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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

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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

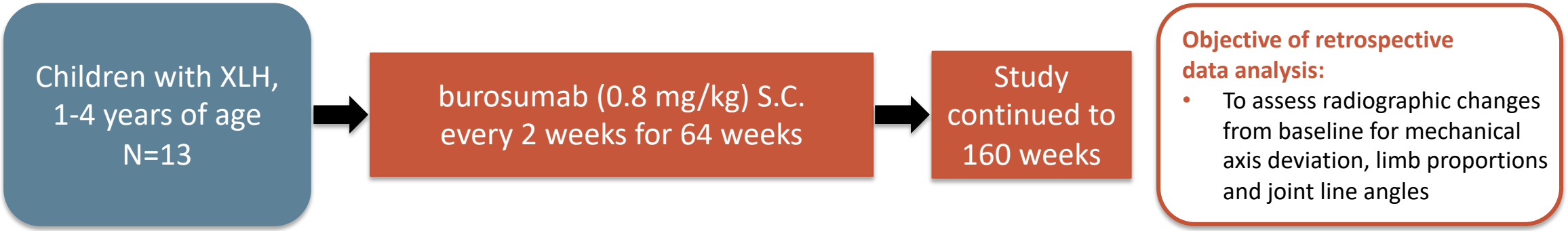
BUROSUMAB IMPROVES LOWER LIMB ALIGNMENT IN CHILDREN WITH XLH

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

XLH, X-linked hypophosphataemia

BACKGROUND AND STUDY DESIGN

- **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

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- 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

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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

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- **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

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- 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/

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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

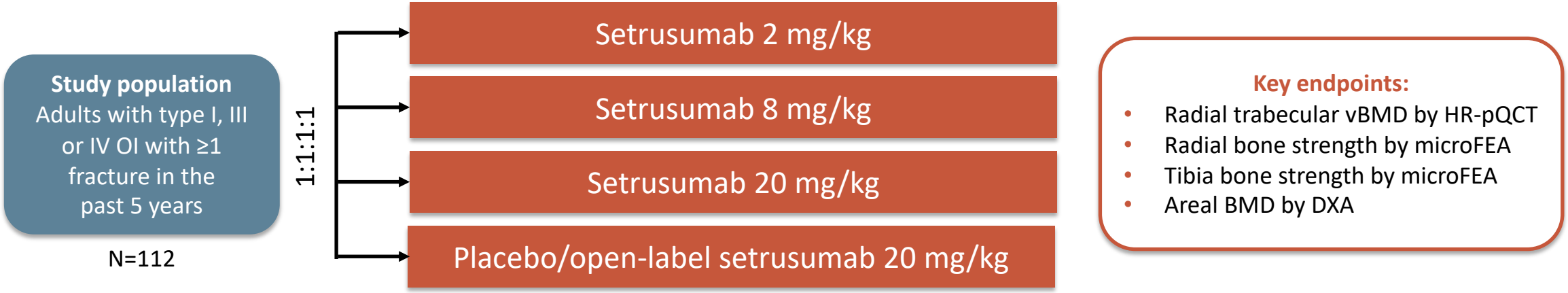
ADH1, autosomal dominant hypocalcaemia type 1
https://cor2ed.com/podcast-rare-bone-disease-highlights-at-asbmr-2021/

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

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- 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/

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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

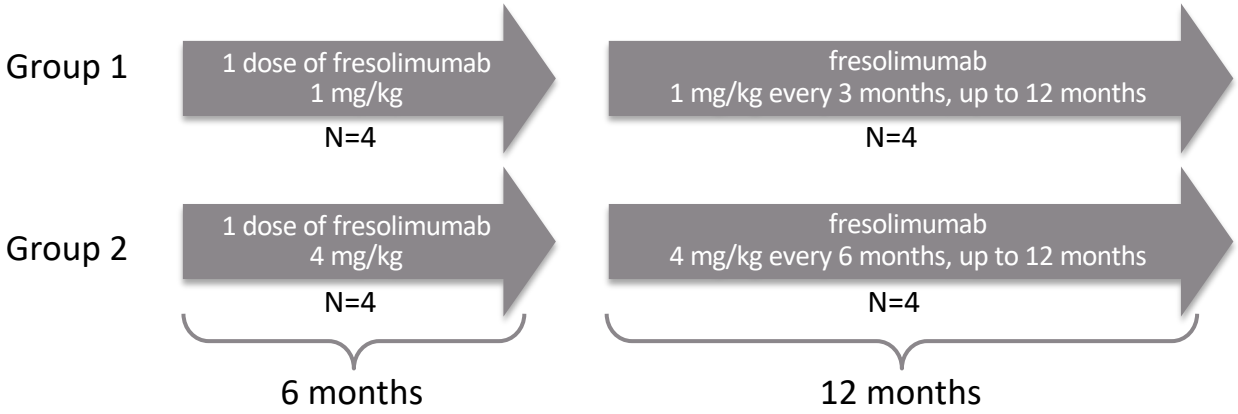
- TGF-β is a protein important in bone formation
- In studies with mice with OI, it has been shown that silencing TGF-β can lead to higher bone mass, quality and strength
- Fresolimumab is a pan–anti-TGF-β antibody

