

Effect of food on selumetinib pharmacokinetics and gastrointestinal tolerability in adolescents with neurofibromatosis type 1-related plexiform neurofibromas

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Abstract

Background. Selumetinib is approved for the treatment of pediatric patients with neurofibromatosis type 1 (NF1) who have symptomatic, inoperable plexiform neurofibromas (PN) in multiple countries, including the USA (≥ 2 years). Until recently, individuals had to take selumetinib twice daily (BID) in a fasted state. This study evaluated the effect of a low-fat meal on selumetinib PK parameters and gastrointestinal (GI) tolerability in adolescent participants with NF1-PN.

Methods. Eligible participants aged ≥ 12 to < 18 years took 25 mg/m² selumetinib BID with a low-fat meal (T1) for 28 days, followed by a 7-day washout, and then administration in a fasted state (T2) for another 28 days. Primary objectives were to evaluate the effect of a low-fat meal on AUC_{0–12,ss} and GI tolerability after multiple selumetinib doses in T1 versus T2. Key secondary objectives were additional PK parameters and adverse events (AEs).

Results. At primary data cut-off, all 24 participants completed T1, and 23 participants completed T2. There were no significant differences in AUC_{0–12,ss} between T1 and T2. In T1 and T2, 29.2% and 33.3% participants, respectively, reported ≥ 1 GI AE. No GI AEs Grade ≥ 3 , or serious AEs, or GI AEs resulting in treatment interruptions, discontinuation, or dose reductions were reported in T1 and T2.

Conclusions. Dosing selumetinib with a low-fat meal had no clinically relevant impact on selumetinib AUC_{0–12,ss} nor GI tolerability in adolescents with NF1-PN.

Trial registration [ClinicalTrials.gov](https://clinicaltrials.gov) ID: NCT05101148.

Key Points

- Low-fat meals had no clinically relevant impact on selumetinib steady-state exposure.
- Selumetinib maintains an acceptable PK/safety profile when taken with a low-fat meal.
- This will allow flexibility in administration of selumetinib with respect to food.

Neurofibromatosis type 1 (NF1) is a genetic disorder that results from a pathological variant in the *NF1* gene, which leads to the loss of function of neurofibromin, a tumor suppressor protein.^{1,2–4} NF1 affects approximately 1 in 3000 worldwide

and is associated with a diverse range of clinical manifestations.⁵ Manifestations characteristic of NF1 include pigmented lesions, cutaneous and subcutaneous neurofibromas, brain tumors, and internal and peripheral nerve sheath tumors

Importance of the Study

Currently, selumetinib is approved for pediatric patients with neurofibromatosis type 1 (NF1) who have symptomatic, inoperable plexiform neurofibromas (PN) in multiple countries. The initial approved label required selumetinib to be taken on an empty stomach with no food 2 h before, and 1 h after each dose. Gastrointestinal (GI) events are common adverse reactions in patients who receive selumetinib. Results from the primary data cut-off for this study show that when

selumetinib is taken with a low-fat meal, no clinically relevant impact on the PK of selumetinib and GI tolerability was observed. These results demonstrate that the current recommended dose of selumetinib can maintain an acceptable pharmacokinetic and safety profile if taken with a low-fat meal. The FDA and EMA have recently approved that selumetinib can now be taken with or without food.

known as plexiform neurofibromas (PN).^{5,6} PN can be debilitating with associated symptoms including pain, disfigurement, and motor dysfunction.² Complete surgical resection is often not possible, as it comes with risks, such as blood loss, nerve damage, and functional impairment.^{7,8} In 1 study, 13% of PN surgeries in patients with NF1 resulted in the manifestation of new symptoms, and 23% of tumors regrew significantly after surgery.⁷

Selumetinib (ARRY-142886, AZD6244) is a potent and highly selective MEK1/2 inhibitor, which blocks the RAS/RAF/MEK/ERK pathway signaling, thereby preventing PN growth and reducing PN volume.^{3,9–11} Selumetinib was first approved by the FDA for pediatric patients (age ≥ 2 years) with NF1 who have symptomatic, inoperable PN, and has since been approved by the regulatory bodies in multiple other countries.^{3,12–15} These approvals were based on results from the pivotal Phase 1/2 SPRINT trial, in which selumetinib demonstrated durable PN shrinkage and improvements in several quality of life measures.^{11–15}

The initial approved label for selumetinib indicated that it must be administered twice daily (BID) on an empty stomach, requiring individuals to fast for 2 h before and 1 h after taking each dose. This dosing schedule resulted in a total of 6 h of fasting per day,^{3,4} which could have been inconvenient. The recommendation for administration of selumetinib while fasting, as indicated on the initial approved label, was based on multiple studies in adults without NF1.^{16,17}

Data from 3 previous food effect studies have demonstrated that consumption of a meal reduces the extent of selumetinib absorption compared with administration in fasted conditions.^{16–18} The food effect studies conducted in healthy participants,¹⁶ and in participants with advanced solid tumors,¹⁷ showed that consumption of a high-fat meal reduced the rate of absorption of selumetinib, but did not reduce the extent of the absorption by an amount that was considered to be clinically relevant.^{16,17} In healthy participants, maximum observed plasma peak drug concentration (C_{\max}) was reduced by 50%, time to reach peak or maximum observed concentration (T_{\max}) was delayed by 1.5 h, and AUC was reduced by 16%.¹⁶ In participants with advanced solid tumors, C_{\max} was reduced by 62%, T_{\max} was delayed by 2.5 h, and AUC was reduced by 19%.¹⁷ A further study conducted in healthy adults showed that consumption of a low-fat, low-calorie meal reduced both the rate and extent of absorption after a single dose of selumetinib; C_{\max} was reduced by 60%, T_{\max} was delayed by 2.5 h, and

AUC was reduced by 38%.¹⁸ Therefore, administration in the fed rather than the fasted state could affect exposure to, and absorption of, selumetinib.

