Development of Recifercept: Potential for use in Achondroplasia

February 2022

We aspire to be the world's leading innovator in rare disease by pioneering breakthrough science that has a profound impact on the lives of underserved patient populations.

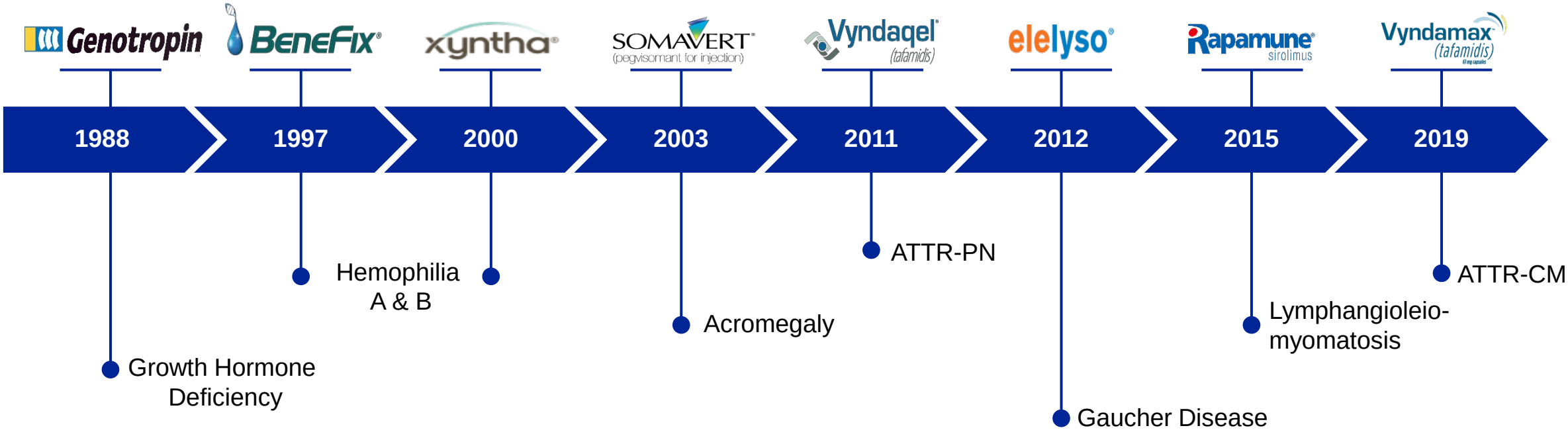
Pfizer Rare Disease:

Breakthroughs that change patients' lives

At Pfizer Rare Disease, we believe that people living with a rare disease, along with the untold number of family members and caregivers who support them, deserve better.

For more than thirty years, we have provided critical treatment options for patients with a range of rare diseases

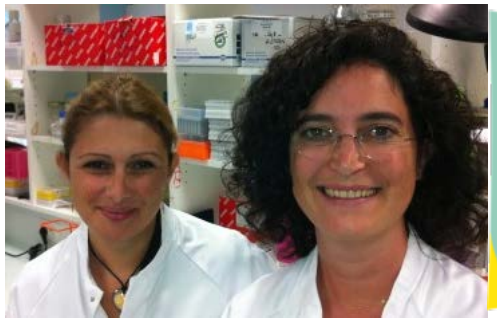
Our industry-leading portfolio of innovative medicines has provided hope to patients with rare diseases and their families for decades.



DISCLAIMER

RECIFERCEPT is an experimental drug still under development and consequently not registered for any therapeutic use.

Recap of the story!



Université Nice Sophia Antipolis

Membre de UNIVERSITÉ CÔTE D'AZUR

Therachon
achieving potential

RESEARCH ARTICLE

RARE DISEASES

Postnatal Soluble FGFR3 Therapy Rescues Achondroplasia Symptoms and Restores Bone Growth in Mice

Stéphanie Garcia,[1,2,3] Béatrice Dirat,[1,3] Thomas Tognacci,[1,3] Nathalie Rochet,[4] Xavier Mouska,[4] Stéphanie Bonnafous,[1,3,5] Stéphanie Patouraux,[1,3,6] Albert Tran,[1,3,5] Philippe Gual,[1,3,5] Yannick Le Marchand-Brustel,[1,3] Isabelle Gennero,[7] Elvire Gouze[1,3]*

