Poster 402P

Phase 1 study of selumetinib in Chinese pediatric and adult patients (pts) with neurofibromatosis type 1 (NF1) and inoperable plexiform neurofibromas (PN): Interim results

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OBJECTIVE

- Here, we report interim results from an ongoing Phase 1 study evaluating selumetinib for the first time in pediatric and adult patients with neurofibromatosis type 1 (NF1) and inoperable plexiform neurofibromas (PN) in China

CONCLUSIONS

- The pharmacokinetics (PK) of selumetinib was generally consistent between the pediatric and adult cohorts, with rapid absorption and no significant accumulation following multiple doses
  - The PK profile of selumetinib in Chinese patients was similar to that seen in the pivotal SPRINT trial[6]
- Based on these interim analysis results from an ongoing Phase 1 study, selumetinib at a dosage of 25 mg/m^2 twice daily was well tolerated with a manageable safety profile in both pediatric and adult patients with NF1 and inoperable PN in China
  - The safety profile was in line with the known safety profile of selumetinib and no new safety concerns were identified
- Selumetinib demonstrated promising efficacy in both pediatric and adult patients with NF1-PN at the interim data cut-off, with most patients experiencing a reduction in target PN volume
- Selumetinib may address an unmet medical need for patients with NF1 and inoperable PN in China

PLAIN LANGUAGE SUMMARY

Why did we perform this research?
Neurofibromatosis type 1 (NF1) is a genetic condition where some people living with it develop non-cancerous tumors around their nerves called plexiform neurofibromas (NF1-PN). NF1-PN can grow very large and cause various problems depending on where they are in the body. Surgery can treat NF1-PN but it is not always possible.[1–4] Selumetinib is a drug that can be used to treat children with NF1-PN who are at least 2 years old in the USA or at least 3 years old in Europe.[5,6] The goal of this study was to investigate selumetinib treatment in children and adults with NF1-PN in China.

How did we perform this research?
This is an ongoing clinical trial that includes 16 children and 16 adults with NF1-PN in China. The aims of this study are to investigate the effect of selumetinib on shrinking the size of NF1-PN, how it can help relieve symptoms associated with them, how the recommended dose of selumetinib works in a Chinese population, and if selumetinib causes any new side effects.

What were the findings of this research and what are the implications?
In both children and adults, selumetinib was able to shrink the size of their NF1-PN, and the side effects were safely managed. In addition, selumetinib improved pain and quality of life for most patients. The recommended dose of selumetinib does not need to be changed for patients in China.

References: 1. Akshintala S et al. *Neuro Oncol* 2020;22:1368–1378; 2. Nguyen R et al. *Orphanet J Rare Dis* 2012;7:75; 3. Tucker T et al. *J Med Genet* 2009;46:81–85; 4. Gross AM et al. *N Engl J Med* 2020;382:1430–1442; 5. AstraZeneca Pharmaceuticals LP. Koselugo (selumetinib) Prescribing Information. 2021; 6. AstraZeneca Pharmaceuticals LP. Koselugo (selumetinib) Summary of Product Characteristics. 2022.

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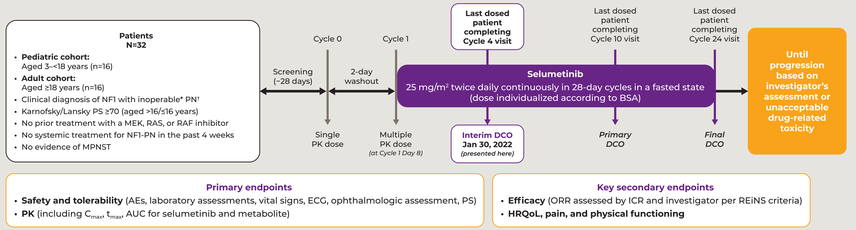
BACKGROUND

