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Safety of Ceftazidime-Avibactam (CZA) in Combination with Aztreonam (ATM) in a Phase I, Open-Label Study in Healthy Adult Subjects (COMBINE)

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ABSTRACT

Background: The combination of CZA-ATM is frequently used to treat patients with metallo-β-lactamase (MBL)-producing Enterobacterales (EB) infections, but its safety has not been established in controlled trials. This phase 1 study evaluated the safety of the optimal CZA-ATM regimens identified in the hollow fiber infection model of MBL-producing EB (PMID: 32464664).

Methods: The phase I, open-label, single center study enrolled healthy adults aged 18-45 years (NCT03978091). Subjects were sequentially assigned to 1 of 6 Cohorts and administered investigational product(s) (IP) for 7 days (**Table 1**). Study safety was monitored by assessments of adverse events (AEs), vital signs, and clinical laboratory safety tests.

Results: Of 48 subjects enrolled, 50% were female and 60% were Black. The mean (SD) age was 33.5 (6.2) years and mean (SD) weight was 75.7 (12.1) kg. The number of subjects who had ≥ 1 AE and experienced ≥ 1 related AE was 46 (96%) and 41 (85%), respectively. Summary of AEs, irrespective of severity and relatedness to study product, that occurred in ≥10% of the safety population by Cohort is shown in **Table 2**. ALT/AST elevations (n=19 subjects) of any relatedness were the most frequent AEs and 89% of ALT/AST elevation AEs occurred in subjects in the ATM alone or CZA-ATM combination cohorts (**Figure 1**). The incidence of ALT/AST elevation AEs were comparable between the ATM alone and CZA-ATM combination cohorts. Two subjects in the ATM CI experienced severe ALT/AST elevation AEs, which halted the study. All subjects with ALT/AST elevations were asymptomatic with no other findings suggestive of liver injury, and all resolved without sequelae. Most other AEs were of mild to moderate severity and were similar across cohorts except prolonged prothrombin time (more frequent in CZA-ATM Cohorts [**Figure 2**]).

Conclusions: Clinicians should only consider using CZA-ATM when the benefits outweigh the risks. If CZA-ATM is prescribed, clinicians are advised to monitor for hepatic injury. Close monitoring of coagulation parameters may also be prudent with CZA-ATM. Future comparator-controlled randomized clinical trials are required to better define the safety and efficacy of the CZA-ATM regimens.

BACKGROUND

- Metallo-β-lactamases (MBLs) have recently emerged as a problematic resistance mechanism among Gram-negative bacteria (PMID: 27593176).
- Several antibiotics with activity against MBL-producing Gram-negative bacteria are in development, but none are anticipated to be available for several years (PMID: 28893690).
- Ceftazidime-avibactam (CZA) with aztreonam (ATM) is often used for MBL-producing Gram-negative infections (PMID: 32427286).
- In the combination of ATM with CZA, avibactam (AVI) inhibits ESBL and KPC beta-lactamases that are often present in MBL-producing Gram-negative bacteria, allowing ATM, which is unaffected by MBLs, to effectively bind to bacterial penicillin binding proteins (PMID: 28167541).
- Safety of CZA-ATM has not been established in controlled trials.

OBJECTIVE

- This phase 1 study evaluated the safety of the optimal CZA-ATM regimens identified in hollow fiber infection models of MBL-producing Enterobacterales (PMID: 32464664).

METHODS

Study Design and Population

- The COMBINE study (ClinicalTrials.gov Identifier: NCT03978091) was a Phase I, open-label, single center study that investigated the safety and PK of 7 days of CZA combined with ATM, CZA alone, and ATM alone in 48 healthy adult male and female volunteers aged 18-45 years.
- Eligible subjects were sequentially assigned to one of 6 dosing Cohorts (**Table 1**).
  - Four were single drug cohorts (CZA alone or ATM alone)
  - Two were combination drug cohorts (CZA-ATM)
- Eligible subjects were admitted to the phase 1 study unit for 7 days to receive study product(s) and the final outpatient follow-up visit was Day 11 +3 days post Day 1 of study product administration.
- The study was approved by the Duke Health Institutional Review Board and the study was conducted in accordance with Good Clinical Practice principles as established by the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH).

