

**Clinical trial results:**

An open label phase II study to evaluate the efficacy and safety of PDR001 in patients with advanced or metastatic, well-differentiated, non-functional neuroendocrine tumors of pancreatic, gastrointestinal (GI), or thoracic origin or poorly-differentiated gastroenteropancreatic neuroendocrine carcinoma (GEP-NEC), that have progressed on prior treatment

Summary

EudraCT number	2016-002522-36
Trial protocol	SE GB DE ES AT NL BE FR IT
Global end of trial date	13 May 2020

Results information

Result version number	v1 (current)
This version publication date	01 April 2021
First version publication date	01 April 2021

Trial information**Trial identification**

Sponsor protocol code	CPDR001E2201
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02955069
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Novartis Pharma AG
Sponsor organisation address	CH-4002, Basel, Switzerland,
Public contact	Clinical Disclosure Office, Novartis Pharma AG, 41 613241111, Novartis.email@novartis.com
Scientific contact	Clinical Disclosure Office, Novartis Pharma AG, 41 613241111, Novartis.email@novartis.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	13 May 2020
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	13 May 2020
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To estimate the antitumor activity of spartalizumab as a single agent in the well-differentiated NET and poorly-differentiated GEP-NEC groups (overall response rate).

Protection of trial subjects:

The study was in compliance with the ethical principles derived from the Declaration of Helsinki and the International Conference on Harmonization (ICH) Good Clinical Practice (GCP) guidelines. All the local regulatory requirements pertinent to safety of trial subjects were also followed during the conduct of the trial.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	14 August 2014
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Germany: 7
Country: Number of subjects enrolled	Spain: 9
Country: Number of subjects enrolled	United States: 36
Country: Number of subjects enrolled	Australia: 2
Country: Number of subjects enrolled	Japan: 9
Country: Number of subjects enrolled	Netherlands: 3
Country: Number of subjects enrolled	Austria: 4
Country: Number of subjects enrolled	Belgium: 4
Country: Number of subjects enrolled	Canada: 4
Country: Number of subjects enrolled	France: 9
Country: Number of subjects enrolled	United Kingdom: 3
Country: Number of subjects enrolled	Italy: 26
Worldwide total number of subjects	116
EEA total number of subjects	62

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)	79
From 65 to 84 years	36
85 years and over	1

Subject disposition

Recruitment

Recruitment details:

Recruitment took place in 35 investigative sites in 12 countries from 14 Feb 2017 to 04 Apr 2018

Pre-assignment

Screening details:

A total of 149 participants were screened. Those participants who met the eligibility criteria entered the treatment period.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Well-differentiated NET

Arm description:

Subjects with advanced or metastatic, well-differentiated non-functional NET of GI, pancreatic or thoracic origin that progressed on or after prior available treatments.

Arm type	Experimental
Investigational medicinal product name	Spartalizumab
Investigational medicinal product code	PDR001
Other name	
Pharmaceutical forms	Powder for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Spartalizumab was supplied as 100 mg powder for solution for infusion. Spartalizumab was administered intravenously at a dose of 400 mg once every 4 weeks (Q4W), given as a 30-minute infusion on Day 1 of every Cycle (Each cycle was 28 days)

Arm title	Poorly-differentiated GEP-NEC
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Arm description:

Subjects with advanced or metastatic poorly-differentiated GEP-NEC that progressed on or after prior available treatments.

Arm type	Experimental
Investigational medicinal product name	Spartalizumab
Investigational medicinal product code	PDR001
Other name	
Pharmaceutical forms	Powder for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Spartalizumab was supplied as 100 mg powder for solution for infusion. Spartalizumab was administered intravenously at a dose of 400 mg once every 4 weeks (Q4W), given as a 30-minute infusion on Day 1 of every Cycle (Each cycle was 28 days)

Number of subjects in period 1	Well-differentiated NET	Poorly-differentiated GEP-NEC
Started	95	21
Full Analysis Set (FAS)	95	21
Safety set	95	21
Pharmacokinetic analysis set (PAS)	94	18
Immunogenicity (IG) prevalence set	94	21
IG incidence set	84	17
Completed	0	0
Not completed	95	21
Adverse event, serious fatal	7	3
Physician decision	10	2
Adverse event, non-fatal	7	2
Study terminated by sponsor	4	-
Subject/Guardian decision	3	1
Progressive disease	64	13

Baseline characteristics

Reporting groups

Reporting group title	Well-differentiated NET
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Reporting group description:

Subjects with advanced or metastatic, well-differentiated non-functional NET of GI, pancreatic or thoracic origin that progressed on or after prior available treatments.

Reporting group title	Poorly-differentiated GEP-NEC
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Reporting group description:

Subjects with advanced or metastatic poorly-differentiated GEP-NEC that progressed on or after prior available treatments.

