the analyses in the mITT population were quite similar to those found in the PP population.

At V2 the microbiological eradication rates were 79.86% in the cefditoren group and 93.04% in the ciprofloxacin group (p= 0.0007). In the late follow-up visit (V3), the eradication rates in cefditoren group were 88.54% and 90.15% in ciprofloxacin group (p= 0.696). Values of clinical response at V2 on mITT population were 88.69% in cefditoren group and 91.49% in ciprofloxacin group (p= 0.266). At V3, response rate was 92.27% in the cefditoren group and 93.1% in the ciprofloxacin group (p=0.749).

Safety

Treatment with either cefditoren pivoxil or ciprofloxacin was safe and well tolerated. No

serious related adverse events were reported during the trial.

There were 193 adverse events reported during the study, 96 from cefditoren group and 97 from ciprofloxacin group. Intensity in all of them was as follows: 163 mild (80 and 83 from cefditoren and ciprofloxacin groups, respectively), 26 moderate (14 from ciprofloxacin group and 12 from cefditoren group) and 4 severe (2 per treatment group).

The incidence of treatment related adverse events was 6.45% and 7.05% in cefditoren and ciprofloxacin respectively. Two patients in the ciprofloxacin group experienced severe adverse events that were considered treatment related. No deaths or other serious adverse events or discontinuations due to adverse events occurred during the study. The analysis of laboratory tests or vital signs did not revealed significant changes.

CONCLUSIONS

The comparison of clinical response between cefditoren and ciprofloxacin showed that both treatments in both PP and mITT populations were efficacious in resolving symptoms of cystitis with no statistically significant differences between treatment arms.

At late follow up visit performed 4-6 weeks post treatment, percentages of sustained microbiological efficacy were very similar in both PP and mITT populations and the non inferiority was demonstrated.

However, regarding microbiological efficacy, the results obtained in the visit at 5-9 days post treatment (V2) showed that cefditoren pivoxil 400 mg od for 3 days was not as efficacious as ciprofloxacin 250 mg bid for 3 days in eradicating bacterial pathogens causative of cystitis and the non-inferiority hypothesis could not be demonstrated. Similar results were obtained in the mITT population.

No differences between cefditoren and ciprofloxacin were found in patients having colony counts $\geq 10^5$ nor in patients under 65 years old were found neither in microbiological eradication nor in clinical response.

Both treatments were safe and well tolerated.

DATE OF REPORT

28-september-2010