



Clinical trial results:

A multi-center, open-label, single-arm Phase I dose-escalation and Phase II dose-expansion study to evaluate the safety, tolerability, PK characteristics and anti-tumor activity of FCN-159 in adult and pediatric participants with neurofibromatosis type 1

Summary

EudraCT number	2021-001572-42
Trial protocol	ES IT PL
Global end of trial date	23 September 2024

Results information

Result version number	v1 (current)
This version publication date	20 February 2026
First version publication date	20 February 2026

Trial information

Trial identification

Sponsor protocol code	FCN-159-002
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04954001
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Shanghai Fosun Pharmaceutical Development Co., Ltd.
Sponsor organisation address	No. 1289, Yishan Road, Xuhui District, Shanghai, China, 200233
Public contact	Project Management, Shanghai Fosun Pharmaceutical Development Co., Ltd., +86 21- 33987558, chenleilei@fosunpharma.com
Scientific contact	Project Management, Shanghai Fosun Pharmaceutical Development Co., Ltd., +86 21- 33987558, chenleilei@fosunpharma.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	11 June 2025
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	23 September 2024
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Phase I:

-To evaluate the safety and tolerability of FCN-159 administered PO daily.

-To determine the maximum tolerated dose (MTD) and recommended Phase II dose (RP2D).

Phase II:

-To assess the efficacy of FCN-159 per REINS criteria.

Protection of trial subjects:

The clinical study protocol, ICF, eCRF, and other relevant materials for this study were approved by the IEC before the start of the study. IEC strictly followed the requirements of relevant laws and regulations to review these materials and issue approval files after approval. The entire trial process of this study complied with relevant laws and regulations, Good Clinical Practice, and the principles of the Declaration of Helsinki (2013). The ICF must be signed and dated by patients or their legal representatives, and the investigator who performs the informed consent process or the representative before any drug administration.

Background therapy:

The commonly used concomitant medications were supportive care for the target disease, corrective medications for adverse events, and treatment of medical history, including dermatological antibiotics and chemotherapy drugs, anti-inflammatory and anti-rheumatic drugs, and systemic anti-bacterial drugs, analgesics and systemic antihistamines, etc.

Evidence for comparator:

Not applicable

Actual start date of recruitment	16 March 2021
Long term follow-up planned	Yes
Long term follow-up rationale	Efficacy, Safety
Long term follow-up duration	35 Months
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	China: 82
Country: Number of subjects enrolled	United States: 3
Country: Number of subjects enrolled	Spain: 1
Worldwide total number of subjects	86
EEA total number of subjects	1

Notes:

Subjects enrolled per age group	
In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	86
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Phase I: a total of 19 Chinese patients (3 in the 4 mg dose group, 4 in the 6 mg dose group, 8 in the 8 mg dose group, and 4 in the 12 mg dose group) and 1 U.S. patient (8 mg dose group); Phase II: 63 Chinese patients and 3 non-Chinese patients (2 U.S. patients and 1 Spanish patient).

Pre-assignment

Screening details:

Adult patients diagnosed with symptomatic Neurofibromatosis type 1 with Plexiform neurofibroma (NF1 with PN) with PNs that was inoperable or had postoperative residual/recurrence.

Period 1

Period 1 title	Treatment period - Phase I and Phase II (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Blinding implementation details:

This is an open-label study

Arms

Are arms mutually exclusive?	Yes
Arm title	Phase I - 4 mg FCN-159

Arm description:

Participants enrolled in Phase I dose-finding clinical trial assigned to receive 4 mg FCN-159.

Arm type	Experimental
Investigational medicinal product name	FCN-159
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

4 mg FCN-159 tablets were orally administered once daily, for continuous use, with 28 days as a cycle.

Arm title	Phase I - 6 mg FCN-159
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Arm description:

Participants enrolled in Phase I dose-finding clinical trial assigned to receive 6 mg FCN-159.

Arm type	Experimental
Investigational medicinal product name	FCN-159
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

6 mg FCN-159 tablets were orally administered once daily, for continuous use, with 28 days as a cycle.

Arm title	Phase I - 8 mg FCN-159
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Arm description:

Participants enrolled in Phase I dose-finding clinical trial assigned to receive 8 mg FCN-159.

Arm type	Experimental
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Investigational medicinal product name	FCN-159
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

8 mg FCN-159 tablets were orally administered once daily, for continuous use, with 28 days as a cycle.

Arm title	Phase I - 12 mg FCN-159
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Arm description:

Participants enrolled in Phase I dose-finding clinical trial assigned to receive 12 mg FCN-159.

