



Hôpitaux
Universitaires
Genève



UNIVERSITÉ
DE GENÈVE



AIDA NITROFURANTOIN VS FOSFOMYCIN FOR ACUTE UTI: STATISTICAL ANALYSIS PLAN v1.0

STATISTICAL ANALYSIS PLAN
Protocol 13-014

AIDA WP2: Randomised clinical trial comparing fosfomycin vs. nitrofurantoin for treatment of uncomplicated lower urinary tract infection in female adults at increased risk of antibiotic-resistant bacterial infection

Prepared by:
Angela Huttner MD,
16 June 2017

Approved by:

Signature

Date

Stephan Harbarth, MD
Principal investigator

16 June 2017

Johan Mouton, MD, PhD
AIDA Coordinator

16/6/2017



Hôpitaux
Universitaires
Genève



UNIVERSITÉ
DE GENÈVE



AIDA: NITROFURANTOIN VS FOSFOMYCIN FOR ACUTE UTI: STATISTICAL ANALYSIS PLAN v1.0

Document history

Version	Date	Reason for change
1.0	16.06.2017	N/A

Table of Contents

1 Introduction & data preparation	3
2 Protocol-defined study outcomes	3
3 Statistical methods	4
3.1 Populations	4
3.2 Analyses and methods.....	4
3.2.1 Baseline demographics and clinical data	4
3.2.2 Clinical efficacy analyses	5
3.2.3 Bacteriologic baseline and efficacy analyses	5
3.2.4 Safety and other secondary outcome analyses	6
3.2.5 Missing data	6
4 Salient protocol definitions	6
5 References	7

AIDA: NITROFURANTOIN VS FOSFOMYCIN FOR ACUTE UTI: STATISTICAL ANALYSIS PLAN v1.0

1 Introduction & data preparation

This document describes the statistical analysis plan for the multicenter superiority trial entitled “Randomized clinical trial comparing fosfomycin vs. nitrofurantoin for treatment of uncomplicated lower urinary tract infection in female adults at increased risk of antibiotic-resistant bacterial infection.” All study outcome measures and analysis populations are reviewed in Sections 2 and 3, respectively. Please refer to the study protocol (v7, 03.11.2014) for all other details on study design. Of note, the superiority hypothesis pertains solely to the primary outcome of clinical response and the secondary outcome of bacteriologic response, and not to any other secondary outcomes.

Data source. The information collected in the case report form (CRF) has been transferred into a dedicated database (SecuTrial). Only data stored within SecuTrial will be analyzed.

Database lock. No data will be exported for analysis until the data have been validated by study investigators and database managers, and the database locked by the study’s data managers in Geneva.

Data-analyst blinding. As described in the study protocol, all data analyses will be conducted in a blinded fashion. Through the aid of data managers, data exports from Secutrial will include “scrambled” (recoded) patient study numbers to avoid recognition of a patient by study investigators, and individual treatment assignments will be coded to ensure masking of group treatment assignment.

2 Protocol-defined study outcomes

Primary outcome. The trial’s primary outcome is the incidence of clinical failure in both study arms in the 28 days following completion of therapy. Clinical response is categorized as follows:

Clinical response	Definition
Clinical cure	Complete resolution of symptoms with no recurrence of symptoms or signs of UTI
Clinical failure	Need for additional, or change in, antibiotic treatment due to a UTI OR discontinuation due to lack of efficacy
Indeterminate	Either persistence of symptoms without objective evidence of infection (absence of bacteriuria or pyuria) OR any extenuating circumstances precluding a classification or clinical cure/failure

Secondary outcomes include clinical response 14 days after completion of therapy, bacteriological response 14 and 28 days after completion of therapy, the incidence of “true UTI” (culture-positive) among all included patients, duration of symptoms after treatment initiation, and the incidence of hospital admission, progression to pyelonephritis or urosepsis (see definitions below), study drug-related adverse events (AE), mortality, and emergence of resistance in the 33-day study period. Bacteriologic response is defined as below:

Bacteriologic response	Definition
Bacteriologic cure	Eradication of the infecting strain with no recurrence of bacteriuria ($<10^3$ cfu/mL) during follow-up
Bacteriologic recurrence	Bacteriuria $\geq 10^3$ cfu/mL However, bacteriologic recurrence without urinary tract symptoms will be designated asymptomatic bacteriuria and left untreated.

3 Statistical methods

3.1 Populations

Efficacy and safety analyses will be conducted on intention-to-treat (ITT), various modified intention-to-treat (mITT), and per-protocol (PP) populations. These are defined as follows:

Intention-to-treat population: All patients randomized constitute this population, whether the patients ultimately received a study antibiotic or not.

Clinical mITT population: This group is comprised of patients who were randomized and received at least one dose of the study antibiotic to which they were randomized.

