Efficacy and safety of selumetinib in adults with neurofibromatosis type 1 and symptomatic, inoperable plexiform neurofibromas (KOMET): a multicentre, international, randomised, placebo-controlled, parallel, double-blind, phase 3 study

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Summary

Background Currently, no worldwide approved therapies exist for adults with neurofibromatosis type 1 (NF1) and symptomatic, inoperable plexiform neurofibromas. The KOMET study aimed to evaluate selumetinib (ARRY-142886, AZD6244) efficacy and safety in this population.

Methods This ongoing multicentre, international, randomised, placebo-controlled, phase 3, parallel, double-blind trial randomly assigned adults with NF1-plexiform neurofibroma 1:1 to 28-day cycles of oral selumetinib 25 mg/m² twice daily, or placebo with crossover to selumetinib at confirmed radiological progression or the end of cycle 12. The primary endpoint was objective response rate (confirmed partial or complete response) established by use of independent central review per Response Evaluation in Neurofibromatosis and Schwannomatosis (REiNS) criteria by cycle 16 (selumetinib *vs* placebo). This study (KOMET) is registered with ClinicalTrials.gov, NCT04924608 and is ongoing.

Findings Overall, of 184 participants enrolled, 145 adults were randomly assigned to selumetinib (n=71) or placebo (n=74). Selumetinib led to a rapid response (median 3·7 months), with an objective response rate of 20% (n=14/71; 95% CI 11·2 to 30·9) by cycle 16 versus 5% (n=4/74; 1·5 to 13·3) with placebo (p=0·011). Participants with baseline chronic pain intensity scores of at least 3 had a greater reduction in score at cycle 12 with selumetinib versus placebo (least-squares mean [SE] –2·0 [0·30] –2·6 to –1·4, *vs* –1·3 [0·29] –1·8 to –0·7; p=0·070), although this did not reach significance; and a clinically meaningful improvement from baseline. Change from baseline to cycle 12 in PlexiQoL total scores between treatment groups was not significant (least-squares mean difference [SE] –0·1 [0·59]; –1·2 to 1·1). Adverse events were consistent with the known selumetinib safety profile.

Interpretation In the first international, randomised, placebo-controlled trial in adults with NF1-plexiform neurofibromas, selumetinib achieved a significant objective response rate versus placebo. No new safety concerns were identified. The observations of reduction in tumour volume by cycle 16, reduction in chronic and spike pain, reduction in analgesia, and decrease in pain interference over placebo show that selumetinib is effective at treating plexiform neurofibromas in adults with NF1.

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Introduction

Neurofibromatosis type 1 (NF1) is a rare, heterogenous, genetic disorder caused by pathogenic variants in the *NF1* tumour suppressor gene (neurofibromin 1), and is associated with an 8–15-year reduction in life expectancy versus the general population.[1–5] The clinical manifestations of NF1 are diverse and typically affect multiple organ systems.[1–4,6] Plexiform neurofibromas are nerve sheath tumours that develop in up to 50% of individuals with NF1.[7–10] Although typically present at birth, plexiform neurofibromas can continue to manifest through late adolescence and adulthood.[10]

Individuals with NF1 could have none, one, or multiple plexiform neurofibromas, which can be associated with clinical symptoms such as chronic pain or spike pain, disfigurement, motor dysfunction, and compression of vital structures, as well as the potential for malignant transformation, all of which can negatively affect quality of life.[7–9,11–14] The unpredictable nature of plexiform

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Research in context

Evidence before this study

We searched PubMed for published articles using the terms "neurofibromatosis type 1" or "NF1" and "plexiform neurofibroma" or "PN", or "NF1-PN", and "adults". Neurofibromatosis type 1 (NF1) is a rare, heterogenous, genetic condition. NF1 has an estimated prevalence of approximately one in 2500 to one in 6000 people. Up to 50% of individuals with NF1 develop plexiform neurofibromas, which can impair quality of life. In addition to plexiform neurofibromas, more than 50% of individuals with NF1 report having substantial pain and discomfort. Selumetinib is a potent, selective, allosteric inhibitor of mitogen-activated protein kinase kinases 1 and 2 that was first approved by the US Food and Drug Administration in April 2020 for children (aged ≥2–17 years) with NF1 and symptomatic, inoperable plexiform neurofibromas, and has since been approved for this patient population by the European Medicines Agency (aged ≥3–17 years old) and the regulatory bodies in multiple other countries (aged ≥2 or 3 years, region dependent), at a dosage of 25 mg/m² twice daily. These approvals were based on the pivotal SPRINT study, in which selumetinib showed an overall response rate of 68% and provided a clinically meaningful reduction in tumour pain intensity. In February, 2025, mirdametinib was approved in the USA for adults and children aged at least 2 years with NF1 and symptomatic plexiform neurofibromas not amenable to complete resection on the basis of the results of a single arm, phase 2b study. However, as of May, 2025, there are no worldwide approvals of medical treatments for adults with NF1 and symptomatic, inoperable plexiform neurofibromas. Further clinical trials of medical treatments in adults are needed given the high burden of disease in this population.

Added value of this study

KOMET is the first and, as of May 2025, the only international, randomised, placebo-controlled trial of an inhibitor of mitogen-activated protein kinase kinases 1 and 2 in adults with NF1 who also have symptomatic, inoperable plexiform neurofibromas. KOMET is an ongoing trial that will assess the effects of selumetinib over a period of at least 24 months of treatment.

Implications of all the available evidence

Data from the primary analysis of KOMET indicate that selumetinib treatment achieved a significant objective response rate versus placebo by cycle 16, a clinically meaningful reduction in chronic target plexiform neurofibroma pain intensity score at cycle 12 compared with baseline in adults with a baseline chronic target plexiform neurofibroma pain intensity score of at least 3, and a decrease in chronic pain medication versus placebo at cycle 12. Selumetinib 25 mg/m² taken orally twice daily had a manageable safety and tolerability profile in adults with NF1-PN; no new safety concerns were identified. The observations of reduction in tumour volume by cycle 16, reduction in chronic and spike pain, reduction in analgesia, and improvement in pain-interfering activities at primary analysis show that selumetinib is effective at treating plexiform neurofibromas in adults with NF1.

neurofibroma-related symptoms can affect the ability of adults with NF1 to work.[12,15]

Plexiform neurofibroma growth rate is inversely correlated with age.[16] However, sustained growth can still be observed in adolescence and early adulthood.[16–18] Although spontaneous plexiform neurofibroma shrinkage can occur in some adults, the regression rate is typically slow.[11,18] Furthermore, spontaneous resolution of symptoms or morbidities associated with stable or growing plexiform neurofibromas is unlikely.[11]

Individuals with NF1 have a higher overall cumulative risk of cancer (25·1% *vs* 0·8% by 30 years; 38·8% *vs* 3·9% by 50 years) than the general population as well as a 15·8% cumulative risk of developing malignant peripheral nerve sheath tumours (MPNST) from pre-existing PN.[19] The risk of developing MPNST with NF1 is higher in adolescents and young adults compared with children.[17,19,20]

For individuals with NF1-plexiform neurofibromas, options within surgery can be limited owing to tumour size, location, and extent.[21–23] Although mirdametinib was recently approved in the USA for adults and children aged at least 2 years with NF1 and symptomatic plexiform neurofibromas not amenable to complete resection on the basis of the results of a single-arm, phase 2b study,[24] there are currently no worldwide approved pharmacological therapies in adults,[25] giving rise to substantial unmet needs in this population. Selumetinib is a potent, selective, allosteric inhibitor of mitogen-activated protein kinase kinases 1 and 2 that was first approved by the US Food and Drug Administration in April, 2020 for children (aged ≥2–17 years) with NF1 and symptomatic, inoperable plexiform neurofibromas, and has since been approved for this patient population by the European Medicines Agency (aged ≥3–17 years old) and the regulatory bodies in multiple other countries (aged ≥2 or 3 years, region dependent), at a dosage of 25 mg/m² twice daily.[26–29] These approvals were based on the primary analysis of the pivotal SPRINT study in children, in which selumetinib showed an overall response rate of 68% and provided a clinically meaningful reduction in tumour pain intensity as assessed by use of the 11-point Numerical Rating Scale (NRS-11).[7] The ongoing international KOMET study evaluates the efficacy and safety of selumetinib versus placebo in adults with NF1-plexiform neurofibromas. This article presents KOMET primary analysis results, when all participants had the opportunity to complete cycle 16.

