



## Clinical trial results:

### Phase IIa/IIb Clinical Trial of NC-6004 in Combination with Pembrolizumab in Subjects with Recurrent or Metastatic Squamous Cell Carcinoma of the Head and Neck Who Have Failed Platinum or a Platinum-containing Regimen

#### Summary

EudraCT number	2018-003959-37
Trial protocol	HU PL CZ HR
Global end of trial date	30 June 2022

#### Results information

Result version number	v1 (current)
This version publication date	15 March 2024
First version publication date	15 March 2024
Summary attachment (see zip file)	CSR Synopsis (2023_01_05_NC-6004-009_CSR Synopsis.pdf)

#### Trial information

##### Trial identification

Sponsor protocol code	NC-6004-009
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##### Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03771820
WHO universal trial number (UTN)	-

Notes:

#### Sponsors

Sponsor organisation name	Nano Carrier Co, Ltd
Sponsor organisation address	Ohnoya-Kyobashi Bldg 1-4-10 Kyobashi, Chuo-ku, Tokyo, Japan, 104-0031
Public contact	Study Director, NanoCarrier Co, Ltd., +81 3-3241-0551, osada@nanocarrier.co.jp
Scientific contact	Study Director, NanoCarrier Co, Ltd., +81 3-3241-0551, osada@nanocarrier.co.jp

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:

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## Results analysis stage

Analysis stage	Final
Date of interim/final analysis	05 January 2023
Is this the analysis of the primary completion data?	No
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Global end of trial reached?	Yes
Global end of trial date	30 June 2022
Was the trial ended prematurely?	Yes

Notes:

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## General information about the trial

Main objective of the trial:

Part 1(Phase IIa):

To assess dose-limiting toxicities (DLTs), and to determine the optimal dose in order to establish the recommended Phase IIb (RPIIb) dose for the combination of NC-6004 plus pembrolizumab.

Part 2 (Phase IIb):

To compare progression-free survival (PFS) between NC-6004 plus pembrolizumab and pembrolizumab alone.

Protection of trial subjects:

The study protocol, consent form, participant recruitment process and other relevant study documents were submitted to involved Ethic Committee (ECs)/Independent Ethic Committees (IECs) and approved prior to study initiation. This study was conducted in accordance with principles of the Declaration of Helsinki, with the current

Good Clinical Practice guidelines and with other applicable local regulations. The investigators and their study staff conducted the study in compliance with the study protocol and further protocol amendments. Interested participants were given an opportunity to discuss the activities and procedures involved in study participation with the principal investigator and their site staff. An EC-approved informed consent form which was given to the potential subject and an opportunity afforded to read the consent form and ask questions. Those individuals interested in participation were requested to sign the informed consent form prior to the performance of any study-related procedures.

The rights, safety, and wellbeing of the study subjects were the most important considerations and prevailed over the interests of science and society.

Identifying any untoward medical occurrence and timely and complete reporting of all AEs was aimed at the most efficient protection of the safety of study subjects.

Patient's personal, medical and sensitive data were protected in line with general (GDPR) and applicable local data protection regulations.

Background therapy:

Platinum compounds are well established agents in the treatment of cancer (Kelland and Sharp 1999). The leading platinum compounds in cancer chemotherapy are cisplatin, carboplatin, and oxaliplatin. They share a number of common structural chemical characteristics; however, they exhibit marked interanalogue differences in pharmacokinetics, side effect profiles, and optimal therapeutic indication. Cisplatin has been widely used for the treatment of cancer, including lung cancer (both small cell lung cancer and NSCLC), head and neck cancer, germ-cell tumors (testicular, ovarian, and extragonadal germ cell tumor), ovarian cancer, testicular tumor, bladder cancer, renal pelvis/ureter tumor, prostate cancer, esophagus cancer, cervical cancer, neuroblastoma, stomach cancer, osteosarcoma, and pleura malignant mesothelioma in monotherapy, and malignant bone tumors, endometrial cancer (adjuvant chemotherapy and chemotherapy for metastasis/recurrence), recurrent/refractory malignant lymphoma, and pediatric malignant solid tumors (rhabdomyosarcoma, neuroblastoma, hepatoblastoma, and other primary malignant liver tumors, medulloblastoma) in combination therapy. The mechanism of action of cisplatin is the inhibition of DNA synthesis induced by the platinum-DNA adduct formed by cross-linking between cisplatin and specific base sequences. This cross-linking inhibits DNA replication and transcription and activates signal transduction pathways leading to apoptosis and cell death (Pinto and Lippard 1985).