Safety Monitoring

- Safety was closely monitored using daily assessments of AEs, vital signs, and symptom-directed physical examinations.
- The type, incidence, relatedness, and severity of AEs and serious adverse events (SAEs) were recorded from start of infusion of the first dose of study product(s) on Day 1 through the Final Study Visit (Day 11 +3).
- AEs were assessed by the investigator using the protocol-defined grading system that was based on the FDA Guidance for Industry for grading of AEs and all AEs after the first dose of study drug(s) were coded using Medical Dictionary for Regulatory Activities Terminology (MedDRA) dictionary version 23.1.
- The number of AEs and the number of subjects with an AE were summarized by MedDRA system organ class (SOC), preferred term (PT), maximum severity, relatedness to treatment, Cohort, and investigational study product(s) received.

Table 1. Investigational Study Drug Cohorts (8 Subjects/Cohort)

Cohort	Investigational Study Drugs
1	CZA 2.5 g intravenously (IV) as 2-hour infusion every 8 hours for 7 days
2	CZA 2.5 g IV as 2-hour infusion x 1, then 0.32 g per hour IV daily as a continuous infusion (CI) (7.5 g/day) for 7 days
3	ATM 2 g IV as 2-hour infusion every 6 hours for 7 days
4	ATM 2 g IV as a 2-hour infusion x 1, then 0.33 g per hour IV daily as a CI (8 g/day) for 7 days
5*	CZA 2.5 g IV as 2-hour infusion every 8 hours for 7 days and ATM 1.5 g IV as 2-hour infusion every 6 hours for 7 days
6*	CZA 2.5 g IV as 2-hour infusion every 8 hours for 7 days and ATM 2 g IV as 2-hour infusion every 6 hours for 7 days

*Cohorts 5 and 6 reflect modified treatment. Initial regimen for Cohort 5 was CZA 2.5 g IV as 2-hour infusion every 8 hours and ATM 2 g IV as 2-hour infusion every 6 hours for 7 days. Initial regimen for Cohort 6 was CZA 2.5 g IV as a 2-hour infusion x 1, then 0.32 g per hour IV daily as CI (7.5 g/day) and ATM 2 g IV as 2-hour infusion x 1, then 0.33 g per hour IV daily as CI (8 g/day) for 7 days. A halting rule was observed in Cohort 4 (2 subjects experienced Grade 3 related ALT/AST elevations). In response to the study halt, the dosing in the Cohorts 5 and 6 be changed, and additional safeguards were incorporated in the study protocol.

RESULTS

Study Safety Population (n=48 subjects)

- 24 subjects (50%) were female and 29 (60%) were Black.
- Mean (SD) age was 33.5 (6.2) years and mean (SD) weight was 75.7 (12.1) kg.

Safety Summary

- 46 subjects (96%) experienced at least one AE in the safety population.
  - 6 subjects experienced a Grade 3 AE (13%), 19 subjects experienced a Grade 2 AE (40%), and 21 subjects (44%) experienced a Grade 1 AE.
- 41 subjects (85%) had ≥1 related AE and 35 subjects (73%) had ≥1 unrelated AE.
- There were no serious adverse events (SAEs) or deaths in any Cohort.
- Summary of AEs of any relatedness and non-clinically significant (NCS) laboratory abnormalities that occurred in ≥10% of subjects by Cohort are shown in **Table 2**.
- The most common AE was ALT/AST elevations (n=19 subjects).
  - 89% of subjects with ALT/AST elevations received ATM or CZA-ATM (**Figure 1**).
  - ALT/AST elevation AEs were comparable between the ATM and CZA-ATM cohorts.
  - Two subjects in the ATM CI (Cohort 4) experienced severe ALT/AST elevation AEs.
  - All subjects with ALT/AST elevations were asymptomatic.
- The second most frequent AEs observed were hematologic and coagulation AEs.
  - Most hematologic and coagulation AEs were of mild to moderate severity and only prolonged prothrombin time AEs were more pronounced in CZA-ATM Cohorts (**Figure 2**).
  - All subjects with hematologic and coagulation AEs were asymptomatic.
- Other related and unrelated AEs were comparable across study Cohorts.
  - Most other AEs were of mild to moderate severity and were comparable across Cohorts.
  - One Grade 3 related increase in blood glucose was observed in 1 subject in Cohort 4.
  - 14 subjects had unrelated infusion site-related AEs (13 Grade 1 and 1 Grade 2), and these were attributed to managing and changing peripheral IV access during dosing.

