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Please note that the results reported in any single trial may not reflect the overall potential risks or benefits of a product which are based on an evaluation of an entire research program.

Before prescribing any Takeda products, healthcare professionals should consult prescribing information for the product approved in their country.
## SYNOPSIS

<table>
<thead>
<tr>
<th>Name of Sponsor</th>
<th>Name of Finished Product</th>
<th>Name of Active Ingredient(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Takeda Pharmaceuticals LLC</td>
<td>Flomoxef, lyophilizate for solution for intravenous infusion/injection, 1.0 g</td>
<td><strong>[Redacted]</strong></td>
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</table>

### Study Title
A phase 3, randomized, double-blind, multicenter study comparing the efficacy and safety of intravenous infusions of Flomoxef versus intravenous infusions of Cefepime in the treatment of subjects with complicated urinary tract infections including pyelonephritis.

### Publication (reference)
Not applicable.

### Studied Period

<table>
<thead>
<tr>
<th>Date of first enrolment</th>
<th>Date of early study termination</th>
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<tbody>
<tr>
<td>01.12.2015</td>
<td>19.05.2016</td>
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### Study Phase
III

### Objectives

**Primary Objective(s)**
To determine if Flomoxef is non-inferior to Cefepime with respect to the proportion of subjects in the microbiological intent to treat (micro-intent to treat (ITT)) population who achieve clinical resolution of symptoms at the End-of-Therapy visit (EOT visit, 7-14 days after the first dose of the drug is administered).

**Secondary Objective(s)**
- Microbiological response rate at the EOT visit (7-14 days)
and TOC visit (7 days after EOT).

- Clinical resolution of symptoms of Flomoxef versus Cefepime at day 3 visit, at the TOC visit and Late Follow Up (LFU) visits.
- Per-pathogen microbiological eradication rates.
- To evaluate the safety profile of Flomoxef in comparison with Cefepime.

### Design/Methodology of Clinical Study

This was a phase 3, randomized, double-blind, multicenter study comparing the efficacy and safety of intravenous infusions of Flomoxef versus intravenous infusions of Cefepime in the treatment of subjects with complicated urinary tract infections including pyelonephritis.

Due to the double-blind design investigators, clinical site team staff involved in subject care or clinical examinations, statistical team, data-management team and subjects were blinded regarding the type of therapy until the database lock. Staff at the pharmacy (study nurse, pharmacist) were not blinded. All bags and infusion system for infusions were closed (not allow the unauthorized opening) in order to maintain blinding.

80 subjects were planned to be randomized in approximately 10 sites in Russia.

Patients were screened (maximum for 24 hours) at the investigative centers after they signed the informed consent document. Eligible patients who fulfilled the requirements of the inclusion and exclusion criteria were randomized. Following the baseline assessments, patients were dosed with the assigned trial medication according to their randomization number (Flomoxef or Cefepime).

Treatment duration: 7 days course of treatment with possible extension up to 14 days.

**Treatment groups:**

- **Flomoxef** (Shionogi, Japan) - intravenous infusion 2 g twice daily (every 12 hours) - 7 days course with possible extension up to 14 days.
- **Cefepime** (Maxipime, Bristol-Myers Squibb) - intravenous infusion 1 g twice daily (every 12 hours) - 7 days course with possible extension up to 14 days.

6 study visits were planned:

- V1 (screening) (24 hours before 1st dose)
- V2 (randomization and 1st dose) Day 1
- V3 (Day 3)
- V4 (End-of-therapy (EOT)) - 7 to 14 days after start of study treatment
- V5 (test-of-cure (TOC) visit) - 7 days after EOT visit
- V6 (Late Follow-up) - 30 days (±3 days) after study start

### Number of Subjects (Planned and Analyzed)

Among 80 patients, planned by protocol, only 13 patients took part in the study due to premature trial termination by the sponsor for administrative/strategic reasons.

A total 13 patients were screened, enrolled and randomised into the study. 6 patients were randomised to receive Flomoxef and 7
patients to receive Cefepime. All patients completed drug administration according to the protocol. No patients withdrew from the study for any reason.

