Therapies on the Horizon: Ongoing phase 2/3 studies

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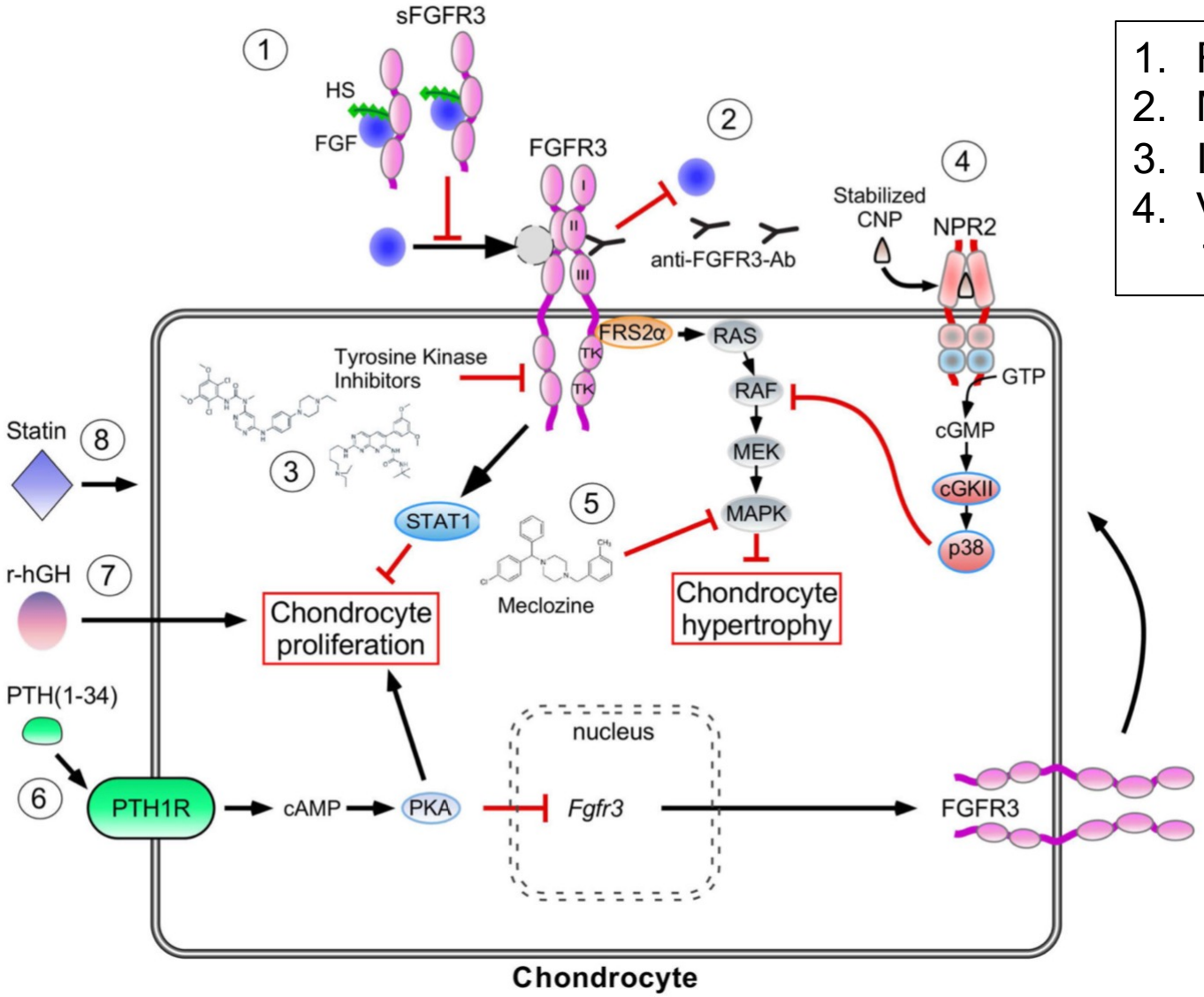
Potential Conflicts of Interest - Disclosure

NAME: Geert Mortier
AFFILIATION: UZ Leuven and KU Leuven

Consultancy fees from pharmaceutical companies:
Pfizer, BioMarin, Alexion, Kyowa Kirin, Mereo BioPharm, Clementia, Sanofi

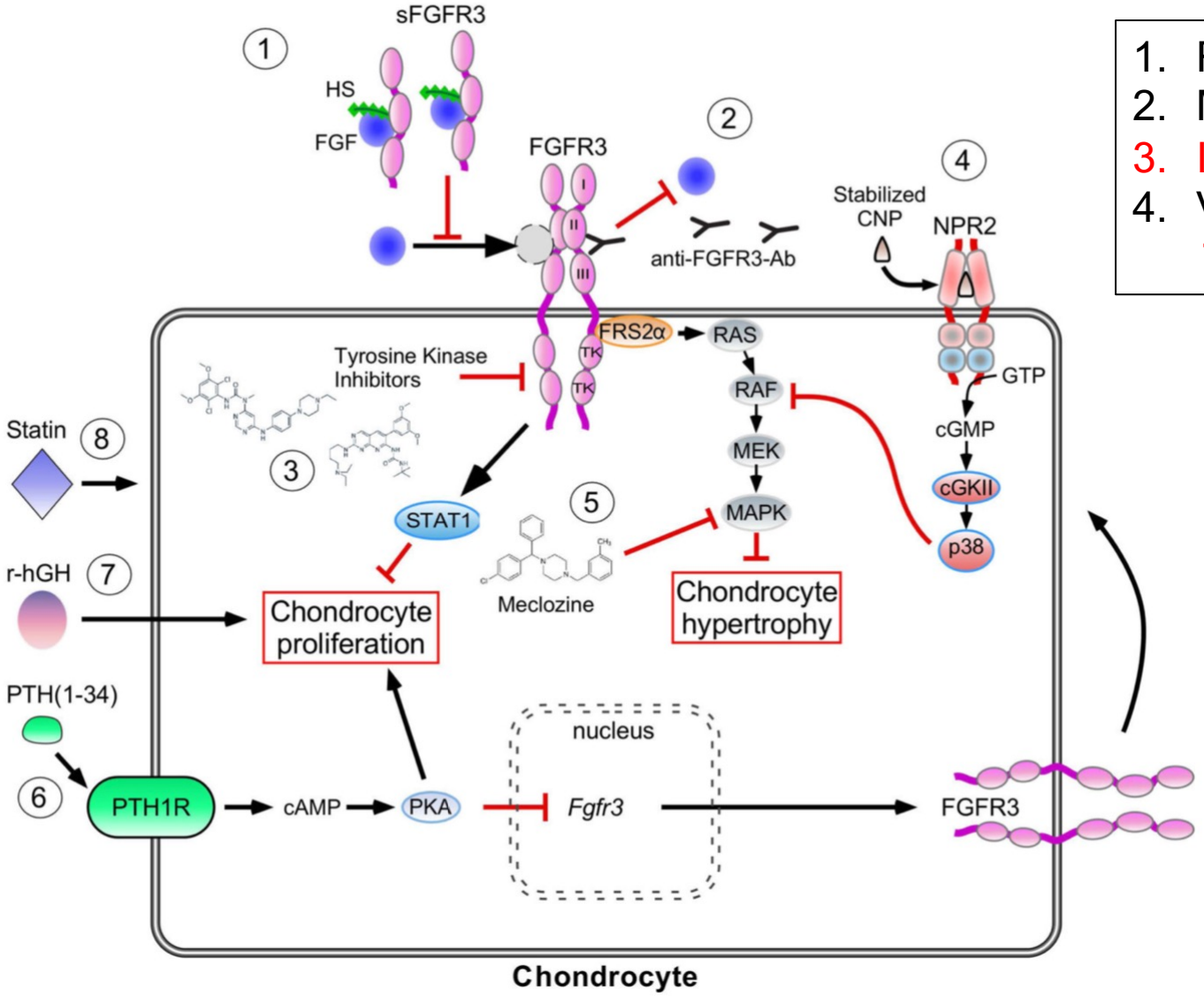
Possible targets for new drug development in achondroplasia



1. Recifercept (Pfizer)
2. Monoclonal Ab (Sanofi)
3. Infigratinib (QED therapeutics)
4. Vosoritide (Biomarin)
   TransCon CNP (Ascendis)