Evidence for comparator:

Immune checkpoint inhibitors, such as pembrolizumab, are approved for treatment in people with recurrent or metastatic head and neck cancer who are currently on or have received platinum-containing chemotherapy. In oncology development, there are many ongoing trials that show better efficacy from combination agents have already been developed, showing an acceptable tolerance with a significant clinical activity.

Actual start date of recruitment	14 June 2019
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

## Population of trial subjects

### Subjects enrolled per country

Country: Number of subjects enrolled	Poland: 15
Country: Number of subjects enrolled	Croatia: 7
Country: Number of subjects enrolled	Czechia: 7
Country: Number of subjects enrolled	Hungary: 9
Country: Number of subjects enrolled	Taiwan: 13
Country: Number of subjects enrolled	Russian Federation: 20
Country: Number of subjects enrolled	Serbia: 38
Country: Number of subjects enrolled	Ukraine: 43
Worldwide total number of subjects	152
EEA total number of subjects	38

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)	152
From 65 to 84 years	0
85 years and over	0

## Subject disposition

### Recruitment

Recruitment details:

A total of 220 subjects were screened in this study, 16 subjects in Phase IIa and 204 subjects in Phase IIb.

Of 204 subjects screened for Phase IIb, 136 subjects were randomized and 68 subjects were screen failure. Of the 136 subjects, 31 subjects were excluded from the Full Analysis Set (FAS) and 105 subjects received treatment.

### Pre-assignment

Screening details:

Days -28 -1: ICF, demographic data, medical/surgical/cancer history, disease status, tumor sampling.

Days -14 -1: height, weight; body surface area, CT/MRI, ECOG Performance Status, audiometry, ophthalmologist, cardiac risk factor, medications, vaccinations, AEs.

Days -7 -1: eligibility criteria, pregnancy test, FSH, physical examination, etc.

### Period 1

Period 1 title	Treatment period (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Blinding implementation details:

Not applicable

### Arms

Are arms mutually exclusive?	Yes
<b>Arm title</b>	NC-6004 and Pembrolizumab

Arm description:

In the first arm patients were treated with NC-6004 and Pembrolizumab.

Arm type	Experimental
Investigational medicinal product name	NC-6004
Investigational medicinal product code	
Other name	Cisplatin-PEG-pGlu
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Subjects were administered with NC-6004 first followed by pembrolizumab in both parts of the study. The Part 1 phase IIa portion, starting dose was 90 mg/m<sup>2</sup>, with subsequent dose escalations to 105 mg/m<sup>2</sup>, 120 mg/m<sup>2</sup>, and 135 mg/m<sup>2</sup>. In phase IIb portion, the dose was to be determined RPII dose in phase IIa portion.

Investigational medicinal product name	Pembrolizumab
Investigational medicinal product code	L01XC18
Other name	KEYTRUDA
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

The recommended dose of pembrolizumab was 200 mg administered as an IV infusion over 30 minutes every 3 weeks.

<b>Arm title</b>	Pembrolizumab
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Arm description:

In the second arm patients were treated with Pembrolizumab alone.

Arm type	Active comparator
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Investigational medicinal product name	Pembrolizumab
Investigational medicinal product code	
Other name	KEYTRUDA
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

The recommended dose of pembrolizumab was 200 mg administered as an IV infusion over 30 minutes every 3 weeks.

<b>Number of subjects in period 1<sup>[1]</sup></b>	NC-6004 and Pembrolizumab	Pembrolizumab
Started	53	52
Completed	0	0
Not completed	53	52
Adverse event, serious fatal	32	24
Physician decision	10	12
Consent withdrawn by subject	7	5
Adverse event, non-fatal	2	5
Lost to follow-up	1	3
Progressive disease	1	3

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.

Justification: A total of 220 subjects were screened at baseline period this study. Only 152 subjects were enrolled.

