KHONDRION

The Mitochondrial Medicine Company

Goal Attainment Scaling in Drug Development

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Asterix Symposium
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SDD consulting
Strategic Drug Development

Topics

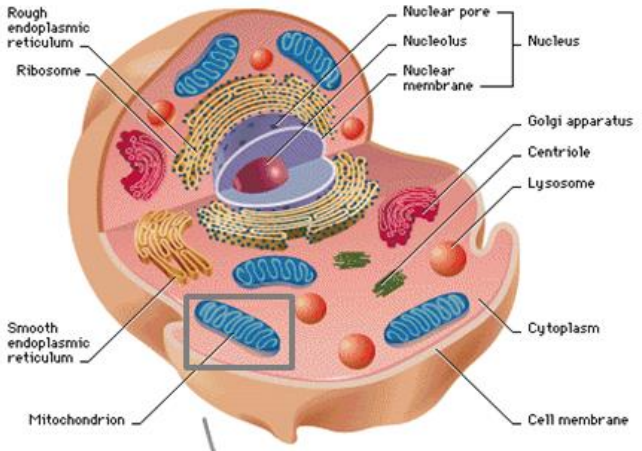
Introduction

Mitochondrial disorders

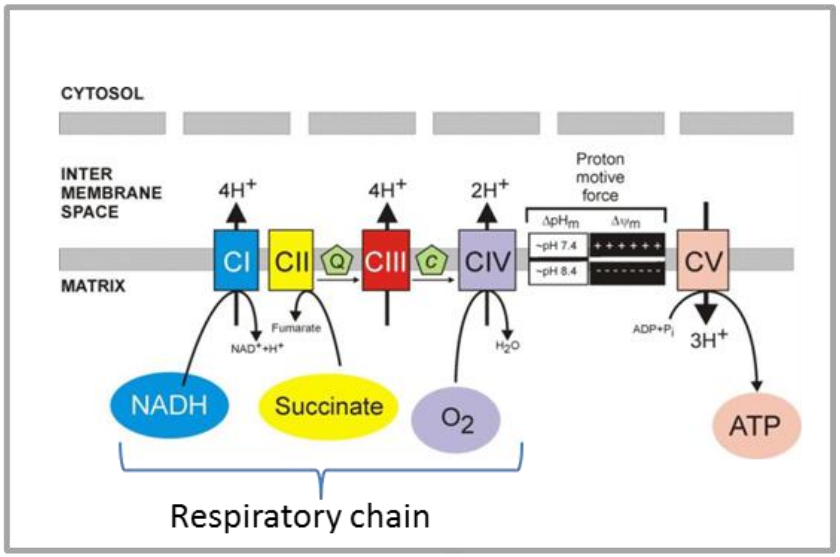
Use of goal attainment scaling

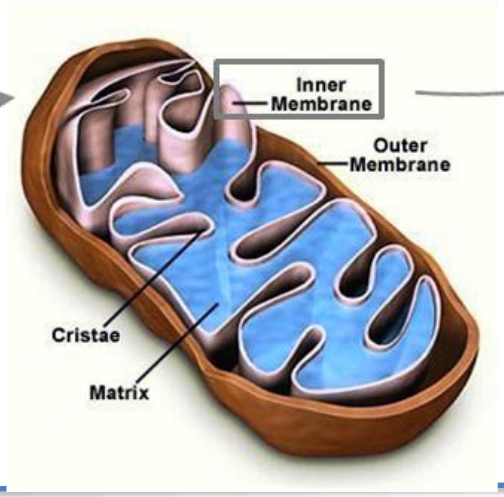
Use of endpoints in different stages of development