Ornitz et al Dev Dyn 2017

Possible targets for new drug development in achondroplasia



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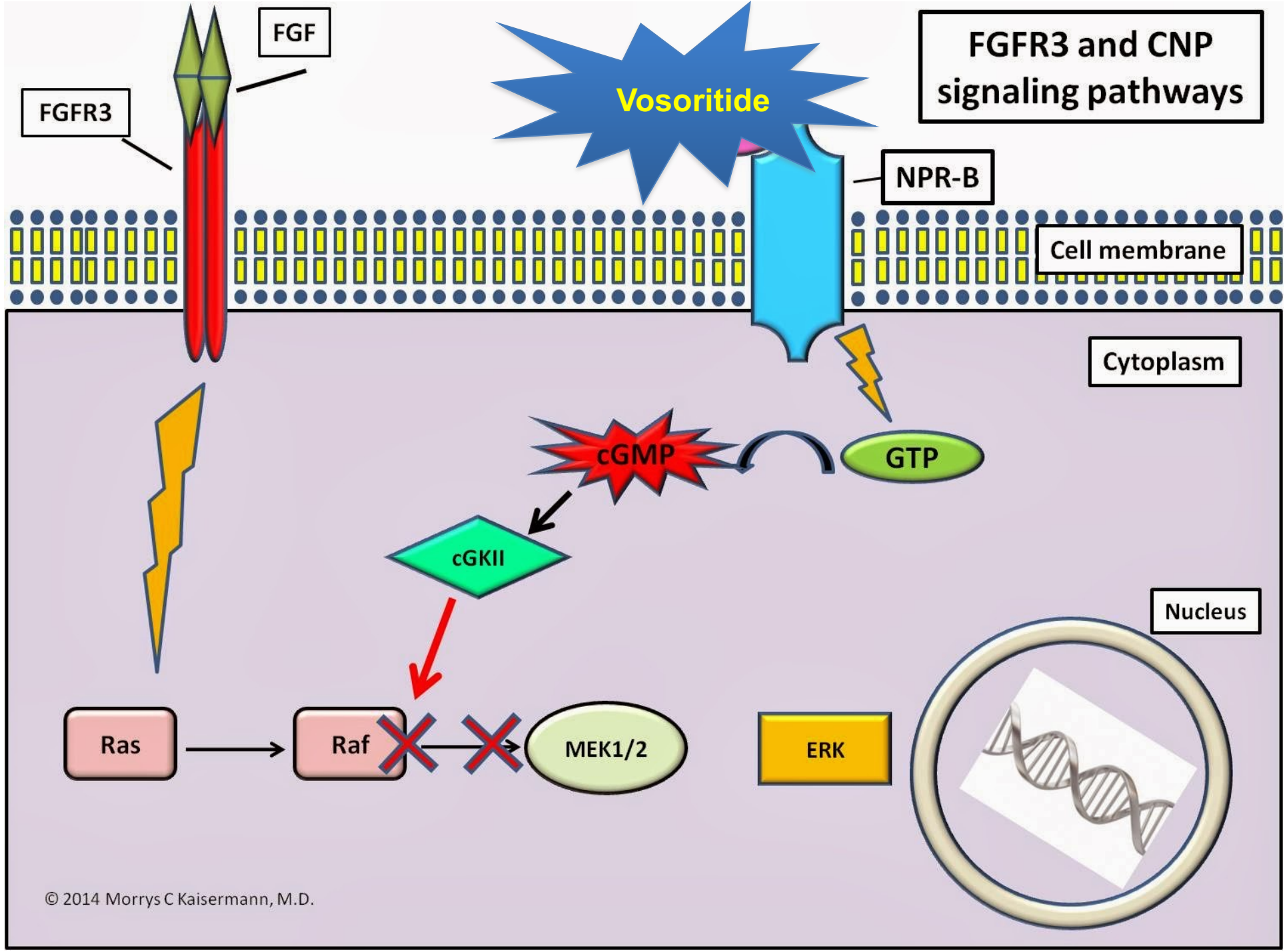
Ornitz et al Dev Dyn 2017


FGFR3 and CNP signaling pathways
FGF
FGFR3
Vosoritide
NPR-B
Cell membrane
Cytoplasm
cGMP
GTP
cGKII
Nucleus
Ras
Raf
MEK1/2
ERK
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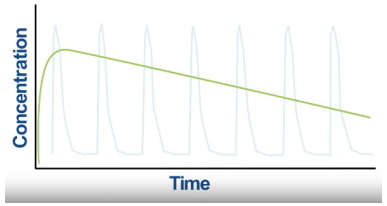
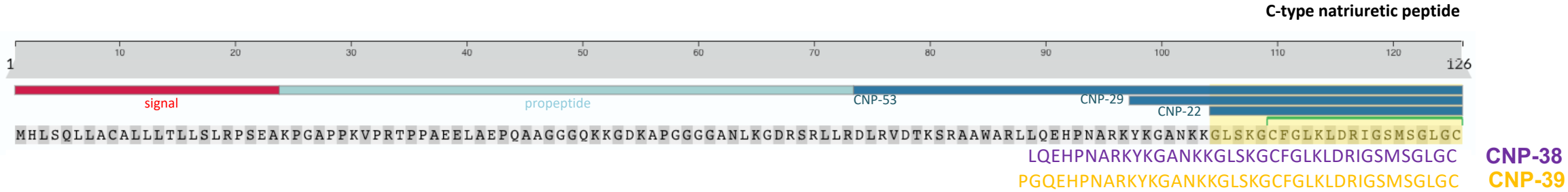
TransCon CNP (Ascendis Pharma)

Rationale: - more continuous exposure and avoidance of high concentrations (reduce side effects)
- reduce degradation by neutral endopeptidase (NEP)

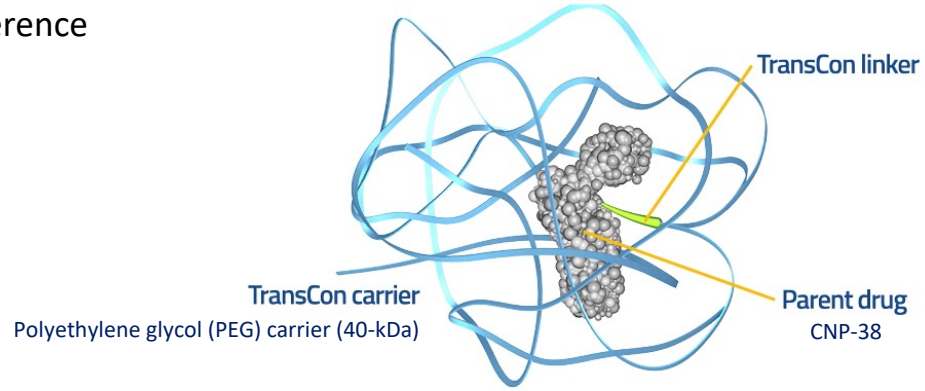


Native CNP (CNP-22) has a half-life of only 2-3 minutes
Vosoritide (CNP-39) has a half-life of 19 to 46 minutes
TransCon CNP (CNP-38) has a half-life of 120 hours



TransCon technology to - enhance efficacy and adherence
- improve convenience
- reduce caregiver burden

sustained release of CNP-38



Reduces renal clearance, proteolytic degradation and binding to NPR-C

Study of TransCon CNP in mice and monkeys

Bone length [millimeters [95% confidence interval] (% change from control)] determined by X-ray after 5 wk of daily bolus injection or continuous infusion of CNP-38 or vehicle control in FVB mice

	Subcutaneous Bolus Injection		Subcutaneous Continuous Infusion	
Measurement	Vehicle Control	CNP-38 203 μg/kg Per Day	Vehicle Control	CNP-38 203 μg/kg Per Day
Femur length[a]	14.2 [13.7; 14.8]	15.0 [14.5; 15.6] (5.5%)*	13.6 [13.0; 14.1]	14.6 [14.1; 15.2] (7.1%)*
Tibia length[b]	17.9 [17.7; 18.1]	18.7 [18.5; 18.9] (4.0%)*	17.6 [17.4; 17.8]	19.8 [19.6; 20.0] (12.2%)*,#
Spine length[c]	53.8 [52.4; 55.2]	59.8 [58.5; 61.2] (11.3%)*	53.6 [52.2; 55.0]	67.0 [65.6; 68.4] (25.0%)*,#

[a]Right femur.
[b]Right tibia.
[c]Lateral view.
*Different from vehicle control; #different from growth under subcutaneous bolus injection (one-factor ANOVA model on logarithmic transformed data); $P < 0.05$.

Estimated relative effects of CNP treatment on growth of body, tail, tibia, and ulna (relative increase in growth compared with vehicle treatment [% (95% confidence interval) in monkeys]

	TransCon CNP 40 μg CNP/kg Per Week	TransCon CNP 100 μg CNP/kg Per Week	Daily CNP-39 Molecule 20 μg CNP/kg Per Day
Body	1.0 (−2.3; 4.4)	4.8 (1.1; 8.5)*	3.3 (0.0; 6.6)*
Tail	1.4 (−2.7; 5.5)	8.6 (3.7; 13.4)*	2.8 (−1.3; 6.9)
Tibia	1.7 (−2.0; 5.4)	6.0 (2.1; 9.9)*	2.9 (−1.0; 6.8)
Ulna	0.9 (−2.8; 4.7)	2.7 (−1.1; 6.5)	0.8 (−2.9; 4.5)

*$P < 0.05$.

Histomorphometry data of the proximal tibial growth plate following weekly administration of TransCon CNP compared with the daily CNP-39 molecule for 26 wk to monkeys (% change from vehicle control)

		Treatment	
	TransCon CNP 40 μg CNP/kg Per Week	TransCon CNP 100 μg CNP/kg Per Week	Daily CNP-39 Molecule 20 μg/kg Per Day
No. animals per group	**4**	**4**	**4**
Bone, tibia (no. measured)	4	4	4
Proliferative zone width	−2	37[a]	16[a]
Hypertrophic zone width	7	38[a]	39[a]
Epiphyseal plate thickness	−4	16[a]	7

[a]Significantly different from control group; $P \leq 0.05$, based on statistical analysis of group means.