- NF1 is an autosomal dominant disorder arising from an *NF1* mutation, affecting 1 in 2000 to 1 in 6000 individuals worldwide[1]
  - PN are nerve sheath tumors that occur in up to 50% of patients with NF1; they can cause severe morbidity and negatively impact patient quality of life[1–4]
- Although surgery is a treatment option for NF1-PN, complete resection is often challenging and residual PN after resection can continue to grow[3,5–8]
- Based on results of the pivotal SPRINT trial,[9] selumetinib (ARRY-142886, AZD6244), an orally available selective MEK1/2 inhibitor, is the only MEK1/2 inhibitor approved by the U.S. Food and Drug Administration (age ≥2 years) and the European Medicines Agency (age ≥3 years) for pediatric patients with NF1 and symptomatic, inoperable PN[10,11]
- In China, patients with NF1 and inoperable PN have a considerable unmet medical need as there are no approved medical treatments

STUDY DESIGN AND METHODS

Figure 1. Study design



Primary endpoints
- **Safety and tolerability** (AEs, laboratory assessments, vital signs, ECG, ophthalmologic assessment, PS)
- **PK** (including C_{max}, t_{max} AUC for selumetinib and metabolite)

Key secondary endpoints
- **Efficacy** (ORR assessed by ICR and investigator per REiNS criteria)
- **HRQoL, pain, and physical functioning**

- This Phase 1, single-arm study was conducted at two centers in China and evaluated selumetinib at a dosage of 25 mg/m^2 twice daily in a capsule formulation in two independent cohorts (pediatric and adult) (**Figure 1**)
- The primary endpoints were safety, tolerability, and pharmacokinetics (PK), and secondary endpoints included efficacy, health-related quality of life, pain, and physical functioning (**Figure 1**)
- The data presented here are from an interim analysis performed after the last dosed patient completed the first post-baseline response assessment at Cycle 4 Day 28 (interim data cut-off Jan 30, 2022)
- All data were analyzed descriptively

*Inoperable PN was defined as PN that cannot be completely removed by surgery without risk of substantial morbidity due to encasement of, or close proximity to, vital structures, invasiveness, or high vascularity of the PN; †Patients must have had ≥1 measurable PN (≥3 cm). The target PN was defined as the most clinically relevant PN; only one non-target lesion could be selected, if any.
Intensive PK samples were collected on Cycle 1 Day 8 for assessment of the 12-hour PK profile at steady state. The SRC evaluated preliminary tolerability and safety data, as well as PK data (if available) after the first six patients in both cohorts had received approximately three cycles of treatment. Additional enrollment was initiated per SRC recommendation. Long-term post-treatment safety follow-up assessments will be conducted for 1 year (at 6 and 12 months post treatment) for pediatric patients only.
AE, adverse event; AUC, area under the concentration–time curve; BSA, body surface area; C_{max}, maximum plasma concentration; DCO, data cut-off; ECG, electrocardiogram; HRQoL, health-related quality of life; ICR, independent central review; MPNST, malignant peripheral nerve sheath tumor; NF1, neurofibromatosis type 1; ORR, objective response rate; PK, pharmacokinetics; PN, plexiform neurofibromas; PS, performance status; REiNS, Response Evaluation in Neurofibromatosis and Schwannomatosis; SRC, Safety Review Committee; t_{max}, time to maximum plasma concentration.

RESULTS

- Overall, 16 pediatric and 16 adult patients received selumetinib, and all patients remained on treatment at interim data cut-off
  - Median actual/total treatment duration was 4.8/4.8 months and 6.7/6.6 months for the pediatric and adult patients, respectively
- Key baseline demographics and clinical characteristics, including target PN-related morbidities and target PN location, are shown in **Table 1**