RESEARCH ARTICLE

In vitro and *in vivo* characterization of Recifercept, a soluble fibroblast growth factor receptor 3, as treatment for achondroplasia

Diogo Gonçalves[1☯], Guylène Rignol[1☯], Pierre Dellugat[1], Guido Hartmann[1,2], Stephanie Sarrazy Garcia[3], Jeffrey Stavenhagen[4], Luca Santarelli[5], Elvire Gouze[6], Christian Czech[1]*

1 Research and Development, Rare Disease Unit, Pfizer, Nice, France, 2 TOLREMO Therapeutics AG, Muttenz, Switzerland, 3 Bionea, Biot, France, 4 Therini Bio, South San Francisco, CA, United States of America, 5 VectivBio, Basel, Switzerland, 6 Université Côte d'Azur, CNRS, Inserm, iBV, Nice, France

☯ These authors contributed equally to this work.
* christian.czech@pfizer.com

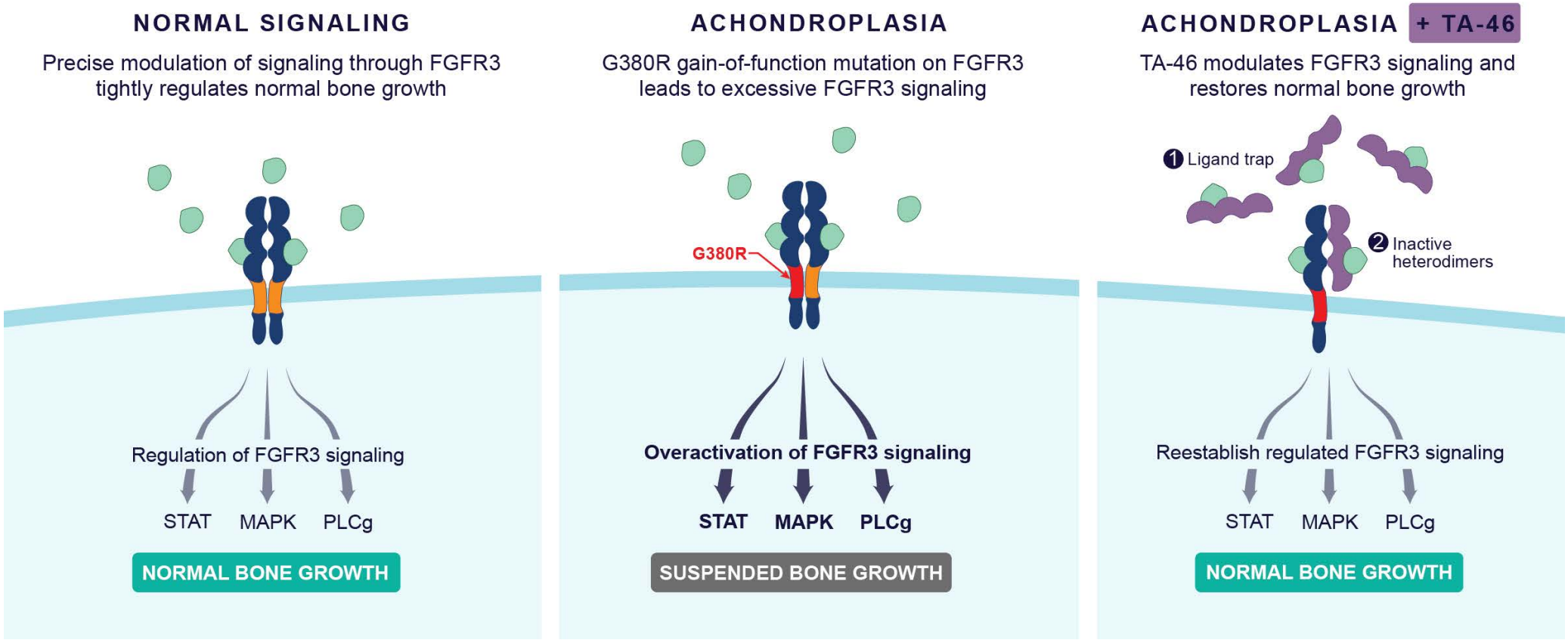
Pfizer Acquires Clinical-Stage Biotech Therachon

