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EMA/24182/2025
Human Medicines Division

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

Koselugo

Selumetinib

Procedure no: EMEA/H/C/005244/P46/007

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**	**Need for discussion**
☐	Start of procedure	19/08/2024	19/08/2024	☐
☐	CHMP Rapporteur Assessment Report	23/09/2024	23/09/2024	☐
☐	CHMP members comments	07/10/2024	07/10/2024	☐
☐	Updated CHMP Rapporteur Assessment Report	10/10/2024	10/10/2024	☐
☒	CHMP adoption of conclusions:	17/10/2024	17/10/2024	☐

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1. Introduction

On July 2024, the MAH submitted a paediatric study for selumetinib (Koselugo), in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

Study D1346C00015 is a Phase I, Single-Arm, Sequential Study to Evaluate the Effect of Food on the Gastrointestinal Tolerability and Pharmacokinetics of Selumetinib after Multiple Doses in Adolescent Children with Neurofibromatosis Type 1 (NF1) Related Plexiform Neurofibromas (PN) conducted by the MAH AstraZeneca to fulfil an FDA Post-Marketing Requirement (PMR 3806-3), and as previously agreed with the PDCO Study 15 used to fulfil PIP Quality Measure 2. The Clinical Study Report for the DCO1 was submitted to the Agency to support the removal of the fasting restriction (EMEA/H/C/005244/II/0013) for which EMA Decision was granted on 19 Oct 23. The MAH AstraZeneca submitted Study D1346C00015 CSR for DCO2, which includes a safety update to fulfil Art.46 requirements.

A short critical expert overview has also been provided.

2. Scientific discussion

2.1. Information on the development program

Study D1346C00015 "A Phase I, Single-Arm, Sequential Study to Evaluate the Effect of Food on the Gastrointestinal Tolerability and Pharmacokinetics of Selumetinib after Multiple Doses in Adolescent Children with Neurofibromatosis Type 1 (NF1) Related Plexiform Neurofibromas (PN)"

2.2. Information on the pharmaceutical formulation used in the study

In Study D1346C00015 (Study 15), the commercially representative selumetinib capsules were used to support submission of clinical pharmacology program.

Assessor's comment:

No complementary biopharmaceutical investigation is needed. The drug products used in the dedicated food effect study 15 (10 and 25 mg capsules) are already approved and deemed suitable for the claimed dosing scheme.

2.3. Clinical aspects

2.3.1. Pharmacokinetics

Selumetinib is used as monotherapy for the treatment of symptomatic, inoperable plexiform neurofibromas (PN) in paediatric patients with neurofibromatosis type 1 (NF1) aged 3 years and above.

The recommended dose of selumetinib is 25 mg/m^2 individualised based on body surface area (BSA) and taken orally twice daily (BID). Dosing is rounded to the nearest achievable 5 mg or 10 mg dose (up to a maximum single dose of 50 mg for BSA ≥ 1.9 m^2). Selumetinib is not recommended in patients with a BSA < 0.55 m^2.

The pharmacokinetic (PK) properties of selumetinib were sufficiently characterized in the initial MAA. Please refer to section 5.2 of the current SmPC.

In the context of this PAM procedure EMEA/H/C/5244/P46, the Applicant submitted an addendum to CSR of **Study D1346C00015** (Study 15): A Phase I, single-Arm, sequential study to evaluate the effect of food on the gastrointestinal tolerability and PK of selumetinib after multiple doses in adolescent children with neurofibromatosis type 1 (NF1) Related Plexiform Neurofibromas (PN).

This updated report included new safety data for patients who continued the treatment until the final data cut-off (DCO; 24 April 2023) in the extension period T2 after the primary DCO (06 April 2022). There is no PK analysis conducted at this final DCO, and therefore, there are no updates to the PK data since the primary analysis.

It is important to underline that PK results of Study 15 were already submitted and assessed in type II variation EMEA/H/C/005244/II/0013. Within this variation, it was concluded that, taking into account both results from the formal and pivotal food effect Study 15 in the target adolescent patients (a reduction in steady state $AUC_{0\text{-}12h,ss}$ and C_{max} by in average 8% and 24% respectively, when administered with a low-fat meal compared with the fasted state) and the supportive findings from the population approach (fed state reduced AUC_{12hss} of selumetinib and the N-desmethyl metabolite by less than 30%), the proposal to remove the fasting restriction from the product information (section 4.2 of the SmPC) and addition of PK results from Study 15 (section 5.2) were agreed.

No new data regarding the food effect of selumetinib are submitted and no change to the product information is proposed within the current PAM under review.

