Phase 2 Trial of High Dose IV trehalose (Cabaletta) for Treatment of Spinocerebellar Ataxia 3 (SCA3)

Zohar Argov MD

Prof (Emeritus) of Neurology at Hadassah-Hebrew University, Jerusalem

CHIEF MEDICAL OFFICER, BIOBLAST PHARMA

BioBlast Pharma

Forward-Looking Statements

- This presentation includes statements that are, or may be deemed, ‘‘forward-looking statements.’’ In some cases, these forward-looking statements can be identified by the use of forward-looking terminology, including the terms “believes,” “estimates,” “anticipates,” “expects,” “plans,” “intends,” “may,” “could,” “might,” “will,” “should,” “approximately,” “potential” or, in each case, their negative or other variations thereon or comparable terminology, although not all forward-looking statements contain these words. They appear in a number of places throughout this presentation and include statements regarding our intentions, beliefs, projections, outlook, analyses or current expectations concerning, among other things, the genetic orphan disease drug market size and its growth potential, our position and potential in the genetic orphan disease drug market, our product pipeline, the timing and cost of trials for our products or whether such trials will be conducted at all, completion and receiving favorable results of trials for our products, regulatory action with respect to our products, our projections for funds required for the development and commercialization of our products, market adoption of our products by physicians and patients, the timing, cost or other aspects of the commercialization and marketing of our products, and future sales of our products or product candidates.

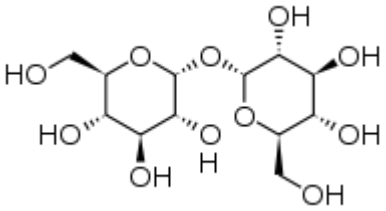
- By their nature, forward-looking statements and their implications, involve risks and uncertainties because they relate to events, competitive dynamics, and healthcare, regulatory and scientific developments and depend on the economic circumstances that may or may not occur in the future or may occur on longer or shorter timelines than anticipated. In addition, historic results of scientific research and clinical and preclinical trials do not guarantee that the conclusions of future research or trials would not suggest different conclusions or that historic results referred to in this presentation would not be interpreted differently in light of additional research and clinical and preclinical trials results. Although we believe that we have a reasonable basis for each forward-looking statement contained in this presentation, we caution you that forward-looking statements are not guarantees of future performance and that our actual results of operations, financial condition and liquidity, and the development of the industry in which we operate may differ materially from the forward-looking statements contained in this presentation as a result of, among other factors, the factors referenced in the “Risk Factors” section of the final prospectus filed with the Securities and Exchange Commission on July 31, 2014 in connection with our initial public offering. In addition, even if our results of operations, financial condition and liquidity, and the development of the industry in which we operate are consistent with the forward-looking statements contained in this presentation, they may not be predictive of results or developments in future periods. Any forward-looking statements that we make in this presentation speaks only as of the date of such statement, and we undertake no obligation to update such statements to reflect events or circumstances after the date of this presentation.

- You should read carefully the factors described in the “Risk Factors” section of the Prospectus contained in the Registration Statement to better understand the risks and uncertainties inherent in our business and underlying any forward-looking statements.

Introduction

- Spinocerebellar ataxia-3 (SCA-3) is an inherited neurodegenerative disorder caused by repeat expansion of polyglutamine in the gene-encoding the protein ataxin-3
- Accumulation of the misfolded abnormal ataxin-3 causes intracellular aggregation and is assumed to be critical in the pathogenesis of SCA3.
- Treatment aimed at reduction of this pathological process may be beneficial to patients