Microbiologically confirmed mITT population: This group is comprised of patients who were randomized, received at least one dose of the study antibiotic to which they were randomized, and had a positive initial urine culture ($\geq 10^3$ cfu/mL).

Microbiologically susceptible mITT population: This group is comprised of patients who were randomized, received at least one dose of the study antibiotic to which they were randomized, and had a positive ($\geq 10^3$ cfu/mL) initial urine culture with a bacterial isolate that was susceptible *in vitro* to that study antibiotic.

Microbiologically study-drug susceptible, otherwise resistant mITT population: This group is comprised of patients who were randomized, received at least one dose of the study antibiotic to which they were randomized, and had a positive ($\geq 10^3$ cfu/mL) initial urine culture with a bacterial isolate with *in vitro* susceptibility to that study antibiotic but acquired resistance to ≥ 1 antibiotic (with special attention to fluoroquinolone resistance and extended-spectrum beta-lactamase (ESBL)-producing Gram-negative bacteria).

Low-count microbiological mITT populations: The three microbiological mITT populations described above will be recreated but will be expanded to include patients whose cultures yielded uropathogen bacterial counts of only $< 10^3$ cfu.

Per-protocol population: This group consists of all patients who were randomized to either antibiotic, received the antibiotic per study protocol (with at least 80% compliance), and for whom (2) no major protocol deviations were documented throughout the study period.

3.2 Analyses and methods

3.2.1 Baseline demographics and clinical data

Baseline demographics and clinical characteristics will be described study-wide and by study site. Demographic data will include age and race. Baseline clinical data include, but are not limited to, baseline risk (see definitions below) for resistant bacterial infections, initial urinary symptomatology, baseline urinalysis results and, where available, liver function and calculated creatinine clearance; baseline microbiologic data include the presence of positive urine culture upon study inclusion and baseline antibiotic resistance profiles. Summary tables (descriptive statistics and/or frequency tables) will be provided for baseline demographic and clinical variables as appropriate. Continuous variables

AIDA: NITROFURANTOIN VS FOSFOMYCIN FOR ACUTE UTI: STATISTICAL ANALYSIS PLAN v1.0

will be summarized with descriptive statistics (mean and standard deviation, median and range). Frequency counts and percentage of subjects within each category will be provided for categorical data. Missing data will be described.

3.2.2 Clinical efficacy analyses

As laid out in the protocol, the alternative hypothesis (H_1) is anticipated: nitrofurantoin is expected to have a 10% advantage over fosfomycin in clinical cure rates 28 days post treatment, assuming clinical success rates of roughly 90% and 80% in the nitrofurantoin and fosfomycin groups, respectively. Clinical efficacy analyses will be performed by intervention group on the PP, ITT and mITT populations. The incidence of clinical failure at days 14 and 28 (primary outcome time point) will be tabulated in the two intervention arms and compared using the Fisher test; statistical tests will be two-sided with a significance level of 0.05.

Univariate analyses will be conducted to assess associations between clinical failure and the following factors:

- age, ethnicity, number and intensity of initial urinary symptoms, study site, study antibiotic received, antibiotic compliance, baseline urine culture (whether positive, number of colony counts, mono- versus polymicrobial infection, baseline resistance in cultured bacterium to study antibiotic)

We will perform a subgroup analysis of treatment efficacy of study drugs on lower UTI caused by fluoroquinolone-resistant and/or EBSL-producing Gram-negative bacteria. Given the probability that this exploratory analysis may be confounded by study group imbalances, we will run uni- and multivariate analyses to determine treatment efficacy, stratified by study allocation (with inclusion of variables emerging from univariate analyses with an arbitrary p value cutoff of $\leq .20$). Fisher exact, Chi square, and Mann-Whitney tests as well as Spearman correlation coefficients will be used to test associations.

Special considerations: a blinded panel to evaluate patients with “indeterminate” clinical outcomes

As described in the study protocol, clinical outcomes may occasionally be difficult to assess (e.g., a patient may report overall improvement but persistent, subclinical dysuria while at the same time denying a need for additional, or change in, antibiotic treatment). Thus cases deemed “indeterminate” will be orally presented to a blinded panel of study investigators (including the AIDA coordinator and investigators from alternate study sites) to determine whether the outcome can be classified more clearly as cure or failure. Investigators will be blinded to the patients’ treatment assignments. Cases defying further classification will remain “indeterminate.”

3.2.3 Bacteriologic baseline and efficacy analyses

First, the incidence of “true” (culture-positive) UTI at study inclusion (baseline) will be described across intervention arms and study sites. (The protocol definition of a positive culture is below.)

Second, the prevalence of “resistant” bacteria and “multidrug-resistant” bacteria (as defined in section 4) in these baseline cultures will be described in both study arms and by site. Special emphasis will be placed on baseline resistance to nitrofurantoin and fosfomycin. Finally, the incidence of emergence of bacterial resistance to study antibiotics at days 14 and 28 after completion of therapy will be compared across intervention arms and study sites.