Arm type	Experimental
Investigational medicinal product name	FCN-159
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

12 mg FCN-159 tablets were orally administered once daily, for continuous use, with 28 days as a cycle.

Arm title	Phase II - 8 mg FCN-159
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Arm description:

Participants enrolled in Phase II dose-expansion clinical trial assigned to receive Recommended Phase II dose (RP2D) of 8 mg FCN-159.

Arm type	Experimental
Investigational medicinal product name	FCN-159
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

8 mg FCN-159 tablets were orally administered once daily, for continuous use, with 28 days as a cycle.

Number of subjects in period 1	Phase I - 4 mg FCN-159	Phase I - 6 mg FCN-159	Phase I - 8 mg FCN-159
Started	3	4	9
Completed	3	4	9
Not completed	0	0	0
Consent withdrawn by subject	-	-	-
Adverse event, non-fatal	-	-	-
Other	-	-	-
Death	-	-	-

Number of subjects in period 1	Phase I - 12 mg FCN-159	Phase II - 8 mg FCN-159
Started	4	66
Completed	3	54
Not completed	1	12
Consent withdrawn by subject	-	8

Adverse event, non-fatal	1	1
Other	-	2
Death	-	1

Baseline characteristics

Reporting groups

Reporting group title	Phase I - 4 mg FCN-159
Reporting group description:	
Participants enrolled in Phase I dose-finding clinical trial assigned to receive 4 mg FCN-159.	
Reporting group title	Phase I - 6 mg FCN-159
Reporting group description:	
Participants enrolled in Phase I dose-finding clinical trial assigned to receive 6 mg FCN-159.	
Reporting group title	Phase I - 8 mg FCN-159
Reporting group description:	
Participants enrolled in Phase I dose-finding clinical trial assigned to receive 8 mg FCN-159.	
Reporting group title	Phase I - 12 mg FCN-159
Reporting group description:	
Participants enrolled in Phase I dose-finding clinical trial assigned to receive 12 mg FCN-159.	
Reporting group title	Phase II - 8 mg FCN-159
Reporting group description:	
Participants enrolled in Phase II dose-expansion clinical trial assigned to receive Recommended Phase II dose (RP2D) of 8 mg FCN-159.	

Reporting group values	Phase I - 4 mg FCN-159	Phase I - 6 mg FCN-159	Phase I - 8 mg FCN-159
Number of subjects	3	4	9
Age categorical			
Units: Subjects			
Adults (18-64 years)	3	4	9
Gender categorical			
Units: Subjects			
Female	0	0	6
Male	3	4	3

Reporting group values	Phase I - 12 mg FCN-159	Phase II - 8 mg FCN-159	Total
Number of subjects	4	66	86
Age categorical			
Units: Subjects			
Adults (18-64 years)	4	66	86
Gender categorical			
Units: Subjects			
Female	3	28	37
Male	1	38	49

End points

End points reporting groups

Reporting group title	Phase I - 4 mg FCN-159
Reporting group description: Participants enrolled in Phase I dose-finding clinical trial assigned to receive 4 mg FCN-159.	
Reporting group title	Phase I - 6 mg FCN-159
Reporting group description: Participants enrolled in Phase I dose-finding clinical trial assigned to receive 6 mg FCN-159.	
Reporting group title	Phase I - 8 mg FCN-159
Reporting group description: Participants enrolled in Phase I dose-finding clinical trial assigned to receive 8 mg FCN-159.	
Reporting group title	Phase I - 12 mg FCN-159
Reporting group description: Participants enrolled in Phase I dose-finding clinical trial assigned to receive 12 mg FCN-159.	
Reporting group title	Phase II - 8 mg FCN-159
Reporting group description: Participants enrolled in Phase II dose-expansion clinical trial assigned to receive Recommended Phase II dose (RP2D) of 8 mg FCN-159.	
Subject analysis set title	Phase II - 8 mg FCN-159 - ITT set
Subject analysis set type	Intention-to-treat
Subject analysis set description: Intent-to-treat (ITT) set: It included patients who signed the informed consent form (ICF) and had received at least one dose of FCN-159 Tablets	

Primary: Phase I - The occurrence of dose-limiting toxicity (DLT)

End point title	Phase I - The occurrence of dose-limiting toxicity (DLT) ^{[1][2]}
End point description: DLT analysis set: All patients who met the DLT evaluation criteria enrolled in the dose escalation part, regardless of whether DLT occurred during the DLT observation period. DLT = Dose-Limited Toxicity * The results present information only for Chinese participants.	
End point type	Primary
End point timeframe: 28 days after the dose of FCN-159	
Notes:	

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: No statistical analysis was done for this end point

[2] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: This end point is applicable only for arms in Phase I.

