COR2ED®

THE HEART OF MEDICAL EDUCATION

MEETING SUMMARY
ASBMR 2021, HYBRID MEETING

Dr. Kassim Javaid, MBBS, BMedSci, MRCP, PhD
Nuffield Centre of Orthopaedics, University of Oxford, Oxford, UK

Dr. Zulf Mughal, MB,ChB, FRCPCH
Hospital Manchester University NHS Foundation Trust, Manchester, UK

RARE BONE DISEASE HIGHLIGHTS FROM DAY 1

OCTOBER 2021

DISCLAIMER AND DISCLOSURES

COR2ED®
THE HEART OF MEDICAL EDUCATION

Please note: The views expressed within this presentation are the personal opinions of the authors and do not necessarily represent the views of the author's academic institution.

This content is supported by an independent educational grant from Ipsen, Kyowa Kirin and Ultragenyx.

Dr Kassim Javaid, MBBS, BMedSci, MRCP, PhD has received financial support/sponsorship for grants and consultation fees from the following companies:

- Kyowa Kirin

Dr Zulf Mughal, MB,ChB, FRCPCH has received financial support/sponsorship for grants, research support and honoraria from the following companies:

- Ipsen, Inozyme Pharma, Kyowa Kirin and Thornton & Ross

BUROSUMAB IMPROVES LOWER LIMB ALIGNMENT IN CHILDREN WITH XLH

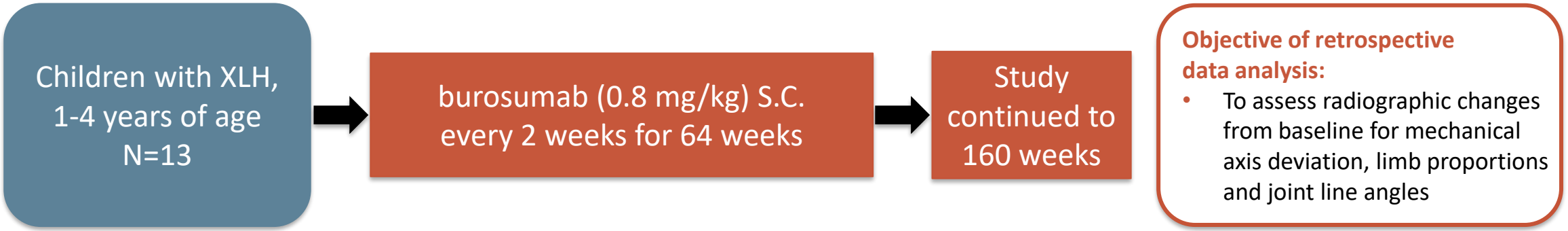
Frumberg D, et al. ASBMR 2021, Abstract #1020

XLH, X-linked hypophosphataemia

BACKGROUND AND STUDY DESIGN

COR2ED®
THE HEART OF MEDICAL EDUCATION

- **X-linked hypophosphataemia (XLH)** is an inherited disease of phosphate metabolism in which inactivating mutations of the *PHEX* gene lead to abnormalities including **impaired growth, rickets, osteomalacia, bone abnormalities, bone pain, spontaneous dental abscesses, hearing difficulties, enthesopathy, osteoarthritis, and muscular dysfunction**
- XLH patients present with **elevated levels of fibroblast growth factor 23 (FGF23)**, which is thought to mediate many of the abnormalities associated with the disease
- **Burosumab** is a recombinant fully human **monoclonal antibody against FGF23**
- Here we present a retrospective analysis of the phase 2 open-label trial (NCT02750618) of children ages 1-4 with XLH treated with burosumab



FGF23, fibroblast growth factor 23; PHEX, phosphate regulating endopeptidase homolog, X-linked; S.C., subcutaneous; XLH, X-linked hypophosphatemia

Beck-Nielsen S, et al. Orphanet J Rare Dis. 2019;14(1):58; Whyte M, et al. Lancet Diabetes Endocrinol. 2019;7(3):189-99; www.clinicaltrials.gov (NCT02750618): accessed 02-Oct-2021; https://cor2ed.com/podcast-rare-bone-disease-highlights-at-asbmr-2021/

KEY FINDINGS

COR2ED®
THE HEART OF MEDICAL EDUCATION

- Marked improvement in the alignment of the children's limbs, leaning towards correction of the normal mechanical axis
- Change from baseline to week 64:
  - Mechanical lateral distal femoral angle: −5°
  - Medial proximal tibial angle: 3.7°
  - Femoral tibial angle: −7.3°
- Improvements in alignment at week 64 continued at week 160
- Longitudinal growth was proportional with no significant change in ratio of tibia to femur length

Frumberg D, et al. ASBMR 2021, Abstract #1020; https://cor2ed.com/podcast-rare-bone-disease-highlights-at-asbmr-2021/

CLINICAL PERSPECTIVES

COR2ED®
THE HEART OF MEDICAL EDUCATION

FROM: DR. KASSIM JAVAID AND DR. ZULF MUGHAL

- Early treatment of toddlers and young children with XLH may:
  - Prevent the bone deformities developing
  - May lead to less need for surgery
  - May translate into less osteoarthritis in adulthood
- Study underlies the importance of early diagnosis and referral to specialist centres to maximise access to treatments
- Data reinforces the positioning of anti-FGF23 antibodies early in the treatment of XLH to reduce the incidence of lower limb deformities

FGF23, fibroblast growth factor 23; XLH, X-linked hypophosphataemia
https://cor2ed.com/podcast-rare-bone-disease-highlights-at-asbmr-2021/

THE EFFECTS OF ENCALERET ON MINERAL PHYSIOLOGY IN ADH1 DEMONSTRATE PROOF-OF-CONCEPT: EARLY RESULTS FROM AN ONGOING PHASE 2B, OPEN-LABEL, DOSE-RANGING STUDY

Gafni R, et al. ASBMR 2021, Abstract #1018

ADH1, autosomal dominant hypocalcaemia type 1

BACKGROUND AND STUDY DESIGN

COR2ED®
THE HEART OF MEDICAL EDUCATION

- **Autosomal dominant hypocalcaemia type 1** (ADH1) is a rare familial disorder characterised by **low serum calcium and low or inappropriately normal serum parathyroid hormone** (PTH). It is caused by activating *calcium sensing receptor* (*CaSR*) mutations, which produces a left-shift in the set point for extracellular calcium
- Treatment with activated **vitamin D analogues and calcium should be reserved for symptomatic patients**, due to the **risk of hypercalciuria and severe complications** such as nephrocalcinosis, nephrolithiasis and renal impairment
- **Encaleret** is an investigational small molecule **antagonist of CaSR** being studied as a potential treatment for ADH1
- Early results of an ongoing open-label, phase 2b, dose ranging study are reported

ADH1, autosomal dominant hypocalcaemia type 1; CaSR, calcium sensing receptor; PTH, parathyroid hormone

Kwan B, et al. Endocrinol Diabetes Metab Case Rep. 2018:18-0107; www.clinicaltrials.gov (NCT04581629): accessed 02-Oct-2021; Gafni R, et al. ASBMR 2021, Abstract #1018; https://cor2ed.com/podcast-rare-bone-disease-highlights-at-asbmr-2021/

KEY FINDINGS

- 13 subjects with 9 different *CASR* variants were included in the study
- At the end of period one (n=6), treatment with encaleret resulted in:
  - Normalisation of blood and urine calcium excretion
    - 3 subjects the 24-hr urine calcium levels normalised
    - 3 subjects the urine calcium level was undetectable
  - Increases in PTH
- At the end of period two (n=13), treatment with encaleret twice daily normalised blood and urine calcium
- Treatment was well tolerated with no serious adverse events

PTH, parathyroid hormone

Gafni R, et al. ASBMR 2021, Abstract #1018; https://cor2ed.com/podcast-rare-bone-disease-highlights-at-asbmr-2021/

CLINICAL PERSPECTIVES

COR2ED®
THE HEART OF MEDICAL EDUCATION

FROM: DR. KASSIM JAVAID AND DR. ZULF MUGHAL

- Encaleret is a unique and physiological way of treating ADH1 which can restore normal calcium and avoid symptoms associated with hypercalcaemia, whilst not putting kidneys at risk
- If results are confirmed at the end of the trial, then this is an important advance in the treatment of ADH1

