Amsterdam, 11 December 2025
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Humans Medicines Division

Assessment report for paediatric studies submitted according to Article 46 of the Regulation (EC) No 1901/2006

Kisplyx

Lenvatinib

Procedure no: EMA/PAM/0000279841

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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Status of this report and steps taken for the assessment			
Current step	**Description**	**Planned date**	**Actual Date**
☐	CHMP Rapporteur AR	25 August 2025	25 August 2025
☐	CHMP comments	8 September 2025	n/a
☐	Updated CHMP Rapporteur AR	11 September 2025	n/a
☐	Request for Supplementary Information	18 September 2025	18 September 2025
☐	Deadline for responses	11 November 2025	11 November 2025
☐	Start date	12 November 2025	12 November 2025
☐	CHMP Rapporteur AR	26 November 2025	24 November 2025
☐	CHMP comments	01 December 2025	28 November 2025
☐	Updated CHMP Rapporteur AR	04 December 2025	03 December 2025
☒	CHMP Outcome	11 December 2025	11 December 2025

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1. Introduction

On 11 June 2025, the MAH submitted the final Clinical Study Report for a completed paediatric study E7080-G000-231 for Kisplyx (and Lenvima), in accordance with Article 46 of Regulation (EC) No1901/2006, as amended. Study 231 is part of the clinical development program for Lenvatinib in the approved Paediatric Investigation Plan (EMEA-001119-PIP03-19-M03). This study was completed on 13 February 2025, which was the final database lock for the study.

2. Scientific discussion

2.1. Information on the development program

Lenvatinib is a receptor tyrosine kinase (RTK) inhibitor that selectively inhibits the kinase activities of vascular endothelial growth factor (VEGF) receptors VEGFR1 (FLT1), VEGFR2 (KDR), and VEGFR3 (FLT4), in addition to other proangiogenic and oncogenic pathway-related RTKs including fibroblast growth factor (FGF) receptors FGFR1, 2, 3, and 4, the platelet derived growth factor (PDGF) receptor PDGFRα, KIT, and RET.

The first approval for lenvatinib was granted on 28 May 2015 in the EU for treatment of patients with locally recurrent or metastatic, progressive, RAI-refractory DTC. Subsequently, lenvatinib has been approved for Hepatocellular Carcinoma (HCC), Endometrial Carcinoma (EC) and the advanced renal cell carcinoma (RCC), either as Lenvima or Kisplyx.

The MAH stated that Study E7080-G000-231/MK-7902-013 (hereafter referred to as HOPSKIP-013), falls within the scope of the Paediatric Regulation; it is identified as Study 2 in the lenvatinib PIP (EMEA-001119-PIP03-19-M03). Study 231 is a Phase 2, open-label, multicenter basket study to evaluate the antitumor activity and safety of Lenvatinib in children, adolescents, and young adults with relapsed or refractory solid malignancies. The study was conducted to evaluate the antitumor activity and safety of lenvatinib in 4 cohorts: HGG, RMS, EWS/peripheral primitive neuroectodermal tumour (pPNET; hereafter referred to as EWS), and any other solid tumours (aside from osteosarcoma). The primary efficacy analysis results for Study 231 were provided in the previously submitted CSR (DCO date: 16-SEP-2022; [Ref. 5.3.5.4: P013V01MK7902]) as part of procedure EMEA/H/C/WS2631. This study was completed on 13 February 2025, which was the final database lock for the study

Within the clinical development scope of Lenvima /Kisplyx in paediatric setting, Study 231 is one of the main clinical studies in PIP EMEA001119-PIP03-19-M03 (condition: solid tumours) approved on December 2023. This Type II variation was submitted for both Lenvima and Kisplyx licenses to include the final results of the paediatric Study 231.

As the MAH is not planning to seek a paediatric indication based on the results of EMEA-001119-PIP03-19-M03 submitted final CRS of Study 231, no changes to the SmPC are proposed in this procedure.

2.2. Information on the pharmaceutical formulation used in the study

Lenvatinib was administered in the E7080-G000-231/MK-7902-013 as hydroxypropyl methylcellulose (HPMC) capsules, which may be suspended in water or apple juice for children unable to swallow capsules.

One of the secondary objectives of the Study E7080-G000-231/MK-7902-013 was to assess the palatability and acceptability of the suspension formulation of lenvatinib. The results based on the palatability questionnaire using a facial hedonic scale were provided in the previous CSR dated 13-JUN-2023 (P013V01MK7902).

2.3. Clinical aspects

2.3.1. Introduction

The MAH submitted a final report for Study E7080-G000-231/MK-7902-013, presenting final disposition, demographics, exposure, and selected safety results collected through LPLV. A final analysis of updated OS data based on all data collected through the end of the study is included in this CSR (DCO date: 13-FEB-2025). No extension of the indication is applied for, and no modifications are proposed to the SmPC by the MAH.

2.3.2. Clinical study

Study E7080-G000-231/MK-7902-013 (hereafter referred to as HOPSKIP-013)

Title: A multicenter, open-label, Phase 2 basket study to evaluate the antitumor activity and safety of lenvatinib in children, adolescents, and young adults between 2 and ≤21 years of age with relapsed or refractory solid malignancies.

