Clinical Study Report Addendum Synopsis	
Drug Substance	Selumetinib
Study Code	D1346C00011
Edition Number	1.0
Date	13 December 2023
NCT Number	NCT04590235

A Phase 1 Open Label Study to Assess the Safety, Tolerability, Pharmacokinetics and Clinical Efficacy of Selumetinib (a Selective Mitogen Activated Protein Kinase Kinase [MEK] 1 Inhibitor) in Chinese Paediatric and Adult Patients with Neurofibromatosis Type 1 (NF1) and Inoperable Plexiform Neurofibromas (PN)

Study dates: First patient enrolled: 16 December 2020
Last patient last visit: 15 August 2023
The analyses presented in this report are based on a clinical data cut-off date of 15 August 2023

Phase of development: Phase I

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

Study Centre(s)

This study was conducted at 2 study centres in China.

Publications

Wang Z et al. Primary analysis of a Phase 1 study of selumetinib in Chinese pediatric and adult patients with neurofibromatosis type 1 and inoperable plexiform neurofibromas. Abstracts of the 2023 Neurofibromatosis (NF) Conference: 2023 Jun 24-27; Arizona, United States. Children's Tumor Foundation; 2023. p.189.

Yuan XJ et al. 402P Phase I study of selumetinib in Chinese pediatric and adult patients (pts) with neurofibromatosis type 1 (NF1) and inoperable plexiform neurofibromas (PN): Interim results. *Ann Oncol.* 2022 Nov 1;33:1599.

Objectives and Criteria for Evaluation

Table S1 Objectives and Endpoints

Objectives	Endpoints
Primary:	
To assess the safety and tolerability of selumetinib in Chinese paediatric and adult patients with NF1 and inoperable PN	**Paediatric and adult cohorts:** Safety and tolerability were evaluated in terms of AEs, clinical safety laboratory assessments, physical examination, vital signs, height/weight, ECG, echocardiogram, ophthalmologic assessment and performance status **Paediatric only:** Safety and tolerability were also evaluated in terms of bone growth and Tanner stages **Assessments related to AEs included:** • Occurrence/frequency • Relationship to IP as assessed by investigator • CTCAE grade • Seriousness • Death • AEs leading to discontinuation of IP • AEs of special interest

Objectives	Endpoints
To characterise the PK of selumetinib and its metabolite (N-desmethyl selumetinib) in Chinese paediatric and adult patients with NF1 and inoperable PN [a]	PK parameters for selumetinib and N-desmethyl selumetinib were derived from following single dose and multiple doses. [a] These included, but were not limited to: **After a single dose:** • AUC • AUC0-12 • AUC0-t • Cmax • tmax • t1/2 **After multiple doses:** • AUC0-12,ss • Cmax,ss • Rac
Secondary:	
To evaluate the clinical efficacy of selumetinib in Chinese paediatric and adult patients with NF1 and inoperable PN on ORR, DoR, PFS, TTP, and TTR	ORR was defined as the proportion of patients who had a complete response or confirmed partial response (defined as a target PN volume decrease ≥ 20% compared to baseline, confirmed by a consecutive scan within 3 to 6 months after first response), as determined by the investigator and independent central review per Response Evaluation in Neurofibromatosis and Schwannomatosis (REiNS) criteria. DoR was defined as the time from the date of first documented response (which was subsequently confirmed) until the date of documented progression or death in the absence of disease progression, as determined by the investigator and independent central review per REiNS criteria. PFS was defined as the time from the date of first dose until progression per REiNS criteria, as assessed by the investigator and independent central review, or death due to any cause. TTP was defined as the time from the date of first dose until progression per REiNS criteria, as assessed by the investigator and independent central review. TTR was defined as the time from the date of first dose until the date of first documented response (which is subsequently confirmed), as determined by the investigator and independent central review per REiNS criteria.

Objectives	Endpoints
To evaluate the effect of selumetinib on pain in Chinese paediatric and adult patients with NF1 and inoperable PN	• FLACC scale (3 years of age) • Faces Pain Scale - revised (4 to 17 years of age) • NRS-11 (adult cohort) • PII (adult cohort; self- and parent-reported in the paediatric cohort) • Pain Medication Survey (self-reported in the adult cohort; parent-reported in the paediatric cohort)
To determine the effect of selumetinib on HRQoL	• PedsQL (paediatric cohort; self- and parent-reported) • EORTC QLQ-C30 and PlexiQoL (adult cohort)
To determine the effect of selumetinib on physical functioning	• PROMIS (upper extremity; self- and parent-reported in the paediatric cohort) • PROMIS (mobility; self- and parent-reported in the paediatric cohort) • PROMIS Physical Function - Short Form 8c 7-day (adult cohort)
Exploratory:	
To evaluate PGIS of symptoms	• PGIS (adult cohort; self- and parent-reported in the paediatric cohort)
To evaluate PGIC in symptoms	• PGIC (adult cohort; self- and parent-reported in the paediatric cohort)
To determine the effect of selumetinib on disfigurement	• Photographic evaluation

[a] Not reported in this CSR. See the interim CSR for results.

AE = adverse event; AUC = area under the concentration-time curve from zero to infinity; AUC0-12 = area under the concentration-time curve from zero to 12 hours; AUC0-12,ss = area under the concentration-time curve from zero to 12 hours at steady-state; AUC0-t = area under the concentration-time curve from zero to the last measurable concentration; Cmax = maximum plasma drug concentration; Cmax,ss = maximum steady-state plasma concentration; CSR = Clinical Study Report; CTCAE = Common Terminology Criteria for Adverse Events; DoR = duration of response; ECG = electrocardiogram; EORTC QLQ-C30 = European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30; FLACC = Face, Legs, Activity, Cry, Consolability; HRQoL = health-related quality of life; IP = investigational product; NF1 = neurofibromatosis type 1; NRS = Numeric Rating Scale; ORR = objective response rate; PedsQL = Paediatric Quality of Life Inventory; PFS = progression-free survival; PGIC = patient's global impression of change; PGIS = patient's global impression of symptom severity; PII = Pain Interference Index; PK = pharmacokinetics; PlexiQoL = Plexiform Neurofibromas Quality of Life Scale; PN = plexiform neurofibroma; PROMIS = Patient-Reported Outcomes Measurement Information System; Rac = accumulation ratio; REiNS = Response Evaluation in Neurofibromatosis and Schwannomatosis; t1/2 = terminal half-life; tmax = time to maximum plasma drug concentration; TTP = time to progression; TTR = time to response.

Study Design

This was an open label, single-arm Phase I study with 2 independent cohorts to assess the safety, tolerability, pharmacokinetics (PK), and clinical efficacy of selumetinib in Chinese paediatric and adult patients with neurofibromatosis type 1 (NF1) and inoperable plexiform neurofibroma (PN) that required treatment due to symptoms or had the potential to develop

significant clinical complications. Approximately 16 patients were planned to be enrolled in each of one paediatric and one adult cohort. The Safety Review Committee evaluated preliminary tolerability, safety, and available PK data after the first 6 patients in both cohorts had been treated for approximately 3 cycles.

Intensive PK samples were collected from patients before and after the first single dose of selumetinib 25 mg/m^2 during Cycle 0 (the first 2 days of treatment were planned with a single-dose regimen of selumetinib before starting with the twice daily [BID] regimen) and pre-dose at Cycle 1, Day 1. From Cycle 1, Day 1, patients were administered multiple doses of selumetinib 25 mg/m^2 twice daily on a continuous schedule (28 days per cycle). Intensive PK samples were collected on Cycle 1, Day 8 in dose intervals for assessment of PK profiles at a steady state.

Safety assessments were performed at screening, at the end of each cycle up to the end of Cycle 4, every 2 cycles up to the end of Cycle 12, every 4 cycles up to the end of Cycle 24, and every 6 cycles thereafter, for as long as the patient remained on study treatment.

Unless clinically indicated otherwise, tumour assessments were obtained at screening and Cycle 4 and were to be obtained every 4 cycles (16 ± 1 weeks) relative to the date of the first dose for the first 2 years (24 cycles). From the end of Cycle 24, tumour assessments were to be performed every 6 cycles (24 ± 1 weeks) for as long as the patient remained on study treatment or until disease progression. Disfigurement assessments were performed at screening and were to be performed at the end of Cycles 8, 16, and 24, so long as the patient remained on study treatment.

Clinical outcome assessments (COAs) were performed at screening, at the end of each cycle up to the end of Cycle 4, every 2 cycles up to the end of Cycle 12, every 4 cycles up to the end of Cycle 24, and every 6 cycles thereafter, for as long as the patient remained on study treatment.