Trehalose is a Known Protein Stabilizer

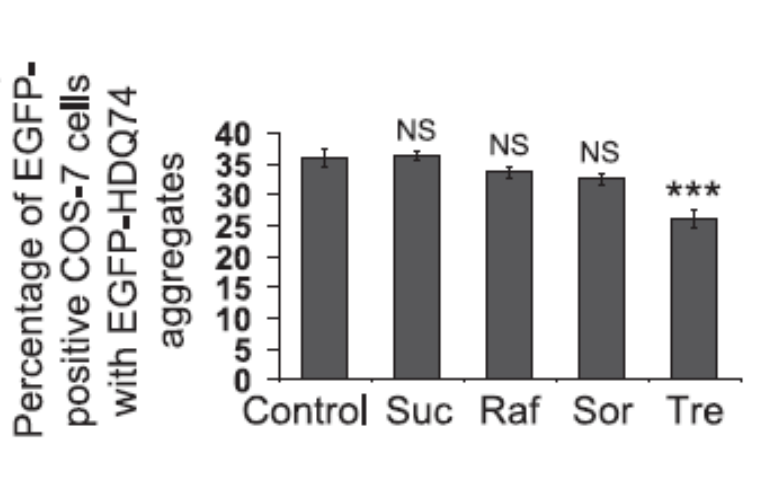


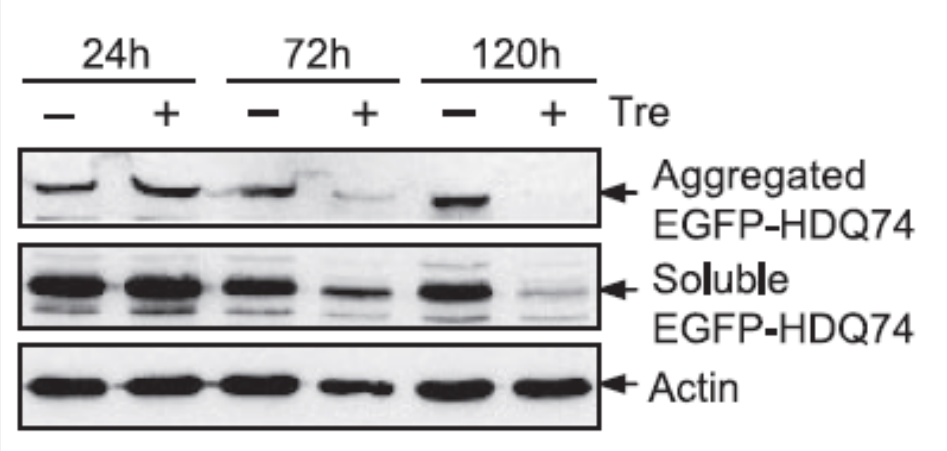
- **Trehalose** is a natural occuring alpha-linked disaccharide formed by an a-a 1,1-glucoside bond between two a-glucose units
- **Trehalose** is known to be an exceptional protein stabilizer
- **Trehalose** is used in the food industry (e.g. for stabilizing frozen food) and is recognized as a food ingredient and registered on the National Formulary.
- **Trehalose** serves as stabilizer of therapeutic parenteral proteins and as an excipient in tablets and IV solutions (e.g. herceptin, avastin)
- **Trehalose** can thus be expected to work as a universal stabilizer of protein conformation

Trehalose is an Autophagy Enhancer

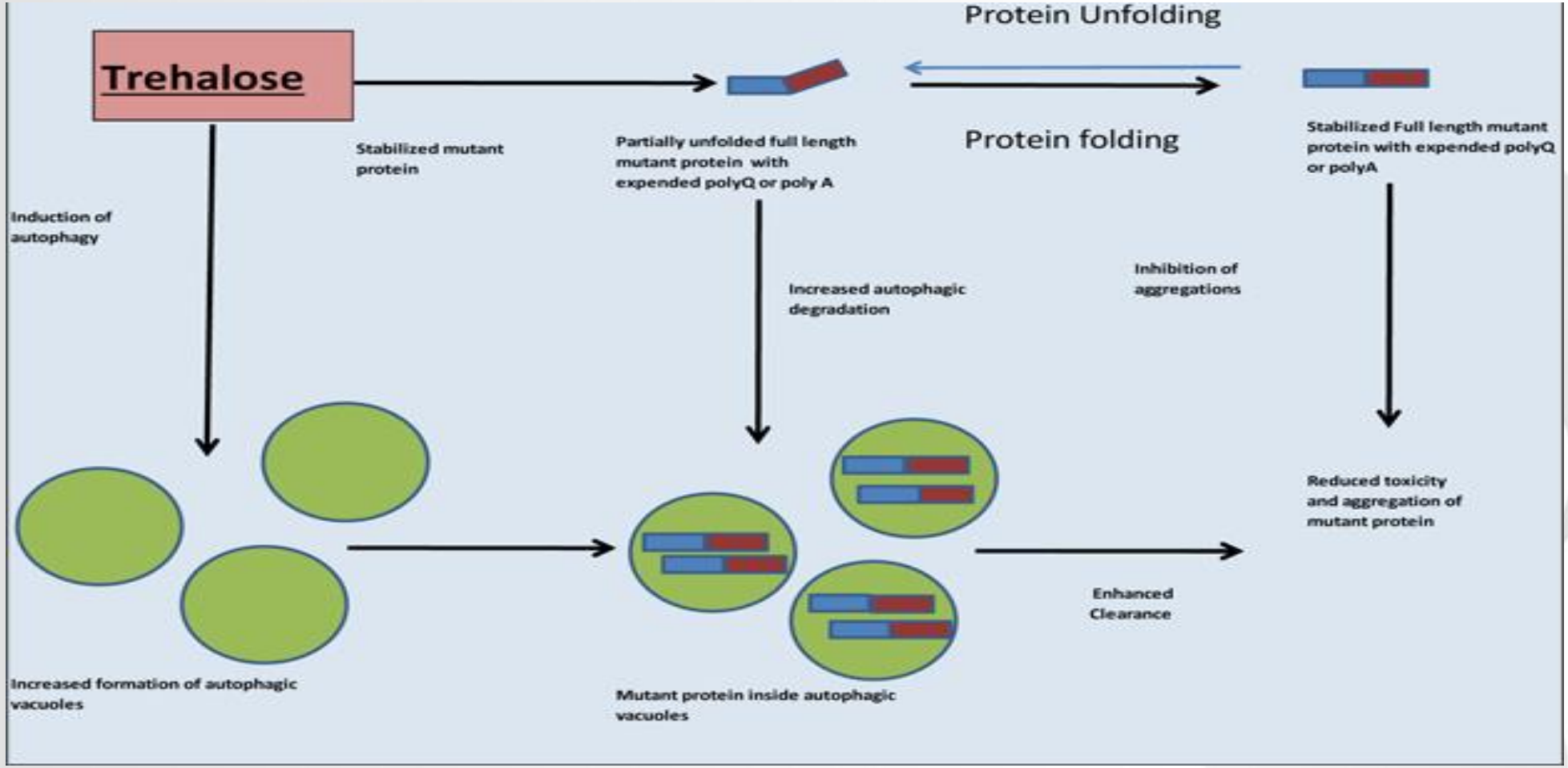
Trehalose, a Novel mTOR-independent Autophagy Enhancer, Accelerates the Clearance of Mutant Huntingtin and a-Synuclein (Sarkar S et al from David Rubinsztein 's lab *JBC 2007)*