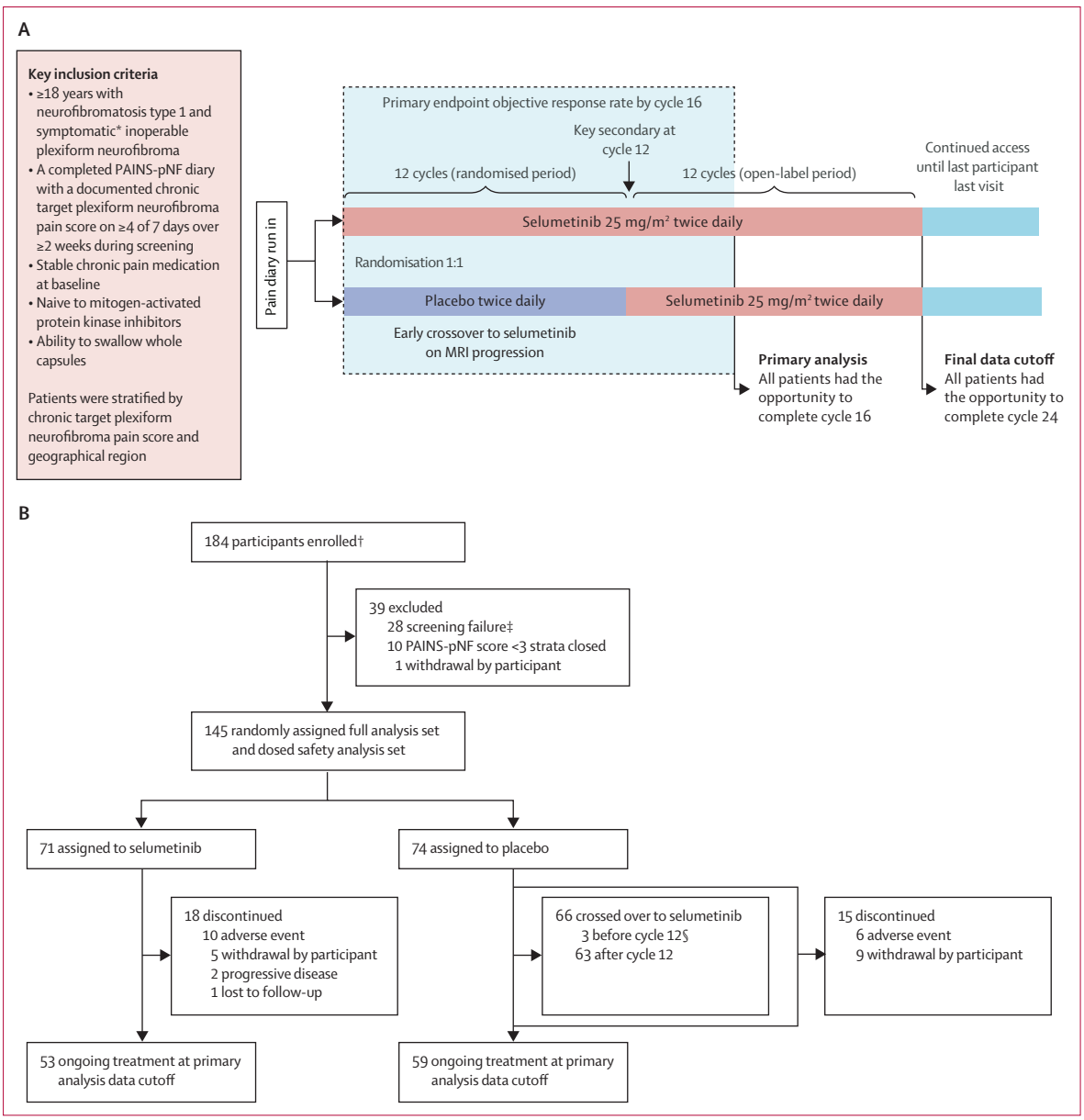


Figure 1: **Study design (A) and study disposition (B)**
(A) The first participant was enrolled in KOMET on Nov 19, 2021. The protocol included an interim analysis data cutoff for the KOMET study when the 100th randomly assigned patient had the opportunity to complete cycle 16. The primary analysis for the KOMET study was done when the last participant had the opportunity to complete their cycle 16 assessment (Aug 5, 2024). (B) The data cutoff was Aug 5, 2024. NF1=neurofibromatosis type 1. PAINS-pNF=Pain Intensity Scale for Plexiform Neurofibromas. *Symptoms could include, but were not limited to, pain, motor morbidity, and disfigurement. †Participants who signed the informed consent form. ‡Non-fulfilment of inclusion or exclusion criteria. §Two due to disease progression and one due to important protocol deviation.

Methods

Study design and participants

KOMET is a multicentre, international, phase 3 study with a parallel, randomised, double-blind, placebo-controlled, two-arm design to assess the efficacy and safety of selumetinib in adults (aged ≥18 years at informed consent) with NF1 and symptomatic, inoperable plexiform neurofibromas (figure 1A). The first participant was enrolled in KOMET on Nov 19, 2021. An interim analysis was planned after the 100th randomly assigned patient had the opportunity to complete their end of cycle 16 assessment (appendix p 4). The primary analysis was done after the last participant had the opportunity to complete their end of cycle 16 assessment (Aug 5, 2024).

See Online for appendix

Participants had at least one measurable plexiform neurofibroma (>3 cm in one dimension with a well defined contour and observable on at least three imaging

slices) and ≥1 other diagnostic criterion for NF1 (figure 1A).[30] Tumour growth history was not part of the eligibility criteria. Full study inclusion and exclusion criteria are detailed in the appendix (p 8).

As the randomised period of this study was of a short duration, the participant population was not considered clinically vulnerable, and the safety profile of selumetinib was well established, an independent data monitoring committee was not deemed necessary for this study. This study was approved by the ethics committees of each study site (see the appendix p 15 for full details) and was done in accordance with the Declaration of Helsinki. Study conduct was consistent with International Council for Harmonisation—Good Clinical Practice, applicable regulatory requirements, and the AstraZeneca bioethics policy. All participants provided written informed consent to be enrolled into KOMET.

This study is registered with ClinicalTrials.gov, NCT04924608 and is active but not recruiting.

Randomisation and masking

Following a screening period of up to 28 days, eligible participants were randomly assigned 1:1 to oral selumetinib 25 mg/m² (capped at 50 mg twice daily for a body surface area ≥1·9 m²) or placebo twice daily. Randomisation was stratified by average baseline Pain Intensity Scale for Plexiform Neurofibromas (PAINS-pNF) chronic target plexiform neurofibroma pain intensity score (capped at 106 participants with an average score ≥3, and 40 participants with an average score <3), and geographical region. Participants must have completed the pain diary for 4 of 7 days for ≥2 weeks to establish their average baseline chronic target plexiform neurofibroma pain intensity score required for stratification.

Placebo participants were crossed over to selumetinib after cycle 12 completion. Earlier crossover was permitted for confirmed progression on imaging as established by independent central review. From cycle 13 onwards, participants in both the selumetinib group and the placebo group entered the open-label group with selumetinib administered in 28-day cycles until a discontinuation criterion was met or until the final data cutoff, whichever was earlier.

Procedures

Participants were instructed to swallow study intervention capsules whole with a glass of water approximately 12 h apart but no less than 6 h apart, on an empty stomach. At the time of initiation of KOMET, the fasting requirement was still specified in the selumetinib label; therefore, no food or drink other than water was permitted for 2 h before and 1 h after dosing. From the end of cycle 24 (cycle 25, day 1), participants were not required to continue to observe the fasting restriction. Dose modifications were permitted in the case of adverse events and dose reductions were mandatory according to the protocol for certain prohibited medications. Complete response was defined as disappearance of the target plexiform neurofibroma, confirmed by a consecutive scan 3–6 months after the first response. Partial response was defined as a ≥20% decrease in target plexiform neurofibroma volume compared with baseline, confirmed by a consecutive scan 3–6 months after the first response. Progressive disease was defined as a ≥20% increase in the target plexiform neurofibroma volume compared with baseline or the time of best response after documenting a partial response. The appearance of a new plexiform neurofibroma that was unequivocally and completely distinct and separate from the target plexiform neurofibroma and the non-target plexiform neurofibroma, or unequivocal progression (≥20% increase in volume) of an existing non-target plexiform neurofibroma, was also considered progressive disease.