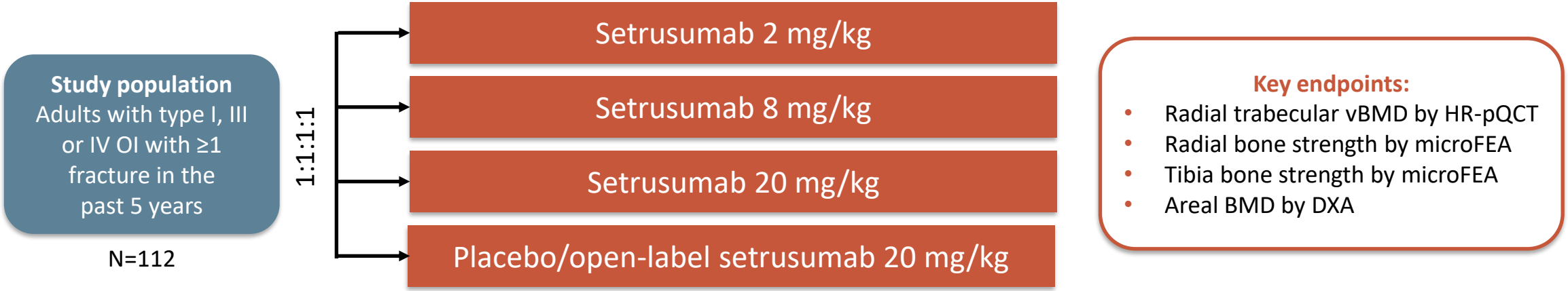
ADH1, autosomal dominant hypocalcaemia type 1
https://cor2ed.com/podcast-rare-bone-disease-highlights-at-asbmr-2021/

SETRUSUMAB FOR THE TREATMENT OF OSTEOGENESIS IMPERFECTA: RESULTS FROM THE PHASE 2B ASTEROID STUDY

Glorieux F, et al. ASBMR 2021, Abstract #1016

BACKGROUND AND STUDY DESIGN

- Osteogenesis imperfecta (OI) is a rare genetic disorder of connective tissues caused by an abnormality in the synthesis or processing of type I collagen. Also known as brittle bone disease, it is characterised by an increased susceptibility to bone fractures and decreased bone density
- Management of patients with OI currently involves medical treatment with bisphosphonates to inhibit bone resorption and facilitate bone formation
- Setrusumab is a fully human monoclonal antibody that inhibits sclerostin and alleviates the inhibitory effect of sclerostin on bone formation, leading to the production of new bone
- ASTEROID was a 12-month double-blind, phase 2b dose-finding study with a 12-month extension period



FEA, finite element analysis; HR-pQCT, high-resolution peripheral quantitative computed tomography; OI, osteogenesis imperfecta; (v)BMD, (volumetric) bone mineral density

Etich J, et al. Mol Cell Pediatr. 2020;7:9; Subramanian S, et al. https://www.ncbi.nlm.nih.gov/books/NBK536957/; www.clinicaltrials.gov (NCT03118570): accessed 02-Oct-2021; https://cor2ed.com/podcast-rare-bone-disease-highlights-at-asbmr-2021/

KEY FINDINGS

COR2ED®
THE HEART OF MEDICAL EDUCATION

- Primary endpoint was not met
  - setrusumab did not significantly improve radial trabecular vBMD by HR-pQCT
- Met co-primary endpoint:
  - setrusumab treatment resulted in statistically significant, dose-dependent, improvements in radial bone strength by microFEA
- Other endpoints:
- Dose-dependent increases in total vBMD as measured by HR-pQCT
  - Both radius and tibia total vBMD achieved statistical significance at the setrusumab 20 mg/kg dose
- Positive improvements in tibia bone strength by microFEA
  - Tibia stiffness significant at setrusumab 20 mg/kg dose
  - Tibia failure load, P=NS
- Dose-dependent increases by usual bone density measurements of DXA
  - Effect was seen not only in type I but also in the more severe (types III and IV) types of OI
- Fracture rates appeared to be lower at higher dose than lower dose but not statistically significant

DXA, dual-energy x-ray absorptiometry; FEA, finite element analysis; HR-pQCT, high-resolution peripheral quantitative computed tomography; NS, non-significant; OI, osteogenesis imperfecta; vBMD, volumetric bone mineral density

Glorieux F, et al. ASBMR 2021, Abstract #1016; https://cor2ed.com/podcast-rare-bone-disease-highlights-at-asbmr-2021/

CLINICAL PERSPECTIVES

COR2ED®
THE HEART OF MEDICAL EDUCATION

FROM: DR. KASSIM JAVAID AND DR. ZULF MUGHAL

- Encouraging results from the adult ASTEROID study
  - Result may have been different if alternative surrogate endpoints were chosen
- Surrogate endpoint studies are useful but a fracture endpoint study in OI would add great value to the field of research
- It would also be interesting to look at the effects of setrusumab in children
  - In OI more fractures occur pre-puberty, after puberty the number of fracture tends to reduce

OI, osteogenesis imperfecta
https://cor2ed.com/podcast-rare-bone-disease-highlights-at-asbmr-2021/

TARGETING TRANSFORMING GROWTH FACTOR-B FOR TREATMENT OF OSTEOGENESIS IMPERFECTA

Nagamani S, et al. ASBMR 2021, Abstract #1017

BACKGROUND AND STUDY DESIGN

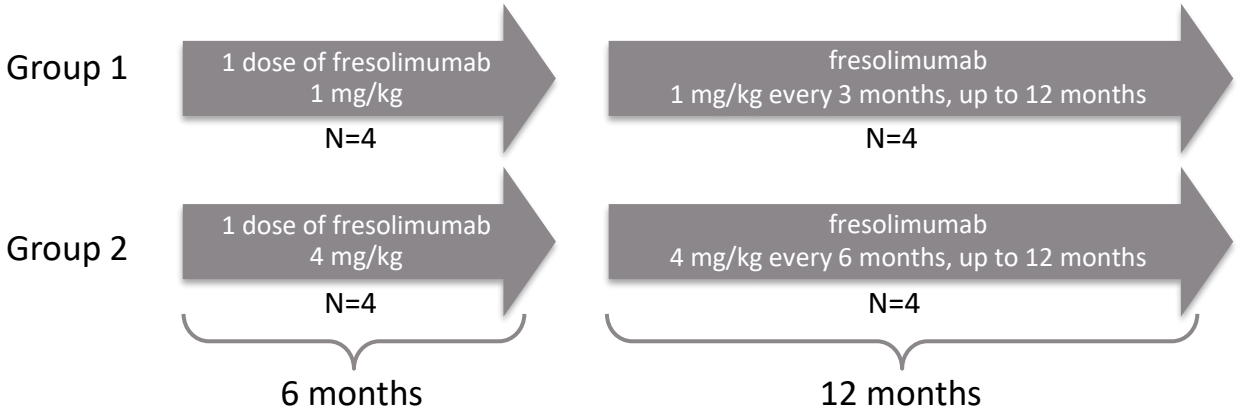
- TGF-β is a protein important in bone formation
- In studies with mice with OI, it has been shown that silencing TGF-β can lead to higher bone mass, quality and strength
- Fresolimumab is a pan–anti-TGF-β antibody

Part 1
Evaluated whether increased TGF-β signalling is observed in bones from children with OI

Bone samples from children:
N=10 with OI
N=4 without OI

Assessed signalling abnormalities using a multi-omic approach

Part 2
Phase 1 clinical trial of TGF-β inhibition through treatment with fresolimumab in patients with OI



OI, osteogenesis imperfecta; TGF, tumour growth factor

Nagamani S, et al. ASBMR 2021, Abstract #1017; www.clinicaltrials.gov (NCT03064074): accessed 02-Oct-2021; https://cor2ed.com/podcast-rare-bone-disease-highlights-at-asbmr-2021/

KEY FINDINGS

- Pre-clinical and human data suggest that inhibiting TGF-β may be beneficial in OI
- In the phase 1 study:
  - Fresolimumab was well tolerated in adults with OI
  - Higher dose of fresolimumab was associated with a decrease in bone turnover
  - Fresolimumab increased LS areal BMD in moderate but not severe OI

BMD, bone mineral density; OI, osteogenesis imperfecta; TGF, tumour growth factor

Nagamani S, et al. ASBMR 2021, Abstract #1017; https://cor2ed.com/podcast-rare-bone-disease-highlights-at-asbmr-2021/

CLINICAL PERSPECTIVES

COR2ED®
THE HEART OF MEDICAL EDUCATION

FROM: DR. KASSIM JAVAID AND DR. ZULF MUGHAL

- Very early stage investigations but promising pre-clinical and in-vitro data
- Potentially an important way of targeting the pathway involved in bone mass and fracture risk in OI
- Warrants further investigation
- Limitations: very small numbers of patients studied at this stage

OI, osteogenesis imperfecta
https://cor2ed.com/podcast-rare-bone-disease-highlights-at-asbmr-2021/

NEUROLOGICAL AND PSYCHIATRIC MANIFESTATIONS OF X-LINKED HYPOPHOSPHATEMIA IN A LONGITUDINAL COHORT STUDY: XLH DISEASE MONITORING PROGRAM (XLH-DMP)

Jan de Beur S, et al. ASBMR 2021, Abstract #1019

BACKGROUND AND STUDY DESIGN

COR2ED®
THE HEART OF MEDICAL EDUCATION

- **X-linked hypophosphataemia** (XLH) is the prototypic **disorder of renal phosphate wasting**, and the **most common form of heritable rickets**
  - Dental abscesses, arthritis, and calcification of tendons and ligaments (enthesopathy) often develop in later life
- **XLH-DMP** is a global, prospective, multicenter, **longitudinal, long-term outcomes program** for subjects on or off any treatment
  - Aims are to characterise XLH disease presentation and progression
    - assess long-term safety and effectiveness of burosumab
    - investigate change over time across biomarker(s), clinical assessments, and patient/caregiver-reported outcome measures
- This analysis **reports neurological and psychological symptoms** in this population

