

SUMMARY OF RESULTS



The Antibacterial Resistance Leadership Group (ARLG) funds, designs, and conducts clinical research that will help prevent, diagnose, and treat infections caused by bacteria that are resistant to antibiotics.

The ARLG, along with the team of study doctors, scientists, and researchers, are pleased to describe the results from a study focused on antibiotic review strategies in community hospitals to prevent overuse of antibiotics.

WHAT IS THE STUDY TITLE?

Ceftazidime-Avibactam in **Combination** with Aztreonam (COMBINE)

Combination regimen of Ceftazidime-Avibactam with Aztreonam Hollow Fiber Infection Model against NDM-1-producing Enterobacteriaceae (COMBINE HFIM)



WHAT IS THE PURPOSE OF THE RESEARCH? WHAT IS THE PRIMARY ENDPOINT?

Doctors have few options for treating infections caused by antibiotic-resistant Gram-negative bacteria. Like many antibiotics, ceftazidime-avibactam (CZA)

and aztreonam (ATM) do not work against some types of bacteria when used alone, but they do work when combined together.

CZA is made up of a β -lactamase inhibitor (avibactam) and an antibiotic (ceftazidime). ATM is another antibiotic treatment option. Both ceftazidime and ATM are β -lactam antibiotics that disturb the bacterial cell wall, which kills the bacteria.

Some antibiotic-resistant Gram-negative bacteria produce enzymes called β -lactamases, which stop β -lactam antibiotics from working. When ceftazidime and ATM do not work, the bacteria do not die.

β -lactamases called metallo- β -lactamases (MBLs) are very difficult to treat, because they inactivate all β -lactam antibiotics except ATM. ATM may not be stopped from working by MBLs, but it is stopped by other β -lactamases. However, ATM is protected by those other β -lactamases by the avibactam part of CZA.

Researchers wondered if combining CZA and ATM could become a new treatment option that is more effective and resilient against the MBLs made by antibiotic-resistant Gram-negative bacteria. CZA and ATM can be prescribed on their own, but doctors do not know when it may be safe to combine the two antibiotics or which doses may work best. To find out, researchers conducted the COMBINE and COMBINE HFIM studies. Researchers performed the COMBINE Hollow-fiber Infection Model (HFIM) Study to see which doses of CZA plus ATM would kill the most bacteria and prevent antibiotic resistance. The HFIM mimics the environment in the human body and allows bacteria to grow continuously. Using the HFIM, researchers can evaluate how different doses may show up in the blood.

Using the effective doses from the HFIM study, researchers performed the COMBINE Study to see how safe these doses were compared to ATM alone and CZA alone. They evaluated safety based on patients' vital signs, blood samples, and physical exams.

Researchers also looked for side effects. A known side effect from ATM is an increase in liver enzymes, which is a sign of liver damage. However, researchers did not know if CZA and ATM given together would cause further increases in liver enzymes compared to ATM alone.



WHEN DID THE RESEARCH TAKE PLACE?

The COMBINE HFIM study took place between January 2018 and February 2019. The phase I COMBINE Study occurred between July 9, 2019 and November 23, 2020.



HOW WILL THE RESULTS HELP PATIENTS AND DOCTORS?

Doctors will use the results to prescribe safe doses of a combination antibiotic that is resilient to antibiotic resistance. Patients may receive fewer antibiotic treatments and recover more quickly from bacterial infections.



MANUSCRIPT OF PRIMARY RESULTS OR CLINICAL STUDY REPORT.



Determining the Optimal Dosing of a Novel Combination Regimen of Ceftazidime/Avibactam with Aztreonam Against NDM-1-producing Enterobacteriaceae Using a Hollow-fibre Infection Model

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

Pharmacokinetics of Ceftazidime-Avibactam in Combination with Aztreonam (COMBINE) in a Phase I, Open-Label Study in Healthy Adult Volunteers

IS THE STUDY REGISTERED WITH CLINICALTRIALS.ORG?

NCT03978091

WHY WAS THIS RESEARCH CONDUCTED? WHAT IS THE RATIONALE?



Researchers are worried about the rising number of infections from the antibiotic-resistant Gram-negative bacteria that produce MBLs. These infections are resistant to nearly all available antibiotics. Patients with these infections may be treated by combining CZA and ATM. However, the best dose for CZA and ATM together was not known.

Additionally, researchers did not know if it was safe to give CZA and ATM together. They knew it was safe to prescribe CZA and ATM by themselves, but it was important to understand their safety when combined. Researchers also needed to learn if the CZA-ATM combination affects the increase in liver enzymes sometimes caused by ATM. Researchers also needed to learn if other side effects occurred.



WHAT WERE THE RESULTS?

In the COMBINE HFIM Study, researchers found that several doses of CZA-ATM killed the most bacteria and suppressed antibiotic resistance.

Researchers for the COMBINE Study found that CZA-ATM given as a 2-hour infusion every 6 to 8 hours for 7 days does not worsen liver damage compared to ATM alone, but they recommended that doctors who prescribe CZA-ATM should monitor liver function and blood clotting.



WHY IS THIS RESEARCH IMPORTANT TO PATIENTS, CLINICIANS, AND OTHER RESEARCHERS?

Doctors will benefit from this research by knowing the safest doses of CZA-ATM to prescribe to patients. Patients will benefit by receiving the safest doses of an antibiotic combination that is effective to treat infections caused by MBL-producing Gram-negative bacteria.



WHO WAS INVOLVED?

The COMBINE HFIM study involved no patients; instead, researchers used bacteria strains of *Escherichia coli* and *Klebsiella pneumoniae* that produced MBLs.

The COMBINE Study involved 48 healthy adult male and female volunteers aged 18 to 45 years.



WHAT HAPPENED DURING THE STUDY?

In the COMBINE HFIM study, researchers grew bacteria strains that produce MBLs. These bacterial strains are resistant to many antibiotics. Then, they tested multiple doses of CZA by itself or with ATM. The doses that killed the most bacteria and suppressed antibiotic resistance were then studied further in the COMBINE clinical trials.

Since COMBINE was a phase I study, the purpose was to help researchers find out if this potential treatment option is safe and which dose may work best.

In the COMBINE Study, healthy participants were randomly assigned (by chance) to receive one of six doses of CZA, ATM, or CZA-ATM combined. Doses were given through infusion either intermittently or continuously over 7 days. Participants gave blood samples for researchers to learn about the antibiotics' pharmacokinetics.

Pharmacokinetic studies explore how a drug moves through and leaves the body. They help doctors understand important information about a drug's dose, including route (by mouth or another method) and frequency (how many times per day the drug is taken).



WHAT'S NEXT?

Researchers will need to conduct additional clinical trials to learn how the safety and efficacy information gathered in the COMBINE and COMBINE HFIM studies about CZA-ATM may apply to people with active antibiotic-resistant infections.