Demonstrated using mutant Huntingtin transfected to COS7 (left) or PC12 (right) cells]





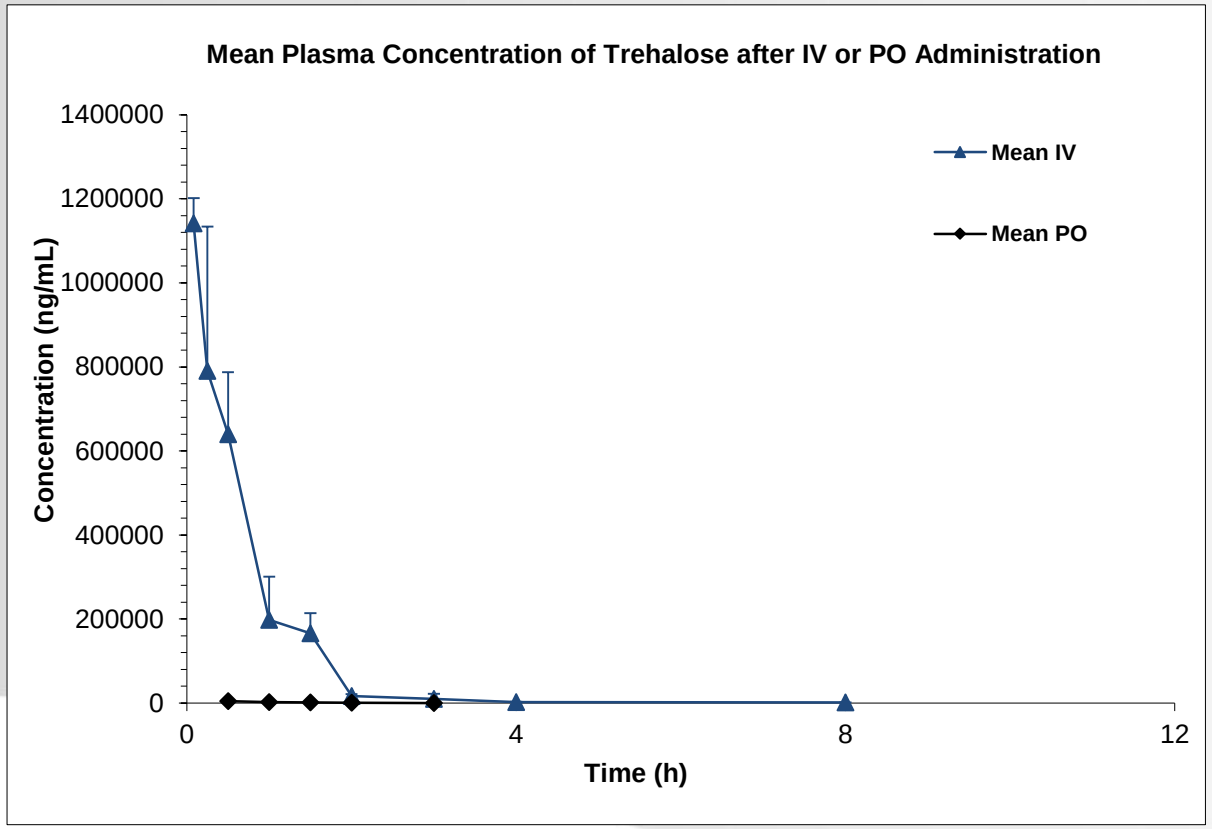
Trehalose biological activity



BioBlast Pharma

Trehalose is not Absorbed when Given Orally in rats and humans, but is absorbed orally in mice