End point values	Phase I - 4 mg FCN-159	Phase I - 6 mg FCN-159	Phase I - 8 mg FCN-159	Phase I - 12 mg FCN-159
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	3	3	6	3
Units: number				
Subjects with any TEAE	0	0	1	3
DLT of Grade 3: folliculitis	0	0	1	3

Statistical analyses

No statistical analyses for this end point

Primary: Phase I - Maximum tolerated dose and recommended Phase II dose (RP2D) in clinical practice

End point title	Phase I - Maximum tolerated dose and recommended Phase II dose (RP2D) in clinical practice ^{[3][4]}
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End point description:

MTD is defined as the maximum dose level with a DLT incidence rate of < 33% (0/3 or 1/6 cases). After integrating the Phase I PK, PD, efficacy, and safety data, it was decided to set the adult RP2D at 8 mg after full discussion at the Safety Management Committee (SMC) meeting.

* The results present information only for Chinese participants.

End point type	Primary
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End point timeframe:

Approximately 6-9 months for MTD and RP2D (phase I duration)

Notes:

[3] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: No statistical analysis was done for this end point

[4] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: This end point is applicable only for arms in Phase I.

End point values	Phase I - 4 mg FCN-159	Phase I - 6 mg FCN-159	Phase I - 8 mg FCN-159	Phase I - 12 mg FCN-159
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	3	3	6	3
Units: percent				
number (not applicable)				
Subjects with any TEAE	0	0	16.7	100

Statistical analyses

No statistical analyses for this end point

Primary: Phase II - ORR assessed by the investigator: Best overall response

End point title	Phase II - ORR assessed by the investigator: Best overall response ^[5]
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End point description:

Objective response rate (ORR) is defined as Proportion of patients achieving confirmed disease response (Complete response (CR) or Partial response (PR)). CR is defined as the disappearance of the target lesion. PR is defined as a ≥20% reduction in the volume of the target PN from baseline. Both CR and PR were confirmed by reassessment over at least 3 months.

* The results present information only for Chinese participants.

End point type	Primary
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End point timeframe:

Through study completion, an average of 2 years

Notes:

[5] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: No statistical analysis was done for this end point

End point values	Phase II - 8 mg FCN-159 - ITT set			
Subject group type	Subject analysis set			
Number of subjects analysed	63			
Units: percent				
number (not applicable)				
Complete response (CR)	0			
Partial response (PR)	42.9			
Stable disease (SD)	52.4			
Stable disease (SD) $\geq$ 6 months	41.3			
Progressive disease (PD)	0			
Not evaluable (NE)	4.8			

Statistical analyses

No statistical analyses for this end point

Primary: Phase II - ORR assessed by the investigator

End point title	Phase II - ORR assessed by the investigator ^[6]
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End point description:

Objective response rate (ORR), defined as the proportion of patients with disease response (Responsive Disease, RD) confirmed using volumetric MRI analysis.

Clinical benefit rate (CBR), defined as assessments including CR, PR, and SD lasting over 6 months.

Disease control rate (DCR), defined as the percentage of cases with best response (PR or CR) and stable disease (SD) after treatment to the number of evaluable cases.

Data includes subject of Intent-to-treat (ITT) set: It included patients who signed the informed consent form (ICF) and had received at least one dose of FCN-159 Tablets.

* The results present information only for Chinese participants.

End point type	Primary
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End point timeframe:

Through study completion, an average of 2 years

Notes:

[6] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: No statistical analysis was done for this end point

End point values	Phase II - 8 mg FCN-159 - ITT set			
Subject group type	Subject analysis set			
Number of subjects analysed	63			
Units: percent				
number (confidence interval 95%)				
Objective Response Rate (ORR)	42.9 (30.5 to 56.0)			

Clinical benefit rate (CBR)	84.1 (72.7 to 92.1)			
Disease control rate (DCR)	95.2 (86.7 to 99.0)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Since the first administered dose till the end of safety follow up period (30 days of the last dose)

Adverse event reporting additional description:

*The results present information only for Chinese participants.

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	26.0
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Reporting groups

Reporting group title	Phase I - 4 mg FCN-159
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Reporting group description:

Participants enrolled in Phase I dose-finding clinical trial assigned to receive 4 mg FCN-159.