Patients of any age with XLH who are either on or off treatment currently

Data collection started 27 June 2018
Data cut-off* for this analysis 01 March 2021
(*N=651)

35 study locations globally

Data collected through patient/caregiver interviews

XLH, X-linked hypophosphatemia

Carpenter T, et al. J Bone Miner Res. 2011;26:1381-8; www.clinicaltrials.gov (NCT03651505): accessed 02-Oct-2021; Jan de Beur S, et al. ASBMR 2021, Abstract #1019; https://cor2ed.com/podcast-rare-bone-disease-highlights-at-asbmr-2021/

KEY FINDINGS

COR2ED®
THE HEART OF MEDICAL EDUCATION

- Psychological burden of XLH disease increases in adolescents and adulthood
  - Higher prevalence of depression (14.8% vs 0.7%) and anxiety (12.1% vs 4.5%) in adults with XLH than in children
- Frequent use of pain medication in adults with XLH (68.7% of adults vs 30.3% of children)
- Severe headaches commonly reported (19.8% adults vs 6.3% children)
- Other commonly reported problems by adults:
  - Tinnitus (34.6%)
  - Hearing loss (29.1%)
  - Spinal stenosis (18.4%)
  - Spinal compression (10.2%)

Jan de Beur S, et al. ASBMR 2021, Abstract #1019; https://cor2ed.com/podcast-rare-bone-disease-highlights-at-asbmr-2021/

CLINICAL PERSPECTIVES

COR2ED®
THE HEART OF MEDICAL EDUCATION

FROM: DR. KASSIM JAVAID AND DR. ZULF MUGHAL

- Headache must be taken serious in XLH patients – could be an indicator for craniosynostosis or Chiari type 1 malformation
- XLH patients are currently not systematically screened for these neurological complications
  - should we be now be doing CT/MRI if they have neuro/psychiatry problems?
- Highlights the value of routine assessment for neurological features and not just musculoskeletal evaluations

CT, computed tomography; MRI, magnetic resonance imaging; XLH, X-linked hypophosphataemia
https://cor2ed.com/podcast-rare-bone-disease-highlights-at-asbmr-2021/

COR2ED®

THE HEART OF MEDICAL EDUCATION

MEETING SUMMARY
ASBMR 2021, HYBRID MEETING

Professor Dr. Oliver Semler, MD
Children´s Hospital, Department of Rare Skeletal Diseases in Childhood
University Hospital Cologne, Germany

RARE BONE DISEASE HIGHLIGHTS FROM DAY 2

OCTOBER 2021

DISCLAIMER AND DISCLOSURES

COR2ED®
THE HEART OF MEDICAL EDUCATION

Please note: The views expressed within this presentation are the personal opinions of the authors and do not necessarily represent the views of the author's academic institution.

This content is supported by an independent educational grant from Ipsen, Kyowa Kirin and Ultragenyx.

Professor Dr Oliver Semler, MD has no disclosures to declare.

ENPP1

ENPP1: BACKGROUND

COR2ED®
THE HEART OF MEDICAL EDUCATION

- Ectonucleotide pyrophosphatase/phosphodiesterase 1 **(ENPP1)** is a membrane-bound glycoprotein that **regulates bone mineralisation** by hydrolysing extracellular nucleotide triphosphates to produce pyrophosphate

- **ENPP1-deficiency results in either lethal arterial calcifications** (Generalised Arterial Calcification of Infancy, GACI), **phosphate wasting rickets, early onset osteoporosis, or progressive spinal rigidity** and a **50% lethality during infancy**
- Patients with moderate phenotypes can present with **rickets-like appearance on x-rays**

ENPP1, ectonucleotide pyrophosphatase/phosphodiesterase 1

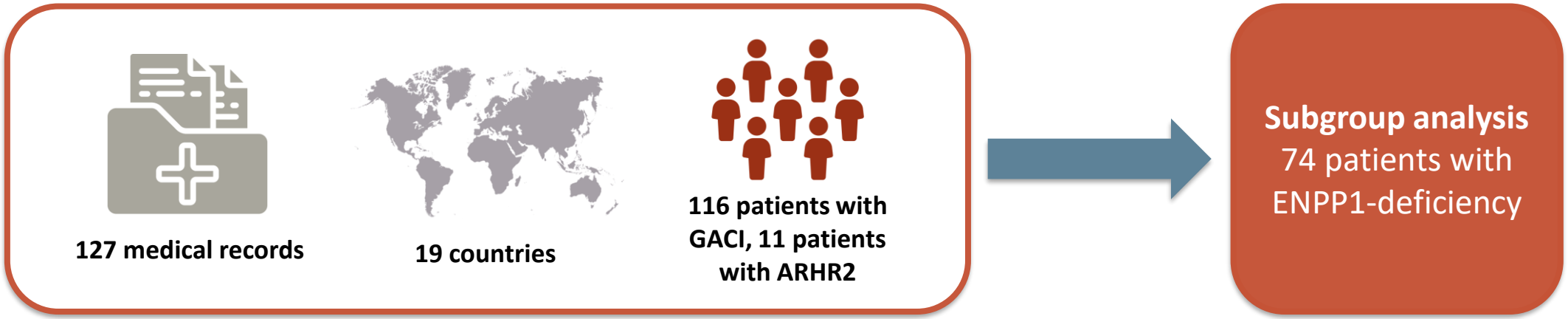
Kato K, et al. Proc Natl Acad Sci USA. 2012;109:16876-81 ; Maulding N, et al. Bone 2021;142:115656; Ferreira C, et al. J Bone Miner Res. 2021. DOI: 10.1002/jbmr.4418; Rutsch F. ASBMR 2021, Abstract #FRI-265 and O'Brien K, et al. ASBMR 2021, Abstract #1037; https://cor2ed.com/podcast-rare-bone-disease-highlights-at-asbmr-2021/

ENPP1-DEFICIENT PATIENTS PRESENT WITH BOTH SKELETAL COMPLICATIONS AND ECTOPIC CALCIFICATION

COR2ED®
THE HEART OF MEDICAL EDUCATION

STUDY DESIGN

- Here we report a cross-sectional, **retrospective study of patients with ENPP1-deficiency**, characterising the prevalence and onset of skeletal complications to accelerate diagnosis and management



ARHR2, autosomal recessive hypophosphataemic rickets type 2; ENPP1, ectonucleotide pyrophosphatase/phosphodiesterase 1; GACI, generalised arterial calcification of infancy

Rutsch F, et al. ASBMR 2021, Abstract #FRI-265; https://cor2ed.com/podcast-rare-bone-disease-highlights-at-asbmr-2021/

ENPP1-DEFICIENT PATIENTS PRESENT WITH BOTH SKELETAL COMPLICATIONS AND ECTOPIC CALCIFICATION

COR2ED®
THE HEART OF MEDICAL EDUCATION

KEY FINDINGS

- 46% presented with findings suggestive of rickets or osteomalacia (ie. altered gait, bowed extremities, metaphyseal cupping or short stature)
  - 25% of patients with skeletal complications did not have a diagnosis of GACI
- Rickets may be the first presentation for these patients and a diagnosis of ENPP1-deficiency should still be considered even if no prior history of calcification or GACI
- Currently the treatment of choice in the patients is an enzyme replacement therapy which prevents calcification of the vessels and may partially restore the skeletal phenotype but this has to be given twice a week
- Gene therapy being explored as a therapeutic option
- ENPP1 Deficiency should be considered as differential diagnosis in cases of rickets-like symptoms without alterations of vitamin D or phosphate levels

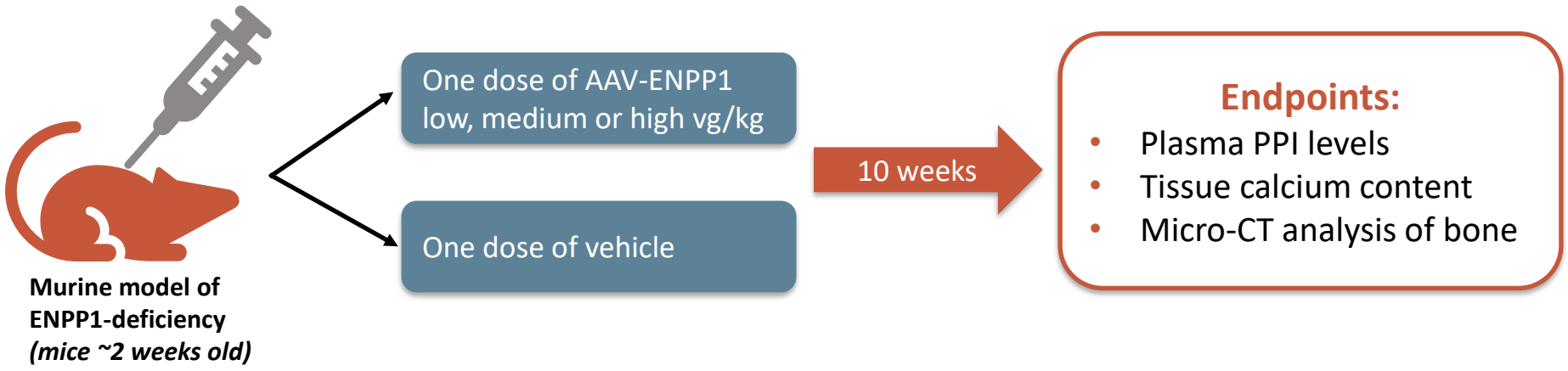
ENPP1, ectonucleotide pyrophosphatase/phosphodiesterase 1; GACI, generalised arterial calcification of infancy
Rutsch F, et al. ASBMR 2021, Abstract #FRI-265; https://cor2ed.com/podcast-rare-bone-disease-highlights-at-asbmr-2021/

