

# mcDs THERAPY

## An international collaboration to develop a new repurposed therapy for metaphyseal chondrodysplasia type Schmid (MCDS)

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- MCDS is an ultra-rare inherited skeletal disorder causing short stature, pain, and bone deformities.
- Investigations into the condition have identified endoplasmic reticulum stress as the key mechanism of disease.
- There is currently no treatment, but a potential therapy, carbamazepine, has been identified through a screen of generic drugs.
- The EU have funded MCDS-Therapy, an international academic-led collaboration, to repurpose carbamazepine for MCDS.
- Results from our clinical trial are expected in 2022, with a subsequent aim of licensing a low-cost therapy.

### WHAT IS MCDS?

MCDS, or metaphyseal chondrodysplasia type Schmid, is an ultra-rare

inherited skeletal disorder affecting less than 1/100,000 of the population. It leads to short stature with disproportionately short arms and legs (called short-limbed dwarfism), as well as curvature, or bowing, of the leg bones. The ends of long bones and ribs can also flare outwards, and there may be hip deformities causing the thigh bone to be angled towards the centre of the body. Some symptoms, like short stature, have little impact on physical health and well-being and can be of limited concern to patients. However, the bone deformations can lead to impaired gait when walking, making movement difficult, as well as pain in the legs and joints throughout life. This burden in pain and disability can lead to poor quality of life and high healthcare costs and should be treated if possible.

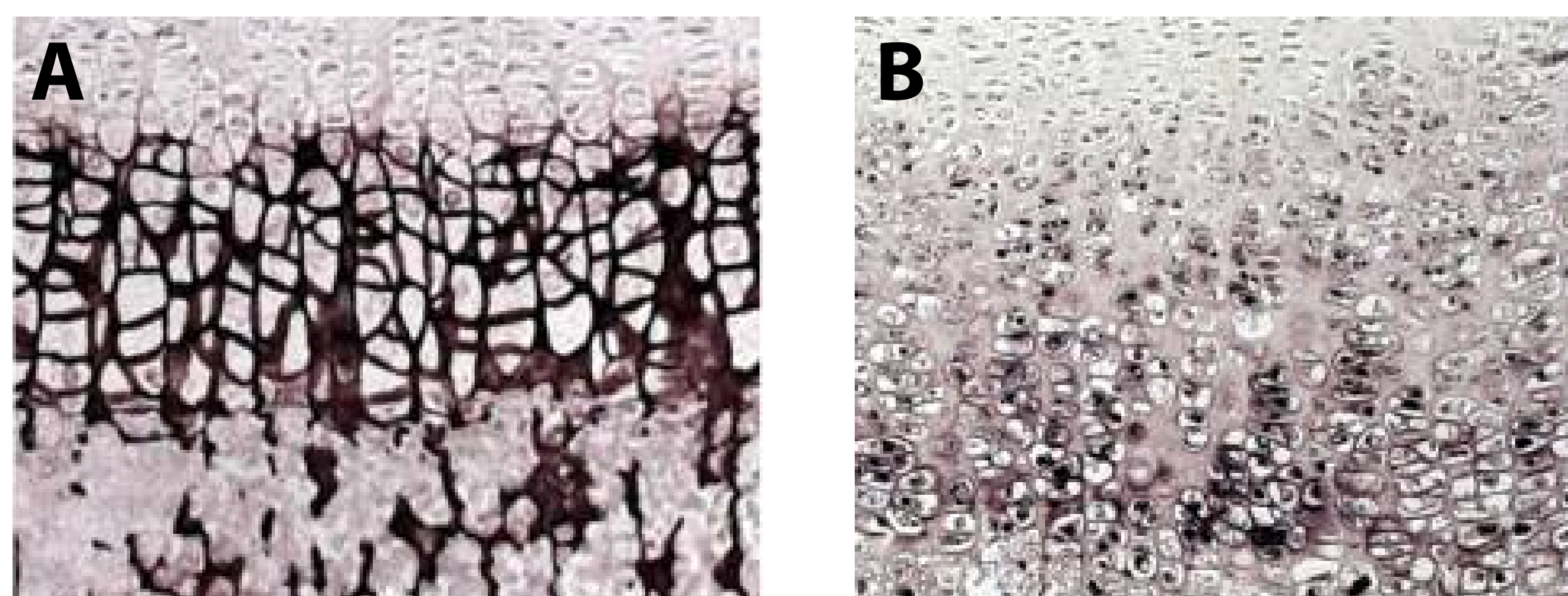


An x-ray showing curvature and flaring in an MCDS patient's leg bones

### WHAT CAUSES MCDS?

MCDS is caused by an error in the body's genetic code. The error is located on the COL10A1 gene which creates a protein

known as collagen X (collagen 10). Collagen is a protein that is used to form the hard structure of bone. This means that to function, it needs to be moved outside of the cells and into the surrounding bony matrix. In MCDS, errors in the gene for collagen X mean that cells build the protein incorrectly. This causes the protein to get trapped inside the cell. Specifically, the protein gets trapped within a part of the cell known as the endoplasmic reticulum (or ER), which becomes stressed (ER stress). Over time this stops the cells functioning in a normal way, and ultimately leads to cell death.



