Clinical trial results:
Open label single arm Phase Ib-II study of pre-operative IPH2201 in patients with locally advanced resectable squamous cell carcinoma of the oral cavity

Summary

EudraCT number	2014-002135-34
Trial protocol	DE
Global end of trial date	26 November 2016

Results information

Result version number	v1 (current)
This version publication date	25 November 2017
First version publication date	25 November 2017

Trial information

Trial identification

Sponsor protocol code	IPH2201-201

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02331875
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	INNATE PHARMA
Sponsor organisation address	117 avenue de luminy, Marseille, France, 13009
Public contact	Dr Pierre Dodion, INNATE PHARMA, +33 4 30 30 30 50, pierre.dodion@innate-pharma.fr
Scientific contact	Dr Pierre Dodion, INNATE PHARMA, +33 4 30 30 30 50, pierre.dodion@innate-pharma.fr

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	20 March 2017
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	26 November 2016
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

To evaluate the antitumor activity of pre-operative IPH2201 in patients with operable squamous cell carcinoma of the oral cavity

Protection of trial subjects:

This study was performed in accordance with the principles stated in the Declaration of Helsinki adopted by the World Medical Association and in accordance with the International Conference of Harmonization (ICH) guidelines on Good Clinical Practice (GCP) (CPMP/ICH/135/95). The safety committee of the study was composed of The international coordinating investigator, One principal investigator per country, The director of the Charité Comprehensive Cancer Center, as Medical Oncologist with high experience in clinical tumor immunology, A medical representative of the sponsor, A radiologist. A methodologist and other principal investigators of sites which has enrolled at least one patient in the trial could join the safety committee as optional members. The safety committee had to review the data for progression and safety, for instance to decide on dose escalation. It could also be involved at any time should a major safety issue occur.

Background therapy:

Patients should receive all necessary supportive care in the form of treatment or prophylaxis as clinically indicated e.g. transfusion of blood products, antibiotics, anti-histaminics, analgesics. No premedication was required. However, from cycle 2, premedication by acetaminophen or anti-histamine drug could be prescribed, at the investigator’s discretion, if the patient experienced any grade 1 to 3 infusion related AE at the previous cycle.

Evidence for comparator:

not applicable

Actual start date of recruitment	18 December 2014
Long term follow-up planned	Yes
Long term follow-up rationale	Efficacy
Long term follow-up duration	2 Years
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Spain: 1
Country: Number of subjects enrolled	Germany: 2
Worldwide total number of subjects	3
EEA total number of subjects	3

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)	1
From 65 to 84 years	2
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Interventional Efficacy and Safety Study, Multi-center, open label single-arm phase Ib-II study including a run-in part. The first 6 patients were to received IPH2201 at a dose of 4 mg/kg q2w x 4, subsequent patients were to be treated at a dose of 10 mg/kg q2w x 4, after escalation approval by safety committee.

Pre-assignment

Screening details:

up to 2 weeks of screening were given to allow site to verify all selection criteria.
Among the 4 patients screened, 3 were treated (1 was screen-failed at sponsor request, in the context of the premature ending of the trial).

Period 1

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

Arms

Arm title	4mg/kg

Arm description:

only treated patients (who received at least one cycle of IPH2201) are taken in account.

Arm type	Experimental
Investigational medicinal product name	monalizumab
Investigational medicinal product code	IPH2201
Other name	NNC0141-0100, anti-NKG2A
Pharmaceutical forms	Powder for injection
Routes of administration	Intravenous use

Dosage and administration details:

