January 30, 2019

Orphazyme reports positive results from full data set of Phase II/III arimoclomol trial in Niemann-Pick disease Type C (NPC)

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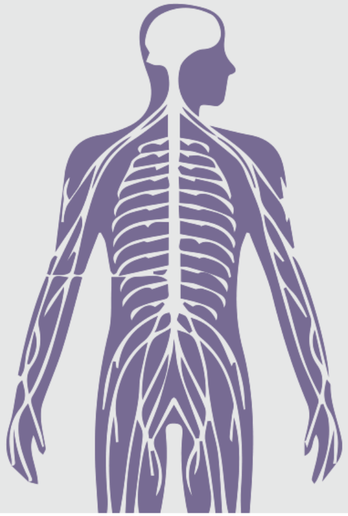
Niemann-Pick Disease Type C (NPC)

WHAT IS NPC? Niemann-Pick Disease Type C

NPC IS A RARE, INHERITED, PROGRESSIVE, AND OFTEN FATAL NEURODEGENERATIVE DISEASE

NPC is a lysosomal storage disorder caused by genetic mutations that often lead to misfolded variants of NPC proteins. Misfolded NPC protein does not function properly and is subject to rapid degradation.

1-2000
people are diagnosed with NPC in the USA and EU



MANIFESTATIONS

The disease affects the brain, liver, spleen and lungs. Often patients succumb to the disease before reaching the end of their teens.

The disease is progressive and patients gradually loses:

- Motor function and coordination
- Speech
- Cognition
- Memory

20 years
is the average life expectancy

95% have mutations in the NPC1 gene

There is NO CURE for NPC

ONLY 1 DRUG
is currently approved to treat NPC (Zavesca).