Target Population and Sample Size

Approximately 16 adult and 16 paediatric eligible Chinese patients with a clinical diagnosis of NF1 and inoperable PN that required treatment due to symptoms or with the potential to develop significant clinical complications, as judged by the investigator, were planned to be enrolled in each cohort in this study. At least 8 to 12 patients per cohort were required; and a minimum (min) of 6 patients each in the 3 to 11- and 12 to 17-year age groups, at the time of enrolment.

Any patient with a life-threatening illness, medical condition, or organ system dysfunction which, in the investigator’s opinion, could compromise the patient's safety, interfere with the absorption or metabolism of selumetinib, or put the study outcomes at undue risk was excluded from the study.

Investigational Product: Dosage, Mode of Administration, and Batch Numbers

Selumetinib was taken orally in a 10 mg (white) or 25 mg (blue) capsule. Eligible patients received a single oral dose of selumetinib 25 mg/m^2 at Cycle 0 and multiple doses of selumetinib were administered at 25 mg/m^2 BID from Cycle 1. The dosage was adjusted for changes in body surface area according to the nomogram.

- Batch numbers for selumetinib 10 mg: 3164167R, 3187749R, 3198867, 3205162
- Batch numbers for selumetinib 25 mg: 3174108R, 3185367R, 3204835

Duration of Treatment

Following the screening period (Day -28 to Day -1), all eligible patients received a single oral dose of selumetinib 25 mg/m^2 (Cycle 0). After a 2-day period following the single dose, patients received oral doses of selumetinib 25 mg/m^2 BID continuously for 28-day cycles starting at Cycle 1. Patients continued to receive selumetinib until progressive disease (PD) based on the investigator's decision or unacceptable drug-related toxicity, whichever occurred first.

Statistical Methods

Safety data were presented using descriptive statistics by cohort. Evaluations of safety included, but were not limited to, adverse events (AEs), clinical safety laboratory assessments, physical examination, vital signs, bone growth (paediatric cohort only), and Tanner stages (paediatric cohort only).

See the interim clinical study report (CSR) (data cut-off [DCO]: 30 January 2022) for details of the PK analysis.

Efficacy endpoints, including objective response rate (ORR), target PN volume change, time to response (TTR), duration of response (DoR), time to progression (TTP), and progression-free survival (PFS), were presented based on investigator and independent central review (ICR) assessment per the Response Evaluation in Neurofibromatosis and Schwannomatosis (REiNS) criteria.

COAs were evaluated and presented for pain, health-related quality of life (HRQoL), physical functioning, patients' global impression of symptom severity (PGIS), and patient's global impression of change (PGIC). The primary analysis of the COAs was based on descriptive statistics. In addition, change from baseline was analysed using a mixed model repeated measures approach.

Study Population

As of this final DCO (15 August 2023), all patients had terminated the study. The Chinese patients enrolled in this study represented the intended target population, as detailed in the interim CSR (DCO: 30 January 2022).

Paediatric Cohort

A total of 20 paediatric patients were enrolled. 16 received at least one dose of selumetinib and were included in the Safety Analysis Set. At the final DCO, all 16 patients had terminated and completed the study; 15 patients were still on treatment with selumetinib; and one patient had an early treatment discontinuation due to PD but completed the study. No patients reported important protocol deviations (IPD).

Adult Cohort

A total of 17 adult patients were enrolled. 16 received at least one dose of selumetinib and were included in the Safety Analysis Set. As of the final DCO, all 16 patients had terminated the study and 13 patients were still on treatment with selumetinib; 13 patients completed the study as planned; 2 discontinued because of 'patient decision', and one discontinued due to 'other' reasons. A total of 5 patients (31.3%) reported IPDs, mainly due to the lack of image acquisition related to the coronavirus disease 2019 (COVID-19) epidemic, however the results support the conclusion that these IPDs had limited impact on this study.

Summary of Efficacy Results

The efficacy results in this CSR provide cumulative data as of the final DCO (15 August 2023), when the last dosed patient had the chance to complete the Cycle 24 assessment.

Overall, selumetinib showed clinical efficacy in ORR, and tumour volume change, and continued to show clinical efficacy in pain intensity, physical function, quality of life (QoL) and disease symptoms in Chinese patients with NF1-PN.