Methods – analysis of data submitted

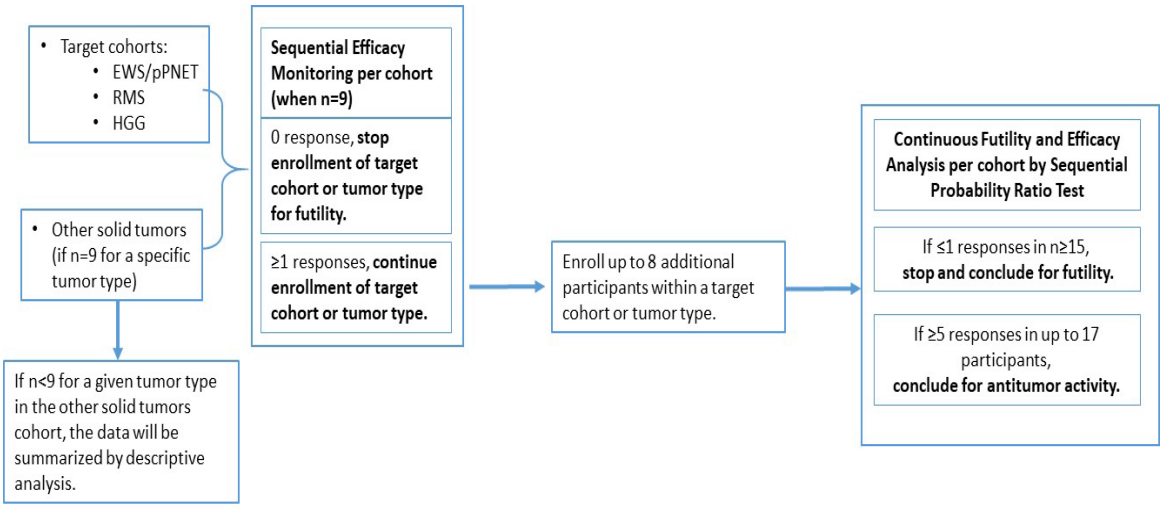


Figure 1 Study 231 design

EWS = Ewing Sarcoma, HGG = high-grade glioma (including anaplastic astrocytoma, anaplastic oligodendroglioma, glioblastoma, mixed glioma, and malignant glioma), pPNET = peripheral primitive neuroectodermal tumor, RMS = rhabdomyosarcoma.

Study participants

Key inclusion criteria were:

- Male/female children, adolescents, and young adult subjects with relapsed or refractory pediatric solid tumors (excluding osteosarcoma) between the ages of 2 and 21 years, inclusive, were to be enrolled in this study.
- Had histologically or cytologically documented relapsed or refractory pediatric solid malignancy excluding osteosarcoma. Subjects with diffuse midline glioma (formerly known as diffuse intrinsic pontine glioma), optic pathway glioma, or pineal tumors with elevated tumor markers (AFP, β-hCG, or hCG) did not require histological or cytological confirmation of diagnosis. Subjects with diffuse midline glioma were not eligible for the HGG cohort and should only be enrolled in the other solid tumors' cohort.

- Had measurable disease as defined by RECIST 1.1 or RANO for HGG, as defined in the study protocol.
- Had a KPS (for subjects >16 years of age) or Lansky play score (for subjects ≤16 years of age) ≥50.
- Neurologic deficits in subjects with primary CNS tumors must have been stable for at least 7 days prior to study enrollment. Subjects who were unable to walk because of paralysis, but who could perform ADL while wheelchair bound, were considered ambulatory for the purpose of assessing the performance score.

Key exclusion criteria were:

- Had a major surgery within 3 weeks prior to Cycle 1 Day 1.
  Note: Adequate wound healing after major surgery must be assessed clinically, independent of time elapsed for eligibility.
- Had CNS tumors with a history of symptomatic tumor hemorrhage.
- Had radiographic evidence of encasement or invasion of a major blood vessel or of intratumoral cavitation.
  Note: The degree of proximity to major blood vessels should be considered for exclusion because of the potential risk of severe hemorrhage associated with tumor shrinkage/necrosis after lenvatinib therapy.
- Had evidence of untreated CNS metastases (exception: subjects with primary CNS tumors and leptomeningeal disease).
- History or current evidence of any condition, therapy, laboratory abnormality that might confound the results of the study, interfere with the subject's participation for the full duration of the study, or is not in the best interest of the subject to participate, in the opinion of the treating investigator.

Treatments

Subjects were administered lenvatinib 14 mg/m2 orally QD and could continue to receive lenvatinib until a treatment discontinuation criterion was met, as described in the study protocol. Planned enrollment was to be a minimum of 36 subjects (9 subjects in each of 4 cohorts: HGG, RMS, EWS, and other solid tumors) and an estimated maximum of approximately 150 subjects.

Arm Name	Intervention Name	Unit Dose Strength(s)	Dosage Level(s)	Route of Administration	Regimen/Treatment Period/Vaccination Regimen	Use
Arm 1	Lenvatinib	1 mg, 4 mg, 10 mg	14 mg/m^2	Oral	Once daily	Test Product

Objectives and endpoints

Objectives	Endpoints
Primary	
To determine the ORR at Week 16, by each tumor type, per RECIST 1.1 or RANO (for HGG only) as assessed by the investigator.	Objective Response, defined as a confirmed (≥4 weeks after initial response) CR or PR.
Secondary	

Objectives	Endpoints
To evaluate ORR, by each tumor type, per RECIST 1.1 or RANO (for HGG only) as assessed by the investigator.	Objective Response, defined as a confirmed (≥4 weeks after initial response) CR or PR.
To evaluate PFS per RECIST 1.1 or RANO (for HGG only), by each tumor type.	PFS defined as the time from the date of the first administration of lenvatinib until the date of first documentation of PD or death (whichever occurs first).
To evaluate the BOR, DOR, DCR, and CBR, by each tumor type.	BOR defined as the subject's best confirmed response (CR or PR) over the treatment period. DOR defined as the time from the date of the first documented CR or PR to the date first documentation of progressive disease or death (whichever occurs first). Disease control defined as a BOR of CR or PR, or SD. To be assigned a BOR of SD, the time from the first administration of study drug until the date of documented SD should be ≥7 weeks. Clinical benefit defined as a BOR of CR or PR, or durable SD (SD duration ≥23 weeks since the first dose of the study treatment).
To evaluate the safety of lenvatinib	AEs, SAEs, clinical laboratory values, vital signs, 12-lead ECGs, urine dipstick, Lansky play scores or KPS scores, physical examination findings, dental examination findings, height, and closure of proximal tibial plates.
To assess the palatability and acceptability of the suspension formulation of lenvatinib.	Palatability questionnaire using a facial hedonic scale.
To characterize the PK of lenvatinib.	Assessment of population-based PK parameters of lenvatinib.
Exploratory	
To explore OS, by each tumor type.	OS defined as the time from the date of the first administration of study drug until the date of death from any cause.