Safety

- No adverse events (AEs) leading to death or discontinuation of selumetinib were reported
- All patients experienced ≥1 AE; the most common AE was blood albumin decreased in pediatric patients (**Table 2**) and dermatitis acneiform in adult patients (**Table 3**)
  - In total, 12 pediatric patients (75%) (**Table 2**) and all adult patients (**Table 3**) experienced ≥1 treatment-related AE
    - One adult patient experienced a grade 3 treatment-related AE (paronychia) leading to dose reduction
  - One pediatric patient experienced a grade 3 serious AE of sepsis leading to selumetinib interruption, which was not considered to be treatment related
  - No grade 4 or 5 AEs were reported

Pharmacokinetics

- **Rapid absorption:** median time to maximum plasma concentration (C_{max}) and time to C_{max} at steady state ($C_{max,ss}$) of 1.5 hours (both) in pediatric patients and 1.0 and 1.5 hours, respectively, in adult patients
- **Higher exposure of selumetinib versus active metabolite:** metabolite:parent ratio of area under the concentration–time curve from 0 hours to 12 hours (AUC_{0-12}) and C_{max} of ≤0.085 in pediatric patients and ≤0.079 in adult patients
- **Rapid elimination:** half-life of 7.20 hours in pediatric patients and 7.49 hours in adult patients
- **No obvious accumulation after multiple dosing:** AUC_{0-12} and C_{max} accumulation ratio of ≤1.52 for pediatric patients and ≤1.34 for adult patients
- **Moderate variability of PK exposure in pediatric patients at steady state:** $AUC_{0-12,ss}$ and $C_{max,ss}$ geometric coefficient of variation (gCV) of 32–44%
  - Geometric mean of $C_{max,ss}$ of 1032 ng/mL and $AUC_{0-12,ss}$ of 2961 hours*ng/mL
- **Low-to-moderate variability of PK exposure in adult patients at steady state:** $AUC_{0-12,ss}$ and $C_{max,ss}$ gCV of 20–32%
  - Geometric mean of $C_{max,ss}$ of 1168 ng/mL and $AUC_{0-12,ss}$ of 3932 hours*ng/mL

Efficacy

- Response and PN volume change assessed by independent central review (ICR) and investigator as per Response Evaluation in Neurofibromatosis and Schwannomatosis criteria are shown in **Table 4**
  - Best percentage change in PN volume with a reduction of ≥20% from baseline reported for:
    - Pediatric patients: 4/16 (25%) per ICR and 12/16 (75%) per investigator (**Figure 2**)
    - Adult patients: 8/15 (53%) per ICR and 5/15 (33%) per investigator
- All non-target lesions were non-progressive by the interim data cut-off in all patients per both ICR and investigator; 1 pediatric patient (100%) and 5/6 adult patients (83%) had a non-target lesion volume reduction as best percentage change
- Most patients experienced an improvement from baseline in PN-related pain, overall pain, and PN-related problems over time

Table 1. Baseline demographics and clinical characteristics

Characteristic	Pediatric patients (n=16)	Adult patients (n=16)
Male, n (%)	9 (56)	9 (56)
Age, median (range), years	11.0 (4–16)	24.5 (18–51)
Time from NF1 diagnosis*, median (range), years	2.7 (0.4–14.3)	4.1 (0.1–34.5)
NF1 diagnostic criteria, n (%)		
Any café-au-lait macules	16 (100)	16 (100)
≥6 café-au-lait macules	16 (100)	16 (100)
Freckling in axilla or groin	16 (100)	15 (94)
≥2 Lisch nodules	10 (63)	12 (75)
A first-degree relative with NF1	1 (6)	8 (50)
A distinctive bony lesion	0	4 (25)
Optic glioma	0	0
Target PN location, n (%)		
Extremity	5 (31)	6 (38)
Trunk	3 (19)	5 (31)
Head and neck	2 (13)	1 (6)
Neck or trunk	1 (6)	0
Trunk or extremity	1 (6)	0
Head	1 (6)	4 (25)
Other	3 (19)	0
Any target PN-related morbidity†, n (%)		
Pain	14 (88)	4 (25)
Disfigurement	5 (31)	2 (13)
Motor	4 (25)‡	4 (25)
Airway obstruction	1 (6)	0
Bowel or bladder dysfunction	1 (6)	0
Vision loss	0	2 (13)
Other§	16 (100)	4 (25)
Target PN volume, median (range), mL	517.4 (47.6–2664.4)	691.7 (46.2–7746.3)
≥1 prior NF1- or PN-related treatment, n (%)	12 (75)	13 (81)
Medical treatment	3 (19)	0
Surgery	10 (63)	13 (81)