## Baseline characteristics

### Reporting groups

Reporting group title	NC-6004 and Pembrolizumab
Reporting group description: In the first arm patients were treated with NC-6004 and Pembrolizumab.	
Reporting group title	Pembrolizumab
Reporting group description: In the second arm patients were treated with Pembrolizumab alone.	

Reporting group values	NC-6004 and Pembrolizumab	Pembrolizumab	Total
Number of subjects	53	52	105
Age categorical			
Males or females aged $\geq 18$ years.			
Units: Subjects			
Adults (18-64 years)	53	52	105
From 65-84 years	0	0	0
85 years and over	0	0	0
Not recorded	0	0	0
Gender categorical			
Units: Subjects			
Female	6	9	15
Male	47	43	90

### Subject analysis sets

Subject analysis set title	Safety Population (SP)
Subject analysis set type	Full analysis
Subject analysis set description: The Safety Population (SP) included all participants who received at least one dose of study drug NC-6004 and/or one dose of pembrolizumab. This population was used for analyses of safety data. It was used for summary of baseline data and analyses of progression free survival (PFS).	
Subject analysis set title	Response Evaluable Population (REP)
Subject analysis set type	Full analysis

Subject analysis set description:

The Response Evaluable Population (REP) included all participants who received at least one dose of study drug NC-6004 and/or one dose of pembrolizumab, had baseline measurable disease (per Response Evaluation Criteria in Solid Tumors version 1.1 [RECIST v1.1]), and had at least one post-baseline radiographic tumor assessment or discontinued study treatment due to clinical progression determined by the site investigator or death if no post-baseline tumor assessment. This population was used for summary of tumor assessment data and analyses of response rates.

Reporting group values	Safety Population (SP)	Response Evaluable Population (REP)	
Number of subjects	105	105	
Age categorical			
Males or females aged $\geq 18$ years.			
Units: Subjects			
Adults (18-64 years)	105	105	
From 65-84 years	0	0	
85 years and over	0	0	

Not recorded	0	0	
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Gender categorical			
Units: Subjects			
Female	15	15	
Male	90	90	

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## End points

### End points reporting groups

Reporting group title	NC-6004 and Pembrolizumab
Reporting group description: In the first arm patients were treated with NC-6004 and Pembrolizumab.	
Reporting group title	Pembrolizumab
Reporting group description: In the second arm patients were treated with Pembrolizumab alone.	
Subject analysis set title	Safety Population (SP)
Subject analysis set type	Full analysis
Subject analysis set description: The Safety Population (SP) included all participants who received at least one dose of study drug NC-6004 and/or one dose of pembrolizumab. This population was used for analyses of safety data. It was used for summary of baseline data and analyses of progression free survival (PFS).	
Subject analysis set title	Response Evaluable Population (REP)
Subject analysis set type	Full analysis
Subject analysis set description: The Response Evaluable Population (REP) included all participants who received at least one dose of study drug NC-6004 and/or one dose of pembrolizumab, had baseline measurable disease (per Response Evaluation Criteria in Solid Tumors version 1.1 [RECIST v1.1]), and had at least one post-baseline radiographic tumor assessment or discontinued study treatment due to clinical progression determined by the site investigator or death if no post-baseline tumor assessment. This population was used for summary of tumor assessment data and analyses of response rates.	

### Primary: To establish the Recommended Phase IIb (RPIIb) dose

End point title	To establish the Recommended Phase IIb (RPIIb) dose <sup>[1]</sup>
End point description: To assess (DLTs), and to determine the optimal dose in order to establish the RPIIb dose for the combination of NC 6004 plus pembrolizumab an Independent Data Monitoring Committee was involved in this part. No statistical analyses planned.	
End point type	Primary
End point timeframe: From the first day of treatment to the end of the follow-up period of the study.	
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: this study was early terminated.	

End point values	NC-6004 and Pembrolizumab	Pembrolizumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	53	52		
Units: number of subjects	53	52		

### Statistical analyses

No statistical analyses for this end point

### Primary: To determine the Progression-Free Survival (PFS) by Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST 1.1)

End point title	To determine the Progression-Free Survival (PFS) by Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST 1.1) <sup>[2]</sup>
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End point description:

To determine the Progression-free survival (PFS) by Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST 1.1) in eligible subjects after treatment with NC-6004 plus pembrolizumab and pembrolizumab alone.