Outcomes

Endpoints, objectives, and estimands are fully described in the appendix (p 12).

The primary endpoint was comparison of the effect of selumetinib versus placebo on confirmed partial and complete response rate (objective response rate) by the end of cycle 16 (approximately 15 months), by use of volumetric MRI analysis as established by masked independent central review per Response Evaluation in Neurofibromatosis and Schwannomatosis (REiNS) criteria.[31] Before starting study treatment, the investigator selected the single most clinically relevant and measurable target plexiform neurofibroma. Volumetric MRI plexiform neurofibroma assessments were conducted at screening, day 28 of every four cycles until cycle 24, and day 28 of every six cycles thereafter. Definitions of complete response, partial response, stable disease, and progressive disease are provided in figure 1 and the appendix (p 4).

Key secondary endpoints were comparison of the effect of selumetinib versus placebo by assessment of: change in chronic target plexiform neurofibroma pain intensity from baseline to cycle 12 (approximately 11 months) in participants with a PAINS-pNF chronic target plexiform neurofibroma pain intensity score of at least 3 at baseline, and change in health-related quality of life from baseline to cycle 12 by use of the Plexiform Neurofibroma Quality of Life scale (PlexiQoL) total score. Further secondary endpoints relating to efficacy, pain, health-related quality of life, health status, physical functioning, and pharmacokinetics will be reported on in the future.

PAINS-pNF is a NF1-plexiform neurofibroma-specific adaptation of the NRS-11 scale[32] developed by the National Cancer Institute (NCI) on the basis of extensive qualitative research to assess plexiform neurofibroma-related pain intensity.[33] PAINS-pNF is undergoing validation with KOMET data, and in an NCI study. It consists of two items to assess participants' experience of chronic target plexiform neurofibroma-related pain (tumour pain that is present most of the time) and spikes of target plexiform

	Selumetinib n=71	Placebo n=74
Age at screening, years		
n	71	74
Mean (SD)	32·6 (11·4)	29·8 (8·7)
Median (IQR)	31·0 (24·0–40·0)	28·0 (24·0–36·0)
Minimum, maximum	18, 60	18, 53
Sex		
Male	33 (46%)	42 (57%)
Female	38 (54%)	32 (43%)
Race		
Asian	22 (31%)	23 (31%)
Black or African American	6 (8%)	3 (4%)
White	38 (54%)	43 (58%)
Other	2 (3%)	3 (4%)
Not reported	3 (4%)	2 (3%)
Region*		
China	11 (15%)	13 (18%)
Japan	7 (10%)	8 (11%)
Europe	31 (44%)	30 (41%)
Rest of the world	22 (31%)	23 (31%)
Time from diagnosis of NF1, years		
n	70†	74
Mean (SD)	23·1 (13·5)	18·6 (12·7)
Median (IQR)	23·0 (14·8–32·1)	18·7 (7·9–27·3
Minimum, maximum	0·06, 60·9	0·04, 47·0
Time from diagnosis of inoperable plexiform neurofibroma, years		
n	70†	74
Mean (SD)	8·69 (11·4)	8·10 (11·3)
Median (IQR)	2·5 (0·3–15·1)	2·3 (0·2–14·4)
Minimum, maximum	0·04, 45·9	0·03, 38·9
Target plexiform neurofibroma overall location		
Neck–trunk	8 (11%)	11 (15%)
Trunk–extremity	16 (23%)	11 (15%)
Head and neck	7 (10%)	5 (7%)
Head	5 (7%)	7 (10%)
Extremity	13 (18%)	18 (24%)
Body	1 (1%)	2 (3%)
Trunk	21 (30%)	19 (26%)
Other	0	1 (1%)
Target plexiform neurofibroma volume, mL		
Mean (SD)	480·91 (1231·0)	539·53 (927·2)
Median (IQR)	91·95 (25·0–355·2)	221·85 (49·7–529·6)
Minimum, maximum	0‡, 6264·3	9·1, 5621·9
Target plexiform neurofibroma symptoms§		
Any symptoms	71 (100%)	74 (100%)
Pain	62 (87%)	61 (82%)
Motor weakness	14 (20%)	19 (26%)
Decreased range of motion	19 (27%)	19 (26%)
Sensory deficit	8 (11%)	13 (18%)
Plexiform neurofibroma-related disfigurement	23 (32%)	17 (23%)
Other symptoms¶	12 (17%)	19 (26%)

(Table 1 continues on next column)

(Continued from previous column)

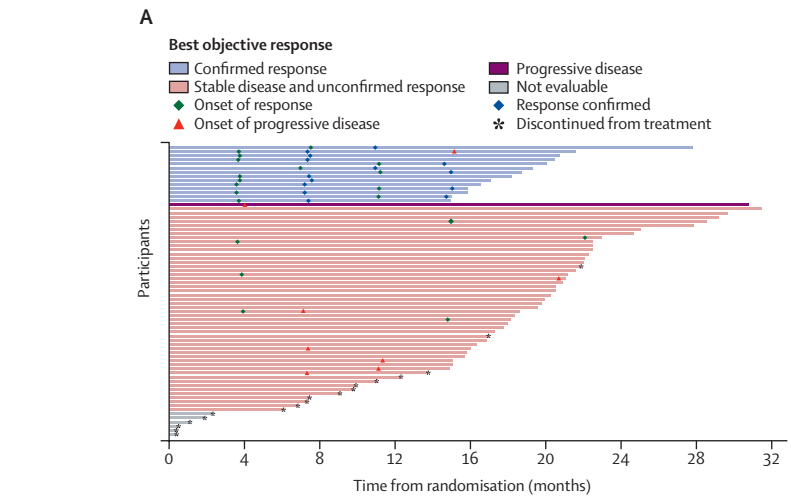
	Selumetinib n=71	Placebo n=74
Baseline PAINS-pNF intensity score		
<3	21 (30%)	21 (28%)
≥3	50 (70%)	53 (72%)
Any non-target plexiform neurofibroma		
No	53 (75%)	44 (59%)
Yes	18 (25%)	30 (41%)
Non-target plexiform neurofibroma overall location		
Neck–trunk	4 (6%)	4 (5%)
Trunk–extremity	2 (3%)	9 (12%)
Head and neck	5 (7%)	2 (3%)
Head	1 (1%)	1 (1%)
Extremity	0	4 (5%)
Trunk	6 (9%)	8 (11%)
Other	0	2 (3%)

Data are n (%) unless stated otherwise. The data cutoff was Aug 5, 2024. Percentages have been rounded up from one decimal place and, therefore, might add up to more than 100%. eCRF=electronic case report form. NF1=neurofibromatosis type 1. PAINS-pNF=Pain Intensity Scale for Plexiform Neurofibromas. *Europe includes France (selumetinib group: n=3; placebo group: n=2), Germany (selumetinib group: n=2; placebo group: n=8), Italy (selumetinib group: n=7; placebo group: n=8), Poland (selumetinib group: n=4; placebo group: n=1), Russia (selumetinib group: n=4; placebo group: n=3), Spain (selumetinib group: n=5; placebo group: n=4), and the U K (selumetinib group: n=6; placebo group: n=4). Rest of the world includes Australia (selumetinib group: n=6; placebo group: n=4), Brazil (selumetinib group: n=7; placebo group: n=13), Canada (selumetinib group: n=6; placebo group: n=3), and the USA (selumetinib group: n=3; placebo group: n=3). †Time from diagnosis of NF1 (years): time from diagnosis of NF1 to start of study intervention was greater than 60 years as it was calculated on the basis of date of birth and age at screening, which was recorded on the eCRF and not calculated. The sample size for time from diagnosis of NF1 was 70 rather than 71 for the selumetinib group because data for one rescreened patient who had provided initial screening information on disease diagnosis were not transferred. The date of diagnosis of NF1 was collected in the eCRF, and the time to diagnosis of NF1 was defined as the difference between the first dose date and the date of diagnosis of NF1. Time from diagnosis of inoperable plexiform neurofibroma (years): Participants could have had more than one NF1 diagnostic criteria. ‡The minimum value of 0 for selumetinib is an error in data from one participant. §A participant could have had multiple symptoms and overall morbidity types. ¶Other symptom categories with less than 10% are not shown in the table.