As reported in previous studies, gastrointestinal (GI) adverse events (AEs) are commonly associated with selumetinib treatment.^{3,11,19} GI disturbances were the most commonly reported AEs in SPRINT, although these were mostly mild to moderate in severity (Grade 1/2)¹¹; the most frequently occurring GI AEs included vomiting, abdominal pain, diarrhea, and nausea.^{3,11} Here, we present results from the primary data cut-off (DCO; April 6, 2022) for this Phase 1 study, which aimed to evaluate the effect of a low-fat meal on steady-state exposure and GI tolerability of selumetinib in adolescents with NF1 who have inoperable PN. This study evaluated the effect of a low-fat meal on selumetinib PK parameters and GI tolerability in adolescent participants with NF1-PN. The data from this study were assessed by the FDA and EMA, which contributed to the removal of the fasting requirement on the selumetinib label.^{3,4,20}

Methods

Study Design and Participants

This was a Phase 1, single-arm, sequential period, food effect study, to evaluate the steady-state systemic exposure of selumetinib and GI tolerability when multiple doses were taken with a low-fat meal compared with a fasted state.

Eligible participants were adolescents aged ≥ 12 to < 18 years diagnosed with NF1 (per National Institutes of Health Consensus Development Conference Statement 1988)²¹ and inoperable PN. Participants who had prior treatment with a MEK inhibitor were eligible; those who had received an investigational medicinal product or other systemic PN treatment were required to undergo a washout period of 4 weeks or equivalent to 5 half-lives. Participants who had received radiotherapy within 6 weeks before selumetinib initiation were excluded. Full inclusion and exclusion criteria are provided in the [Supplementary Material](#).

Participants were administered 25 mg/m² selumetinib BID ([Figure 1](#)). A 28-day screening period was followed by a 28-day treatment period, during which participants were dosed in a fed state (T1; fed treatment period). During T1, participants were given selumetinib with a light meal or

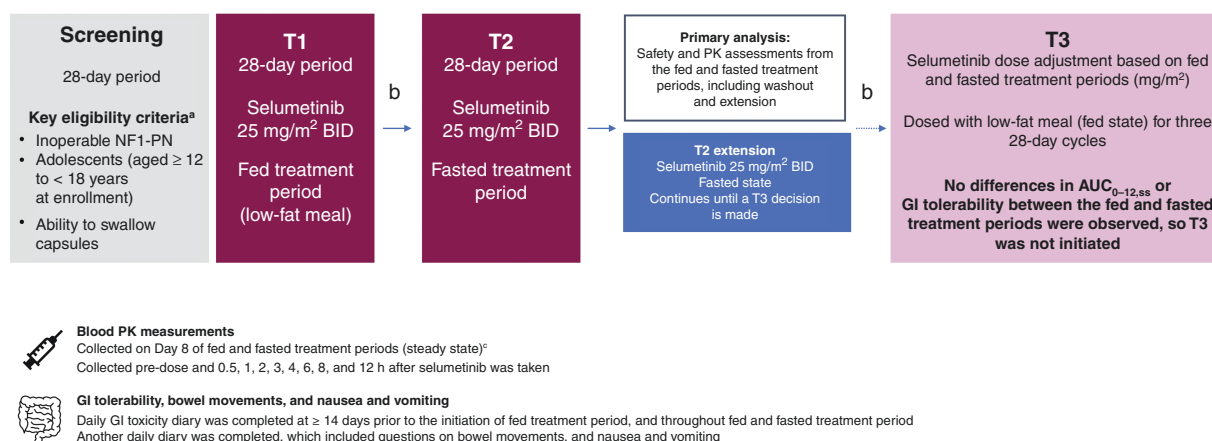


Figure 1. Study design. ^aFull lists of the inclusion and exclusion criteria are included in the [Supplementary Material](#); ^b7-day washout period (could be extended up to 21 days at the investigator's discretion for GI-related AEs to return to baseline); ^cPK blood measurements were targeted for Day 8 but could be taken on any day between Days 4 and 14, assuming the participant had received at least 1 consecutive day of dosing immediately prior to the day the PK sample was taken on. AE, adverse event; AUC_{0-12,ss}, area under the concentration-time curve from time zero to 12 h at steady state; BID, twice daily; GI, gastrointestinal; NF1, neurofibromatosis type 1; PK, pharmacokinetic; PN, plexiform neurofibroma.

snack of approximately 500 calories containing < 15 g fat. Other than this low-fat meal, participants did not consume any other food in the 2 h before, and the 1 h after their dose of selumetinib. T1 was followed by a 7-day washout period. If any GI-related AEs had not recovered or returned to baseline after 7 days of washout, this period could be extended to 21 days at the discretion of the investigator. This washout period was followed by another 28-day treatment period, during which participants were dosed BID in a fasted state (T2; fasted treatment period), as per the initial approved label.^{3,4} Following this, an extension in the fasted state was initiated (T2 extension; fasted treatment period extension), which continued until results from the primary analysis (safety and PK assessments from the fed and fasted treatment periods) were available. In the T2 and T2 extension treatment periods, participants did not eat or drink (other than water) in the 2 h before, and 1 h after receiving selumetinib. Doses of selumetinib were taken approximately 12 h apart.

Following T1 and T2, a third treatment period (T3) was embedded in the initial protocol development, whereby an adjustment of selumetinib dosing could be administered based on PK analyses of T1 and T2; as such, T3 would only occur if required (based on results from T1 and T2). By considering the flat exposure–response relationship at the investigated dose range of 20–30 mg/m², the observed range of exposure, and the variability in SPRINT, it was expected that a $< 30\%$ change in AUC₀₋₁₂ would not alter the benefit–risk profile of selumetinib. A significant reduction in exposure was defined as a $> 30\%$ decrease in the AUC of selumetinib when dosed with a low-fat meal compared with fasted treatment. Therefore, if the fed/fasted AUC geometric mean ratio (GMR) showed a $\geq 20\%$ decrease and the lower 90% confidence interval (CI) of the ratio showed a $\geq 30\%$ decrease in the fed state compared to fasted, then the effect of the low-fat meal on selumetinib exposure would have been considered clinically relevant, which would have triggered initiation of T3.

Participants who had stopped taking selumetinib for any reason other than death, loss to follow-up, or withdrawal of consent, would have had an end of treatment assessment, on the day of, or up to 7 days after, the day they stopped taking selumetinib and a safety follow-up assessment 30 days after the end-of-treatment visit. Details of the withdrawal criteria for this study are in the [Supplementary Material](#).