Reporting group title	Phase I - 6 mg FCN-159
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Reporting group description:

Participants enrolled in Phase I dose-finding clinical trial assigned to receive 6 mg FCN-159.

Reporting group title	Phase I - 8 mg FCN-159
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Reporting group description:

Participants enrolled in Phase I dose-finding clinical trial assigned to receive 8 mg FCN-159.

Reporting group title	Phase I - 12 mg FCN-159
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Reporting group description:

Participants enrolled in Phase I dose-finding clinical trial assigned to receive 12 mg FCN-159.

Reporting group title	Phase II - 8 mg FCN-159
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Reporting group description:

Participants enrolled in Phase II dose-expansion clinical trial assigned to receive Recommended Phase II dose (RP2D) of 8 mg FCN-159.

Serious adverse events	Phase I - 4 mg FCN-159	Phase I - 6 mg FCN-159	Phase I - 8 mg FCN-159
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 3 (33.33%)	0 / 4 (0.00%)	0 / 8 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Injury, poisoning and procedural complications			
Head injury			
subjects affected / exposed	0 / 3 (0.00%)	0 / 4 (0.00%)	0 / 8 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Spinal compression fracture			

subjects affected / exposed	0 / 3 (0.00%)	0 / 4 (0.00%)	0 / 8 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Scapula fracture			
subjects affected / exposed	0 / 3 (0.00%)	0 / 4 (0.00%)	0 / 8 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ankle fracture			
subjects affected / exposed	0 / 3 (0.00%)	0 / 4 (0.00%)	0 / 8 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	0 / 3 (0.00%)	0 / 4 (0.00%)	0 / 8 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Vertebrobasilar artery dissection			
subjects affected / exposed	0 / 3 (0.00%)	0 / 4 (0.00%)	0 / 8 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Hemolytic anemia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 4 (0.00%)	0 / 8 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eye disorders			
Rhegmatogenous retinal detachment			
subjects affected / exposed	1 / 3 (33.33%)	0 / 4 (0.00%)	0 / 8 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Duodenal ulcer			

subjects affected / exposed	0 / 3 (0.00%)	0 / 4 (0.00%)	0 / 8 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemorrhoidal haemorrhage			
subjects affected / exposed	0 / 3 (0.00%)	0 / 4 (0.00%)	0 / 8 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Drug-induced liver injury			
subjects affected / exposed	0 / 3 (0.00%)	0 / 4 (0.00%)	0 / 8 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Pneumothorax spontaneous			
subjects affected / exposed	0 / 3 (0.00%)	0 / 4 (0.00%)	0 / 8 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
IgA nephropathy			
subjects affected / exposed	0 / 3 (0.00%)	0 / 4 (0.00%)	0 / 8 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Soft tissue infection			
subjects affected / exposed	0 / 3 (0.00%)	0 / 4 (0.00%)	0 / 8 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
COVID-19			
subjects affected / exposed	0 / 3 (0.00%)	0 / 4 (0.00%)	0 / 8 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Upper respiratory tract infection			

subjects affected / exposed	0 / 3 (0.00%)	0 / 4 (0.00%)	0 / 8 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary tuberculosis			
subjects affected / exposed	0 / 3 (0.00%)	0 / 4 (0.00%)	0 / 8 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Phase I - 12 mg FCN-159	Phase II - 8 mg FCN-159	
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 4 (25.00%)	13 / 63 (20.63%)	
number of deaths (all causes)	0	1	
number of deaths resulting from adverse events	0	0	
Injury, poisoning and procedural complications			
Head injury			
subjects affected / exposed	0 / 4 (0.00%)	1 / 63 (1.59%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal compression fracture			
subjects affected / exposed	0 / 4 (0.00%)	1 / 63 (1.59%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Scapula fracture			
subjects affected / exposed	0 / 4 (0.00%)	1 / 63 (1.59%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ankle fracture			
subjects affected / exposed	0 / 4 (0.00%)	1 / 63 (1.59%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Atrial fibrillation			

subjects affected / exposed	0 / 4 (0.00%)	1 / 63 (1.59%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Vertebrobasilar artery dissection			
subjects affected / exposed	1 / 4 (25.00%)	0 / 63 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Hemolytic anemia			
subjects affected / exposed	0 / 4 (0.00%)	1 / 63 (1.59%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Rhegmatogenous retinal detachment			
subjects affected / exposed	0 / 4 (0.00%)	0 / 63 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Duodenal ulcer			
subjects affected / exposed	0 / 4 (0.00%)	1 / 63 (1.59%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhoidal haemorrhage			
subjects affected / exposed	0 / 4 (0.00%)	1 / 63 (1.59%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Drug-induced liver injury			
subjects affected / exposed	0 / 4 (0.00%)	1 / 63 (1.59%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Pneumothorax spontaneous			