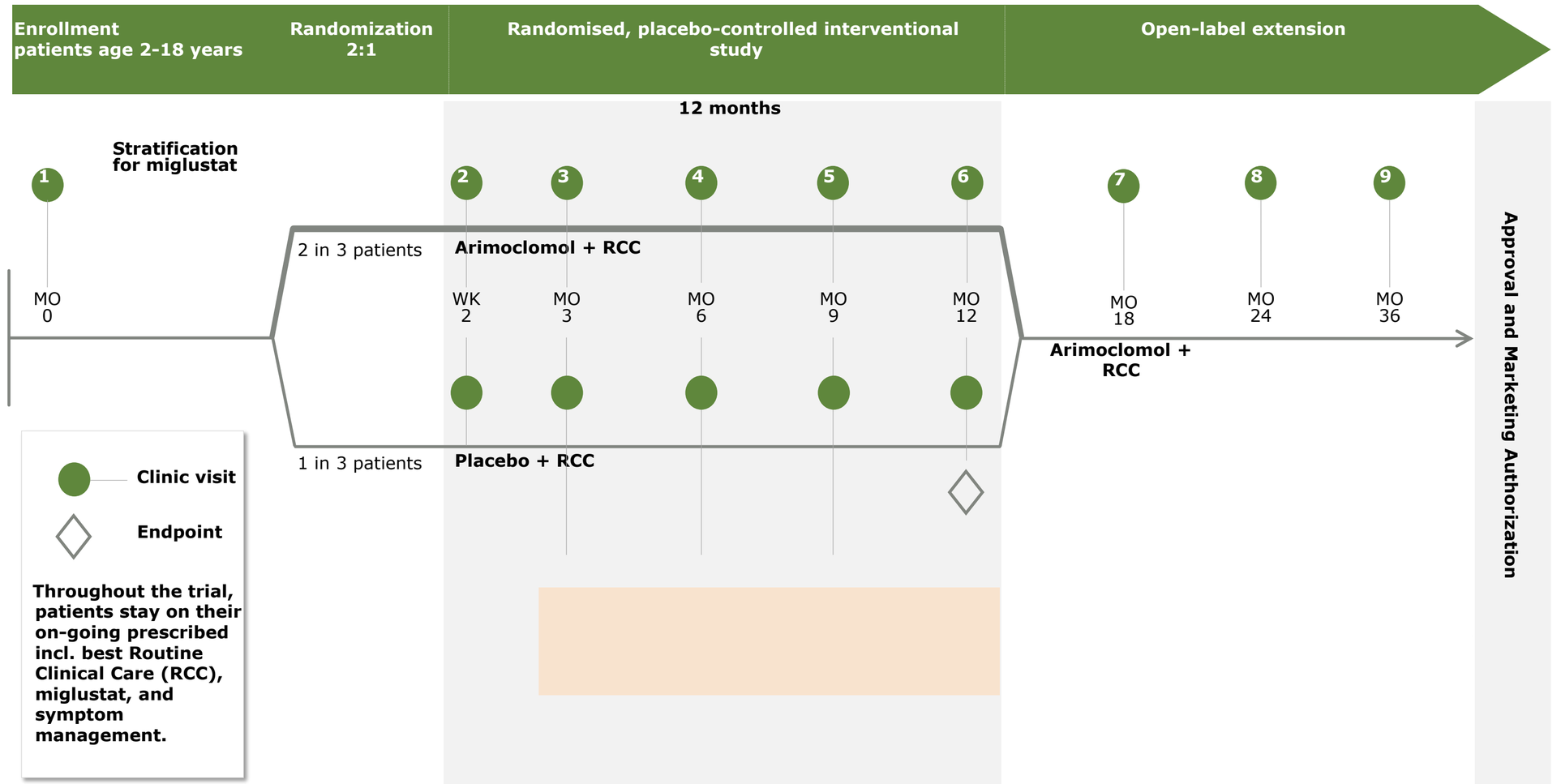
DIAGNOSIS

Difficult to diagnose, NPC is often diagnosed by ruling out other diseases, which may take years.

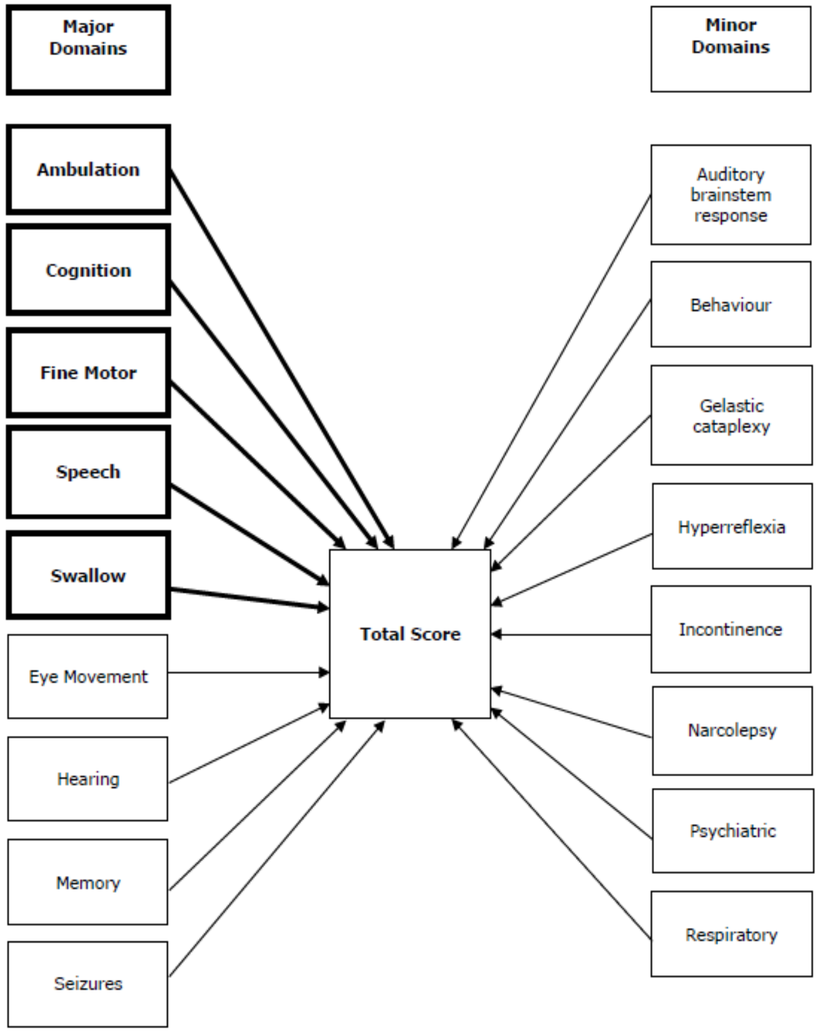
Key Results

- **Baseline demographics and characteristics**: Comparable between treatment arms
- **Pharmacokinetics (PK)**: Preliminary assessment of population PK indicates good compliance
- **Safety:** Arimoclomol was safe and well-tolerated
- **Efficacy:**
  - Primary endpoint 5-domain NPC-Clinical Severity Scale (NPC-CSS) shows -1.34 treatment effect in favor of arimoclomol over placebo, p=0.0506
  - Signal enhancement in:
    - Patients ≥4 years: -1.68 treatment effect in favor of arimoclomol over placebo, p=0.0219
    - Patients on background miglustat treatment: -2.00 treatment effect in favor of arimoclomol over placebo control, p=0.0071
  - Clinical Global Impression of Improvement (CGI-I) responder endpoint (no change or improved) not met, however further analysis of CGI-I indicates supportive evidence
- **Biomarkers:** Demonstrate statistically significant biological effect