AE = adverse event, BOR = best overall response, CBR = clinical benefit rate, CR = complete response, DCR = disease control rate, DOR =duration of clinical response, HGG= high grade glioma, KPS = Karnofsky Performance Status, ORR = objective response rate, OS = overall survival, PD = progressive disease/disease progression, PK = pharmacokinetic, PFS = progression-free survival, PR = partial response, RANO = Response Assessment in Neuro-Oncology, RECIST = Response Evaluation Criteria in Solid Tumors, RMS = rhabdomyosarcoma, RP2D = recommended Phase 2 dose, SAE = serious adverse event, SD = stable disease.

Randomisation and blinding (masking)

Not applicable, the study is open-label.

Statistical Methods

The primary efficacy population was the EAS, which included all evaluable participants, who had measurable disease present at baseline and at least 1 post baseline efficacy assessment, unless they discontinued prior to the first efficacy assessment due to progressive disease.

Objective responses counted only confirmed (≥4 weeks after initial response) complete response (CR) and partial response (PR) at Week 16. Estimated objective response rate (ORR) and its exact 95% confidence interval (CI) using the method of Clopper and Pearson were presented. The ORR, disease control rate (DCR), and clinical benefit rate (CBR) were provided with exact 95% CIs using the method of Clopper and Pearson, and the duration of response (DOR) was analyzed for responders using Kaplan-Meier approach.

PFS was analyzed using Kaplan-Meier product-limit estimates. The cumulative progression-free survival (PFS) probabilities were plotted over time as appropriate.

The primary safety population was the Safety Analysis Set, which included all participants who received at least 1 dose of the study drug. Count and percentage of adverse events (AE) by system organ class and preferred term are provided.

Results

The DCO date of EoT is 13-FEB-2025.

Efficacy results (ORR, BOR, DCR, DOR, PFS, palatability, and OS) from the primary analysis were provided in the previous CSR dated 13-JUN-2023 (P013V01MK7902) and are briefly summarized in this report for completeness. OS was formally analysed and presented in the previous CSR; however, due to additional follow-up, a final analysis of OS was performed and is included in this CSR (DCO date: 13-FEB-2025).

A total of 4 cohorts were evaluated: HGG, RMS, EWS/peripheral primitive neuroectodermal tumor (pPNET; hereafter referred to as EWS), and any other solid tumors (aside from osteosarcoma).

Participant Disposition:

- As of the data cutoff date, 127 allocated (9 in EWS, 17 in RMS, 8 in HGG, 9 each in diffuse midline glioma, medulloblastoma, and ependymoma, and 66 in other solid tumors cohort), 127 treated, 127 discontinued treatment, 0 ongoing on treatment, 0 completed study, 127 discontinued study, 0 ongoing in the study.

Table 1 Study Population

	Ewing Sarcoma	Rhabdomyosarcoma	High Grade Glioma	Diffuse Midline Glioma	Medulloblastoma	Ependymoma	Other Solid Tumors Excluding Osteosarcoma, Diffuse Midline Glioma, Medulloblastoma and Ependymoma	Total
Number of Subjects Screened								144
Number of Subjects Allocated	9	17	8	9	9	9	66	127
Number of Subjects Received Treatment (Safety Analysis Set)	9	17	8	9	9	9	66	127
Number of Subjects Allocated and Did not Receive Treatment	0	0	0	0	0	0	0	0
Number of Evaluable Subjects (Evaluable Analysis Set)	9	17	6	9	9	9	65	124
Number of Subjects Discontinued Study Medication	9	17	8	9	9	9	66	127
Number of Deaths	9	17	8	9	8	9	55	115
Subjects Allocated include subjects who received allocation numbers. Database Cutoff Date: 13FEB2025.								

Demographics and Baseline Characteristics:

- **Overall Median Age (Range):** 14.0 years (2 to 21 years)
- **Sex:** 67 (52.8%) male, 60 (47.2%) female
- **Ethnicity:** 77 (60.6%) not Hispanic or Latino, 13 (10.2%) Hispanic or Latino, 37 (29.1%) not reported/unknown/missing
- **Race:** 22 (17.3%) Asian, 3 (2.4%) American Indian or Alaska Native, 4 (3.1%) Black or African American, 2 (1.6%) Native Hawaiian or Other Pacific Islander, 1 (0.8%) multiple, 63 (49.6%) White, 32 (25.2%) missing
- **Lansky or Karnofsky Scores:** 50 (11 [8.7%]), 60 (13 [10.2%]), 70 (13 [10.2%]), 80 (17 [13.4%]), 90 (34 [26.8%]), 100 (39 [30.7%])

Extent of Exposure:

The median duration of exposure to study treatment was 104.0 days (range: 8.0 to 627.0). A total of 32 participants had a median duration of exposure based on person-months of ≥6 months. The median dose intensity was 13.8 mg/m2/day (range: 6.3 to 14.0 mg/m2/day)

Efficacy results

Primary efficacy endpoint:

- Although objective responses occurred in some participants, antitumor activity could not be concluded for any cohort in this study based on investigator assessment of ORR at Week 16 per RECIST 1.1 or RANO (for HGG only).
- The ORR at Week 16 per RECIST 1.1 or RANO (for HGG only) was 22.2% in the EWS, 11.8% in the RMS, and 7.7% in the other solid tumors cohorts. No antitumor activity was observed in participants with HGG, diffuse midline glioma, medulloblastoma, and ependymoma.

