



OTSUKA MARYLAND RESEARCH INSTITUTE, INC.

2440 Research Boulevard
Rockville, Maryland 20850
Telephone 301.417.0900
Facsimile 301.990.0036

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Contact:	Debra Kaufmann	Kara Vonasek
	240.683.3568	202.955.6222 ext. 2532
	301.252.3582 (on site in Orlando)	508.981.1613 (on site in Orlando)
	debrak@otsuka.com	kvonasek@spectrumscience.com

OTSUKA'S TOLVAPTAN SHOWS DECREASED FLUID RETENTION IN HOSPITALIZED PATIENTS WITH WORSENING CONGESTIVE HEART FAILURE

*Data on Novel Phase III Agent Presented at Late Breaking Clinical Trials Session
During American Heart Association's Scientific Sessions 2003*

ORLANDO, FL, November 10, 2003 – Results presented from a study of the therapeutic impact of tolvaptan in congestive heart failure at the American Heart Association's Scientific Sessions 2003 (November 9-12) showed that tolvaptan significantly decreased fluid retention for hospitalized patients with worsening heart failure. More than 1,000,000 hospitalizations occur for worsening congestive heart failure in the U.S. each year, totaling nearly \$25 billion in direct health care costs annually and producing up to a 30 percent readmission rate within two months. Tolvaptan is a phase III compound currently being studied by Otsuka Maryland Research Institute, Inc. (OMRI).

The study, "ACTIV in CHF" (Acute and Chronic Therapeutic Impact of a Vasopressin 2 Antagonist [Tolvaptan] in Congestive Heart Failure), randomized 319 patients into four groups. Along with conventional CHF therapy, tolvaptan was orally administered once a day during hospitalization at one of three dosage levels (30, 60 or 90 milligrams). Treatment with tolvaptan was continued for seven weeks after discharge. Data shows statistically significant body weight reductions in patients receiving tolvaptan compared to patients given placebo, after 24 hours. These differences were maintained over time.

"Randomized, controlled trials are extremely rare in hospitalized patients with worsening heart failure," said ACTIV in CHF lead investigator, Mihai Gheorghide, MD, Associate Chief, Division of Cardiology, Northwestern University Feinberg School of Medicine, Chicago, IL. "These results are encouraging and may provide hope for a field that has not seen a new treatment option in a long time."

Tolvaptan is believed to work by blocking the vasopressin V2 receptor in the kidney. Vasopressin is a neurohormone responsible for water reabsorption. By blocking the V2 receptor, tolvaptan appears to reduce fluid build up or congestion in patients.

At present, diuretics are the preferred congestive heart failure therapy for reducing fluid build up in the body. Unfortunately, diuretics may exhibit negative side effects, such as potassium loss and impaired kidney function.

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Another study presented at the American Heart Association's Scientific Sessions 2003 compared the effects of tolvaptan and furosemide on renal physiology and hemodynamics. In this study, the increased urine production observed with tolvaptan appears to be associated with enhanced renal blood flow, and glomerular filtration rate, and decreased renal vascular resistance. This second tolvaptan study was sponsored by Otsuka and conducted by the Mayo Clinic.

"The results of these studies encourage us to continue looking closely at tolvaptan for congestive heart failure," said Cesare Orlandi, MD, Vice President, Clinical Development, Otsuka Maryland Research Institute, Inc. "An international study investigating tolvaptan's impact on congestive heart failure and survival is currently underway, (EVEREST) Efficacy of Vasopressin Antagonism in Heart Failure: Outcome Study with Tolvaptan."

In both studies, the most commonly observed adverse events were those associated with the pharmacological action of the compound, including thirst, polyuria and dry mouth.

Tolvaptan has been studied in more than 350 healthy people in Japan, the United Kingdom and United States. Tolvaptan has been studied in over 700 people with congestive heart failure and in 135 people with low blood sodium. Clinical studies have shown that a by-product of the drug breakdown can build up in the body. The long-term effects of this product in humans are unknown. The known side effects related to tolvaptan (OPC-41061) are the following: dry mouth, increased thirst, increased heart rate, abdominal pain, headache, low energy, soft stool, dizziness, increased white blood cell count, sore throat, increased urine flow, rectal bleeding, abnormal rapid heartbeats, abnormal heart rhythm, and high sodium levels in the blood.

Otsuka Maryland Research Institute, Inc. (OMRI) is involved in conducting all phases of clinical research and development of innovative healthcare products to address unmet medical needs. OMRI is well established in the scientific community as a globally focused organization that plays a leadership role in the research and development of Otsuka's ethical healthcare products. The company is dedicated to the improvement of the quality of life and health of patients around the world. OMRI is part of the Otsuka Pharmaceutical Group.

Founded in 1964, Otsuka Pharmaceutical Co., Ltd. is a diversified health care company guided by its philosophy: "Otsuka - people creating new products for better health worldwide" and dedicated to the research and development of innovative medical, pharmaceutical, and nutritional consumer products to improve the quality of human life. Otsuka has a diverse portfolio including central nervous system, cardiovascular, circulatory, gastro-intestinal, respiratory, dermatological, ophthalmologic, and anti-cancer therapies, and is pursuing research in genomics and protein function. The Otsuka Pharmaceutical Group is composed of 51 businesses around the world and 22,000 employees, earning total revenues of \$4.3 billion annually.

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