Reporting group values	Well-differentiated NET	Poorly-differentiated GEP-NEC	Total
Number of subjects	95	21	116
Age categorical			
Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	63	16	79
From 65-84 years	31	5	36
85 years and over	1	0	1
Age Continuous			
Units: Years			
arithmetic mean	59.4	57.4	
standard deviation	± 11.21	± 8.56	-
Sex: Female, Male			
Units: Participants			
Female	43	4	47
Male	52	17	69
Race/Ethnicity, Customized			
Units: Subjects			
Caucasian	59	16	75
Black	4	0	4
Asian	7	3	10
Native American	1	0	1
Black or African American	2	0	2
White	15	1	16
Unknown	3	1	4
Other	3	0	3
Missing	1	0	1

End points

End points reporting groups

Reporting group title	Well-differentiated NET
Reporting group description:	
Subjects with advanced or metastatic, well-differentiated non-functional NET of GI, pancreatic or thoracic origin that progressed on or after prior available treatments.	
Reporting group title	Poorly-differentiated GEP-NEC
Reporting group description:	
Subjects with advanced or metastatic poorly-differentiated GEP-NEC that progressed on or after prior available treatments.	

Primary: Overall response rate (ORR) by RECIST 1.1 and as per Blinded Independent Central Review (BIRC).

End point title	Overall response rate (ORR) by RECIST 1.1 and as per Blinded Independent Central Review (BIRC). ^[1]
End point description:	
ORR is defined as the proportion of patients with best overall response (BOR) of complete response (CR) or partial response (PR), according to BIRC radiological assessment by RECIST 1.1. CR: disappearance of all non-nodal target lesions. In addition, any pathological lymph nodes assigned as target lesions must have a reduction in short axis to < 10 mm. PR: at least a 30% decrease in the sum of diameter of all target lesions, taking as reference the baseline sum of diameters.	
End point type	Primary
End point timeframe:	
From baseline up to approximately 1.5 years	

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

End point values	Well-differentiated NET	Poorly-differentiated GEP-NEC		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	95	21		
Units: Percentage of participants				
number (confidence interval 95%)	7.4 (3.0 to 14.6)	4.8 (0.1 to 23.8)		

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of response (DOR) by RECIST 1.1 and as per BIRC

End point title	Duration of response (DOR) by RECIST 1.1 and as per BIRC
End point description:	
DOR is defined as the time between the date of first documented response (CR or PR) and the date of first documented disease progression by RECIST 1.1 and as per BIRC or death due to underlying cancer. For DOR analysis, participants continuing without progression or death due to underlying cancer were	

censored at the date of their last adequate tumor assessment. An adequate tumour assessment is a tumour assessment with an overall response other than unknown.

CR: disappearance of all non-nodal target lesions. In addition, any pathological lymph nodes assigned as target lesions must have a reduction in short axis to < 10 mm.

PR: at least a 30% decrease in the sum of diameter of all target lesions, taking as reference the baseline sum of diameters.

End point type	Secondary
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End point timeframe:

From the date of first documented response (CR or PR) until the first documented disease progression or death, whichever comes first, assessed up to approximately 1.5 years

End point values	Well-differentiated NET	Poorly-differentiated GEP-NEC		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	7	1		
Units: Days				
median (full range (min-max))	250 (49 to 288)	270 (270 to 270)		

Statistical analyses

No statistical analyses for this end point

Secondary: Disease Control Rate by RECIST 1.1 and as per BIRC

End point title	Disease Control Rate by RECIST 1.1 and as per BIRC
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End point description:

Disease control rate is defined as the proportion of patients with best overall response of CR, PR or stable disease (SD) according to RECIST 1.1 criteria and as per BIRC.

CR: disappearance of all non-nodal target lesions. In addition, any pathological lymph nodes assigned as target lesions must have a reduction in short axis to < 10 mm.

PR: at least a 30% decrease in the sum of diameter of all target lesions, taking as reference the baseline sum of diameters.

SD: neither sufficient shrinkage to qualify for PR or CR nor an increase in lesions which would qualify for progressive disease.

End point type	Secondary
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End point timeframe:

From baseline up to approximately 1.5 years

End point values	Well-differentiated NET	Poorly-differentiated GEP-NEC		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	95	21		
Units: Percentage of participants				
number (confidence interval 95%)	64.2 (53.7 to 73.8)	19.0 (5.4 to 41.9)		

Statistical analyses

No statistical analyses for this end point

Secondary: Time to response (TTR) by RECIST 1.1 and as per BIRC

End point title	Time to response (TTR) by RECIST 1.1 and as per BIRC
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End point description:

TTR is defined as the time from the date of start of treatment to the first documented response of either CR or PR, which must be subsequently confirmed. TTR was evaluated according to RECIST 1.1 and as per BIRC.

CR: disappearance of all non-nodal target lesions. In addition, any pathological lymph nodes assigned as target lesions must have a reduction in short axis to < 10 mm.

PR: at least a 30% decrease in the sum of diameter of all target lesions, taking as reference the baseline sum of diameters.

End point type	Secondary
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End point timeframe:

From baseline to the first documented response, assessed up to approximately 1.5 years

End point values	Well-differentiated NET	Poorly-differentiated GEP-NEC		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	7	1		
Units: Days				
median (full range (min-max))	110 (52 to 218)	53 (53 to 53)		

Statistical analyses

No statistical analyses for this end point

Secondary: Progression-free survival (PFS) by RECIST 1.1 and as per BIRC

End point title	Progression-free survival (PFS) by RECIST 1.1 and as per BIRC
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End point description:

PFS is defined as the time from the date of first dose to the date of the first documented radiological progression or death due to any cause. PFS was evaluated according to RECIST 1.1 and as per BIRC. For participants who had not progressed or died at the analysis cut-off date, PFS was censored at the date of the last adequate tumor evaluation date. An adequate tumour assessment is a tumour assessment with an overall response other than unknown.