2.3.2. Clinical study

Clinical study number and title

Study code: D1346C00015

EudraCT Number: 2020-005648-52

NCT Number: NCT05101148

Title:A Phase I, Single-Arm, Sequential Study to Evaluate the Effect of Food on the Gastrointestinal Tolerability and Pharmacokinetics of Selumetinib after Multiple Doses in Adolescent Children with Neurofibromatosis Type 1 (NF1) Related Plexiform Neurofibromas (PN)

Summary of the study description following addendum of the CSR

This is a clinical study report (CSR) addendum for Study D1346C00015. Study D1346C00015 was initiated in adolescent children, aged ≥ 12 and < 18 years with neurofibromatosis Type 1 (NF1)-related symptomatic inoperable plexiform neurofibroma (PN), to evaluate the effect of a low-fat meal on steady state selumetinib pharmacokinetic (PK) exposure; to assess the effect on gastrointestinal (GI) tolerability when selumetinib is dosed under fed and fasted conditions; and, potentially, to confirm an appropriate dosing recommendation of selumetinib with a low-fat meal that maintained efficacy with acceptable safety and tolerability.

A Data Review Committee (DRC) reviewed the PK and safety data from treatment period 1 (T1) cycle 1 (C1) and treatment period 2 (T2) C1 to determine whether treatment period 3 (T3) was to be initiated, should a significant reduction in PK exposure have been observed when selumetinib was given with a low-fat meal compared to the fasted state; T3 was deemed not necessary and was not initiated. The T2 extension period continued until the final data cut-off (DCO; 24 April 2023), and included new data for participants who continued study treatment in the T2 extension period after the primary DCO (06 April 2022).

Objective

The primary analysis of the primary PK and safety endpoints for this study compared T1 C1 (fed) with T2 C1 (fasted) and included the comparison of GI tolerability in the fed and fasted states; the T2 extension period was not included in this comparison. The new safety data reported in this clinical study report (CSR) addendum are for participants who remained in the T2 extension period after the primary

DCO, to further assess the safety profile of selumetinib administered in adolescent children with NF1-related PN in the fasted state.

Study design

This was a Phase I, single arm, multiple dose, uncontrolled, sequential, two or three period study in adolescent children aged ≥ 12 to < 18 years at study entry with a clinical diagnosis of NF1-related PN.

The study was designed to evaluate the steady state systemic exposure and safety (especially GI toxicity) of selumetinib 25 mg/m^2 bid given with a low-fat meal versus the same dose given in a fasted state.

This sequential study consisted of a screening period lasting up to 28 days, a 28 day (one cycle) treatment period (T1) in a fed state, a 7 day washout period (for PK and safety) that could be extended up to 21 days at the discretion of the Investigator if GI related adverse events (AEs) had not recovered or returned to baseline, a further 28 day (one cycle) treatment period (T2) in a fasted state, and an extension to T2 which continued until the final DCO (24 April 2023).

Prior to the start of dosing in T2, the Investigator reviewed all AEs, vital signs, laboratory assessments and concomitant medications to confirm that the participant was able to continue in the study.

For at least 14 days during screening and throughout T1 C1 and T2 C1, participants completed a diary on a daily basis to confirm that selumetinib was taken according to the instructions and to rate GI symptoms (bowel movements, vomiting, nausea). In addition, at the end of each cycle, participants were asked to rate the convenience of taking selumetinib with a low-fat meal versus the same dose given in a fasted state; at the end of the study, participants were asked to indicate how they preferred taking selumetinib.

A third treatment period (T3) was planned to be added if a significant reduction in PK exposure was observed when selumetinib was given with a low-fat meal compared to the fasted; T3 was to evaluate the PK and safety of an adjusted dose of selumetinib when given with a low-fat meal. Based on a DRC assessment of data from T1 and T2, T3 was not initiated.

The final DCO (24 April 2023) included new data for participants who continued treatment in the T2 extension period after the primary DCO (06 April 2022). In addition, there were minor updates to the database for participants treated in T1 C1 plus the washout period and T2 C1; these updates are also reported in this CSR addendum.

Approximately 20 adolescent children aged ≥ 12 to < 18 years with a clinical diagnosis of NF1-related PN were planned to be enrolled to ensure 16 evaluable participants completing T2. A total of 25 participants were actually enrolled (aged between 12 and 17 years), of whom 24 participants were evaluable for safety (defined as all participants who received at least one dose of selumetinib) and 24 participants were included in the PK Analysis Set (defined as all participants who received at least one dose of selumetinib and who had at least one post-dose quantifiable plasma concentration and did not have any important protocol deviations that would affect the PK analysis). One participant screen failed due to inclusion criterion 6 (participants must have a body surface area [BSA] ≥ 1.3 and ≤ 2.5 m^2); the participant's BSA was measured as 1.09 m^2.

Duration of Treatment

This sequential study consisted of a screening period lasting up to 28 days, a 28 day (one cycle) treatment period (T1) in a fed state, a 7 day washout period (for PK and safety) that could be extended up to 21 days at the discretion of the Investigator if GI related AEs had not resolved or returned to baseline, a further 28 day (one cycle) treatment period (T2) in a fasted state, an extension to T2 which continued until results from the primary analysis were available, and a recommendation had been made as to whether a third treatment period (T3) in a fed state was required.

