

## **Summary - MMPOWER Update Reenie McCarthy - CEO, Stealth BioTherapeutics**

A joint message between MitoAction, UMDF, and the Foundation for Mitochondrial Medicine for the benefit of the mitochondrial disease community.

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On December 6, 2016, Reenie McCarthy participated in an online presentation to the mitochondrial disease community to provide an update on Stealth BioTherapeutics' clinical development program for primary mitochondrial myopathy. Following is a summary of the information presented during this event.

Stealth BioTherapeutics is committed to developing therapies for genetic mitochondrial diseases as well as more common diseases of aging that involve mitochondrial function. Our lead programs are in genetic mitochondrial diseases.

### **BACKGROUND**

Stealth hopes to help establish mitochondrial medicine as an innovative approach to the treatment of human disease.

### **ELAMIPRETIDE**

Stealth's lead compound, elamipretide (previously known as Bendavia, MTP-131, or SS31), preferentially targets the mitochondria. Elamipretide diffuses across the cell and outer mitochondrial membranes, binding to cardiolipin in the inner mitochondrial membrane. Mechanistically, Stealth believes that elamipretide's binding affinity with cardiolipin may help to protect cardiolipin from the degradative effects of excess ROS, and thus help to preserve more functional ETC performance in situations where oxidative stress (due to excess ROS caused by disease or other factors) is compromising mitochondrial function. However, Stealth continues to conduct studies to better characterize the mechanism of its compounds.

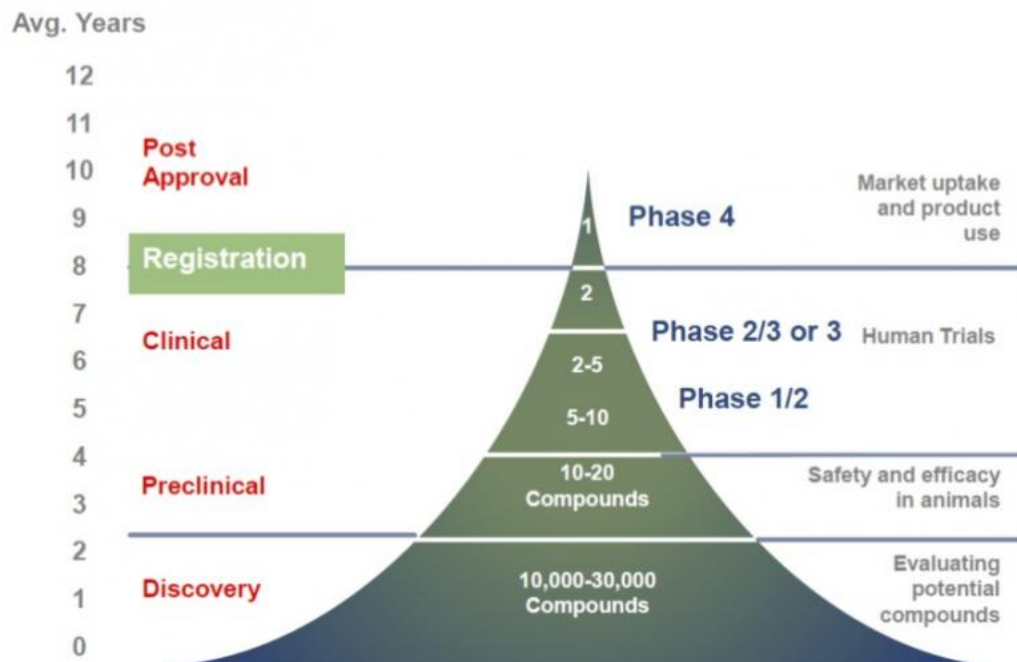
From a clinical perspective, Stealth has focused on the systems in the body with the highest demand for energy, which are:

- active muscle
- the heart - producing about 6 kilograms of ATP per day
- the kidneys
- the eye
- the brain

Stealth has preclinical data, ongoing clinical programs, and/or clinical data in diseases/conditions impacting each of these systems. These include genetic mitochondrial diseases such as mitochondrial myopathy (MM), Barth's syndrome (BHTS), Leber's hereditary optic neuropathy (LHON), as well as common diseases of aging, such as heart failure.