Arimoclomol prospective double-blind, randomized, placebo-controlled trial in patients diagnosed with NPC



Selection of 5 Domains out of Full 17-Domain NPC-CSS for Primary Endpoint



5-Domain NPC-CSS

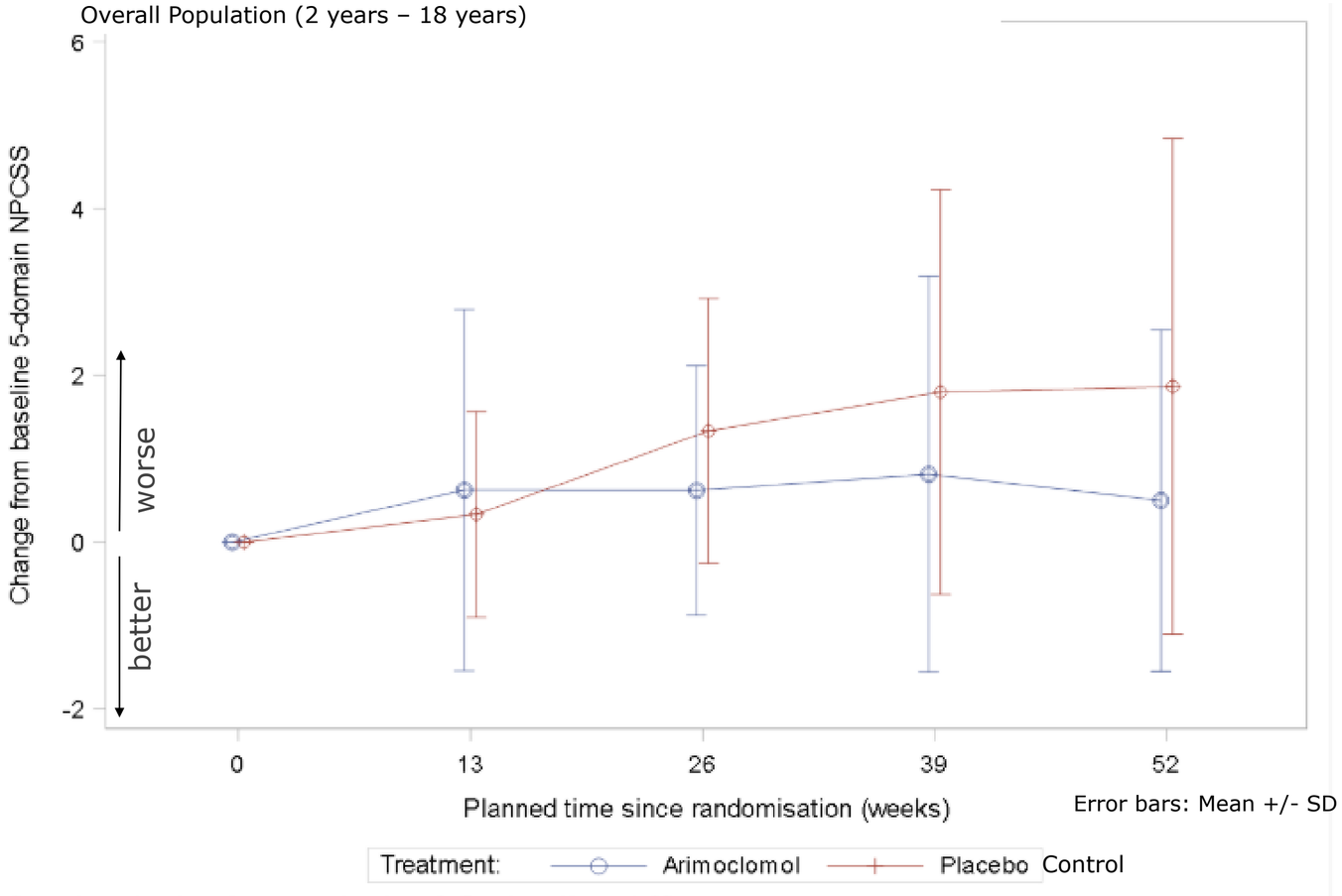
- Captures key aspects of disease important to patients and clinicians
- Range:
  - Individual domain 0 (normal) – 5 (worst)
  - Total score range 0 (normal) -25 (worst)
- Correlation between total score of 5-domain NPC-CSS and full NPC-CSS is 0.93
- Sensitive to change
  - In observational trial annualized mean change: 1.5 points/year