Table 1: **Baseline demographics and disease characteristics**

neurofibroma-related pain (sudden bursts of tumour pain). Participants completed a daily e-diary to rate their worst target plexiform neurofibroma chronic and spike tumour pain intensity over approximately the past 24 h by selecting a number between 0 (no tumour pain) and ten (worst tumour pain possible). Plexiform neurofibroma pain medication use (with chronic pain medication scored with the WHO Modified Analgesic Ladder; appendix p 4), and study treatment intakes were recorded by participants on the same device.

The Pain–Interference index—plexiform neurofibroma (PII-pNF) tool is a 12-item measure based on qualitative research with participants and medical experts.[33] PII-pNF assesses the extent to which plexiform neurofibroma-related pain interferes with aspects of daily life (physical, social-emotional, and physiological). Responses are on a



	Target plexiform neurofibroma volume, best percentage change	
Participants randomly assigned to selumetinib	Participants with an objective response by C16 (n=14)	Participants who had not reached an objective response by C16 (n=51)
Mean	−36·6	−9·9
Median (minimum, maximum)	−33·9 (−58·1 to −22·6)	−11·4 (−26·7 to 24·0)

***Figure 2*: Best response* in participants randomly assigned to selumetinib (swimmer plot), full analysis set (A) and target plexiform neurofibroma volume and best percentage change at the primary analysis data cutoff—waterfall plot, full analysis set (B)**

FAS=full analysis set. NF1=neurofibromatosis type 1. REiNS=Response Evaluation in Neurofibromatosis and Schwannomatosis. (A) *Best objective response is the response a participant had following the start of intervention, but before starting any subsequent NF1-PN therapy and up to and including progression or the last evaluable MRI assessment in the absence of progression. The on-treatment MRI volumetric assessment period was from the first dose until discontinuation or data cut-off (whichever occurs first), excluding data during prolonged study intervention interruption (>28 continuous days of no study intervention). According to REiNS criteria, a sustained response is at least 6 months. (B) Data cutoff was Aug 5, 2024. Waterfall pre-planned visualisation. Table data are from post-hoc analyses. SD of the mean was 11·3 for responders and 10·5 for non-responders. For responders, quartile 1 was −46·5 and quartile 3 was −28·1. For non-responders, quartile 1 was −17·3 and quartile 3 was −11·4. C16=cycle 16, etc.

7-point Likert-style scale with anchors of "Not at All" and "Completely". Total score is derived by averaging the responses to each of the 12 items.

PlexiQoL is a needs-based quality-of-life measure specific to adults with NF1-associated plexiform neurofibroma, which was developed by Heaney and colleagues 2020 and requires validation in the clinical trial setting.[34] PlexiQoL comprises 18 dichotomous items covering appearance, relationships, independence, role fulfilment, and pleasure.[34] Each item is given a score of 1 (=true) or 0 (=not true); a total score is obtained by summing all items (range 0–18), lower scores indicate better quality of life. In KOMET, PlexiQoL was done by use of an electronic tablet during clinic visits at baseline, day 28 of cycle 2, and then day 28 of every four cycles until cycle 24, and day 28 of every six cycles thereafter.

Safety assessments, including adverse events, serious adverse events, protocol-defined adverse events of special interest (AESIs; defined in the appendix p 13), laboratory markers, and physical examinations, were done at screening, baseline, day 28 of cycles 1, 2, 4, 6, 8, 10, 12, 16, 20, 24, and 30, end of treatment, and 30 days after last dose (appendix p 5).

Statistical analysis

Primary analysis on the comparison of objective response rate between groups was made by use of Fisher's exact test. Objective response rates were presented with corresponding two-sided exact 95% CIs on the basis of the Clopper–Pearson method.[35] Risk difference and 95% CI based on the Miettinen–Nurminen (score) method[36] were calculated.

Patient-reported outcome data were analysed by use of a Mixed Model for Repeated Measures approach, which included treatment, cycle number, and geographical region as categorical fixed effects; baseline patient-reported outcome score as a continuous covariate; and treatment-by-cycle number and baseline patient-reported outcome score-by-cycle number interactions.

At a two-sided α level of 5%, 73 participants per group were required to detect a difference between selumetinib and placebo for objective response rate (20% *vs* 0%) with >99% power. A total of 42 participants per group were required to detect a treatment difference of at least 2 for change in PAINS-pNF chronic target PN pain intensity score (assuming SD of 2·8) in favour of selumetinib with 90% power. To allow for approximately 20% dropout (ie, participants without ≥1 post-baseline average cycle PAINS-pNF chronic target plexiform neurofibroma pain score), 106 participants with baseline PAINS-pNF chronic target plexiform neurofibroma pain score of at least 3 were required to be randomly assigned to treatment with a 1:1 selumetinib:placebo allocation. To detect a treatment difference of at least 1·2 for PlexiQoL total score (assuming SD of 2·3) in favour of selumetinib with 80% power, 58 participants were required.

A multiple hierarchical testing procedure was employed to control for type 1 errors. All other p values are nominal (see appendix pp 5, 27 for more information).

Adverse events were coded by use of the Medical Dictionary for Regulatory Activities (version 26.1). Treatment-emergent adverse events were defined as events with onset or worsening after the first dose and within 30 days of the last dose or up to the day before the start of subsequent therapy.

Dropout was defined as "(patients discontinued from treatment at cycle 12 or patients discontinued from treatment at the primary analysis data cutoff divided by

total patients randomly assigned) multiplied by 100" (see appendix p 4 for more information).

Study populations are defined in the appendix p 14.

Any change, divergence, or departure from the approved protocol was considered a protocol deviation. Important deviations were defined as any non-compliance that might significantly affect the reliability of the study data or that might significantly affect a participant's rights, safety, or well-being. None of the important protocol deviations were considered to have affected the safety of the participants or the reliability of the study data.

Role of the funding source

The study sponsor (AstraZeneca) was responsible for study design, funded medical writing assistance, and provided formal review of the publication. Authors retain control and final authority of publication content and decisions, including journal choice.

	Selumetinib		Placebo		Selumetinib *vs* placebo	
	n	Least-squares mean	n	Least-squares mean	Least-squares mean difference	p value
Pain full analysis set*	42	−2·0 (0·30; −2·6 to −1·4)	42	−1·3 (0·29; −1·8 to −0·7)	−0·8 (0·41; −1·6 to −0·1)	0·07
Baseline PAINS-pNF level						
≥2	45	−2·0 (0·28; −2·6 to −1·5)	44	−1·2 (0·28; −1·7 to −0·6)	−0·9 (0·39; −1·6 to −0·1)	0·03 (nominal)
≥1	50	−1·9 (0·26; −2·4 to −1·3)	49	−1·0 (0·26; −1·5 to −0·5)	−0·8 (0·36; −1·5 to −0·1)	0·02 (nominal)
Full analysis set	57	−1·6 (0·22; −2·0 to −1·1)	62	−0·9 (0·21; −1·3 to −0·5)	−0·7 (0·30; −1·3 to −0·1)	0·02 (nominal)

Data are mean (SE; 95% CI). Statistical analysis model: Mixed Model for Repeated Measures with randomised treatment, cycle, baseline score, geographical region, pain strata, treatment group by cycle number, and baseline PAINS-pNF score by cycle number. Unstructured covariance matrix. Scale meaningful score difference ≤−2 points. PAINS-pNF=Pain Intensity Scale for Plexiform Neurofibromas. *Pain FAS (baseline PAINS-pNF ≥3), first key secondary endpoint, confirmatory analysis; baseline PAINS-pNF ≥1, ≥2, post-hoc analyses; Full analysis set (all participants regardless of baseline PAINS-pNF score), preplanned supplementary exploratory analysis.

Table 2: **Change from baseline in PAINS-pNF chronic target plexiform neurofibroma pain intensity score at cycle 12, according to population analysed**

Results

Participants were enrolled from 33 sites in 13 countries (Australia, Brazil, Canada, China, France, Germany, Italy, Japan, Poland, Russia, Spain, the UK, and the USA). The preplanned primary analysis at cycle 16 included the study period from Nov 19, 2021, to Aug 5, 2024 (primary analysis data cutoff).

Overall, of 184 participants enrolled, 145 were randomly assigned (selumetinib 71; placebo 74) and received at least one dose of study intervention (figure 1B). In the placebo group, 66 participants crossed over to selumetinib. Of these 66 participants, 63 crossed over to selumetinib at cycle 12 and three crossed over at an earlier timepoint. The study dropout rate was 22 (15%) of 145 before the end of cycle 12 and 31 (21%) at the primary analysis data cutoff (appendix p 18, figure 1B). The median duration of selumetinib exposure was 554 days (IQR 454–657) for the selumetinib group and 267 days (IQR 181–343) for the placebo–selumetinib group. Details of Important protocol deviations can be found in the appendix p 6.