*To start of selumetinib treatment; †Patients may have more than one target PN-related morbidity; ‡All cases were reduced range of motion; §Details of other target PN-related morbidities are not available.
NF1, neurofibromatosis type 1; PN, plexiform neurofibroma.

Table 2. AE profile in pediatric patients at interim data cut-off (Jan 30, 2022; after the last dosed patient completed Cycle 4 Day 28)

Patients experiencing AEs, n (%)	Pediatric patients (n=16)	
	All	Treatment related
Any AE (any grade)	16 (100)	12 (75)
Any AE (grade ≥3)	1 (6)*	0
AEs leading to dose modifications†	3 (19)‡	2 (13)‡
AEs occurring in ≥10% of patients		
Blood albumin decreased	5 (31)	4 (25)
Pyrexia	4 (25)	0
Alanine aminotransferase increased	2 (13)	1 (6)
Aspartate aminotransferase increased	2 (13)	1 (6)
Cough	2 (13)	0
Hemoglobin decreased	2 (13)	2 (13)
Hyperuricemia	2 (13)	0
Ocular hypertension	2 (13)	2 (13)
Rash	2 (13)	2 (13)
Rhinorrhea	2 (13)	0
Stomatitis	2 (13)	1 (6)
Upper respiratory tract infection	2 (13)	0
Vomiting	2 (13)	0

*Grade 3 sepsis not considered to be treatment related; †Interruption or reduction; ‡Grade 3 sepsis, grade 2 ocular hypertension, and grade 1 rash; §Grade 2 ocular hypertension and grade 1 rash.
AE, adverse event.

Table 3. AE profile in adult patients at interim data cut-off (Jan 30, 2022; after the last dosed patient completed Cycle 4 Day 28)

Patients experiencing AEs, n (%)	Adult patients (n=16)	
	All	Treatment related
Any AE (any grade)	16 (100)	16 (100)
Any AE (grade ≥3)	1 (6)*	1 (6)
AEs leading to dose modifications†	2 (13)‡	2 (13)‡
AEs occurring in ≥10% of patients		
Dermatitis acneiform	12 (75)	12 (75)
Hyperphosphatemia	9 (56)	9 (56)
Conjunctivitis	6 (38)	3 (19)
Aspartate aminotransferase increased	5 (31)	5 (31)
Blood alkaline phosphatase increased	4 (25)	4 (25)
Blood creatine phosphokinase increased	4 (25)	4 (25)
Blood lactate dehydrogenase increased	4 (25)	4 (25)
Hyperuricemia	4 (25)	4 (25)
Alanine aminotransferase increased	3 (19)	3 (19)
Paronychia	3 (19)	3 (19)
Trichiasis	3 (19)	1 (6)
Anemia	2 (13)	2 (13)
Diarrhea	2 (13)	2 (13)
Dry mouth	2 (13)	2 (13)
Dry skin	2 (13)	2 (13)
Edema peripheral	2 (13)	2 (13)
Skin ulcer	2 (13)	2 (13)

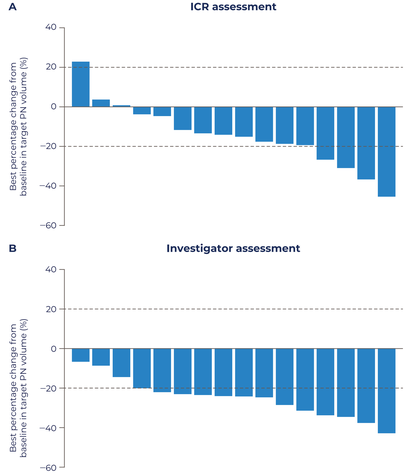
*Grade 3 paronychia considered to be treatment related; †Interruption or reduction; ‡Grade 3 paronychia and grade 2 hematoma.
AE, adverse event.