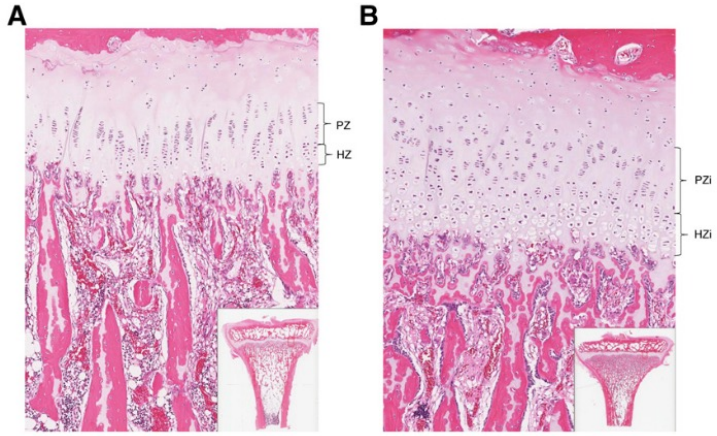


Fig. 4. Histomorphometry imaging of the proximal tibial physis following weekly administration of (A) vehicle control compared with (B) TransCon CNP (100 μg CNP/kg per week) for 26 weeks to monkeys. Footnote: PZ, proliferative zone; HZ, hypertrophic zone; PZi, increased cellularity and width of proliferative zone; HZi, increased cellularity and width of hypertrophic zone.

Breinholt VM et al. J Pharmacol Exp Ther 2019;370:459

In mice and monkeys, sustained exposure to CNP via TransCon CNP was more efficacious in stimulating bone growth than intermittent CNP exposure

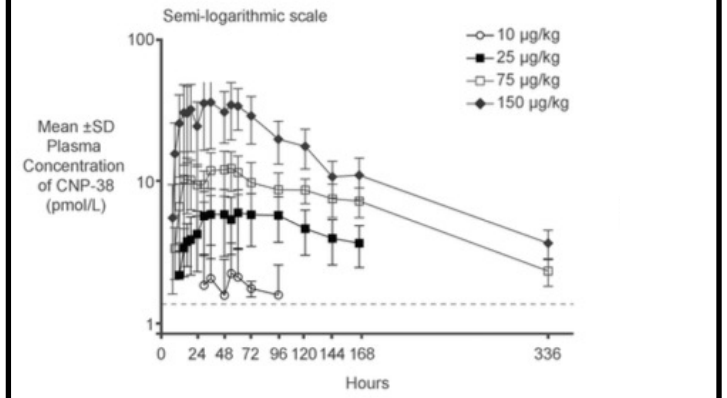
Phase 1 safety, tolerability, pharmacokinetics and pharmacodynamics results of a long-acting C-type natriuretic peptide prodrug, TransCon CNP

Breinholt VM et al. Br J Clin Pharmacol 2022;88:4763

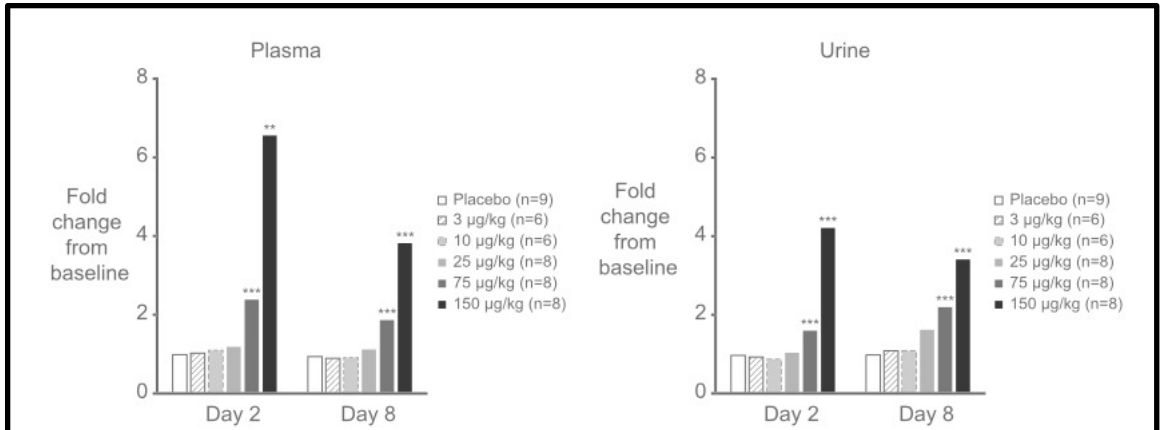
- Phase 1, first in human, randomized, double-blind, placebo controlled, single-ascending dose trial
- To evaluate safety, tolerability, pharmacodynamics and pharmacokinetics of SC administered TransCon CNP
- 44 healthy adult males (36 received the drug, 8 received placebo)
- Five dosing cohorts (up to 10 subjects per cohort: 6-8 received drug, 1-2 received placebo)
- Ascending doses: 3-10-25-75-150 ug CNP/kg
- Safety observational period of 4 weeks

Phase 1 safety, tolerability, pharmacokinetics and pharmacodynamics results of a long-acting C-type natriuretic peptide prodrug, TransCon CNP

Breinholt VM et al. Br J Clin Pharmacol 2022;88:4763



CNP-38 plasma concentration following single-dose administration of 10, 25, 75 and 150 µg/kg CNP to adult male subjects.



Normalized levels of cGMP (fold change from baseline) measured in both plasma and urine samples collected post-dose at days 2 and 8. **P < .01, *** P < .001.

TABLE 3 Summary of treatment-emergent adverse events

AE, n (%)	Dose cohort 3 µg CNP/kg (N = 6)	10 µg CNP/kg (N = 6)	25 µg CNP/kg (N = 8)	75 µg CNP/kg (N = 8)	150 µg CNP/kg (N = 8)	Placebo[a] (N = 9)	Total TransCon CNP subjects (N = 36)
Subject experienced any AE	5 (83.3)	4 (66.7)	5 (62.5)	8 (100)	6 (75.0)	7 (77.8)	28 (77.8)
Subject experienced any drug-related AE[b]	3 (50.0)	3 (50.0)	2 (25.0)	6 (75.0)	6 (75.0)	2 (22.2)	20 (55.6)
Discontinued trial participation due to an AE	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Subject experienced any moderate/severe AE	2 (33.3)	1 (16.7)	0 (0)	6 (75.0)	3 (37.5)	2 (22.2)	12 (33.3)
Subject experienced any SAE	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Subject death	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)

Note: Only TEAEs are presented (defined as an event with the date of AE onset being later than or equal to the date/time of the first injection of the dose).
[a]Consists of pooled dosage placebo groups. Moderate/severe AE: contact dermatitis; headache
[b]Defined as the causal relationship being definite, probable or possible as reported by the investigator.

SUMMARY

- Continuous exposure to CNP over at least 1 week
- Average half-life of approximately 120 hrs
- Sustained activation of NPR-B (cGMP) for at least 7 days after administration (>75 ug/kg)
- No major safety or tolerability concerns
- No cardiovascular side effects
- No evidence of an immunogenic response (anti-CNP Ab) was observed

ACcomplisH (NCT04085523): phase 2 clinical trial
A multicenter, double-blinded, randomized, placebo-controlled, dose escalation trial

- Evaluation of safety and efficacy of TransCon CNP administered SC
- Children received drug/placebo once a week for 12 months
- Actual enrollment: 57 participants (update 22/12/22)
- Study started in June 24, 2020

ACcomplisH (NCT04085523): phase 2 clinical trial
A multicenter, double-blinded, randomized, placebo-controlled, dose escalation trial

TransCon CNP: Phase 2 Trial Design

ACcomplisH TRIAL

Up to 60 children (ages 2–10 years) with achondroplasia

TransCon CNP vs. placebo (3:1 randomization)

12 subjects randomized in each dose cohort in a blinded manner

6 µg/kg → 20 µg/kg → 50 µg/kg → 100 µg/kg → >100 µg/kg

Data Monitoring Committee reviews blinded data after each dose cohort

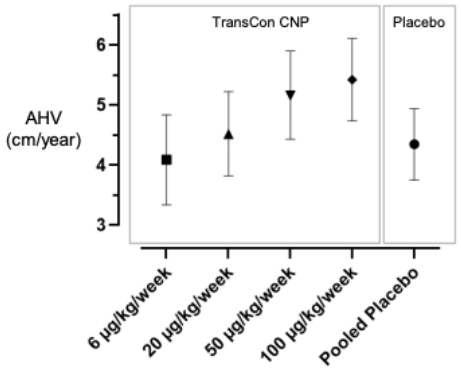
Open Label Extension Period to evaluate long-term safety and efficacy

Primary Endpoint
- Annualized height velocity

Key Secondary/Additional Endpoints
- Change in body proportionality
- Patient reported outcome (PRO) measures
- Exploratory biomarkers evaluated

TransCon CNP 100 µg/kg/week Demonstrated Superiority in AHV Compared to Placebo

Treatment Group (TransCon CNP Dose Levels or Placebo)	AHV (cm/year), n LS Mean [95% CI]	p-value (TransCon CNP vs. Pooled Placebo)
6 µg/kg/week	4.09, n=10 [3.34, 4.84]	0.6004
20 µg/kg/week	4.52, n=11 [3.82, 5.22]	0.7022
50 µg/kg/week	5.16, n=10 [4.43, 5.90]	0.0849
100 µg/kg/week	5.42, n=11 [4.74, 6.11]	0.0218
Pooled Placebo	4.35, n=15 [3.75, 4.94]	NA