Participant demographics and disease characteristics at baseline (table 1) were generally well balanced between treatment groups except for median plexiform neurofibroma tumour volume (selumetinib 91·95 mL [IQR 25·0–355·2]; placebo 221·85 mL [IQR 49·7–529·6]), presence of non-target plexiform neurofibroma tumours (selumetinib 18 [25%] of 71; placebo 30 [41%] of 74), and investigator-assessed target plexiform neurofibroma-related disfigurement (selumetinib 23 [32%] of 71; placebo 17 [23%] of 74).

At baseline, 87% of selumetinib participants and 82% of placebo participants had target plexiform neurofibroma-related pain. Overall, 70% in the selumetinib group and 72% in the placebo group had a baseline PAINS-pNF chronic pain intensity score of at least 3.

The primary endpoint was met: selumetinib objective response rate by cycle 16 was significant versus placebo in the full analysis set (appendix p 28). Overall, 14 (20%) of 71 participants (95% CI 11·2 to 30·9) responded to selumetinib versus four (5%) of 74 placebo participants (1·5 to 13·3); p=0·011. The estimated difference in objective response rate between the selumetinib and the placebo group was 14% (95% CI 3·8 to 25·8). The 5% objective response rate observed in the placebo group was due to four participants who had a confirmed partial response by the end of cycle 16. Of these, two participants had a confirmed partial response at cycle 12 day 28 while receiving only placebo. The other two participants had a confirmed partial response at cycle 16 day 28 after four cycles (almost 4 months) of selumetinib treatment. In these two participants, tumour reductions were 22% and 23% at the end of the placebo period and improvements in tumour volume were observed after crossing over to selumetinib treatment resulting in reductions of 44% and 31% at the end of cycle 16 after four cycles of selumetinib treatment. The age and baseline tumour volume of the two responders on placebo only were 42 years and 940·0 mL for one participant and 36 years and 25·5 mL for the second participant.

A rapid onset of response evident at a scheduled visit for the first planned staging evaluation (median: 3·7 months; 95% CI 3·6 to 11·1) was observed for participants randomly assigned to the selumetinib group. Selumetinib showed clinically meaningful, sustained responses in most participants. Amongst those with a confirmed objective response to selumetinib (n=14), 86% remained in response for at least 6 months and the remaining 14% had been followed up for less than 6 months from the onset of response but remained in response at the time of the last evaluable MRI before data cutoff.

The best response in participants randomly assigned to selumetinib is shown in figure 2A. At cycle 16, 14 (20%)

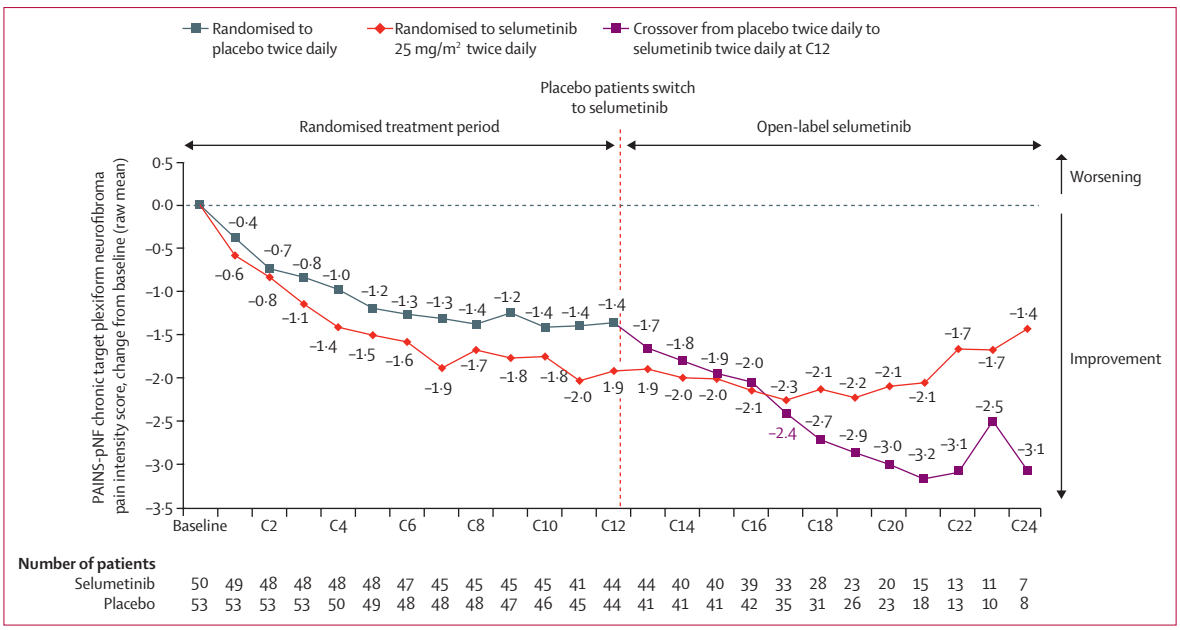


Figure 3: **Change from baseline in PAINS-pNF chronic target plexiform neurofibroma pain intensity score over time, pain full analysis set***
Supplementary analysis. Descriptive analysis. Three placebo participants crossed over to selumetinib before cycle 12. PAINS-pNF=Pain Intensity Scale for Plexiform Neurofibromas. *Pain full analysis set—participants randomly assigned to study intervention with a baseline pain intensity score of at least 3.

of 71 participants in the selumetinib group had a confirmed partial response, 50 (70%) of 71 had stable disease,one (1%) had progressive disease, and six (8%) were not evaluable because of early discontinuation due to adverse events (n=3), withdrawal of consent (n=2), and loss to follow-up (n=1). In the placebo group, 63 (85%) of 74 participants had stable disease, five (7%) of 74 had progressive disease, and two (3%) of 74 were not evaluable because of early discontinuation due to adverse events (appendix p 7).

Post-hoc analyses of participants in the selumetinib group who showed an objective response (n=14) showed a mean −36·6% target plexiform neurofibroma volume reduction from baseline to cycle 16 (figure 2B). The mean target plexiform neurofibroma volume reduction from baseline to cycle 16 in participants in the selumetinib group who had not shown an objective response (n=51) was −9·9%.

In the full analysis set, when compared with placebo (by cycle 12) a difference was observed in best percentage change from baseline in target plexiform neurofibroma volume in the selumetinib group (lease-squares mean difference −11·1%; 95% CI −15·5% to −6·8%; nominal p<0·0001; appendix p 7). Additionally, selumetinib had a continuous effect on target plexiform neurofibroma tumour volume reduction over time, extending beyond cycle 12 (appendix p 29). Placebo participants switching to selumetinib after cycle 12 also responded to treatment (eight of 66 participants by the primary analysis data cutoff; median exposure time 267 days; appendix p 32).

Participants with a baseline chronic pain score of at least 3 had a greater reduction in PAINS-pNF chronic target plexiform neurofibroma pain intensity score with selumetinib (least-squares mean −2·0; 95% CI −2·6 to −1·4) versus placebo (least-squares mean −1·3; −1·8 to −0·7), although this did not reach significance (least-squares mean difference −0·8; 95% CI −1·6 to 0·1; p=0·070; pain full analysis set; table 2). The reduction in PAINS-pNF chronic pain score observed in the selumetinib group was clinically meaningful (scale meaningful score difference ≤−2 points).[37,38] There was consistent improvement in chronic pain following selumetinib treatment across populations with different baseline pain thresholds (table 2).

In addition, a consistent effect on chronic pain reduction over time and after crossover was observed (pain full analysis set; figure 3). The crossover group had a maximum mean reduction of 1·4 during the randomised period; the mean reduction only surpassed the meaningful score difference of at least 2 points after participants switched from placebo to selumetinib. A greater proportion of chronic target plexiform neurofibroma pain palliation responders (appendix p 4) was observed in the selumetinib versus the placebo group starting at cycle 3 and throughout the randomised period (appendix p 33).

A greater decrease was observed in spike pain scores with selumetinib versus placebo (full analysis set; appendix p 34). A difference was observed in PAINS-pNF spike target plexiform neurofibroma pain intensity at the end of the randomised period between the selumetinib (least-squares mean: −2·5; 95% CI −3·1 to −1·9) and the placebo group (least-squares mean −1·5; −2·0 to −0·9), as established by the difference in mean change in

PAINS-pNF spike target plexiform neurofibroma pain intensity score from baseline (least-squares mean difference –1·1; 95% CI –1·8 to –0·3; nominal p=0·0085).