End point type	Secondary
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End point timeframe:

From baseline until the date of the first documented radiological progression or death due to any cause, whichever comes first, assessed up to approximately 1.5 years

End point values	Well-differentiated NET	Poorly-differentiated GEP-NEC		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	95	21		
Units: Months				
median (confidence interval 95%)	3.8 (3.6 to 5.5)	1.8 (1.5 to 2.0)		

Statistical analyses

No statistical analyses for this end point

Secondary: Immune related Overall Response Rate (irORR) by irRECIST and as per BIRC

End point title	Immune related Overall Response Rate (irORR) by irRECIST and as per BIRC
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End point description:

irORR is the proportion of patients with a best overall response of immune related Complete Response (irCR) or immune related partial response (irPR), according to BIRC assessment by irRECIST.

irCR: Complete disappearance of all measurable and non-measurable lesions. In addition, any pathological lymph nodes must have a reduction in short axis to < 10 mm.

irPR: At least 30% decrease in the total measurable tumor burden (TMTB) compared to baseline and not qualifying for irCR or immune related progressive disease (irPD).

End point type	Secondary
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End point timeframe:

From baseline up to approximately 1.5 years

End point values	Well-differentiated NET	Poorly-differentiated GEP-NEC		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	95	21		
Units: Percentage of participants				
number (confidence interval 95%)	7.4 (3.0 to 14.6)	4.8 (0.1 to 23.8)		

Statistical analyses

No statistical analyses for this end point

Secondary: Immune related Duration of Response (irDoR) by irRECIST and as per BIRC.

End point title	Immune related Duration of Response (irDoR) by irRECIST and as per BIRC.
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End point description:

irDOR is defined as the time from first documentation of irCR or irPR until the time of first documentation of progression per irRECIST based on BIRC assessment. Participants continuing without progression or death due to underlying cancer were censored at the date of their last adequate tumor assessment. An adequate tumour assessment is a tumour assessment with an overall response other than unknown for irRECIST.

irCR: Complete disappearance of all measurable and non-measurable lesions. In addition, any pathological lymph nodes must have a reduction in short axis to < 10 mm.

irPR: At least 30% decrease in the TMTB compared to baseline and not qualifying for irPD or irCR

End point type	Secondary
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End point timeframe:

From the date of first documented confirmed response (irCR or irPR) until the first documented progression, assessed up to approximately 1.5 years

End point values	Well-differentiated NET	Poorly-differentiated GEP-NEC		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	7	1		
Units: Days				
median (full range (min-max))	228 (49 to 288)	270 (270 to 270)		

Statistical analyses

No statistical analyses for this end point

Secondary: Immune related Time to Response (irTTR) by irRECIST and as per BIRC

End point title	Immune related Time to Response (irTTR) by irRECIST and as per BIRC
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End point description:

irTTR is defined as the time between date of start of treatment until first documented response (confirmed irCR or irPR) by irRECIST and as per BIRC.

irCR: Complete disappearance of all measurable and non-measurable lesions. In addition, any pathological lymph nodes must have a reduction in short axis to < 10 mm.

irPR: At least 30% decrease in the TMTB compared to baseline and not qualifying for irPD or irCR.

End point type	Secondary
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End point timeframe:

From baseline to the first documented response, assessed up to approximately 1.5 years

End point values	Well-differentiated NET	Poorly-differentiated GEP-NEC		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	7	1		
Units: Days				
median (full range (min-max))	110 (52 to 218)	53 (53 to 53)		

Statistical analyses

No statistical analyses for this end point

Secondary: Immune related Disease Control Rate (irDCR) by irRECIST and as per BIRC

End point title	Immune related Disease Control Rate (irDCR) by irRECIST and as per BIRC
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End point description:

irDCR is defined as the proportion of patients with a best overall response of irCR or irPR or immune related stable disease (irSD) according to irRECIST and as per BIRC.

irCR: Complete disappearance of all measurable and non-measurable lesions. In addition, any pathological lymph nodes must have a reduction in short axis to < 10 mm.

irPR: At least 30% decrease in the TMTB compared to baseline and not qualifying for irPD or irCR.

irSD: Neither a sufficient shrinkage to qualify for irPR or irCR, nor an increase in lesions, or a clear and unequivocal progression of existing nontarget or new non-measurable lesions that would qualify for irPD.

End point type	Secondary
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End point timeframe:

From baseline up to approximately 1.5 years

End point values	Well-differentiated NET	Poorly-differentiated GEP-NEC		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	95	21		
Units: Percentage of participants				
number (confidence interval 95%)	66.3 (55.9 to 75.7)	19.0 (5.4 to 41.9)		

Statistical analyses

No statistical analyses for this end point

Secondary: Immune related Progression Free Survival (irPFS) by irRECIST and as per BIRC

End point title	Immune related Progression Free Survival (irPFS) by irRECIST and as per BIRC
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End point description:

irPFS is defined as the time from date of start of treatment to the date of event defined as the first documented assessment of immune related progression that is confirmed or death due to any cause. If a patient has not had an event, immune related progression-free survival was censored at the date of last adequate tumor assessment. An adequate tumor assessment is a tumor assessment with overall response other than unknown for irRECIST.