subjects affected / exposed	0 / 4 (0.00%)	1 / 63 (1.59%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
IgA nephropathy			
subjects affected / exposed	0 / 4 (0.00%)	1 / 63 (1.59%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Soft tissue infection			
subjects affected / exposed	0 / 4 (0.00%)	2 / 63 (3.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
COVID-19			
subjects affected / exposed	0 / 4 (0.00%)	1 / 63 (1.59%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper respiratory tract infection			
subjects affected / exposed	0 / 4 (0.00%)	1 / 63 (1.59%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary tuberculosis			
subjects affected / exposed	0 / 4 (0.00%)	1 / 63 (1.59%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Phase I - 4 mg FCN-159	Phase I - 6 mg FCN-159	Phase I - 8 mg FCN-159
Total subjects affected by non-serious adverse events			
subjects affected / exposed	0 / 3 (0.00%)	4 / 4 (100.00%)	8 / 8 (100.00%)
Investigations			
Blood creatine phosphokinase increased			

subjects affected / exposed	0 / 3 (0.00%)	3 / 4 (75.00%)	5 / 8 (62.50%)
occurrences (all)	0	3	5
Blood lactate dehydrogenase increased			
subjects affected / exposed	0 / 3 (0.00%)	2 / 4 (50.00%)	1 / 8 (12.50%)
occurrences (all)	0	2	1
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 3 (0.00%)	2 / 4 (50.00%)	0 / 8 (0.00%)
occurrences (all)	0	2	0
Urinary occult blood positive			
subjects affected / exposed	0 / 3 (0.00%)	1 / 4 (25.00%)	3 / 8 (37.50%)
occurrences (all)	0	1	3
Weight increased			
subjects affected / exposed	0 / 3 (0.00%)	1 / 4 (25.00%)	3 / 8 (37.50%)
occurrences (all)	0	1	3
Blood alkaline phosphatase increased			
subjects affected / exposed	0 / 3 (0.00%)	1 / 4 (25.00%)	4 / 8 (50.00%)
occurrences (all)	0	1	4
Alanine aminotransferase increased			
subjects affected / exposed	0 / 3 (0.00%)	2 / 4 (50.00%)	1 / 8 (12.50%)
occurrences (all)	0	2	1
Blood fibrinogen increased			
subjects affected / exposed	0 / 3 (0.00%)	0 / 4 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Protein urine present			
subjects affected / exposed	0 / 3 (0.00%)	3 / 4 (75.00%)	3 / 8 (37.50%)
occurrences (all)	0	3	3
Electrocardiogram T wave abnormal			
subjects affected / exposed	0 / 3 (0.00%)	1 / 4 (25.00%)	0 / 8 (0.00%)
occurrences (all)	0	1	0
Blood uric acid increased			
subjects affected / exposed	0 / 3 (0.00%)	3 / 4 (75.00%)	2 / 8 (25.00%)
occurrences (all)	0	3	2
pH urine decreased			

subjects affected / exposed	0 / 3 (0.00%)	3 / 4 (75.00%)	4 / 8 (50.00%)
occurrences (all)	0	3	4
Specific gravity urine increased			
subjects affected / exposed	0 / 3 (0.00%)	3 / 4 (75.00%)	4 / 8 (50.00%)
occurrences (all)	0	3	4
Bile acids increased			
subjects affected / exposed	0 / 3 (0.00%)	2 / 4 (50.00%)	0 / 8 (0.00%)
occurrences (all)	0	2	0
Blood urea increased			
subjects affected / exposed	0 / 3 (0.00%)	3 / 4 (75.00%)	2 / 8 (25.00%)
occurrences (all)	0	3	2
Urobilinogen urine increased			
subjects affected / exposed	0 / 3 (0.00%)	3 / 4 (75.00%)	2 / 8 (25.00%)
occurrences (all)	0	3	2
QRS axis abnormal			
subjects affected / exposed	0 / 3 (0.00%)	1 / 4 (25.00%)	1 / 8 (12.50%)
occurrences (all)	0	1	1
Urine ketone body present			
subjects affected / exposed	0 / 3 (0.00%)	1 / 4 (25.00%)	3 / 8 (37.50%)
occurrences (all)	0	1	3
pH urine increased			
subjects affected / exposed	0 / 3 (0.00%)	2 / 4 (50.00%)	1 / 8 (12.50%)
occurrences (all)	0	2	1
Blood bilirubin increased			
subjects affected / exposed	0 / 3 (0.00%)	3 / 4 (75.00%)	2 / 8 (25.00%)
occurrences (all)	0	3	2
Immunoglobulins increased			
subjects affected / exposed	0 / 3 (0.00%)	1 / 4 (25.00%)	2 / 8 (25.00%)
occurrences (all)	0	1	2
Prealbumin decreased			
subjects affected / exposed	0 / 3 (0.00%)	0 / 4 (0.00%)	2 / 8 (25.00%)
occurrences (all)	0	0	2
White blood cells urine positive			
subjects affected / exposed	0 / 3 (0.00%)	1 / 4 (25.00%)	2 / 8 (25.00%)
occurrences (all)	0	1	2
Cardiac disorders			