Safety and Tolerability

- Overall incidence of AEs similar for arimoclomol (88.2%) and placebo (81.3%)
- 3 patients withdrew due to AEs – all in the arimoclomol group (n=3, 8.8%)
- SAEs occurred less frequently in arimoclomol group (14.7%) compared to placebo (37.5%)
  - 1 patient died due to cardiopulmonary arrest assessed as not related to arimoclomol

Primary Endpoint: 5-Domain NPC-CSS Mean Change from Baseline – Full Analysis Set

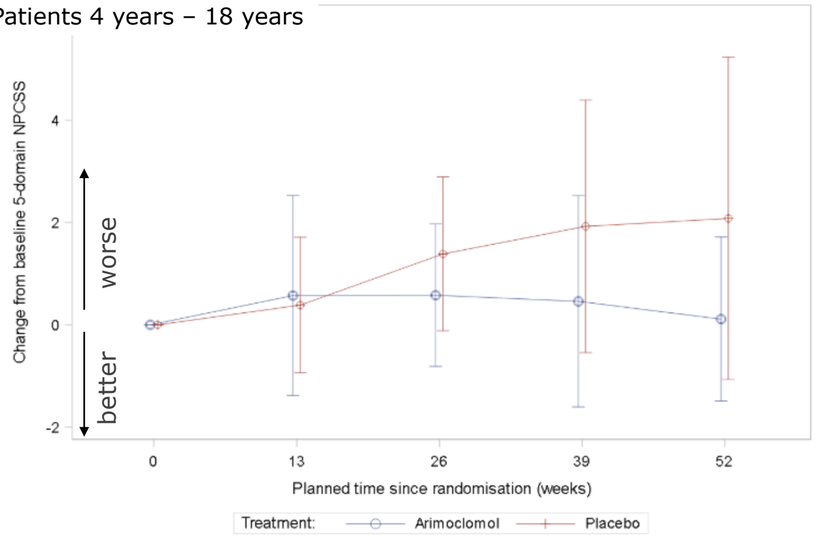
Overall Population (2 years – 18 years)



Error bars: Mean +/- SD

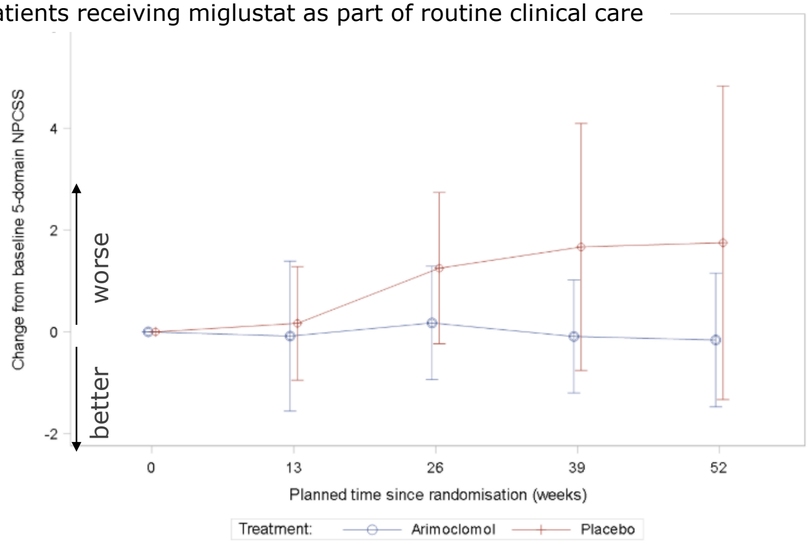
General Linear MMRM Treatment Effect -1.34 (-2.69, 0.00) p=0.0506

Patients 4 years – 18 years



General Linear MMRM Treatment Effect -1.68 (-3.11, -0.26) p=0.0219

Patients receiving miglustat as part of routine clinical care



General Linear MMRM Treatment Effect -2.00 (-3.42, -0.58) p=0.0071

Individual Domains on NPC-CSS

- Generally, most change observed on 4 out of 5 Domains from primary endpoint over 12 months, changes in placebo control arm comparable to NPC-001 observational study