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/

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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

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- **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

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- 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/

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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
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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

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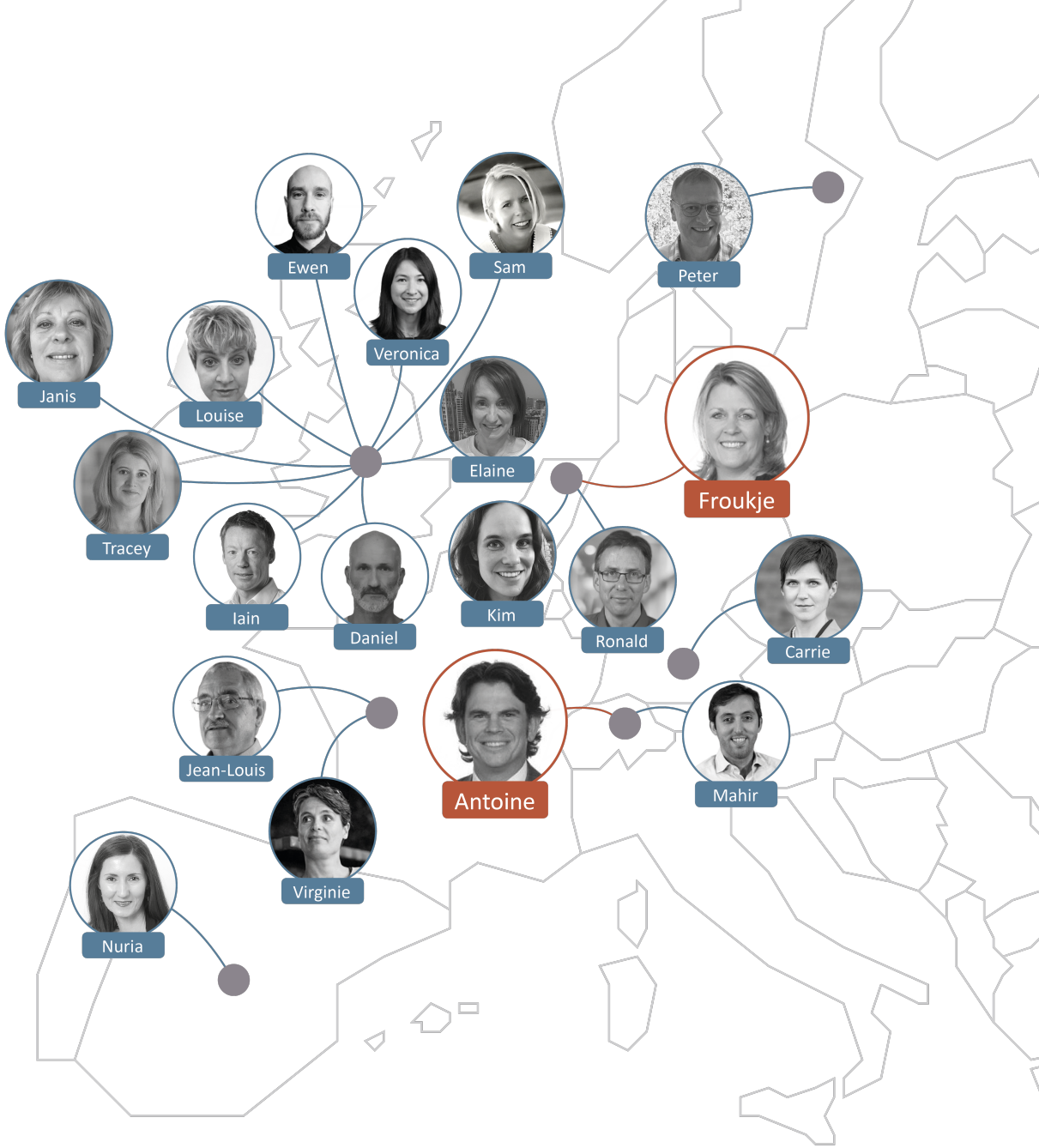

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