End point type	Primary
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End point timeframe:

From the first day of treatment to the end of the follow-up period of the study.

Notes:

[2] - 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: this study was early terminated.

End point values	NC-6004 and Pembrolizumab	Pembrolizumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	53	52		
Units: number of subjects	53	52		

## Statistical analyses

No statistical analyses for this end point

## Secondary: Incidences and severity of SAEs, TEAEs, and discontinuation because of TEAEs

End point title	Incidences and severity of SAEs, TEAEs, and discontinuation because of TEAEs
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End point description:

Incidences and severity of serious adverse events (SAEs), treatment-emergent adverse events (TEAEs), and discontinuation because of TEAEs

End point type	Secondary
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End point timeframe:

From the first day of treatment to the end of the follow-up period of the study.

End point values	NC-6004 and Pembrolizumab	Pembrolizumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	53	52		
Units: number of subjects	9	5		

## Statistical analyses

No statistical analyses for this end point

## Secondary: Incidence and severity of laboratory abnormalities

End point title	Incidence and severity of laboratory abnormalities
End point description: Incidence and severity of laboratory abnormalities (hematology and biochemistry) according to National Cancer Institute - Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 5.0.	
End point type	Secondary
End point timeframe: From the first day of treatment to the end of the follow-up period of the study.	

<b>End point values</b>	NC-6004 and Pembrolizumab	Pembrolizumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0 <sup>[3]</sup>	0 <sup>[4]</sup>		
Units: number of subjects				

Notes:

[3] - Not done.

[4] - Not done.

### Statistical analyses

No statistical analyses for this end point

### Secondary: Change from baseline in vital sign measurements

End point title	Change from baseline in vital sign measurements
End point description: Change from baseline in vital sign measurements (blood pressure, heart rate, respiratory rate, and temperature)	
End point type	Secondary
End point timeframe: From the first day of treatment to the end of the follow-up period of the study.	

<b>End point values</b>	NC-6004 and Pembrolizumab	Pembrolizumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	53	52		
Units: number of subjects	53	52		

### Statistical analyses

No statistical analyses for this end point

### Secondary: Change from baseline in electrocardiogram (ECG) findings

End point title	Change from baseline in electrocardiogram (ECG) findings
End point description:	

End point type	Secondary
End point timeframe:	
From the first day of treatment to the end of the follow-up period of the study.	

End point values	NC-6004 and Pembrolizumab	Pembrolizumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	53	52		
Units: number of subjects	53	52		

## Statistical analyses

No statistical analyses for this end point

## Secondary: Overall survival subjects

End point title	Overall survival subjects
End point description:	
OS is defined as the time from randomization/inclusion to death due to any cause or last contact.	
End point type	Secondary
End point timeframe:	
From the first day of treatment to the end of the follow-up period of the study.	

End point values	NC-6004 and Pembrolizumab	Pembrolizumab	Response Evaluable Population (REP)	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	0 <sup>[5]</sup>	0 <sup>[6]</sup>	0 <sup>[7]</sup>	
Units: Rate				
number (confidence interval 95%)	( to )	( to )	( to )	

Notes:

[5] - Not done.

[6] - Not done.

[7] - Not done.

## Statistical analyses

No statistical analyses for this end point

## Secondary: Overall response rate (ORR)

End point title	Overall response rate (ORR)
End point description:	
ORR is defined as the proportion of subjects who have a complete response (CR) defined as a disappearance of all target lesions with pathological lymph nodes having a reduction in short axis to <10 mm, or partial response (PR) defined as at least a 30% decrease in the sum of diameters of target lesions, using the baseline sum diameters as a reference.	

ORR was assessed by performing study imaging at 6 weeks (42 days  $\pm$  7 days) and again at 12 weeks (84 days  $\pm$  7 days) from the date of first study dose. Subsequent tumor imaging was performed every 9 weeks (63 days  $\pm$  7 days) after the last imaging or more frequently if clinically indicated. After 48 weeks, subjects who remain on treatment had imaging performed every 12 weeks (84 days  $\pm$  7 days) after the last imaging.