The median total treatment duration (intended) and the median actual treatment duration (total minus treatment interruptions) were equal for both T1 C1 (28 days) and T2 C1 (29 days). Median relative dose intensity during both T1 C1 and T2 C1 was 100%.

In total, 23 participants had completed the study at the addendum DCO (24 April 2023). Since the primary analysis, median total (intended) treatment exposure in T2 C1 plus extension period had increased from 91.5 to 417.5 days and median actual treatment exposure (total minus treatment interruptions) had increased from 80.0 to 412.0 days.

Statistical Methods

All statistical analyses and production of tables, figures and listings were performed using Statistical Analysis Software (SAS)® Version 9.4.

There was no PK analysis conducted at the final DCO. The safety analyses were based on the Safety Analysis Set. Safety data were analysed based on summary statistics.

Efficacy results

There were no efficacy endpoints in this study.

Safety results

Exposure

At the time of the primary CSR DCO (06 April 2022), 25 participants were enrolled into the study and 24 participants received treatment. No additional participants were enrolled or received treatment between the primary CSR DCO and the final CSR addendum DCO (24 April 2023).

- Treatment Period 1 (Cycle 1 Plus Washout Period): Since the primary analysis, there were no updates to the duration of exposure data for participants during T1 (Section 9 and see Table 14.3.1.2).

- Treatment Period 2 (Cycle 1 Plus Extension Period): The duration of exposure for participants during T2 is presented in Table 5. Since the primary analysis, median total (intended) treatment exposure had increased from 91.5 to 417.5 days and median actual treatment exposure had increased from 80.0 to 412.0 days in the T2 C1 plus extension period.

Table 5 Duration of Exposure During T2 (Safety Analysis Set)

		T2 [a] 25 mg/m² fasted (N = 24)
Total (or intended) exposure (days) [b]	n	24
	Mean (SD)	433.6 (63.65)
	Median (Min-Max)	417.5 (284-547)
Actual exposure (days) [c]	n	24
	Mean (SD)	428.4 (64.93)
	Median (Min-Max)	412.0 (284-547)
Relative dose intensity (%) [d]	n	24
	Mean (SD)	98.5 (3.10)
	Median (Min-Max)	100.0 (90-100)

[a] T2 includes T2 C1 plus the extension period.

[b] Total (or intended) exposure = min (last dose date in treatment period where dose > 0 mg, death date) – first dose date in treatment period + 1.

[c] Actual treatment duration = intended exposure – total duration of drug interruptions. Drug interruptions were counted in days; a single missed dose = 0.5 days.

[d] Relative dose intensity is the percentage of the actual cumulative dose delivered relative to the intended cumulative dose.

A treatment period ran from the first dose to the first dose of the following treatment period or 30 days after the end of treatment.

DCO: 24 April 2023.

C = cycle; DCO = data cut-off; Max = maximum; Min = minimum; N = number of participants in analysis set; n = number of participants included in analysis; SD = standard deviation; T2 = Treatment Period 2.

Adverse events

For information on AEs in any category during T1 C1, T2 C1, T1 C1 plus washout period, and T2 C1 plus extension period at the time of the primary analysis, see Section 12.2.1 of the primary CSR.

- Treatment Period 1 (Cycle 1 Plus Washout Period)

Since the primary analysis, the only updated data for AEs in any category for T1 was an increase in the number of participants with AESIs, from 15 participants (62.5%) to 16 participants (66.7%).

- Treatment Period 2 (Cycle 1 Plus Extension Period)

Adverse events were reported for 23 participants during the T2 extension period; 4 additional participants since the primary analysis (Table 7). Of these, 18 participants had an AE assessed by the Investigator to be possibly related to study treatment; 5 additional participants since the primary analysis. Six participants had an AE of Grade 3 or higher during the T2 extension period; 5 additional participants since the primary analysis, with one additional participant reporting an AE of Grade 3 or higher that was possibly related to study treatment.

The table 7 displayed adverse events in any category during T2:

Table 7 Adverse Events in Any Category During T2 and the Study Overall (Safety Analysis Set)

AE category	Number (%) of participants [a]	
	T2 [b] 25 mg/m^2 fasted (N = 24)	Overall [c] (N = 24)
Any AE	23 (95.8)	24 (100)
Any AE possibly related to treatment [d]	18 (75.0)	22 (91.7)
Any AE of CTCAE Grade 3 or higher	6 (25.0)	6 (25.0)
Any AE of CTCAE Grade 3 or higher, possibly related to treatment [b]	2 (8.3)	2 (8.3)
Any AE with an outcome of death	0	0
Any SAE	5 (20.8)	5 (20.8)
Any SAE, possibly related to treatment [d]	1 (4.2)	1 (4.2)
Any AE leading to discontinuation of study treatment	0	0
Any AE leading to interruption of study treatment	3 (12.5)	3 (12.5)
Any AE leading to dose reduction of study treatment	1 (4.2)	2 (8.3)
Any AEs of special interest	18 (75.0)	24 (100)
Any other significant AE [e]	0	0

[a] Participants with multiple events in the same category were counted only once in that category. Participants with events in more than one category were counted once in each of those categories.