Expands Pfizer's rare disease portfolio with potential first-in-class therapy for achondroplasia, a genetic condition and the most common form of short-limb dwarfism

Pfizer

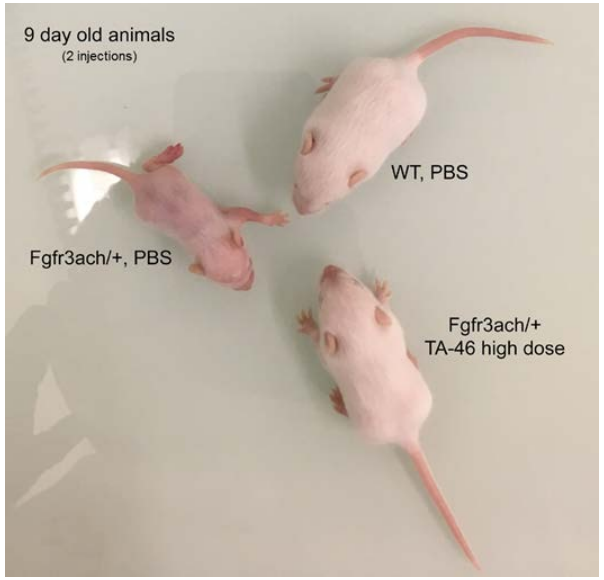
Recifercept targets mutated FGFR3 and normalises bone growth

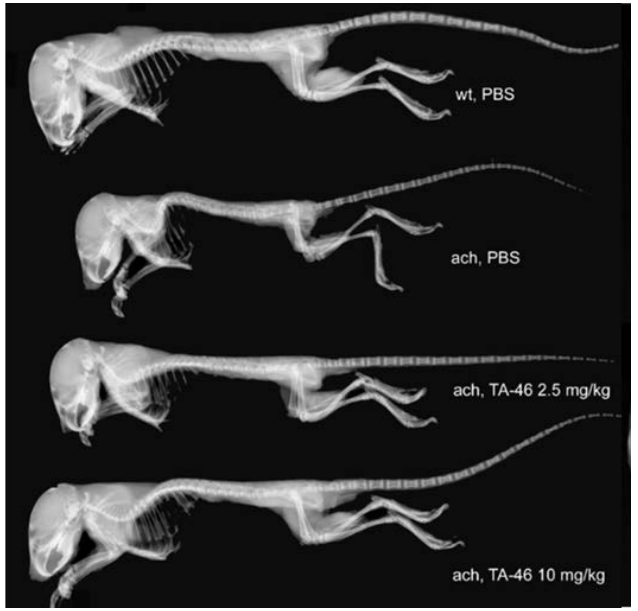
- FGFR3 is a key inhibitory regulator of linear bone growth
- ~97% of achondroplasia cases caused by G380R dominant gain-of-function point mutation
- The resulting over-activation of FGFR3 impairs bone development