TREATMENT WITH AN AAV VECTOR EXPRESSING ENPP1-FC PREVENTS ECTOPIC TISSUE CALCIFICATION AND RESTORES BONE PARAMETERS IN ENPP1 DEFICIENT MICE

COR2ED®
THE HEART OF MEDICAL EDUCATION

STUDY DESIGN

- An adeno-virus vector was developed expressing a modified human ENPP1-Fc as a potential treatment for ENPP1-deficiency, AAV-ENPP1
- The aim of this research was to develop a one-dose gene therapy to treat ENPP1-deficiency



AAV, adeno-virus vector; CT, computed tomography; ENPP1, ectonucleotide pyrophosphatase/phosphodiesterase 1; PPI, inorganic pyrophosphate; vg, vector genomes
O'Brien K, et al. ASBMR 2021, Abstract #1037; https://cor2ed.com/podcast-rare-bone-disease-highlights-at-asbmr-2021/

TREATMENT WITH AN AAV VECTOR EXPRESSING ENPP1-FC PREVENTS ECTOPIC TISSUE CALCIFICATION AND RESTORES BONE PARAMETERS IN ENPP1 DEFICIENT MICE

COR2ED®
THE HEART OF MEDICAL EDUCATION

KEY FINDINGS

- Positive response to correct ENPP1-deficiency with this viral treatment
- After administration of a single dose of AAV-ENPP1 there was:
  - An increase in PPI levels
  - Decreased tissue calcification and improved mineralisation of the bones
  - An improved rickets-like phenotype
- Next steps would be to determine the lowest effective dose and conduct a safety assessment followed by clinical trials

ENPP1, ectonucleotide pyrophosphatase/phosphodiesterase 1; PPI, inorganic pyrophosphate
O'Brien K, et al. ASBMR 2021, Abstract #1037; https://cor2ed.com/podcast-rare-bone-disease-highlights-at-asbmr-2021/

ENPP1: CLINICAL PERSPECTIVES

COR2ED®
THE HEART OF MEDICAL EDUCATION

FROM: DR. SEMLER

- Normally a rickets-like X-ray is only conducted due to bowing of long bones or in cases of impaired bone mineralisation defects (vitamin D deficiency or phosphate wasting).
- X-rays of metaphyseal areas need to be taken also in cases of ectopic calcification
- Data presented at ASBMR show that ENPP1 has to be considered as a differential diagnosis for a rickets-like X-ray to distinguish between ENPP1-deficiency rickets and other hypophosphataemic rickets
- Genetic testing for *ENPP1*-deficiency should therefore be used as a routine part of clinical practice in the future in the workup of unclear rickets.

ENPP1, Ectonucleotide pyrophosphatase/phosphodiesterase 1
https://cor2ed.com/podcast-rare-bone-disease-highlights-at-asbmr-2021/

FIBRODYSPLASIA OSSIFICANS PROGRESSIVA (FOP)

FOP: BACKGROUND

COR2ED®
THE HEART OF MEDICAL EDUCATION

- **Fibrodysplasia ossificans progressiva** (FOP) is **a rare and disabling autosomal dominant disease** involving extraskeletal bone formation
- **Characterised by congenital deformity of the great toes** and progressive heterotopic ossification
- **Heterotopic ossifications occur after painful inflammatory flare-ups** that can arise spontaneously or can be triggered by minor trauma. Each flare-up ultimately causes restriction of related-joints, and along with the others eventually leads to immobility
- The **causative gene of FOP is *activin A receptor type 1* (*ACVR1*)**, a bone morphogenetic protein-signaling component, which normally acts to inhibit osteoblastogenesis
- **Currently, there are no curative interventions**, and the mainstay of treatment is focused on symptomatic relief using brief courses of high-dose corticosteroids for flare-ups

ACVR1, activin A receptor type 1 ; FOP, fibrodysplasia ossificans progressiva

Kaplan F, et al. Bone 2020; 140:115539; Akyuz G, et al. Curr. Opin. Pediatr 2019;31:716-22; Pignolo R, et al. Front Endocrinol (Lausanne). 2020;10:908; https://cor2ed.com/podcast-rare-bone-disease-highlights-at-asbmr-2021/

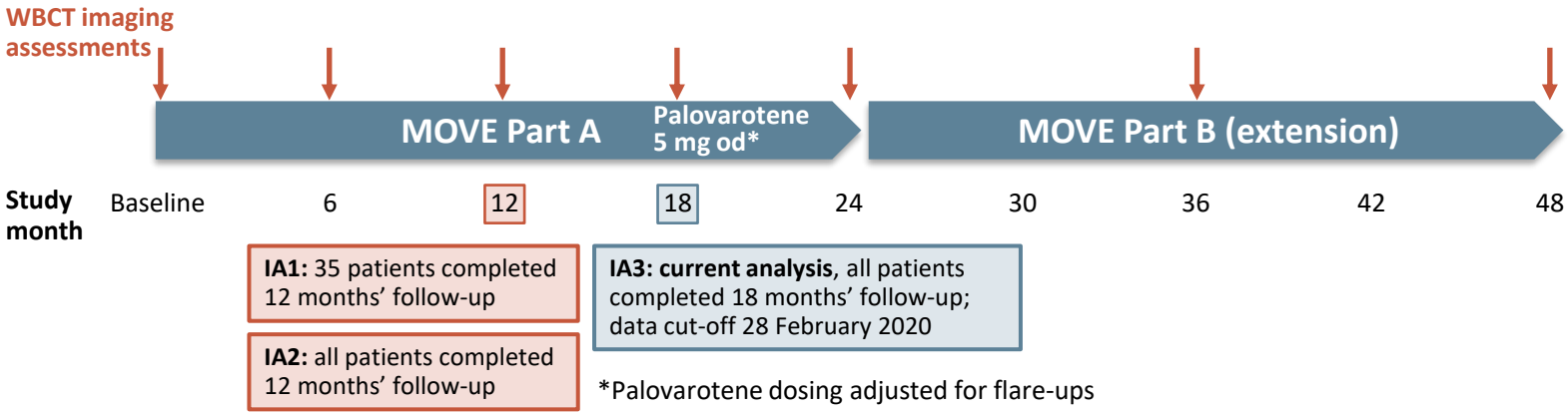
PALOVAROTENE FOR THE TREATMENT OF FOP IN FEMALES AGED ≥8 AND MALES ≥10 YEARS: DATA FROM THE PHASE 3 MOVE TRIAL

COR2ED®
THE HEART OF MEDICAL EDUCATION

STUDY DESIGN

- Palovarotene is retinoic acid receptor gamma (RARγ) agonist
- MOVE trial (NCT03312634) – an efficacy and safety study of palovarotene for the treatment of FOP
  - Compared data from the MOVE trial with data from the Natural History Study (NHS; NCT02322255)
  - Data presented for females ≥8 years and males ≥10 years of age

Study population:
FOP pts ≥4 years of age with R206H ACVR1 mutation or other FOP associated with progressive HO



Endpoint:
Change in new HO volume assessed by low-dose WBCT

ACVR1, activin A receptor type 1; FOP, fibrodysplasia ossificans progressive; HO, heterotopic ossifications; IA, interim analysis; od, once daily; RARγ, retinoic acid receptor gamma; WBCT, whole body computed tomography

Pignolo R, et al. ASBMR 2021, Abstract #FRI-264; www.clinicaltrials.gov (NCT03312634); https://cor2ed.com/podcast-rare-bone-disease-highlights-at-asbmr-2021/

PALOVAROTENE FOR THE TREATMENT OF FOP IN FEMALES AGED ≥8 AND MALES ≥10 YEARS: DATA FROM THE PHASE 3 MOVE TRIAL

COR2ED®
THE HEART OF MEDICAL EDUCATION

KEY FINDINGS

- 79 patients aged ≥8/10 years of age with a documented ACVR R206H mutation were enrolled in MOVE
- 88 subjects aged ≥8/10 years of age were treated in the NHS
- Mean annualised new HO volume was 57% lower in treated group after 18-month treatment period (consistent with the results from the overall MOVE population) versus the NHS
- The most common TEAEs were mucocutaneous events associated with retinoic acid
- Mucocutaneous treatment-emergent side effects were reported most commonly in the MOVE trial
- Premature physeal closure occurred in a number of patients (led to temporary hold of trial). Treatment is therefore limited until after closure of growth plates