[b] T2 includes T2 C1 plus the extension period.

[c] Overall includes T1 C1 plus the washout period and T2 C1 plus the extension period.

[d] As assessed by the Investigator.

[e] Any AEs, other than SAEs and those AEs leading to discontinuation of study treatment, which were of particular clinical importance, were identified and classified as Other Significant AEs by the sponsor.

A treatment period ran from the first dose to the first dose of the following treatment period, or 30 days after the end of treatment. Adverse events were assigned to a treatment period based on date of onset. Overall period was defined as AEs started between first and last dose + 30 days.

CTCAE Version 5.0; MedDRA Version 25.1.

DCO: 24 April 2023.

AE = adverse event; C = cycle; CTCAE = Common Terminology Criteria for Adverse Events; DCO = data cut-off; MedDRA = Medical Dictionary for Regulatory Activities; N = number of participants in analysis set; SAE = serious adverse event; T1 = Treatment Period 1; T2 = Treatment Period 2.

- Treatment Period 1 (Cycle 1 Plus Washout Period)

Since the primary analysis, the following AE data for participants in T1 has been updated: One additional participant was reported with acne, increasing from one participant (4.2%) to 2 participants (8.3%). This increased the number of participants with AEs in the SOC of Skin and Subcutaneous Tissue Disorders from 16 participants (66.7%) to 17 participants (70.8%).

▪ Treatment Period 2 (Cycle 1 Plus Extension Period)

The SOCs that had a > 20% increase in participants during the T2 extension period since the primary analysis were:

- Infections and Infestations (from 7 participants [29.2%] to 14 participants [58.3%]; increase of 29.1%);

- Nervous System Disorders (from 2 participants [8.3%] to 8 participants [33.3%]; increase of 25.0%);

- Gastrointestinal Disorders (from 9 participants [37.5%] to 14 participants [58.3%]; increase of 20.8%); and

- Skin and Subcutaneous Tissue Disorders (from 9 participants [37.5%] to 14 participants [58.3%]; increase of 20.8%).

The most common AEs (occurring in ≥ 25% of participants during the T2 extension period) were: paronychia (8 participants [33.3%]), COVID-19 (7 participants [29.2%]), and dermatitis acneiform and vomiting (6 participants [25.0%] each.

The AEs that had a > 10% increase in participants during the T2 extension period since the primary analysis were:

- Paronychia (from 2 participants [8.3%] to 8 participants [33.3%]; increase of 25.0%);

- Dry skin (from one participant [4.2%] to 5 participants [20.8%]; increase of 16.6%);

- Headache (from one participant [4.2%] to 5 participants [20.8%]; increase of 16.6%); and

- Blood CPK increased (from 2 participants [8.3%] to 5 participants [20.8%]; increase of 12.5%).

Treatment related adverse events

For information on AEs by relation to study treatment during T1 C1, T2 C1, T1 C1 plus washout period, and T2 C1 plus extension period at the time of the primary analysis, see Section 12.2.3 of the primary CSR.

▪ Treatment Period 1 (Cycle 1 Plus Washout Period)

Since the primary analysis, the following data for AEs assessed by the Investigator as possibly related to study treatment for participants in T1 has been updated (Section 9):

One additional participant was reported with acne, increasing from one participant (4.2%) to 2 participants (8.3%). This increased the number of participants with AEs assessed by the Investigator as possibly related to study treatment in the SOC of Skin and

Subcutaneous Tissue Disorders from 14 participants (58.3%) to 15 participants (62.5%).

▪ Treatment Period 2 (Cycle 1 Plus Extension Period)

Adverse events, occurring in > 5% participants overall, assessed by the Investigator as possibly related to study treatment during the study, are presented by SOC and PT in Table 9.

Since the primary analysis, AEs assessed by the Investigator as possibly related to study treatment were reported for 5 additional participants during the T2 extension period, totalling 18 participants (75.0%) during T2.

The only SOC that had a > 20% increase in participants during the T2 extension period since the primary analysis was Infections and Infestations (from 2 participants [8.3%] to 7 participants [29.2%]; increase of 20.9%).

The most common AEs, assessed by the Investigator as possibly related to study treatment (occurring in ≥ 20% of participants during the T2 extension period) were: paronychia (7 participants [29.2%]), dermatitis acneiform (6 participants [25.0%]), and blood CPK increased and dry skin (5 participants [20.8%] each; Table 9).

The AEs that had a > 10% increase in participants during the T2 extension period since the primary analysis were:

- Paronychia (from 2 participants [8.3%] to 7 participants [29.2%]; increase of 20.9%);
- Dry skin (from one participant [4.2%] to 5 participants [20.8%]; increase of 16.6%);
- Blood CPK increased (from 2 participants [8.3%] to 5 participants [20.8%]; increase of 12.5%); and
- Dermatitis acneiform (from 3 participants [12.5%] to 6 participants [25.0%]; increase of 12.5%).