Domain	Arimoclomol	Placebo control
Ambulation	0.2	0.3
Speech	-0.2	0.3
Swallow	0.0	0.5
Fine Motor	0.2	0.6
Cognition	0.2	0.1

CGI-I

- In agreement with FDA, treatment response defined as no change or improved on the Clinical Global Impression of Improvement scale (CGI-I) included as a co-primary endpoint

		Arimoclomol (N=34)	Placebo (N=16)	Total (N=50)	p-value
Responder at 12 months	N	34	16	50	
	Yes	20 (58.8%)	9 (56.3%)	29 (58.0%)	
	No	14 (41.2%)	7 (43.8%)	21 (42.0%)	
	Chi-squared test				1.0000

- However, when considering patients who severely progressed during the trial, only 10.7% of the arimoclomol treated patients got ‘much worse’ or ‘very much worse’ compared to 26.7% in the placebo control group supporting an effect of arimoclomol in preventing severe progression over a 12-months observation period

CGI-I Cumulative Distribution

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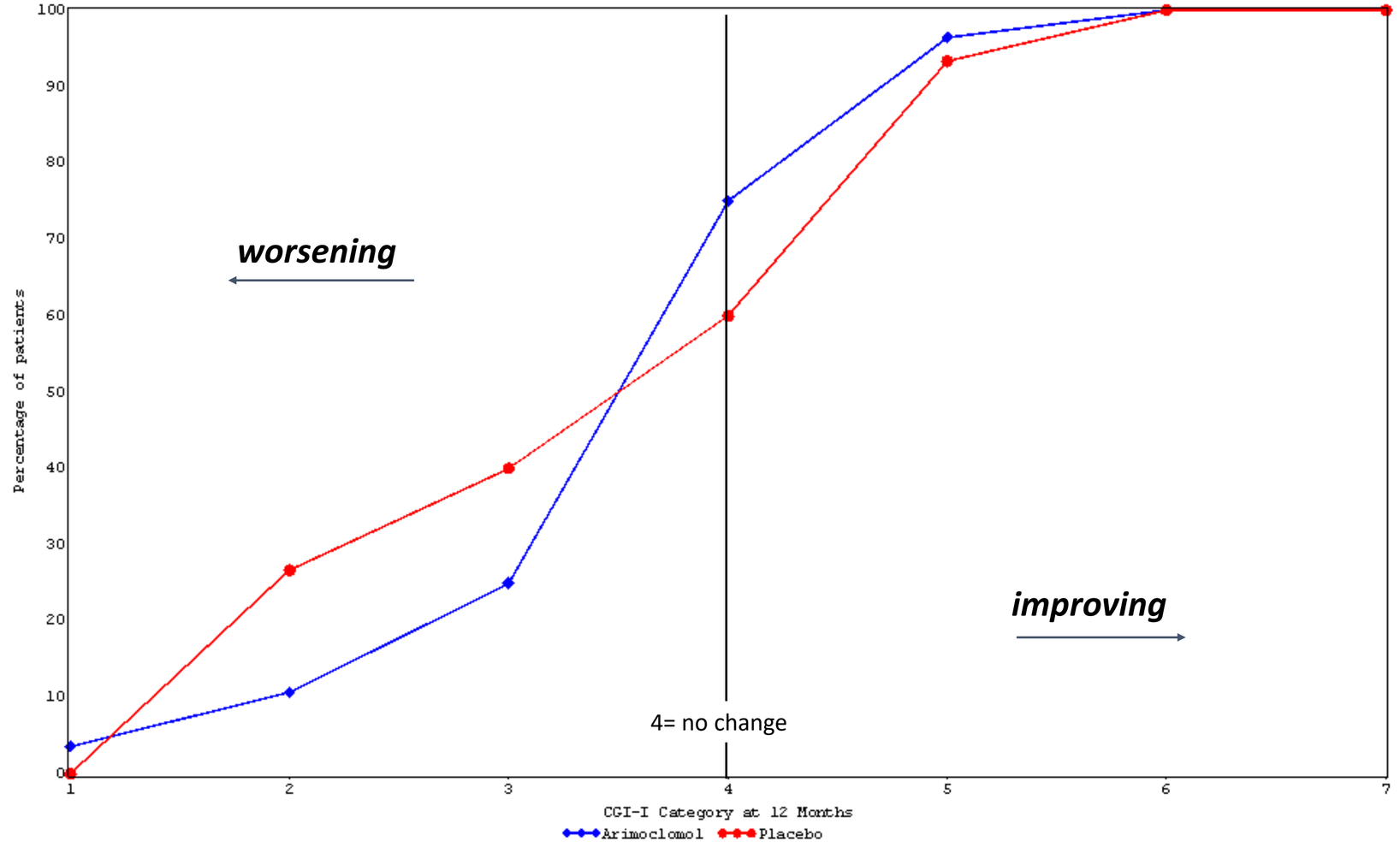
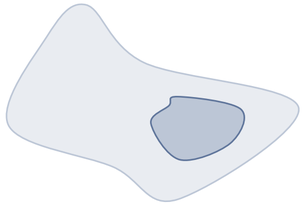
Figure 2.2.2 Cumulative Distribution Curve of CGI-I at 12 Months (Full Analysis Set)