Paediatric Cohort

According to the REiNS Criteria, based on investigator assessment, ORR was 81.3% (95% confidence interval [CI]: 54.4%, 96.0%), and BOR was as follows: no patient achieved complete response (CR), 13 patients (81.3%) achieved confirmed partial response (cPR), 2 patients (12.5%) achieved unconfirmed partial response (uPR), one patient (6.3%) achieved stable disease (SD), and no patient had PD documented as BOR based on the REiNS Criteria. Based on ICR assessment, ORR was 62.5% (95% CI: 35.4%, 84.8%), and BOR was as follows: no patient achieved CR, 10 patients (62.5%) achieved cPR, one patient (6.3%) achieved uPR, 4 patients (25.0%) achieved SD, and one patient (6.3%) had PD documented as BOR based on the REiNS Criteria. The difference in BOR assessment between the

investigator and ICR was mainly due to the judgement of uPR versus SD (2 cases). There were also 13 cPRs by investigator and 10 by ICR (ICR concluded the other 3 investigator cPRs were one uPR, one SD, and one PD).

According to the best change in target PN volume from baseline collected from the first dose to this DCO, tumour volume was reduced compared to baseline in 16/16 (100%) and 14/16 (87.5%) patients as per investigator assessment and ICR assessment, respectively. The mean (standard deviation [SDev]) best change in target PN volume from baseline was -42.30% (15.95%) based on investigator assessment and -29.56% (22.62%) based on ICR assessment.

As of this DCO, the median TTR was 3.7 (95% CI: 3.55, 7.39) months based on investigator assessment and 8.7 (95% CI: 3.55, 9.30) months based on ICR assessment; the median DoR, PFS, and TTP were not reached based on investigator or ICR assessment.

The COA questionnaires assessed the changes in pain management, physical function, HRQoL, and symptom severity of patients before and after receiving selumetinib. The Faces Pain Scale showed that the pain intensity of patients was lower than baseline during the treatment period, with a mean (SDev) change from baseline in pain score of -0.9 (1.03) at Cycle 24; the total score of the Pain Interference Index (PII) showed a decreasing trend of interference of pain on daily activities from baseline (mean [SDev] change from baseline at Cycle 24: -0.83 [0.86], self-reported; -0.64 [1.08] parent-reported); the Patient-Reported Outcomes Measurement Information System (PROMIS) showed a trend toward slight improvement in mobility and upper extremity physical function compared with baseline (mean [SDev] change from baseline at Cycle 24: self-reported mobility score of 3.0 [3.83] and upper extremity score of 0.4 [1.65]; parent-reported mobility score of 1.4 [3.71] and upper extremity score of 1.6 [2.41]); the Paediatric Quality of Life Inventory scale showed an improvement trend of patients' HRQoL compared with baseline during the treatment period (self- and parent-reported); PGIS and PGIC showed that the proportion of patients who reported no symptoms or very mild symptoms in terms of tumour pain, overall pain, and tumour-related problems increased during the treatment period compared with baseline, and most patients reported improvements in symptoms compared with baseline.

Adult Cohort

According to the REiNS Criteria, based on investigator assessment, the ORR was 37.5% (95% CI: 15.2%, 64.6%), and the BOR was as follows: no patient achieved CR, 6 patients (37.5%) achieved cPR, 5 patients (31.3%) achieved uPR, 5 patients (31.3%) achieved SD, and no patient had PD documented as BOR. Based on ICR assessment, the ORR was 31.3% (95% CI: 11.0%, 58.7%), and the BOR was as follows: no patient achieved CR, 5 patients (31.3%) achieved cPR, 3 patients (18.8%) achieved uPR, 7 patients (43.8%) achieved SD, and one patient (6.3%) had PD documented as BOR based on the REiNS Criteria. The difference

in BOR assessment between the investigator and ICR mainly lies in the judgment of uPR versus SD. The 5 patients with investigator-assessed uPR all received their first documented response of PR at their final assessment, thus did not have the opportunity to have the PR confirmed.

According to the best percent change in target PN volume from baseline collected from the first dose to this DCO, tumour volume was reduced compared to baseline in 16/16 (100%) and 14/16 (87.5%) patients as per investigator assessment and ICR assessment, respectively. At the end of Cycle 24, the mean (SDev) best change in target PN volume from baseline was -22.03% (10.64%) based on investigator assessment and -18.00% (29.19%) based on ICR assessment.

As of this DCO, the median TTR was 3.9 (95% CI: 3.55, not calculated [NC]) months based on investigator assessment and 7.9 (95% CI: 3.81, NC) months based on ICR assessment; the median DoR, PFS, and TTP were not reached based on either investigator or ICR assessment.