Mitochondrial disorders

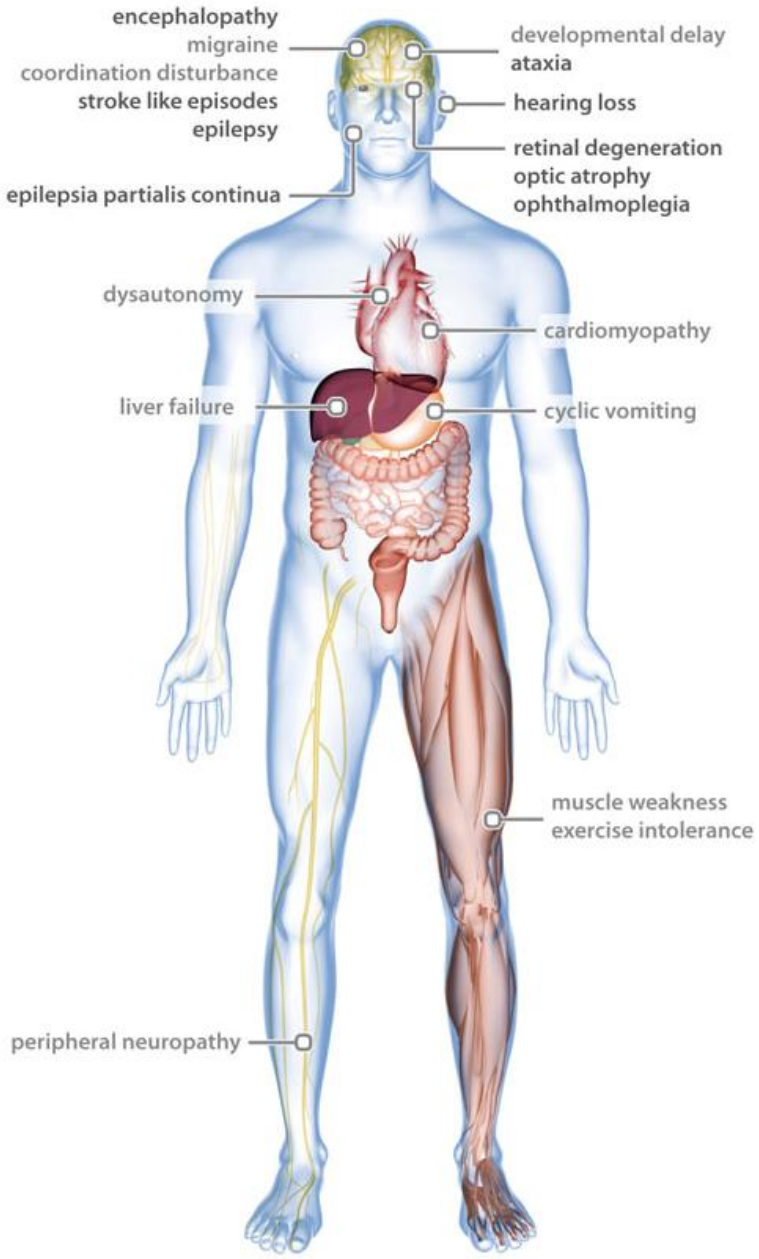


OXPHOS system





Mitochondrial disorders



Heterogeneous multisystem disorder

Prevalence 1 : 10.000

Any organ or tissue

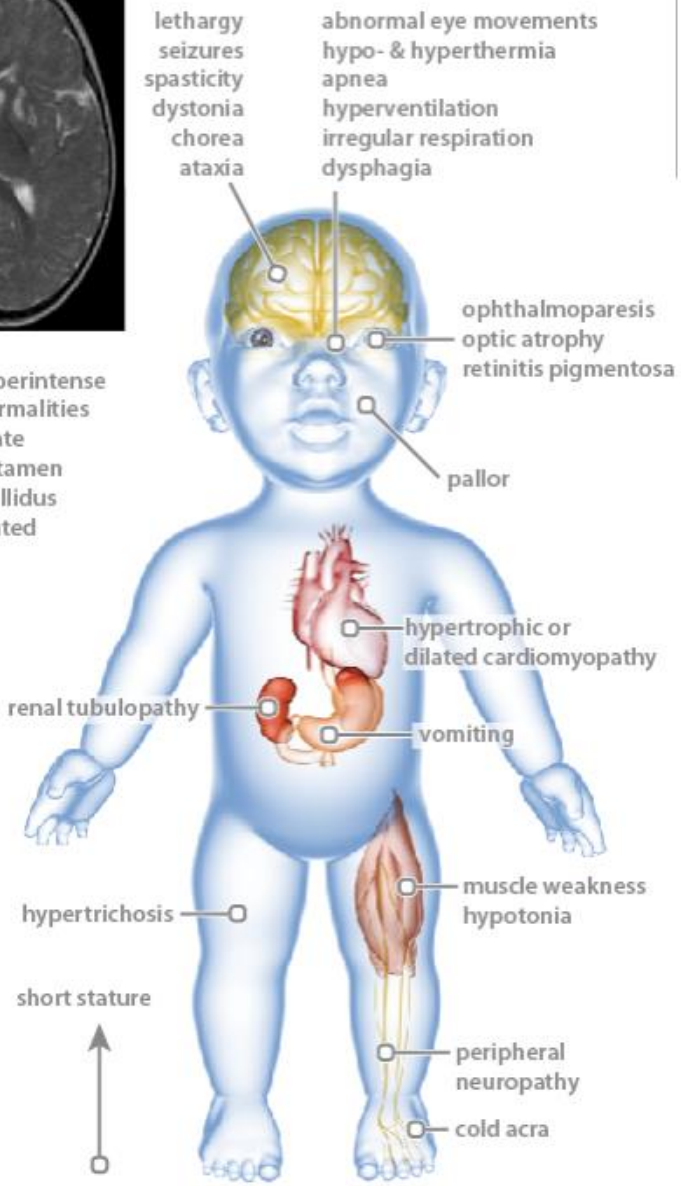
Any mode of inheritance

Any Age

Devastating, often early fatal

Mitochondrial disorders

Bilateral hyperintense signal abnormalities in the caudate nucleus, putamen & globus pallidus on T2 weighted images



Very heterogeneous

Leigh, MELAS, MIDD, NARP, Kearns-Sayre, Alpers-Huhenlocher, Pearson, Fatal infantyl Lactic Acidosis, mitochondrial myopathies, mitochondrial encephalopathies, ...

