Amsterdam UMC
University Medical Centers

Rare Bone Disease Center
Amsterdam UMC

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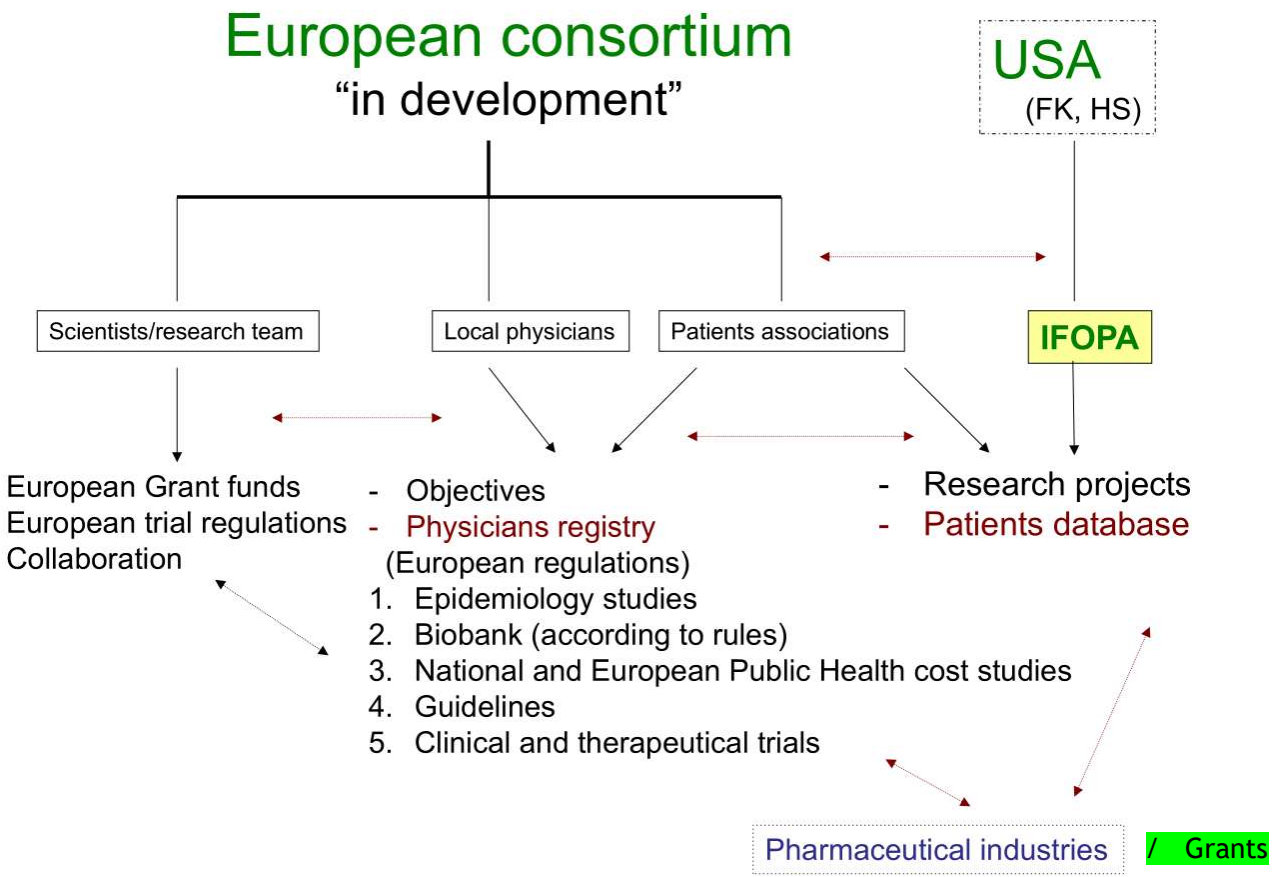
Disclosure of speaker's interests

(Potential) conflict of interest	None/See below:
- Sponsorship or research funding EU IMI, AZ, Ipsen, Regeneron, Incyte, (Lilly)	Board membership: Amsterdam Bone Center Rare Bone Disease Center NVE BoNe ASBMR committee ERN BOND
- Fee or other (financial) payment IFOPA, Dutch FOP patients organization	Task Force (2 committees) Marker consortium Gene therapy consortium Tissue working group
- Other relationship, i.e. … Board / membership: ICC on FOP, Medical Advisory Board IFOPA patient registry, European FOP Consortium	

Collaboration in FOP!

