Bayesian Adaptive Dose-Response Studies in Complicated and Uncomplicated Urinary Tract Infection

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Poster 36

BACKGROUND

- Challenges to safe clinical development include minimizing exposure of patients to excessive or ineffective doses during dose ranging, while maximizing assessment of efficacy
- Adaptive-design methods incorporate evidence-guided decision gates at pre-specified interim analyses[1,2]
  - Decisions follow scientifically driven rules that are formulated at the design stage to result in a potentially safer and more efficient study, compared with traditional designs
    - Although no dose regimens tested would be considered unsafe, some doses may have better tolerability than others
- In Phase 2, incorporating Bayesian methods in the elucidation of the dose-response function is beneficial in preventing subsequent dose changes or failure in Phase 3 due to inappropriate dose selection[3]
- Adaptive trials have particular operational and logistical challenges that must be evaluated and planned for, in order to facilitate successful study implementation
- We present two statistical designs for proof-of-concept and dose-selection Phase 2 studies of omadacycline (OMC) for treating adult female patients with uncomplicated urinary tract infection (uUTI; NCT03425396) or acute pyelonephritis (AP; NCT03757234)[4]
- The decision to utilize these adaptive study designs was due to the lower rate of urinary excretion for OMC relative to biliary excretion,[4] the lack of informative pre-clinical models, and the historically limited support for use of tetracyclines in these indications

METHODS

Interim Analysis Study Design

- Both designs were randomized, double-blind, adaptive, dose-response studies with three per-protocol interim analyses
  - Efficacy data (investigator assessment of clinical response at post treatment evaluation) for 40, 80, and 100 patients (planned enrollment, N≥200 per study)
- In both studies, an unblinded Data Monitoring Committee (DMC) monitored safety, tolerability, and efficacy using pre-defined decision rules to initiate or drop OMC treatment group(s), or modify the randomization ratio

uUTI Study (17201; NCT03425396)

- Goal:
  - To evaluate efficacy of three regimens of oral OMC compared with a standard oral regimen of nitrofurantoin (NTF) (**Table 1**)
- Planned patient participation:
  - ≤37 days, including 7 days' total duration of test article exposure
- Efficacy outcome:
  - Clinical success rate (CSR, i.e., investigator assessment of clinical response) at Day 14, assessed using logistic regression with a prior Beta distribution for the NTF group

METHODS

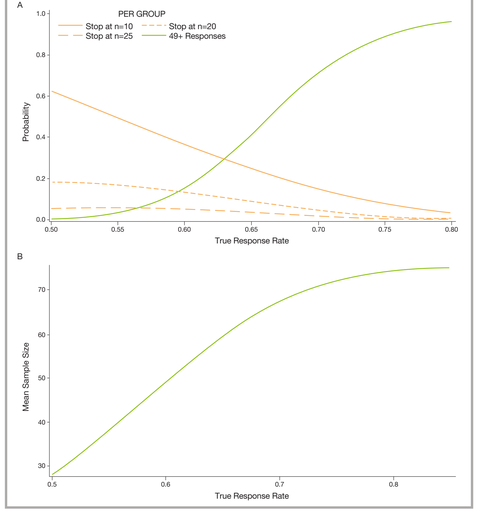
Table 1. Initial Planned Treatment Groups, n=50 per group (Study 17201)

Group	Test Article	Study Day 1	Study Days 2-7
1 – Low dose	Omadacycline	Low oral q12h	Low oral q24h
2 – Middle dose	Omadacycline	High oral q12h	Low oral q24h
3 – High dose	Omadacycline	High oral q12h	High oral q24h
4 – Comparator	Nitrofurantoin	100 mg oral q12h	100 mg oral q12h

q12h = every 12 hours; q24h = every 24 hours

- Design was to enroll 200 patients into four groups (**Table 1**):
  - Initial allocation to treatment arms was equal
  - Assumption at outset was 1:1:1:1 randomization, with n=50 per group
- Response criteria were targeted toward estimating the probability that CSR for each dose group was within 10% of the comparator group, based on Bayesian logistics regression
  - Rules were based using a prior Beta distribution (12.00, 3.27) that has a better mean square error for all n≤75 over the range 0.6-0.9
  - Success was defined as ≥49 responders out of 75 patients (**Fig. 1**)

Figure 1. (A) Probability of Each Decision Node, Given the True Response Rate for a Dose; (B) Mean Sample Size Based on Various Response Rates (Study 17201)



METHODS

- Modifications to OMC dosing regimens and treatment arms were based on efficacy rules and tolerability (**Fig. 2**)
  - Dropping a dose group was considered if the predictive probability of success was <50%
- Dose group enrollment could be stopped based on safety and tolerability at interim analyses or at any point during the study

Figure 2. Dose Group Allocation Rules (Study 17201)

DMC = Data Monitoring Committee

In the case of lower doses achieving efficacy, higher doses are not excluded. Likewise, intolerability in lower doses may lead to dropping higher doses.