1 = Very much worse; 2 = Much worse; 3 = Minimally worse; 4 = No change; 5 = Minimally improved; 6 = Much improved; 7 = Very much improved

Page 1/1

Biomarker Analysis – What Are We Measuring and Why?



- Skin cells

- Peripheral blood mononuclear cells (PBMCs)
- Serum

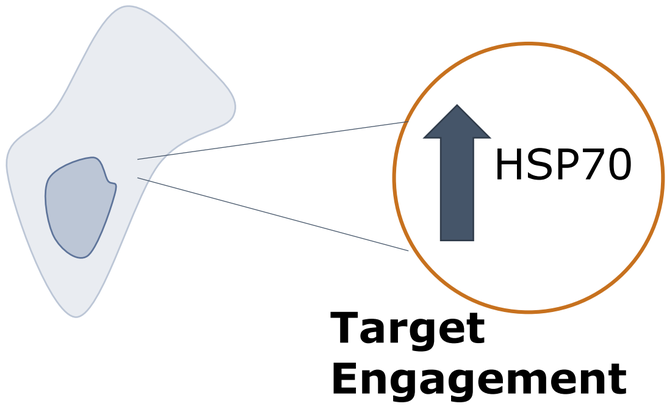
Target engagement/PD

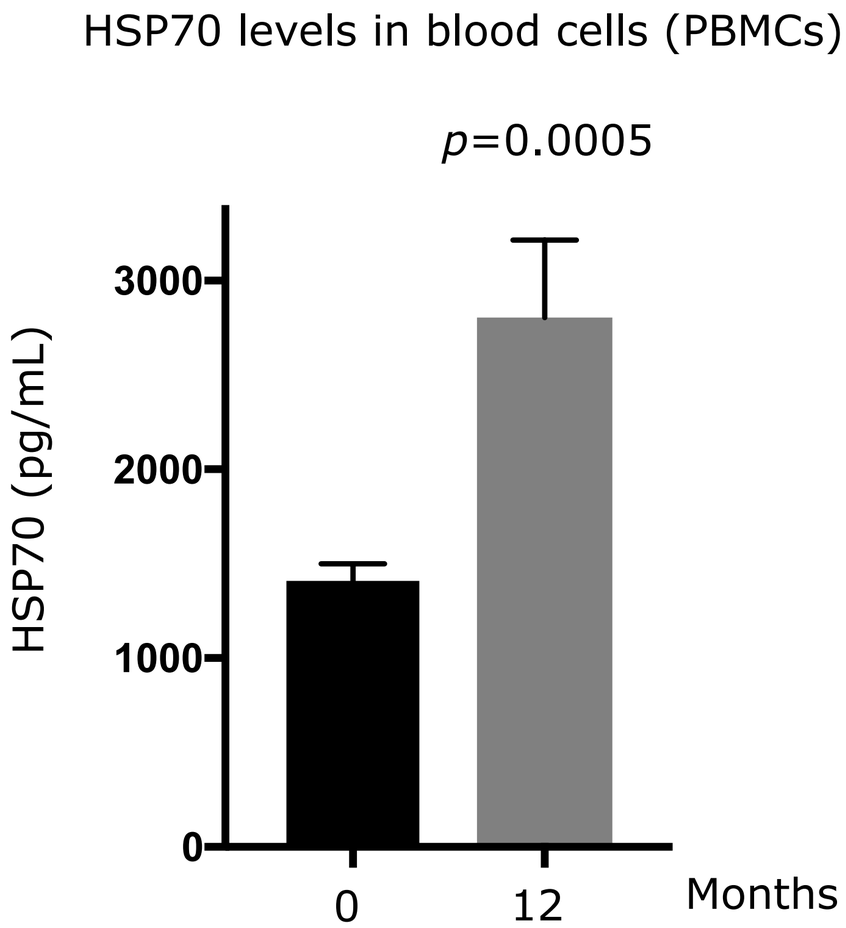
- HSP70 (in PBMCs)