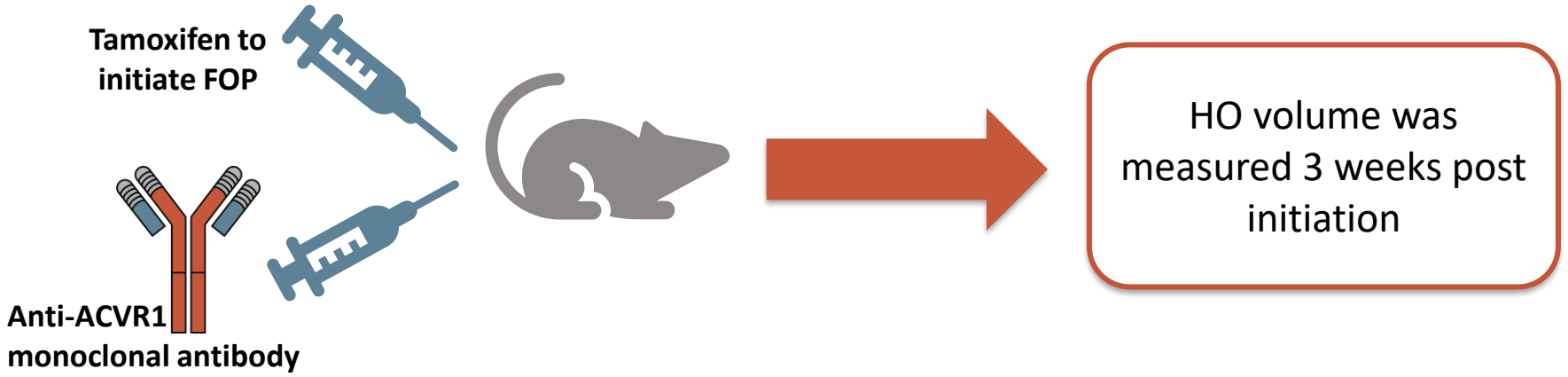
ACVR, activin A receptor; FOP, fibrodysplasia ossificans progressive; HO, heterotopic ossifications; NHS, natural history study
Pignolo R, et al. ASBMR 2021, Abstract #FRI-264; https://cor2ed.com/podcast-rare-bone-disease-highlights-at-asbmr-2021/

ACVR1 ANTIBODIES EXACERBATE HETEROTOPIC OSSIFICATION IN FOP

COR2ED®
THE HEART OF MEDICAL EDUCATION

STUDY DESIGN

- Previous results showed that HO in FOP is dependent on activation of FOP-mutant ACVR1 by a ligand, activin A
- The dependence on induction by activin A ligand suggested that inhibition of ligand-ACVR1 interaction using ACVR1 antibodies should have the same effect as inhibition of activin A
- It was hypothesised that a human antibody to activin A may be a potential therapeutic approach for FOP



ACVR1, activin A receptor type 1; CT, computed tomography; FOP, fibrodysplasia ossificans progressive; HO, heterotopic ossifications

ACVR1 ANTIBODIES EXACERBATE HETEROTOPIC OSSIFICATION IN FOP

COR2ED®
THE HEART OF MEDICAL EDUCATION

KEY FINDINGS

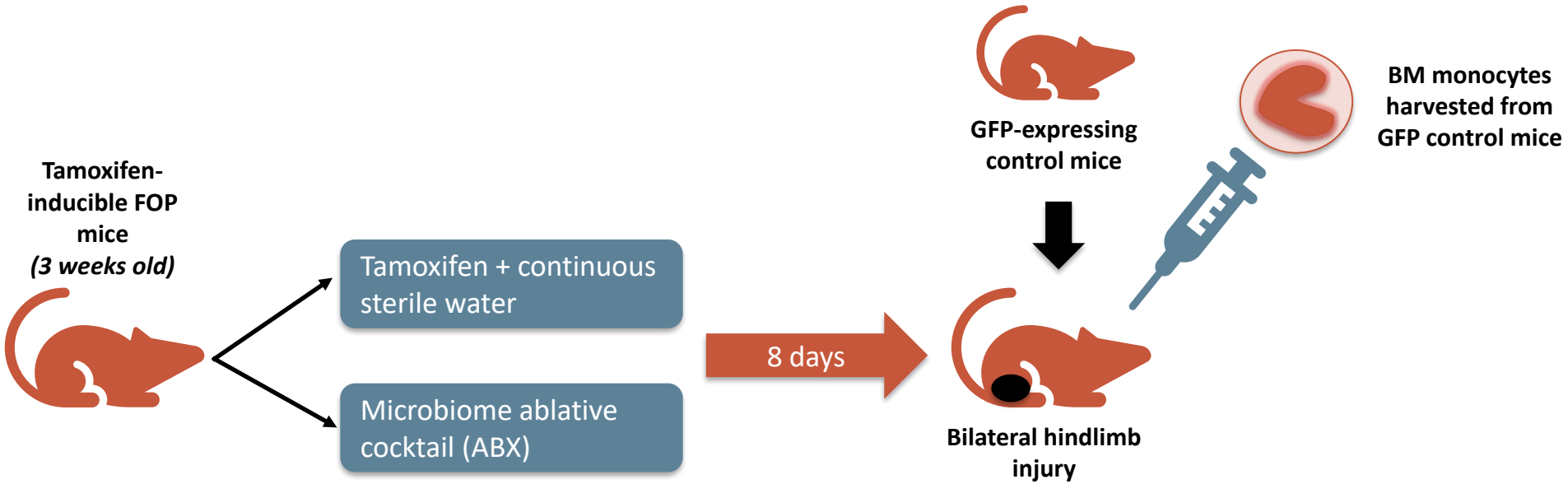
- **Increase** of HO in the FOP mouse model
  - ACVR1 antibodies exacerbated HO in FOP
  - Therefore ACVR1 antibodies are definitely **not** a therapeutic option for FOP patients

ACVR1, activin A receptor type 1; FOP, fibrodysplasia ossificans progressive; HO, heterotopic ossifications
Wang L, et al. ASBMR 2021, Abstract #1038; https://cor2ed.com/podcast-rare-bone-disease-highlights-at-asbmr-2021/

THE MICROBIOME CONTRIBUTES TO ENDOCHONDRAL HETEROTYPIC OSSIFICATION IN FOP MICE BY REGULATING INNATE IMMUNE CELL RECRUITMENT AND POLARISATION

STUDY DESIGN

- Inflammation and innate immune cells contribute to FOP flares and HO
  - Inflammatory environmental factors could therefore contribute to disease variability in FOP patients
- Aim of this study was to reduce the HO formation by reducing the inflammatory activities in the mice and to determine whether ABX reduction in HO is mediated by changes in monocytes



ABX, ablative antibiotic cocktail; BM, bone marrow; FOP, fibrodysplasia ossificans progressive; GFP, green fluorescent protein; HO, heterotopic ossifications

Pierce J, et al. ASBMR 2021, Abstract #1039; https://cor2ed.com/podcast-rare-bone-disease-highlights-at-asbmr-2021/

THE MICROBIOME CONTRIBUTES TO ENDOCHONDRAL HETEROTYPIC OSSIFICATION IN FOP MICE BY REGULATING INNATE IMMUNE CELL RECRUITMENT AND POLARISATION

COR2ED®
THE HEART OF MEDICAL EDUCATION

KEY FINDINGS

- Microbiome-ablative ABX reduced HO in ABX-treated FOP mice
- Treatment decreased the expression of proinflammatory chemokines and receptors in injured FOP muscles
- Transplanting BM monocytes from control mice restored the HO phenotype in ABX-treated FOP mice
- Reducing the inflammatory process in FOP mice seems to have a beneficial therapeutic effect on HO formation

ABX, ablative antibiotic cocktail; BM, bone marrow; FOP, fibrodysplasia ossificans progressive; HO, heterotopic ossifications
Pierce J, et al. ASBMR 2021, Abstract #1039; https://cor2ed.com/podcast-rare-bone-disease-highlights-at-asbmr-2021/

FOP: CLINICAL PERSPECTIVES

COR2ED®
THE HEART OF MEDICAL EDUCATION

FROM: DR. SEMLER

- A lot of activity and good ideas presented at ASBMR as to how to improve the care of FOP patients
- Some approaches have been shown to be more beneficial than others, e.g. palovarotene is one of the most developed and best approaches
- Other ways to influence the signalling pathway in the cell need to be further investigated. Initial results suggest regulating inflammation may be beneficial
- Very pleased that there is so much research ongoing in the rare bone disease area which is new
- Many studies in the pre-clinical stage that have promising data
- There is hope that a better treatment can be offered to these patients in the future

FOP, fibrodysplasia ossificans progressive
https://cor2ed.com/podcast-rare-bone-disease-highlights-at-asbmr-2021/

MEETING SUMMARY
ASBMR 2021, HYBRID MEETING

Dr. Eric Rush, MD, FAAP, FACMG, CCD

Children's Mercy, Kansas City, MO, USA

Assoc. Prof. Marelise Eekhoff, MD

Amsterdam University Medical Centers, Vumc, The Netherlands

ROUND UP OF RARE BONE DISEASE HIGHLIGHTS

OCTOBER 2021

DISCLAIMER AND DISCLOSURES

COR2ED®
THE HEART OF MEDICAL EDUCATION

Please note: The views expressed within this presentation are the personal opinions of the authors and do not necessarily represent the views of the author's academic institution.