Table 9 **Adverse Events (Occurring in > 5% of Participants Overall, Assessed by Investigator as Possibly Related to Study Treatment) by SOC and PT During T2 and Overall (Safety Analysis Set)**

System Organ Class Preferred Term	Number (%) of participants [a] T2 [b] 25 mg/m^2 fasted (N = 24)	Overall [c] (N = 24)
Participants with any possibly related AE [d]	**18 (75.0)**	**22 (91.7)**
Skin and Subcutaneous Tissue Disorders	12 (50.0)	20 (83.3)
Dermatitis acneiform	6 (25.0)	15 (62.5)
Dry skin	5 (20.8)	5 (20.8)
Alopecia	2 (8.3)	4 (16.7)
Acne	2 (8.3)	3 (12.5)
Rash	2 (8.3)	3 (12.5)

System Organ Class Preferred Term	Number (%) of participants [a] T2 [b] 25 mg/m^2 fasted (N = 24)	Overall [c] (N = 24)
Eczema	2 (8.3)	2 (8.3)
Gastrointestinal Disorders	6 (25.0)	10 (41.7)
Nausea	3 (12.5)	4 (16.7)
Abdominal pain	2 (8.3)	3 (12.5)
Diarrhoea	0	2 (8.3)
Infections and Infestations	7 (29.2)	9 (37.5)
Paronychia	7 (29.2)	8 (33.3)
Investigations	8 (33.3)	8 (33.3)
Blood creatinine phosphokinase increased	5 (20.8)	5 (20.8)
Ejection fraction decreased	2 (8.3)	2 (8.3)
General Disorders and Administration Site Conditions	2 (8.3)	2 (8.3)
Fatigue	2 (8.3)	2 (8.3)
Respiratory, Thoracic and Mediastinal Disorders	2 (8.3)	2 (8.3)
Epistaxis	2 (8.3)	2 (8.3)

[a] Number (%) of participants with any possibly related AE, sorted by incidence and then alphabetically for SOC and PT. Participants with multiple events in the same PT were counted only once in that PT. Participants with events in more than one PT were counted once in each of those PTs.

[b] T2 includes T2 C1 plus the extension period.

[c] Overall includes T1 C1 plus the washout period and T2 C1 plus the extension period.

[d] Possibly related, as assessed by the Investigator.

A treatment period ran from the first dose to the first dose of the following treatment period, or 30 days after the end of treatment. Adverse events were assigned to a treatment period based on date of onset. Overall period was defined as AEs started between first and last dose + 30 days.

MedDRA Version 25.1.

AE = adverse event; C = cycle; MedDRA = Medical Dictionary for Regulatory Activities; N = number of participants in analysis set; PT = preferred term; SOC = system organ class; T1 = Treatment Period 1; T2 = Treatment Period 2.

Serious adverse event

At the time of the primary analysis, no SAEs had been reported during the study (see Section 12.3.2 of the primary CSR).

- Treatment Period 1 (Cycle 1 Plus Washout Period):

Since the primary analysis, no data updates have been made for participants with SAEs during T1 (Section 9 and see Table 14.3.4.2).

- Treatment Period 2 (Cycle 1 Plus Extension Period)

Serious AEs are presented by SOC and PT in Table 15. Since the primary analysis, Five (5) participants (20.8%) had reported a total of 6 SAEs during the T2 extension period:

- One participant (4.2%) reported an SAE of hypertension that was assessed by the Investigator as possibly related to study treatment. For key information regarding these SAEs, see Table 14.3.4.5.

- One participant reported an SAE of hypertension on Day 116, graded as CTCAE Grade 1 and assessed by the Investigator as possibly related to study treatment. Study treatment was not interrupted and the dose was not changed. The participant recovered and the SAE resolved on Day 121.

- One participant reported an SAE of COVID-19 on Day 225, graded as CTCAE Grade 2 and assessed by the Investigator as unrelated to study treatment. Study treatment was not interrupted and the dose was not changed. The participant received treatment, recovered, and the SAE resolved on Day 233. The participant also reported an SAE of loss of consciousness that was assessed by the Investigator as unrelated to study treatment (CTCAE Grade 3; see Section 12.2.4). The participant recovered and the SAE resolved on the same day.

- One participant reported an SAE of suicidal ideation on Day 189, graded as CTCAE Grade 2 and assessed by the Investigator as unrelated to study treatment. Study treatment was not interrupted and the dose was not changed. The participant recovered and the SAE resolved on the same day. The participant also reported a second SAE of suicidal ideation that was assessed by the Investigator as unrelated to study treatment (Day 339; CTCAE Grade 3). The participant recovered and the SAE resolved on the same day.

- One participant reported an SAE of injury (reported term: multi-site trauma; CTCAE Grade 3).

- One participant reported an SAE of torsion of urethra (CTCAE Grade 4).