End point type	Secondary
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End point timeframe:

From baseline until the date of the first documented immune related progression or death due to any cause, whichever comes first, assessed up to approximately 1.5 years

End point values	Well-differentiated NET	Poorly-differentiated GEP-NEC		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	95	21		
Units: Months				
median (confidence interval 95%)	3.8 (3.6 to 5.5)	1.8 (1.5 to 2.0)		

Statistical analyses

No statistical analyses for this end point

Secondary: Overall survival (OS)

End point title	Overall survival (OS)
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End point description:

OS is defined as the time from the start of treatment date to the date of death, due to any cause. If a patient was not known to have died, then OS was censored at the latest date the patient was known to be alive.

Note: 999999 indicates value is not evaluable.

End point type	Secondary
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End point timeframe:

From baseline until death due to any cause, assessed up to approx. 3 years

End point values	Well-differentiated NET	Poorly-differentiated GEP-NEC		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	95	21		
Units: Months				
median (confidence interval 95%)	23.4 (19.2 to 999999)	6.8 (4.0 to 8.6)		

Statistical analyses

No statistical analyses for this end point

Secondary: Changes from baseline in Chromogranin A (CgA) levels

End point title	Changes from baseline in Chromogranin A (CgA) levels
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End point description:

Blood samples were collected for assessment of CgA level. Change from Baseline at a particular visit was

calculated as the CgA level at that visit minus Baseline. Only those participants with evaluable data at the specified time points for this outcome measure were analyzed (represented by n=X / Y in the category titles).

Note: 999999 indicates value is not evaluable.

End point type	Secondary
End point timeframe:	
Baseline, day 1 of each cycle from cycle 2 to end of treatment, assessed up to approx. 1.5 years.	
Cycle=28 days.	

End point values	Well-differentiated NET	Poorly-differentiated GEP-NEC		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	95	21		
Units: microgram/liter (ug/L)				
arithmetic mean (standard deviation)				
Cycle 2 Day 1, n= 87 / 14	874.6 (± 6694.64)	6466.9 (± 23760.13)		
Cycle 3 Day 1, n= 77 / 8	-1811.7 (± 21413.11)	706.5 (± 2294.87)		
Cycle 4 Day 1, n= 69 / 6	579.9 (± 13437.06)	1544.5 (± 2712.23)		
Cycle 5 Day 1, n= 53 / 5	598.2 (± 11724.93)	1306.6 (± 3125.84)		
Cycle 6 Day 1, n= 47 / 3	1337.6 (± 7106.32)	4531.7 (± 8694.65)		
Cycle 7 Day 1, n= 41 / 2	-564.5 (± 12643.71)	11089.5 (± 17551.10)		
Cycle 8 Day 1, n= 29 / 2	3726.0 (± 18813.63)	9103.5 (± 14759.44)		
Cycle 9 Day 1, n= 27 / 1	22522.2 (± 94054.85)	-1342.0 (± 999999)		
Cycle 10 Day 1, n= 26 / 1	54301.5 (± 250229.27)	-1376.0 (± 999999)		
Cycle 11 Day 1, n= 21 / 1	84634.7 (± 344244.60)	-1393.0 (± 999999)		
Cycle 12 Day 1, n= 18 / 1	8177.6 (± 36820.47)	-1362.0 (± 999999)		
Cycle 13 Day 1, n= 16 / 1	-379.8 (± 1509.95)	-1377.0 (± 999999)		
Cycle 14 Day 1, n= 15 / 0	398.3 (± 1866.56)	999999 (± 999999)		
Cycle 15 Day 1, n= 12 / 0	13.1 (± 1120.60)	999999 (± 999999)		
Cycle 16 Day 1, n= 4 / 0	-81.0 (± 1583.99)	999999 (± 999999)		
Cycle 17 Day 1, n= 1 / 0	-176.0 (± 999999)	999999 (± 999999)		
Cycle 18 Day 1, n= 1 / 0	42.0 (± 999999)	999999 (± 999999)		
End of treatment, n= 34 / 7	30115.3 (± 131958.16)	3899.6 (± 7991.40)		

Statistical analyses

Secondary: Change from baseline in neuron specific enolase (NSE) levels

End point title	Change from baseline in neuron specific enolase (NSE) levels
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End point description:

Blood samples were collected for assessment of NSE level. Change from Baseline at a particular visit was calculated as the NSE level at that visit minus Baseline. Only those participants with evaluable data at the specified time points for this outcome measure were analyzed (represented by n=X / Y in the category titles).

Note: 999999 indicates value is not evaluable.

End point type	Secondary
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End point timeframe:

Baseline, day 1 of each cycle to end of treatment, assessed up to approx. 1.5 years. Cycle=28 days.

