Analysis of bone health in pediatric and adult patients with TRK fusion solid tumors treated with larotrectinib

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BACKGROUND

- Tropomyosin receptor kinase (TRK) signaling plays a crucial role in bone homeostasis, regulating bone formation and remodeling through nerve growth factor-activated signalling.[1–4]
- The effect of TRK inhibition on bone homeostasis is not fully understood; however, serious fractures with or without trauma or injury have been reported in patients who received TRK inhibitor treatment for TRK fusion cancer, particularly in pediatric patients.[2–9]
- Larotrectinib is a first-in-class, highly selective, central nervous system (CNS)-active TRK inhibitor with marketing approval for tumor-agnostic use in pediatric and adult patients with TRK fusion cancer.[10,11]
- While other TRK inhibitors also target the TRKA, TRKB, and TRKC receptors, their kinase selectivity profiles differ.[6–11]
  - Larotrectinib was designed to avoid the off-target inhibition of kinases, such as ALK, ROS1, JAK2, and FGFR1, observed with other marketed TRK inhibitors.[6–11]
- This study evaluated the fracture incidence and bone health of pediatric and adult patients with locally advanced or metastatic TRK fusion cancer treated with larotrectinib.

METHODS

- Following protocol amendments in 2021 in the NAVIGATE (NCT02576431) and SCOUT (NCT02637687) clinical trials, bone health data were prospectively collected in newly enrolled patients in both studies and in ongoing patients in SCOUT who reconsented for inclusion in the bone health cohort.
- Both adult and pediatric patients with locally advanced or metastatic TRK fusion cancer were included.
- The bone health analysis population included all treated patients (in each trial) with ≥1 valid dual-energy X-ray absorptiometry (DXA) or serum bone marker assessment.
- Assessments included:
  - Bone mineral density (BMD) or content (BMC) by DXA (Z-scores in children and young adults, and T-scores in adults).
  - Bone maturation by X-ray (SCOUT only).
  - Bone turnover and bone mineral metabolism serum markers.
  - Fracture incidence and severity (graded by Common Terminology Criteria for Adverse Events v4.03).
  - Height (NAVIGATE) and growth curves (SCOUT).

RESULTS

Patient characteristics

- Among 369 patients enrolled in SCOUT (0–21 years old) and NAVIGATE (≥18 years old) at data cutoff (July 20, 2024), 67 patients (35 pediatric and 32 adult patients) had bone health data and were included in the bone health cohort (**Table 1**).
- Median larotrectinib exposure prior to first bone health assessment was 39.6 (range 11.0–74.5) months in patients who were ongoing in SCOUT (**Table 1**).
- The most common primary tumor types at baseline were CNS primary (25%, n=17) and soft tissue sarcoma (22%, n=15) (**Table 1**).
- Twenty-one patients (31%) in the bone health cohort had a prior history of a medical condition affecting bone health, including prior fracture, osteoporosis/osteopenia, arthritis, menopause, vitamin D deficiency, malabsorption, and parathyroid disorder (**Table 1**).

Table 1. Demographics and baseline characteristics

	NAVIGATE bone health cohort (n=29)	SCOUT bone health cohort (n=38)	Total bone health cohort (n=67)	Overall study population (N=369)
Sex, n (%)				
Female	21 (72)	18 (47)	39 (58)	195 (53)
Male	8 (28)	20 (53)	28 (42)	174 (47)
Median age (range), years				
At baseline	66 (24–83)	6.5 (0.1–19.0)	15.0 (0.1–83)	33.0 (0.1–90.0)
At first bone health assessment	66 (24–83)	8.9 (1.7–22.4)	18.3 (1.7–83)	NA
Treatment exposure,† median (range), months	NA	NA	39.6 (11.0–74.5)	NA
Median bone health observation period (range), months	5.6 (0.0–24.0)	18.0 (0.0–28.8)	15.8 (0.0–28.8)	NA
Primary tumor type, n (%)				
CNS primary	4 (14)	13 (34)	17 (25)	65 (18)
Soft-tissue sarcoma	1 (3)	14 (37)	15 (22)	70 (19)
Colon	6 (21)	0	6 (9)	25 (7)
IFS	0	6 (16)	6 (9)	49 (13)
Lung	5 (17)	0	5 (8)	32 (9)
Breast	4 (14)	0	4 (6)	17 (5)
Thyroid	1 (3)	3 (8)	4 (6)	34 (9)
Other‡	8 (28)	2 (5)	10 (15)	77 (21)
Medical bone history,§ n (%)	19 (66)	2 (5)	21 (31)	NA