Tricuspid valve incompetence subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	3 / 4 (75.00%) 3	3 / 8 (37.50%) 3
Mitral valve incompetence subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	3 / 4 (75.00%) 3	2 / 8 (25.00%) 2
Sinus arrhythmia subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	1 / 4 (25.00%) 1	2 / 8 (25.00%) 2
Blood and lymphatic system disorders Anemia subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	0 / 4 (0.00%) 0	2 / 8 (25.00%) 2
Gastrointestinal disorders Mouth ulceration subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	0 / 4 (0.00%) 0	1 / 8 (12.50%) 1
Diarrhoea subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	2 / 4 (50.00%) 2	3 / 8 (37.50%) 3
Constipation subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	0 / 4 (0.00%) 0	4 / 8 (50.00%) 4
Stomatitis subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	2 / 4 (50.00%) 2	5 / 8 (62.50%) 5
Respiratory, thoracic and mediastinal disorders Epistaxis subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	0 / 4 (0.00%) 0	1 / 8 (12.50%) 1
Cough subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	0 / 4 (0.00%) 0	0 / 8 (0.00%) 0
Pulmonary mass subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	3 / 4 (75.00%) 3	0 / 8 (0.00%) 0

Skin and subcutaneous tissue disorders			
Folliculitis			
subjects affected / exposed	0 / 3 (0.00%)	1 / 4 (25.00%)	4 / 8 (50.00%)
occurrences (all)	0	1	4
Paronychia			
subjects affected / exposed	0 / 3 (0.00%)	2 / 4 (50.00%)	3 / 8 (37.50%)
occurrences (all)	0	2	3
Dermatitis			
subjects affected / exposed	0 / 3 (0.00%)	0 / 4 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Alopecia			
subjects affected / exposed	0 / 3 (0.00%)	1 / 4 (25.00%)	4 / 8 (50.00%)
occurrences (all)	0	1	4
Urticaria			
subjects affected / exposed	0 / 3 (0.00%)	0 / 4 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Dry skin			
subjects affected / exposed	0 / 3 (0.00%)	0 / 4 (0.00%)	1 / 8 (12.50%)
occurrences (all)	0	0	1
Pruritus			
subjects affected / exposed	0 / 3 (0.00%)	0 / 4 (0.00%)	2 / 8 (25.00%)
occurrences (all)	0	0	2
Rash			
subjects affected / exposed	0 / 3 (0.00%)	2 / 4 (50.00%)	2 / 8 (25.00%)
occurrences (all)	0	2	2
Drug eruption			
subjects affected / exposed	0 / 3 (0.00%)	2 / 4 (50.00%)	2 / 8 (25.00%)
occurrences (all)	0	2	2
Infections and infestations			
Upper respiratory tract infection			
subjects affected / exposed	0 / 3 (0.00%)	2 / 4 (50.00%)	1 / 8 (12.50%)
occurrences (all)	0	2	1
COVID-19			
subjects affected / exposed	0 / 3 (0.00%)	3 / 4 (75.00%)	2 / 8 (25.00%)
occurrences (all)	0	3	2
Pharyngitis			

subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	0 / 4 (0.00%) 0	0 / 8 (0.00%) 0
Metabolism and nutrition disorders			
Hypercholesterolemia			
subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	0 / 4 (0.00%) 0	0 / 8 (0.00%) 0
Dyslipidaemia			
subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	2 / 4 (50.00%) 2	2 / 8 (25.00%) 2
Hypophosphataemia			
subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	2 / 4 (50.00%) 2	1 / 8 (12.50%) 1