## THE PROCESS OF RARE DISEASE DRUG DEVELOPMENT

The following pyramid illustrates the rare disease drug development process, and the time various stages of development typically entail.



The drug development process typically takes 10 years or more for rare diseases and may take much longer for more common disorders.

Stealth is conducting a continuation study (**MMPOWER 2**) in which only MMPOWER participants are eligible to enroll. This study is a "crossover study" in which participants are assigned to study drug or placebo for an initial 4-week dosing period, after which they will "crossover" into the other treatment arm after a 4 week washout period. Dosing in MMPOWER2 is once daily subcutaneous injection of elamipretide or placebo. There will be additional efficacy endpoints measured in this trial in addition to the 6-minute walk test. Among the objectives of MMPOWER2 are to evaluate elamipretide subcutaneous dosing, to evaluate longer dosing, and to develop additional endpoints in this population. MMPOWER2 is being conducted at the same clinical sites as MMPOWER (Massachusetts General Hospital, University of California-San Diego, University of Pittsburgh Medical Center and Akron Children's Hospital).

Stealth plans to move forward with a Phase 3 clinical program in MM. Stealth's Phase 3 program will begin with a **Multinational Phase 3 Pre-trial Registry**. The primary objective of this pre-trial registry is to better understand the relationship between genetic test results and how individuals with mitochondrial disease present with their symptoms of myopathy, to understand how mitochondrial disease is commonly treated and to help us identify potential participants for a future trial with an investigational product made by Stealth for people with mitochondrial disease that have symptoms of myopathy. Information about this trial will be posted on [www.clinicaltrials.gov](http://www.clinicaltrials.gov) in 2017. Stealth anticipates the following details with respect to this trial, but protocols are still being finalized so this is subject to change:

- *Who will be eligible?*

- o Individuals aged 16-65 with genetic confirmation of mitochondrial disease
- o Individuals must experience symptoms of myopathy (skeletal muscle weakness, fatigue, exercise intolerance)
- o Individuals without genetic confirmation of mito can have genetic testing performed at no cost if the investigators deem necessary and with such individuals' consent

- *What will it entail?*

- o One site visit at an approved site, to perform tests including 6-minute walk test and other screening tests
- o Permission to collect health information to see if you may be eligible to participate in a future Stealth trial

- *When and where?*

- o Recruiting likely to start the first half of 2017 in the United States and Europe

Participants in the **MMPOWER 3 REGISTRY** will be potentially eligible to participate in the second part of the MMPOWER Phase 3 trial, the Multinational Phase 3 Clinical Trial. Information about this trial will be posted on [www.clinicaltrials.gov](http://www.clinicaltrials.gov) in 2017. Stealth anticipates the following details with respect to this trial, but protocols are still being finalized so this is subject to change:

- *Who will be eligible?*

- o Individuals enrolled in the MMPOWER Phase 3 Pre-Trial Registry with genetic confirmation of mitochondrial disease
- o Additional inclusion criteria still to be determined

- *What will it entail?*

- o Anticipated 6-month study with daily SQ injections of elamipretide or placebo
- o Assessments including 6-minute walk test
- o Anticipated open label extension

- *When and where?*

- o Recruiting likely to begin Q3 2017
- o Multiple sites in United States and Europe

Patients interested in/eligible for the MMPOWER 3 study should visit [www.clinicaltrials.gov](http://www.clinicaltrials.gov) as well as stay engaged with mitochondrial disease advocacy organizations for additional information