This content is supported by an independent educational grant from Ipsen, Kyowa Kirin and Ultragenyx.

Dr Eric Rush, MD has received financial support/sponsorship for grants and research support, consultation fees and honoraria from the following companies:

- Alexion, Ascendis, Biomarin, Inozyme, Ultragenyx

Dr Marelise Eekhoff, MD, PhD has received financial support/sponsorship for grants and research support, consultation fees and honoraria on the research budget at Amsterdam UMC:

- Regeneron, EU IMI/ AZ, IFOPA, Ipsen, Telethon

THE PATIENT CLINICAL JOURNEY AND SOCIOECONOMIC IMPACT OF OSTEOGENESIS IMPERFECTA: A SYSTEMATIC REVIEW

Rauch F, et al. ASBMR 2021, Abstract #SUN-280

BACKGROUND AND STUDY DESIGN

- **Osteogenesis imperfecta (OI) is a rare genetic disorder of connective tissues** caused by an abnormality in the synthesis or processing of type I collagen. Also known as brittle bone disease, it is **characterised by an increased susceptibility to bone fractures and decreased bone density**
- **A review of OI-related publications from Jan 1995-Dec 2020 was conducted.** The aim of the review was to identify and quantify published literature related to clinical, humanistic, economic impact of OI on patients, families and society

9 databases:
MEDLINE
EMBASE
CENTRAL
PsycINFO
NHS EED
CEA Registry
PEDE
ScHARRHUd
Orphanet

Grey literature

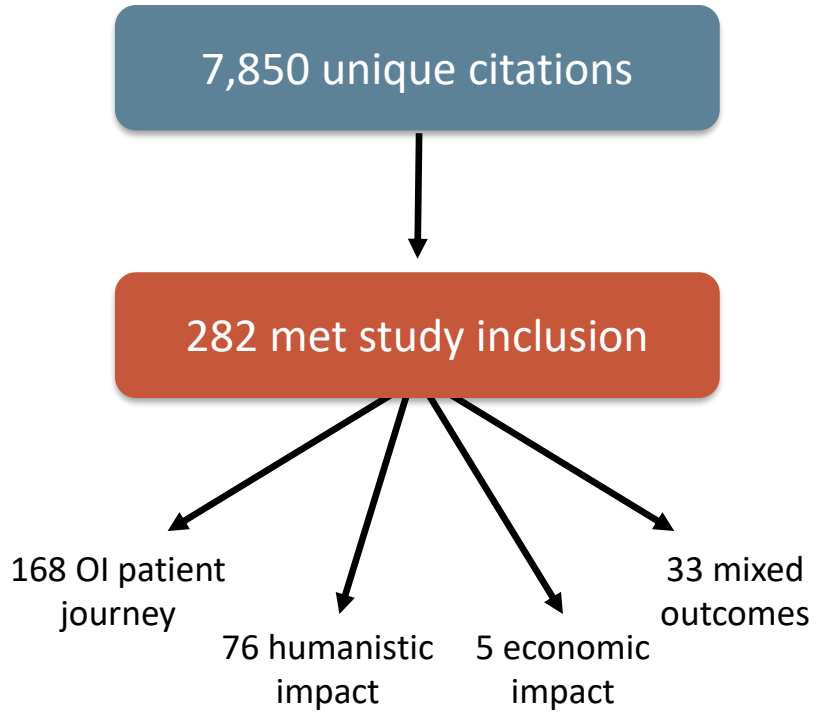
January 1995-December 2020

Studies included reported on the following for OI:
- Clinical events and conditions
- OI healthcare
- HRQoL
- Direct and indirect costs
- Healthcare resource use

HRQoL, health-related quality of life; OI, osteogenesis imperfecta

Etich J, et al. Mol Cell Pediatr. 2020;7:9; Subramanian S, et al. StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2021. https://www.ncbi.nlm.nih.gov/books/NBK536957/; Rauch F, et al. ASBMR 2021, Abstract #SUN-280; https://cor2ed.com/podcast-rare-bone-disease-highlights-at-asbmr-2021/

KEY FINDINGS



- Significant data gaps identified
- Few studies reported on:
  - Standard of OI care
  - Diagnosis and monitoring
  - Interactions with the healthcare system
  - Transition of care from child to adult services
  - The social and economic impact of OI on patients and caregivers
- Further research required to capture and quantity the full impact of OI

OI, osteogenesis imperfecta

Rauch F, et al. ASBMR 2021, Abstract #SUN-280; https://cor2ed.com/podcast-rare-bone-disease-highlights-at-asbmr-2021/

CLINICAL PERSPECTIVES

COR2ED®
THE HEART OF MEDICAL EDUCATION

FROM: DR. ERIC RUSH

- Interesting data focussing on the patient journey and humanistic and economic impacts of OI
- This area is not explored as often as it should be given the pressures that patients and caregivers endure in medical and non-medical aspects of their lives
- There is a lack of clinical guidelines which incorporate a lot of these elements
- The study found a lot of different guidance with limitations and gaps in literature as to how to care for these patients. Also focused on Northern European and US publications so data from other areas of the world is lacking
- Reflects what we see in clinical practice in the US as payors vary significantly and this impacts the way they receive care

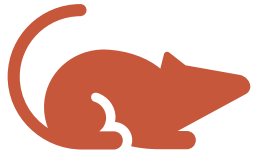
OI, osteogenesis imperfecta
Rauch F, et al. ASBMR 2021, Abstract #SUN-280; https://cor2ed.com/podcast-rare-bone-disease-highlights-at-asbmr-2021/

OSTEOGENESIS IMPERFECTA CAUSES INTRINSIC RESPIRATORY SYSTEM CHANGES: A STUDY IN MOUSE MODELS OF OI

Morello R, et al. ASBMR 2021, Abstract #FRI-284

BACKGROUND AND STUDY DESIGN

- **Osteogenesis imperfecta (OI) is a rare genetic disorder of connective tissues** caused by an abnormality in the synthesis or processing of type I collagen. Also known as brittle bone disease, it is **characterised by an increased susceptibility to bone fractures and decreased bone density**
- **OI is generally caused by dominant mutations in *COL1A1* and *COL1A2* genes**, encoding the a1 and a2 chain of type I collagen
- **OI is a systemic disease** with skeletal and extraskeletal manifestations **that affect many organ systems, including the lungs**, due to type I collagen being expressed in most tissues
- This study sought to understand the effects of type 1 collagen alterations on respiratory function



OI mouse model	Affected gene	Type of mutation	Clinical OI type (I-V) modelled
*Crtap*KO	*Crtap*	Loss of function-recessive	Moderate to severe (III/IV)
Col1A2$^{+/G610C}$ (Amish)	*Col1A2*	Gly substitution-dominant	Mild to moderate (I/IV)
Oim/oim	*Col1A2*	C-propeptide frameshift-semi-dominant	Severe (III)

Histological and invasive studies of respiratory mechanics, using the forced oscillation technique were used

COL1A1, collagen type I alpha 1 chain; COL1A2, collagen type I alpha 2 chain; *Crtap*KO, cartilage-associated protein knockout; Gly, glycine; OI, osteogenesis imperfecta
Etich J, et al. Mol Cell Pediatr. 2020;7:9; Subramanian S, et al. Subramanian S, et al. StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2021. https://www.ncbi.nlm.nih.gov/books/NBK536957/; Morello R, et al. ASBMR 2021, Abstract #FRI-284 (Poster presentation); https://cor2ed.com/podcast-rare-bone-disease-

KEY FINDINGS

COR2ED®
THE HEART OF MEDICAL EDUCATION

- Pulmonary histology showed alveolar simplification and enlarged acinar airspace indicating defective alveolarization
- Found changes in the respiratory system resistance, including reduced compliance and increased elastance in *Crtap*KO and oim/oim mice indicating increased lung/thoracic cage rigidity
  - these defects are found in *Crtap*KO and oim/oim but not in $Col1A2^{+/G610C}$, suggesting that that the impact of OI on lung function positively correlates with the severity of the skeletal phenotype
- Results suggested that OI not only causes brittle bones but also primary lung defects and altered respiratory mechanics. Further investigation required

OI, osteogenesis imperfecta
Morello R, et al. ASBMR 2021, Abstract #FRI-284; https://cor2ed.com/podcast-rare-bone-disease-highlights-at-asbmr-2021/