2012 First European FOP Consortium Amsterdam

Collaboration



Fibrodysplasia Ossificans Progressiva (FOP)

- Amsterdam UMC Center for Rare Bone Diseases:
  - Participate in all studies on FOP to find a cure (international referral center)
  - ->STOPFOP Trial

Marelise Eekhoff
(Amsterdam)

Richard Keen
(London)

Clemens Stockklausner
(Garmisch, Germany)

STOPFOP

Saracatinib trial TO Prevent FOP "STOPFOP"

A Phase 2A Clinical Trial

Alex Bullock
(Oxford)

Paul Yu
(Boston)

(AstraZeneca,
Sweden)

imi innovative medicines initiative

efpia

Fibrodysplasia Ossificans Progressiva

- Rare, genetic disease in which heterotopic bone forms in muscle, ligaments and tendons

- 1 in 2.000.000 people

- Autosomal dominant inheritance, most often spontaneous mutation
  - c.617G>A; R206H
  - Gain of function
  - BMP/activin A hypersensitivity

https://commons.wikimedia.org/wiki/File:Fibrodysplasia_ossificans_progressiva.jpg

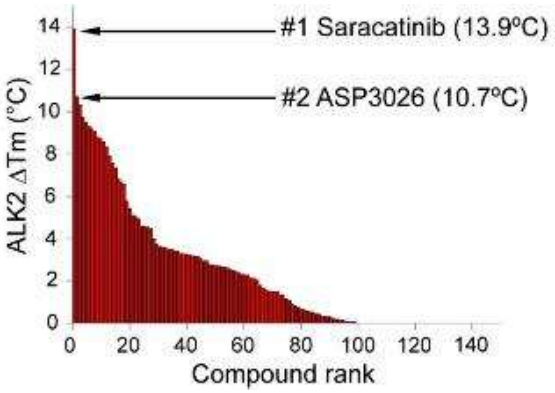
STOPFOP

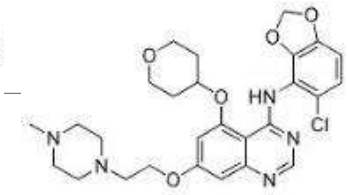
- **S**aracatinib **T**rial **TO** **P**revent **FOP**

- Investigator initiated
  - Sponsored by EU: Innovative Medicines Initiative

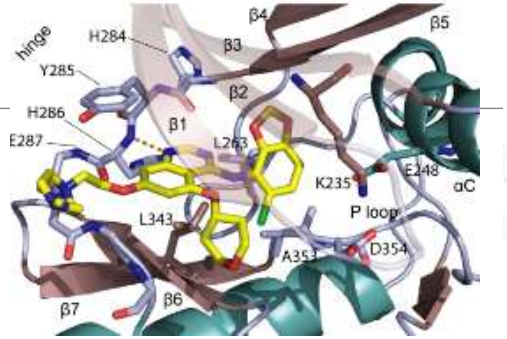
- Partners
  - Consortium of several academic centers and AstraZeneca
  - Stakeholders board
    - IFOPA
    - National patients organisations of The Netherlands, United Kingdom, Germany, France, Italy and Sweden

Screen of clinical kinase inhibitors identifies the SRC inhibitor Saracatinib as 6.7 nM ALK2 inhibitor