Study Objectives and Assessments

The primary objectives were: (1) to evaluate the effect of a low-fat meal on the AUC_{0-12,ss} of selumetinib capsules, and (2) to investigate GI tolerability after multiple selumetinib doses in adolescent patients with NF1 and inoperable PN. The secondary objectives were additional PK parameters in the fed and fasted states, and additional safety measures (including non-GI AEs, laboratory variables, and vital signs). Additional PK (fed vs fasted treatment period) endpoints were observed plasma concentrations and PK parameters for both selumetinib and its metabolite (N-desmethyl selumetinib) after multiple-dose administration. These included C_{max} , the area under the concentration–time curve from zero to the last quantifiable concentration (AUC_{last}), T_{max} , and time to last observed quantifiable concentration (T_{last}). Additional PK parameters for selumetinib only included apparent total clearance of drug from plasma after extravascular administration (CL_{ss}/F), and apparent volume of distribution at a steady-state following extravascular administration (V_{ss}/F).

Pharmacokinetics

The primary PK parameter was assessed using GMR (1-sided 90% CI) of selumetinib AUC_{0-12,ss} for the fed versus the fasted treatment period. In both treatment periods, blood PK measurements were collected pre-dose on Day

8 and then at 0.5, 1, 2, 3, 4, 6, 8, and 12 h after selumetinib was taken. Although measurements were targeted for Day 8, these could be taken on any day between Days 4 and 14, assuming the participant had received at least 1 consecutive day of dosing immediately prior to the day the PK sample was taken.

Selumetinib has a relatively short-half-life of 6.2 h and reaches steady state in approximately 1–2 days, with minimal accumulation.³ To be evaluable for PK analyses, participants must have received selumetinib, as per the dosing requirements (please see the [Study Design and Participants](#) section) the day prior to, and on the multiple-dose PK sampling day with no protocol deviations that could have affected the PK analysis; participants must also have had ≥ 1 post-dose quantifiable plasma concentration.

PK parameters were derived from plasma concentrations using non-compartmental methods in Phoenix® WinNonlin® Version 8.1.1.

Safety and Tolerability

GI symptoms were collected through a daily diary, and usage of GI concomitant medication(s) per the WHODrug Global B3-format.²² The daily GI diary incorporated the modified Bristol Stool Form Scale for Children²³ (mBSFS-C) and the Nausea and Vomiting Symptom Rating Scale (adapted from the Children's Cancer and Leukaemia Group).²⁴ Bowel movements were assessed using the mBSFS-C scale.²³ Nausea and vomiting were assessed by severity, frequency, and interference with daily life, based on the Nausea and Vomiting Symptom Rating Scale.²⁴ Clinical safety assessments (clinical chemistry, hematology, urinalysis) and physical examinations were conducted. Weight, vital signs, electrocardiogram, echocardiogram or cardiac MRI, ophthalmologic assessment, and performance status were also assessed. AE-related assessments included occurrence/frequency, relationship to study intervention, and AEs leading to discontinuation of study intervention. All AEs were coded using MedDRA Version 24.1 and graded using Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0. For each participant, only the occurrence with the highest observed grade for each AE was reported. AEs were assigned to a treatment period based on onset date; if an AE emerged in the fed treatment period and continued into the fasted treatment period, it would not be re-counted. However, if the AE emerged in the fed treatment period, resolved, and re-emerged in the fasted treatment period, it would be counted in both treatment periods.

Data and Statistical Analysis

All statistical analyses were performed using Statistical Analysis Software (SAS)® Version 9.4. PK analyses were based on the PK analysis set, which consisted of all participants who received at least 1 dose of selumetinib and had at least 1 post-dose quantifiable plasma concentration without any protocol deviations that affected PK analysis. PK analyses were performed on both selumetinib and N-desmethyl selumetinib analytes.

For comparison between fed and fasted conditions of $AUC_{0-12,SS}$, AUC_{last} , and C_{max} , a mixed-effects analysis of variance (ANOVA) was performed with log-transformed PK parameter as the response variable, treatment as a fixed effect, and participant as a random effect. The estimate of the difference in means on the log scale from the mixed-effects ANOVA was back-transformed to obtain the GMR (fed treatment period/fasted treatment period) and its 1-sided 90% CI. The geometric least squares (LS) mean for each period and the corresponding 2-sided 95% CIs were derived similarly. Comparison between fed and fasted conditions of T_{max} was analyzed with the Hodges–Lehmann point estimate of median difference and associated 2-sided 90% CI. CL_{ss}/F and V_{ss}/F were descriptively summarized and no statistical comparison between the treatment periods was made. Geometric mean selumetinib plasma concentration–nominal time profiles under fed and fasted conditions were plotted on a semi-logarithmic scale.

Safety analyses were based on the safety analysis set, which included all participants who received at least 1 dose of selumetinib. There were no inferential analyses for safety results; summary statistics were provided for safety endpoints.

Ethics

This study was performed in accordance with the Declaration of Helsinki, and was consistent with the International Council for Harmonisation Good Clinical Practice guidelines, applicable regulatory requirements, and the AstraZeneca policy on bioethics.

Informed Consent

Mandatory provision of signed and dated parent/legal guardian consent for the study along with the pediatric assent form (or consent form if the participant was deemed a “young adult” [aged 16 to 18 years]) was required, when applicable. For participants who reached the age of legal consent during the clinical study, notification was required, and a new consent form needed to be signed by the participant.

Results

The study started on July 21, 2021, and the primary DCO for this analysis was April 6, 2022.²⁵ Results from the primary DCO (fed vs fasted) are presented herein.²⁵ Additional analyses from this dataset may be available in future publications.

Participant Demographics and Baseline Characteristics

Overall, 25 participants were enrolled at 9 sites across 4 countries (Poland, Russia, Spain, and the USA). One participant failed screening; therefore, 24 participants were

Table 1. Participant demographics and clinical characteristics at baseline (safety analysis set)