CLINICAL PERSPECTIVES

COR2ED®
THE HEART OF MEDICAL EDUCATION

FROM: DR. MARELISE EEKHOFF

- Really impressed by design as the group managed to carry out extensive lung function test in mice mimicking type III OI but also looked at lung tissues
- Sheds new light on previously identified lung function issues which were previously attributed to abnormalities of the chest wall
- Supports a review performed by Dr. Eekhoff's group which showed that lung function in OI patients can be explained in part by the chest wall but there is also an intrinsic alveolar factor involved. This is now being investigated further through histology

OI, osteogenesis imperfecta
Morello R, et al. ASBMR 2021, Abstract #FRI-284; https://cor2ed.com/podcast-rare-bone-disease-highlights-at-asbmr-2021/

NEUROLOGICAL AND PSYCHIATRIC MANIFESTATIONS OF X-LINKED HYPOPHOSPHATAEMIA IN A LONGITUDINAL COHORT STUDY: XLH DISEASE MONITORING PROGRAM (XLH-DMP)

Jan de Beur S, et al. ASBMR 2021, Abstract #1019

BACKGROUND AND STUDY DESIGN

COR2ED®
THE HEART OF MEDICAL EDUCATION

- **X-linked hypophosphataemia** (XLH) is the prototypic **disorder of renal phosphate wasting**, and the **most common form of heritable rickets**
  - Dental abscesses, arthritis, and calcification of tendons and ligaments (enthesopathy) often develop in later life
- **XLH-DMP** is a global, prospective, multicenter, **longitudinal, long-term outcomes program** for subjects on or off any treatment
  - Aims are to characterise XLH disease presentation and progression
    - assess long-term safety and effectiveness of burosumab
    - investigate change over time across biomarker(s), clinical assessments, and patient/caregiver-reported outcome measures
- This analysis **reports neurological and psychological symptoms** in this population

Patients of any age with XLH who are either on or off treatment currently

Data collection started 27 June 2018
Data cut-off* for this analysis 01 March 2021
(*N=651)

35 study locations globally

Data collected through patient/caregiver interviews

XLH, X-linked hypophosphataemia

Carpenter T, et al. J Bone Miner Res. 2011;26:1381-8; www.clinicaltrials.gov (NCT03651505): accessed 02-Oct-2021; Jan de Beur S, et al. ASBMR 2021, Abstract #1019; https://cor2ed.com/podcast-rare-bone-disease-highlights-at-asbmr-2021/

KEY FINDINGS

COR2ED®
THE HEART OF MEDICAL EDUCATION

- Psychological burden of XLH disease increases in adolescents and adulthood
  - Higher prevalence of depression (14.8% vs 0.7%), anxiety (12.1% vs 4.5%) and insomnia (7.7% vs 1.0%) in adults with XLH than in children
- Frequent use of pain medication in adults with XLH (68.7% of adults vs 30.3% of children)
- Severe headaches commonly reported (19.8% adults vs 6.3% children)
- Other commonly reported problems by adults:
  - Tinnitus (34.6%)
  - Hearing loss (29.1%)
  - Spinal stenosis (18.4%)
  - Spinal cord compression (10.2%)

XLH, X-linked hypophosphataemia
Jan de Beur S, et al. ASBMR 2021, Abstract #1019; https://cor2ed.com/podcast-rare-bone-disease-highlights-at-asbmr-2021/

CLINICAL PERSPECTIVES

COR2ED®
THE HEART OF MEDICAL EDUCATION

FROM: DR. ERIC RUSH

- Hadn’t appreciated that depression and anxiety are seen this much more in XLH patients than in the general public
- Significant rate of insomnia in these patients and this is of note especially given known risk for restless leg syndrome
- Information is actionable immediately in clinical practice. Screen more intentionally for headaches, depression, and anxiety going forward

XLH, X-linked hypophosphataemia
https://cor2ed.com/podcast-rare-bone-disease-highlights-at-asbmr-2021/

THE MICROBIOME CONTRIBUTES TO ENDOCHONDRAL HETEROTYPIC OSSIFICATION IN FOP MICE BY REGULATING INNATE IMMUNE CELL RECRUITMENT AND POLARISATION

Pierce J, et al. ASBMR 2021, Abstract #1039

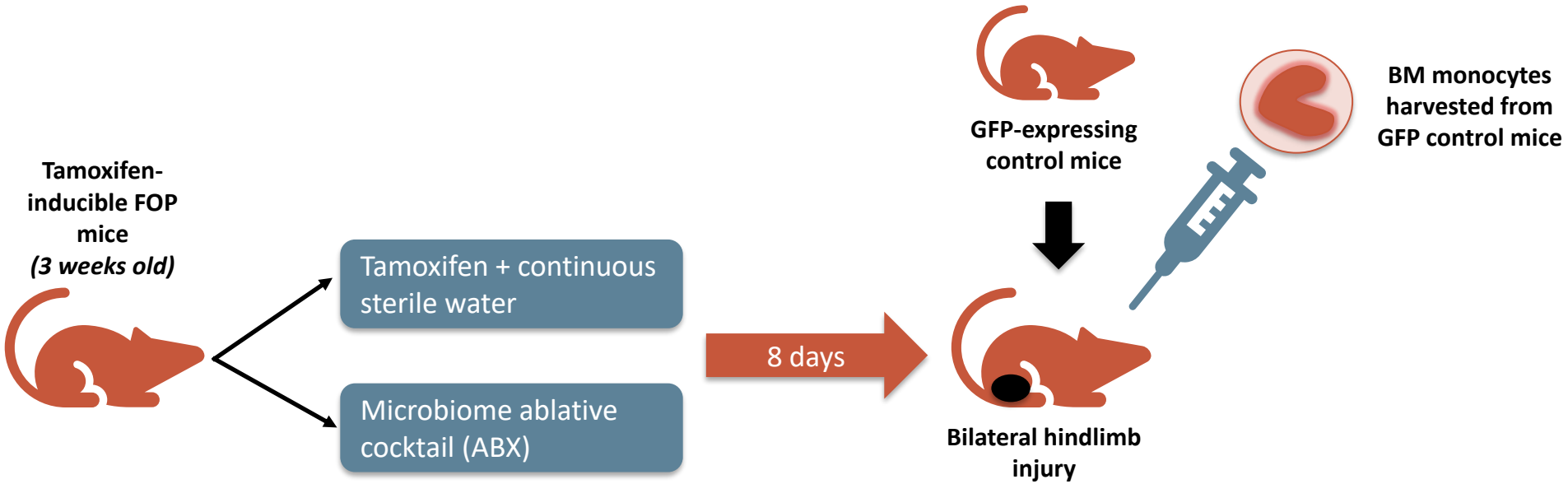
FOP, fibrodysplasia ossificans progressiva

BACKGROUND AND STUDY DESIGN

COR2ED®
THE HEART OF MEDICAL EDUCATION

STUDY DESIGN

- **Inflammation and innate immune cells contribute to FOP flares and HO**
  - Inflammatory environmental factors could therefore contribute to disease variability in FOP patients
- **Aim of this study was to reduce the HO formation by reducing the inflammatory activities** in a FOP mouse model and to **determine whether ABX reduction in HO is mediated by changes in monocytes**



ABX, ablative antibiotic cocktail; BM, bone marrow; FOP, fibrodysplasia ossificans progressive; GFP, green fluorescent protein; HO, heterotopic ossification

Pierce J, et al. ASBMR 2021, Abstract #1039; https://cor2ed.com/podcast-rare-bone-disease-highlights-at-asbmr-2021/

COR2ED®
THE HEART OF MEDICAL EDUCATION

KEY FINDINGS

- Microbiome-ablative ABX reduced HO in ABX-treated FOP mice
- Treatment decreased the expression of proinflammatory chemokines and receptors in injured FOP muscles
- Transplanting BM monocytes from control mice restored the HO phenotype in ABX-treated FOP mice
- Reducing the inflammatory process in FOP mice seems to have a beneficial therapeutic effect on HO formation

ABX, ablative antibiotic cocktail; BM, bone marrow; FOP, fibrodysplasia ossificans progressive; HO, heterotopic ossifications
Pierce J, et al. ASBMR 2021, Abstract #1039; https://cor2ed.com/podcast-rare-bone-disease-highlights-at-asbmr-2021/

CLINICAL PERSPECTIVES

COR2ED®
THE HEART OF MEDICAL EDUCATION

FROM: DR. MARELISE EEKHOFF

- Monocytes play an important role in FOP flare ups and in bone formation. Here, a totally new concept is used to demonstrate the role of the microbiome as well as the importance of monocytes in this process that needs further investigation.
- Interesting to consider ways that you may be able to influence the gut microbiome in ways that could impede heterotopic ossification in these patients in the future

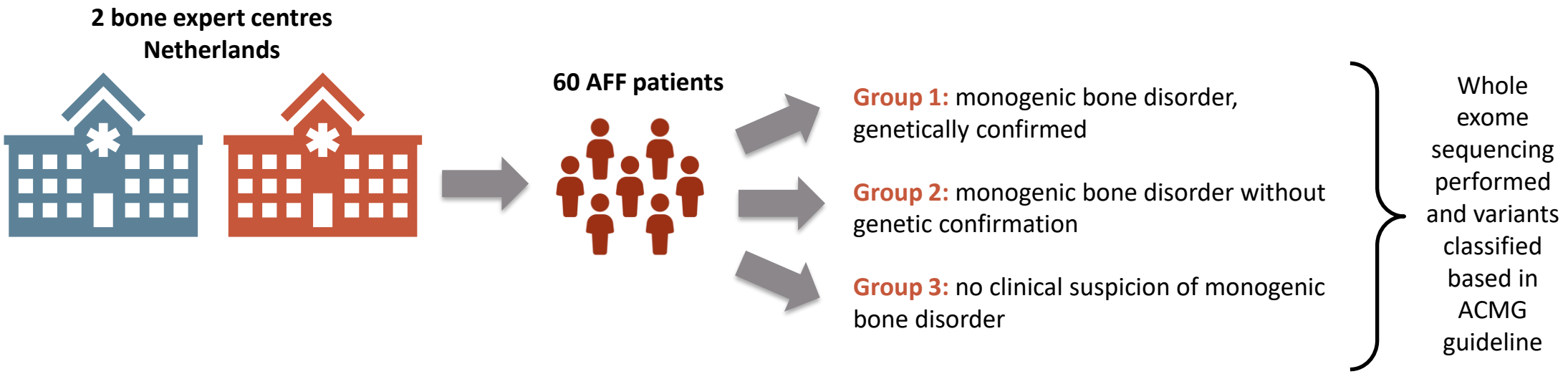
Pierce J, et al. ASBMR 2021, Abstract #1039; https://cor2ed.com/podcast-rare-bone-disease-highlights-at-asbmr-2021/

PREVALENCE OF MONOGENIC BONE DISORDERS IN A DUTCH COHORT OF AFF PATIENTS

Zhou W, et al. ASBMR 2021. Abstract #1051

BACKGROUND AND STUDY DESIGN

- **Atypical femur fracture (AFF),** is a **rare type of fracture** with characteristic radiological features and a suspected relation to treatment with bisphosphonate (BP)
- **Patients with monogenic bone disorders,** such as osteogenesis imperfecta and hypophosphatasia, **have reported AFFs** with or without bisphosphonates use. **The association of AFFs with these monogenic bone disorders remains unclear**



ACMG, American College of Medical Genetics and Genomics; AFF, atypical femur fracture; BP, bisphosphonate

Andersen J, et al. Osteoporos Int. 2019;30:513-7; Zhou W, et al. ASBMR 2021. Abstract #1051; https://cor2ed.com/podcast-rare-bone-disease-highlights-at-asbmr-2021/

KEY FINDINGS

	AFF patients N (%)
Group 1	7 (12)
Group 2	21 (35)
Group 3	-

- Approximately 50% of AFF patients have a clinically suspected monogenic bone disorder
  - 1/3 were genetically confirmed
    - This supports the hypothesis of a genetic cause of AFF

AFF, atypical femur fracture

Zhou W, et al. ASBMR 2021. Abstract #1051; https://cor2ed.com/podcast-rare-bone-disease-highlights-at-asbmr-2021/

CLINICAL PERSPECTIVES

COR2ED®
THE HEART OF MEDICAL EDUCATION

FROM: DR. MARELISE EEKHOFF

- New concepts and new treatments are needed for all these rare bone diseases
- This study is interesting as it could lead to potentially new diagnostic procedures
- When patients with rare bone diseases present with a fracture, we need to look further into the underlying mechanism and should consider genetic testing
- The question also remains whether AFF is also a problem in polygenic bone disorders

AFF, atypical femur fracture
Zhou W, et al. ASBMR 2021. Abstract #1051; https://cor2ed.com/podcast-rare-bone-disease-highlights-at-asbmr-2021/

FUTURE RESEARCH

COR2ED®
THE HEART OF MEDICAL EDUCATION

FROM: DR. ERIC RUSH

- Over the past decade there has been a lot of progress in the field of rare bone disease and there is a lot of cause for optimism going forward for our patients
- Interesting future studies include:
  - Setrusumab trial in children with OI
    - Seen promising data for setrusumab in adults
  - INZ-701 in adults with ENPP1 deficiency
    - Condition with significant morbidity and mortality so it's exciting to see a potential targeted therapy for these patients

ENPP1, ectonucleotide pyrophosphatase/phosphodiesterase 1; OI, osteogenesis imperfecta

COR2ED®

THE HEART OF MEDICAL EDUCATION

COR2ED
Bodenackerstrasse 17
4103 Bottmingen
SWITZERLAND

Dr. Froukje Sosef MD

+31 6 2324 3636

froukje.sosef@cor2ed.com

Dr. Antoine Lacombe Pharm D, MBA

+41 79 529 42 79

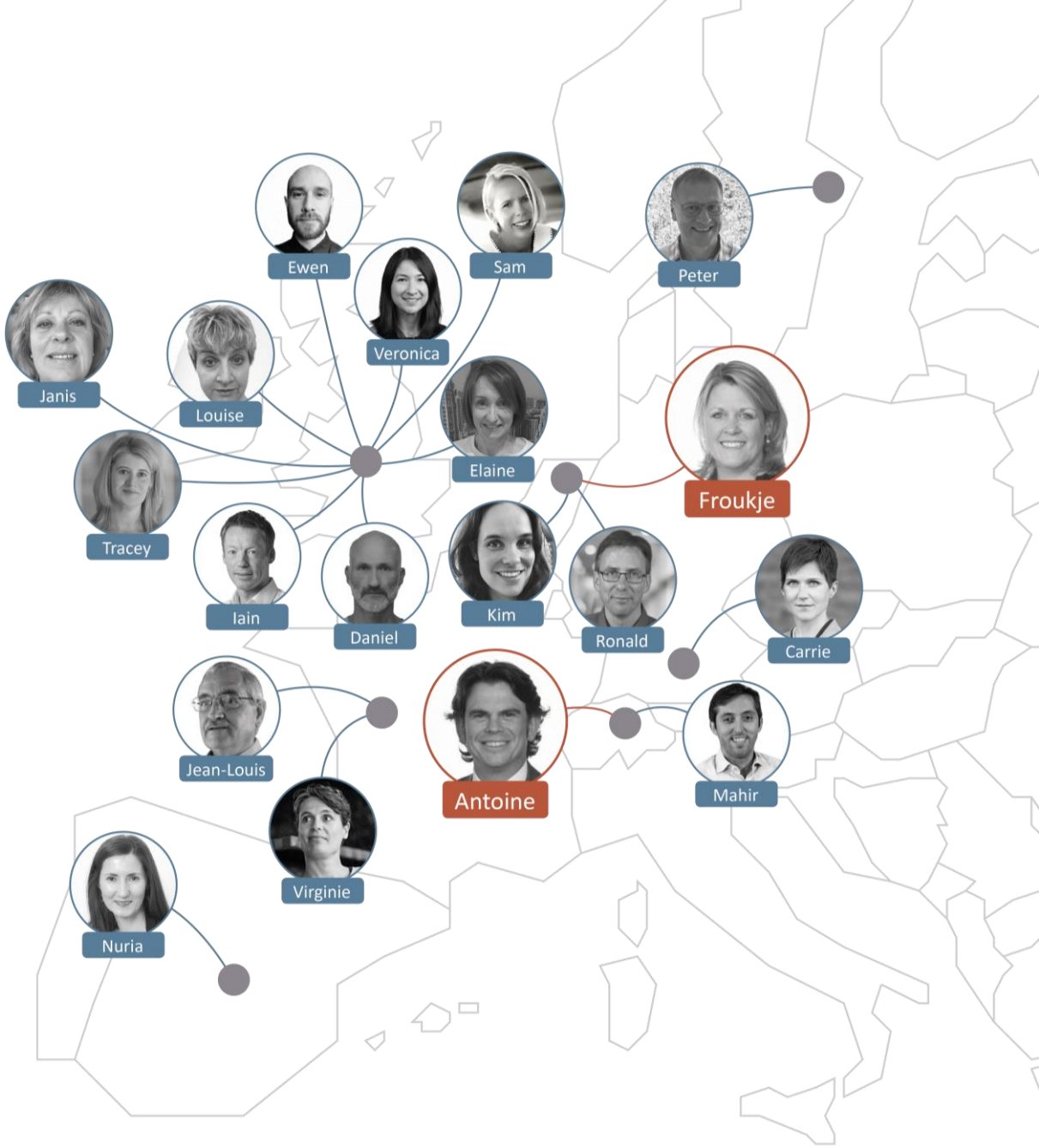
antoine.lacombe@cor2ed.com

Connect on
LinkedIn @COR2ED

Watch on
Vimeo @COR2ED

Visit us at
cor2ed.com

Follow us on
Twitter @COR2EDMedEd



Heading to the heart of Independent Medical Education Since 2012