The ITT population include all subjects who were randomized. The micro-ITT population include all subjects who were randomized who had a baseline bacterial pathogen on culture of urine that causes UTI against which the investigational drug has antibacterial activity. The micro-ITT population was considered as the primary analysis population. The Safety Population include all subjects received any dose of planned study medication.

All 13 (100%) subjects were included in the Safety population Analysis Set and in the Intent-to-treat population (ITT) Set. Patient 00090001 (Flomoxef group), who had no bacterial pathogen determined in a baseline urine culture, was excluded from the Micro-ITT analysis Set. So there were 12 (92.3%) patients in the Micro-ITT analysis Set.

**Diagnosis and Main Criteria for Inclusion**

Only the patients with the following applied conditions were included:

1. The subject is man or woman and aged 18 to 70 years, inclusive.
2. Subject has pyuria (white blood cell [WBC] count > 10/pL in unspun urine or > 10 per high power field in spun urine).
3. Subject has clinical signs and/or symptoms of Complicated lower UTI and/or Acute pyelonephritis that include one or more of the following: fever (i.e., axillary temperature greater than 37.7 degrees Celsius), chills, malaise, flank pain, back pain, and/or costo-vertebral angle pain or tenderness and/or any of dysuriac symptoms (dysuria, urinary urgency, urinary frequency, suprapubic discomfort, new urinary incontinence or worsening of pre-existing incontinence) that occur in the presence of a functional or anatomical abnormality of the urinary tract or in the presence of catheterization
4. Subject has a pretreatment baseline urine culture specimen obtained within 24 hours before the start of administration of the first dose of study drug.
5. Subject requires IV antibacterial therapy for the treatment of the presumed cUTI.
6. In the opinion of the investigator, the subject is capable of understanding and complying with protocol requirements.
7. The subject or, when applicable, the subject’s legally acceptable representative signs and dates a written, informed consent form and any required privacy authorization prior to the initiation of any study procedures. A male subject who is nonsterilized and sexually active with a female partner of childbearing potential agrees to use adequate contraception from signing of the informed consent throughout the duration of the study and for 12 weeks after last dose.
8. A female subject of childbearing potential who is sexually active with a nonsterilized male partner agrees to routinely use
adequate contraception from signing of the informed consent throughout the duration of the study.
9. Subject is willing and able to comply with study procedures.

| Test Product, Dose and Mode of Administration, Batch Number | **FLOMOXEF**, lyophilize for preparation of the solution for intravenous administration 1.0 g, in 14-ml vial. 2.0 g of FLOMOXEF was dissolved in 8.0 ml of 0.9% sodium chloride solution and well shaken. Before each infusion, the prepared 8-ml solution of FLOMOXEF was diluted further in 0.9% sodium chloride - the final volume of 100.0 mL. Containing 2.0 g FLOMOXEF 100-ml solution immediately after its preparation was infused intravenously in 1 hour to a subject. Test product batch number: 5008-P1 |
| Duration of Treatment with the Test Product | Treatment course: intravenous infusion 2 g twice daily (every 12 hours) - 7 days course with possible extension up to 14 days. |
| Reference Product, Dose and Mode of Administration, Batch Number | **CEFEPIME** (MAXIPIME, Bristol-Myers Squibb) lyophilize for preparation of the solution for intravenous administration 1.0 g in vial. 1.0 g of MAXIPIME was dissolved in 10.0 ml of 0.9% sodium chloride solution and well shaken. Before each infusion, the prepared 10.0-ml solution of MAXIPIME was diluted further in 0.9% sodium chloride - the final volume of 100.0 mL. Containing 1.0 g MAXIPIME 100-ml solution immediately after its preparation was infused intravenously in 1 hour to a subject. Reference product batch number: 4D 02695 |
| Duration of Treatment with the Reference Product | Treatment course: intravenous infusion 1 g twice daily (every 12 hours) - 7 days course with possible extension up to 14 days. |
| Criteria for evaluation: Efficacy | **Primary Efficacy Endpoint**  
The proportion of subjects who are assessed based on resolution of clinical symptoms of cUTI present at trial entry and no new symptoms at EOT Visit (7 days - 14 days after first dose of study drug administration), i.e., none of the following:  
- No pyuria.  
- No fever (i.e., axillar temperature greater than 37.7 degrees Celsius) and chills.  
- No malaise, flank pain, back pain, and/or costo-vertebral angle pain or tenderness.  
- No any of dysuriac symptoms (dysuria, urinary urgency, urinary frequency, suprapubic discomfort, new urinary incontinence or worsening of pre-existing incontinence).  
**Secondary Efficacy Endpoints**  
- Microbiological response is determined by the results of cultures obtained at baseline, after the EOT visit and the TOC visit. We define microbiological success as the demonstration that the bacterial uropathogen found at trial entry is reduced to less than 10^4 colony forming units per milliliter (CFU/mL) on urine culture. The number and
percentage of subjects in each treatment group recorded as a microbiological eradication or persistence or indeterminate or new infection or superinfection.