Univariate analyses will be conducted to assess associations between baseline (presence of positive culture) and endpoint (emergence of bacterial resistance) observations and the following factors:

- For presence of positive urine culture at baseline: age, ethnicity, number and intensity of initial urinary symptoms, baseline risk for resistant bacterial infection (see above), and study site

AIDA: NITROFURANTOIN VS FOSFOMYCIN FOR ACUTE UTI: STATISTICAL ANALYSIS PLAN v1.0

- This will be repeated specifically for presence of *E. coli*-positive urine culture at baseline
- For emergence of bacterial resistance in post-treatment urine cultures: age, ethnicity, baseline risk for resistant bacterial infection (see above), study site, compliance with antibiotic therapy, study antibiotic received
 - This will be repeated specifically for emergence of *E. coli* resistance in post-treatment cultures

Multivariate logistic regression will be performed and will include variables emerging from univariate analyses with an arbitrary p value cutoff of ≤ 0.20 . Fisher exact, Chi square, and Mann-Whitney tests as well as Spearman correlation coefficients will be used to test associations.

3.2.4 Safety and other secondary outcome analyses

Frequency and severity grade of AE considered possibly, probably or definitely related to the study antibiotic will be described by system organ class and by Medical Dictionary for Regulatory Activities (MedDRA) preferred term. Frequency of AEs will be reported and compared among intervention groups with Fisher's exact or the Chi-square test, as appropriate.

Other outcomes such as duration of symptoms after treatment initiation and the incidence of hospital admission, progression to pyelonephritis or urosepsis, and mortality will be compared by intervention arm and by site. All statistical tests will be two-sided with a significance level of 0.05.

3.2.5 Missing data

For clinical and bacteriologic outcome measures, Bayesian multiple imputation (MI) methods will be applied to deal with missing data. In this model, if one or more observations of "X" is missing, values are simulated from their complete conditional distribution given other X values. For each of the X values (observed and possibly simulated), a MI analysis is conducted. The reported estimates are averaged over all these simulations, and thereby incorporate the error due to "missingness" in a natural and principled manner.

Such may be the primary analysis, but for sensitivity purposes, the following sensitivity analyses would be conducted:

- 1) Assume all missing observations under treatment (fosfomycin) and control (nitrofurantoin) had the best possible outcome
- 2) Assume all missing observations under treatment and control had the worst possible outcome
- 3) Assume all missing observations under treatment had the best possible outcome and all missing observations under the control had the worst possible outcome
- 4) Assume all missing observations under treatment had the worst possible outcome and all missing observations under the control had the best possible outcome

4 Salient protocol definitions

Increased risk for a resistant bacterial infection is defined in the study protocol as follows:

- Any systemic antibiotic exposure (\geq one dose) in the previous twelve months
- Hospitalization in an acute or long-term-care centre in the previous twelve months
- The present episode of suspected UTI fulfils criteria for healthcare-associated infection¹

AIDA: NITROFURANTOIN VS FOSFOMYCIN FOR ACUTE UTI: STATISTICAL ANALYSIS PLAN v1.0

- Current or recent (in the preceding twelve months) carriage of resistant organisms (e.g., MRSA, ESBL, quinolone-resistant E. coli)
- Recent stay in a high-risk country:
 - Residence for at least one month in the preceding twelve months in the following countries:
 - Any country in the Mediterranean basin, excluding France
 - South Asia
 - Southeast Asia
 - Middle East
 - Africa
 - Central & South America

Lower urinary tract infection includes infection of the urethra (urethritis), bladder (cystitis), and ureters. A “true” infection requires symptoms and/or signs consistent with UTI as well as a positive urine culture ($\geq 10^3$ colony forming units (cfu) /ml).²

Resistant bacterium. A bacterium with acquired (not intrinsic) resistance to at least one agent in one class of antibacterial agents.

Multidrug-resistant bacterium. In accordance with the European Centre for Disease Prevention and Control’s recent proposal for standard definitions of acquired resistance, we define a multidrug-resistant pathogen as one that is resistant to at least one agent in ≥ 3 classes of antimicrobial agents.³

5 References

1. Horan TC, Andrus M, Dudeck MA. CDC/NHSN surveillance definition of health care-associated infection and criteria for specific types of infections in the acute care setting. *Am J Infect Control*. 2008;36(5):309-332.
2. Nicolle LE. Uncomplicated urinary tract infection in adults including uncomplicated pyelonephritis. *Urol Clin North Am*. 2008;35(1):1-12, v.
3. Magiorakos AP, Srinivasan A, Carey RB, et al. Multidrug-resistant, extensively drug-resistant and pandrug-resistant bacteria: an international expert proposal for interim standard definitions for acquired resistance. *Clin Microbiol Infect*. 2012;18(3):268-281.