Non-serious adverse events	Phase I - 12 mg FCN-159	Phase II - 8 mg FCN-159	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	4 / 4 (100.00%)	63 / 63 (100.00%)	
Investigations			
Blood creatine phosphokinase increased			
subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	25 / 63 (39.68%) 25	
Blood lactate dehydrogenase increased			
subjects affected / exposed occurrences (all)	3 / 4 (75.00%) 3	25 / 63 (39.68%) 25	
Aspartate aminotransferase increased			
subjects affected / exposed occurrences (all)	1 / 4 (25.00%) 1	28 / 63 (44.44%) 28	
Urinary occult blood positive			
subjects affected / exposed occurrences (all)	1 / 4 (25.00%) 1	20 / 63 (31.75%) 20	
Weight increased			
subjects affected / exposed occurrences (all)	3 / 4 (75.00%) 3	17 / 63 (26.98%) 17	
Blood alkaline phosphatase increased			
subjects affected / exposed occurrences (all)	2 / 4 (50.00%) 2	18 / 63 (28.57%) 18	

Alanine aminotransferase increased subjects affected / exposed occurrences (all)	1 / 4 (25.00%) 1	17 / 63 (26.98%) 17
Blood fibrinogen increased subjects affected / exposed occurrences (all)	4 / 4 (100.00%) 4	18 / 63 (28.57%) 18
Protein urine present subjects affected / exposed occurrences (all)	1 / 4 (25.00%) 1	13 / 63 (20.63%) 13
Electrocardiogram T wave abnormal subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	14 / 63 (22.22%) 14
Blood uric acid increased subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	10 / 63 (15.87%) 10
pH urine decreased subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	5 / 63 (7.94%) 5
Specific gravity urine increased subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	5 / 63 (7.94%) 5
Bile acids increased subjects affected / exposed occurrences (all)	1 / 4 (25.00%) 1	9 / 63 (14.29%) 9
Blood urea increased subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	8 / 63 (12.70%) 8
Urobilinogen urine increased subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	5 / 63 (7.94%) 5
QRS axis abnormal subjects affected / exposed occurrences (all)	3 / 4 (75.00%) 3	5 / 63 (7.94%) 5
Urine ketone body present subjects affected / exposed occurrences (all)	2 / 4 (50.00%) 2	3 / 63 (4.76%) 3

pH urine increased subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	5 / 63 (7.94%) 5	
Blood bilirubin increased subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	2 / 63 (3.17%) 2	
Immunoglobulins increased subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	2 / 63 (3.17%) 2	
Prealbumin decreased subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	3 / 63 (4.76%) 3	
White blood cells urine positive subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	1 / 63 (1.59%) 1	
Cardiac disorders Tricuspid valve incompetence subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	12 / 63 (19.05%) 12	
Mitral valve incompetence subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	11 / 63 (17.46%) 11	
Sinus arrhythmia subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	8 / 63 (12.70%) 8	
Blood and lymphatic system disorders Anemia subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	13 / 63 (20.63%) 13	
Gastrointestinal disorders Mouth ulceration subjects affected / exposed occurrences (all)	3 / 4 (75.00%) 3	37 / 63 (58.73%) 37	
Diarrhoea subjects affected / exposed occurrences (all)	2 / 4 (50.00%) 2	28 / 63 (44.44%) 28	
Constipation			

subjects affected / exposed occurrences (all)	2 / 4 (50.00%) 2	11 / 63 (17.46%) 11	
Stomatitis subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	5 / 63 (7.94%) 5	
Respiratory, thoracic and mediastinal disorders			
Epistaxis subjects affected / exposed occurrences (all)	1 / 4 (25.00%) 1	15 / 63 (23.81%) 15	
Cough subjects affected / exposed occurrences (all)	1 / 4 (25.00%) 1	13 / 63 (20.63%) 13	
Pulmonary mass subjects affected / exposed occurrences (all)	1 / 4 (25.00%) 1	6 / 63 (9.52%) 6	
Skin and subcutaneous tissue disorders			
Folliculitis subjects affected / exposed occurrences (all)	4 / 4 (100.00%) 4	49 / 63 (77.78%) 49	
Paronychia subjects affected / exposed occurrences (all)	3 / 4 (75.00%) 3	35 / 63 (55.56%) 35	
Dermatitis subjects affected / exposed occurrences (all)	3 / 4 (75.00%) 3	25 / 63 (39.68%) 25	
Alopecia subjects affected / exposed occurrences (all)	3 / 4 (75.00%) 3	20 / 63 (31.75%) 20	
Urticaria subjects affected / exposed occurrences (all)	1 / 4 (25.00%) 1	18 / 63 (28.57%) 18	
Dry skin subjects affected / exposed occurrences (all)	2 / 4 (50.00%) 2	14 / 63 (22.22%) 14	
Pruritus			