Disease pathology-relevant biomarkers

- UE Cholesterol (in PBMCs)
- UE Cholesterol (in skin cells)
- Oxysterol (in serum)

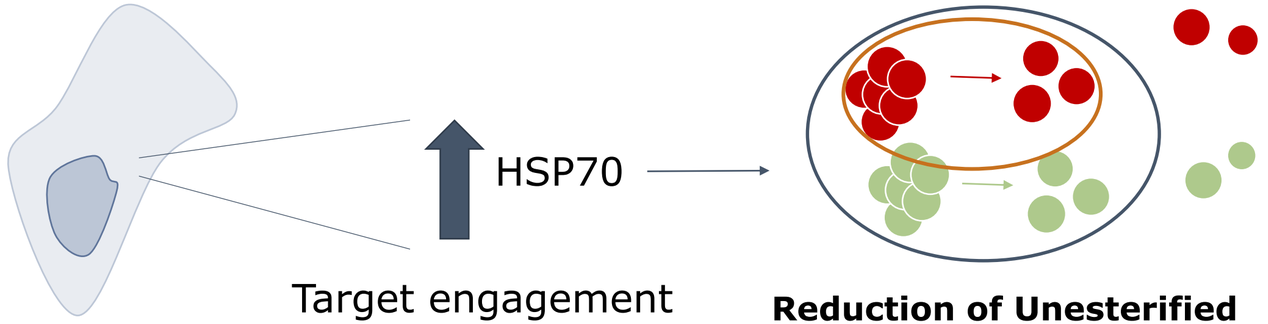
Biomarker Analysis: Target Engagement – HSP70 Levels Increase