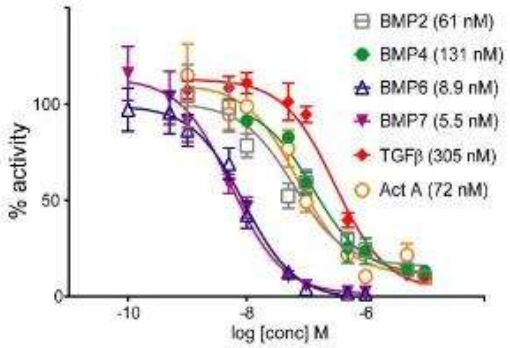




Saracatinib (AZD0530)
Screening hit
IC_{50} = 6.7 nM

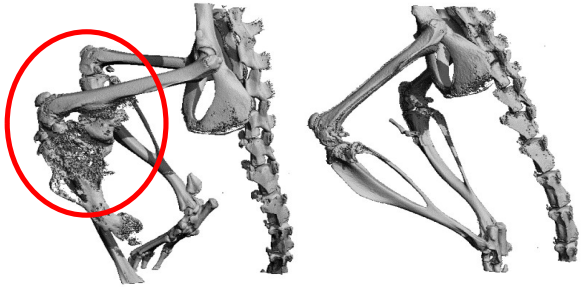


ALK2-saracatinib co-structure



BMP signalling inhibition in C2C12 cells

Saracatinib shows efficacy in FOP mouse models (ALK2 R206H)