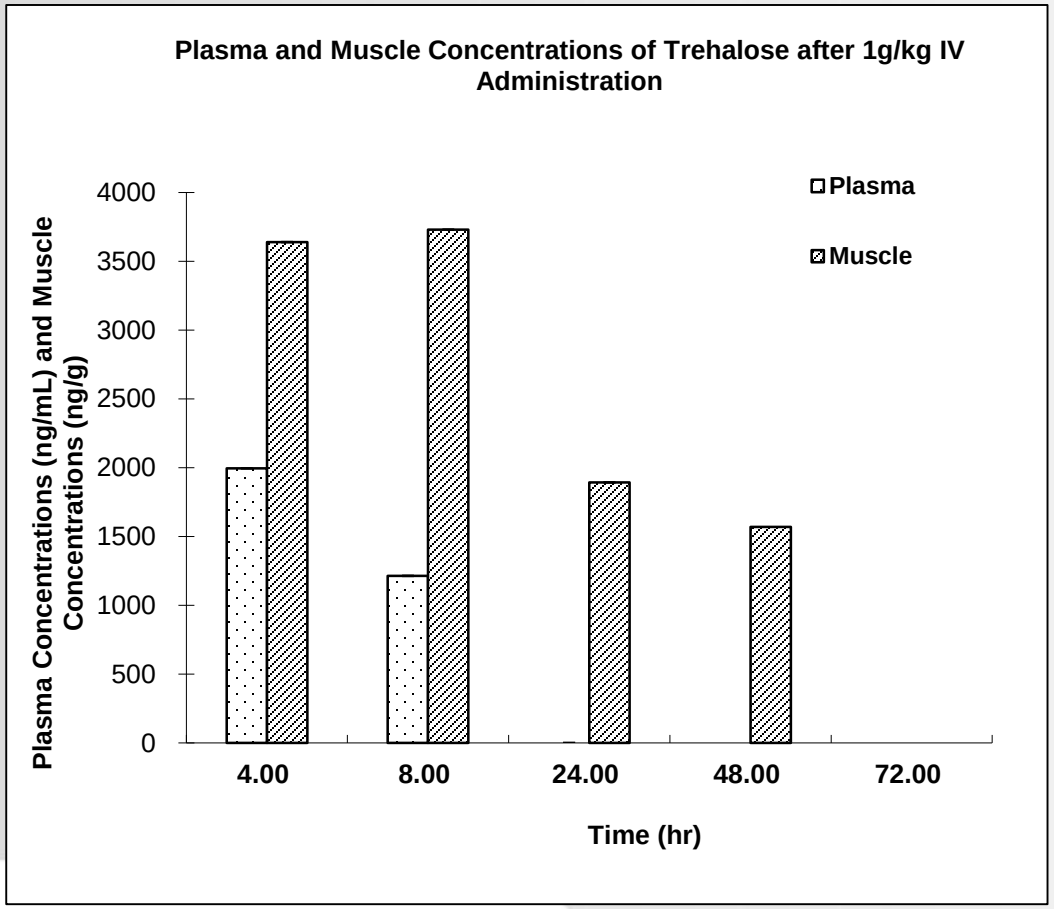
PK Study in rats:
(1 gr/kg administered IV and PO, plasma and muscle samples analysed)



Human and rat: Trehalose is metabolized at the intestinal epithelial brush border into two D-glucose molecules. Less than 0.5% of ingested Trehalose is absorbed.

In mice: Trehalose is absorbed by pinocytosis and if given in drinking water (2%) tissue (**brain** and liver) penetration is well documented (Tanaka M et al Nature Med 2004)

IV administration of trehalose enables high tissue content for long duration (BioBlast studies in rats)