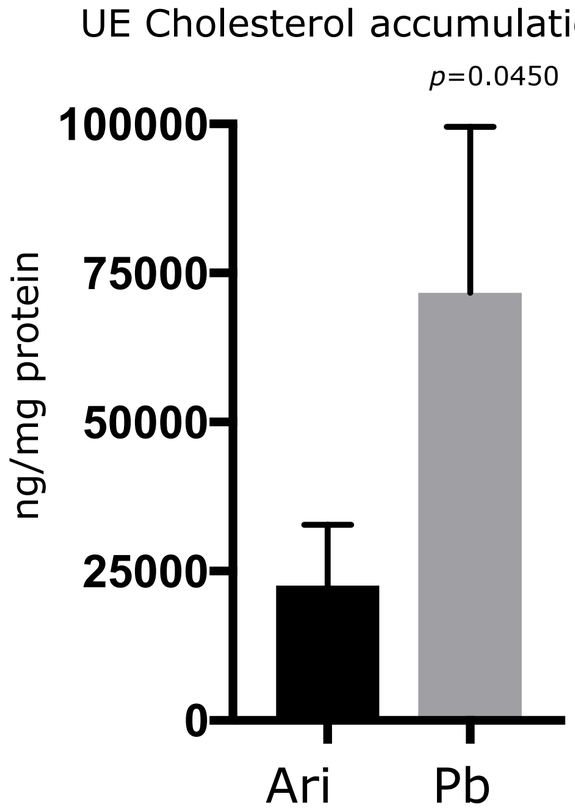


HSP70 levels increase over time in arimoclomol-treated patients

Biomarker Analysis: Reduced Accumulation of Cholesterol in Blood and Skin Cells



Reduction of Unesterified Cholesterol in blood and skin cells



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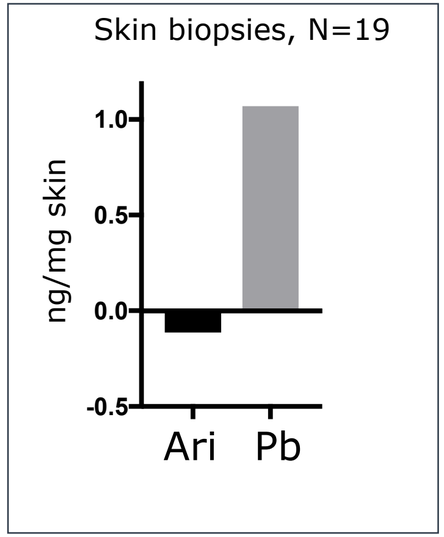
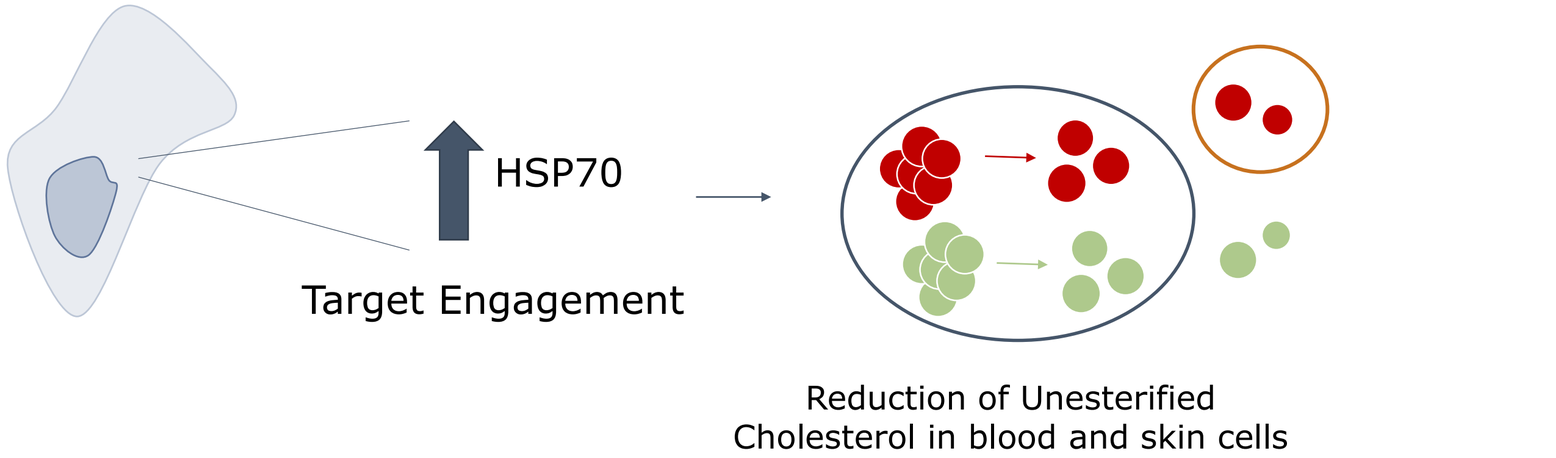
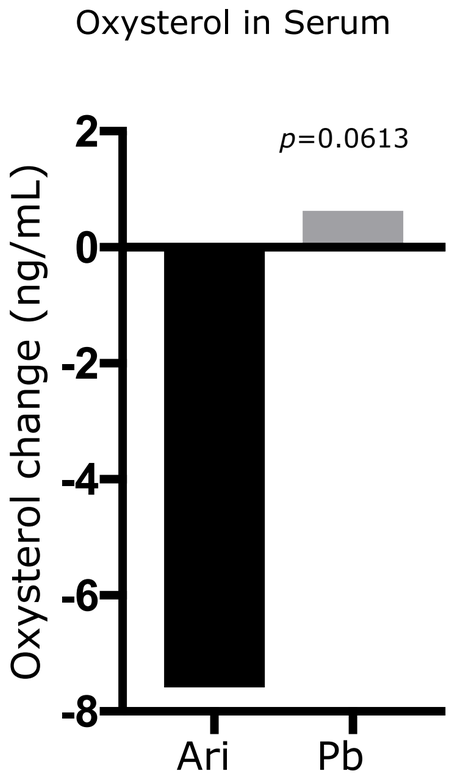


Biomarker Analysis: Reduction of Oxysterol in Blood





Conclusions

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  - CGI-I responder endpoint (no change or improved) not met, however further analysis of CGI-I indicates supportive evidence
- **Biomarkers:** Demonstrate statistically significant biological effect

Next Steps

- Initiate filing preparations and seek to meet with US Food and Drug Administration and European Medicines Agency mid-2019 to discuss path to approval
- 24-month data will become available from on-going open-label extension of the trial in Q3 2019
- Orphazyme expects filing in the US and EU in H1 2020, with potential approval in H2 2020