TransCon CNP demonstrated a dose-response in AHV across the four dose groups

Safety Results Summary (Double-Blind Period)

- TransCon CNP was generally well tolerated, with no discontinuations
  - Frequency of TEAEs in each dose group was similar to placebo
- No serious AEs (SAEs) related to treatment were reported
  - Two unrelated SAEs were reported (febrile convulsion and viral infection)
- 95% of TransCon CNP patients and 93% of placebo patients reported TEAEs
  - 95% of TransCon CNP TEAEs were assessed as mild (Grade 1) in severity
- Injections were generally well tolerated with low frequency of injection site reactions
- No reported events of symptomatic hypotension
- For body proportionality, induced growth was proportional across all groups at Week 52

Observed safety results support continued development of TransCon CNP for children with achondroplasia

Open Label Extension (OLE) Efficacy and Safety Results*

- 57 of 57 patients completed the blinded period of ACcomplisH and continued in the OLE on 100 µg/kg/week with 100% retention
- Patients treated ≥6 months at 100 µg/kg/week in the blinded or OLE period demonstrated a consistent and sustained response with mean AHV of 5.39 cm/year (n=40)
- TransCon CNP continued to be well tolerated in the OLE period with safety results consistent with those observed in the blinded period for all patients

Open-label extension data confirms target product profile for once-weekly TransCon CNP 100 µg/kg/week

* Preliminary ACcomplisH Trial live database snapshot as of October 27, 2022.

Executive Summary

- In the Phase 2 ACcomplisH Trial in children with achondroplasia aged 2-10, once-weekly TransCon CNP demonstrated the potential to meet patient and caregiver needs for a safe, effective, tolerable, and convenient treatment
- The primary endpoint, annualized height velocity (AHV) at Week 52, demonstrated superiority of TransCon CNP at 100 µg/kg/week compared to placebo (p=0.0218)
- TransCon CNP was generally well tolerated with low frequency of injection site reactions; all 57 randomized children continued, with the longest treatment duration beyond two years
- Data showed robust and consistent results in prespecified analyses across age groups and dose levels, supporting continued development at the selected dose of 100 µg/kg/week

Next Steps

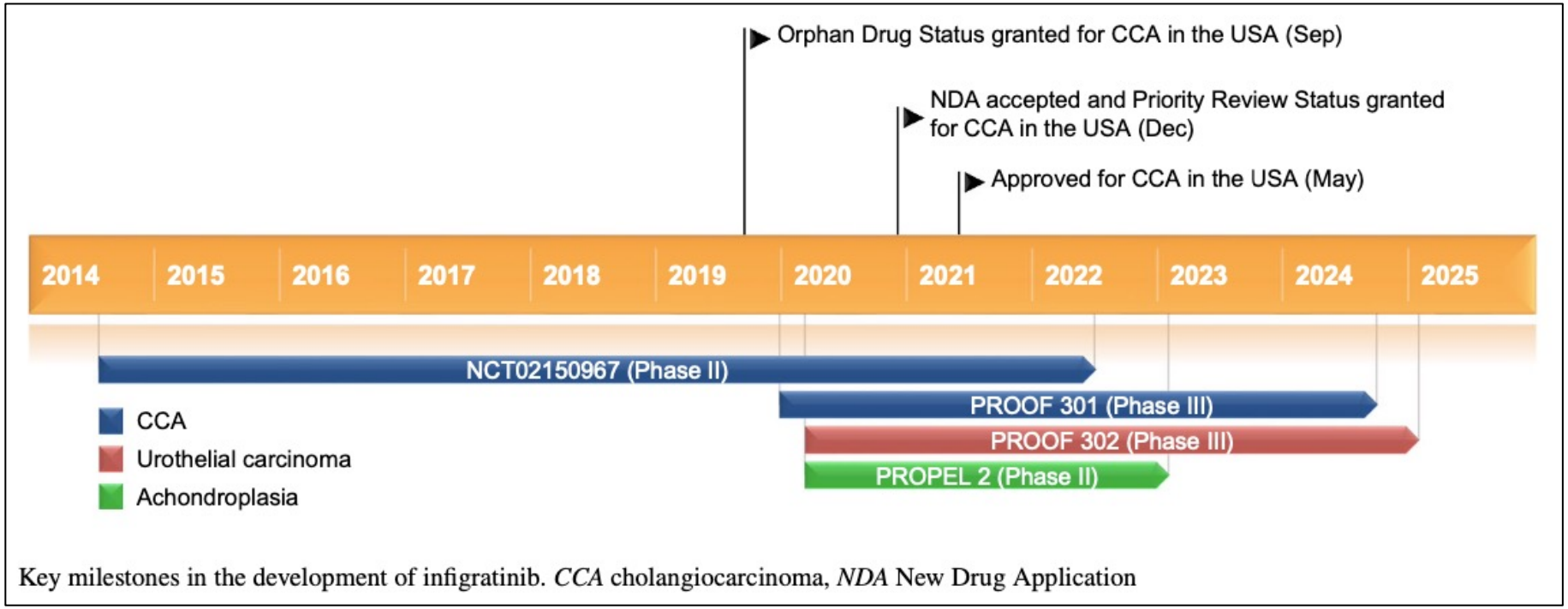
- IND submitted for ApproaCH, a global Phase 2b trial in 80 children with achondroplasia aged 2-11; enrollment targeted for completion in early 2023
  - TransCon CNP 100 µg/kg/week vs. Placebo (2:1)
- End of Phase 2 meetings with FDA and EMA planned
- Plan to file IND or similar for TransCon CNP in infants (age 0-2)
- Plan to file IND or similar for a combination trial with TransCon hGH and TransCon CNP
- Expand global reach with finalizing trial in China* and initiating trial in Japan

Infigratinib (QED Therapeutics)

Features and properties of infigratinib	
Alternative names	BBP-831; BGJ-398; BGJ-398 phosphate; Infigratinib phosphate; NVP-BGJ398; TRUSELTIQ
Class	Aniline compounds, Antineoplastics, Chlorobenzenes, Methylurea compounds, Phenyl ethers, Piperazines, Pyrimidines, Small molecules
Mechanism of action	Fibroblast growth factor receptor (FGFR)-specific tyrosine kinase inhibitor that inhibits tumour angiogenesis and proliferation, leading to tumour cell death
Route of administration	Oral
Pharmacodynamics	Inhibits FGFRs, which are involved in malignant cell proliferation in tumours with *FGFR* alterations, thereby reducing tumour growth; exhibited anti-tumour activity in xenograft models of cholangiocarcinoma
Pharmacokinetics	Exhibits non-linear pharmacokinetics in patients with cholangiocarcinoma; drug exposure increased following food; t_{max} 6 h; mainly protein-bound; terminal $t_{1/2}$ 33.5 h; mainly metabolised by CYP3A4
Adverse reactions	
Most frequent (> 40%)	Nail toxicity, stomatitis, dry eye, fatigue
Laboratory abnormalities (> 50%)	Increased: creatinine, phosphate, alkaline phosphate, alanine aminotransferase Decreased: phosphate, haemoglobin
Special warnings and precautions	Retinal pigment epithelial detachment, hyperphosphatemia and soft tissue mineralization, embryo-foetal toxicity
ATC codes	
WHO ATC code	L01X-E (Protein kinase inhibitors)
EphMRA ATC code	L1H (Protein Kinase Inhibitor Antineoplastics)
Chemical name	3-(2,6-dichloro-3,5-dimethoxyphenyl)-1-[6-[4-(4-ethylpiperazin-1-yl)phenylamino]pyrimidin-4-yl]-1-methylurea phosphate (1:1)

Kang C. Drugs 2021;81:1355

Clinical trials of infigratinib



Key milestones in the development of infigratinib. *CCA* cholangiocarcinoma, *NDA* New Drug Application

Key clinical trials of infigratinib

Indication	Phase	Status	Location(s)	Identifier	Sponsor(s)
Cholangiocarcinoma	III	Ongoing	Global	NCT03773302, EudraCT2018-004004-19, PROOF 301	LianBio, QED Therapeutics
Cholangiocarcinoma	II	Ongoing	Global	NCT02150967, EudraCT2013-005085-19	Novartis Pharmaceuticals, QED Therapeutics
Urothelial carcinoma	III	Ongoing	Global	NCT04197986, EudraCT2019-003248-63, PROOF 302	QED Therapeutics
Achondroplasia	II	Ongoing	Global	NCT04265651, EudraCT2019-002954-21, PROPEL 2	QED Therapeutics