Table 2. Summary of AEs of Any Relatedness and Grade 1 NCS Laboratory Abnormalities that Occurred in ≥10% of Safety Population by Cohort

Adverse Event	Cohort 1 (N=8)	Cohort 2 (N=8)	Cohort 3 (N=8)	Cohort 4 (N=8)	Cohort 5 (N=8)	Cohort 6 (N=8)	All (N=48)
Hemoglobin Decreased	5 (63)	4 (50)	5 (63)	4 (50)	**3 (38)**	**3 (38)**	24 (50)
AST Increased	1 (13)	1 (13)	5 (63)	2 (25)	**4 (50)**	**5 (63)**	18 (38)
ALT Increased	1 (13)	-	5 (63)	3 (38)	**3 (38)**	**5 (63)**	17 (35)
Prothrombin Time Increased	-	1 (13)	1 (13)	3 (38)	**4 (50)**	**7 (88)**	16 (33)
Bradycardia	2 (25)	2 (25)	4 (50)	2 (25)	**4 (50)**	**2 (25)**	16 (33)
Infusion Site Reaction	2 (25)	2 (25)	3 (38)	2 (25)	**2 (25)**	**4 (50)**	15 (31)
Neutrophils Decreased	2 (25)	1 (13)	1 (13)	2 (25)	**3 (38)**	**2 (25)**	11 (23)
Abdominal Discomfort	2 (25)	1 (13)	2 (25)	-	**2 (25)**	**1 (13)**	8 (17)
Headache	1 (13)	1 (13)	2 (25)	1 (13)	**2 (25)**	-	7 (15)
Blood Glucose Increased	3 (38)	-	2 (25)	2 (25)	-	-	7 (15)
ECG QT Prolonged	1 (13)	2 (25)	-	1 (13)	**1 (13)**	-	5 (10)
Phlebitis	1 (13)	-	1 (13)	-	**1 (13)**	**2 (25)**	5 (10)

Footnote: N reflects number of subjects (% of subjects) in Each Cohort. Abbreviations: ALT: alanine transaminase; AST: aspartate transaminase; ECG: Electrocardiogram. *Bradycardia included bradycardia and sinus bradycardia.

Figure 1. Individual and Mean ALT and AST Values by Study Product Cohort

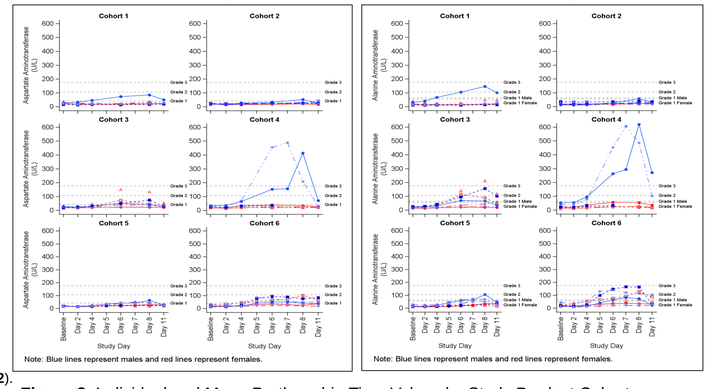
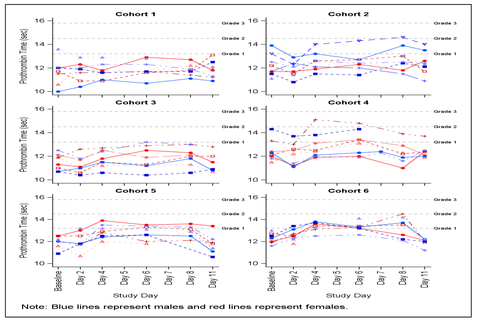


Figure 2. Individual and Mean Prothrombin Time Values by Study Product Cohort



CONCLUSIONS

- Administration of 2-hour intermittent infusions of CZA-ATM was safe, and some caution should be exercised with use of continuous infusion ATM.
- Clinicians should only consider using CZA-ATM when the benefits outweigh the risks.
- If CZA-ATM is prescribed, clinicians are advised to monitor liver function, hematologic, and coagulation parameters.
- Future controlled studies are required to better define the safety and efficacy of the CZA-ATM regimens evaluated in this Phase 1 study.

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