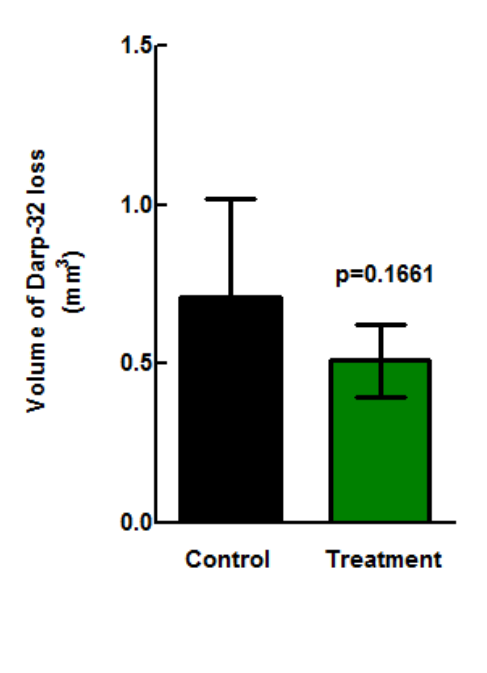


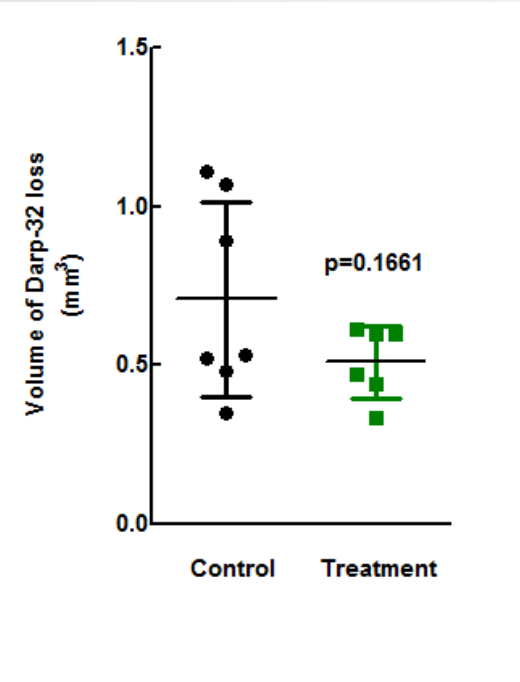
- C_{max} plasma was 2000 ng/mL at 4 hours post IV
- C_{max} muscle was 3730 ng/gr at 8 hours post IV
- Elimination half life from muscle was 33.8 hours.
- Trehalose was present in tissue for at least 48 hours

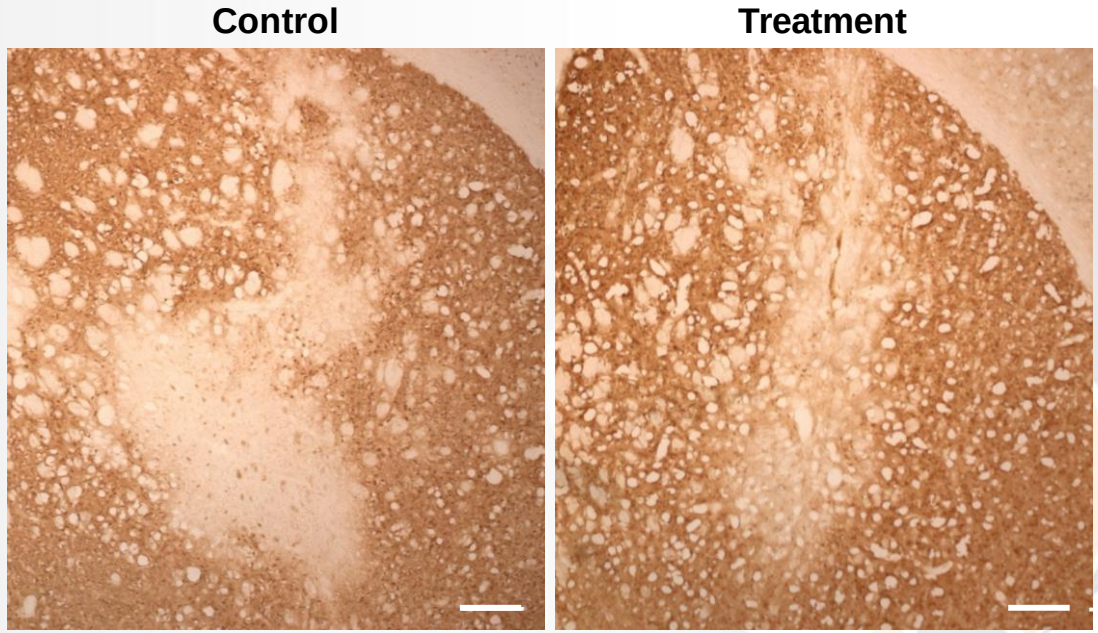
Proof of concept of trehalose in SCA3 animal models (BioBlast supported work)

- Study was conducted by:
  - Prof. Luís Pereira de Almeida
  - Magda M. Santana, Pharm.D, Ph.D.
- Two mouse models were used (trehalose was given in drinking water for 24 weeks)
- Lentiviral-based MJD mouse model was used for measurements of brain changes:
  - Reduction of cellular aggregations
  - Reduction of brain lesion volume
- Transgenic mouse model with truncated ataxin-3 was used for functional studies:
  - Rotarod
  - Beam walking
  - Swimming