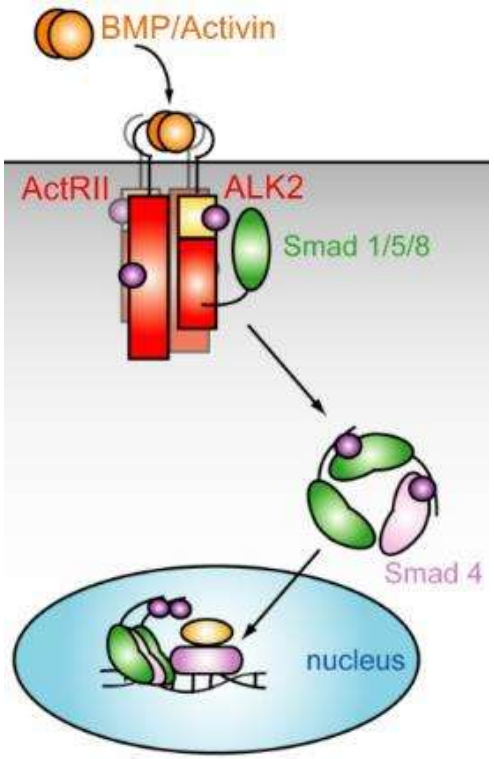


Vehicle

Saracatinib

E. Williams et al JCI insight, 2021 Apr 22; 6(8): e95042

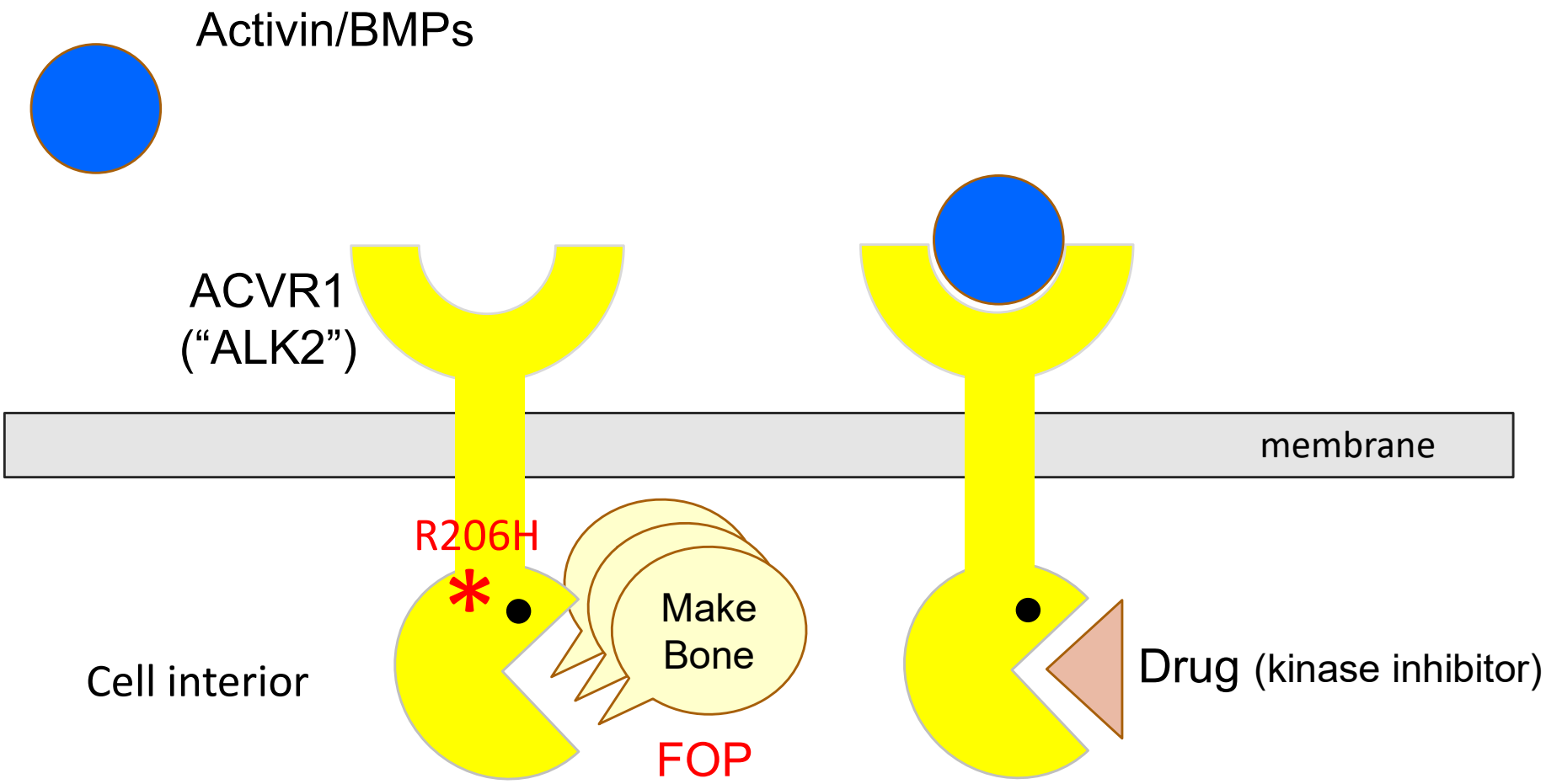
Rationale for inhibiting the FOP receptor ALK2 directly



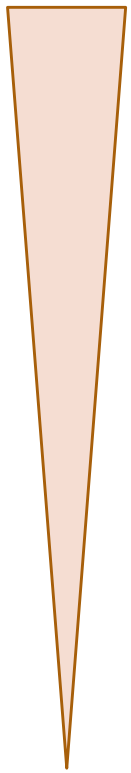
- Directly blocks region affected by mutation
- Potentially most robust inhibition of FOP
  - Block Activin neofunction
  - Block BMP hypersensitivity
  - Block any leaky signaling