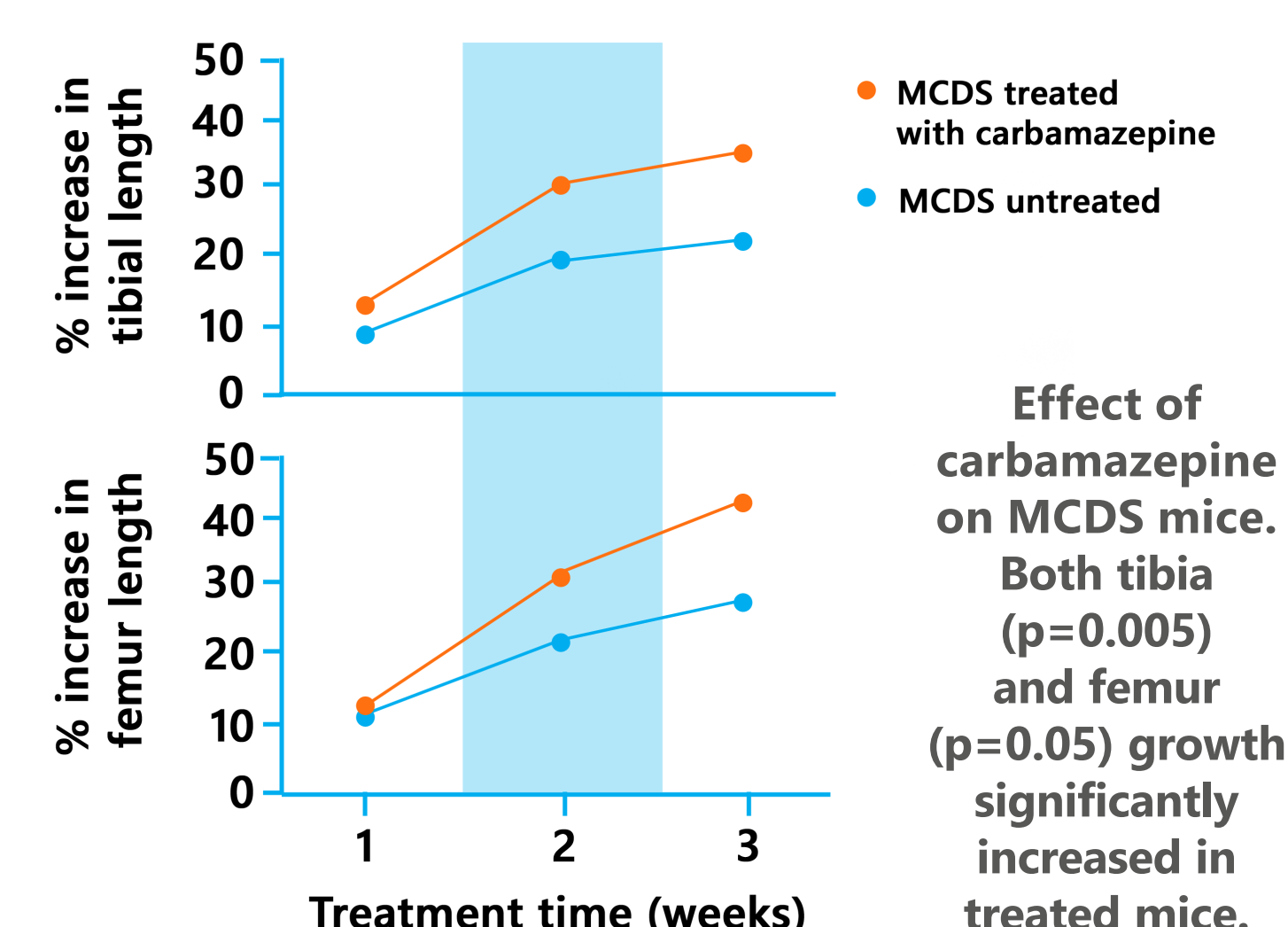
Stained sections of the growth plate in a person unaffected (A) and affected (B) by MCDS. In a normal growth plate collagen X (stained black) sits outside the cells, creating a net-like pattern. In a MCDS growth plate collagen X gets trapped inside the cells, so you see dark spots within the bone cells, with very little sign of the collagen net around them.

Collagen X is only produced at the ends of bones in the cartilage growth plate. This is where cartilage is turned into bone when bones are growing. In MCDS patients, ER stress hampers the growth of the bones as the cells in the growth plate stop changing – also known as differentiating – from cartilage to bone. This causes the characteristics of the condition: shortened limbs, bowed long bones, and flaring of the bone ends.

### CAN MCDS BE TREATED?

There is currently no licensed treatment for MCDS, and no active clinical trial. However, a potential repurposed treatment has been identified. Carbamazepine is a generic drug that lowers ER stress, and is approved for use in epilepsy. Based on its action on ER stress it was tested in a mouse model of MCDS, as well as in a cell system.