The extent to which plexiform neurofibroma-related pain interfered with daily functioning decreased with selumetinib treatment, as shown by change in PII-pNF scores over time (full analysis set; appendix p 35). At the end of the randomised period, a difference in PII-pNF pain interference total score in the full analysis set (least-squares mean difference –0·5; 95% CI –0·9 to –0·1; nominal p=0·023) was observed between the selumetinib (least-squares mean –0·9; 95% CI –1·3 to –0·6) and the placebo group (least-squares mean –0·5; –0·8 to –0·1).

At cycle 12, a relative reduction from baseline in pain medication usage of 27% was observed in the selumetinib group, versus 14% in the placebo group (full analysis set; appendix p 35). In the selumetinib group, 47% of participants had no analgesia for chronic plexiform neurofibroma pain at baseline versus 70% at the end of the randomised period. Corresponding proportions for the placebo group were 51% at baseline and 65% at the end of the randomised period (full analysis set; appendix p 20).

No significant differences were observed for selumetinib versus placebo in PlexiQoL total score (least-squares mean change from baseline [95% CI] –0·4 [–1·3 to 0·5] for selumetinib and –0·3 [–1·2 to 0·6] for placebo; nominal p=0·92; appendix p 21).

Overall, 100% of selumetinib participants and 92% of placebo participants reported at least one adverse event (table 3). The most frequently reported adverse events in the selumetinib group were dermatitis acneiform (42 [59%] of 71), increased blood creatine phosphokinase (32 [45%]), and diarrhoea (30 [42%]). The most frequently reported adverse events in the placebo group were COVID-19 (15 [20%] of 74), nausea (12 [16%]), and fatigue (10 [14%]). Overall, 96% of selumetinib participants and 57% of placebo participants had adverse events assessed by the investigator as possibly related to treatment.

Most adverse events were grade 1/2 (table 3). Overall, 27% of participants in the selumetinib group and 15% of participants in the placebo group had at least one grade 3 adverse event. The percentage of participants who had at least one adverse event of at least grade 3 was higher in the selumetinib (32%) versus the placebo group (18%). In the selumetinib group, five (7%) participants had grade 3 increased blood creatine phosphokinase. All other adverse events of at least grade 3 in the selumetinib group occurred in no more than two participants. Overall, 20% and 1%, respectively, had adverse events of at least grade 3 that were assessed by the investigator as possibly related to study intervention (appendix p 22). No grade 5 adverse events were reported.

No notable differences in the frequency of serious adverse events were observed between the selumetinib (14%) and placebo groups (12%; appendix p 24). Four (6%) participants in the selumetinib group and one (1%) placebo participant had serious adverse events assessed by the investigator as possibly treatment-related (table 3). In the selumetinib group, one participant with a preexisting medical history of psychiatric disorder had a worsening of symptoms that led to a grade 3 psychiatric decompensation or deterioration on day 186 and subsequent treatment discontinuation (event not resolved at data cutoff); another participant had grade 3 cellulitis on day 279 leading to treatment discontinuation (event was resolved); one participant had grade 3 cellulitis

	Selumetinib n=71	Placebo n=74
Any adverse events	71 (100%)	68 (92%)
Adverse event, possibly related*	68 (96%)	42 (57%)
Adverse event, CTCAE grade 3 or higher	23 (32%)	13 (18%)
CTCAE grade 3 or higher, possibly related*	14 (20%)	1 (1%)
Outcome of death	0	0
Serious adverse event (including events with outcome of death)	10 (14%)	9 (12%)
Serious adverse event (including events with outcome of death), possibly related*	4 (6%)	1 (1%)
Serious adverse event leading to discontinuation	4 (6%)	4 (5%)
Serious adverse event leading to discontinuation, possibly related*	2 (3%)	0
Adverse event leading to discontinuation	9 (13%)	5 (7%)
Adverse event leading to discontinuation, possibly related*	6 (8%)	1 (1%)
Adverse event leading to dose modification†	27 (38%)	10 (14%)
Adverse event leading to dose interruption	19 (27%)	8 (11%)
Adverse event leading to dose reduction	10 (14%)	3 (4%)
Any AESIs‡	47 (66%)	16 (22%)
Any other significant adverse events§	0	0
Maximum reported CTCAE grade		
1	16 (23%)	22 (30%)
2	32 (45%)	33 (45%)
3	19 (27%)	11 (15%)
4	4 (6%)	2 (3%)
System organ class with a higher percentage of participants with adverse events in the selumetinib group		
Infections and infestations	38 (54%)	33 (45%)
Psychiatric disorders	7 (10%)	2 (3%)
Nervous system disorders	20 (28%)	20 (27%)
Eye disorders	12 (17%)	9 (12%)
Ear and labyrinth disorders	6 (8%)	4 (5%)
Respiratory, thoracic, and mediastinal disorders	12 (17%)	12 (16%)
Gastrointestinal disorders	53 (75%)	32 (43%)
Hepatobiliary disorders	3 (4%)	2 (3%)
Skin and subcutaneous tissue disorders	64 (90%)	26 (35%)
Musculoskeletal and connective tissue disorders	19 (27%)	17 (23%)
Renal and urinary disorders	6 (8%)	5 (7%)
Reproductive system and breast disorders	5 (7%)	3 (4%)
Congenital, familial, and genetic disorders	1 (1%)	0
General disorders and administration-site conditions	36 (51%)	21 (28%)
Investigations	44 (62%)	21 (28%)
Injury, poisoning, and procedural complications	11 (15%)	9 (12%)

(Table 3 continues in next column)

	Selumetinib n=71	Placebo n=74
(Continued from previous column)		
Adverse events had by ≥10% of participants in either treatment group by preferred term		
Dermatitis acneiform	42 (59%)	8 (11%)
Diarrhoea	30 (42%)	9 (12%)
Blood creatine phosphokinase increased	32 (45%)	4 (5%)
Nausea	18 (25%)	12 (16%)
Vomiting	18 (25%)	6 (8%)
Fatigue	14 (20%)	10 (14%)
Alopecia	13 (18%)	8 (11%)
Dry skin	13 (18%)	4 (5%)
Aspartate aminotransferase increased	13 (18%)	4 (5%)
COVID-19	11 (15%)	15 (20%)
Oedema peripheral	11 (15%)	1 (1%)
Alanine aminotransferase increased	11 (15%)	5 (7%)
Rash	11 (15%)	3 (4%)
Paronychia	9 (13%)	3 (4%)
Headache	8 (11%)	9 (12%)
Stomatitis	7 (10%)	3 (4%)
Constipation	7 (10%)	1 (1%)
Pruritus	7 (10%)	5 (7%)
Anaemia	5 (7%)	8 (11%)
Pain in extremity	5 (7%)	8 (11%)
Arthralgia	3 (4%)	8 (11%)
Decreased appetite	1 (1%)	8 (11%)

Data are n (%). Randomised period: first dose date until earliest of last dose of cycle 12, crossover, 30 days after discontinuation, day before the start of subsequent therapy, or data cutoff. Percentages have been rounded up from one decimal place and, therefore, might add up to more than 100%. AESI=adverse event of special interest. CTCAE=Common Terminology Criteria for Adverse Events (version 5.0). *As assessed by the investigator. †Action taken either a drug interruption or a dose reduction, or both. ‡Per protocol, AESIs included ocular toxicity, hepatotoxicity, muscular toxicity, and cardiac toxicity events (see appendix p 13, 25). §Significant adverse events, other than serious adverse events and those adverse events leading to discontinuation of study intervention, which are of particular clinical importance are identified and classified as other significant adverse events.

Table 3: **Number of participants with adverse events in the randomised period, safety analysis set**

on day 339 leading to treatment interruption (event was resolved); and one participant had two events of grade 3 headache on day 74 and day 77. Both events led to treatment interruption and were resolved. One placebo participant had grade 3 bacterial urinary tract infection on day 63, leading to dose reduction (event was resolved).