Trehalose Effect on Brain lesion Volume



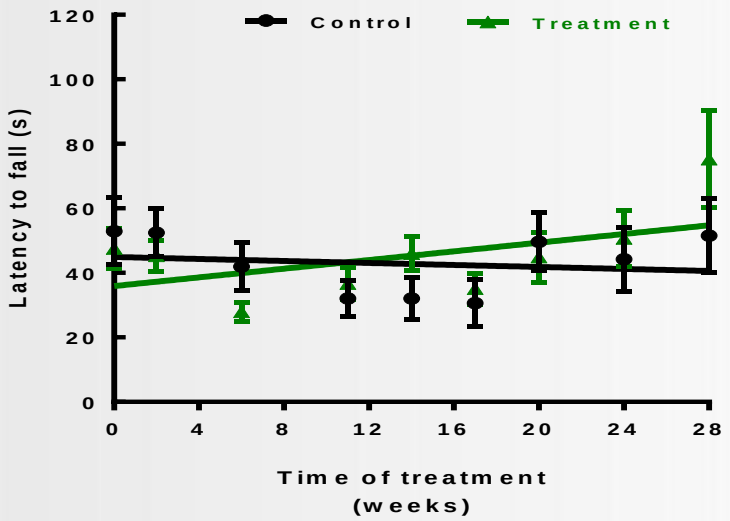




SCA3 transgenic mice performance on stationary rotarod (differences between females and males)