The COA questionnaire assessed the pain management, physical function, HRQoL and symptom severity of patients before and after treatment with selumetinib. The NRS-11 and PII scores of patients were generally maintained over time (NRS-11 overall pain and PII total score mean [SDev] change from baseline at Cycle 24: -1.0 [NC] and -0.21 [0.71], respectively); the overall results of the PROMIS scale showed that fluctuations were observed until Cycle 12, after which maintenance was observed; the EORTC QLQ-C30 scale showed a general deterioration trend, but the PlexiQoL scale showed an improvement trend in the HRQoL of patients (mean [SDev] change from baseline at Cycle 24: -0.9 [2.43]); PGIS showed that most patients had no worsening in severity of tumour pain, overall pain, and tumour-related problems compared with baseline; PGIC showed that most patients reported improvement in tumour pain, overall pain, and tumour-related problems at each time point compared with baseline.

Summary of PK Results

See the interim CSR (DCO: 30 January 2022) for details.

Summary of Safety Results

Overall, selumetinib monotherapy administered at 25 mg/m^2 BID was well tolerated and the safety was manageable in Chinese patients with NF1-related inoperable PN. No new safety concerns were identified during the study.

Paediatric Cohort

At this DCO, the median (min, maximum [max]) actual treatment duration was 22.80 (18.5, 30.8) months and the median total treatment duration was 23.26 (18.5, 30.8) months.

All 16 patients had at least one AE. The most common AEs (> 30%) were COVID-19, pyrexia, upper respiratory tract infection, blood albumin decreased, hyperuricaemia, paronychia, and rash. Except for COVID-19, most were known adverse drug reactions (ADRs) for selumetinib.

All 16 patients reported at least one treatment-related adverse event (TRAE).

Most reported AEs were Common Terminology Criteria for Adverse Events (CTCAE) Grade 1 or 2. There were 6 AEs of CTCAE Grade 3 that were reported in 3 (18.8%) patients. There were 3 (18.8%) patients with 5 AEs that were classed as serious adverse events (SAEs). All were assessed as not related to treatment. There were no CTCAE Grade 4 or 5 AEs. No deaths were reported.

No patients experienced AEs which led to study treatment discontinuation or dose reduction. A total of 10 (62.5%) patients experienced AEs which led to dose interruption.

7 patients (43.8%) reported adverse events of special interest (AESIs), most of which were known ADRs of selumetinib and none of which were CTCAE Grade 3 or higher.

No trends of unexpected clinically significant changes were observed in clinical laboratory evaluation, vital signs, electrocardiogram (ECG)/ echocardiogram (ECHO), and Tanner stages.

Adult Cohort

At this DCO, the median (min, max) actual treatment duration was 23.69 (7.5, 30.9) months and the median total treatment duration was 25.08 (8.6, 31.3) months.

All 16 patients had at least one AE. The most common AEs (> 40%) were dermatitis acneiform, hyperphosphatemia, AST increased, conjunctivitis, and hyperuricaemia, most of which were known ADRs for selumetinib.

All 16 patients reported at least one TRAE.

Most reported AEs were CTCAE Grade 1 or 2. AEs of CTCAE Grade 3 were reported in 4 (25.0%) patients (one event in each patient); 2 were considered possibly related to treatment. 2 (12.5%) patients reported 2 SAEs; both were considered unrelated to treatment. There were no CTCAE Grade 4 or 5 AEs. No deaths were reported.

No patients experienced AEs that led to study treatment discontinuation. 7 (43.8%) patients experienced AEs that led to dose interruption. One (6.3%) patient reported an AE of paronychia of CTCAE Grade 3 which was assessed to be treatment related and led to permanent dose reduction.

A total of 13 patients (81.3%) reported AESIs, all of which were known ADRs of selumetinib.

No trends of unexpected clinically significant changes were observed in clinical laboratory evaluation, vital signs, ECG, and ECHO.

Conclusions

As of the final DCO of this study, ie, when the last dosed patient had the chance to complete the Cycle 24 assessment, no new safety concerns were identified. Selumetinib monotherapy administered at 25 mg/m^2 BID was well tolerated and had a manageable safety profile in both paediatric and adult Chinese patients with NF1-related inoperable PN.

After continuous treatment with selumetinib, almost all patients experienced tumour shrinkage. Other supportive clinical outcome data showed that patients were relatively stable or improved compared with baseline in terms of pain, physical function, QoL, and pain interference. The results confirm the clinical efficacy of selumetinib (25 mg/m^2 BID) in Chinese paediatric and adult patients with NF1-related inoperable PN.