End point type	Secondary
End point timeframe:	
From the first day of treatment to the end of the follow-up period of the study.	

<b>End point values</b>	NC-6004 and Pembrolizumab	Pembrolizumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	53	52		
Units: number of subjects	53	52		

## Statistical analyses

No statistical analyses for this end point

## Secondary: Complete response (CR)/ Partial response (PR)

End point title	Complete response (CR)/ Partial response (PR)
End point description:	
CR defined as disappearance of all target and all non-target lesions. All pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10mm. PR defined as at least 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum of diameters.	
End point type	Secondary
End point timeframe:	
From the first day of treatment to the end of the follow-up period of the study.	

<b>End point values</b>	NC-6004 and Pembrolizumab	Pembrolizumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	53	52		
Units: number of subjects	53	52		

## Statistical analyses

No statistical analyses for this end point

## Secondary: Stable disease (SD)

End point title	Stable disease (SD)
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End point description:

SD defined as neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for progressive disease (PD).

End point type	Secondary
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End point timeframe:

From the first day of treatment to the end of the follow-up period of the study.

End point values	NC-6004 and Pembrolizumab	Pembrolizumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0 <sup>[8]</sup>	0 <sup>[9]</sup>		
Units: number of subjects				

Notes:

[8] - Not done.

[9] - Not done.

### Statistical analyses

No statistical analyses for this end point

### Secondary: Duration of response (DOR)

End point title	Duration of response (DOR)
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End point description:

DOR defined as subjects who demonstrated confirmed CR or PR. DOR is defined as the time from first documented evidence of CR or PR until disease progression or death.

End point type	Secondary
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End point timeframe:

From the first day of treatment to the end of the follow-up period of the study.

End point values	NC-6004 and Pembrolizumab	Pembrolizumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0 <sup>[10]</sup>	0 <sup>[11]</sup>		
Units: number of subjects				

Notes:

[10] - Not done.

[11] - Not done.

### Statistical analyses

No statistical analyses for this end point

### Secondary: Time to response (TTR)

End point title	Time to response (TTR)
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End point description:

TTR defined as subject's first documented response from the date of randomization/inclusion.

End point type	Secondary
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End point timeframe:

From the first day of treatment to the end of the follow-up period of the study.

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<b>End point values</b>	NC-6004 and Pembrolizumab	Pembrolizumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0 <sup>[12]</sup>	0 <sup>[13]</sup>		
Units: days				
number (not applicable)				

Notes:

[12] - Not done.

[13] - Not done.

### **Statistical analyses**

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No statistical analyses for this end point

## Adverse events

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### Adverse events information<sup>[1]</sup>

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Timeframe for reporting adverse events:

From screening to the end of the study.

Assessment type	Systematic
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### Dictionary used

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Dictionary name	MedDRA
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Dictionary version	24
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Frequency threshold for reporting non-serious adverse events: 3 %

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#### Notes:

[1] - There are no non-serious adverse events recorded for these results. It is expected that there will be at least one non-serious adverse event reported.

Justification: The analysis included only TEAEs, i.e., AEs that started or worsened after the start of IMP. All TEAEs, related TEAEs (i.e., TEAEs probably or possibly related to the IMP), and serious TEAEs were summarized and tabulated according to MedDRA primary system organ class and preferred term.

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
21 February 2019	Protocol updated with regards to the exclusion criteria in connection with comments received from the Hungarian regulatory authority (OGYEI).
26 November 2019	Protocol submitted only in Taiwan and then updated in line with comments received from Taiwanese FDA, which resulted in creation of Protocol version 4.0 submitted globally.
04 May 2020	Main changes: <ul style="list-style-type: none"><li>• Clarification of study objectives and endpoints</li><li>• Clarification of inclusion criteria</li><li>• Clarification and addition of exclusion criteria upon TFDA request</li><li>• Change to adaptive randomization</li><li>• Change in reasons for patient withdrawal from the study due to toxicity upon TFDA request</li><li>• Change in dose-limiting toxicity criteria upon TFDA request</li><li>• Clarification of efficacy assessments</li><li>• Change in prophylactic medication as per FDA recommendation and the Sponsor's medical monitors recommendation</li></ul>

Notes:

### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

None
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Notes: