Clinical Study Report Addendum Synopsis	
Drug Substance	Selumetinib
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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)

Study dates: First subject enrolled: 21 July 2021
Last subject last visit: 24 April 2023
The analyses presented in this report are based on a database lock date of 06 June 2023.

Phase of development: Clinical pharmacology (I)

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This study was performed in compliance with Good Clinical Practice, including the archiving of essential documents.

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).

Study Centre(s)

The study was conducted by 9 Investigators at 9 sites in 4 countries (Poland, Russia, Spain, and the United States of America).

Publications

Viskochil D. A Phase I Study to Assess the Effect of Food on the Pharmacokinetics and Gastrointestinal Tolerability of Selumetinib in Adolescents with Neurofibromatosis Type 1-Related Plexiform Neurofibromas. Presented at the Neurofibromatosis European Meeting, 10 October 2022. Available at URL: https://www.convenzis.co.uk/events/neurofibromatosis-european-meeting-manchester#eventagenda

Viskochil D. A Phase I Study to Assess the Effect of Food on the Pharmacokinetics and Gastrointestinal Tolerability of Selumetinib in Adolescents with Neurofibromatosis Type 1-Related Plexiform Neurofibromas. Children's Tumour Foundation Neurofibromatosis Conference, June 2023. Available at URL: https://drive.google.com/file/d/1UL3uh3ICuGP3bp5OIp5kmk8cwXra5v2E/view

Objectives and Criteria for Evaluation

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.

Table S1 Objectives and Endpoints

Objectives	Endpoints
Primary	
• To investigate the effect of a low-fat meal on the PK of selumetinib capsules after multiple doses at 25 mg/m^2.	• Geometric mean ratio and 90% CI of selumetinib $AUC_{0\text{-}12,SS}$ for T1 (fed) versus T2 (fasted).
• (If T3 is conducted) To investigate the effect of a low-fat meal on the PK of selumetinib capsules after multiple doses at the adjusted dose (T3). [a]	• Geometric mean ratio and 90% CI of selumetinib $AUC_{0\text{-}12,SS}$ for T3 (fed) versus T2 (fasted).
• To investigate the GI toxicity of selumetinib capsules after multiple doses under fed conditions (T1 and T3) compared to fasted conditions (T2). [a]	• Gastrointestinal AEs graded by CTCAE Version 5.0. • Gastrointestinal toxicity diary incorporating the mBSFS-C and Nausea and Vomiting Symptom Rating Scale (adapted from the Children's Cancer and Leukaemia Group). • Usage of GI concomitant medication.
Secondary	
• To further assess the safety and tolerability of selumetinib capsules by assessment of all AEs, laboratory variables, and vital signs.	• Safety and tolerability was evaluated in terms of AEs, clinical safety laboratory assessments (clinical chemistry, haematology, urinalysis), physical examination, weight, vital signs, ECG, ECHO or cardiac MRI, ophthalmologic assessment, and performance status. • Assessments related to AEs included: occurrence/frequency; relationship to study intervention; CTCAE grade; seriousness; death; AEs leading to discontinuation of study intervention; and AEs of special interest.
• To further evaluate the PK of selumetinib and N-desmethyl selumetinib metabolite after multiple doses under fed conditions, compared to fasted conditions.	• Plasma concentrations and PK parameters of selumetinib and N-desmethyl selumetinib after multiple dose administration, including, but not limited to, C_{mas}, AUC_{last}, t_{max}, and t_{last}.
Exploratory	
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Table S1 Objectives and Endpoints

Objectives	Endpoints
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[a] Treatment period 3 was not conducted.

[b] In the primary CSR, there was a minor change of wording for an CCI. The original wording in the CSP was: CCI This change was made to improve accuracy in the scientific text and there was no impact on this rewording between the CSP and the CSR. Please note: CCI, if performed, will be reported outside of this CSR.

AE = adverse event; $AUC_{0\text{-}12,SS}$ = area under the concentration-time curve from time zero to 12 hours at steady state; AUC_{last} = area under the concentration-time curve from time zero to time of last quantifiable concentration; CI = confidence interval; C_{max} = maximum observed plasma (peak) drug concentration; CSP = Clinical Study Protocol; CSR = Clinical Study Report; CTCAE = Common Terminology Criteria for Adverse Events; ECG = electrocardiogram; ECHO = echocardiogram; GI = gastrointestinal; mBSFS-C = modified Bristol Stool Form Scale for children; MEK = mitogen activated protein kinase; MRI = magnetic resonance imaging; NF1 = neurofibromatosis type 1; PK = pharmacokinetic; PN = plexiform neurofibroma; CCI T1 = Treatment Period 1; T2 = Treatment Period 2; T3 = Treatment Period 3; t_{last} = time to last observed (quantifiable) concentration; t_{max} = time to reach peak or maximum observed concentration.

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.

Target Participant Population and Sample Size

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 PPD and PPD 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.