Secondary efficacy endpoints:

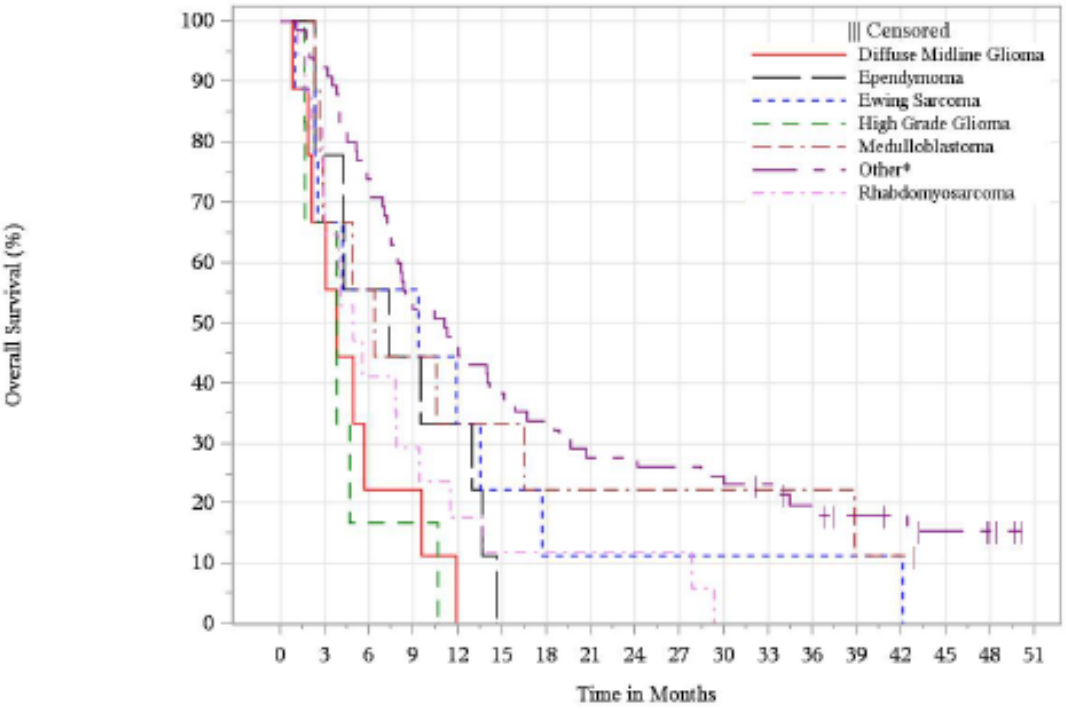
- The ORR per investigator assessment using RECIST 1.1 or RANO (for HGG only) was 22.2% in the EWS, 11.8% in the RMS, and 7.7% in the other solid tumors cohorts as of the DCO date.

No objective responses were observed in participants with HGG, diffuse midline glioma, medulloblastoma, and ependymoma.

- The DCR was 66.7% in the EWS, 52.9% in the RMS, 33.3% in the HGG, 22.2% in the diffuse midline glioma, 55.6% in the medulloblastoma, 55.6% in the ependymoma, and 64.6% in the other solid tumors cohorts. The CBR was 33.3%, 29.4%, 11.1%, 44.4%, 33.3%, and 40.0% in the EWS, RMS, diffuse midline glioma, medulloblastoma, ependymoma, and the other solid tumors cohorts, respectively.
- The median DOR was not reached in the EWS cohort; the median DOR was 4.6 months each in RMS and other solid tumors cohorts. The median TTR was 2.8, 1.8, and 1.9 months in the EWS, RMS, and other solid tumors cohorts, respectively.
- The median PFS was 3.0, 2.6, 1.9, 1.8, 3.4, 2.5, and 3.8 months in the EWS, RMS, HGG, diffuse midline glioma, medulloblastoma, ependymoma, and other solid tumors cohorts, respectively.
- The median OS was 9.4, 4.9, 3.8, 3.8, 6.3, 7.4, and 10.4 months in the EWS, RMS, HGG, diffuse midline glioma, medulloblastoma, ependymoma, and the other solid tumors cohorts, respectively.

Final Analysis of OS

- With a median follow-up duration of 7.9 months (range 0.9 to 50.4), the median OS (months) was 9.4 (95% CI: 1.0, 17.7) in EWS, 4.9 (95% CI: 2.8, 9.4) in RMS, 3.8 (95% CI: 1.6, NR) in HGG, 3.8 (95% CI: 0.9, 9.6) in diffuse midline glioma, 6.3 (95% CI: 2.3, 38.8) in medulloblastoma, 7.4 (95% CI: 2.3, 13.6) in ependymoma, and 11.1 (95% CI: 7.7, 15.1) in other solid tumors cohorts.



At Risk

Diffuse Midline Glioma	9	6	2	2	0	0	0	0	0	0	0	0	0	0	0	0	0
Ependymoma	9	7	5	4	3	0	0	0	0	0	0	0	0	0	0	0	0
Ewing Sarcoma	9	6	5	5	3	2	1	1	1	1	1	1	1	1	0	0	0
High Grade Glioma	6	4	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0
Medulloblastoma	9	6	5	4	3	3	2	2	2	2	2	2	2	1	1	0	0	0
Other*	65	60	48	35	30	25	22	18	18	17	16	14	11	8	7	5	4	0
Rhabdomyosarcoma	17	11	7	5	3	2	2	2	2	2	0	0	0	0	0	0	0	0

Figure 2 Kaplan-Meier Plot of Overall Survival (Evaluable Analysis Set)

Safety results

Adverse Events

With an additional 29 months of follow-up, all AE safety data collected throughout the study (FPFV through LPLV) were analysed for this report (DCO date: 13-FEB-2025). Adverse events for lenvatinib as a single-agent (Study 231) are discussed below.