Clinical:
SIMILAR PHENOTYPE: DIFFERENT BIOCHEMISTRY
SIMILAR PHENOTYPE: DIFFERENT GENE DEFECTS
SIMILAR PHENOTYPE: DIFFERENT DISEASE EXPRESSION
SIMILAR PHENOTYPE: DIFFERENT DISEASE COURSE

Biochemical
SIMILAR BIOCHEMISTRY: DIFFERENT PHENOTYPES
SIMILAR BIOCHEMISTRY: DIFFERENT GENE DEFECTS

Genetic
SIMILAR GENE DEFECT: DIFFERENT PHENOTYPE
SIMILAR GENE DEFECT: DIFFERENT BIOCHEMISTRY

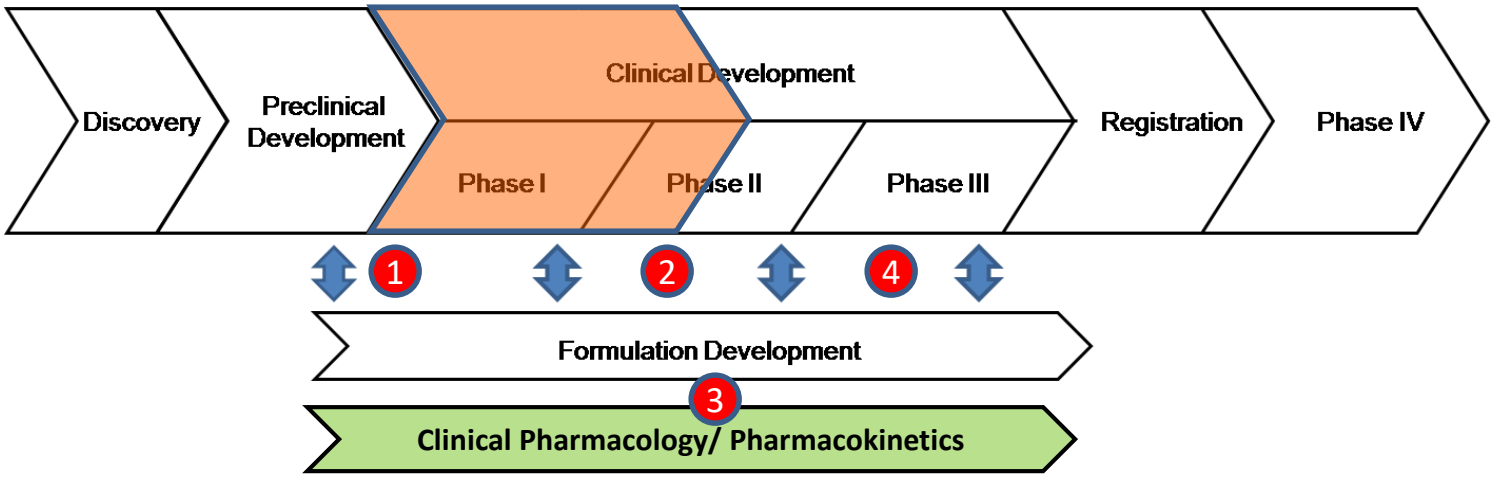
Challenges: Endpoints in Clinical Trials

6 minutes walk test:
- regulatory reference
- Variable, slight motivation: 30 % difference
- Sensitive?
- Only for the ones that can walk!