Activating genomic alterations in FGFR signaling resulting in cancer

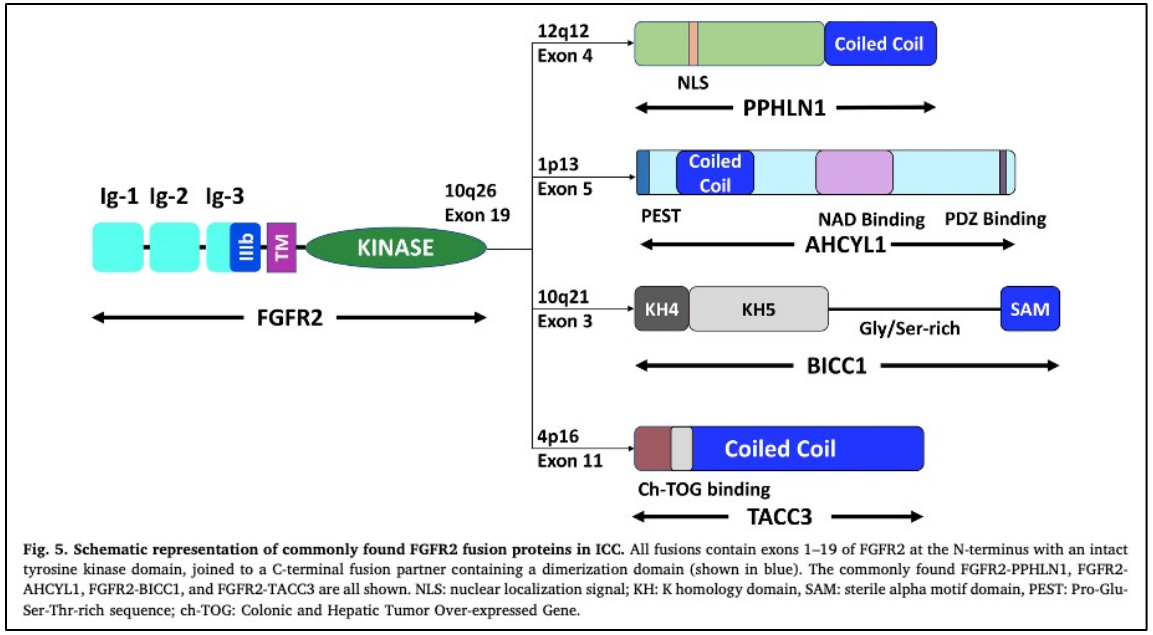


Fig. 5. Schematic representation of commonly found FGFR2 fusion proteins in ICC. All fusions contain exons 1–19 of FGFR2 at the N-terminus with an intact tyrosine kinase domain, joined to a C-terminal fusion partner containing a dimerization domain (shown in blue). The commonly found FGFR2-PPHLN1, FGFR2-AHCYL1, FGFR2-BICC1, and FGFR2-TACC3 are all shown. NLS: nuclear localization signal; KH: K homology domain, SAM: sterile alpha motif domain, PEST: Pro-Glu-Ser-Thr-rich sequence; ch-TOG: Colonic and Hepatic Tumor Over-expressed Gene.

FGFR2 fusions in cholangiocarcinoma

Fangda L et al. Cytokine Growth Factor Rev 2020;52:56

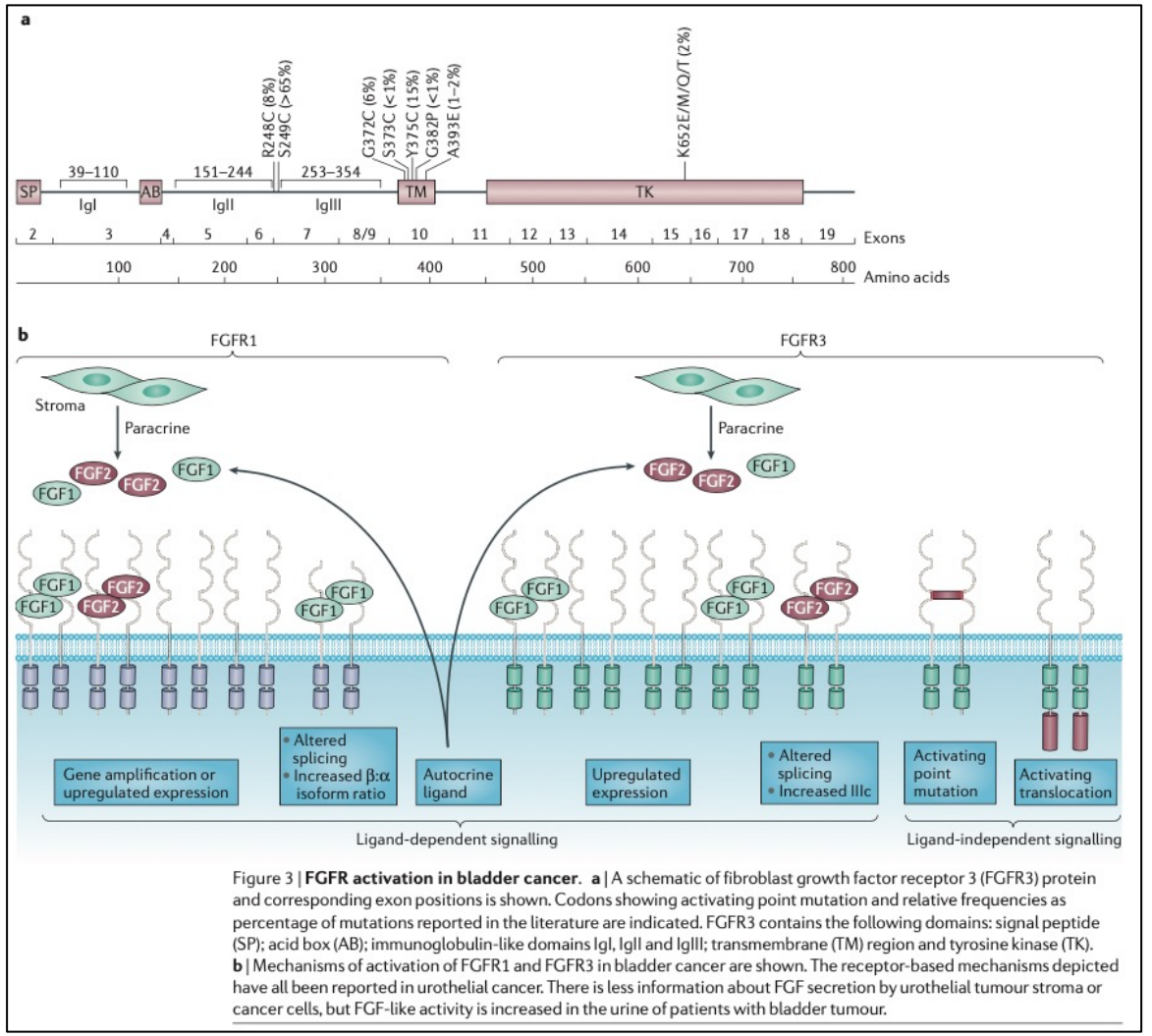
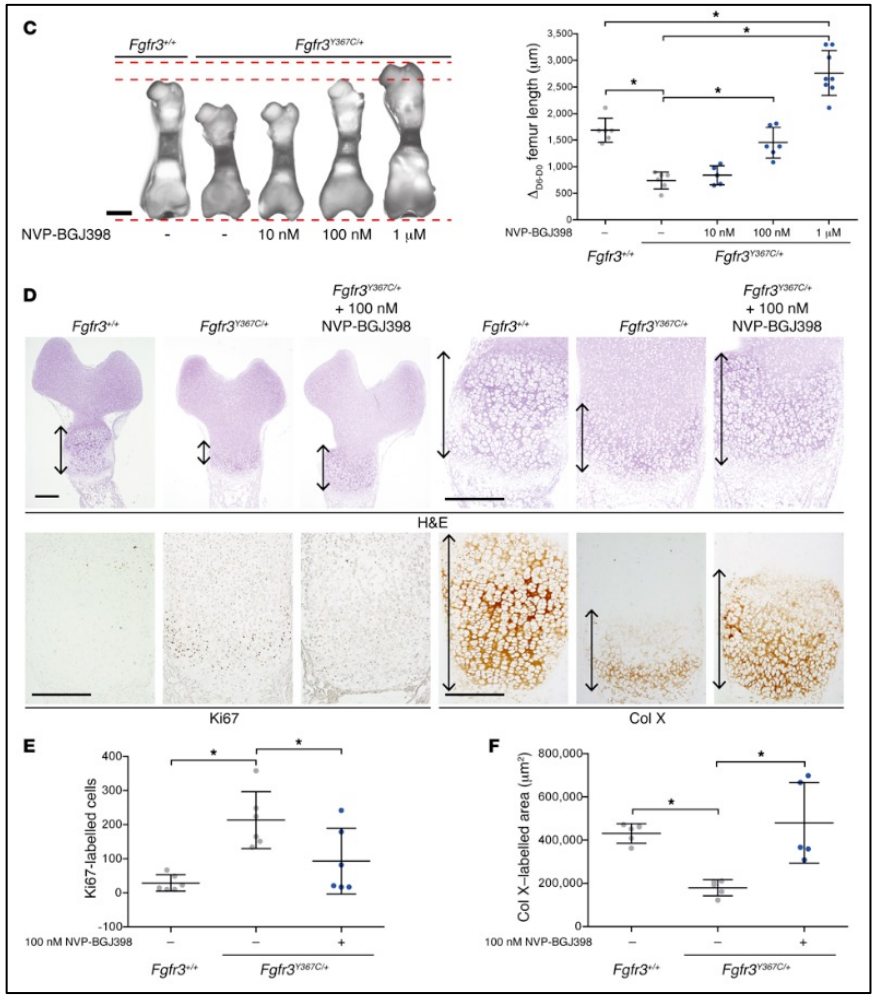


Figure 3 | **FGFR activation in bladder cancer.** **a** | A schematic of fibroblast growth factor receptor 3 (FGFR3) protein and corresponding exon positions is shown. Codons showing activating point mutation and relative frequencies as percentage of mutations reported in the literature are indicated. FGFR3 contains the following domains: signal peptide (SP); acid box (AB); immunoglobulin-like domains IgI, IgII and IgIII; transmembrane (TM) region and tyrosine kinase (TK). **b** | Mechanisms of activation of FGFR1 and FGFR3 in bladder cancer are shown. The receptor-based mechanisms depicted have all been reported in urothelial cancer. There is less information about FGF secretion by urothelial tumour stroma or cancer cells, but FGF-like activity is increased in the urine of patients with bladder tumour.