End point values	Well-differentiated NET	Poorly-differentiated GEP-NEC		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	95	21		
Units: microgram/liter (ug/L)				
arithmetic mean (standard deviation)				
Cycle 2 Day 1, n= 81 / 13	0.8 (± 29.71)	27.9 (± 40.77)		
Cycle 3 Day 1, n= 73 / 7	2.5 (± 29.33)	32.6 (± 56.87)		
Cycle 4 Day 1, n= 66 / 2	-0.1 (± 14.98)	21.9 (± 21.64)		
Cycle 5 Day 1, n= 48 / 4	4.8 (± 30.34)	31.8 (± 56.39)		
Cycle 6 Day 1, n= 43 / 2	-3.6 (± 19.18)	151.6 (± 204.21)		
Cycle 7 Day 1, n= 41 / 2	7.6 (± 39.44)	-3.0 (± 17.75)		
Cycle 8 Day 1, n= 25 / 1	1.0 (± 22.19)	40.4 (± 999999)		
Cycle 9 Day 1, n= 25 / 1	2.6 (± 8.64)	-12.7 (± 999999)		
Cycle 10 Day 1, n= 21 / 1	10.3 (± 33.74)	-15.0 (± 999999)		
Cycle 11 Day 1, n= 18 / 0	2.3 (± 8.89)	999999 (± 999999)		
Cycle 12 Day 1, n= 17 / 1	-2.4 (± 23.04)	-12.3 (± 999999)		
Cycle 13 Day 1, n= 14 / 1	-3.9 (± 24.22)	-17.8 (± 999999)		
Cycle 14 Day 1, n= 15 / 0	-4.5 (± 22.71)	999999 (± 999999)		
Cycle 15 Day 1, n= 11 / 0	-3.4 (± 29.73)	999999 (± 999999)		
Cycle 16 Day 1, n= 3 / 0	26.5 (± 35.38)	999999 (± 999999)		
Cycle 17 Day 1, n= 1 / 0	15.1 (± 999999)	999999 (± 999999)		
Cycle 18 Day 1, n= 1 / 0	13.8 (± 999999)	999999 (± 999999)		
End of treatment, n= 33 / 7	47.7 (± 136.78)	44.3 (± 66.73)		

Statistical analyses

No statistical analyses for this end point

Secondary: PDR001 plasma concentration

End point title	PDR001 plasma concentration
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End point description:

Blood samples will be taken to evaluate the pharmacokinetics by assessing plasma concentration of PDR001 at selected time points. Only those participants with evaluable data at the specified time points for this outcome measure were analyzed (represented by n=X / Y in the category titles).

Note: 999999 indicates value is not evaluable.

End point type	Secondary
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End point timeframe:

Cycle(C)1 Day(D)1 pre-dose and 30min post-infusion,C2D1 Pre-dose,C3D1 Pre-dose and 30min post-infusion,D1 pre-dose from C4 to C13, assessed up to approx. 1.5 years. Cycle=28 days.

End point values	Well-differentiated NET	Poorly-differentiated GEP-NEC		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	94	18		
Units: nanogram/mililiter (ng/mL)				
arithmetic mean (standard deviation)				
Cycle 1 Day 1 pre-dose, n= 89 / 17	0 (± 0)	0 (± 0)		
Cycle 1 Day 1 30 min post-dose, n= 87 / 14	106 (± 32.9)	100 (± 52.2)		
Cycle 2 Day 1 Pre-dose, n= 85 / 14	26.8 (± 9.76)	25.8 (± 9.30)		
Cycle 3 Day 1 pre-dose, n= 72 / 9	43.7 (± 18.9)	42.3 (± 19.6)		
Cycle 3 Day 1 30 min post-dose, n= 73 / 9	140 (± 46.7)	142 (± 44.3)		
Cycle 4 Day 1 pre-dose, n= 64 / 4	52.8 (± 25.1)	40.7 (± 17.2)		
Cycle 5 Day 1 pre-dose, n= 49 / 4	52.0 (± 32.3)	41.8 (± 8.88)		
Cycle 6 Day 1 pre-dose, n= 42 / 1	58.2 (± 31.6)	49.9 (± 999999)		
Cycle 7 Day 1 pre-dose, n= 36 / 2	64.3 (± 37.6)	66.9 (± 30.1)		
Cycle 8 Day 1 pre-dose, n= 28 / 2	59.6 (± 38.2)	64.7 (± 31.4)		
Cycle 9 Day 1 pre-dose, n= 23 / 1	65.1 (± 38.1)	93.7 (± 999999)		
Cycle 10 Day 1 pre-dose, n= 25 / 0	70.2 (± 40.2)	999999 (± 999999)		
Cycle 11 Day 1 pre-dose, n= 19 / 1	69.2 (± 39.1)	99.0 (± 999999)		
Cycle 12 Day 1 pre-dose, n= 14 / 1	71.7 (± 38.1)	111 (± 999999)		
Cycle 13 Day 1 pre-dose, n= 13 / 0	91.8 (± 46.0)	999999 (± 999999)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire-Core 30 (QLQ-C30) global health status/quality of life score

End point title	Change from baseline in European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire-Core 30 (QLQ-C30) global health status/quality of life score
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End point description:

The EORTC QLQ-C30 is a patient completed 30 item questionnaire that is composed of both multi-item scales and single-item measures. These include five functional scales, three symptom scales, six single items and a global health status/QoL scale. Global health status/QoL response options are 1 to 4. Scores were averaged and transformed to 0 to 100. Higher scores indicate better functioning. Change from Baseline was calculated by subtracting Baseline value from the selected visit value. A positive change from Baseline indicates improvement. Only those participants with evaluable data at the specified time points for this outcome measure were analyzed (represented by n=X / Y in the category titles).