Exercise testing
Muscle strength
Biochemical biomarkers
Disease scales (patient and investigator rated)
QoL scales
Cognitive testing
Specific organ functioning (eye, heart, etc)
…..

Goal Attainment Scaling

Drug Development Overview: Exploratory Development

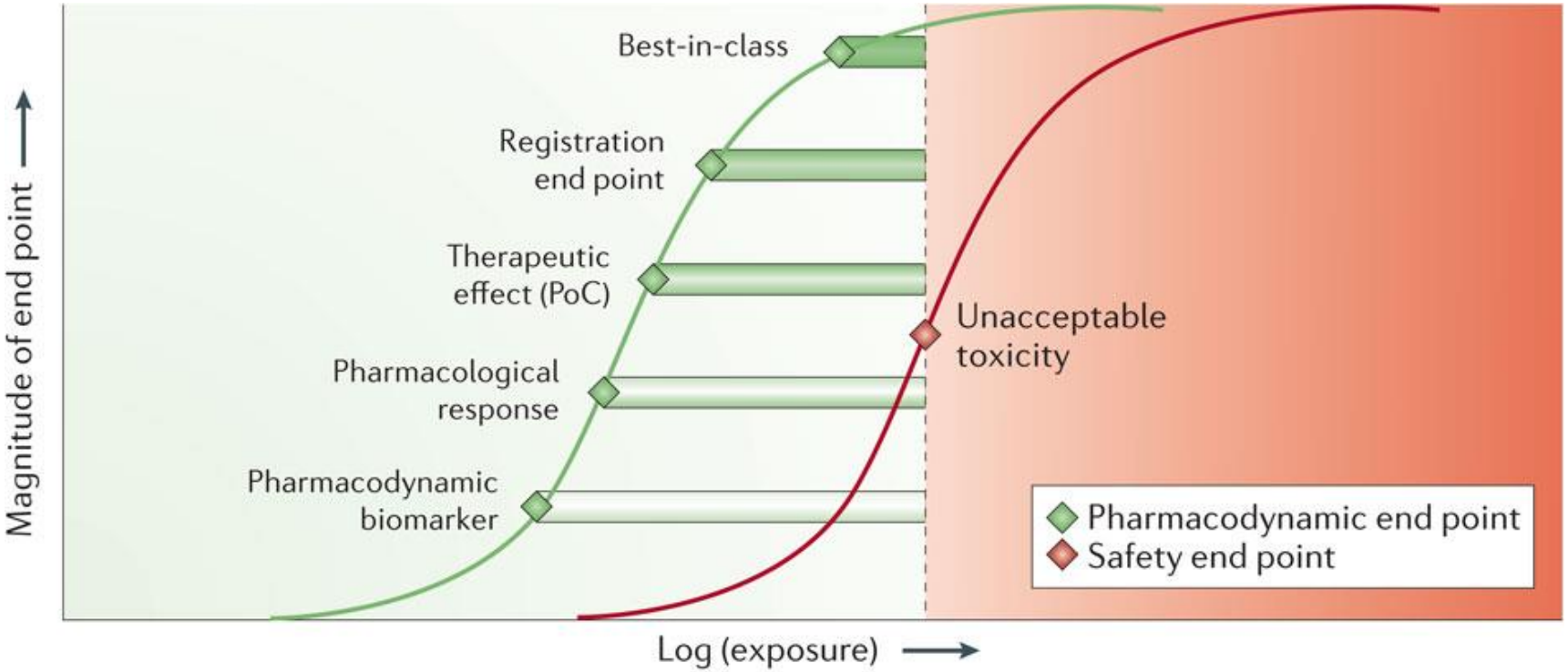


Orange: **Exploratory** Clinical Development;

From '*First in Man*' (1) studies up to '*Proving the Concept' (2).*

1. First-in-human study
2. Proof-of-concept study (POC)
3. Clinical pharmacology/PK studies (also regarded as "Phase I")
4. Pivotal Studies

Translational Considerations in exploratory development: Get the dose right!!