All except 1 subject (99.2%) experienced at least 1 AE; the majority (91.3%) experienced AEs that were considered treatment-related and 72.4% experienced AEs that were Grade ≥3 in severity .

Table 2: Adverse Event Summary (Safety Analysis Set)

	Total	
	n	(%)
Participants in population	127	
with one or more adverse events	126	(99.2)
with no adverse event	1	(0.8)
with drug-related[a] adverse events	116	(91.3)
with toxicity grade 3-5 adverse events	92	(72.4)
with toxicity grade 3-5 drug-related adverse events	63	(49.6)
with serious adverse events	66	(52.0)
with serious drug-related adverse events	28	(22.0)
with any dose reduction due to an adverse event	50	(39.4)
with any dose interruption due to an adverse event	53	(41.7)
with any dose interruption due to an drug-related adverse event	36	(28.3)
with any dose modification[b] due to an adverse event	76	(59.8)
who died	3	(2.4)
who died due to a drug-related adverse event	1	(0.8)
discontinued drug due to an adverse event	10	(7.9)
discontinued drug due to a drug-related adverse event	6	(4.7)
discontinued drug due to a serious adverse event	8	(6.3)
discontinued drug due to a serious drug-related adverse event	5	(3.9)

[a] Determined by the investigator to be related to the drug.
[b] Dose modification includes dose reduction or drug interruption.
Non-serious and serious adverse events up to 30 days following the last dose are included.
MedDRA preferred terms "Neoplasm progression", "Malignant neoplasm progression" and "Disease progression" not related to the drug are excluded.
Grades are based on NCI CTCAE version 5.0.
Database Cutoff Date: 13FEB2025.

Source: [P013MK7902: adam-adsl: adae]

The most frequently reported TEAEs (>20% incidence) were hypothyroidism (65.4%), hypertension (39.4%), decreased appetite (32.3%), proteinuria (32.3%), diarrhea (31.5%), vomiting (29.9%), weight decreased (22.8%), and abdominal pain (22.8%), AST increase (21.3%).

Grade ≥3 Adverse Events

Ninety subjects (72.4%) experienced at least one Grade ≥3 AE. The most frequently reported (incidence ≥5%) Grade ≥3 AEs were proteinuria (12.6%), hypertension (11.8%), decreased appetite (7.9%), alanine aminotransferase (ALT) increased (8.7%), Aspartate aminotransferase AST increased (5.5%), Pneumothorax(5.5%), and anemia (7.1%). Three subjects had a Grade 5 AE.

Serious Adverse Events

A total of 66 (52.0%) subjects experienced at least 1 SAE during the study. The most frequently reported SAEs (incidence ≥2%) were pneumothorax (6.3%); abdominal pain(3.9%); pyrexia, urinary tract infection, headache (3.1% each); and pneumonia aspiration , sepsis, intracranial pressure increased, and hypertension (2.4% each).

Death

Grade 5 (fatal) TEAEs occurred in 3 subjects during the study, consisting of sepsis, intracranial pressure increased, and device dislocation in 1 subject each. One death, intracranial pressure increased, which occurred in the other solid tumors cohort, was the only death assessed as related to

study treatment by the investigator. No new deaths due to AE were reported since the prior DCO (16-SEP-2022).

Drug-Related Adverse Events Resulting in Treatment Discontinuation / Treatment Interruption / Dose Reduction /Treatment Modification

10 subjects (7.9%) discontinued study drug for an AE. The drug-related adverse events resulting in treatment discontinuation occurred in total of 6 subjects (4.7%), and duodenal perforation , musculoskeletal pain, hemorrhage intracranial, intracranial pressure increased, pneumothorax, and hypertension in 1 subject each.

36 subjects (21.8%) interrupted the treatment from the study for a drug-related AE as assessed by the investigator. 48 subjects (37.8%) and 76 subjects (59.8%) experienced dose reduction and treatment modification due to a drug-related AE, respectively.

Clinically Significant Adverse Events for Lenvatinib

Approximately 2/3 CSAEs were Grade 1 or 2 in severity, and no participants died due to a CSAE.

Table 3: Adverse Event Summary CSAE Overall (Safety Analysis Set)

	Total	
	n	(%)
Participants in population	127	
with one or more adverse events	112	(88.2)
with no adverse event	15	(11.8)
with drug-related[a] adverse events	101	(79.5)
with toxicity grade 3-5 adverse events	44	(34.6)
with toxicity grade 3-5 drug-related adverse events	36	(28.3)
with serious adverse events	15	(11.8)
with serious drug-related adverse events	7	(5.5)
with any dose reduction due to an adverse event	28	(22.0)
with any dose interruption due to an adverse event	22	(17.3)
with any dose interruption due to an drug-related adverse event	14	(11.0)
with any dose modification[b] due to an adverse event	42	(33.1)
who died	0	(0.0)
who died due to a drug-related adverse event	0	(0.0)
discontinued drug due to an adverse event	5	(3.9)
discontinued drug due to a drug-related adverse event	3	(2.4)
discontinued drug due to a serious adverse event	3	(2.4)
discontinued drug due to a serious drug-related adverse event	2	(1.6)

[a] Determined by the investigator to be related to the drug.
[b] Dose modification includes dose reduction or drug interruption.
Non-serious and serious adverse events up to 30 days following the last dose are included.
Grades are based on NCI CTCAE version 5.0.
Database Cutoff Date: 13FEB2025.