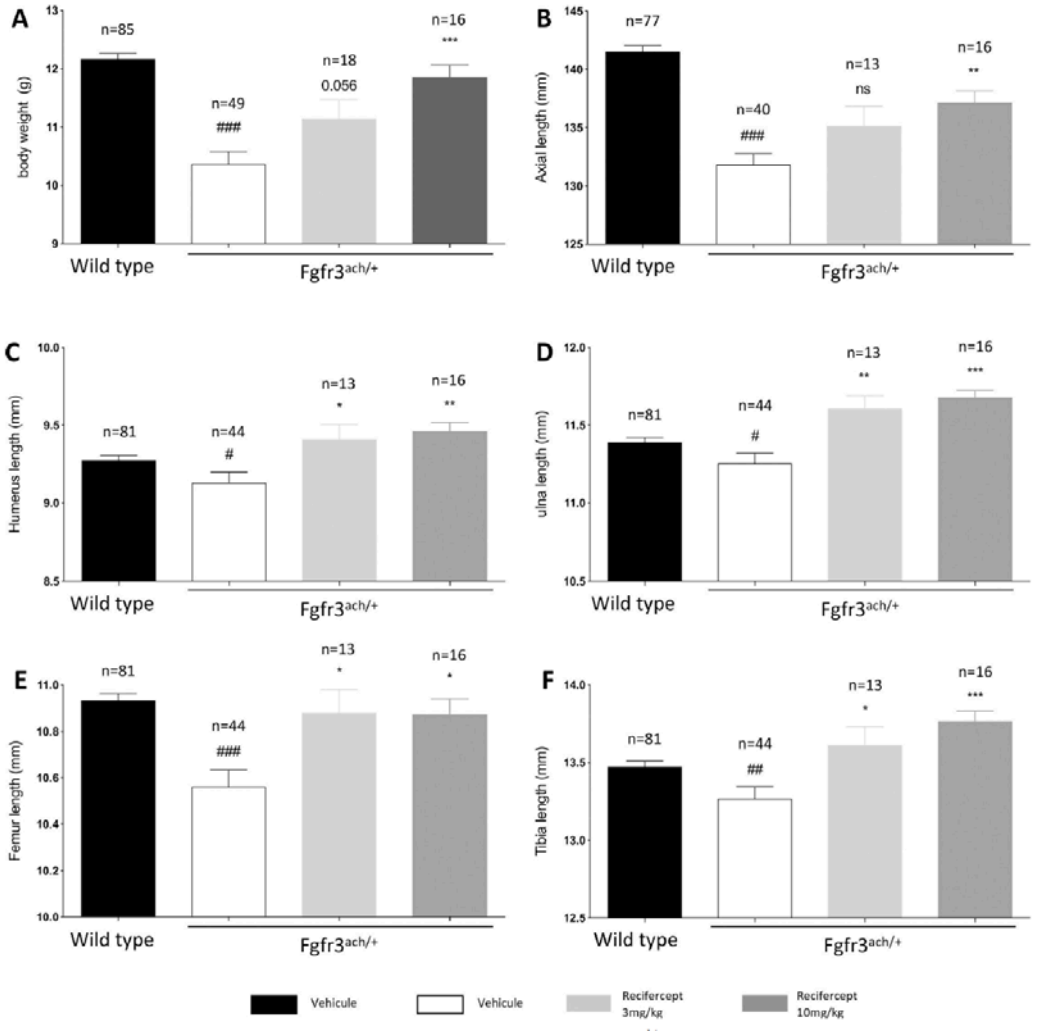


Recifercept treatment improves body weight, axial length and long bones length in transgenic mice

- WT and Fgfr3ach/+ mice received subcutaneous injection of vehicle or Recifercept at 3 or 10 mg/kg.
- Growth was characterized by body weight (A), total length (B), and long bones measurements (C-F).