AESIs were selected (appendix p 13) on the basis of known class effects of mitogen-activated protein kinase (MEK) inhibitors to increase understanding of important potential risks of selumetinib.[39] Most AESIs were grade 1–2 (appendix p X). The most frequently reported AESI was increased blood creatine phosphokinase (32 [45%]) for selumetinib and increased alanine aminotransferase (ALT; five [7%]) for placebo. Four (6%) selumetinib participants had AESIs with maximum severity of grade 3 (increased blood creatine phosphokinase, decreased left ventricular ejection fraction [LVEF], increased ALT, and increased aspartate aminotransferase [AST]). Two additional participants had increased blood creatine phosphokinase with a maximum severity of grade 4; neither were serious or led to discontinuation and only one of these two grade 4 events led to interruption with restart of treatment at a reduced dose. Three placebo participants had AESIs with a maximum severity of grade 3 (increased blood creatine phosphokinase, and muscular weakness). No myopathy or rhabdomyolysis were reported. Ocular toxicity events were grade 1. No central serous retinopathy, retinal vein occlusion, or retinal pigment epithelial detachment were reported. One selumetinib participant (1%) had a grade 3 LVEF decrease from 59% at baseline to 50% that was non-serious, and did not require dose modification. No participants had overlapping decreased LVEF with peripheral oedema or swelling, and oedema. No cardiac AESIs were serious or led to discontinuation.

Dose interruptions or reductions due to adverse events were more frequent with selumetinib than placebo (table 3; appendix p 26). Nineteen (27%) of 71 participants in the selumetinib group had adverse events leading to dose interruptions versus eight (11%) of 74 participants in the placebo group. The most common adverse events leading to dose interruption were increased blood creatine phosphokinase (three [4%]); and COVID-19, headache, abdominal pain, and nausea (two [3%] each) in the selumetinib group. All other interruptions in the selumetinib group occurred in only one participant each (appendicitis, cellulitis, folliculitis, influenza, paronychia, decreased appetite, syncope, periorbital oedema, dyspnoea, diarrhoea, lip swelling, vomiting, dermatitis acneiform, rash papular, myalgia, chest discomfort, peripheral swelling, swelling face, LVEF decreased, international normalised ratio increased, lipase increased, weight decreased, and joint dislocation). The most common adverse event leading to dose interruption in the placebo group was vomiting (two [3%]). All other interruptions in the placebo group occurred in only one participant each (COVID-19, gastrointestinal infection, influenza, urinary tract infection, anaemia, thrombocytopenia, decreased appetite, dysaesthesia, superficial vein thrombosis, acute respiratory failure, dental caries, diarrhoea, muscular weakness, and ovarian cyst). Dose reductions due to adverse events occurred in ten (14%) participants in the selumetinib groupand three (4%) in the placebo group. The most common adverse events leading dose reductions were alopecia, paronychia, increased ALT, increased AST, and increased blood creatinine phosphatase in the selumetinib group (two [3%] each), and bacterial urinary tract infection, thrombocytopenia, dyspnoea, nausea, and malaise in the placebo group (one [1%] each). No new safety concerns were identified during assessment of laboratory results, vital signs, electrocardiograms, or ophthalmological examinations.

Discussion

Adults with NF1 and symptomatic, inoperable plexiform neurofibromas have a considerable unmet need for pharmacological treatments.[21–23] The ongoing,

international KOMET study is the first, and as of May, 2025, the largest trial done in adult participants with NF1-PN that has a placebo-controlled group. The placebo control, which was limited to 12 cycles for ethical reasons, provides a comparative analysis of the primary endpoint of objective response rate and both key secondary endpoints. By evaluating efficacy and safety of selumetinib versus placebo, insights can be obtained into the natural regression in adults with NF1-PN. The crossover phase of the study increases the robustness of the design by allowing the benefit of selumetinib in patients with progressing tumour on placebo to be assessed. KOMET met its primary endpoint showing the efficacy of selumetinib in reducing plexiform neurofibroma volume in this population.

Some between-group differences in disease characteristics at baseline were observed (target plexiform neurofibroma tumour volume, target plexiform neurofibroma-related disfigurement, and non-target plexiform neurofibroma tumours). Notably, there was substantial variation in the time from diagnosis of inoperable plexiform neurofibroma at enrolment. This reflects the heterogeneous nature of NF1-PN and the global practice pattern of the study; enrolment of a more homogenous population would have represented a substantial challenge in the context of NF1 being classified as a rare disease.

In KOMET, the magnitude of tumour volume reduction seen in participants who responded to selumetinib (median: −33·9%; IQR −46·5 to 28·1) was significant and clinically relevant for the treatment duration of 16 cycles. The efficacy of selumetinib in adults with NF1-PN has also been investigated in a phase 2 study done in Korea and a phase 2 NCI-led study.[40,41] In these two non-randomised studies, most participants treated with selumetinib had a reduction in target plexiform neurofibroma volume, with improvements in pain and quality of life.[40,41] When taken in the context of these other findings, the observed reductions in plexiform neurofibroma volume noted during the KOMET primary analysis reinforce the evidence of selumetinib efficacy in adults. Although final analysis of KOMET will occur when the last participant has had the opportunity to complete 24 cycles, it should be noted that a response was observed in some KOMET participants who had only received 4 months of selumetinib treatment (placebo crossover group).

The objective response rate for selumetinib was reported as 68% in the phase 2 SPRINT paediatric study,[7] 63% in the phase 2 NCI-led open-label adult study,[41] and 20% in the primary analysis of KOMET. Given that all three studies used volumetric MRI assessment by REiNS criteria, this probably reflects differences in study design and the fact that the primary endpoint for KOMET was assessed after a shorter time period (16 cycles *vs* a median number of treatment cycles of 36 at the primary analysis data cutoff for SPRINT and a median duration of treatment of 28 months at data cutoff for the open-label adult study).[7,41] Furthermore, the SPRINT study was conducted in paediatric patients with a median age of 10 years at enrolment, whereas the open-label adult study and KOMET were conducted in adults (aged ≥18 years at enrolment).[7,41] Notably, some of the patients in KOMET could have enrolled at a later stage of disease than others depending on resources available in their country to help manage NF1-plexiform neurofibromas.

Pain is a frequent symptom of NF1,[43] and over 80% of KOMET participants had plexiform neurofibroma-related chronic pain at baseline, as assessed by use of the PAINS-pNF measure, which uses a standard NRS-11 scale for evaluating chronic and spike pain intensity associated with the target plexiform neurofibroma. Use of PAINS-pNF to assess pain intensity, rather than the original NRS-11 scale, which is not disease-specific, was a key strength of the KOMET study. Furthermore, KOMET is the first randomised trial in NF1-plexiform neurofibroma to incorporate a placebo control group. Notably, other studies of MEK inhibitors have used a single-arm design without a comparator (NCT03231306),[25,44] and inclusion of a placebo control group in KOMET allowed pain data to be more easily interpreted, accounting for the placebo effect. Therefore, it is important to note that decreases in target plexiform neurofibroma pain scores were detected with selumetinib treatment.

Participants in the placebo group reported some pain reduction before crossover to selumetinib. This observation could have been owing to a placebo effect caused by increased surveillance and patient awareness of pain throughout KOMET through use of a daily e-diary capturing aspects related to this target plexiform neurofibroma manifestation. Notably, meaningful score difference (2-point decrease in PAINS-pNF score) was not seen in the placebo group until after crossover to selumetinib, supporting the placebo effect in the first 12 cycles.

Although the PAINS-pNF and PII-pNF measures are pending psychometric validation, these tools were specifically developed to capture target plexiform neurofibroma-related pain rather than all possible sources of pain that adults with NF1 can have. KOMET data support chronic and spike target plexiform neurofibroma pain reduction following selumetinib treatment and suggest that the PAINS-pNF tool can distinguish between spike and chronic pain in the context of a clinical trial. Consistent improvement in chronic target plexiform neurofibroma pain across populations with different baseline pain thresholds was observed, along with a higher proportion of chronic pain responders and a greater decrease in spike pain scores for selumetinib versus placebo. A greater reduction in the use of chronic pain medication was observed for participants on selumetinib versus placebo. A greater proportion of chronic target plexiform neurofibroma

pain palliation responders was observed in the selumetinib group than the placebo group starting at cycle 3 through the duration of the randomised period, although this was not significant; a reduction in the extent to which plexiform neurofibroma-related pain interfered with daily functioning was also observed.