Table 15 Serious AEs by SOC and PT During the Study (Safety Analysis Set)

System Organ Class Preferred Term	Number (%) of participants [a] T2 [b] 25 mg/m^2 fasted (N = 24)	Overall [c] (N = 24)
Participants with any SAE	**5 (20.8)**	**5 (20.8)**
Infections and Infestations	1 (4.2)	1 (4.2)
COVID-19	1 (4.2)	1 (4.2)
Psychiatric Disorders	1 (4.2)	1 (4.2)
Suicidal ideation	1 (4.2)	1 (4.2)
Nervous System Disorders	1 (4.2)	1 (4.2)
Loss of consciousness	1 (4.2)	1 (4.2)
Vascular Disorders	1 (4.2) [d]	1 (4.2) [d]
Hypertension	1 (4.2) [d]	1 (4.2) [d]
Renal and Urinary Disorders	1 (4.2)	1 (4.2)
Torsion of the urethra	1 (4.2)	1 (4.2)

Table 15 Serious AEs by SOC and PT During the Study (Safety Analysis Set)

System Organ Class Preferred Term	Number (%) of participants [a] T2 [b] 25 mg/m^2 fasted (N = 24)	Overall [c] (N = 24)
Injury, Poisoning and Procedural Complications	1 (4.2)	1 (4.2)
Injury	1 (4.2)	1 (4.2)

[a] Number (%) of participants with any SAE, sorted by incidence and then alphabetically for SOC and PT. Participants with multiple SAEs in the same PT were counted only once in that PT. Participants with SAEs in more than one PT were counted once in each of those PTs.

[b] T2 includes T2 C1 plus the extension period.

[c] Overall includes T1 C1 plus the washout period and T2 C1 plus the extension period.

[d] Possibly related to study treatment, as assessed by the Investigator.

A treatment period ran from the first dose to the first dose of the following treatment period, or 30 days after the end of treatment. Adverse events were assigned to a treatment period based on date of onset. Overall period was defined as SAEs started between first and last dose + 30 days.

MedDRA Version 25.1.

AE = adverse event; C = cycle; COVID-19 = coronavirus disease 2019; MedDRA = Medical Dictionary for Regulatory Activities; N = number of participants in analysis set; PT = preferred term; SAE = serious adverse event; SOC = system organ class; T1 = Treatment Period 1; T2 = Treatment Period 2.

One participant reported an SAE of suicidal ideation on Day 339, graded as CTCAE Grade 3 and assessed by the Investigator as unrelated to study treatment. The participant recovered from the Grade 3 episode and the SAE resolved on the same day.

Death

No AEs with fatal outcome had been reported during the study

Adverse events of special interest

Adverse events of special interest during T2 and overall are presented by grouped term and PT in Table 14:

Table 14 Adverse Events of Special Interest by Grouped Term and PT During T2 and Overall (Safety Analysis Set)

Grouped Term Preferred Term	Number (%) of participants [a] T2 [b] 25 mg/m^2 fasted (N = 24)	Overall [c] (N = 24)
Participants with any AESI	**18 (75.0)**	**24 (100)**
Acneiform Rash	9 (37.5)	21 (87.5)
Dermatitis acneiform	6 (25.0)	17 (70.8)
Acne	2 (8.3)	3 (12.5)
Acne cystic	1 (4.2)	1 (4.2)
Nail Disorder Events	8 (33.3)	9 (37.5)
Paronychia	8 (33.3)	9 (37.5)
CPK Increased	5 (20.8)	6 (25.0)
Blood creatinine phosphokinase increased	5 (20.8)	6 (25.0)
Non Acneiform Rash	5 (20.8)	6 (25.0)
Rash	3 (12.5)	4 (16.7)
Pruritus	2 (8.3)	2 (8.3)
Rash maculo-papular	0	1 (4.2)
Ejection Fraction Decreased	3 (12.5)	3 (12.5)
Ejection fraction decreased	3 (12.5)	3 (12.5)
Oral Mucositis	3 (12.5)	3 (12.5)
Stomatitis	2 (8.3)	2 (8.3)
Aphthous ulcer	1 (4.2)	1 (4.2)
Erythropenic Event	1 (4.2)	1 (4.2)
Anaemia	1 (4.2)	1 (4.2)
Leukopenic Events	1 (4.2)	1 (4.2)
Leukopenia	1 (4.2)	1 (4.2)
Muscle Events	1 (4.2)	1 (4.2)
Muscular weakness	1 (4.2)	1 (4.2)

[a] Number (%) of participants with any AESI, sorted by incidence and then alphabetically for grouped term and then PT. Participants with multiple AESIs in the same PT were counted only once in that PT. Participants with AESIs in more than one PT were counted once in each of those PTs.

[b] T2 includes T2 C1 plus the extension period.

[c] Overall includes T1 C1 plus the washout period and T2 C1 plus the extension period.

A treatment period ran from the first dose to the first dose of the following treatment period, or 30 days after the end of treatment. Adverse events were assigned to a treatment period based on date of onset. Overall period was defined as AESIs started between first and last dose + 30 days.

MedDRA Version 25.1.

