

Bone Remodeling QSP to Guide Clinical Trial Design of WNT pathway inhibitors design

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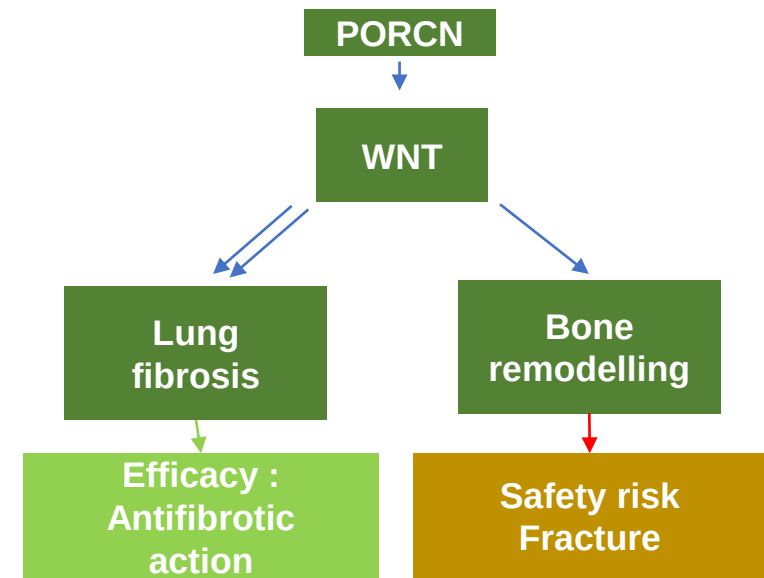
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Targeting Wnt pathways for anti-fibrotic therapeutic strategies

- Targeting WNT signalling pathways has emerged as an attractive strategy to prevent fibrosis, maintain lung function, improve symptoms and decrease mortality in idiopathic pulmonary fibrosis (IPF) patients
- Inhibiting PORCN, which reduces WNT, has been attempted with small-molecule in Oncology (e.g. WNT974, CGX1321, ETC-159).
- However, WNT has critical roles in bone remodeling and for any drug there will be a question of separation between bone loss and efficacy
- During a Phase 1 trial, bone remodeling biomarkers can be evaluated to understand safety and target engagement
- Anticipating changes prior to the FiH can help trial design



A QSP approach has been developed to anticipate changes in bone remodelling biomarkers and inform a FTIH trial

Existing literature showed that a number of academic groups attempted to model bone remodelling

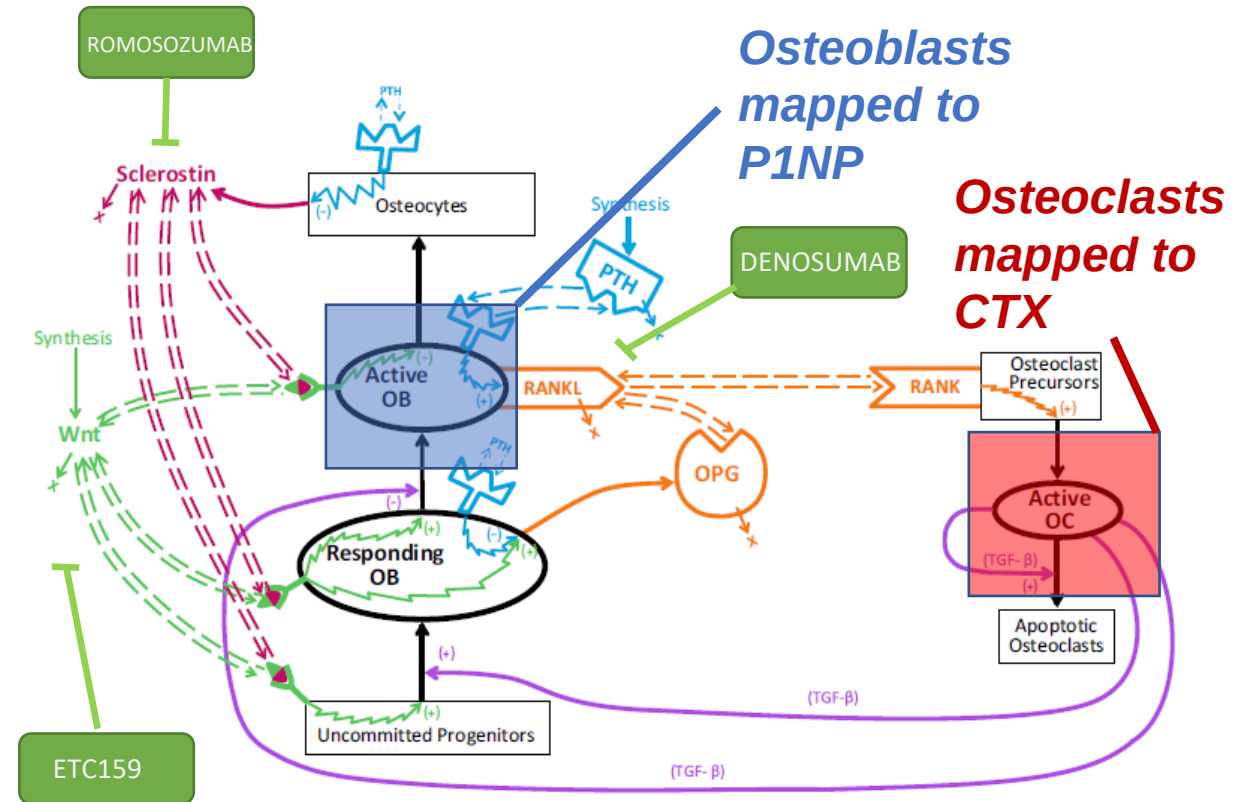
Due to the absence of robust information about future changes in bone biomarkers, it was proposed to combine mechanistic modelling and available clinical data to inform the FiH.

The strategy involved:

- Reviewing the literature and identifying suitable models
- Reviewing public clinical data that could be used
- Adapting the model to the problematic and integrating the public data
- Simulating predicted changes and inform trial design

Systems Modeling by Combining Physiology Understanding & Public External Clinical Data

- The Lemaire et al. (2019) model of bone remodelling is a biochemical model in which bone cell activities are coupled by a multitude of relevant biochemical factors.
- We identified this model as capturing essential bone processes while avoiding excessive complexity
- Public clinical data from Denosumab (an anti-RANKL), Romosozumab (an anti-Sclerostin), and ETC159 (an Oncology PORCNI) which affect the remodelling pathways in different ways were used
- We linked cell activities to bone biomarkers, resulting in a QSP model which captured CTX (bone resorption) and P1NP (bone formation)



The Lemaire model is based on several qualitative behaviours

Experiment

Monitoring cell densities

Addition of active osteoblasts

Addition of active osteoclasts

Addition of responding osteoblasts

Lowering active osteoblasts

Lowering active osteoclasts

Lowering responding osteoblasts

Continuous administration of PTH

Intermittent administration of PTH

Administration of OPG

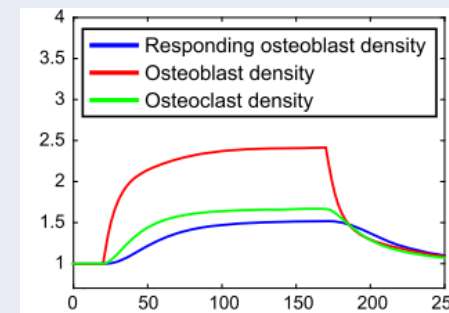
Administration of RANKL

Model: *continuously adding active osteoblasts*

Qualitative expected outcomes:

- *Responding Osteoblasts increase*
- *Active Osteoblasts increase*
- *Osteoclasts increase*
- *The ratio of Osteoclasts to Osteoblasts go down*
- *Steady state reached in less than 1 year*

Simulation:



We validated our implementation against all these virtual experiments

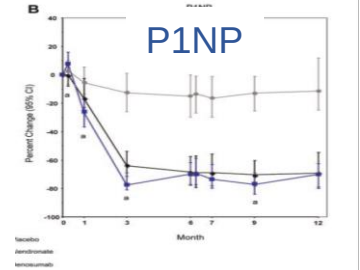
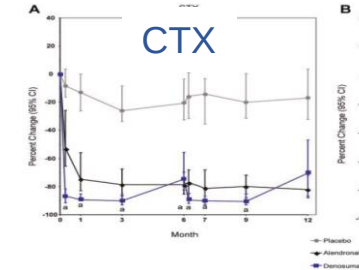
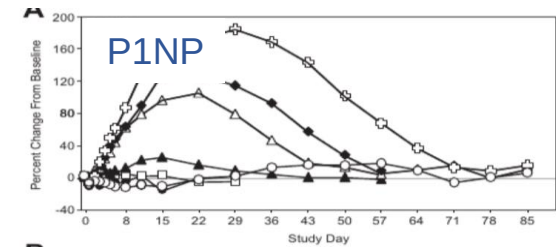
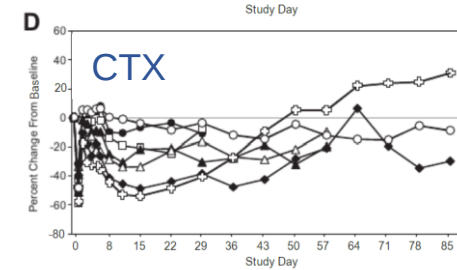
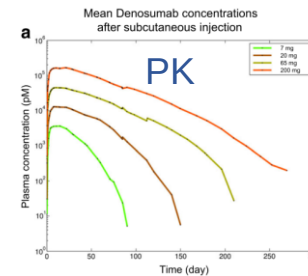
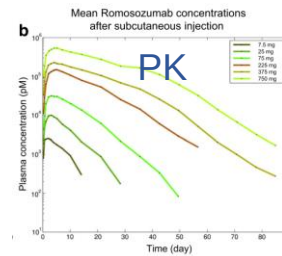
The model was further developed in a quantitative way by leveraging on published clinical data