AP Study (17202; NCT03757234)

- Goal:
  - To evaluate four once-daily intravenous (IV) or IV-to-oral dose regimens of OMC compared with a once-daily standard regimen of IV-to-oral levofloxacin (LEV) (**Table 2**)
- Planned patient participation:
  - ≤30 days, including 7-10 days' total duration of test article exposure (IV and oral combined)
- Efficacy outcome:
  - Composite clinical and microbiological success rate compared with LEV at Day 21
- Design was to enroll ~200 patients into five groups (**Table 2**)
  - Assumption at outset was 1:1:1:1:1 randomization, with n~40 per group
  - For interim decisions, dose groups 2-4 were combined as one set

METHODS

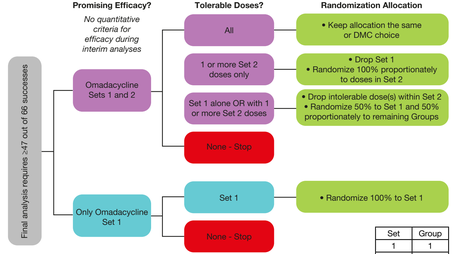
Table 2. Initial Planned Treatment Groups, n~40 per group (Study 17202)

Group	Test Article	Study Day 1	Study Days 2-7	Study Days 8-10
(Set 1) – 1	Omadacycline	High IV	High IV	High IV
(Set 2) – 2	Omadacycline	High IV	Low IV	Low IV
(Set 2) – 3	Omadacycline	High IV	Low oral or low IV	Low oral or low IV
(Set 2) – 4	Omadacycline	High IV	High oral or low IV	High oral or low IV
5	Levofloxacin	750 mg IV	750 mg oral or 750 mg IV	750 mg oral or 750 mg IV

IV = intravenous

- Tolerability was the prime basis for decisions on randomization reallocation and/or dropping dose groups at interim analyses (**Fig. 3**):
  - Efficacy was only considered for dose reallocation if DMC deemed the response rates as too low to proceed with enrollment
  - Efficacy was not pre-planned with statistical decision criteria due to high variability in small sample sizes
- DMC could also recommend continued enrollment of >200 participants

Figure 3. Dose Group Allocation Rules (Study 17202)



Set	Group
1	1
2	2
2	3
2	4

DMC = Data Monitoring Committee

In the case of lower doses achieving efficacy, higher doses will not be excluded. Likewise, intolerability in lower doses may lead to dropping higher doses.

CHALLENGES

- Scientific challenges included expected dose-response relationships, i.e., monotonicity, and grouping of doses to improve decision making
- Operational challenges were similar in both studies and included fast enrollment, fewer than expected patients with complete microbiologic data at time of DMC meetings
  - Rapid enrollment for study 17202 made DMC meetings very close together, creating pressures in terms of data cleaning and output generation
- Study decisions required microbiological data that were unavailable until the patient completed the study; consequently, enrollment continued for ≥1 month before decisions could be made

OVERCOMING LOGISTICAL CHALLENGES

Considerations for successful execution of adaptive trials

- Adaptive trials often include many groups, and randomization allocation may change during the trial; therefore, drug supply must be carefully managed by:
  - Increasing quantities of study drug (to account for allocations across study arms), which may increase drug wastage
  - Planning for overages and budgeting appropriately for necessary quantities
  - Controlling the number of sites and site activations
  - Including the clinical supply manager in DMC meetings, to facilitate rapid awareness of allocation changes
- Appropriately paced enrollment (allowing time to react to changes) or stopping the study (to wait for data to catch up) must be balanced with timeline constraints
- Clear understanding of endpoint/data required (e.g., microbiological data, imaging) for decision making, and speed of any data analysis or transfer is critical, to determine feasibility of an adaptive approach
  - Alignment on how complete data must be in order to support DMC analysis and decision making

CONCLUSIONS

- Bayesian adaptive designs in Phase 2 dose-selection studies allow more patients to enroll in the more effective and tolerable dosing groups, maximizing precision and value of evidence, and utilizing the most efficient sample size
- Modeling and simulation efforts upfront, along with knowing the strength of evidence requirement, can help to mitigate challenges
- Adaptive trials require careful planning; there are challenges unique to these studies that, if not planned for, could hinder the ability of the research team to adapt effectively
- In adaptive trials, baseline assumptions must be regularly monitored throughout trial execution, and necessary adjustments should be made

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