When MCDS mice are treated with carbamazepine, less collagen X is retained in the cells at the growth plate. This means that the growth plate becomes shorter as the bones grow at a normal rate. Physically the mice are much larger – only a little smaller than non-MCDS mice. Furthermore, their pelvises lack any distortion, providing further evidence that carbamazepine can have a therapeutic effect on MCDS.



#### WANT TO LEARN MORE?

Mullen et al. 2017 - Increased intracellular proteolysis reduces disease severity in an ER stress-associated dwarfism *The Journal of Clinical Investigation* 127: 3861–3865.

### WHAT IS MCDS-THERAPY?

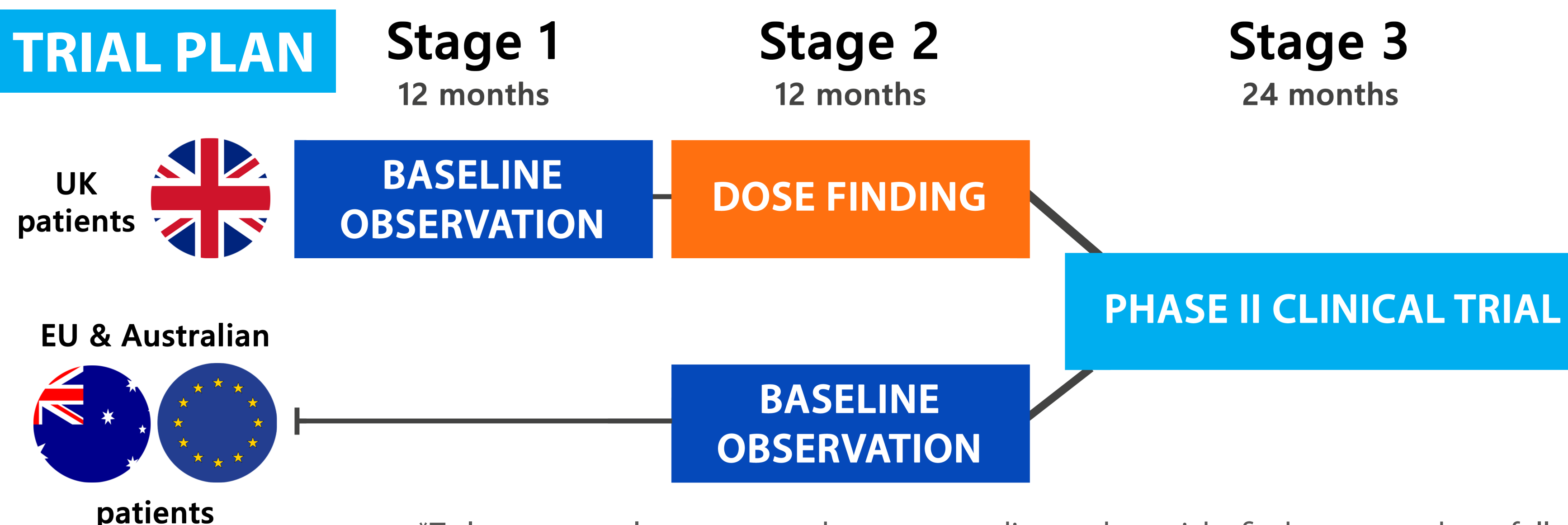
MCDS-Therapy is a scientist-led international collaboration of 11 organisations launched in December 2017, after receiving funding from the European Union Horizon 2020 scheme (EU/3/16/1746). Our objective is to deliver a worldwide, multicentre, phase 2a/2b clinical trial to repurpose carbamazepine for MCDS.

*The MCDS-Therapy team are working to alleviate the pain and bone malformations that patients with the rare genetic skeletal condition MCDS live with on a daily basis.*

We are working closely with patients to deliver the treatment and hope to help develop the global community of MCDS patients through our work. Ultimately, we plan to pioneer an academic drug repurposing pathway, capable of delivering a low-cost, transformative treatment for a rare patient population from bench to bedside, independent of the pharmaceutical industry.



### TRIAL PLAN



\*To learn more please contact the corresponding author - rick@findacure.org.uk - or follow our project online and on social media.

The phase 2a/2b trial will launch in 2018 using a before-after study design, as approved during EMA protocol assistance. The phase 2a component will be conducted in the UK while the phase 2b component will involve additional partner sites in the EU and Australia. We aim to enroll 40 patients in total, all of whom will receive carbamazepine. The basic trial plan is outlined in the figure. Final results are expected in late 2022.

MCDS-Therapy also includes projects to develop new MCDS biomarkers and to assess the health economics of the condition. By running these projects alongside the clinical trial we plan to deliver an innovative and affordable repurposed therapy for MCDS alongside both the tools to provide diagnosis and prognosis and a compelling argument for drug reimbursement around the EU.

[www.mcDs-therapy.eu](http://www.mcDs-therapy.eu)

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MCDS-Therapy Project has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement Number 754825