- The proportion of subjects who have a clinical resolution of symptoms of cUTI present at trial entry and no new symptoms at the day 3 visit, the TOC visit and LFU visit.
- For each unique uropathogen, the number and percentage of subjects in each treatment group recorded as a microbiologic eradication or persistence or new infection or superinfection for that particular pathogen at baseline, the EOT visit and TOC visit.

### Safety Endpoint
- Safety was evaluated in the safety population by presenting summaries of AEs, laboratory evaluations (coagulation, hematology, chemistry evaluations, and urinalysis), vital signs, and physical examinations in the 2 treatment groups (evaluated at all study visits through the Late Follow Up (30 +/- 3 Days after start of study drug administration).

### Statistical Methods
Due to premature trial termination and small sample size only descriptive statistics was used.
Continuous data were summarised using the following descriptive statistics: n (number of observations), arithmetic mean (average), SD (standard deviation), median, maximum, minimum. Categorical variables were summarised using the following descriptive statistics: n (frequency) and percentage (%) of patients in each category. Data were summarised for each treatment group and for all patients (total), where applicable. The two applicable treatment groups were referred to in the text, tables and listings as: “Flomoxef” and “Cefepime”.

### Results:
#### Efficacy Results
At the End-of-therapy (EOT) Visit (7-14 days after first dose of study drug administration) 3/5 (60.0%) patients in the Flomoxef treatment group and 3/7 (42.9%) patients in the Cefepime treatment group reported to be symptoms free (resolution of clinical symptoms of cUTI).

At the End-of-therapy Visit (Visit 4) bacterial uropathogen eradication was reported in 10/12 (83.3%) patients in the total patient population, in 4/5 (80.0%) patients in the Flomoxef treatment group and in 6/7 (85.7%) patients in the Cefepime treatment group. Infection persistence was reported in 2/12 (16.7%) patients in the total patient population, in 1/5 (20.0%) patient in the Flomoxef treatment group and in 1/7 (14.3%) patient in the Cefepime treatment group. New infection and superinfection cases were reported only in the Cefepime treatment group in 1/7 (14.3%) patient, each.

At the test-of-cure (TOC) Visit (Visit 5) bacterial uropathogen eradication was reported in 10/12 (83.3%) patients in the total patient population, in 4/5 (80.0%) patients in the Flomoxef treatment group and in 6/7 (85.7%) patients in the Cefepime treatment group and in 6/7 (85.7%) patients in the Cefepime
New infection was reported in 2/12 (16.7%) patients in the total patient population, in 1/5 (20.0%) patient in the Flomoxef treatment group and in 1/7 (14.3%) patient in the Cefepime treatment group. Superinfection was reported in 4/12 (33.3%) patients in the total patient population, in 2/5 (20.0%) patients in the Flomoxef treatment group and in 2/7 (28.6%) patients in the Cefepime treatment group. Infection persistence was reported only in the Cefepime treatment group in 1/7 (14.3%) patient.