Various drugs interacting with bone remodelling pathways have been brought to the clinic in the past

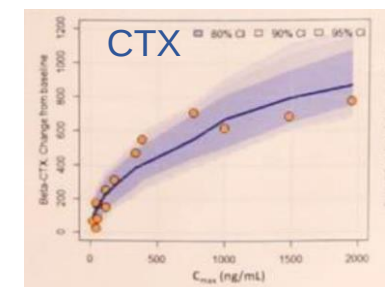
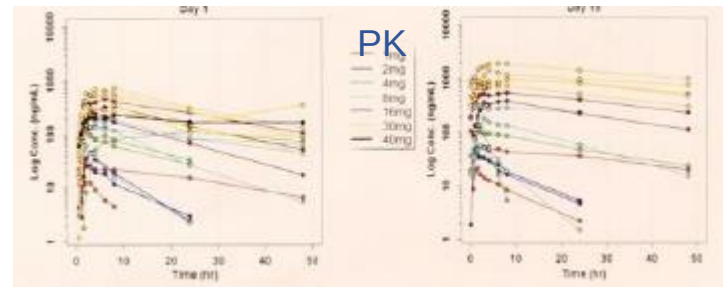
We identified reports of clinical trials with Denosumab (an anti-RANKL) Romosozumab (an anti-Sclerostin) and ETC159 (an Oncology PORCNI) which offered valuable data

These 3 drugs affects the remodelling pathways in different ways, thus providing a robust clinical and quantitative basis.