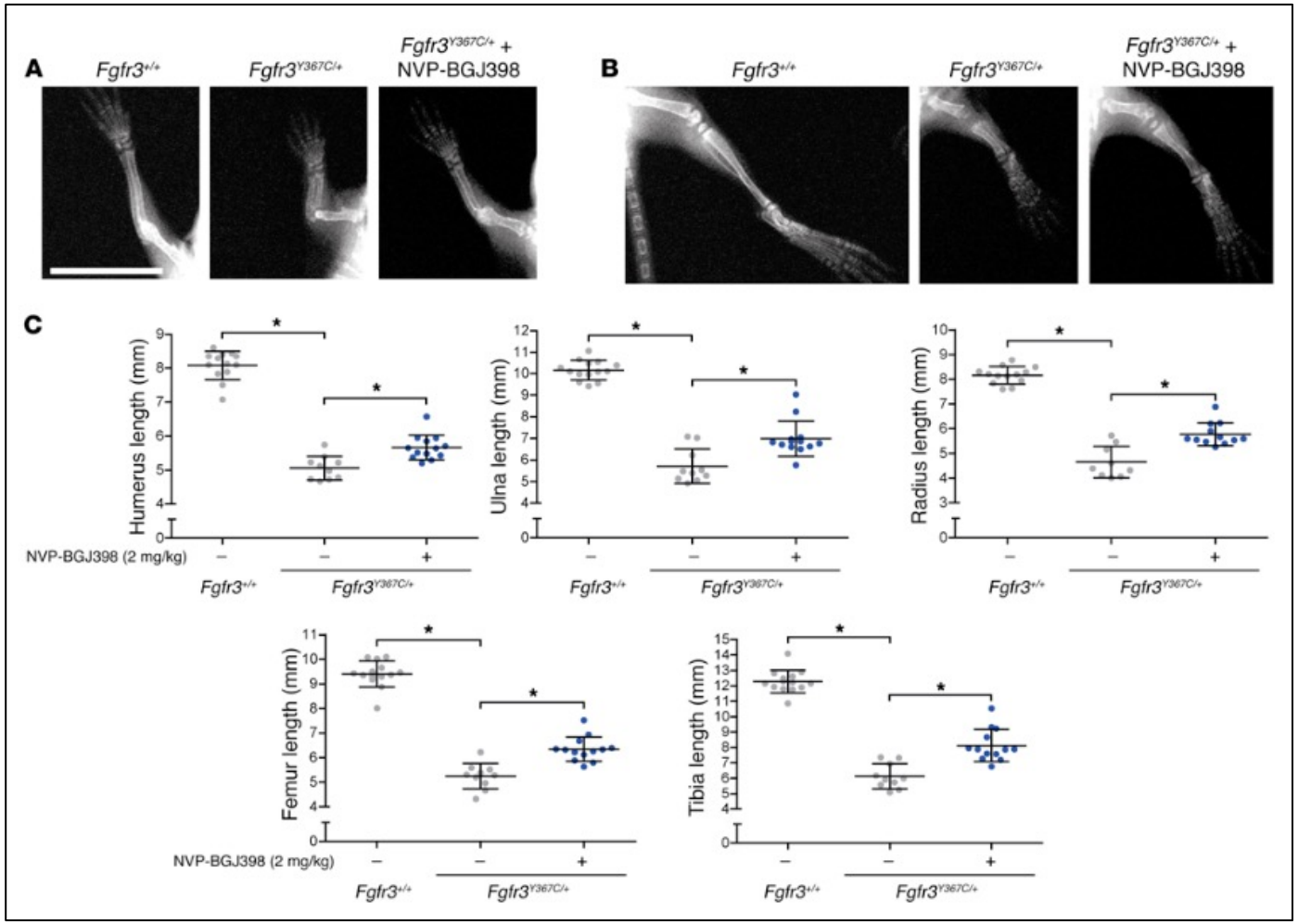
Activation of FGFR1/FGFR3 in bladder cancer

Knowles MA and Hurst CD. Nat Rev Cancer 2015;15:25

NVP-BGJ398 inhibits FGFR3 signaling and rescues endochondral and intramembranous ossification in an ACH mouse model



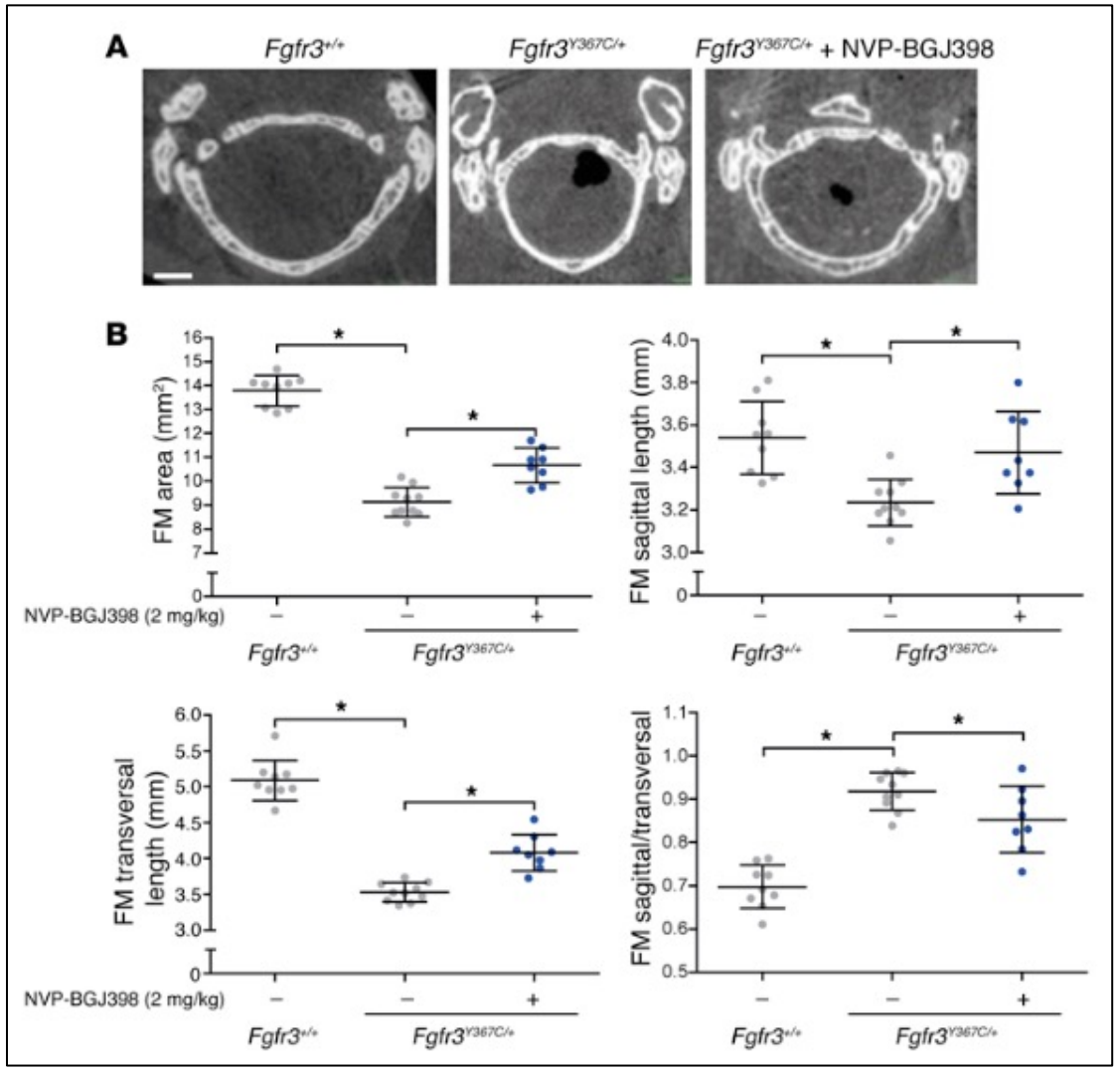
NVP-BGJ398 restores bone growth in *Fgfr3*$^{Y367C/+}$ embryonic femurs (after 6 days in "ex vivo" cultures)