†Prior to first bone health assessment (only for ongoing SCOUT patients). ‡Other tumor types included appendix, bone sarcoma, cancer of unknown primary, cervical, cholangiocarcinoma, congenital mesoblastic nephroma, duodenal, esophageal, Ewing's sarcoma, external auditory canal, GIST, gastric, hepatic, lipofibromatosis, melanoma, neuroblastoma, pancreas, prostate, rectal, salivary gland, testicular cancer, thymus, urothelial, and uterus. §Medical bone history was defined in the bone health cohort only as prior fracture, osteoporosis/osteopenia, arthritis, menopause, vitamin D deficiency, malabsorption, or parathyroid disorder.
CNS, central nervous system; GIST, gastrointestinal stromal tumor; IFS, infantile fibrosarcoma; NA, not available.

Fractures

- Fractures occurred in 30/369 (8%) patients in the overall cohort and 6/67 patients (9%) within the bone health cohort (**Table 2**). Median time to first fracture in the overall cohort was 13.2 months.
- All fractures in the bone health cohort occurred in pediatric patients and resulted from falls or trauma during play/sports activities; the maximum grade for fractures was Grade 2 (**Table 2**). Median time to first fracture in this cohort was 39.5 months.
- Two cases (3%) were considered treatment-related by the investigators primarily because the trial drug was a TRK inhibitor:
  - A 10-year-old patient with soft tissue sarcoma had a Grade 2 fracture of the thumb, which the investigator reported was most likely from a fall or rough contact while playing soccer.
  - A 6-year-old patient with soft tissue sarcoma had a Grade 2 patella fracture. This patient sustained knee injuries from falls while playing, with ongoing knee joint effusion, and was subsequently found to have a fracture.
- No fracture was considered serious. No fracture resulted in dose modification or treatment discontinuation.

BMD

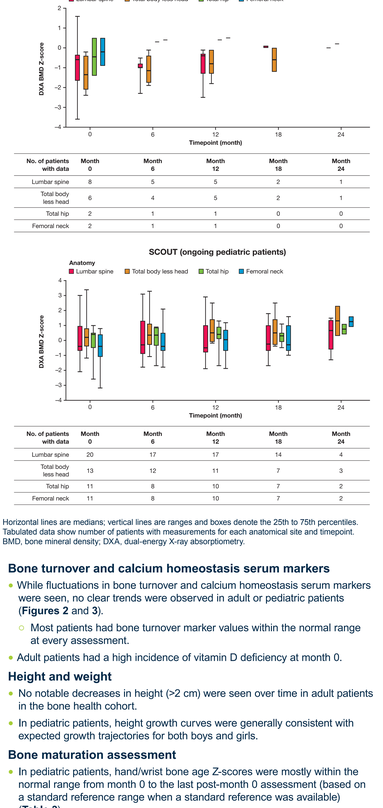
- There were no observable longitudinal trends in DXA BMD values in the adult patients from NAVIGATE or pediatric patients from SCOUT (**Figure 1**).
  - There was no worsening of Z- or T-scores at any anatomical site in adult or pediatric patients.
  - No adult patient's BMD declined into the osteoporotic range.
- Trends in BMC showed similar patterns to BMD.