DENOSUMAB ROMOSUZUMAB

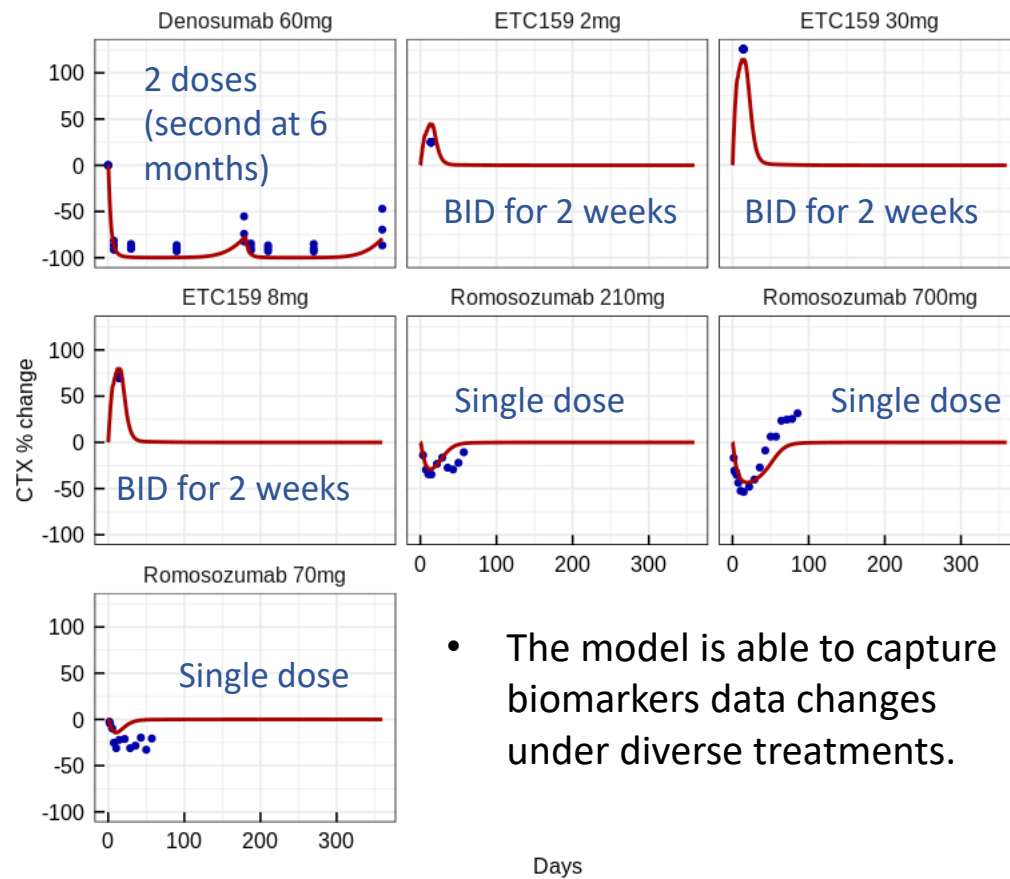


ETC159



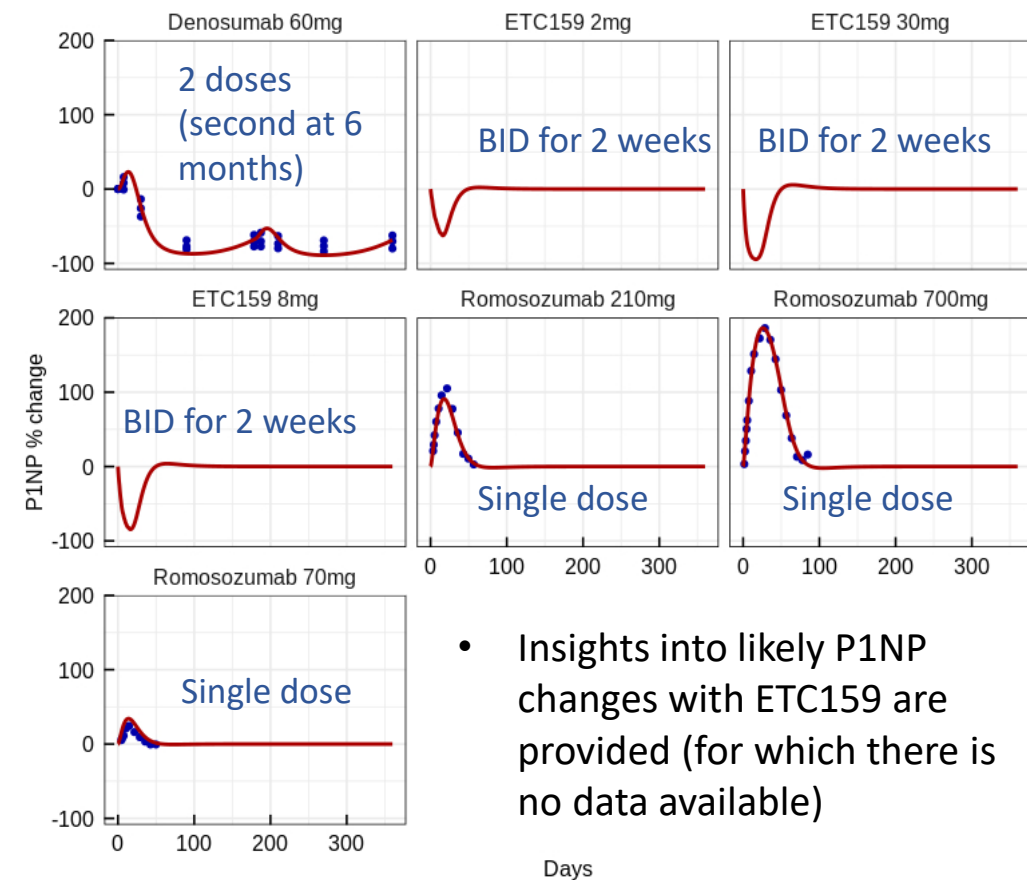
The model simultaneously capture all clinical data and provides insights in terms of unobserved bone formation biomarkers upon WNT inhibition

CTX



- The model is able to capture biomarkers data changes under diverse treatments.