The first 6 patients were to received IPH2201 as single agent, at a dose of 4 mg/kg q2w x 4 in a 1 hour IV administration – batch IPH2201-BLDS001. IPH2201 (monalizumab) treatment period duration was of a maximum of 8 weeks. Cycle 1 administration was to be performed during the 2 weeks following the screening visit.
Administrations at cycle 2, cycle 3 and cycle 4 were performed 14 days +/- 3 after the previous cycle.
One delay of up to 1 week in the treatment schedule was authorized in the absence of resolution to a grade 2 or lower of any grade ≥ 3. For a delay of more than 1 week, the investigator had to contact sponsor.
It was followed by standard treatment :
Surgical procedure: Standard Surgery to be done after the end of treatment with monalizumab, according to standard recommendations in the relevant country.
Postsurgical Adjuvant Therapy : Radiation and/ or Chemotherapy, realized after the standard surgery, according to standard recommendations in the relevant country

Number of subjects in period 1	4mg/kg
Started	3
Completed	1
Not completed	2
SPONSOR DECISION	1

DISEASE PROGRESSION	1

Baseline characteristics

Reporting groups	
Reporting group title	overall

Reporting group description: -

Reporting group values	overall	Total	
Number of subjects	3	3	
Age categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	1	1	
From 65-84 years	2	2	
85 years and over	0	0	
Gender categorical Units: Subjects			
Female	0	0	
Male	3	3	
Histological grade Units: Subjects			
Grade2	3	3	
AJCC STAGE Units: Subjects			
II	0	0	
III	0	0	
IV	0	0	
IVa	3	3	
TNM Stage Units: Subjects			
cT4a, cN2, cM0	2	2	
cT4a, cN1, cM0	1	1	

End points

End points reporting groups

Reporting group title	4mg/kg
Reporting group description:	
only treated patients (who received at least one cycle of IPH2201) are taken in account.	

Primary: Response before surgery

End point title	Response before surgery[1]
End point description:	
Best response during treatment period	
End point type	Primary
End point timeframe:	
up to End of Treatment visit	

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: The decision to stop the recruitment of patients was taken on Sept. 28, 2016, based on the low accrual rate in this trial. Thus, efficacy endpoints were analysed in a descriptive manner only, and no statistical analysis performed.

End point values	4mg/kg			
Subject group type	Reporting group			
Number of subjects analysed	3			
Units: nb patient				
complete response	0			
progressive or relapsed disease	0			
stable disease	3			

Statistical analyses

No statistical analyses for this end point

Secondary: complete response

End point title	complete response
End point description:	

End point type	Secondary
End point timeframe:	
after EOT visit	

End point values	4mg/kg			
Subject group type	Reporting group			
Number of subjects analysed	3			
Units: nb patient				
yes	2			
no	1			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

AEs were collected from consent signature date to the end of study visit.

Adverse event reporting additional description:

after the first patient, reporting rules were changed : From the day of surgery, an event was reported if it was an SAE or if related to IPH2201 treatment (whatever grade) or has a grade ≥ 3 (irrespective of the relationship with IPH2201 treatment).

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	14.1

Reporting groups

Reporting group title	4mg/kg

Reporting group description:

only treated patients (who received at least one cycle of IPH2201) are taken in account.

Serious adverse events	4mg/kg		
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 3 (100.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Vascular disorders			
Thromboangiitis obliterans			
subjects affected / exposed	1 / 3 (33.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Diabetic hyperosmolar coma			
subjects affected / exposed	1 / 3 (33.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	1 / 3 (33.33%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			

Abdominal pain			
subjects affected / exposed	1 / 3 (33.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Hypoxia			
subjects affected / exposed	1 / 3 (33.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Muscular weakness			
subjects affected / exposed	1 / 3 (33.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Encephalitis viral			
subjects affected / exposed	1 / 3 (33.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	4mg/kg		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	3 / 3 (100.00%)		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Tumour pain			
subjects affected / exposed	2 / 3 (66.67%)		
occurrences (all)	2		
Investigations			
Weight decreased			
subjects affected / exposed	1 / 3 (33.33%)		
occurrences (all)	1		
Vascular disorders			