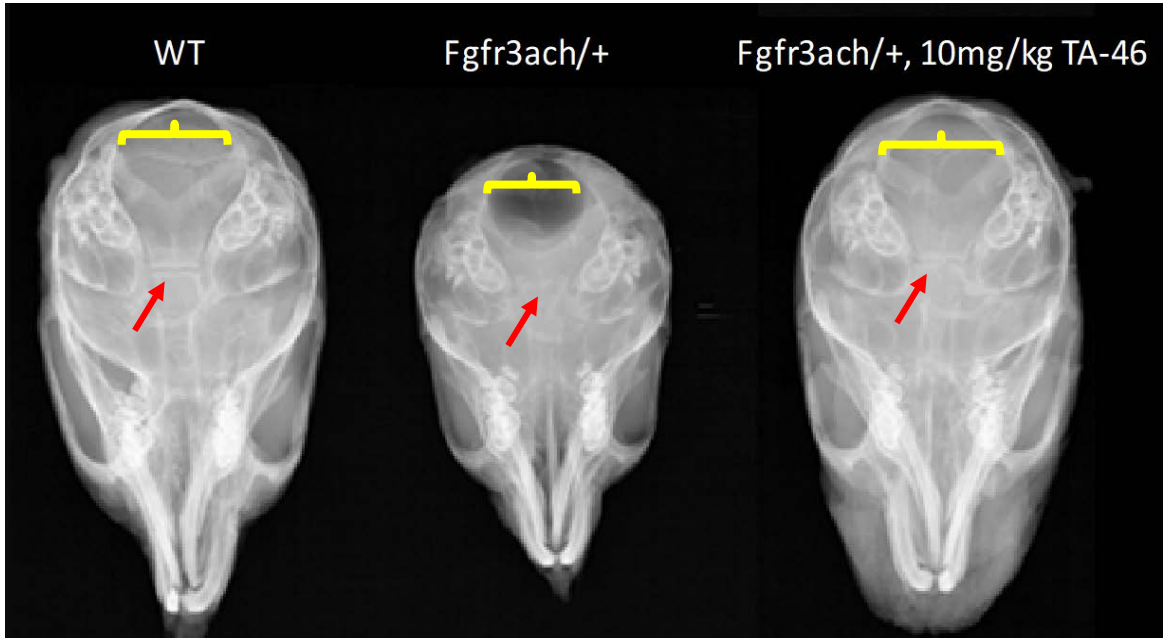




P < 0.05, P < 0.01, P < 0.001 versus Fgfr3ach/+ vehicle-treated mice,
# p< 0.05, ## p< 0.01, ### p< 0.001 versus WT vehicle-treated

Gonzalves and Rignol et al, 2021, PlosOne

Recifercept has pronounced effect on skull development in transgenic ach mice



Restoration of foramen magnum size

Preservation of synchondrosis patency

Clinical Development Program of Recifercept

Natural History Study will provide baseline and longitudinal data for phase 2

Purpose of the studies

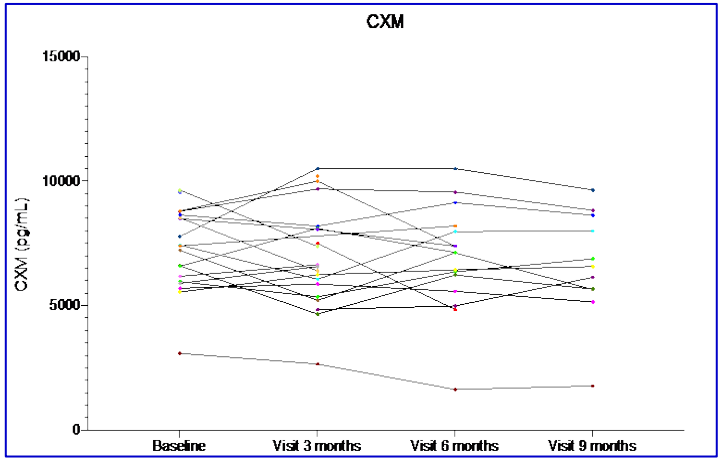
- Provide baseline anthropometric data for those entering interventional trials
- Refine the choice of measurements and the measurement technique for later trials
- Identify high performing sites (in terms of recruitment and data quality) for inclusion in phase 2/3 trials
- Identify and recruit families to the Achondroplasia programme
- Natural history data on biomarker

C4181003 (TA46-010) study in Copenhagen, 1 site, completed

- 23 children (age 2-14y), 3 monthly biomarker sampling and anthropometry (standing/sitting height and arm span)
- Establish relationship between biomarkers and growth velocity in Achondroplasia

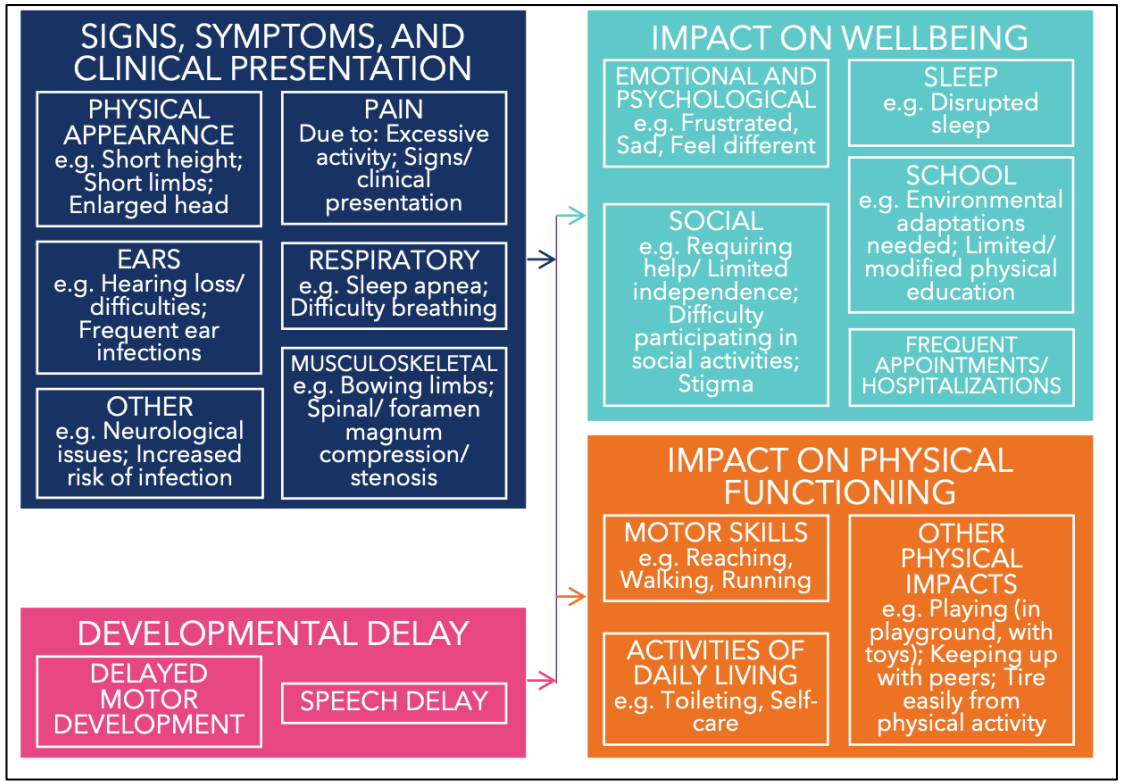
C4181001 (TA46-002) feeder study, 24 sites