Note: 999999 indicates value is not evaluable.

End point type	Secondary
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End point timeframe:

Baseline, every 8 weeks from Cycle 3 Day 1 for the first 13 cycles and every 12 weeks from Cycle 13 Day 1 thereafter and end of treatment, assessed up to approx. 1.5 years. Cycle=28 days.

End point values	Well-differentiated NET	Poorly-differentiated GEP-NEC		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	95	21		
Units: score on a scale				
arithmetic mean (standard deviation)				
Cycle 3 Day 1, n= 67 / 9	-1.00 (± 19.491)	-11.11 (± 27.003)		
Cycle 5 Day 1, n= 48 / 4	-1.91 (± 27.838)	-4.17 (± 17.347)		
Cycle 7 Day 1, n= 34 / 2	1.96 (± 29.945)	25.00 (± 35.355)		
Cycle 9 Day 1, n= 25 / 1	1.67 (± 31.823)	33.33 (± 999999)		
Cycle 11 Day 1, n= 21 / 0	-1.19 (± 28.048)	999999 (± 999999)		
Cycle 13 Day 1, n= 17 / 1	1.96 (± 27.088)	41.67 (± 999999)		
Cycle 16 Day 1, n= 3 / 0	-16.67 (± 16.667)	999999 (± 999999)		
End of Treatment, n= 40 / 8	-6.46 (± 23.607)	-22.92 (± 23.465)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in EQ-5D-5L index score

End point title	Change from baseline in EQ-5D-5L index score
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End point description:

The EQ-5D-5L descriptive system provides a profile of the participant's health state in 5 dimensions (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression). For each of these dimensions, the participant self-assigned a score: from 1 (no problems) to 5 (extreme problems). The 5 digit health states obtained for each dimension was converted into a single mean index value based on the EQ-5D crosswalk value set for the UK using the time trade-off method. This index ranges from -0.594 (worst health) to 1.0 (best health). Change from Baseline was calculated by subtracting Baseline value from the selected visit value. A positive change from baseline indicates improvement. Only those participants with evaluable data at the specified time points for this outcome measure were analyzed (represented by n=X / Y in the category titles).

Note: 999999 indicates value is not evaluable.

End point type	Secondary
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End point timeframe:

Baseline, every 8 weeks from Cycle 3 Day 1 for the first 13 cycles and every 12 weeks from Cycle 13 Day 1 thereafter, and end of treatment, assessed up to approx. 1.5 years. Cycle=28 days.

End point values	Well-differentiated NET	Poorly-differentiated GEP-NEC		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	95	21		
Units: score on a scale				
arithmetic mean (standard deviation)				
Cycle 3 Day 1, n= 66 / 8	0.03 (± 0.169)	-0.09 (± 0.157)		
Cycle 5 Day 1, n= 48 / 4	-0.02 (± 0.247)	0.02 (± 0.111)		
Cycle 7 Day 1, n= 33 / 2	-0.04 (± 0.241)	0.16 (± 0.135)		
Cycle 9 Day 1, n= 25 / 1	0.02 (± 0.247)	0.02 (± 999999)		
Cycle 11 Day 1, n= 21 / 0	0.02 (± 0.262)	999999 (± 999999)		
Cycle 13 Day 1, n= 16 / 1	-0.03 (± 0.299)	0.03 (± 999999)		
Cycle 16 Day 1, n= 3 / 0	-0.17 (± 0.085)	999999 (± 999999)		
End of treatment, n= 40 / 8	-0.10 (± 0.209)	-0.30 (± 0.263)		

Statistical analyses

No statistical analyses for this end point

Secondary: PDR001 Anti-drug antibodies (ADA) prevalence at baseline

End point title	PDR001 Anti-drug antibodies (ADA) prevalence at baseline
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End point description:

ADA prevalence at baseline was calculated as the proportion of participants who had an ADA positive result at baseline

End point type	Secondary
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End point timeframe:

Baseline

End point values	Well-differentiated NET	Poorly-differentiated GEP-NEC		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	88	17		
Units: Participants				
number (not applicable)	1.1	0		

Statistical analyses

No statistical analyses for this end point

Secondary: PDR001 ADA incidence on-treatment

End point title	PDR001 ADA incidence on-treatment
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End point description:

ADA incidence on treatment was calculated as the proportion of participants who were treatment-induced ADA positive (post-baseline ADA positive with ADA-negative sample at baseline) and treatment-boosted ADA positive (post-baseline ADA positive with titer that is at least the fold titer change greater than the ADA-positive baseline titer)

End point type	Secondary
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End point timeframe:

Cycle(C)1 Day(D)1 pre-dose and 30min post-infusion,C2D1 Pre-dose,C3D1 Pre-dose and 30min post-infusion,D1 pre-dose from C4 to C13 and every 6 cycles until C25, and end of treatment, assessed up to approx. 1.5 years. Cycle=28 days.

End point values	Well-differentiated NET	Poorly-differentiated GEP-NEC		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	84	17		
Units: Participants				
number (not applicable)	11.9	11.8		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events were collected from first dose of study treatment until end of study treatment plus 30 days post treatment, up to maximum duration of approximately 3 years.

