TITLE: Phase I Study of CB5083 in Patients with VCP Inclusion Body Myopathy

Abstract

VCP disease (OMIM 167320) first described by Kimonis et al. (2000) comprises of Inclusion Body Myopathy associated with Paget’s disease of the bone and Frontotemporal Dementia (IBMPFD) and other phenotypes including amyotropic lateral sclerosis and Parkinson’s disease[1-5]. It is caused by dominantly inherited mutations in the Valosin Containing Protein (VCP) gene mapped to the human chromosomal region 9p13.3-12 [6-9]. To date, more than 40 disease mutations have been identified in the VCP gene the A232E mutation being associated with a more severe clinical phenotype[10]. VCP disease is an underdiagnosed disease that has been reported in >100 families worldwide mainly from the United States and Europe. Al-Obeidi E et. al. (2017) recently reported clinical findings in 231 individuals (118 males, 113 females) from 36 families carrying 15 different VCP mutations from Dr. Kimonis’ cohort.

One of the main functions of the protein is as a chaperone for proteosomal protein degradation and autophagic dysfunction leading to protein aggregation[11-14]. Several studies have indicated that the mechanism for VCP disease is gain of function of the mutant allele. Niwa et al. (2012) reported that ATPase levels were the highest with A232E and R155C mutations, these being associated with a more severe clinical progression when compared to other VCP mutations[15]. Recently Zhang et al. (2017)[16] showed that the common VCP disease mutation act as hyperactive alleles with respect to regulation of Mitofusin which is involved with mitochondrial fusion. Importantly, VCP inhibitors were shown to suppress mitochondrial defects, muscle tissue damage and cell death associated with VCP mutations in Drosophila. These inhibitors also suppressed mitochondrial fusion and respiratory defects in patient fibroblasts. Blythe et al. (2017) [17] showed that mutant VCP is associated with overactive segregase or protein unfolding activity and CB-5083 the newest compound restored activity to normal. These results support prior studies showing that VCP disease mutations cause IBMPFD through a gain-of-function mechanism, and that VCP inhibitors will have therapeutic value.

We propose a Phase I study of CB5083, a VCP inhibitor in 10 individuals with the R155H mutation associated inclusion body limb girdle myopathy. This inhibitor has been tested in a phase 1 dose escalation study for oncology indications in 85 patients and has a known safety profile. Cleave, Inc. holds the IND for CB5083 and have offered the drug free to my patients VCP associated inclusion body myopathy since the company is not pursuing this drug for this indication. Since the mechanism is now conclusively known to be related to the action of the hyperactive allele VCP inhibitors for the first time offer hope to patients with this devastating progressive disease. This phase 1 safety study will provide proof of principle of the safety of CB5083. Additionally analysis of secondary endpoints will help design a more robust Phase II study to study the efficacy of CB5083 in clearing the aggregates and thus provides hope that this progressive muscle weakness may be ameliorated.