Nature Reviews | Drug Discovery

Muller PY, Milton MN, Nat Rev Drug Discov. 2012 Oct;11(10):751-61

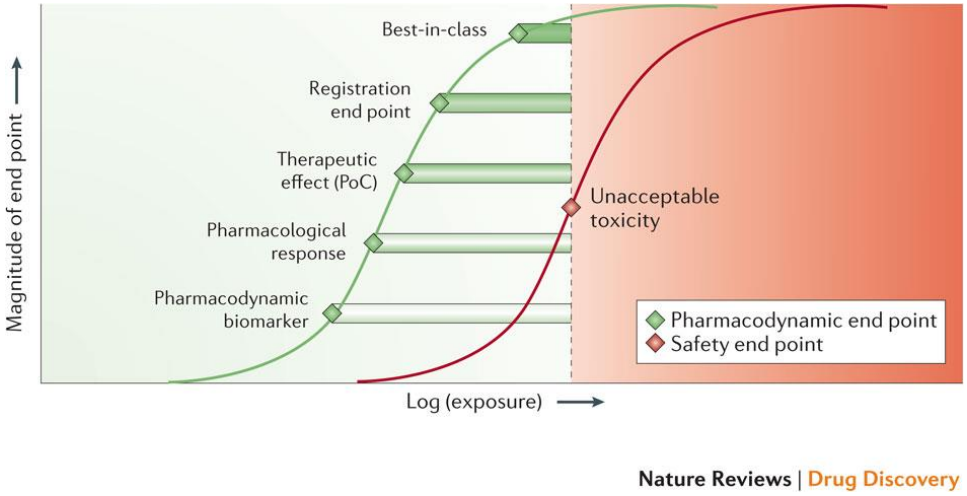
The therapeutic index in relation to the pharmacodynamic endpoint

Needs in Exploratory Development:

Signal detection to justify large studies

Goal:
- Get the dose right
- Justification for large studies

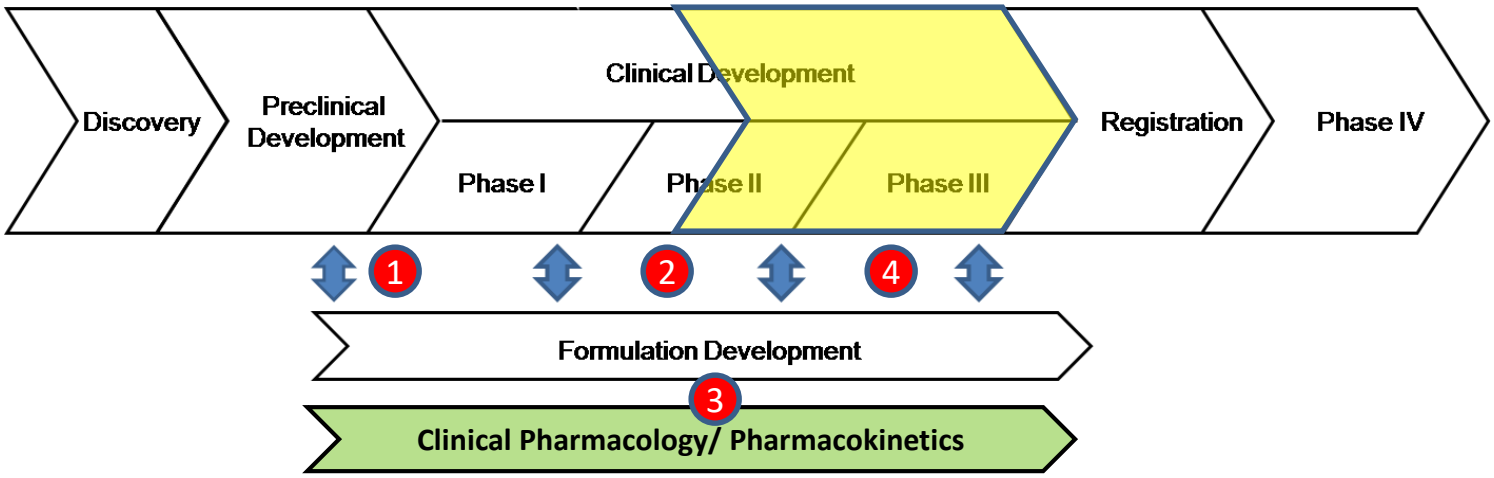
Patient Population:
- Sensitive to treatment
- Measurable disease
- Homogeneous