Hope to
-Block both flare ups and HO
-Enable surgery in long term

Our strategy to stop FOP

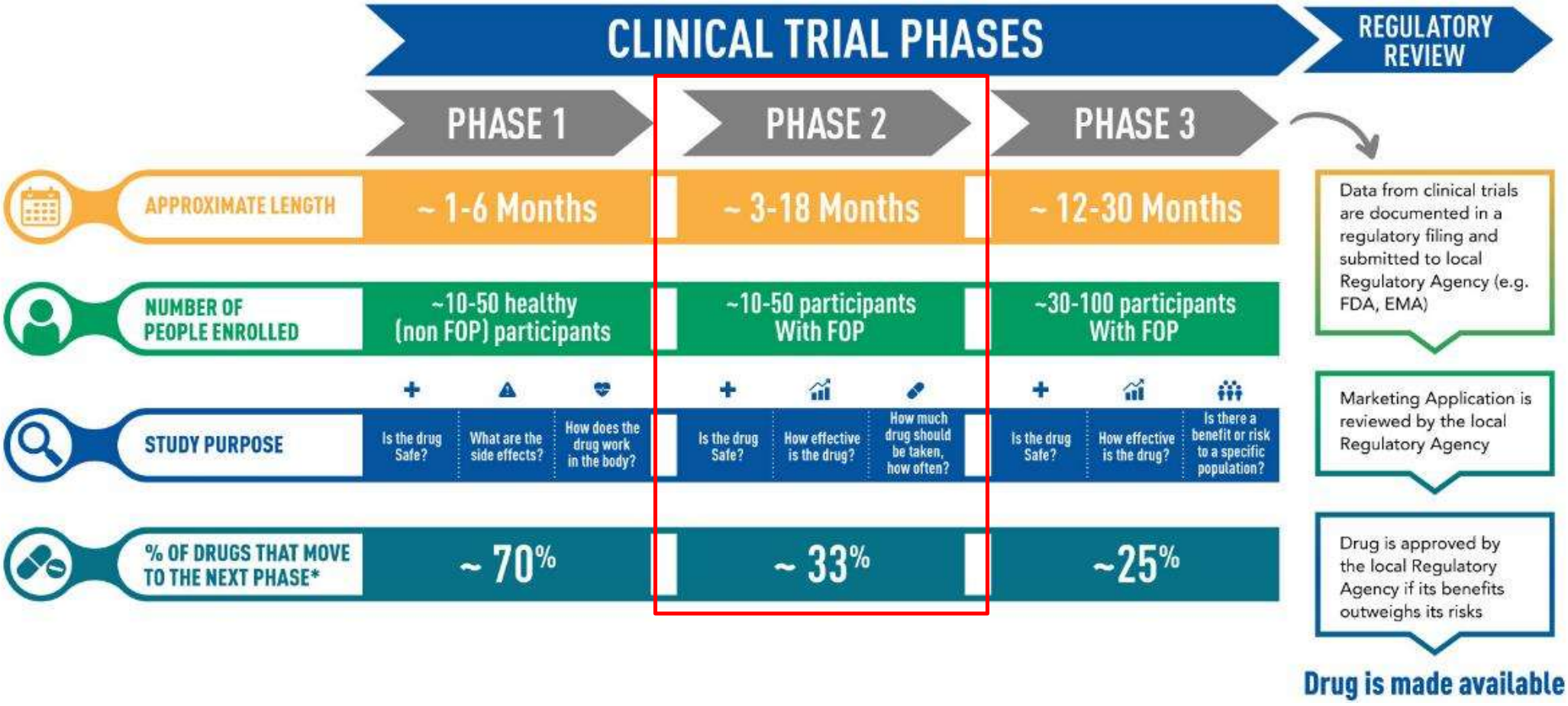


History of Saracatinib in clinical trials (>700 patients)



Dose	Disease	Clinical trial phase	Observations
grams per day			
1.000	**Healthy volunteers**	phase 1	Maximum tolerated single dose
0.175	**Cancer**	phase 2, 3	Treatment for 4-6 weeks with chemotherapy >600 patients
0.125	**Alzheimer's disease** **LAM lung disease**	phase 2	Treatment for 9-12 months >100 patients (100-125 mg dose)
0.100	**STOPFOP**	phase 2	New clinical trial

HOW A DRUG MOVES THROUGH CLINICAL TRIALS
AND GETS TO PEOPLE WITH FOP



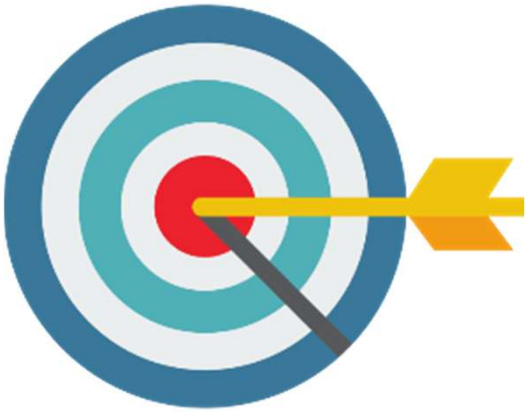
Aim

To investigate:

- The **effectiveness** of Saracatinib on FOP
  - PET-CT
  - Questionnaires/diary/mobility

- The **safety** of Saractinib in people with FOP
  - Side-effects
  - Blood results

<u>In order to discover an effective medicine to stop FOP</u>



Locations

3 clinical sites
- Netherlands (Amsterdam)
- Germany (Garmisch-Partenkirchen)
- United Kingdom (London)

Participation from patients outside of these countries is possible

- European Union
- Case-by-case basis

Study Design

- 6 month Randomised controlled trial
  - 50% chance of treatment with Saracatinib
  - 50% chance of treatment with placebo (fake drug)

- 12 month open label extension phase
  - 100% chance of treatment with Saracatinib

- *Saracatinib can be continued after study period*

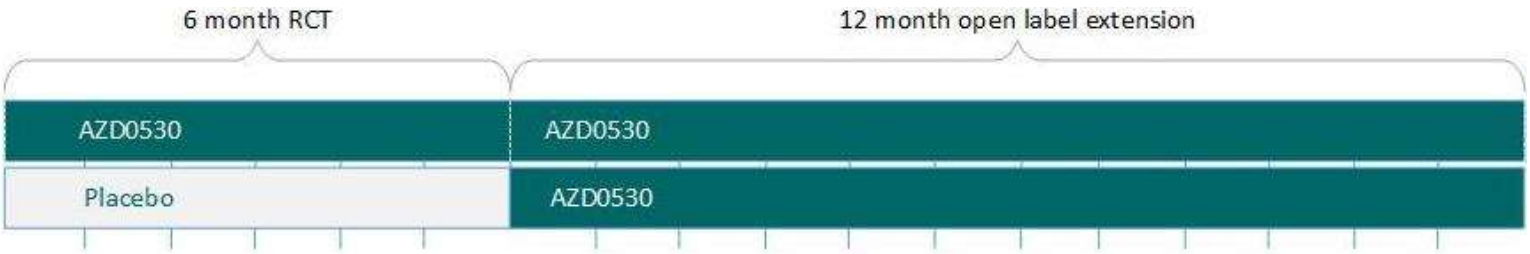
Study Design

Visits

-Screening

-3 weeks

-Every 3 months



Participants

- 17 FOP patients 18y-65y
  - Classic (R206H) mutation
  - Willing and able to participate (e.g. fit in CT-scanner)
  - Little other health issues

Study Design (2)

-Daily oral administration of Saracatinib
  - Medication can be crushed

- Diary
- Blood and urine collection
- Pulmonary and cardiac tests
- Questionnaires
- PET-CT → In Amsterdam for German patients