For inclusion in the study, participants had to fulfil the following key criteria:

- Male and female participants aged ≥ 12 to < 18 years at the time of signing the informed consent.
- All study participants must have been diagnosed with (i) NF1 per National Institutes of Health Consensus Development Conference Statement and (ii) inoperable PN. Inoperable PN was defined as PN that cannot be completely surgically removed without a risk of substantial morbidity due to encasement of, or close proximity to, vital structures, invasiveness, or high vascularity of the PN.
- Participants must have required treatment for NF1 and inoperable PN due to actual symptoms or because of the potential to develop significant clinical complications, as judged by the Investigator, including but not limited to: head and neck lesions that could

compromise the airway or great vessels; paraspinal lesions that could cause myelopathy; brachial or lumbar plexus lesions that could cause nerve compression and loss of function; lesions that would result in major deformity (eg, orbital lesions) or are significantly disfiguring; lesions that cause limb hypertrophy or loss of function; and painful lesions.

- Participants who had prior treatment with any mitogen activated protein kinase inhibitor (MEKi; including selumetinib) were considered for inclusion in this study.

The following were regarded as a key exclusion criterion for the study:

- Evidence or suspicion of optic glioma, malignant glioma, malignant peripheral nerve sheath tumours, or other cancer that required treatment with chemotherapy or radiation therapy.
- Prior malignancy that required active treatment (except for adequately treated basal cell or squamous cell skin cancer, in situ cervical cancer, or other cancer from which the participant had been disease free for ≥ 2 years or which would not have limited survival to < 2 years).
- Had received or were receiving an investigational medicinal product (IMP) or other systemic PN target treatment (including chemotherapy, hormonal therapy, radiation therapy, immunotherapy, biologic therapy or MEKi) within 4 weeks prior to the first dose of study intervention, or within a period during which the IMP or systemic PN target treatment had not been cleared from the body (eg, a period of 5 'half-lives'), whichever was the most appropriate and as judged by the Investigator.

Investigational Product and Comparator(s): Dosage, Mode of Administration, and Batch Numbers

Selumetinib was supplied by AstraZeneca as CCI mg (white) and CCI mg (blue) capsules. Each bottle was labelled in accordance with Good Manufacturing Practice Annex 13 and per country regulatory requirement. Labels were prepared in accordance with Good Clinical Practice Ordinance.

Selumetinib 25 mg/m^2 was administered orally bid (approximately every 12 hours). The capsules were not to be crushed or broken and were to be swallowed whole.

For both T1 and T2, participants were to fast for 2 hours pre-dose and 1 hour post-dose, for both daily doses of selumetinib; this is the currently approved method of selumetinib treatment for the treatment of NF1-related PN. In T1 C1 (fed), selumetinib was administered with a low-fat meal. Appropriate examples of low-fat meals (approximately 500 calories, < 15 g fat) were provided in Section 5.3.1 of the Clinical Study Protocol (CSP).

Dosing was performed based on BSA, and doses were rounded to the nearest CCI to CCI mg using a dosing nomogram. Selumetinib dosing was capped at CCI mg when BSA was ≥ 1.9 m^2.

A range of commercially representative batches of selumetinib capsules ([redacted] and [redacted] mg) were used in the study. The individual batch numbers of selumetinib used were [redacted], [redacted], [redacted], [redacted], [redacted], [redacted], and [redacted].

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.

Study Population

In total, 25 participants were enrolled in the study; 24 received treatment with selumetinib 25 mg/m^2. Participants were aged between [redacted] and [redacted] years, with a median age of 15.0 years. Twelve participants were male and 12 participants were female; 23 participants were White and one participant was Asian.

All 24 participants who received treatment completed T1 C1, and 23 participants completed T2 C1; one participant did not complete T2 C1 per the CSP, due to receiving a reduced dose from Day 36, and was moved to the T2 extension on Day 50. Twenty-three participants completed the study and one participant had terminated the study. One participant completed the study but discontinued selumetinib at the end of treatment visit (declined further selumetinib with commercial supply after study completion).

Since the primary analysis, an additional 6 participants developed study-specific withdrawal criteria (ie, had a dose reduction or prolonged interruption for more than 7 days and therefore may have been withdrawn from the study) totalling 9 participants overall. These participants continued in the T2 extension period until the end of the study.

Summary of Efficacy Results

Not applicable. There were no efficacy endpoints in this study.

Summary of Pharmacokinetic Results

There was no PK analysis conducted at the final DCO, and therefore, there are no updates to the PK data since the primary analysis.

Summary of Safety Results

At the time of the primary analysis, data from 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 GI AEs, or any other AEs, in this study.

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 GI 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.

Conclusion(s)

At the time of the primary analysis, the following conclusions were drawn:

- Selumetinib capsules at 25 mg/m^2 bid administered with a low-fat meal (compared to fasted) did not show clinically relevant differences in selumetinib $AUC_{0\text{-}12,SS}$, based on a GMR of 0.9190 and the lower bound of the one-sided 90% CI being > 0.7.
- 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 GI AEs, or any other AEs, in this study.
- The data from this study in adolescent children with NF1-related PN show that selumetinib exposure is not impacted when selumetinib capsules are administered with a low-fat meal compared with selumetinib capsules administered in the fasted state.

At the time of the final DCO, after one additional year of exposure to selumetinib in the T2 extension period, the following conclusions were reviewed and remain supported:

- The reported AEs remained consistent with the known safety profile of selumetinib.
- No new safety signals or safety concerns were identified throughout the study.