Hypertension			
subjects affected / exposed	1 / 3 (33.33%)		
occurrences (all)	1		
General disorders and administration site conditions			
Oedema peripheral			
subjects affected / exposed	1 / 3 (33.33%)		
occurrences (all)	1		
Pyrexia			
subjects affected / exposed	1 / 3 (33.33%)		
occurrences (all)	1		
Pain			
subjects affected / exposed	1 / 3 (33.33%)		
occurrences (all)	1		
Disease progression			
subjects affected / exposed	1 / 3 (33.33%)		
occurrences (all)	1		
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	2 / 3 (66.67%)		
occurrences (all)	3		
Nausea			
subjects affected / exposed	2 / 3 (66.67%)		
occurrences (all)	3		
Stomatitis			
subjects affected / exposed	1 / 3 (33.33%)		
occurrences (all)	1		
Proctitis			
subjects affected / exposed	1 / 3 (33.33%)		
occurrences (all)	1		
Infections and infestations			
Bronchitis			
subjects affected / exposed	1 / 3 (33.33%)		
occurrences (all)	1		
Metabolism and nutrition disorders			
Hypercholesterolaemia			

subjects affected / exposed occurrences (all)	1 / 3 (33.33%) 1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
03 July 2015	- Change of the title: from "Open label single arm Phase Ib-II study of pre-operative IPH2201 in patients with resectable intermediate or high risk (stage IIIIVa) squamous cell carcinoma of the oral cavity" to "Open label single arm Phase Ib-II study of pre-operative IPH2201 in patients with locally advanced resectable squamous cell carcinoma of the oral cavity" - Modification of inclusion criteria: the inclusion of large cT2 tumors and some stage IVB cases is now allowed: -"Stage II with large (≥ 3 cm and≤4cm) cT2cN0cM0tumors or any cT2cN0cM0 tumor invading neighboring structures" -"Stage IV with a primary tumor(cT)of any stage and an adenopathy assessed as cN3 considered as resectable by the investigator surgeon and no clinically or radiologically detectable metastasis" - Modification of the exclusion criteria relative to other malignancy - Expansion of study sites number: changed from monocentric to "up to 4 sites located in Germany"
15 October 2015	- Expansion of study sites number: changed from "up to 4 sites located in Germany" to "Approximately 12 sites in Europe" - Expansion of study duration: LPLV changed from December 2017 to June 2018 -Change in contraception requirements during the study: male and female patients must use a highly effective contraception method throughout the study and up to 5 months after treatment discontinuation (previously up to 16 weeks). Pregnancy reporting rules have also been updated consequently. - New reporting rules for AEs: "From the day of surgery, an event was reported if it was an SAE or if related to IPH2201 treatment (whatever grade) or has a grade ≥ 3 (irrespective of the relationship with IPH2201 treatment)". -New reporting rules for concomitant medications: "All concomitant medications given to a patient prior to surgery are to be reported. From the surgery day, a concomitant treatment has to be reported if it is corticosteroid, or given to treat a AE (as defined above) or a condition described in medical history" - Change of safety committee member list, to include one principal investigator per country, other principal investigator and other principal investigator of sites which have enrolled at least one patient in the trial)

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date

28 September 2016	The decision to stop the recruitment of patients has been taken on September 28, 2016 after consultation and in agreement with the study coordinators, based on the low accrual rate in this trial since its start in December 2014. At the time of interruption of recruitment, the study was active in Germany (one active site; Dr Jan D. Raguse, Charité University Medicine Berlin, serving as the International Coordinating Investigator) and in Spain (4 active sites - with Dr Ricard N. Mesia, Instituto Catalan de Oncologia - L'Hospitalet, serving as national coordinator for Spain). Since the start of the trial, only 3 patients had been treated (two in Germany and one in Spain), out of the 43 patients planned in this study. two were still on study at this date, but had ended their treatment period. Last visit performed by the last patient occured the 26th of November 2016.	-

Notes:

Limitations and caveats

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

Overall, the limited number of patients treated in this study does not allow concluding on primary and secondary objectives. Efficacy endpoints were analysed in a descriptive manner only, and no statistical analysis performed.

Notes: