Repurposing of carbamazepine for metaphyseal chondrodysplasia, type Schmid

Mike Briggs
Professor of Skeletal Genetics
Skeletal Research Group

Drug Repurposing for Rare Diseases
27th February 2018 - The Royal College of Nursing, London
Genetic (Rare) Skeletal Diseases

- Extensive clinical and genetic heterogeneity
- Short-limbed dwarfism
- Over 450 unique phenotypes
- ~1/4000 incidence
- **GSDs are difficult to diagnose**
- **There are currently no treatments**
- Significant burden in **pain** and **disability** leads to **poor quality of life** and **high healthcare costs**
Drug repurposing for rare bone diseases: from pre-clinical studies to clinical trials

- Pre-clinical cell & mouse studies completed: **Sept 2015**
- UK Priority Patent filed: **March 2016**
- Orphan Drug Designation granted: **Oct 2016**
- International Patent filed: **March 2017**
- Preclinical data published in Mullen *et al* JCI: **Sept 2017**
- Horizon 2020-funded clinical trial: **Dec 2017**
- Protocol assistance received from EMA: **Dec 2017**
Increased intracellular proteolysis reduces disease severity in an ER stress–associated dwarfism

Lorna A. Mullan,1,2 Ewa J. Mularczyk,1,2 Louise H. Kung,1,2,3 Mitra Forouhan,1,2 Jordan M. A. Wragg,1,2 Royston Goodacre,4 John F. Bateman,3 Eileithya Swanton,2 Michael D. Briggs,5 and Raymond P. Boot-Handford1,2

1Wellcome Trust Centre for Cell-Matrix Research, 2Faculty of Biology, Medicine and Health, 3Bolton Academic Health Science Centre, Manchester, United Kingdom. 4Murdoch Childrens Research Institute, Parkville, Victoria, Australia. 5School of Chemistry and Manchester Institute of Biotechnology, Faculty of Science and Engineering, University of Manchester, Manchester, United Kingdom.

4Institute of Genetic Medicine, Newcastle University, Newcastle upon Tyne, United Kingdom.
Metaphyseal chondrodysplasia, type Schmid MCDS
Col10a1 N617K mouse recapitulates MCDS phenotype

A

wt/wt  wt/m  m/m

B

Weight (grams)

Age (days)

wt/wt  wt/m  m/m

C

wt/wt  wt/m  m/m

D

i

wt/wt  m/m

ii

wt/wt  m/m

Rajpar et al 2009
Retained mutant type X collagen causes ER stress and an enlarged hypertrophic zone

Retention of mutant collagen X

Rajpar et al 2009
Route to potential therapy for MCDS

ER stress is a core disease mechanisms in MCDS......

......and other genetic skeletal diseases

ER stress can be targeted through the use of drugs/molecules

↓ misfolding & aggregation

↑ folding capacity of cell

↑ degradation (ERAD/autophagy)
Reduction of ER stress by chemical modulation

SPB = sodium phenyl butyrate (salt)
CBZ = carbamazepine
TUDCA = tauroursodeoxycholic acid (bile acid)
Verapamil = calcium channel blocker
Quercetin = plant pigment (flavonoid - red wine)

Mullen et al 2017
Improvement of growth plate pathology in MCDS mice following cbz treatment

- Width of HZ zone
- BiP = ER stress
- Retention of mutant collagen X

Mullen et al. 2017
Restoration of bone growth in MCDS mice
Carbamazepine is a long established & safe medicine

- Carbamazepine was discovered by chemist Walter Schindler in 1953 & marketed to treat epilepsy in 1963
- Used as an anticonvulsant & antiepileptic in UK since 1965 & US since 1968
- Available as a **generic medication** & **not very expensive**
- On the World Health Organization's “List of Essential Medicines”; the **most effective** and **safe medicines** needed in a health system
- The wholesale cost is approx. £ per dose
Orphan Drug Designation granted in 2016

Public summary of opinion on orphan designation
Carbamazepine for the treatment of metaphyseal chondrodysplasia, Schmid type

On 14 October 2016, orphan designation (EU/3/16/1746) was granted by the European Commission to University of Newcastle upon Tyne, United Kingdom, for carbamazepine for the treatment of metaphyseal chondrodysplasia, Schmid type.

What is metaphyseal chondrodysplasia, Schmid type?
Metaphyseal chondrodysplasia, Schmid type is an inherited disease of the bone. It is due to mutations (changes) in the genes responsible for making collagen X, a protein important in the development of cartilage and bone. As a result, abnormal forms of collagen X are produced that build up and interfere with bone development. Abnormal development of the bones causes patients to have short arms and legs, bowing of the legs and abnormal gait. Other bones may also be affected and the patient may have hip deformities.