Characteristic	Participants (N = 24)
Sex, n (%)	
Female	12 (50.0)
Male	12 (50.0)
Age, median (range), years	15 (12, 17)
Height, median (range), cm	158.5 (146.0, 178.4)
Weight, median (range), kg	50.2 (41.0, 86.0)
Body surface area, median (range), m ²	1.5 (1.3, 2.0)
Ethnic group, n (%)	
Hispanic or Latino	2 (8.3)
Not Hispanic or Latino	22 (91.7)
Race, n (%)	
Asian	1 (4.2)
White	23 (95.8)
Country, n (%) ^a	
Poland	9 (37.5)
Russia	7 (29.2)
Spain	4 (16.7)
USA	4 (16.7)
NF1 diagnostic criteria, n (%) ^b	
Six or more café-au-lait macules	20 (83.3)
Freckling in axilla or groin	18 (75.0)
Two or more Lisch nodules	18 (75.0)
First-degree relative with NF1	10 (41.7)
Optic glioma	6 (25.0)
A distinctive osseous lesion	4 (16.7)
Reasons for inoperable PN, n (%) ^c	
Close proximity to vital structures	15 (62.5)
Invasiveness	13 (54.2)
Encasement of vital structures	9 (37.5)
High vascularity	3 (12.5)
Lansky performance status score, median (range) ^d	n=22 90 (80, 100)
Time from diagnosis of NF1 to start of selumetinib, median (range), y ^e	11.7 (0, 16)
Time from diagnosis of inoperable PN to start of selumetinib, median (range), y	5.4 (0, 12)
Previous PN-directed treatments, n (%) ^f	14 (58.3)
Medical therapy ^g	7 (29.2)
Surgery	9 (37.5)

^aTotal percentage may not equal 100% due to rounding; ^bParticipants could have had more than 1 NF1 diagnostic criterion; ^cParticipants could have had more than 1 reason for inoperable PN; ^dThe Lansky scale was completed for participants aged ≤ 16 years at study entry. The Karnofsky scale was completed for participants aged ≥ 16 years at study entry. Both the Karnofsky and Lansky performance status scores range from 10 to 100, with higher scores indicating better functioning. Only participants with Karnofsky/Lansky scores ≥ 70 at enrollment were included in the study. Karnofsky scores were recorded for 2 participants included in the study for which the median (range) was 90.0 (80 to 100); ^eThe "start of selumetinib" refers to participants who received selumetinib treatment as part of the study, not participants who had received selumetinib as prior therapy; ^fParticipants could have had more than 1 modality; ^gSix of 7 participants who had previously received PN-directed medical therapy had received selumetinib. NF1, neurofibromatosis type 1; PN, plexiform neurofibroma.

included in the safety and PK analysis sets. Participant demographics and baseline characteristics are shown in [Table 1](#).

Participant Disposition

All 24 participants completed the fed treatment period (T1), and 23 participants completed the fasted treatment period (T2). The maximum dose of 50 mg BID (for participants with a body surface area [BSA] of ≥ 1.9 m² at baseline^{3,4}) was administered to 3 participants in the study. One participant did not complete T2 due to a dose reduction and was entered into the extension part of the study. However, as this patient started T2, data for all 24 participants are presented for both treatment periods in all text, tables, and figures, unless otherwise stated. Over the course of the study (including the fed treatment period, washout, fasted treatment period, and fasted treatment period extension), 3 participants (12.5%) met the withdrawal criteria ([Supplementary Material](#)); of these, 2 participants had a prolonged interruption for > 7 days while in the fasted treatment period extension, and the remaining participant had a dose reduction while in the fasted treatment period. Therefore, although these 3 participants continued to receive selumetinib in the fasted treatment period extension, and treatment was ongoing at data cut-off, these participants did not complete the fasted treatment period; consequently, PK statistical comparisons to the fed treatment period were not possible. No other participants had a dose reduction or prolonged dose interruption during either of the 28-day treatment periods. Participants with dose modifications were not included in the PK analysis as the doses that they received in the fed and fasted treatment periods were not comparable; however, these participants were included in the safety analysis as they received selumetinib in both treatment periods.

Pharmacokinetics

Full PK results for selumetinib are shown in [Table 2](#) and full PK results for N-desmethyl selumetinib are shown in [Supplementary Table 1](#). The geometric mean plasma concentration–time profiles following multiple doses of selumetinib under fed and fasted conditions are shown in [Figure 2](#).

Of the 24 participants included in the PK analysis set, 19 (79.2%) were eligible for the PK statistical comparison analysis, having been compliant with the study protocol and provided evaluable PK data including the last required PK sample in both the fed and fasted treatment periods. The reasons for exclusion of 5 participants from the PK statistical comparison analysis have been included in the [Supplementary Material](#).

There were no notable differences in AUC_{0–12,SS} and AUC_{last} for selumetinib in the fed and fasted treatment periods, with GMRs of 0.919 and 0.931, respectively. The lower bounds of the 1-sided 90% CI for both parameters were above 0.7 (AUC_{0–12,SS} 0.841, AUC_{last} 0.850), and therefore within the 30% threshold for a clinically relevant change ([Table 2](#)). The GMRs for AUC_{0–12,SS} and AUC_{last} for N-desmethyl selumetinib were 1.008 and 1.022; the lower bounds of the 1-sided 90% CI

Table 2. Summary of selumetinib PK parameters in the fed (T1) versus fasted (T2)^a treatment periods at primary DCO (PK analysis set)

PK parameter (n = 19)		Geometric LS mean (95% CI)	Geometric mean ratio (fed vs fasted, 1-sided 90% CI lower bound)
AUC _{0–12,ss} (h*ng/mL)	Fed (T1)	2910 (2508, 3376)	0.919 (0.841)
	Fasted (T2)	3166 (2729, 3674)	
AUC _{last} (h*ng/mL)	Fed (T1)	2909 (2500, 3385)	0.931 (0.850)
	Fasted (T2)	3124 (2685, 3636)	
C _{max} (ng/mL)	Fed (T1)	851 (709, 1021)	0.763 (0.667)
	Fasted (T2)	1116 (929, 1339)	
		Geometric mean (geometric CV%)	
CL _{ss} /F (L/h)	Fed (T1)	13.2 (32.6) ^b	–
	Fasted (T2)	12.3 (34.9) ^b	
V _{ss} /F (L)	Fed (T1)	87.6 (37.9) ^c	–
	Fasted (T2)	74.6 (38.7) ^b	
		Median (range)	Estimated median difference (2-sided 90% CI)
T _{max} (h)	Fed (T1)	2.00 (0.92, 3.00) ^b	0.57 (0.46, 1.00)
	Fasted (T2)	1.00 (0.55, 2.07) ^b	

^aClinically implausible high concentrations of selumetinib were reported for 3 participants at 12 h post-dose in the fasted treatment period. The plasma concentration–time profiles for each participant from the last timepoint with a measurable concentration (8 h) to 12 h post-dose to estimate the AUC_{0–12,ss} values were extrapolated. As the percentage extrapolation was small, and to maximize the data used in the statistical assessment of food effect, the AUC_{0–12,ss} values for these 3 participant's T2 selumetinib profiles were considered to be representative of the primary endpoint parameter and, therefore, were included in the statistical analysis; ^bn = 21; ^cn = 20.