AESI = adverse event of special interest; C = cycle; CPK = creatine kinase; MedDRA = Medical Dictionary for Regulatory Activities; N = number of participants in analysis set; PT = preferred term; T1 = Treatment Period 1; T2 = Treatment Period 2.

Since the primary analysis, AESIs have been reported for 5 additional participants during the T2 extension period, totalling 18 participants (75.0%) during T2.

The grouped terms that had a > 10% increase in participants during the T2 extension period since the primary analysis included:

- Nail disorder events (from 2 participants [8.3%] to 8 participants [33.3%]; increase of 25.0%);
- Non acneiform rash (from one participant [4.2%] to 5 participants [20.8%]; increase of 16.6%);
- CPK increased (from 2 participants [8.3%] to 5 participants [20.8%]; increase of 12.5%).

The PTs that had a > 10% increase in participants during the T2 extension period since the primary analysis included:

- Paronychia (from 2 participants [8.3%] to 8 participants [33.3%]; increase of 25.0%) and
- Blood CPK increased (from 2 participants [8.3%] to 5 participants [20.8%]; increase of 12.5%).

New PTs that were not reported for any participants at the primary analysis, but were reported for at least one participant at the final DCO during the T2 extension period, included: anaemia, aphthous ulcer, and muscular weakness (one participant [4.2%] each).

Gastro-intestinal adverse events

Table 13 Gastrointestinal AEs by SOC and PT During T2 and Overall (Safety Analysis Set)

Preferred Term	Number (%) of participants [a]	
	T2 [b] 25 mg/m^2 fasted (N = 24)	Overall [c] (N = 24)
Participants with any GI AE	**14 (58.3)**	**19 (79.2)**
Vomiting	6 (25.0)	8 (33.3)
Nausea	4 (16.7)	6 (25.0)
Diarrhoea	2 (8.3)	5 (20.8)
Abdominal pain	2 (8.3)	3 (12.5)
Haemorrhoids	2 (8.3)	2 (8.3)
Stomatitis	2 (8.3)	2 (8.3)
Abdominal distension	1 (4.2)	1 (4.2)
Abdominal pain upper	1 (4.2)	1 (4.2)
Aphthous ulcer	1 (4.2)	1 (4.2)
Constipation	1 (4.2)	1 (4.2)
Dry mouth	1 (4.2)	1 (4.2)

[a] Number (%) of participants with any GI AE, sorted by overall frequency for PT. Participants with multiple events in the same PT were counted only once in that PT. Participants with events in more than one PT were counted once in each of those PTs.

[b] T2 includes T2 C1 plus the extension period.

[c] Overall includes T1 C1 plus the washout period and T2 C1 plus the extension period.

A treatment period ran from the first dose to the first dose of the following treatment period, or 30 days after the end of treatment. Adverse events were assigned to a treatment period based on date of onset. Overall period was defined as GI AEs started between first and last dose + 30 days.

MedDRA Version 25.1.

AE = adverse event; C = cycle; GI = gastrointestinal; MedDRA = Medical Dictionary for Regulatory Activities; N = number of participants in analysis set; PT = preferred term; SOC = system organ class; T1 = Treatment Period 1; T2 = Treatment Period 2.

Treatment interruption

Treatment Period 2 (Cycle 1 Plus Extension Period): Since the primary analysis, an additional 4 participants had a treatment interruption during the T2 extension period (Table 6). The reasons for these treatment interruptions were: AE (one additional participant [paronychia], and 'other' (3 additional participants). An additional 5 participants had a dose reduction during the T2 extension period (Table 6);

the reasons for these dose reductions were: AE (one additional participant [dermatitis acneiform], protocol-specified dose change (3 additional participants), and 'other' (one additional participant).

Table 6 Treatment Interruptions and Dose Reductions During T2 (Safety Analysis Set)

		Number (%) of participants
		T2 [a] 25 mg/m^2 fasted (N = 24)
Received planned starting dose	Yes	24 (100)
No interruption		18 (75.0)
Number of participants with an interruption	Any	6 (25.0)
	1 interruption	5 (20.8)
	2 interruptions	1 (4.2)
Reason for interruption [b]	AE	3 (12.5)
	Other	3 (12.5)
No prolonged interruption [c]		19 (79.2)
Number of participants with a prolonged interruption [c]	Any	5 (20.8)
	1 interruption	5 (20.8)
Reason for prolonged interruption [b, c]	AE	3 (12.5)
	Other	2 (8.3)
No dose reduction		18 (75.0)
	Any	6 (25.0)
Number of participants with a dose reduction	1 reduction	5 (20.8)
	2 reductions	1 (4.2)
Reason for dose reduction [b]	AE	3 (12.5)
	Protocol specified dose change	3 (12.5)
	Other	1 (4.2)

[a] T2 includes T2 C1 plus the extension period.

[b] Reasons were not mutually exclusive for participants with multiple occurrences, although were counted only once per category.

[c] Prolonged interruption was defined as any interruption lasting more than 7 days.

Drug interruptions were counted in days; a single missed dose = 0.5 days.