- ≈ 300 children (age 0-15y), 1 yearly biomarker sampling and anthropometry
- Identify high performing sites (recruitment and data quality) for inclusion in phase 2/3 trials, identify and recruit families to the program
- Estimated Study Completion Date : September 6, 2028

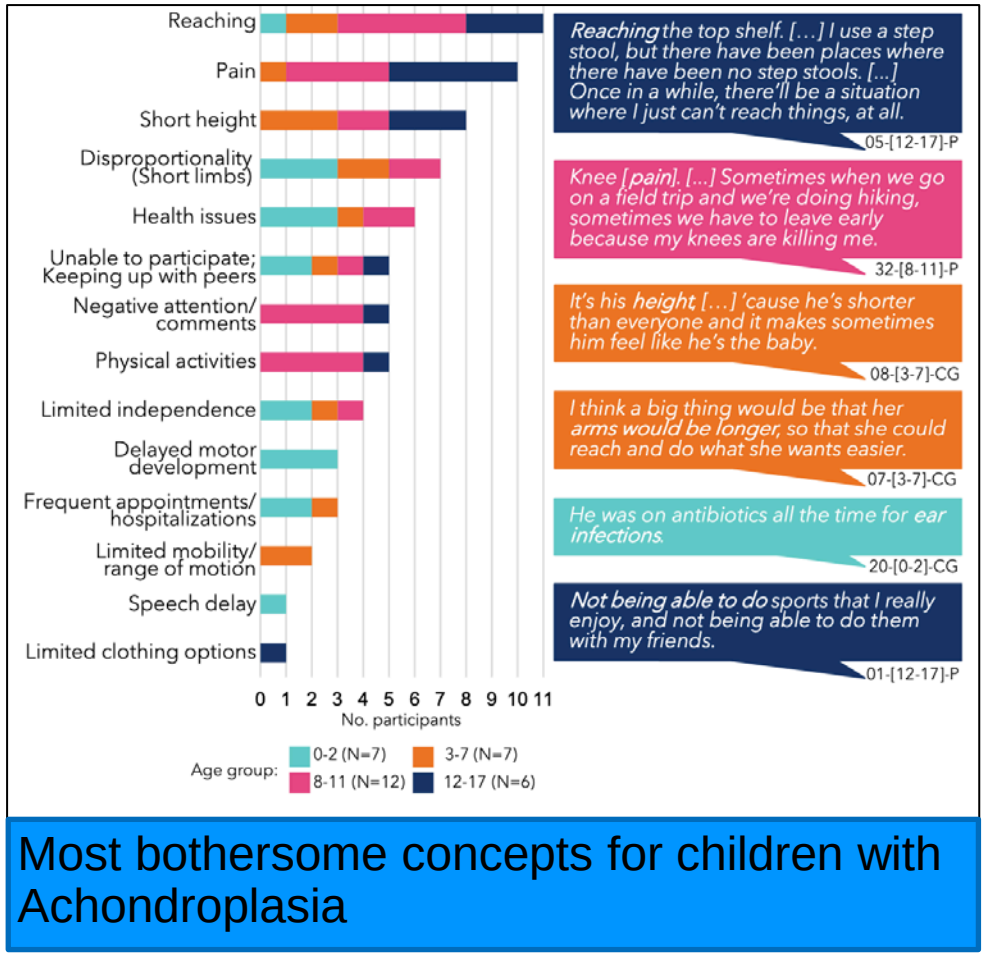


Biomarker study: CXM levels in children

Clinical outcome assessment in Achondroplasia clinical trials to better understand treatment effect.