subjects affected / exposed occurrences (all)	2 / 4 (50.00%) 2	10 / 63 (15.87%) 10	
Rash subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	4 / 63 (6.35%) 4	
Drug eruption subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	3 / 63 (4.76%) 3	
Infections and infestations Upper respiratory tract infection subjects affected / exposed occurrences (all)	3 / 4 (75.00%) 3	37 / 63 (58.73%) 37	
COVID-19 subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	17 / 63 (26.98%) 17	
Pharyngitis subjects affected / exposed occurrences (all)	2 / 4 (50.00%) 2	13 / 63 (20.63%) 13	
Metabolism and nutrition disorders Hypercholesterolemia subjects affected / exposed occurrences (all)	1 / 4 (25.00%) 1	13 / 63 (20.63%) 13	
Dyslipidaemia subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	5 / 63 (7.94%) 5	
Hypophosphataemia subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	1 / 63 (1.59%) 1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
10 December 2020	Protocol, Version 2.1 • Data summary from the first-in-human study of FCN-159 in patients with melanoma (including clinical PK and safety data for 0.2 mg-6 mg) was added as the basis for FCN-159 dose bridging in patients with NF1 • The starting dose was increased from 1 mg to 4 mg based on updated FCN-159 data in patients with melanoma • The last 13 lung cancer-specific questions were deleted from the EORTC QLQ-C30 (V3.0) quality-of-life scale in Attachment 12.
19 February 2021	Protocol, Version 3.0 • Patient numbers were increased (42 adults in Phase I, 55 adults in Phase II) • Study sites were expanded (~10 sites for Phase I, ~30 sites for Phase II) • CYP2C9 enzyme polymorphism testing was added. • Treatment duration was modified to "the administration of FCN-159 Tablets was continued until progressive disease or other criteria for termination of treatment were met" • Tumor assessment frequency was adjusted from "every 3 cycles in the first year, every 6 cycles thereafter" to "every 4 cycles in the first 2 years, every 6 cycles thereafter" • Functional scales were added
19 March 2021	Protocol, Version 3.1 • Safety Management Committee (SMC) was added • Management and prevention of adverse events (e.g., skin toxicity, hepatotoxicity, gastrointestinal events, LVEF, ocular toxicity) were refined
22 May 2021	Protocol, Version 3.2 • PD testing was added in Phase I to better analyze dose-response relationships and determine the optimal recommended phase II dose • The patient age range was revised to ">18 and ≤70 years • Both Phase I and II enrollment populations were revised to "patients with symptomatic plexiform fibroma" • Strong CYP2C8 and CYP2C9 inhibitors or inducers (including moderate inducers) as prohibited drugs were added • PK sampling times were adjusted based on tumor assessment cycles • It was specified that efficacy assessment would follow REINS criteria
13 October 2021	Protocol, Version 4.0 • 3D laser scanning for NF1 with PNs evaluation was deleted • The adult RP2D of 8 mg was confirmed by the SMC meeting based on Phase I data, and this information was added • Specific ophthalmologic examination items were added to avoid inconsistent items in eye examination of each site • A single ECG was changed to three ECGs, and ECG frequency was reduced in Phase II

11 June 2022	Protocol, Version 5.0 • The administration under fasting was adjusted to not requiring fasting state based on the food effect test. • Family history of sudden cardiac death, acute neurological events, and concurrent use of anticoagulants were added as exclusion criteria. • Pharmacokinetic blood collection time points were updated. • ERK phosphorylation inhibition assessment was updated. • Amylase testing was replaced with lipase testing during the screening/baseline period. • Ophthalmologic function and airway function evaluations for orbital PN were deleted. • Delete impulse concussion pulmonary function methodImpulse oscillometry was deleted. • Assessments for plexiform neurofibromas affecting speech/swallowing were deleted
29 December 2023	Protocol, Version 6.2 • The investigator-assessed ORR was adjusted to the primary endpoint, while the IRC-assessed ORR was adjusted to a secondary endpoint

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

<http://www.ncbi.nlm.nih.gov/pubmed/37400844>