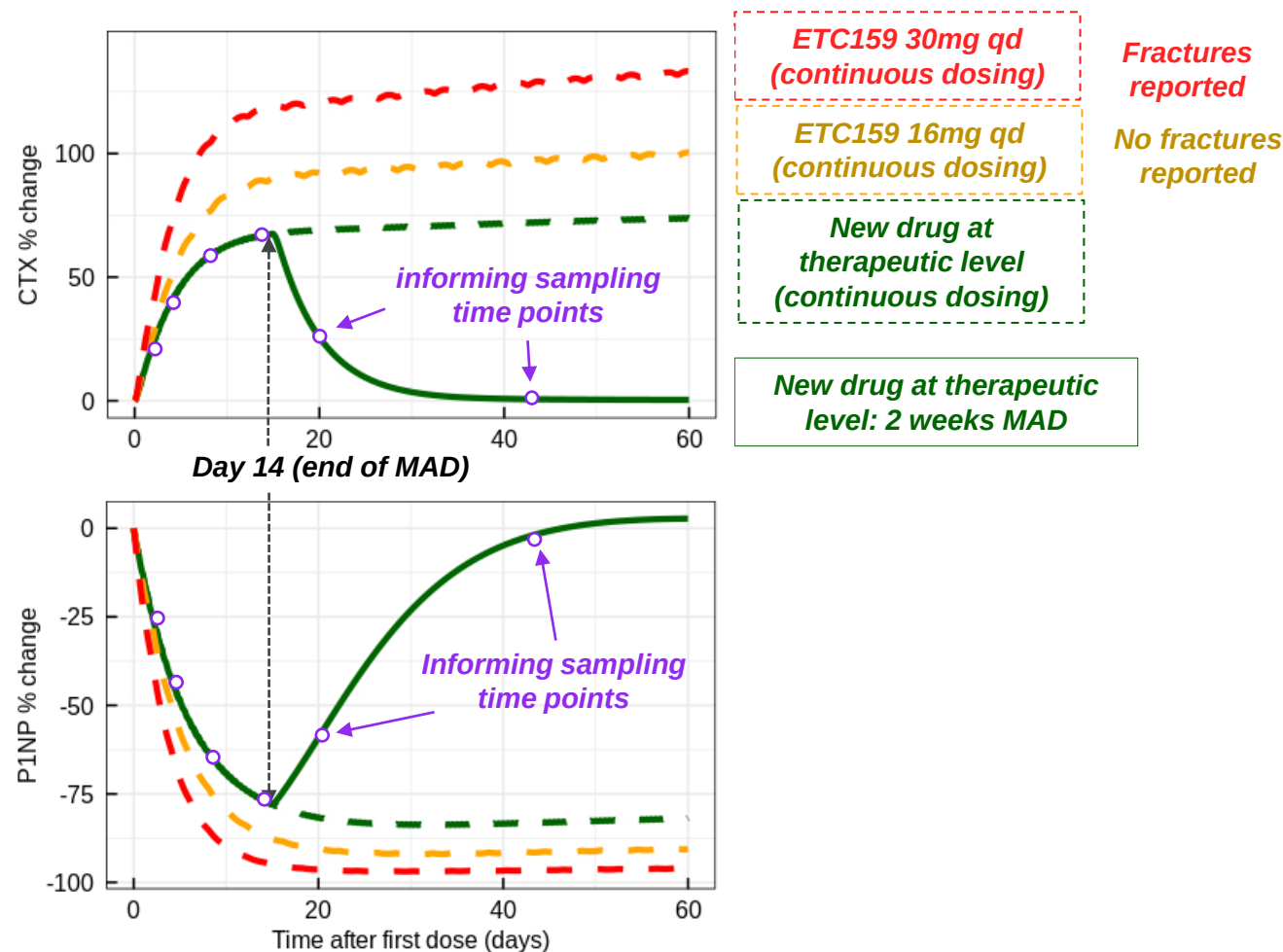
P1NP



- Insights into likely P1NP changes with ETC159 are provided (for which there is no data available)

Study Duration & Biomarker Sampling Times optimization via QSP

- Simulations predict bone biomarkers time courses for a new PORCN inhibitor
- Predictions enabled:
 - Recommending a 2-week MAD study
 - Recommending a bone biomarkers sampling schedule
- Additionally, changes in CTX and P1NP levels can be predicted across modalities
- For example, changes for a new drug can be contrasted to changes with ETC159 30mg qd (report of fractures at 30mg) and ETC159 16mg qd (no report of fractures during the window of assessment)
- Overall, the QSP strategy provided an opportunity to improve the chances of collecting informative target engagement and safety measurements to help plan further clinical studies.



Bone biomarker changes for a new drug at therapeutic level (green, for 2 weeks MAD study and upon hypothetical continuation) and 10mg or 30mg ETC159 QD dosing (red and amber, shown long term). A MAD sampling schedule for CTX and P1NP is also shown (purple circles)

Investing in the QSP strategy to inform later phase trials

A number of additional steps are being considered:

- Links with and quantification of bone demineralization and fracture risks (e.g. Peterson and Riggs, Eudy-Byrne et al.)
- Integration of future clinical data into an updated version of the model to assess study variability and strengthen predictions
- Modelling of combinations with osteoporosis drugs (e.g. Denosumab)