NEWS RELEASE

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Astellas Provides Update on Phase 3 Study Evaluating Isavuconazole in Patients with Candidemia and Other Invasive *Candida* Infections

NORTHBROOK, Ill., July 30, 2015 – Astellas today announced topline results from the Phase 3 ACTIVE study evaluating the efficacy and safety of intravenous (IV) and oral isavuconazole, commercially known as CRESEMBA® (isavuconazonium sulfate), under development for adults with candidemia and other invasive *Candida* infections. Results from the study demonstrated that the trial did not meet its primary endpoint of non-inferiority in overall treatment response in isavuconazole-treated patients at the end of IV therapy compared to caspofungin. The key secondary endpoint of IV isavuconazole followed by either IV or oral isavuconazole versus IV caspofungin followed by either IV caspofungin or oral voriconazole was comparable between groups. The overall safety profile for isavuconazole was similar to caspofungin and consistent with safety data seen in the previously reported Phase 3 studies with isavuconazole.

"We had hoped for a different outcome, as this is a patient population that would benefit from additional treatment options. We look forward to understanding these data following further analysis," said Bernie Zeiher, M.D., president, Global Development at Astellas. "CRESEMBA remains an important treatment option for the approved indications of invasive aspergillosis and invasive mucormycosis in the United States."

The overall response at the end of IV in the modified intent-to-treat population (N=400) was 60.3 percent in the isavuconazole treatment group and 71.1 percent in the caspofungin group with an adjusted treatment difference of -10.8 percent (95 percent CI; -19.9 percent, -1.8 percent). The lower bound of the 95 percent confidence interval of the treatment difference between isavuconazole and caspofungin exceeded the pre-specified non-inferiority margin of -15 percent.

CRESEMBA is approved in the United States to treat invasive aspergillosis and invasive mucormycosis in adults and is being co-developed with Basilea Pharmaceutica International Ltd.

About ACTIVE
ACTIVE is a Phase 3, double-blind, randomized study of 440 adult patients with candidemia and other invasive *Candida* infections at multiple sites globally. The primary endpoint of the trial was to compare the overall treatment response to isavuconazole versus caspofungin at the end of IV therapy as determined by the independent, blinded Data Review Committee (DRC). The key secondary endpoint was to assess the success rate of overall treatment response at the first follow up visit (two weeks after the end of therapy) for isavuconazole treatment versus the comparator regimen. For the primary endpoint, success rate of overall response at EOIV (i.e., end of intravenous therapy of isavuconazole or caspofungin) was derived based on the DRC assessments of positive clinical and mycological responses, as well as no need for alternative systemic antifungal therapy (SAT). For the key secondary endpoint, success rate was defined as overall response at follow-up one (i.e., two weeks after the end of all

treatment) as derived based on the DRC assessments of positive clinical and mycological responses as well as no SAT use and no recurrent or emergent infection.

The trial was designed to evaluate isavuconazole at a loading dose of 200 mg IV every eight hours for the first 48 hours followed by a maintenance dose of 200 mg IV once-daily Day 3 through Day 10 compared to caspofungin at 70 mg IV on Day 1 as a loading dose and 50 mg IV maintenance dose once-daily Day 2 through Day 10. After Day 10, patients had the option to continue IV therapy or switch to oral therapy. Isavuconazole patients were switched to 200 mg once-daily oral isavuconazole and caspofungin patients were switched to 400 mg twice-daily oral voriconazole Day 11 through end of treatment (maximum 56 days).

About *Candida* Infections
While rare as exemplified by the orphan designation, invasive *Candida* infections are known for their high mortality rates of 40 percent in the United States. [i, ii]

About CRESEMBA®
CRESEMBA (isavuconazonium sulfate) is the prodrug containing the active antifungal agent isavuconazole, an azole antifungal indicated for use in the treatment of invasive aspergillosis and invasive mucormycosis in adults.

Important Safety Information for CRESEMBA® (isavuconazonium sulfate)
CRESEMBA is contraindicated in persons with known hypersensitivity to isavuconazole.

Coadministration of strong CYP3A4 inhibitors, such as ketoconazole or high-dose ritonavir (400 mg every 12 hours), with CRESEMBA is contraindicated because strong CYP3A4 inhibitors can significantly increase the plasma concentration of isavuconazole.