Table 2. Summary of fracture events

	NAVIGATE bone health cohort (n=29)	SCOUT bone health cohort (n=38)	Overall study population (N=369)
Patients with fracture events, n (%)	0	6 (16)	30 (8)
Number of fracture events (EAIR)	0 (0)	7 (5)	38 (4.5)
Fracture events, n (%)			
Related to larotrectinib	0	2 (5)	2 (<1)
Grade 3 or 4	0	0	9 (2)
Leading to discontinuation of trial drug	0	0	0
Fracture by region, n (%)			
Rib	0	0	7 (2)
Fibula	0	1 (3)	4 (1)
Foot	0	1 (3)	3 (<1)
Wrist	0	0	3 (<1)
Femur	0	0	2 (<1)
Tibia	0	0	2 (<1)
Ulna	0	1 (3)	2 (<1)
Upper limb	0	1 (3)	2 (<1)
Cervical vertebra	0	0	1 (<1)
Compression fracture	0	0	1 (<1)
Craniofacial	0	0	1 (<1)
Femoral neck	0	0	1 (<1)
Hand	0	1 (3)	1 (<1)
Hip	0	0	1 (<1)
Humerus	0	1 (3)	1 (<1)
Patella	0	1 (3)	1 (<1)
Pathological fracture	0	0	1 (<1)
Spinal compression fracture	0	0	1 (<1)
Spine	0	0	1 (<1)
Sternum	0	0	1 (<1)

EAIR is defined as the number of events/sum of exposure times, where the sum of exposure times equals the sum of treatment duration and time at risk after treatment end.
EAIR, exposure-adjusted incidence rate (per 100 patient–years).

Figure 1. BMD Z-score trends over time



NAVIGATE (adults) No. of patients with data	Month 0	Month 3	Month 6	Month 12	Month 18	Month 24
Lumbar spine	23	3	8	8	1	2
Total hip	22	3	8	8	1	2
Femoral neck	22	3	8	8	1	2

SCOUT (newly enrolled pediatric patients) No. of patients with data	Month 0	Month 6	Month 12	Month 18	Month 24
Lumbar spine	8	5	5	2	1
Total body less head	6	4	5	2	1
Total hip	2	1	1	0	0
Femoral neck	2	1	1	0	0

SCOUT (ongoing pediatric patients) No. of patients with data	Month 0	Month 6	Month 12	Month 18	Month 24
Lumbar spine	20	17	17	14	4
Total body less head	13	12	11	7	3
Total hip	11	8	10	7	2
Femoral neck	11	8	10	7	2

Horizontal lines are medians; vertical lines are ranges and boxes denote the 25th to 75th percentiles. Tabulated data show number of patients with measurements for each anatomical site and timepoint.
BMD, bone mineral density; DXA, dual-energy X-ray absorptiometry.

Bone turnover and calcium homeostasis serum markers

- While fluctuations in bone turnover and calcium homeostasis serum markers were seen, no clear trends were observed in adult or pediatric patients (**Figures 2** and **3**).
  - Most patients had bone turnover marker values within the normal range at every assessment.
- Adult patients had a high incidence of vitamin D deficiency at month 0.

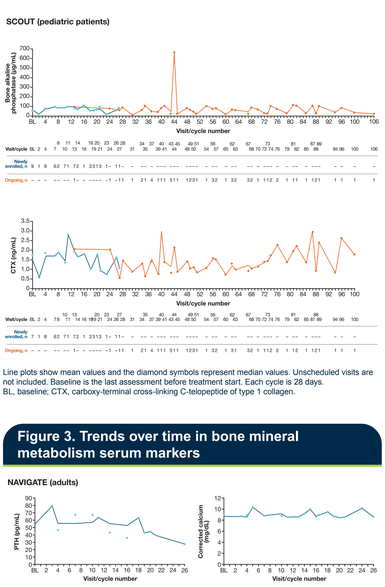
Height and weight

- No notable decreases in height (>2 cm) were seen over time in adult patients in the bone health cohort.
- In pediatric patients, height growth curves were generally consistent with expected growth trajectories for both boys and girls.