AUC_{0–12,ss}, area under the concentration–time curve from time zero to 12 h at steady state; AUC_{last}, area under the concentration–time curve from time zero to time of last quantifiable concentration; CI, confidence interval; CL_{ss}/F, apparent total clearance of drug from plasma after extravascular administration; C_{max}, maximum observed plasma drug concentration; CV, coefficient of variation; DCO, data cut-off; LS, least squares; PK, pharmacokinetic; T_{max}, time to reach peak or maximum observed concentration; V_{ss}/F, apparent volume of distribution at steady state following extravascular administration.

for both parameters were above 0.9 (AUC_{0–12,ss} 0.910, AUC_{last} 0.918) (Supplementary Table 1).

For selumetinib, the GMR for C_{max} was 0.763, with a lower bound of the 1-sided 90% CI of 0.667 (Table 2). For N-desmethyl selumetinib, the GMR for C_{max} was 0.839, with a lower bound of the 1-sided 90% CI of 0.723 (Supplementary Table 1). The median differences in T_{max} between the fed and fasted treatment periods indicated that there was a delay in the T_{max} for selumetinib of 0.57 h (90% CI: 0.46, 1.00) (Table 2). For N-desmethyl selumetinib, the median differences in T_{max} between the fed and fasted treatment periods indicated that there was a delay in the T_{max} of 0.49 h (90% CI: 0.44, 1.00) (Supplementary Table 1).

Clinically implausible high concentrations of selumetinib were reported for 3 participants at 12 h post-dose in the fasted treatment period, with values for selumetinib between 11- and 16-fold higher than at 8 h post-dose concentrations. The corresponding values for N-desmethyl selumetinib were between 7- and 10-fold higher than concentrations at 8 h post-dose. These anomalous concentrations could not be attributed to bioanalytical issues, nor was there any correspondence available from the study site to explain these values. These concentrations, for both selumetinib and N-desmethyl selumetinib, were excluded from PK parameter calculations, as well as concentration

summary tables and figures. WinNonlin® software was used to extrapolate the plasma concentration–time profile from the last timepoint with a measurable concentration (8 h) to 12 h post-dose to estimate the AUC_{0–12,ss} value. The resultant extrapolated areas from AUC_{last} ranged from approximately 6% to 11%. As the percentage extrapolation was small, and to maximize the data used in the statistical assessment of food effect, the AUC_{0–12,ss} values for these 3 participants' T2 selumetinib profiles were considered to be representative of the primary endpoint parameter and, therefore, were included in the statistical analysis. A sensitivity analysis was performed where the statistical analysis that compared fed versus fasted PK parameters was conducted with these 3 participants excluded. This analysis showed that exclusion of these participants had no impact on the overall conclusion regarding a lack of food effect.

Exposure

In the fed and fasted treatment periods, the mean (SD) total (intended treatment length) days of exposure were 28.3 (1.12) and 28.3 (3.03), respectively. The mean (SD) actual (total intended minus dose interruptions) days of exposure were 28.3 (1.12) and 28.3 (3.03) in the fed and fasted treatment periods, respectively.