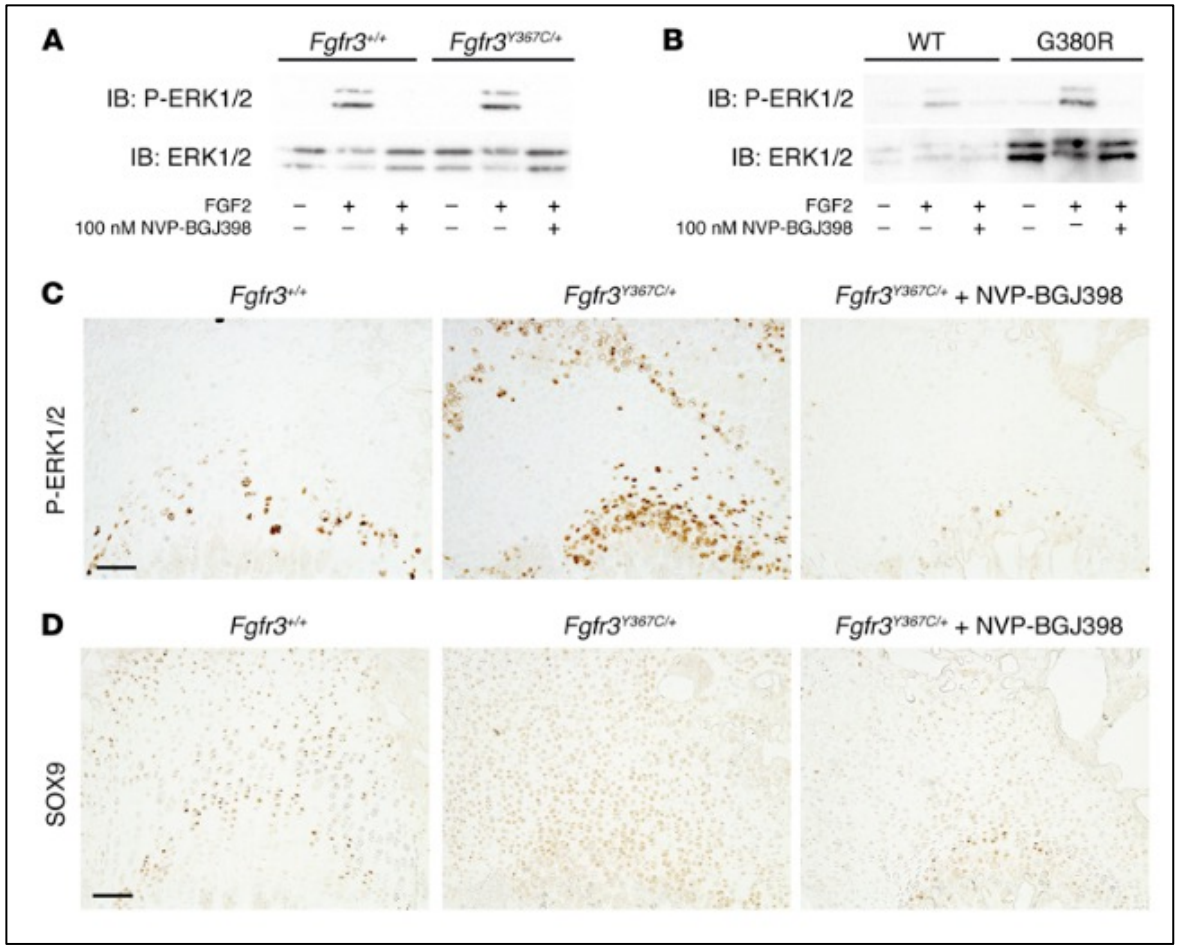
NVP-BGJ398 improves growth of the appendicular skeleton in *Fgfr3*$^{Y367C/+}$ mice (treatment of newborn mice daily with SC injections at 2mg/kg/d for 15 days)

Komla-Ebri D et al. J Clin Invest 2016;126:1871

NVP-BGJ398 inhibits FGFR3 signaling and rescues endochondral and intramembranous ossification in an ACH mouse model



NVP-BGJ398 increases FM size in *Fgfr3*$^{Y367C/+}$ mice
(treatment of newborn mice daily with SC injections at 2mg/kg/d for 15 days)



NVP-BGJ398 rescues defective FGFR3 signaling
(mouse primary chondrocytes (A); human primary chondrocytes (B); mouse growth plates (C))

Komla-Ebri D et al. J Clin Invest 2016;126:1871

PROPEL program to investigate the safety and efficacy of infigratinib in achondroplasia

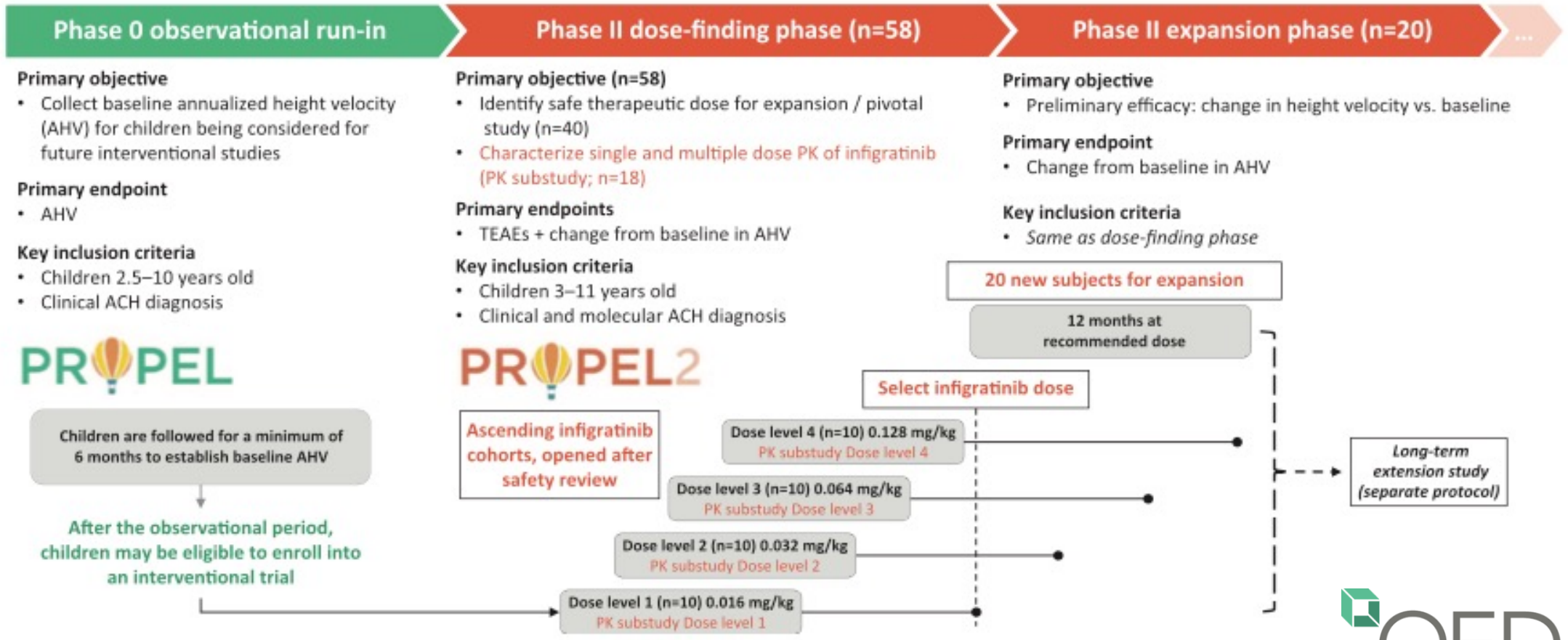
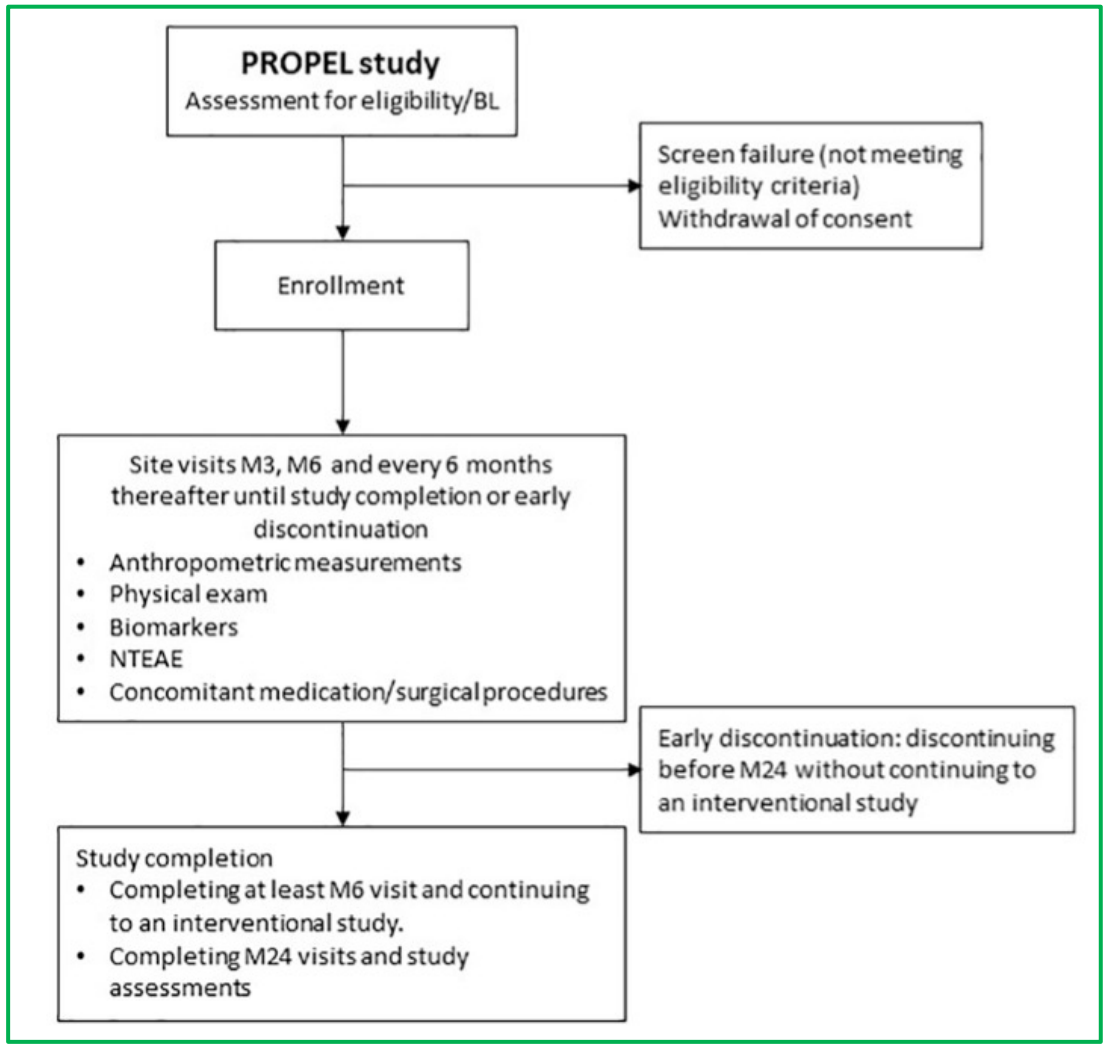
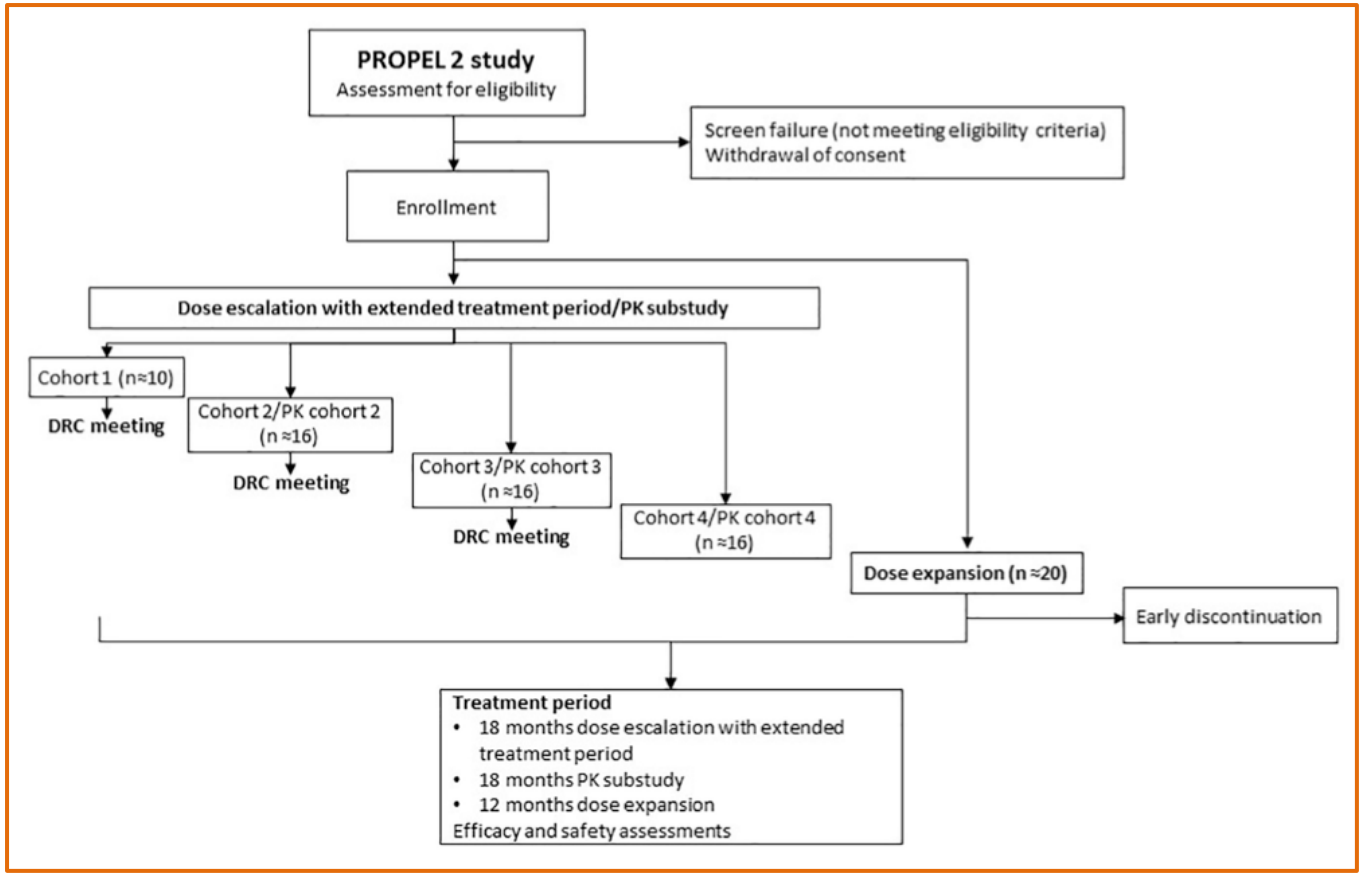