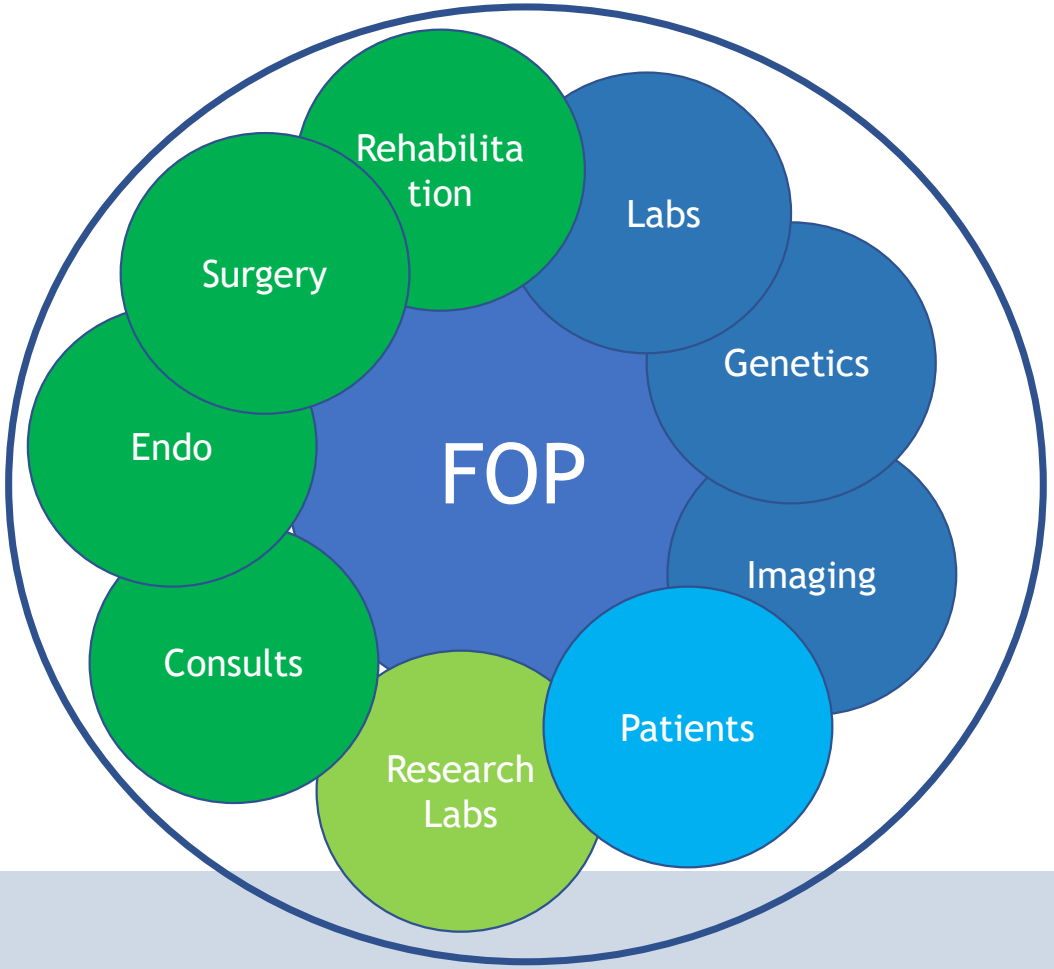
Update..

- **Study is running well (17 patients)**
  - **Amsterdam and Garmish Partenkirchen**
  - **8 countries**

- COVID 19
  - Extra safety measures

-Delay Brexit/COVID
  - EU agreed to extend the study for 2.5 years!

Rare Bone Disease care



-Genetic preclinical research
*genetic databases
*fibroblast cultures
]
-Translational research
*Imaging diagnostics

-Treatment ‘search”
*trials

Rare Bone Disease Center ‘’film”

- https://youtu.be/hyS6sCGUf4o

Amsterdam UMC
Universitair Medische Centra

Zeldzame Botziekten Centrum

Collaboration is based on trust in each other
but you can only achieve a goal if you know where you are heading to.

Mutual inspiration, wonder and the desire to improve (life of patients).

International collaboration

Studies

- Universities
- Farmaceutical companies

Organisations

- European FOP consortium
- ICC International Clinical Counsel on FOP
- Medical advisory board FOP Patient registry
- IFOPA