PlexiQoL is a relatively new quality-of-life measure specifically for adults with NF1-plexiform neurofibromas that has previously only been used in one phase 1 clinical trial;[45] therefore, sensitivity to change had not been examined until the psychometric validation work completed within KOMET.[15,34,45] No significance was observed for the change from baseline in PlexiQoL total score at cycle 12 for selumetinib versus placebo. The psychometric analysis done in the context of KOMET data has indicated that PlexiQoL items might not be able to accurately discriminate between situations where participants report very good or very poor quality of life.[45] With evidence showing that selumetinib improves quality of life and is an established and effective treatment intervention for NF1-plexiform neurofibroma,[7,40,41] the lack of observed effects assessed by PlexiQoL suggests that the dichotomous nature of the response scales (yes or no) might not be sensitive enough to capture the effects of plexiform neurofibroma treatment within the period (12 cycles; approximately 11 months) of assessment from baseline. Therefore, use of PlexiQoL in KOMET represents a study limitation, and additional validation of this measure in the context of clinical trials is warranted before widespread use.[34]

KOMET was conducted in multiple countries providing an international perspective on adult NF1-plexiform neurofibromas, which could have increased the overall diversity of the included population, and differentiates KOMET from the adult open-label study conducted only in the USA. Notably, the KOMET study safety results for the primary analysis were consistent with the known safety profile of selumetinib.[7,28] Most adverse events were grade 1 or 2. Many of the reported adverse events were observed at a similar frequency in both the selumetinib and the placebo group, indicating that some adverse events might be predominantly disease-related rather than treatment-related. Most adverse events where differences between the selumetinib and the placebo groups were found are adverse events described as adverse drug reactions on the basis of other studies done in the paediatric population; only constipation was added as an adverse drug reaction for selumetinib on basis of the KOMET study findings. Most adverse events that led to dose interruptions in both treatment groups were single events. Differences in treatment interruptions between the two groups were driven by the known safety profile of selumetinib and encompassed adverse events classified as infections and infestations (10% for selumetinib *vs* 4% for placebo); blood and lymphatic system disorders (0% *vs* 2%); metabolism and nutrition disorders (1% each); nervous system disorders (4% *vs* 1%); eye disorders (1% *vs* 0%), vascular disorders (0% *vs* 1%); respiratory, thoracic, and mediastinal disorders (1% *vs* 1%); gastrointestinal disorders (7% *vs* 4%); skin and subcutaneous tissue disorders (3% *vs* 0%); musculoskeletal and connective tissue disorder (1% *vs* 1%); reproductive system and breast disorders (0% *vs* 1%); general disorders and administration site conditions (4% *vs* 0%); investigations (9% *vs* 0%); injury, poisoning, and procedural complications (1% *vs* 0%).[28,41]

It is important to note that the findings presented here are primary analysis results with further data beyond cycle 16 to follow as the KOMET study progresses. Further follow-up of the crossover participants will aid assessment of the effect of the switch to selumetinib and its timing on tumour growth rate, pain response, and quality of life as well as providing further safety and tolerability data for selumetinib in the adult population who have NF1-plexiform neurofibroma. Further safety data obtained from the next data cutoff for KOMET after 24 cycles of treatment will allow comparisons to be made with the adverse events reported in the open-label adult study whereby grade 3 treatment-related adverse events had reduced to one instance each of elevated creatinine phosphokinase and elevated lipase, and the incidence of grade 4 adverse events had reduced to zero after cycle 24.[41]

In the first international, randomised, placebo-controlled trial in adults with NF1-plexiform neurofibroma, selumetinib 25 mg/m² twice daily taken orally achieved a clinically and significant objective response rate versus placebo, a clinically meaningful reduction in chronic target plexiform neurofibroma pain intensity score at cycle 12 compared with baseline, and a manageable safety–tolerability profile with no new safety concerns. The observations of reduction in tumour volume by cycle 16, reduction in chronic and spike pain, reduction in analgesia, and decrease in pain interference over placebo show that selumetinib is effective at treating plexiform neurofibromas in adults with NF1.

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APC, GO'SC, SF, IB, RL, RdlRR, SJD, ED, and PW conceived the study. APC, GO'SC, PLW, SM, SF, IB, ZC, LGD, JRW, YN, and IH provided study resources. Data were curated by GO'SC, IB, ZC and RdlRR. Study data were analysed by RL, RdlRR, AA, and NL; IH also provided data interpretation, including key messages and conclusions. The study was supervised by APC, GO'SC, SF, LGD, ME, JRW, RL (for the biometrics components), RdlRR, IH, SJD, ED, and PW. GO'SC, LGD and IH were responsible for acquiring funding for the project. The data were validated and verified by APC, GO'SC, LGD, YN, RL, RdlRR, IH, ED, and PW. The investigations were done by APC, GO'SC, SF, IB, ZC, LGD, ME, JRW, YN, and AA. APC, IB, ZC, LGD, RL, RdlRR, AA, IH, and PW did the data visualization. The methodology was designed by

APC, SF, RL, RdlRR, IH, and ED; IH also provided the definition for post-hoc analysis. The project was coordinated and administered by SF, RL (for the biometrics components), RdlRR, IH, and ED. All authors were involved in preparation of the initial draft of the manuscript and were responsible for reviewing and editing the manuscript. All authors had full access to all study data and accept responsibility to submit for publication. The KOMET investigators included in the study collected and analysed clinical and molecular data of the patients they enrolled and critically reviewed the final manuscript.

Declaration of interests

PLW, SM, and ED receive research support from the Intramural Research Program of the National Institutes of Health and worked on this project as an official duty activity. PLW and SM also received funding from the Neurofibromatosis Therapeutics Acceleration Program for their work on developing and validating the PAINS-pNF and PII-pNF measures. SF has received speaker honoraria from Alexion, AstraZeneca Rare Disease and compensation for advice or lecturing from Alexion, AstraZeneca Rare Disease, and SpringWorks Therapeutics. IB received consultancy fees from Alexion, AstraZeneca Rare Disease and SpringWorks Therapeutics. LDG received consultancy fees from Alexion and AstraZeneca Rare Disease. ME received consultancy fees from Alexion, AstraZeneca Rare Disease. YN received honoraria from Ono, Alexion, AstraZeneca Rare Disease, Daiichi-Sankyo, Hisamitsu, Zimmer-Biomet, and Stryker, and received consulting or advisory role fees from AstraZeneca, Alexion, AstraZeneca Rare Disease, Boehringer, and Seikagaku. RL, RdlRR, AA, IH, and NL are employees of, and own stocks in, Alexion, AstraZeneca Rare Disease. SD is an employee of Merck Sharp & Dohme, a subsidiary Merck, Rahway, NJ, USA and owns stocks in Merck & Rahway, NJ, USA. PW received consultation fees from Alexion, AstraZeneca Rare Disease, AstraZeneca, and SpringWorks Therapeutics.APC received support from AstraZeneca for this study that was paid to the National Cancer Institute.; has received support for attending meetings from the America Association for Cancer Research, AstraZeneca, and Genentech; has a patent pending with Genentech; owns stock in Vanguard Healthcare; declares that the National Cancer Institute has received drugs from AstraZeneca, Genentech, Karyopharma, Pfizer, and Cybrexa, and is Chief Specialty Editor for *Precision Medicine Frontiers in Medicine*. GO'SC declares support from AstraZeneca for this study paid to the National Cancer Institute. GO'SC declares support from AstraZeneca for this study that was paid to the National Cancer Institute. ZC has received support from AstraZeneca paid to his institution (Sun Yat-sen University Cancer Center) for this study. JRW has received grants paid to his institution from NHMRC, Medical Research Future Fund, Cancer Council Victoria, Anheart therapeutics, Flicker of Hope, and Perpeutual; has received payment or honoraria for lectures, presentations, or speaker bureaus from AnHeart therapeutics, Roche and MSD; has participated on a data safety monitoring board of advisory board for Telix Pharmaceuticals.; and declares an unpaid leadership role in the management committee COGNO and the research advisory committee for the Mark Hughes Foundation.

Data sharing

AstraZeneca will consider requests for disclosure of clinical study participant-level data provided that participant privacy is assured through methods such as data de-identification, pseudonymisation, or anonymisation (as required by applicable law), and if such disclosure was included in the relevant study informed consent form or similar documentation. Qualified academic investigators can request participant-level clinical data and supporting documents (statistical analysis plan and protocol) pertaining to Alexion-sponsored studies. Further details regarding data availability and instructions for requesting information are available in the Alexion Clinical Trials Disclosure and Transparency Policy at https://www.alexionclinicaltrialtransparency.com/data-requests/.

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