Endpoints:
Objectively Measurable endpoints
Sensitive endpoints
Quantifyable endpoints, both in positive and negative directions
Preferably wide range of response

Goal Attainment Scaling?? Maybe

Drug Development Overview: Confirmatory Development

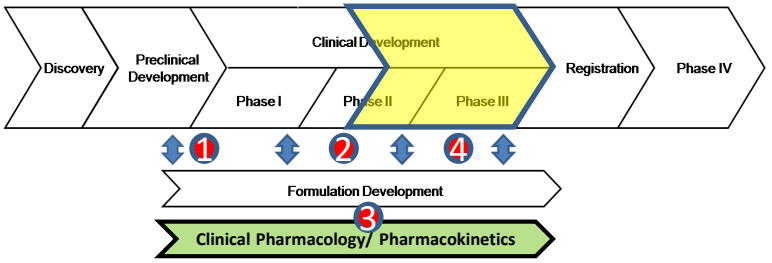


Yellow: Confirmatory Development (4)

From '*Proving the concept'* up to *'filing the dossier'.*

Drug Development Overview: Confirmatory Development

Regulatory driven:
- 6 minutes walk test as anchor
- Other endpoints to be validated



Endpoints:
- Clinically meaningfull
- Patient involvement
- QoL

Yellow: Confirmatory Development (4)

From '*Proving the concept*' up to *'filing the dossier'*.

Patient Population:
- Representative for the intented population

Goal Attainment Scaling? Definately!

Questions?

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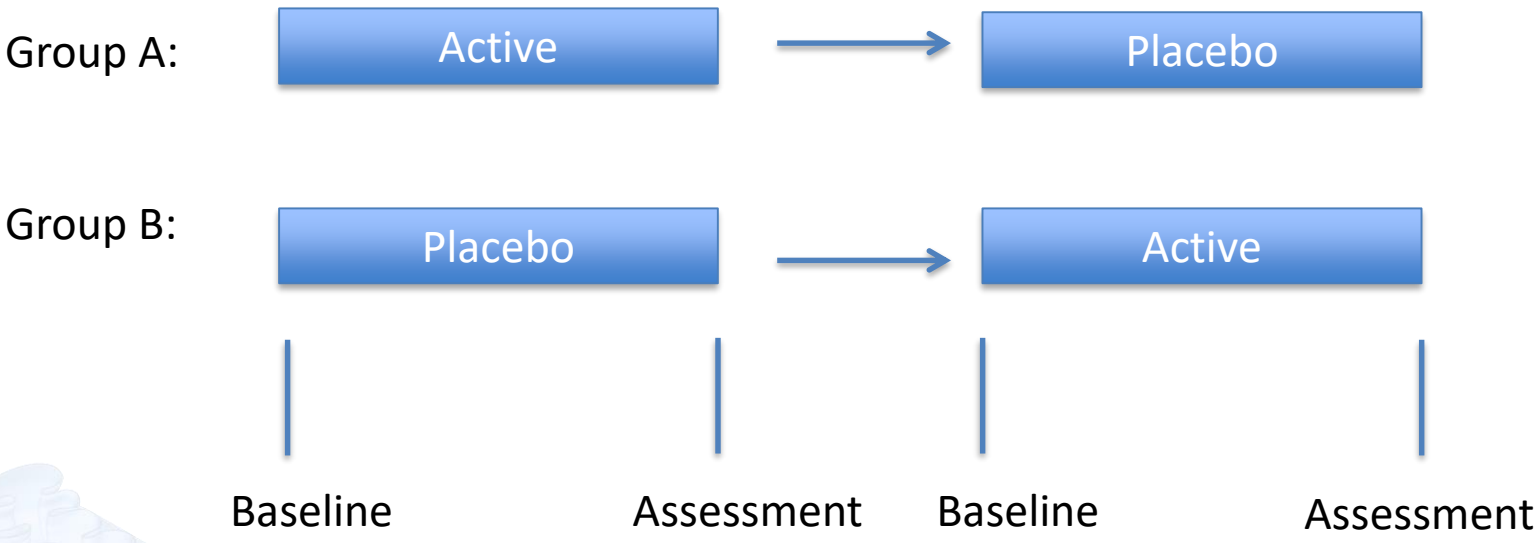
The KHENERGY study

An exploratory, double-blind, randomized, **placebo-controlled**, single-center, **two-way cross-over** study with KH176 in patients with the mitochondrial DNA $tRNA^{Leu(UUR)}$ m.3243A>G mutation and clinical signs of mitochondrial disease