Bone maturation assessment

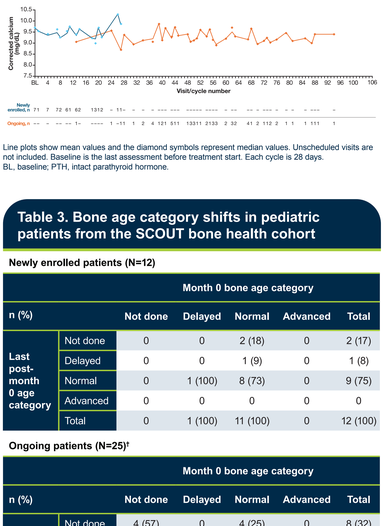
- In pediatric patients, hand/wrist bone age Z-scores were mostly within the normal range from month 0 to the last post-month 0 assessment (based on a standard reference range when a standard reference was available) (**Table 3**).
  - Thus, the bone age of pediatric patients was generally consistent with the chronological age for each patient.

Figure 2. Trends over time in bone turnover markers



Line plots show mean values and the diamond symbols represent median values. Unscheduled visits are not included. Baseline is the last assessment before treatment start. Each cycle is 28 days.
BL, baseline; CTX, carboxy-terminal cross-linking C-telopeptide of type 1 collagen.

Figure 3. Trends over time in bone mineral metabolism serum markers



Line plots show mean values and the diamond symbols represent median values. Unscheduled visits are not included. Baseline is the last assessment before treatment start. Each cycle is 28 days.
BL, baseline; PTH, intact parathyroid hormone.

Table 3. Bone age category shifts in pediatric patients from the SCOUT bone health cohort

Newly enrolled patients (N=12)

		Month 0 bone age category				
n (%)		**Not done**	**Delayed**	**Normal**	**Advanced**	**Total**
Last post-month 0 age category	Not done	0	0	2 (18)	0	2 (17)
	Delayed	0	0	1 (9)	0	1 (8)
	Normal	0	1 (100)	8 (73)	0	9 (75)
	Advanced	0	0	0	0	0
	Total	0	1 (100)	11 (100)	0	12 (100)

Ongoing patients (N=25)†

		Month 0 bone age category				
n (%)		**Not done**	**Delayed**	**Normal**	**Advanced**	**Total**
Last post-month 0 age category	Not done	4 (57)	0	4 (25)	0	8 (32)
	Delayed	0	1 (100)	0	0	1 (4)
	Normal	3 (43)	0	11 (69)	1 (100)	15 (60)
	Advanced	0	0	1 (6)	0	1 (4)
	Total	7 (100)	1 (100)	16 (100)	1 (100)	25 (100)

For patients with valid month 0 scan but no valid subsequent scan(s), the last post-month 0 age category was assigned to "Not done".
Month 0 corresponded to true baseline scan for SCOUT newly enrolled patients.
Unscheduled scans were included.
†One patient did not receive any X-rays for bone maturation assessment.

CONCLUSIONS

- **In this subset of patients assessed for bone health parameters from 2 clinical trials, larotrectinib did not adversely affect bone health in adult or pediatric patients with TRK fusion cancers.**
  - **There was no increase in the incidence of fractures relative to that expected for patients with cancer.[12–15]**
  - **No detrimental effects on BMD Z- or T-scores were observed over time.**
  - **Larotrectinib did not appear to have a negative impact on biochemical markers of bone remodeling or bone health in children or adults, nor on growth or development in pediatric patients.**
- **These results reinforce the favorable risk–benefit profile of larotrectinib as a standard-of-care therapy for patients with TRK fusion cancers.**

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