Work in Progress

Males + Females

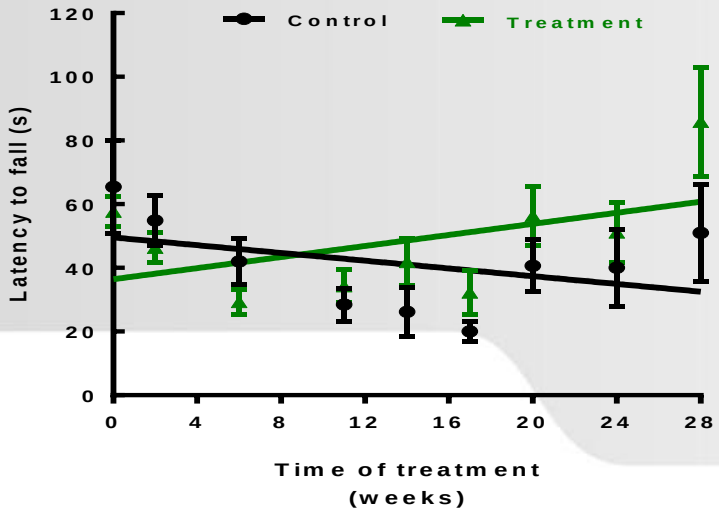


p=0.04894

Slope = 0.6725 ± 0.2740
R^2 = 0.05846

Slope = -0.1551 ± 0.3156
R^2 = 0.002536

Females

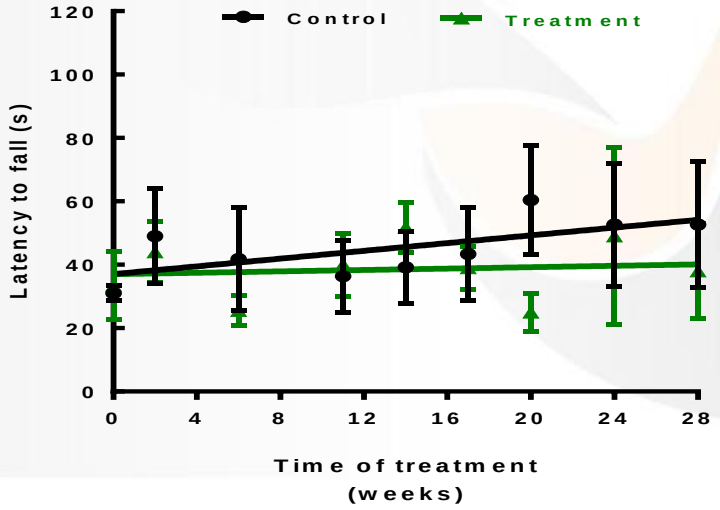


p=0.005828

Slope = 0.8690 ± 0.3620
R^2 = 0.08763

Slope = -0.6082 ± 0.3820
R^2 = 0.04407

Males



p=0.4602

Slope = 0.6115 ± 0.5349
R^2 = 0.03325

Slope = 0.1099 ± 0.3918
R^2 = 0.002244

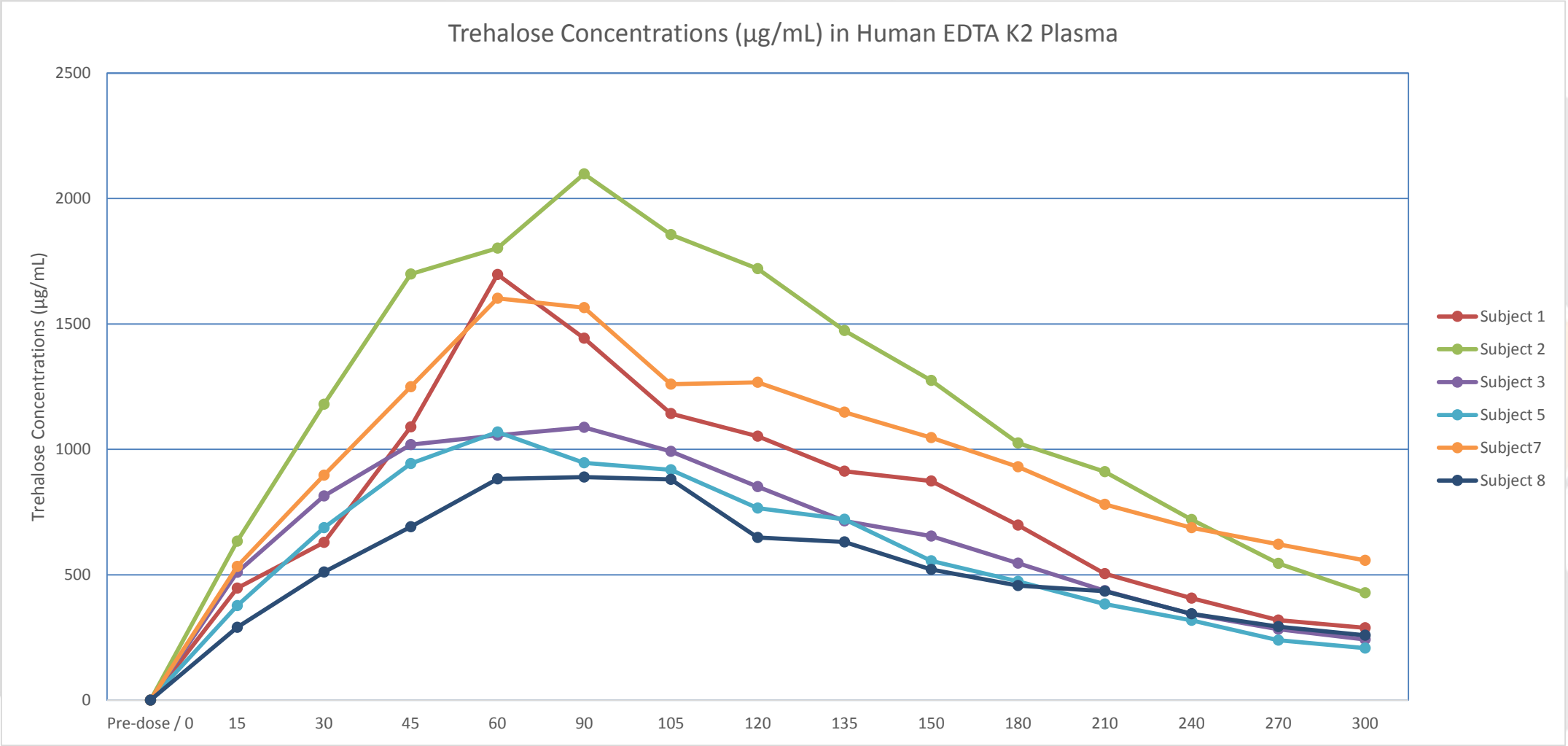
Human studies of Cabaletta (IV trehalose preparation)

- **Ongoing once weekly IV of 30 gr. in OPMD**
  - Two active centers, one with 24 weeks results (14 patients) and the other started recently (8 patients)

- **Open label IV 15 or 30 gr once weekly in MJD (safety & tolerability)**
  - 1 center started (6 patients already dosed)

Trehalose blood levels conforms with animal levels- ensuring penetration into muscle cells