A treatment period ran from the first dose to the first dose of the following treatment period or 30 days after the end of treatment. An interruption or dose reduction was assigned to a treatment period based on the start date of the interruption or dose reduction.

DCO: 24 April 2023.

AE = adverse event; DCO = data cut-off; T2 = Treatment Period 2.

Table 11 Adverse Events Leading to Study Treatment Interruption by SOC and PT During T2 and Overall (Safety Analysis Set)

System Organ Class Preferred Term	Number (%) of participants [a] T2 [b] 25 mg/m^2 fasted (N = 24)	Overall [c] (N = 24)
Participants with any AE leading to study treatment interruption [d]	**3 (12.5)**	**3 (12.5)**
Infections and Infestations	1 (4.2)	1 (4.2)
Paronychia	1 (4.2)	1 (4.2)
Skin and Subcutaneous Tissue Disorders	2 (8.3)	2 (8.3)
Alopecia	1 (4.2)	1 (4.2) [e]
Dermatitis acneiform	0	1 (4.2) [e]
Rash	1 (4.2)	1 (4.2)

[a] Number (%) of participants with AE leading to study treatment interruption, sorted by overall frequency for PT. Participants with multiple events in the same PT were counted only once in that PT. Participants with events in more than one PT were counted once in each of those PTs.

[b] T2 includes T2 C1 plus the extension period.

[c] Overall includes T1 C1 plus the washout period and T2 C1 plus the extension period.

[d] Action taken: Drug interrupted.

[e] One participant reported an AE of dermatitis acneiform that had an onset during T1, but was unresolved until the T2 extension period. They also reported an AE of alopecia in the T2 extension period, which led to study treatment interruption. The study treatment interruption was attributed to both AEs (see Section 12.2.5 of the primary CSR for more details).

A treatment period ran from the first dose to the first dose of the following treatment period, or 30 days after the end of treatment. Adverse events were assigned to a treatment period based on date of onset. Overall period was defined as GI AEs started between first and last dose + 30 days.

Table 12 Adverse Events Leading to Dose Reduction by SOC and PT During T2 and Overall (Safety Analysis Set)

System Organ Class Preferred Term	Number (%) of participants [a] T2 [b] 25 mg/m² fasted (N = 24)	Overall [c] (N = 24)
Participants with any AE leading to dose reduction [d]	**1 (4.2)**	**2 (8.3)**
Skin and Subcutaneous Tissue Disorders	1 (4.2)	2 (8.3)
Dermatitis acneiform	1 (4.2)	2 (8.3)

[a] Number (%) of participants with AE leading to dose reduction, sorted by overall frequency for PT. Participants with multiple events in the same PT were counted only once in that PT. Participants with events in more than one PT were counted once in each of those PTs.

[b] T2 includes T2 C1 plus the extension period.

[c] Overall includes T1 C1 plus the washout period and T2 C1 plus the extension period.

[d] Action taken: Dose reduced.

A treatment period ran from the first dose to the first dose of the following treatment period, or 30 days after the end of treatment. Adverse events were assigned to a treatment period based on date of onset. Overall period was defined as GI AEs started between first and last dose + 30 days.

MedDRA Version 25.1.

AE = adverse event; C = cycle; GI = gastrointestinal; MedDRA = Medical Dictionary for Regulatory Activities; N = number of participants in analysis set; PT = preferred term; SOC = system organ class; T1 = Treatment Period 1; T2 = Treatment Period 2.

At the time of the primary analysis, data from the study D1346C00015 demonstrated that consumption of a low-fat meal with administration of selumetinib capsules, compared with selumetinib capsules administered in the fasted state, showed no difference in the occurrence and/or management of ggastrointrsinal adverse events, or any other AEs.

Overall, since the primary analysis, the one additional year of selumetinib exposure for participants remaining in the T2 extension period led to the following safety findings:

- The reported AEs remained consistent with those reported at the primary analysis and the known safety profile of selumetinib, with minimal changes in the AE categories.

- The gastrointestinal AEs reported were consistent with those reported at the primary analysis. There were no clinically important changes noted in laboratory values or vital signs in participants throughout the study.

- No new safety signals or safety concerns were identified throughout the study.

2.3.3. Discussion on clinical aspects

The safety data from the study D1346C00015 had been assessed in the type II variation EMEA/H/C/005244/II/0013. In the context of this PAM procedure EMEA/H/C/5244/P46, the Applicant submitted an addendum to its clinical study report. This updated report included new safety data for patients who continued the treatment until the final data cut-off (DCO; 24 April 2023) in the extension period T2 after the primary DCO (06 April 2022).

After one additional year of exposure to selumetinib in the T2 extension period, the reported AEs remained consistent with the known safety profile of selumetinib. No new safety signals or safety concerns were identified throughout the study.

3. Rapporteur's overall conclusion and recommendation

Based on the data provided by the MAH regarding the results of D1346C00015 study, no new safety concerns have been identified as compared to previous studies and experiences in patients treated with Koselugo®.

☒ **Fulfilled:**

No regulatory action required.