

An Update on the Clinical Studies Using Arimoclomol as a Potential Treatment for Sporadic Inclusion Body Myositis Presented to Myositis Support & Understanding (MSU)

Presented by

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Our discussion today



Brief overview of sporadic Inclusion Body Myositis (sIBM)



Sporadic in this context means not inherited based on known simple gene defect

Muscle cell pathology suggests that protein dysfunction may be a major underlying cause of IBM



A lack of success targeting inflammatory components of the disease prompted us to consider repairing protein dysfunction as potential therapeutic target

A leading theory of the underlying problem in IBM is **the body's inability to process proteins**, leading to the formation of inclusion bodies (protein aggregates) in cells



Activating a natural defense mechanism



Our bodies already know how to try to "**fix**" or restore cells when stressed by a disease.

Arimoclomol is being evaluated to understand its role in **amplifying this natural defense mechanism.** Our cells prefer their environment to be in constant balance—a condition called homeostasis.

- When cells are **challenged by pathological stressors**, they produce "**rescue proteins**" to try to protect the cells and restore homeostasis.
- Such stressors could be caused by protein aggregation, a hallmark of IBM
- The release of these rescue proteins is called the heat shock response, but also known as the stress response.

The stress response and the rescue protein Heat Shock Protein 70 (HSP 70) have been well-studied for many years.



What we know about arimoclomol



Researchers wondered what if you could simply trigger the body to activate its own rescue proteins?

- We tested arimoclomol in the pilot study (before the current Phase II/III study), which has previously been shown activity to amplify the body's own rescue proteins when under stress
- The theory was that if you could increase the production of rescue proteins, such as HSP70, then the affected cells could be repaired or "rescued" and could function properly
- The results of the animal studies indicate that arimoclomol may clear the protein trapped in the muscle cells, i.e., inclusion bodies



Arimoclomol improved IBM-like pathology in mutant VCP mice with IBM hallmarks

VCP stands for Valosin containing protein.

The mVCP is a mutant mouse that carries the mutation known to cause one of the forms of hereditary IBM.

How arimoclomol is thought to help in IBM

Arimoclomol is thought to work by amplifying "rescue" proteins when cells are under pathological stress by protein aggregation and restoring balance

Resulting in clearance of toxic misfolded proteins such as TDP-43 and improved future protein folding to minimize aggregation.



Clinical development of arimoclomol in IBM: **Pilot Trial**

Pilot Trial

Phase II /III Trial

Open-Label Extension Study

24 patients randomized **2:1** in a double-blind placebocontrolled study. Patients in the treatment arm received 100 mg of arimoclomol citrate 3x a day

Timeline: 4 months treatment with an additional 8 months follow-up with no treatment.

Topline Results:

- Trend toward a slower deterioration in treated patients as measured by IBM Functional Rating Scale (IBMFRS) at 8 months
- No statistical difference observed in secondary endpoints
- Arimoclomol had similar adverse events occurring among those treated vs. placebo
- Results supported further research of arimoclomol in IBM

Clinical development of arimoclomol in IBM: **Promising Pilot Trial Results**

Pilot Trial Results (n=24)

2:1 Placebo-Controlled, 12-Month, Double-Blinded, Randomized, 4-Months of Treatment



RESPONDER ANALYSIS THIS IS A POST HOC ANALYSIS

Stabilization of disease* 4 months after end of treatment in 83% of arimoclomol-treated patients vs. 25% in the placebo cohort

*Progression rate <1.5 points/8 months – natural history studies predict a progression rate: 2 to 2.5 points lost per 8 months (Source: Cortese et *al.*, Neuromuscul. Disord. 2013, Morrow et *al.* Lancet Neurol. 2016).

Clinical development of arimoclomol in IBM: Phase II/III Interventional Trial



Clinical development of arimoclomol in IBM: Phase II/III Interventional Trial



Clinical development of arimoclomol in IBM: **Open-Label Extension Study**

Phase II /III Trial

Pilot Trial

Open-Label Extension Study

Plan is for patients who complete the 20month interventional trial to be offered the **option of participating in an open-label extension**

All patients would receive arimoclomol and continue on their routine clinical care

Primary goal of study: continue to assess the long-term safety and efficacy of arimoclomol

Patients would continue on arimoclomol until they are rolled into an Expanded Access Program or until it becomes commercially available for the treatment of IBM

Key points to **remember**

1	Evidence suggests that the underlying problem in IBM may be due to the body's - inability to process proteins, leading to the formation of inclusion bodies (protein aggregates) in muscle cells
2	We have a natural defense mechanism called the stress response (or heat shock response) - that can activate rescue proteins, known as heat shock proteins, which have the ability to restore balance, repair the dysfunctional protein processing and clear protein aggregation
3	_ Studies have shown that we can harness this mechanism to get the body to produce its own rescue proteins
4	Success of those studies led to the development of arimoclomol, an - investigational oral medication that is being evaluated in patients with IBM (and other diseases caused by misfolded proteins)
5	_ The safety database on people being exposed to arimoclomol is growing and, to date, few safety concerns have been observed in IBM or in studies of other diseases
6	Enrollment has been brisk in the Phase II/III clinical trial and with results expected in the first half of 2021



Thank you!

The following questions will be asked by MSU in a guided Q&A discussion

Frequently Asked Questions (MSU to Facilitate FAQ)

- What is the recruitment status of the phase II/III arimoclomol study? Is the study still enrolling patients?
- How were the trial sites selected?
- Why is there a limit to the number of patients who can participate at each site?
- Why did some people begin the trial in 2017 and some are just now starting?
- Why is the trial limited to patients who can still get out of a chair? If I am doing worse, don't I need the drug more?
- How was the dosing for the trial determined?
- Does arimoclomol have known side effects? Will these be monitored after the study has ended?
- For those participating in the trial, when will they be able to see their data? Will they be informed of whether they received arimoclomol or placebo?

- What is a phase 2/3 trial? How does it differ from a phase 3 trial?
- There is an interim analysis planned for the phase 2/3 study in 2020. What does this mean for trial participants?
- Assuming the Phase II/III study shows positive results, when might we expect this to be available?
- Arimoclomol is being investigated in other diseases, such as Niemann-Pick Type C. What does this mean for the clinical development timeline in IBM?
- Will I be able to access arimoclomol if it is approved for another indication?
- Can you describe the difference between Orphan Drug Designation, Fast Tracking and Early/ Expanded Access Program (EAP)? Will I be able to access arimoclomol through an EAP?
- Are there other trials for patients with IBM being planned?