Trehalose Concentrations (µg/mL) in Human EDTA K2 Plasma



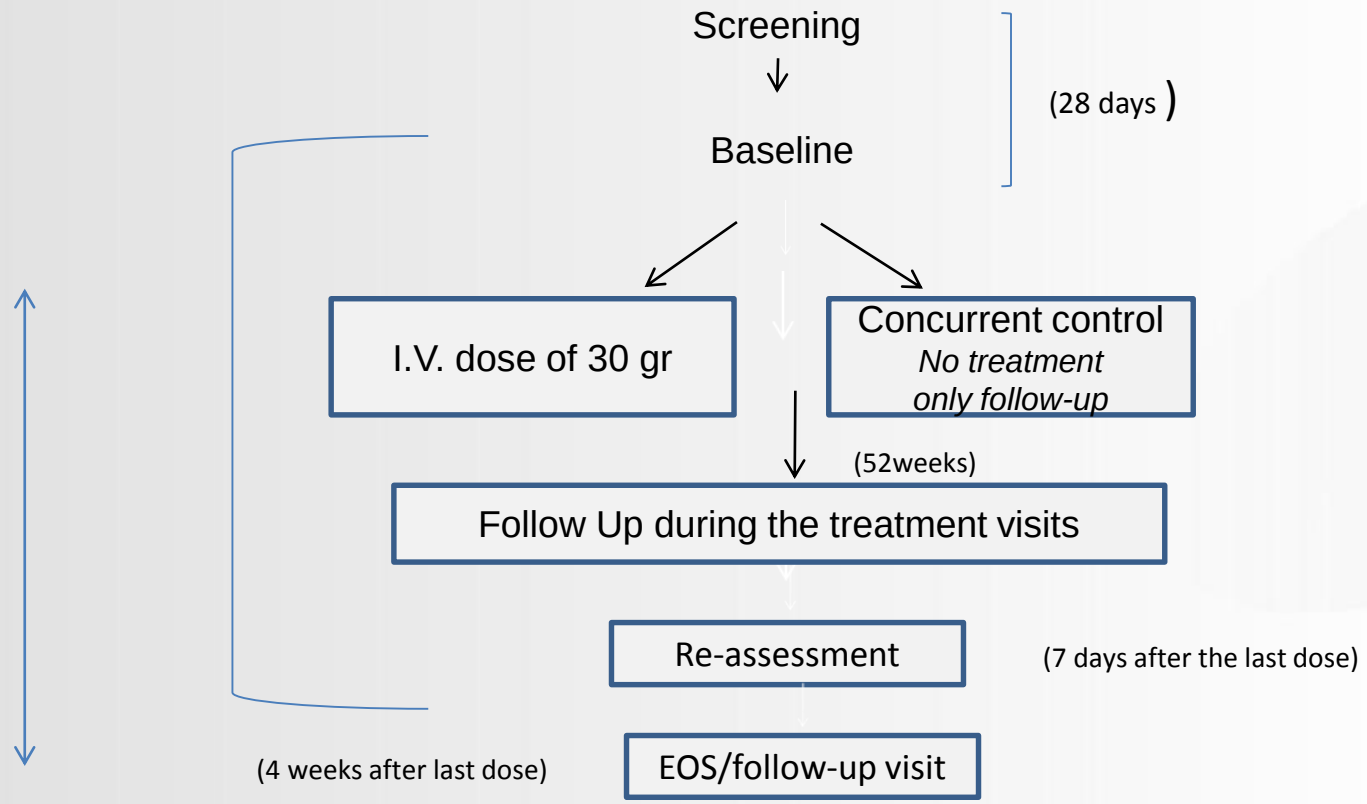
Safety of Cabaletta IV in humans

- No drug-related adverse effects in 20 OPMD patients
- Quality of Life questioner in 11 patients- study subjects report “feeling well”

Planned SCA 3 Study (Bioblast Pharma)

- A Pivotal, Multicenter, Open-label, Randomized, Non-treatment Concurrent Control, Parallel Group Study, to Assess the Safety, Tolerability, and Efficacy of Intravenous Cabaletta® in Patients with Machado-Joseph Disease / Spinocerebellar Ataxia 3 (SCA3)

STUDY SCHEMA



Primary endpoint

Changes in the Scale for the Assessment and Rating of Ataxia (SARA)

Based on data from:
Europe Consortium study showing annual increase by 1.6+0.12 (Jacobi et al 2011)
USA Consortium study showing increase by 1.14+0.4 (Ashizawa et al 2013)

Secondary Endpoints
Changes in several SCA disease markers

- Neurological examination Score for Spinocerebellar Ataxia (NESSCA). Based on natural history data from Brazil (L. Jardim group)
- Changes in Spinocerebellar well-studied Ataxia Functional Tests:
  - 9 hole peg test (9HPT)-two sides
  - 8-meter (25 feet) walk (8MW)
- Quality of life as assessed by:
  - the World Health Organization Quality-of-Life Questionnaire-BREF (WHOQOL-BREF)
  - EQ5L
  - EFACTS- ADL
- Change in weight (BMI)

Study Criteria

- **Inclusion (main):**
  - Age 18-75
  - Genetic confirmation
  - Ambulate for at least 8 m
  - Stable medication for 30 days
  - BMI>20
  - Able to consent

- **Exclusion (main):**
  - Diabetics
  - No major active disease
  - Marked depression

Team and Authors

- BioBlast Pharma
  - Dalia Megiddo MD- Dir. Drug development
  - Hagar Greif PhD- Dir. Preclinical studies
  - Irit Gliko-Kabir- Dir. Clinical trials
- Meir Medical Center (Neurology), Kefar Saba, Israel (MJD safety trial)
  - Carlos Gordon MD
  - Roi Zaltsman MD
- Hadassah University Hospital (CRC), Jerusalem (OPMD trial)
  - Yossi Caraco MD
  - Yael Feinsod Meiri
  - Hadassa Vornovitsky MD