Adverse event reporting additional description:

Consistent with EudraCT disclosure specifications, Novartis has reported under the Serious adverse events field "number of deaths resulting from adverse events" all those deaths, resulting from serious adverse events that are deemed to be causally related to treatment by the investigator

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	23.0
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Reporting groups

Reporting group title	PDR001 400mg Q4w@well-differentiated NET
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Reporting group description:

PDR001 400mg Q4w@well-differentiated NET

Reporting group title	All subjects
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Reporting group description:

All subjects

Reporting group title	PDR001 400mg Q4w@poorly-differentiated GEP-NEC
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Reporting group description:

PDR001 400mg Q4w@poorly-differentiated GEP-NEC

Serious adverse events	PDR001 400mg Q4w@well- differentiated NET	All subjects	PDR001 400mg Q4w@poorly- differentiated GEP- NEC
Total subjects affected by serious adverse events			
subjects affected / exposed	29 / 95 (30.53%)	35 / 116 (30.17%)	6 / 21 (28.57%)
number of deaths (all causes)	1	2	1
number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Tumour necrosis			
subjects affected / exposed	1 / 95 (1.05%)	1 / 116 (0.86%)	0 / 21 (0.00%)
occurrences causally related to treatment / all	1 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Peripheral ischaemia			
subjects affected / exposed	1 / 95 (1.05%)	1 / 116 (0.86%)	0 / 21 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

General disorders and administration site conditions			
Generalised oedema			
subjects affected / exposed	1 / 95 (1.05%)	1 / 116 (0.86%)	0 / 21 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Malaise			
subjects affected / exposed	1 / 95 (1.05%)	1 / 116 (0.86%)	0 / 21 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyrexia			
subjects affected / exposed	3 / 95 (3.16%)	3 / 116 (2.59%)	0 / 21 (0.00%)
occurrences causally related to treatment / all	2 / 3	2 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Immune system disorders			
Insulin autoimmune syndrome			
subjects affected / exposed	1 / 95 (1.05%)	1 / 116 (0.86%)	0 / 21 (0.00%)
occurrences causally related to treatment / all	1 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Bronchial obstruction			
subjects affected / exposed	1 / 95 (1.05%)	1 / 116 (0.86%)	0 / 21 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dyspnoea			
subjects affected / exposed	2 / 95 (2.11%)	2 / 116 (1.72%)	0 / 21 (0.00%)
occurrences causally related to treatment / all	1 / 2	1 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemoptysis			
subjects affected / exposed	1 / 95 (1.05%)	1 / 116 (0.86%)	0 / 21 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia aspiration			

subjects affected / exposed	0 / 95 (0.00%)	1 / 116 (0.86%)	1 / 21 (4.76%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 1
Pneumonitis			
subjects affected / exposed	2 / 95 (2.11%)	2 / 116 (1.72%)	0 / 21 (0.00%)
occurrences causally related to treatment / all	1 / 2	1 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary haemorrhage			
subjects affected / exposed	1 / 95 (1.05%)	1 / 116 (0.86%)	0 / 21 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Product issues			
Device occlusion			
subjects affected / exposed	0 / 95 (0.00%)	1 / 116 (0.86%)	1 / 21 (4.76%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	1 / 95 (1.05%)	1 / 116 (0.86%)	0 / 21 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Femur fracture			
subjects affected / exposed	1 / 95 (1.05%)	1 / 116 (0.86%)	0 / 21 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Post procedural haemorrhage			
subjects affected / exposed	0 / 95 (0.00%)	1 / 116 (0.86%)	1 / 21 (4.76%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin laceration			
subjects affected / exposed	1 / 95 (1.05%)	1 / 116 (0.86%)	0 / 21 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Cardiac disorders			
Torsade de pointes			
subjects affected / exposed	1 / 95 (1.05%)	1 / 116 (0.86%)	0 / 21 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Dizziness			
subjects affected / exposed	1 / 95 (1.05%)	1 / 116 (0.86%)	0 / 21 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatic encephalopathy			
subjects affected / exposed	1 / 95 (1.05%)	1 / 116 (0.86%)	0 / 21 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neuropathy peripheral			
subjects affected / exposed	1 / 95 (1.05%)	1 / 116 (0.86%)	0 / 21 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Post herpetic neuralgia			
subjects affected / exposed	1 / 95 (1.05%)	1 / 116 (0.86%)	0 / 21 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Seizure			
subjects affected / exposed	0 / 95 (0.00%)	1 / 116 (0.86%)	1 / 21 (4.76%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 95 (1.05%)	1 / 116 (0.86%)	0 / 21 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thrombocytopenia			

subjects affected / exposed	1 / 95 (1.05%)	1 / 116 (0.86%)	0 / 21 (0.00%)
occurrences causally related to treatment / all	1 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	6 / 95 (6.32%)	7 / 116 (6.03%)	1 / 21 (4.76%)
occurrences causally related to treatment / all	1 / 7	1 / 8	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal pain upper			
subjects affected / exposed	1 / 95 (1.05%)	1 / 116 (0.86%)	0 / 21 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Constipation			
subjects affected / exposed	2 / 95 (2.11%)	2 / 116 (1.72%)	0 / 21 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diarrhoea			
subjects affected / exposed	1 / 95 (1.05%)	1 / 116 (0.86%)	0 / 21 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastric haemorrhage			
subjects affected / exposed	0 / 95 (0.00%)	1 / 116 (0.86%)	1 / 21 (4.76%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vomiting			
subjects affected / exposed	1 / 95 (1.05%)	2 / 116 (1.72%)	1 / 21 (4.76%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Cholestasis			
subjects affected / exposed	0 / 95 (0.00%)	1 / 116 (0.86%)	1 / 21 (4.76%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatorenal syndrome			