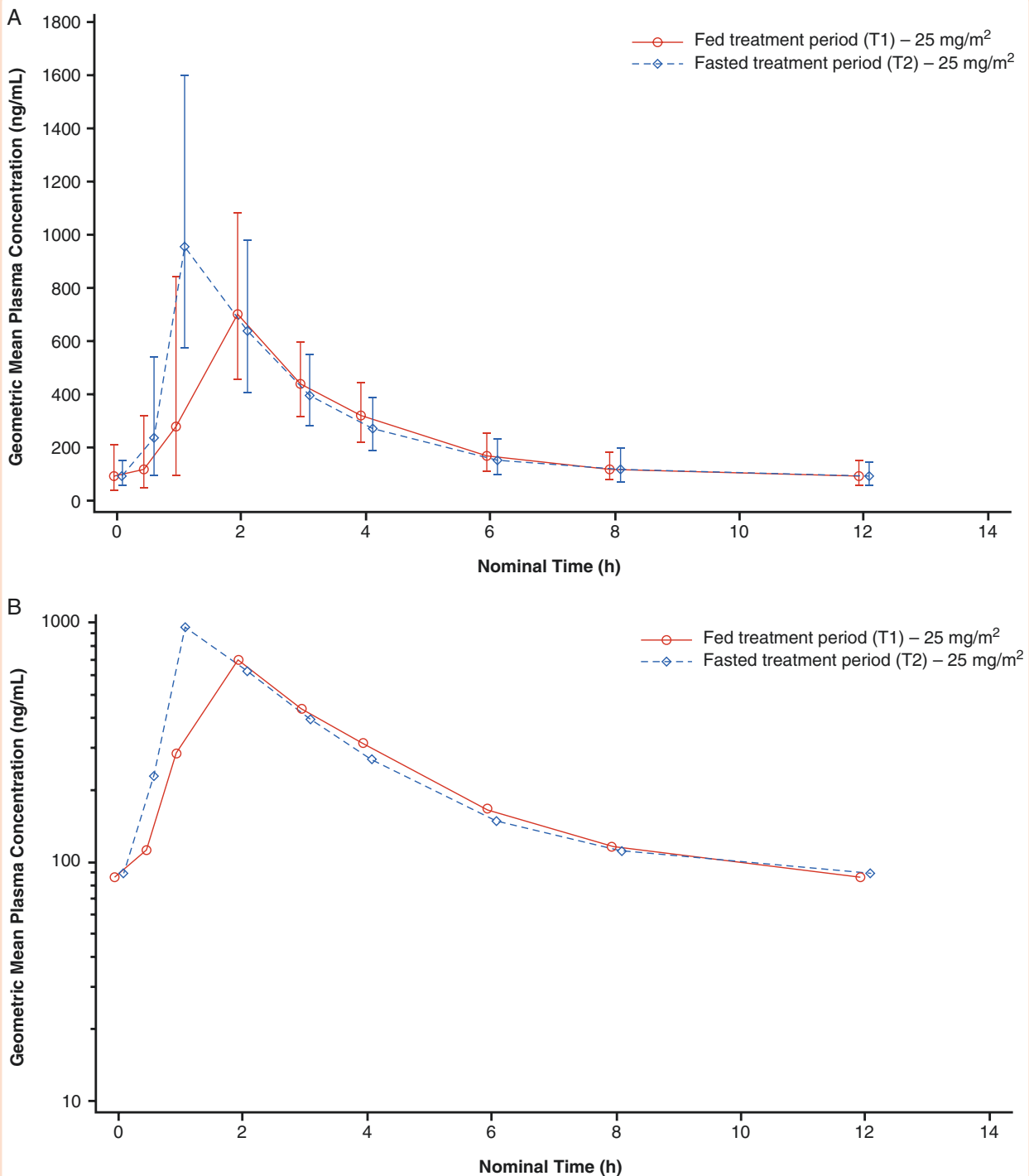


Figure 2. Geometric mean plasma concentrations of selumetinib versus time—multiple dose (A. Linear; B. Semi-logarithmic).^a

^aClinically implausible high concentrations of selumetinib were reported for 3 participants at 12 h post-dose in the fasted treatment period. The plasma concentration–time profiles for each participant from the last timepoint with a measurable concentration (8 h) to 12 h post-dose to estimate the $AUC_{0-12,SS}$ values were extrapolated. As the percentage extrapolation was small, and to maximize the data used in the statistical assessment of food effect, the $AUC_{0-12,SS}$ values for these 3 participants' T2 selumetinib profiles were considered to be representative of the primary endpoint parameter and, therefore, were included in the statistical analysis. $AUC_{0-12,SS}$ area under the concentration–time curve from time zero to 12 h at steady state.

GI AEs

GI AEs for the fed treatment period plus washout and the fasted treatment period plus extension are included in [Supplementary Table 2](#).

The incidence of GI AEs was similar in both treatment periods ([Table 3](#)). Seven participants (29.2%) in the fed treatment period reported any GI AE; 3 of these participants also reported any GI AE in the fasted treatment period. In the fasted treatment period, 8 participants (33.3%) reported

Table 3. Summary of AEs reported in fed (T1) and fasted (T2) treatment periods at primary DCO (safety analysis set)

Participants with AE, n (%) ^a	Fed treatment period (T1; N = 24)	Fasted treatment period (T2; N = 24)
Any AE	19 (79.2)	14 (58.3)
Any AE of CTCAE Grade 3 or higher	0	0
Any AE resulting in death	0	0
Any SAE (including events with an outcome of death)	0	0
Any AE leading to discontinuation	0	0
Any AE leading to interruption	1 (4.2) ^b	0
Any AE leading to dose reduction	1 (4.2) ^c	0
Any GIAE	7 (29.2)	8 (33.3)
Vomiting	3 (12.5)	3 (12.5)
Nausea	2 (8.3)	3 (12.5)
Diarrhea	2 (8.3)	1 (4.2)
Abdominal pain	1 (4.2)	1 (4.2)
Abdominal pain upper	0	1 (4.2)
Constipation	0	1 (4.2)
Dry mouth	0	1 (4.2)
Stomatitis	0	1 (4.2)
Non-GI AE^d		
Skin and subcutaneous lesions	16 (66.7)	6 (25.0)
Dermatitis acneiform	12 (50.0)	4 (16.7)
Alopecia	2 (8.3)	0
Infections and infestations	3 (12.5)	2 (8.3)
COVID-19	1 (4.2)	2 (8.3)
Any AE possibly related to treatment ^e	16 (66.7)	8 (33.3)
Skin and subcutaneous tissue lesions	14 (58.3)	4 (16.7)
Dermatitis acneiform	10 (41.7)	3 (12.5)
Acne	1 (4.2)	1 (4.2)
Alopecia	2 (8.3)	0
Pruritis	1 (4.2)	0
Rash	1 (4.2)	0
Rash maculo-papular	1 (4.2)	0
GI disorders	4 (16.7)	3 (12.5)
Nausea	2 (8.3)	2 (8.3)
Abdominal pain	1 (4.2)	1 (4.2)
Abdominal pain upper	0	1 (4.2)
Diarrhea	1 (4.2)	0
Dry mouth	0	1 (4.2)
Vomiting	1 (4.2)	0
Infections and infestations	2 (8.3)	1 (4.2)
Paronychia	1 (4.2)	1 (4.2)
Folliculitis	1 (4.2)	0
Tinea pedis	1 (4.2)	0
Investigations	0	2 (8.3)
Blood creatine phosphokinase increased	0	1 (4.2)
Ejection fraction decreased	0	1 (4.2)

Table 3. Continued

Participants with AE, n (%) ^a	Fed treatment period (T1; N = 24)	Fasted treatment period (T2; N = 24)
Musculoskeletal and connective tissue disorders	1 (4.2)	0
Soft tissue swelling	1 (4.2)	0

AEs for the fed treatment period plus washout and the fasted treatment period plus fasted treatment period extension have been included in [Supplementary Table S2](#).

^aParticipants who reported multiple events in the same category were only counted once in that category, and participants with events in more than 1 category were counted once in each of those categories; ^bThis dose interruption was attributed to the onset of Grade 2 dermatitis acneiform during the fed state treatment period, and the onset of Grade 2 alopecia during the fasted treatment period extension; the dose interruption itself occurred during the fasted treatment period extension; ^cThe dose reduction occurred on Day 16 of the fed state treatment period, due to the onset of dermatitis acneiform; ^dOccurring in more than 5% of participants in either treatment period; ^eAs assessed by investigator.

AE, adverse event; COVID-19, coronavirus disease 2019; CTCAE, Common Terminology Criteria for Adverse Events; DCO, data cut-off; GI, gastrointestinal; SAE, serious adverse event.

at least 1 GI AE. No Grade ≥ 3 GI AEs were reported over the course of the study. There were no serious GI AEs or GI AEs resulting in treatment interruptions, discontinuation, or dose reduction.

The most frequently occurring GI AE experienced in both the fed and fasted treatment periods was vomiting (12.5%, 3 participants each). Nausea was reported by 2 participants (8.3%) and 3 participants (12.5%) in the fed and fasted treatment periods, respectively. In the fed treatment period, 2 participants (8.3%) experienced diarrhea; 1 participant (4.2%) reported diarrhea in the fasted treatment period. Upper abdominal pain, constipation, dry mouth, and stomatitis were all reported by 1 participant (4.2%) in the fasted treatment period; there were no reports of these AEs in the fed treatment period. Abdominal pain was reported by 1 participant (4.2%) in each treatment period.