Source: [P013MK7902: adam-adsl; adae]

Pneumothorax

Pneumothorax is a known risk for lenvatinib in different tumour types. The total incidence of pneumothorax at DCO (13-FEB-2025) in Study 231 was 6.3% (n=8). Since the previous CSR, one more patient with pneumothorax was reported as previously pneumothorax occurred in 7 patients (5.5%).

All 8 cases were diagnosed as SAEs. For 4 subjects (3.1%), the pneumothorax was considered as treatment-related by the investigator. For 7 patients grade 3-5 pneumothorax was reported (6 patients previously). Six subjects (4.7%) had study treatment interrupted for the event; 1 subject discontinued treatment for pneumothorax.

Clinical Laboratory Evaluations

No updated results on clinical laboratory evaluations are submitted since previous CSR (DCO date: 16-SEP-2022).

Vital Signs, Physical Examination Findings, and Other Observations Related to Safety

The updated results since previous CSR (DCO date: 16-SEP-2022) have not been submitted. However, according to the submitted tables in the final CSR (P013MK7902), no more hypertension cases were apparently reported as a CSAE during this additional follow-up period.

Post marketing Data

Lenvatinib is not approved for any indication in the paediatric population. For post marketing data for lenvatinib, refer to the most recent periodic safety update report (lenvatinib PSUR).

2.4. Discussion on clinical aspects

The target tumour types in Study 231 were RMS, EWS, and HGG; in addition, Study 231 permitted the enrolment of patients with any solid tumour type with the exception of osteosarcoma. In line with the approved PIP, this study population included patients aged 2 to 21 years.

The primary endpoint results (ORR at W16 based on investigator assessment) were consistent with the previous report: there were no objective responses observed in patients with HGG, diffuse midline glioma, medulloblastoma, or ependymoma. Two PRs were observed in both the EWS and RMS cohorts for an ORR at Week 16 of 22.2% and 11.8%, respectively. Five PRs were observed among all other solid tumours for an ORR at Week 16 of 7.7%.

The final OS results have been provided by the MAH. The median follow-up duration was 7.9 months. The median OS (months) was 9.4 in EWS, 4.9 in RMS, 3.8 in HGG, 3.8 in diffuse midline glioma, 6.3 in medulloblastoma, 7.4 in ependymoma, and 11.1 in other solid tumours cohorts.

Overall, the final efficacy OS results of Study 231 were consistent to the primary analysis previously reported. The interpretation of OS results is hampered by the study design (single arm trial).

Lenvatinib appears to have, based on limited data, an acceptable safety profile in cancer patients aged 2 to 21 years when treatment is administered at 14 mg/m2 QD (based on BSA, maximum 24 mg/day) and adjusted by a dose-titration algorithm to manage toxicity.

A total of 127 subjects were enrolled and treated with lenvatinib in Study 231.

Since the previous CSR (DCO 16-Sep-2022), no new fatal AEs were reported. No new safety concerns were identified.

However, *no updated results on clinical laboratory evaluations as well as vital signs and physical examination findings were submitted since previous CSR (DCO date: 16-SEP-2022), so the MAH is asked to provide the above information and include any relevant new data in the final CSR (P013MK7902).*

Most participants discontinued treatment with lenvatinib. The primary reason for treatment discontinuation was PD (n=85 [66.9%]). As of final CSR DCO (13-Feb-2025), all participants completed study, there were no patients still receiving study treatment.

The adverse events reported in the final CSR are consistent with the known safety profile of single-agent lenvatinib in adult cancer populations and paediatric patients (Study E7080-G000-207), and those reported at the previous CSR (DCO 16-Sep-2022). No new safety signals were identified.

However the incidence of pneumothorax of 6.3% is higher than that observed previously with single-agent lenvatinib in adults (DTC lenvatinib monotherapy, 1.1%; non-DTC lenvatinib monotherapy, 0.5%).

Pneumothorax occurred in 8 subjects (6.3%). Since the previous CSR, one more patient with pneumothorax was reported as previously pneumothorax occurred in 7 patients (5.5%).

As at least one additional case of pneumothorax was reported in paediatric patients, the MAH is asked to provide description/narrative of this case and to suggest an update of the SmPC section 4.8 ("Paediatric population" part), to be subsequently implemented in the scope of a work-sharing procedure for Lenvima and Kisplyx.

Overall, a total of 66 (52.0%) subjects experienced at least 1 SAE during the study. The most frequently reported SAEs (incidence ≥2%) were pneumothorax (6.3%); abdominal pain(3.9%); pyrexia, urinary tract infection, headache (3.1% each); and pneumonia aspiration , sepsis, intracranial pressure increased, and hypertension (2.4% each). Of 28 (22.0%) subjects experienced SAEs that were assessed as related to study drug by the investigator. The most frequently reported treatment-related SAEs were pneumothorax and hypertension. Serious AEs appeared to be partly due to lenvatinib.

As required per protocol, the management of lenvatinib toxicities (Grade 3 or 4 and intolerable Grade 2) required an interruption until resolution of event, followed by restarting treatment at a lower dose of lenvatinib (dose reduction) once the toxicity returned to baseline level or improved to Grade 0 or 1. 36 subjects (21.8%) interrupted had an interruption of study treatment for a drug-related AE. The most commonly reported AEs leading to study treatment interruption were pneumothorax and proteinuria. A total of 48 subjects (37.8%) and 76 subjects (59.8%) experienced dose reduction and treatment modification due to a drug-related AE, respectively. The most frequently reported AEs resulting in lenvatinib dose reduction were proteinuria and hypertension.