Conceptual model



Most bothersome concepts for children with Achondroplasia

Development of assement tools to monitor treatment effect on these concepts

A Phase 2 Multiple Dose, Randomized Study To Assess The Safety, Tolerability, Pharmacokinetics and Efficacy of Recifercept in Children with Achondroplasia

Sponsor:	Pfizer Inc.
First child enrolled:	Dec 2020
Countries/Sites:	Denmark (1), Belgium (1), Spain (1), Italy (1), Portugal (1), US (3), Australia (1), Japan (3)
Number of sites:	12
Number of children:	63

Enrollment

- Enrollment will follow an age and dose-staggered approach (descending age and ascending dose) with review of safety and PK data by the study team before progression to the next enrollment block
  - Ages cohorts: 6 - <11 y; 2 - <6 y; 3 m - <2 y
- Progression to the next enrollment block will be after review of safety and PK data
- External DMC (eDMC) review is required for proceeding from Block A to Block B, and then only if safety signals are identified.
- Anthropometrist should be blinded to dose assignment. There will be no additional blinding.

Study Rationale & Design

- Participants will be children diagnosed with achondroplasia, already participating in study C4181001 natural history study and aged ≥3 months to ≤11 years
- 63 participants *(57+6 Japanese Cohort)* will be randomized to one of three doses;
  - Low Dose
  - Medium Dose
  - High Dose
- Enrollment will progress in an age and dose staggered manner (descending age and ascending dose).
- Participants will receive treatment with recifercept for 12 months. All participants who complete the study will be offered to enroll into an open-label extension (OLE) study.
- An interim analysis will be performed when at least 15 participants per dose aged ≥2 to <11 years have received 12 months of treatment with recifercept.

Phase 2 study for safety and efficacy of Recifercept: Endpoints

Primary endpoint (efficacy)

- Increase in height growth above expected

Primary endpoint (safety)

- Adverse events, labs, ECG, physical examination
- Injection site reactions as AESI – only safety signal from FIH
- Immunogenicity

Secondary endpoints

Growth

- Annualised growth velocity (height)
- Change in z-score (achondroplasia and normal stature reference)

Pharmacokinetics

- 2-3 PK samples after 1st dose followed by sparse sampling

Proportionality

- Sitting/standing height,
- Arm span:height
- Knee:lower segment (rhizomelia)
- Skull morphology (head circumference z-score, ratio of cranial measurements)

Secondary endpoints (cont.)

Comorbidities

- Sleep disordered breathing (polysomnography)

Patient-centred outcomes

- TBD

Biomarker

- CXM change from baseline

Exploratory endpoints

Comorbidities

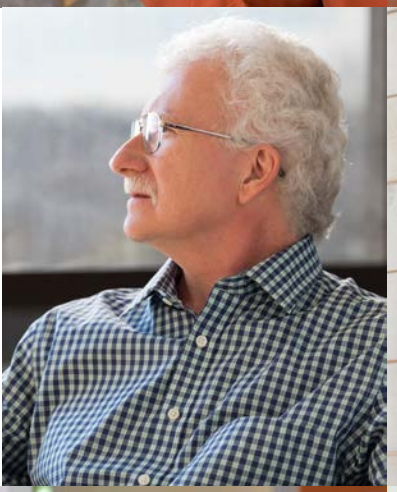
- Rates of surgical intervention
- Metabolic (anthropometric measurements, BMI)

Biomarker

- Change from baseline in serum growth biomarkers (P1NP, CTX, Pro-CNP)

0-2y cohort

- Safety and tolerability of recifercept in children with achondroplasia aged 0-2y
- Efficacy of recifercept in children with achondroplasia aged 0-2y






Thank You

Breakthroughs that change patients' lives