Figure 1. Design of the PROPEL and PROPEL 2 studies.
ACH, achondroplasia; PK, pharmacokinetic; TEAE, treatment-emergent adverse event.

QED therapeutics
a bridgebio company

PROPEL program to investigate the safety and efficacy of infigratinib in achondroplasia



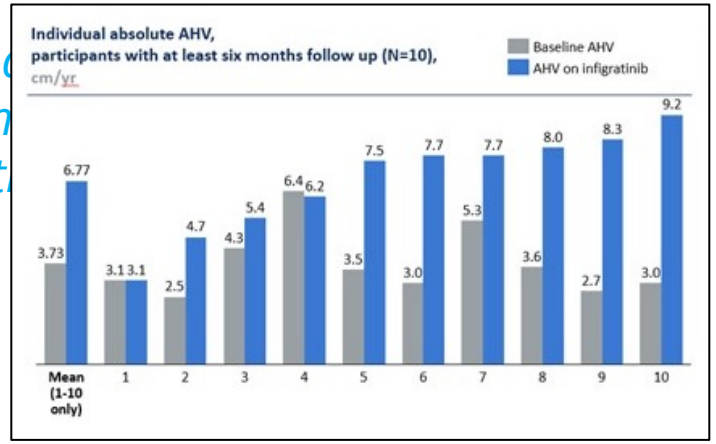


First child enrolled in August 2019
Expected sample size: 200

First dose administered in July 2020

QED therapeutics
a bridgebio company

PALO ALTO, Calif., March 06, 2023 (GLOBE NEWSWIRE) -- BridgeBio Pharma, Inc., biopharmaceutical company focused on genetic diseases and cancers, today ann PROPEL2, a Phase 2 trial of the investigational therapy infigratinib in children wit



Key results from the clinical trial include:

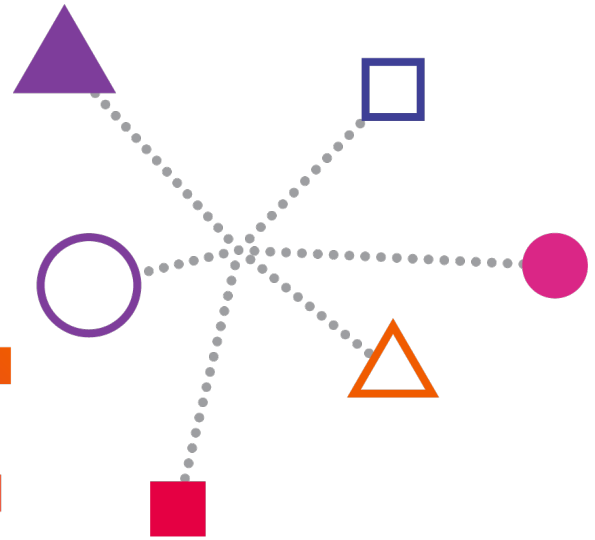
- Mean increase from baseline in AHV (cohort 5 – 0,25 mg/kg) was +3.04 cm/yr (p = 0.0022)
- Average change from baseline in AHV was +3.81 cm/yr for the 8 responders
- Previously reported change from baseline in AHV (cohort 4) was +1.52 cm/yr
- Statistically significant increase from baseline in collagen X levels (cohort 5) (p=0.03)
- No serious adverse events (SAEs) or discontinuations due to AEs were reported in any cohort

TAKE HOME MESSAGE

- TransCon CNP:
  - Phase 2 study (ACcomplisH)
  - Age group 2-10 yrs; n=57; longest period is 2 years
  - 100 ug/kg weekly SC
  - Mean AGV: 5.4 cm (comparable to vosoritide)
  - Well tolerated (no SAEs)

- Infigratinib:
  - Phase 2 study (PROPEL2)
  - Age group 3-11 yrs; n=50; longest period is 6 months (?)
  - 0,25 mg/kg daily oral
  - Mean AGV: 6.77 cm (2x effect of vosoritide)
  - Well tolerated (no SAEs)

Thank you for your attention!



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