Table 4. Response assessed by ICR and investigator as per REiNS criteria at interim data cut-off (Jan 30, 2022; after the last dosed patient completed Cycle 4 Day 28)

Response assessment	Pediatric patients (n=16)		Adult patients (n=16)	
	ICR	Investigator	ICR	Investigator
ORR, n (%)	2 (13)	1 (6)	2 (13)	4 (25)
Best response, n (%)				
CR	0	0	0	0
Confirmed PR*	2 (13)	1 (6)	2 (13)	4 (25)
Unconfirmed PR†	2 (13)	11 (69)	6 (38)	1 (6)
SD	11 (69)	4 (25)	6 (38)	10 (63)
PD	1 (6)	0	1 (6)	0
Not evaluable	0	0	1 (6)	1 (6)
Patients with target PN volume reduction‡, n (%)	n=16 13 (81)	n=16 16 (100)	n=15§ 12 (80)	n=15§ 15 (100)
Best percentage change from baseline in target PN volume, mean (± standard deviation)	n=16 −14 (±16)	n=16 −25 (±10)	n=15§ −19 (±23)	n=15§ −15 (±13)

*PR was defined as a decrease in volume of the target PN by ≥20% compared with baseline, a response of non-PD in the non-target PN, and no new lesions. PR was considered unconfirmed at the first detection until observed again within 3–6 months; †PR achieved but either no confirmation assessment performed or a confirmation assessment performed but response not confirmed; ‡A negative change in target PN volume as best response; §n=15 had ≥1 post-baseline assessment. All non-target lesions were non-progressive by the interim data cut-off in all patients per both ICR and investigator; 1 pediatric patient (100%) and 5/6 adult patients (83%) had a non-target lesion volume reduction as best percentage change.
CR, complete response; ICR, independent central review; ORR, objective response rate; PD, progressive disease; PN, plexiform neurofibroma; PR, partial response; REiNS, Response Evaluation in Neurofibromatosis and Schwannomatosis; SD, stable disease.

Figure 2. Best percentage change from baseline in target PN volume in pediatric patients per (A) ICR and (B) investigator



Each bar represents one patient's best percentage change in target PN volume. Bars are ordered from the largest increase to the largest decrease of PN volume assessed by ICR or investigator. The order of the bars per ICR and investigator assessment do not correspond.
ICR, independent central review; PN, plexiform neurofibroma.

References
1. Bergqvist C et al. *Orphanet J Rare Dis* 2020;15:37.
2. Ferner RE et al. *J Med Genet* 2007;44:81–88.
3. Wolters PL et al. *Am J Med Genet A* 2015;167A:2103–2113.
4. Copley-Merriman C et al. *Adolesc Health Med Ther* 2021;12:55–66.
5. Gross AM et al. *Neuro Oncol* 2018;20:1643–1651.
6. Dombi E et al. *N Engl J Med* 2016;375:2550–2560.
7. Nguyen R et al. *Orphanet J Rare Dis* 2012;7:75.
8. Williams VC et al. *Pediatrics* 2009;123:124–133.
9. Gross AM et al. *New Engl J Med* 2020;382:1430–1442.
10. AstraZeneca Pharmaceuticals LP. Koselugo (selumetinib) Prescribing Information. 2021.
11. AstraZeneca Pharmaceuticals LP. Koselugo (selumetinib) Summary of Product Characteristics. 2022.

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