Participant-Reported GI Outcomes

In both the fed and fasted treatment periods, the most commonly reported mBSFS-C type was 3 ([Table 4](#)).

Based on diary entries, no participants reported nausea that prevented them from eating and drinking concurrently in either the fed or fasted treatment period ([Table 4](#)). There were 2 participants (8.3%) in each treatment period who reported 2 to 5 episodes of vomiting over a 24-h period ([Table 4](#)).

Use of GI Medications

No GI medications were initiated by any participant to treat GI-related AEs in the fed treatment period. Two participants (8.3%) initiated medication to treat GI-related AEs in the fasted treatment period. One participant received macrogol (for 3 days from Day 51 of the study), to treat Grade 1 constipation. The other participant received almagate (for 7 days from Day 44 of the study) and esomeprazole (for 5 days from Day 50 of the study) to treat Grade 2 epigastric pain.

Non-GI AEs

[Table 3](#) presents non-GI AEs reported by at least 5% of participants in either treatment period. AEs for the fed treatment

period plus washout and the fasted treatment period plus extension are presented in [Supplementary Table 2](#).

Skin and subcutaneous lesions were reported in 16 participants (66.7%) and 6 participants (25.0%) in the fed and fasted treatment periods, respectively, and were also the most commonly reported AEs categorized as possibly related to selumetinib treatment (fed: 14 participants [58.3%]; fasted: 4 participants [16.7%]; [Table 3](#)). For most patients who experienced dermatitis acneiform, this AE emerged in the fed treatment period and continued through the fasted treatment period and into the fasted treatment period extension.

Although there were no reports of alopecia in the fasted treatment period, 2 participants (8.3%) reported alopecia in the fed treatment period. Two participants (8.3%) in the fed treatment period and 1 participant (4.2%) in the fasted treatment period reported infections and infestations that were possibly related to treatment.

All AEs

[Table 3](#) describes AEs, serious AEs, treatment-related AEs, and AEs that led to dose interruptions and reductions for the fed and fasted treatment periods. A summary of AEs occurring during the fed treatment period plus washout and fasted treatment period plus extension are presented in [Supplementary Table 2](#). No new safety signals were observed in this study, and no clinically important changes were noted in laboratory values or vital signs.

Of the 24 participants evaluable for safety, 19 (79.2%) and 14 (58.3%) reported at least 1 AE in the fed and fasted treatment periods, respectively; none of these were Grade ≥ 3 . In the fed and fasted treatment periods, 16 participants (66.7%) and 8 participants (33.3%), respectively, had at least 1 AE possibly related to study treatment. No AE resulted in discontinuation of study treatment or death. One participant experienced interruption of selumetinib treatment in the fasted treatment period extension due to Grade 2 dermatitis acneiform (onset during the fed treatment period; Day 13 of the study) and Grade 2 alopecia (onset during fasted treatment period extension; Day 96 of the study). Both AEs led to prolonged interruption of > 7 days, and the AE of alopecia led to a dose reduction.

Table 4. GI PROs in the fed (T1) and fasted (T2) treatment periods at primary DCO (safety analysis set)

PRO n (%)	Fed treatment period (T1; N = 24)	Fasted treatment period (T2; N = 24)
Type of mBSFS-C ^a		
Type 1	12 (50.0)	8 (33.3)
Type 2	15 (62.5)	14 (58.3)
Type 3	19 (79.2)	19 (79.2)
Type 4	13 (54.2)	9 (37.5)
Type 5	6 (25.0)	7 (29.2)
Nausea		
No	24 (100.0)	23 (95.8)
Yes, able to eat ok	12 (50.0)	9 (37.5)
Yes, able to eat but not as normal	6 (25.0)	8 (33.3)
Yes, I couldn't eat but I could drink	0	2 (8.3)
Yes, I couldn't eat or drink	0	0
Vomiting		
None	24 (100.0)	23 (95.8)
1 vomit in 24 h	7 (29.2)	5 (20.8)
2 to 5 vomits in 24 h	2 (8.3)	2 (8.3)
6 to 10 vomits in 24 h	0	0
> 10 vomits in 24 h	0	0

Percentages in each arm may not total 100% as it was possible for participants to report more than 1 symptom at different timepoints throughout the treatment period.

^aFor each participant, average bowel movements per day in an mBSFS type was calculated by the total number of bowel movements in that mBSFS-C type recorded in his/her diary in the period divided by actual total number of diary days of the participant in the treatment period. Results > 9 are imputed as 9 for analyses.

AE, adverse event; DCO, data cut-off; GI, gastrointestinal; mBSFS-C, modified Bristol Stool Form Scale; PRO, participant-reported outcome.

Another participant experienced prolonged dose interruption because of a Grade 3 rash (onset during fasted treatment extension period; Day 78 of study). This was the only Grade ≥ 3 AE reported at primary DCO.

One participant (4.2%) experienced Grade 2 dermatitis acneiform (Day 8), which resulted in a dose reduction during the fed treatment period (Day 16 of the study). The participant's dose was reduced from 35 mg BID to 25 mg BID, which remained the same until the end of the fed treatment period. The participant continued receiving 25 mg selumetinib BID throughout the fasted treatment period but did not complete this treatment period, and they were moved to the fasted treatment period extension on Day 50 of the study.

