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ZENSUN

FACT SHEETS:

NEUCARDIN™: A NOVEL FIRST IN CLASS THERAPY TO TREAT CHRONIC HEART FAILURE

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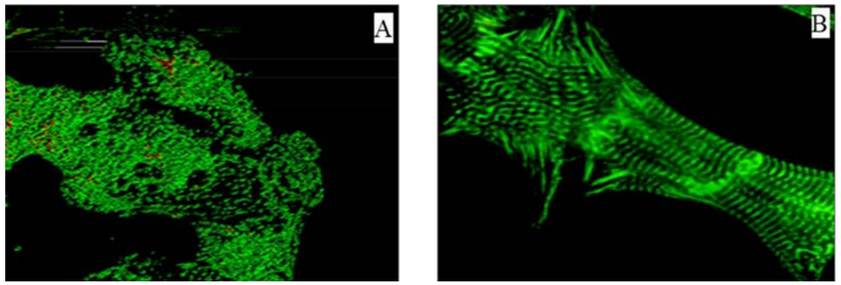
OVERVIEW: Zensun is developing a novel treatment for moderate and severe Chronic Heart Failure (CHF). CHF affects ~5.5 million people in the United States of America and cardiovascular death is the number one single cause of death in the world. There are no treatments for CHF other than heart transplantation that is extremely limited in number.

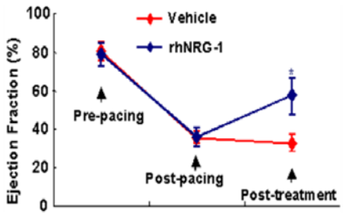
WHAT IS NEUCARDINTM? Neucardin^{TM} is a portion of a naturally occurring protein known as Neuregulin-1β2α. Neuregulin-1 is found in the heart and by binding to receptors known as ErbB4 and ErbB2 found on cardiac muscle cells neuregulin-1 activates downstream signaling pathways important for cardiac function and structure. The presence of neuregulin-1 and its receptors has also been shown to be critical for normal heart development.

COMPOSITION AND ADMINISTRATION: After recombinant expression and purification Neuregulin-1 β2α is formulated for parenteral administration via the subcutaneous route. Its appearance is as a white or whitish lyophilized powder. It is reconstituted in Sterile Water for Injection according to the subjects' body weight and administered using a small external mini pump infusion device. During treatment, subjects can move freely.

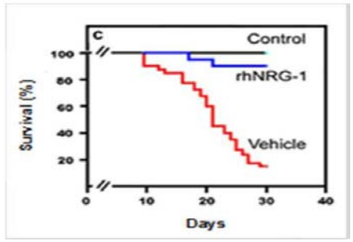
HOW DOES NEUCARDINTM WORK? The reasons for the hearts inability to pump blood to the body are complex, but include structural abnormalities in the cell known as myofibril disarray **(A)**. Once bound to ErbB4, Neucardin^{TM} activates many key molecules that are involved in restoration of an ordered cardiac muscle cell structure and this includes strengthening of the connections between the cells by reorganization of the intercalated discs, thereby increasing contractile function **(B)**.



In various animal models of heart failure, such as dogs with rapid pacing induced heart failure **(C)**, Neucardin^{TM} has been shown to reverse dilated cardiomyopathy, increase heart function and improve hemodynamics. In other animal models such as doxorubicin induced heart failure, Neucardin^{TM} significantly increases survival rates **(D)**.



(C)



(D)

WHAT IS THE PHASE OF CLINICAL DEVELOPMENT OF NEUCARDINTM? Neucardin^{TM} is in Phase III clinical development in China and is now in Phase II clinical trials in the United States of America.

WHAT ARE THE RESULTS OF CLINICAL STUDIES? Neucardin^{TM} has been given to over 400 people with CHF and over 1200 people have been involved in clinical trials in China, Australia and the United States of America. Phase II clinical studies demonstrate that NeucardinTM increases heart function in people with heart failure for up to 3 months following treatment (absolute ejection fraction increase of 5%), reduces left ventricular end systolic volume, and has a significant survival benefit compared with placebo in an enriched heart failure population.

WHAT ARE THE SIDE EFFECTS OF NEUCARDINTM? The main side effects are gastrointestinal disorders, such as nausea, vomiting and diarrhea. Some subjects also suffer from headaches and other nervous system disorders. Importantly, the side effects are alleviated after cessation of study drug administration.

WHAT ARE THE CONTRAINDICATIONS OF NEUCARDINTM? Neucardin^{TM} should not be administered to cancer or pregnant patients or persons under the age of 18 years.

If you have any technical questions, please contact Bhawanjit Brar Ph.D. Senior Director for Product Development at bbrar@ZensunUSA.com

SELECTED ZENSUN PUBLICATIONS

Jabbour A, Hayward CS, Keogh AM, Kotlyar E, McCrohon JA, England JF, Amor R, Liu X, Li X-Y, Zhou MD, Graham RM, Macdonald PS. Parental administration of recombinant human neuregulin-1 to subjects with stable chronic heart failure produces favourable acute and chronic haemodynamic responses. *Transplantation.* 2011 May 15;91(9):961-7.

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Gao R, Zhang J, Cheng L, Wu X, Dong W, Yang X, Li T, Liu X, Xu Y, Li X, Zhou M. A Phase 2, randomized, double-blind, multicenter, based on standard therapy, placebo-controlled study of the efficacy and safety of recombinant human neuregulin-1 in subjects with chronic heart failure. *J Am Coll Cardiol.* 2010; 55(18):1907-14.

Gu X, Liu X, Xu D, Li X, Yan M, Qi Y, Yan W, Wang W, Pan J, Xu Y, Xi B, Cheng L, Jia J, Wang K, Ge J, Zhou M. Cardiac functional improvement in rats with myocardial infarction by upregulating cardiac myosin light chain kinase with neuregulin. *Cardiovasc Res*. 2010; 88(2):334-43

Liu X, Gu X, Li Z, Li X, Li H, Chang J, Chen P, Jin J, Xi B, Chen D, Lai D, Graham RM, Zhou M. Neuregulin-1/erbB-activation improves cardiac function and survival in models of ischemic, dilated, and viral cardiomyopathy. *J Am Coll Cardiol.* 2006. 48(7):1438-47.

Liu X, Hwang H, Cao L, et al. Domain-specific gene disruption reveals critical regulation of neuregulin signaling by its cytoplasmic tail. *Proc Natl Acad Sci U S A.* 1998; 95:13024–9.

IMPORTANT PUBLICATION

Crone SA, Zhao YY, Fan L, et al. ErbB2 is essential in the prevention of dilated cardiomyopathy. Nat Med 2002;8:459–65.