At Visit 3 (Day 3) only 1/7 (14.3%) patient in the Cefepime treatment group reported to be symptoms free (resolution of clinical symptoms of cUTI).

At the test-of-cure (TOC) visit 3/5 (60.0%) patients in the Flomoxef treatment group and 2/7 (28.6%) patients in the Cefepime treatment group were symptoms free.

At the Late Follow-up (LFU) visit 3/5 (60.0%) patients in the Flomoxef treatment group and 4/7 (57.1%) patients in the Cefepime treatment group were symptoms free.

Due to premature trial termination and small sample size such secondary efficacy endpoint, as eradication for particular pathogen numbers in different time periods was not determined.

A total of 4 Treatment-emergent-adverse events (TEAEs) (2 in the Flomoxef treatment group and 2 in the Cefepime treatment group) were reported by 2/6 (33.3%) patients in the Flomoxef treatment group and 2/7 (28.6%) patients in the Cefepime treatment group.

In the Flomoxef treatment group there were 1 case of Influenza (SOC - Infections and infestations) in 1/6 (16.7%) patient and 1 case of Thrombophlebitis (SOC - Vascular disorders) in 1/6 (16.7%) patient.

In the Cefepime treatment group there were 1 case of Pyrexia (SOC - General disorders and administration site conditions) in 1/7 (14.3%) patient and 1 case of Arthralgia (SOC - Musculoskeletal and connective tissue disorders) in 1/7 (14.3%) patient.

There were no patients with permanently discontinued study medication and patients withdrawn from the study due to TEAEs.

There were no patients who reported SAEs or who died during the study.

Clinical significant abnormal laboratory values in the hematology test in the Flomoxef treatment group were: abnormal (above the normal ranges) white blood cells level in 2 patients at baseline (BL) and in 1 patient in Visit 4, abnormal (above the normal ranges) neutrophils level in 1 patient at baseline (BL) and in Visit 4. While in the Cefepine treatment group: abnormal (above the normal ranges) white blood cells level in 1 patient at baseline (BL) and abnormal (above the normal ranges) neutrophils level in 1 patient at baseline (BL).

Clinical significant abnormal laboratory values in the blood
chemistry test include abnormal (above the normal ranges) C-reactive protein level at baseline (BL) and in Visit 3 in 1 patient in the Flomoxef treatment group and in 1 patient in the Cefepine treatment group.

Clinical significant abnormal laboratory values in the urinalysis include abnormal baseline bacteria level at baseline (BL) in 2 patients in the Flomoxef treatment group and in 3 patients in the Cefepine treatment group.

Clinical significant abnormal findings during Vital Signs include abnormal Body Temperature (°C) in 3/6 (50%) patients in Visit 1 and 2/6 (33.3%) patients in Visit 2 in the Flomoxef treatment group. While in the Cefepine treatment group abnormal findings were in 2/7 (28.6%) patients in Visit 1, 2/7 (28.6%) patients in Visit 2 and 1/7 (14.3%) patient in Visit 3.

Clinical significant abnormal findings during Physical Examinations include abnormal Cardiovascular system abnormal findings in 1/6 (16.7%) patient in Visits 4 and 5 in the Flomoxef treatment group, Genitourinary system abnormal findings in 6/6 (100%) patients in Visits 1 and 2 and in 3/6 (50%) patients in Visit 3 in the Flomoxef treatment group, and Genitourinary system abnormal findings in 7/7 (100%) patients in Visits 1 and 2, in 6/7 (85.7%) patients in Visit 3 and in 1/7 (14.3%) patient in Visits 4 and 5 in the Cefepine treatment group.

**Conclusion**

Overall, due to premature trial termination and small sample size only descriptive statistics was used for all efficacy endpoints. No conclusions about Flomoxef and Cefepime efficacy comparison (non-inferiority) could be done.

In this small study population Flomoxef and Cefepime were well tolerated, and there were no unexpected safety findings. The incidence of treatment-emergent adverse events did not show any relevant differences and no subjects experienced any serious adverse events. Future studies with larger sample size are warranted.