Primary Objective

- To evaluate the effect of KH176 on gait (Gaitrite®) parameters: step-length and variability in step-time and step-width in patients with a m.3243A>G mutation

Secondary Objectives

- To explore the effect of KH176 on biomarkers of mitochondrial functioning in patients with an m.3243A>G mutation.
- To explore the effect of KH176 on functional clinical measures of mitochondrial disease in patients with an m.3243A>G mutation.
- To investigate the tolerability and safety of KH176 following 28 days of oral administration to patients with an m.3243A>G mutation.
- To investigate the multiple dose pharmacokinetics of KH176 following 28 days of oral administration in patients with an m.3243A>G mutation.

Safety parameters:

Change from baseline for vital signs (supine and standing blood pressure, and heart rate).
Change from baseline for ECG variables
Change from baseline for clinical laboratory variables
Treatment-emergent laboratory abnormalities up to Follow-up
Treatment-emergent ECG abnormalities up to Follow-up
Treatment-emergent abnormalities in cardiac monitoring (bedsite/Holter registration)
Treatment-emergent AEs up to Follow-up
Treatment-emergent AEs leading to discontinuation of study drug
Treatment-emergent SAEs up to 28 days after last study drug intake

The KHENERGY study: study parameters

Pharmacokinetics:

Blood/urine collection

Plasma concentrations to derive: C_{max}, t_{max}, and AUCtau, AUC_{0-t} and time to reach steady state

Pharmacodynamics:

Blood/urine collection:

- bioanalysis of Glutathione (GSH/GSSG)
- bioanalysis of FGF21, GDF15 and PRDX1
- a whole metabolome analysis
- Oxidative stress platform analysis

Note:

- exact sampling time is mandatory
- Register: time of dosing (precisely) and sampling time (precisely)
- Urine volumes

The KHENERGY study: study parameters

Efficacy parameters:

Change from baseline (defined as the value measured at pre-dose Day -2 and -1) in:

Gait parameters: cadence, walking speed, right and left step and stride lengths, and times
NMDAS Score
Spirometric parameters: FVC, FEV1, PEF, MIP, MEP
30-Seconds sit – stand test: Number of standings
Handgrip dynamometry: Maximum grip strength
6 Minutes Chewing test: VAS pain, VAS tiredness, Rate of Mastication, quality of movement
6 Minutes Walk Test (part of the gait evaluation protocol): Distance and Distance/minute
RAND-SF36 score
Hospital Anxiety and Depression Scale (HAD), supplemented with a Beck Depression Index (BDI)
Checklist Individual Strenght (CIS)
Test of Attentional Performance (TAP): Alertness and Mental Flexibility

In addition:
an assessment of a Goal Attainment Scale (GAS)
a diary of Diet and Gastro-Intestinal Functioning
and a continuous registration of motor activity and sleeping pattern

Flow-chart

Treatment A and B

Assessment			Treatment A and B							
	Screening	Training	Baseline (Day-2/-1)	Week 1 (Day 1-3)	Week 1 (Day 4-6)	Week 2	Week 3	Week 4 (up to day 26)	Week 4 Day 27/28	Follow up
KH176 BID dosing				x	x	x	x	x	x	
Hospitalization (5)			x	x					x	
Ambulant visits (2)	x					x	x	x		x
Adverse events recording(6)	x	x	x	x	x	x	x	x	x	x
ECG recording(7)			x	x		x	x		x	x
Cardiac evaluation, incl echo	x									x
Safety evaluation block(1)			x	x		x	x	x		x
Holter registration			Continuous(8)							
Sampling for biomarker assessments (4)			x						x	

Hospitalization (5)			x	x					x	
Ambulant visits (2)	x					x	x	x		x
Adverse events recording(6)	x	x	x	x	x	x	x	x	x	x
ECG recording(7)			x	x		x	x		x	x
Cardiac evaluation, incl echo	x									x
Safety evaluation block(1)			x	x		x	x	x		x
Holter registration			Continuous(8)							
Sampling for biomarker assessments (4)			x						x	
Questionnaires (home based)			x						x	
Clinical Evaluation block		x	x						x	
Nutritional/ BMI/bio-impedance	x		x			x			x	x
Diary (diet)			x	x	x	x	x	x	x	
Accelerometer				X	X	X	X	X	X	
PK sampling (3)				x		x	x	x	x	