Discussion

Until recently, selumetinib was approved for administration in the fasted state based on previous studies showing potential differences in PK parameters between fed and fasted states, as well as differences in the incidence of GI AEs.^{3,4,16-18} This study evaluated the effects of a low-fat meal on the steady-state exposure and GI tolerability of selumetinib in adolescents with NF1 and inoperable

PN. By the primary DCO for this study, administration of selumetinib in the fed state compared with the fasted state had no clinically relevant effect on PK parameters. Although taking selumetinib with a low-fat meal slightly reduced the rate of absorption (estimated median difference [2-sided 90% CI] for T_{max} , 0.57 [0.46, 1.00]; GMR [1-sided 90% CI] for C_{max} , 0.763 [0.667]), it did not affect the overall extent of absorption, as the $AUC_{0-12,ss}$ was only slightly lower in the fed treatment period compared with the fasted treatment period (GMR [1-sided 90% CI] for $AUC_{0-12,ss}$ was 0.919 [0.841]). As the lower bound of the 90% CI of the GMR was > 0.7, no clinically relevant effect of a low-fat meal on selumetinib $AUC_{0-12,ss}$ and AUC_{last} was observed. Overall, as no clinically relevant difference in $AUC_{0-12,ss}$ between the fed and fasted treatment periods was observed, T3 was not initiated (Figure 1). The extrapolated $AUC_{0-12,ss}$ values from the T2 selumetinib profiles of the 3 participants with clinically high concentrations at 12 h post-dose were considered to be representative of the primary endpoint parameter. Similar conclusions on the effect of a low-fat meal on the PK parameters for N-desmethyl selumetinib were drawn from the selumetinib data obtained here. The concentration of metabolite was low, and it was excreted quickly. Therefore, although N-desmethyl selumetinib has a 3- to 5-fold greater potency for MEK1 inhibition than selumetinib, due to the lower systemic

exposure in relation to selumetinib, the metabolite was not expected to contribute to the overall activity of selumetinib in patients with NF1-PN.²⁶

Although previous studies evaluated the potential effect of food on selumetinib PK parameters, there were differences that included the evaluation of PK after a single dose, and study populations that were either healthy volunteers or adult patients who had advanced solid tumors.^{16–18} A recent pooled population PK analysis that included data from 15 clinical studies also demonstrated that selumetinib administration with a low-fat meal did not have a clinically relevant effect on selumetinib exposure. The same analysis demonstrated that selumetinib administration with a high-fat meal did not significantly affect selumetinib exposure, suggesting that these PK results were unlikely to be dependent on the fat content of the food when taken together with selumetinib; however, the population PK analysis did not assess the effect of food on GI tolerability.²⁷

Data presented here demonstrate that administration of selumetinib capsules with a low-fat meal compared with administration in the fasted state showed no clinically relevant difference in terms of the occurrence of GI and non-GI AEs. Previous studies have indicated that AEs affecting the GI system are among the most common AEs associated with selumetinib treatment.^{11,19,28} In our study, a similar number of participants reported at least 1 GI AE in the fed and fasted treatment periods by the primary DCO. The GI AEs reported in this study were generally consistent with those commonly associated with selumetinib treatment³; for example, vomiting, nausea, diarrhea, and abdominal pain were commonly reported in both the fed and fasted treatment periods.

Although 14 participants (58.3%) reported at least 1 GI AE from the initiation of selumetinib treatment, including the washout period and the fasted treatment period extension, skin and subcutaneous AEs were the most commonly reported type of AE occurring in 20 participants (83.3%) (Supplementary Table 2). Dermatitis acneiform was the most commonly reported non-GI AE, and this AE has also been frequently reported in previous selumetinib studies.^{11,16,18,29} No new safety signals for selumetinib were identified; the AEs reported were similar in both the fed and fasted treatment periods and were comparable to previous studies.^{11,17}

Given that previous PK analyses had indicated a flat PK–efficacy relationship, efficacy was not assessed as an endpoint in this study. By restricting this study to adolescents, the range of BSA bands in the cohort was reduced, thereby limiting any variability in dose levels. The fixed sequential treatment periods meant that it is not possible to rule out any potential sequencing effect. However, it would have made the study more complex for the young participants to comply with first taking selumetinib in the fasted state for 28 days, then switching to taking it with a light meal for another 28 days, before switching back to the fasting posology again. Furthermore, it would have required a greater number of participants to be accrued from adolescent patients in a rare disease population. Another limitation is that the AE collection method may have confounded safety results for the overall study (including washout and fasted treatment period extension).

It should also be noted that blood PK measurements were only taken from each participant once in each treatment period; this was a patient-centric decision to ensure that participants and their caregivers, who often had to travel long distances to attend a specialist center for blood measurements, were not required to take extended periods out of school and work, thereby reducing any burden on them.

Based on results from previous studies,^{11,16,30} the initial approved label stated that selumetinib must be taken BID on an empty stomach with no food or drink 2 h before dosing and 1 h after dosing. However, results from the primary DCO of this study show that multiple dosing of selumetinib with a low-fat meal has no clinically relevant impact on selumetinib exposure or GI tolerability in adolescents with NF1-PN. Based on the contribution of these data, patients can now take selumetinib with or without food,^{3,4} without compromising PK or GI tolerability. Flexibility in dosing with respect to food could improve adherence to treatment, as fasting can be burdensome for young patients.

Supplementary Material

Supplementary material is available online at *Neuro-Oncology* (<https://academic.oup.com/neuro-oncology>).

Keywords

gastrointestinal tolerability | neurofibromatosis type 1 | pharmacokinetics | plexiform neurofibroma | selumetinib

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Conflict of interest statement

D.V. received advisory support from AstraZeneca, grants or contracts from SpringWorks Therapeutics, Soleno Therapeutics, Levo Therapeutics, NFlection Therapeutics, and Takeda Pharmaceuticals; consulting fees from Sanofi Genzyme as well as payment or honoraria from SpringWorks Therapeutics and AstraZeneca. M.W. reports no conflicts of interest. H.S.H. has received advisory fees from AstraZeneca. M.L., P.S., K.S., and A.E. report employment at AstraZeneca. A.E., M.L., and K.S. own AstraZeneca stocks. F.L. owns AstraZeneca and AbbVie stocks.

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Authorship statement

Conceptualization: M.W., M.L., P.S., K.S., A.E., and F.L.; resources: M.W., M.L., K.S., P.S., A.E., and F.L.; data curation: D.V., M.W., M.L., P.S., K.S., A.E., and F.L.; software: F.L.; formal analysis: D.V., M.L., P.S., K.S., A.E., and F.L.; supervision: M.W., M.L., K.S., P.S., A.E., H.S.H.; validation: M.W., M.L., P.S., K.S., A.E., and F.L.; investigation: D.V., M.W., M.L., P.S., A.E., and H.S.H.; visualization: M.W., M.L., P.S., K.S., A.E., F.L., and H.S.H.; methodology: M.L., P.S., K.S., A.E., and F.L.; writing—original draft: M.W., M.L., P.S., K.S., A.E., and F.L.; writing—review and editing: D.V., M.W., M.L., P.S., K.S., A.E., F.L., and H.S.H.

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