In the Study 231, the most frequently reported (≥15%) adverse drug reactions were hypothyroidism, hypertension, decreased appetite, proteinuria, diarrhoea, vomiting, abdominal pain, weight decreased, aspartate aminotransferase increased, alanine aminotransferase increased, constipation, platelet count decreased, fatigue, headache, nausea and anaemia. The MAH is asked to suggest an update of the SmPC section 4.8 ("Paediatric population" part) accordingly, to be subsequently implemented in the scope of a work-sharing procedure for Lenvima and Kisplyx.

The safety profile of lenvatinib in the final analysis is consistent with the known safety profile of lenvatinib and consistent with the previously reported safety profile from this study. No new safety concerns were identified.

Conclusions

This procedure presents the final analysis on efficacy (final OS analysis) and safety data of lenvatinib monotherapy from one paediatric clinical trial (Study 231). The safety profile observed for lenvatinib as single-agent (Study 231) was overall consistent with the known safety profile of the individual agents. No new safety signals were detected. TEAEs were manageable using standard clinical management together with protocol-defined dose modifications.

2.4.1. Changes to the Product Information

No changes to the SmPC are suggested by the MAH. Please refer to discussion above and RSI.

3. Rapporteur's overall conclusion and recommendation

Fulfilled.

No regulatory action required.

4. Request for supplementary information

Based on the data submitted, the MAH should address the following questions as part of this procedure:

1) No updated results on clinical laboratory evaluations as well as vital signs and physical examination findings were submitted since previous CSR (DCO date: 16-SEP-2022), so the MAH is asked to provide the above information and include any relevant new data in the final CSR (P013MK7902).

2) As at least one additional case of pneumothorax was reported in paediatric patients, the MAH is asked to provide description/narrative of this case and to suggest an update of the SmPC section 4.8 ("Paediatric population" subsection), to be subsequently implemented in the scope of a work-sharing procedure for Lenvima and Kisplyx.

3) In the Study 231, the most frequently reported (≥15%) adverse drug reactions were hypothyroidism, hypertension, decreased appetite, proteinuria, diarrhoea, vomiting, abdominal pain, weight decreased, aspartate aminotransferase increased, alanine aminotransferase increased, constipation, platelet count decreased, fatigue, headache, nausea and anaemia. The MAH is asked to suggest an update of the SmPC section 4.8 ("Paediatric population" subsection) accordingly, to be subsequently implemented in the scope of a work-sharing procedure for Lenvima and Kisplyx.

The timetable is a 30-day response timetable with clock stop.

5. Assessment of the MAH responses to the RSI

1) No updated results on clinical laboratory evaluations as well as vital signs and physical examination findings were submitted since previous CSR (DCO date: 16-SEP-2022), so the MAH is asked to provide the above information and include any relevant new data in the final CSR (P013MK7902).

Summary of the MAH's response

The final clinical study report (CSR) with the primary efficacy analysis results for Study 231 was submitted as part of procedure EMEA/H/C/WS2631 (data cutoff [DCO] date: 16-SEP-2022). The 'End of Trial' DCO occurred on 13-Feb-2025 and a synoptic CSR (sCSR) was prepared to fulfill Article 46 of the EU Paediatric Regulation (EC No 1901/2006). The sCSR presents final disposition, demographics, exposure, and selected safety results collected through to the last participant's last visit. A final analysis of updated overall survival (OS) data based on all data collected through the end of the study was also included.

Given that clinically meaningful abnormalities in laboratory evaluations, vital signs, and physical examinations are reported as adverse events (AEs) (see sCSR Section 12.4 and Table 2-14 to Table 2-

35), and a review of all safety data at the end of trial concluded that safety results remain consistent with those reported at the primary analysis (DCO date: 16-SEP-2022), tables with updated results on clinical laboratory evaluations, vital signs, and physical examination findings were not included in the sCSR. Of note, this approach is consistent with that taken for paediatric Study E7080-G000-230 - A Multicenter, Open-label, Randomized Phase 2 Study to Compare the Efficacy and Safety of Lenvatinib in Combination with Ifosfamide and Etoposide versus Ifosfamide and Etoposide in Children, Adolescents and Young Adults with Relapsed or Refractory Osteosarcoma (OLIE) Lenvatinib (submitted on 11 FEB 2024 under procedure numbers EMA/H/C/003727/P46/023 and EMA/H/C/004224/P46/020).

Assessment of the MAH's response

The applicant mentioned only a synoptic CSR (sCSR) in this procedure was submitted (DCO date: 13-FEB-2025). For the safety part, the updated adverse events (AEs) were summarised in the tables instead of listing the updated clinical laboratory evaluations, vital signs, and physical examination findings. The same approach was also used in procedure EMA/H/C/003727/P46/023 and EMA/H/C/004224/P46/020 for paediatric Study E7080-G000-230 (submitted on 11 FEB 2024)

Conclusion

Issue Not Pursued

2) As at least one additional case of pneumothorax was reported in paediatric patients, the MAH is asked to provide description/narrative of this case and to suggest an update of the SmPC section 4.8 ("Paediatric population" subsection), to be subsequently implemented in the scope of a work-sharing procedure for Lenvima and Kisplyx.

Summary of the MAH's response

As requested by the Agency, a description of the additional case of pneumothorax is provided below. Accordingly, Section 4.8 of the SmPC has been updated to include this additional case of pneumothorax.

Subject, was diagnosed with synovial sarcoma 4 months and 13 days prior to the first dose of study medication. At Screening, the participant's Lansky Play Score was 70 and tumour assessments showed lung metastases. The participant was enrolled with refractory disease following first-line therapy (ifosfamide and doxorubicin [administered Day -88 to Day -36]) and had no prior history of radiation or anticancer procedures to the chest.

On Study Day 1, study medication with lenvatinib 14 mg/m2 per day was initiated. On Day 426, the participant attended a routine chest CT scan and tension pneumothorax (Grade 4) was identified. The participant was asymptomatic, did not have thorax trauma before, and was admitted to the hospital. A chest drain was placed. Lenvatinib was interrupted in response to AEs of increased Aspartate Aminotransferase (AST) (Grade 1), increased pancreatic enzymes (Grade 1), and hyponatremia (Grade 1). On Day 426, lenvatinib was discontinued due to pneumothorax, with the last dose on Day 425 (Cycle 15). The participant entered the study Follow-up period.

On Day 429, a chest x-ray showed normal results, the lungs appeared clear with no more fluid and the chest drain was removed. The adverse event (AE) of pneumothorax was considered resolved. On Day 433, the participant was discharged with the diagnosis of tension pneumothorax drainage. On Day 454, the participant was considered to be in good condition and there was no pneumothorax recurrence. Events of increased AST, pancreatic enzymes, and hyponatremia were also considered resolved.

On Day 1016, the participant died; the primary reported cause of death was malignant neoplasm progression.

The investigator considered pneumothorax related to study medication. Baseline disease characteristics of clinical relevance for this patient included lung metastases.

Assessment of the MAH's response

The applicant submitted the case details of the additional patient with pneumothorax and modify the Section 4.8 of the SmPC to include this case of pneumothorax per requeeat.

Paediatric population

In the paediatric Studies 207, 216, 230, and 231 (see section 5.1), the overall safety profile of lenvatinib as a single agent or in combination with either ifosfamide and etoposide or everolimus was consistent with that observed in adults treated with lenvatinib.

In patients with relapsed/refractory osteosarcoma, pneumothorax was reported at a frequency higher than that observed in adults with DTC, HCC, RCC and EC. In Study 207, pneumothorax occurred in 6 patients (10.9%) treated with single -agent lenvatinib and 7 patients (16.7%) treated with lenvatinib in combination with ifosfamide and etoposide. Overall, 2 patients discontinued study treatment due to pneumothorax. In Study 230, pneumothorax was reported in a total of 14 patients (11 patients [28.2%] treated with lenvatinib plus ifosfamide and etoposide, and 3 patients [7.7%] treated with ifosfamide and etoposide). In Study 216, pneumothorax was reported in 3 patients (4.7%) with Ewing sarcoma, rhabdomyosarcoma (RMS) and Wilms tumour; all 3 patients had lung metastases at baseline. In Study 231, pneumothorax was reported in ~~7~~8 patients (~~5.5~~6.3%) with spindle cell sarcoma, undifferentiated sarcoma, RMS, malignant peripheral nerve sheath tumour, synovial sarcoma, spindle cell carcinoma, and malignant fibromyxoid ossifying tumour; all ~~7~~8 patients had lung metastases or primary disease in the chest wall or pleural cavity at baseline. For Studies 216~~,~~ and 230~~, and 231~~, no patient discontinued study treatment due to pneumothorax; in Study 231, one patient discontinued study treatment due to pneumothorax. Pneumothorax occurrence appeared to be mainly associated with pulmonary metastases and underlying disease.

Conclusion

Issue Resolved

3) In the Study 231, the most frequently reported (≥15%) adverse drug reactions were hypothyroidism, hypertension, decreased appetite, proteinuria, diarrhoea, vomiting, abdominal pain, weight decreased, aspartate aminotransferase increased, alanine aminotransferase increased, constipation, platelet count decreased, fatigue, headache, nausea and anaemia. The MAH is asked to suggest an update of the SmPC section 4.8 ("Paediatric population" subsection) accordingly, to be subsequently implemented in the scope of a work-sharing procedure for Lenvima and Kisplyx.

Summary of the MAH's response

To ensure consistency in the presentation of safety data in SmPC section 4.8, the summary for Study E7080-G000-231 includes the most common treatment-related AEs i.e., adverse drug reactions, in alignment with the data previously presented and agreed for Study E7080-A001-216 in the SmPC under procedure numbers EMEA/H/C/003727/P46/022 and EMEA/H/C/004224/P46/019. This approach has been adopted to support consistent interpretation of safety data across studies. Given that there are no changes to the list of most common adverse drug reactions (≥15%) at the time of the sCSR (see Table 2-17), no changes are proposed to SmPC section 4.8.

Assessment of the MAH's response

The applicant clarified the updated data of the most common adverse drug reactions (≥15%) in Study 231 was presented in Table 2-17 of the sCSR, including hypothyroidism, hypertension, proteinuria, decreased appetite, diarrhoea, and platelet count decreased (see below). As there are no updates to this list, the corresponding context in SmPC section 4.8 ("Paediatric population" part") can remain unchanged.

Table 2-17
Participants With Drug-Related Adverse Events (Sorted by Decreasing Incidence) (Incidence ≥ 5%)
(Safety Analysis Set)

	Total	
	n	(%)
Participants in population	127	
with one or more adverse events	116	(91.3)
with no adverse events	11	(8.7)
Hypothyroidism	81	(63.8)
Hypertension	48	(37.8)
Proteinuria	39	(30.7)
Decreased appetite	34	(26.8)
Diarrhoea	32	(25.2)
Platelet count decreased	19	(15.0)
Abdominal pain	18	(14.2)
Fatigue	18	(14.2)
Weight decreased	18	(14.2)
Vomiting	15	(11.8)
Nausea	14	(11.0)
Aspartate aminotransferase increased	13	(10.2)
Alanine aminotransferase increased	12	(9.4)
Headache	11	(8.7)
Myalgia	10	(7.9)
Pain in extremity	9	(7.1)
Epistaxis	8	(6.3)
Palmar-plantar erythrodysaesthesia syndrome	8	(6.3)

Conclusion

Issue Resolved