Metaphyseal chondrodysplasia, Schmid type is debilitating in the long term because it causes pain, and hip and knee deformity.

What is the estimated number of patients affected by the condition?
At the time of designation, metaphyseal chondrodysplasia, Schmid type affected less than 0.1 in 10,000 people in the European Union (EU). This is equivalent to a total of fewer than 500 people, and is below the ceiling for orphan designation, which is 5 people in 10,000. This is based on the information provided by the sponsor and the knowledge of the Committee for Orphan Medicinal Products (COMP).
MCDS-Therapy Project has received funding from the European Union’s Horizon 2020 research and innovation programme under grant agreement No 754825
Horizon 2020: personalized medicine call 2016-2017

Research and Innovation actions (2-stage application process)

SC1-PM-02-2017: New concepts in patient stratification
SC1-PM-07-2017: Promoting mental health and well-being in the young
SC1-PM-08-2017: New therapies for rare diseases
SC1-PM-10-2017: Comparing the effectiveness of existing healthcare interventions

➔ Total Budget €173 million (€65 million to ‘new therapies’)

Oct 2016
Number of proposals submitted to 1st stage = 668
Number of proposal above threshold = 101 (15%)

April 2017
Number of proposals invited to 2nd stage = 97
Number of proposals above threshold = 37 (38%)
“Support will be provided to clinical trials on substances where orphan designation has been given............where the proposed clinical trial design takes into account recommendations from protocol assistance given by the European Medicines Agency”

April 2017: Preliminary approach to EMA – withdrawn

May ‘17: Employ an expert to help – Envestia (~£90/hr)

4 Sept ‘17: Letter of intent and briefing pack sent to EMA for validation

15 Sept ‘17: Submission of “Carbamzepine scientific advice request” to EMA

20 Sept ‘17: Confirmation of Scientific Advice Working Party (SWAP) membership

1st Nov ‘17: Received “List of Issues adopted by the SAWP”

13th Nov ‘17: Response to “SWAP issues” submitted

29th Nov ‘17: SWAP discussion meeting at EMA (London)

18th Dec ‘17: Committee for Medicinal Products Human Use (CHMP) ‘advice’ received
Question 1
Does the agency agree that the **statistical basis and sample size** for the dose-finding element are appropriate?

Question 2
Does the agency agree than an **open-label**, non-comparative design is appropriate for the main study?

Question 3
Does the agency agree with the **proposed sample size** and statistical basis for the main study?

Question 4
Does the agency agree with **proposed primary endpoint**?

Question 5
Does the agency agree with the **proposed secondary endpoints** for the study?

Question 6
Does the Agency agree with the **proposed duration of treatment**?
EMA: “Therefore for this advice you will be charged €63,500 - 75% (orphan fee reduction) = €15,875” – subsequently waived because it is deemed paediatric advice

Envista: £3200 (1/5 – 31/8), £1800 (1-30/9), outstanding...
Repurposing of carbamazepine for treatment of skeletal dysplasia

“MCDS-Therapy”

- Phase 2/2b clinical trial
- Health economics
- Public/patient engagement
- Biomarker discovery

MCDS-Therapy Project has received funding from the European Union’s Horizon 2020 research and innovation programme under grant agreement No 754825
Repurposing of carbamazepine for treatment of skeletal dysplasia

**Stage 1 and 2:**
- Newcastle
- London

**Stage 2:**
- Antwerp
- Paris
- Freiburg
- Bologna
- Melbourne

**Additional partners:**
- Findacure (patient advocacy/drug repurposing)
- Finovatis (project management)
- Sciomics (proteomic biomarkers)

**MCDS-Therapy Project has received funding from the European Union’s Horizon 2020 research and innovation programme under grant agreement No 754825**
The ‘skeletal genetics’ family tree
20 years of EU-funded Collaborative Research in Rare Skeletal Diseases

**FP5** The European Skeletal Dysplasia Network @ESDN_news: 2002-2005

**FP6** European Growth Plate Consortium (EuroGrow): 2007-2010

**FP7** Systems biology for the functional validation of genetic determinants of skeletal diseases @SYBIL_News: 2013-2018

Horizon 2020 Repurposing of carbamazepine for treatment of skeletal dysplasia @MCDS_Therapy: 2018-2022
MCDS-Therapy Project has received funding from the European Union’s Horizon 2020 research and innovation programme under grant agreement No 754825

Michael Wright
Marta Bertoli
Laura Rush/Joe Hedley

Ray Boot-Handford
Lorna Mullen