Coadministration of strong CYP3A4 inducers, such as rifampin, carbamazepine, St. John's wort, or long acting barbiturates with CRESEMBA is contraindicated because strong CYP3A4 inducers can significantly decrease the plasma concentration of isavuconazole.

CRESEMBA shortened the QTc interval in a concentration-related manner. CRESEMBA is contraindicated in patients with familial short QT syndrome.

Hepatic Adverse Drug Reactions (e.g., elevations in ALT, AST, alkaline phosphatase, total bilirubin) have been reported in clinical trials and were generally reversible and did not require discontinuation of CRESEMBA. Cases of severe hepatic adverse drug reactions including hepatitis, cholestasis or hepatic failure including death have been reported in patients with serious underlying medical conditions (e.g., hematologic malignancy) during treatment with azole antifungal agents, including CRESEMBA. Evaluate liver tests at the start and during therapy. Monitor patients who develop liver abnormalities during CRESEMBA therapy for severe hepatic injury. Discontinue if clinical signs and symptoms consistent with liver disease develop that may be attributable to CRESEMBA.

Infusion-related reactions including hypotension, dyspnea, chills, dizziness, paresthesia, and hypoesthesia were reported during intravenous administration of CRESEMBA. Discontinue the infusion of CRESEMBA if these reactions occur.

Serious hypersensitivity and severe skin reactions, such as anaphylaxis or Stevens Johnson syndrome, have been reported during treatment with other azole antifungal agents. Discontinue CRESEMBA if a patient develops a severe cutaneous adverse reaction. Caution should be used when prescribing CRESEMBA to patients with hypersensitivity to other azoles.

During pregnancy, CRESEMBA may cause fetal harm when administered, and should be used during pregnancy only if the potential benefit to the patient outweighs the risk to the fetus. Women who become pregnant while receiving CRESEMBA are encouraged to contact their physician.

Following dilution, CRESEMBA intravenous formulation may form precipitate from the insoluble isavuconazole. Administer CRESEMBA through an in-line filter.

The most frequent adverse events among CRESEMBA-treated patients were: nausea (26 percent), vomiting (25 percent), diarrhea (22 percent), headache (17 percent), elevated liver chemistry tests (16 percent), hypokalemia (14 percent), constipation (13 percent), dyspnea (12 percent), cough (12 percent), peripheral edema (11 percent), and back pain (10 percent).

The adverse reactions which most often led to permanent discontinuation of CRESEMBA therapy during the clinical trials were: confusional state (0.7 percent), acute renal failure (0.7 percent), increased blood bilirubin (0.5 percent), convulsion (0.5 percent), dyspnea (0.5 percent), epilepsy (0.5 percent), respiratory failure (0.5 percent), and vomiting (0.5 percent).

For Full Prescribing Information in the U.S., please visit www.astellas.us/docs/cresemba.pdf.

About Astellas Infectious Disease
Astellas is committed to the field of infectious diseases. Astellas is expanding the knowledge base of this therapeutic area and empowering physicians to make evidence-based clinical decisions.

Astellas' proud history of collaborating with investigators around the world provides ideal environments to study compounds that have the potential for significant breakthroughs for patients. In fact, Astellas has performed some of the world's largest clinical trials in fungal infections.

About Astellas
Astellas is a pharmaceutical company dedicated to improving the health of people around the world through provision of innovative and reliable pharmaceuticals. For more information on Astellas, please visit our website at www.astellas.us. Follow us on Twitter at www.twitter.com/AstellasUS. Visit our Facebook page at www.facebook.com/AstellasUS.

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[i] Isavuconazole (BAL8557) in the Treatment of Candidemia and Other Invasive Candida Infections. https://clinicaltrials.gov/ct2/show/NCT00413218?term=candidiasis&lead=astellas&rank=9. Accessed July 2015.
[ii] Pfaller MA, Diekema DJ. Epidemiology of Invasive Candidiasis: a Persistent Public Health Problem. *Clinical Microbiology Reviews*. 2007;20(1):133-163. doi:10.1128/CMR.00029-06.