### **Barth's Syndrome (BHTS)**

BHTS is an ultra-orphan disease, affecting an estimated 150 individuals worldwide. BHTS is characterized by dilated cardiomyopathy, skeletal muscle weakness and neutropenia. BHTS is caused by a genetic defect in the gene encoding for tafazzin, an enzyme involved in cardiolipin metabolism, resulting in deficient/altered composition. Stealth anticipates launching a clinical trial in this population in Q1 2017. Information about this trial will be posted on [www.clinicaltrials.gov](http://www.clinicaltrials.gov) in 2017. Stealth anticipates the following details with respect to this trial, but protocols are still being finalized so this is subject to change:

- *Who will be eligible?*
  - o Individuals ages 15 years and older with confirmed BHTS
  - o Additional inclusion criteria still to be determined
  
- *What will it entail?*
  - o Anticipated 8-month crossover design study with an initial 3-month treatment period entailing daily SQ injections of elamipretide or placebo, a 1-month washout period, and a subsequent 3-month treatment period entailing daily SQ injections of the other treatment option (i.e., participants on placebo in treatment period 1 receive elamipretide in treatment period 2, and vice versa)
  - o Assessments including 6-minute walk test
  - o Anticipated open label extension
  
- *When and where?*
  - o Recruiting likely to begin Q1 2017
  - o McKusick-Nathans Institute of Genetic Medicine, Johns Hopkins University School of Medicine

### **Leber's Hereditary Optic Neuropathy (LHON)**

The visual system, as the highest energy consumer in the brain, may be vulnerable to mitochondrial dysfunction. LHON is an ATP and ROS mediated mitochondrial optic neuropathy causing optic nerve atrophy and blindness. Stealth's double-masked, placebo controlled, ReSIGHT Clinical Trial, involving twice daily elamipretide topical ophthalmic drops and placebo, is currently enrolling LHON participants with confirmed G11778A mutation. Information about this trial is posted on [www.clinicaltrials.gov](http://www.clinicaltrials.gov) in 2017. The trial involves the following components, with full details available at the referenced link:

- *Who is eligible?*

- o Individuals ages 18-50 years old at the time of loss of vision in the second to be affected eye and with confirmed diagnosis of LHON based on clinical and ophthalmic functional/anatomic test findings, and satisfactory documentation of the mitochondrial DNA genotype m.11778G>A BHTS

- o Loss of vision in both eyes of  $\geq 1$  year but  $\leq 10$  years' duration

- o Other inclusion/exclusion criteria as specified at the referenced link.

- *What will it entail?*

- o 9-mos twice daily topical ophthalmic drops, with 4-week follow up

- o Visits as specified at the referenced link

- o Assessments as specified at the referenced link

- *When and where?*

- o Doheny Eye Institute at the University of California, Los Angeles

- o CURRENTLY RECRUITING

## **COMMON DISEASES OF AGING**

Mitochondrial dysfunction increases with aging and is associated with certain diseases of aging including heart failure, macular degeneration, and kidney disease. While Stealth's lead programs are in primary genetic mitochondrial diseases, Stealth is also studying its compounds in more common diseases of aging. Stealth has early clinical data in early Phase 1/2 trials of elamipretide in heart failure and acute kidney injury populations, and is currently progressing three Phase 2 clinical trials in heart failure

## **CONCLUSION**

Stealth is committed to developing therapies for primary mitochondrial disease and more common diseases of aging in which mitochondrial function is impaired. Additional trials will be required to further assess the elements of efficacy, safety, and tolerability, which are required for approval of new therapeutics.

Stealth extends thanks to MitoAction, UMDF, and the Foundation for Mitochondrial Medicine for hosting this webinar. Stealth also extends heartfelt thanks to the Mito community for its dedication, determination, and fortitude in supporting advocacy, academic, medical, and industry initiatives to advance therapeutic initiatives for the treatment of primary mitochondrial disease.

Learn more about elamipretide and Stealth BioTherapeutics at [www.stealthbt.com](http://www.stealthbt.com) and learn more about mitochondrial disease and clinical trials to support individuals suffering from mitochondrial disorders at [www.mitoaction.org](http://www.mitoaction.org), [www.umdf.org](http://www.umdf.org), and [www.mitochondrialdiseases.org](http://www.mitochondrialdiseases.org).