subjects affected / exposed	0 / 95 (0.00%)	1 / 116 (0.86%)	1 / 21 (4.76%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	0 / 95 (0.00%)	1 / 116 (0.86%)	1 / 21 (4.76%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	1 / 95 (1.05%)	1 / 116 (0.86%)	0 / 21 (0.00%)
occurrences causally related to treatment / all	2 / 2	2 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Back pain			
subjects affected / exposed	2 / 95 (2.11%)	2 / 116 (1.72%)	0 / 21 (0.00%)
occurrences causally related to treatment / all	1 / 2	1 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bone pain			
subjects affected / exposed	1 / 95 (1.05%)	1 / 116 (0.86%)	0 / 21 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Muscular weakness			
subjects affected / exposed	1 / 95 (1.05%)	1 / 116 (0.86%)	0 / 21 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Candida infection			
subjects affected / exposed	1 / 95 (1.05%)	1 / 116 (0.86%)	0 / 21 (0.00%)
occurrences causally related to treatment / all	1 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Febrile infection			
subjects affected / exposed	1 / 95 (1.05%)	1 / 116 (0.86%)	0 / 21 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Gastroenteritis			
subjects affected / exposed	0 / 95 (0.00%)	1 / 116 (0.86%)	1 / 21 (4.76%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Influenza			
subjects affected / exposed	1 / 95 (1.05%)	1 / 116 (0.86%)	0 / 21 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	1 / 95 (1.05%)	1 / 116 (0.86%)	0 / 21 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory tract infection			
subjects affected / exposed	1 / 95 (1.05%)	1 / 116 (0.86%)	0 / 21 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Septic shock			
subjects affected / exposed	1 / 95 (1.05%)	1 / 116 (0.86%)	0 / 21 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Systemic infection			
subjects affected / exposed	0 / 95 (0.00%)	1 / 116 (0.86%)	1 / 21 (4.76%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Hypercalcaemia			
subjects affected / exposed	1 / 95 (1.05%)	2 / 116 (1.72%)	1 / 21 (4.76%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypoglycaemia			
subjects affected / exposed	1 / 95 (1.05%)	1 / 116 (0.86%)	0 / 21 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyponatraemia			

subjects affected / exposed	1 / 95 (1.05%)	1 / 116 (0.86%)	0 / 21 (0.00%)
occurrences causally related to treatment / all	1 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	PDR001 400mg Q4w@well- differentiated NET	All subjects	PDR001 400mg Q4w@poorly- differentiated GEP- NEC
Total subjects affected by non-serious adverse events			
subjects affected / exposed	86 / 95 (90.53%)	104 / 116 (89.66%)	18 / 21 (85.71%)
Vascular disorders			
Hypertension			
subjects affected / exposed	12 / 95 (12.63%)	12 / 116 (10.34%)	0 / 21 (0.00%)
occurrences (all)	16	16	0
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	12 / 95 (12.63%)	14 / 116 (12.07%)	2 / 21 (9.52%)
occurrences (all)	14	16	2
Fatigue			
subjects affected / exposed	36 / 95 (37.89%)	39 / 116 (33.62%)	3 / 21 (14.29%)
occurrences (all)	44	47	3
Oedema peripheral			
subjects affected / exposed	14 / 95 (14.74%)	17 / 116 (14.66%)	3 / 21 (14.29%)
occurrences (all)	15	18	3
Pain			
subjects affected / exposed	2 / 95 (2.11%)	4 / 116 (3.45%)	2 / 21 (9.52%)
occurrences (all)	2	4	2
Pyrexia			
subjects affected / exposed	24 / 95 (25.26%)	26 / 116 (22.41%)	2 / 21 (9.52%)
occurrences (all)	32	34	2
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	14 / 95 (14.74%)	16 / 116 (13.79%)	2 / 21 (9.52%)
occurrences (all)	17	19	2
Dyspnoea			

subjects affected / exposed occurrences (all)	9 / 95 (9.47%) 10	15 / 116 (12.93%) 16	6 / 21 (28.57%) 6
Psychiatric disorders			
Anxiety			
subjects affected / exposed	7 / 95 (7.37%)	7 / 116 (6.03%)	0 / 21 (0.00%)
occurrences (all)	7	7	0
Insomnia			
subjects affected / exposed	3 / 95 (3.16%)	5 / 116 (4.31%)	2 / 21 (9.52%)
occurrences (all)	3	5	2
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	3 / 95 (3.16%)	6 / 116 (5.17%)	3 / 21 (14.29%)
occurrences (all)	3	6	3
Amylase increased			
subjects affected / exposed	5 / 95 (5.26%)	6 / 116 (5.17%)	1 / 21 (4.76%)
occurrences (all)	5	6	1
Aspartate aminotransferase increased			
subjects affected / exposed	1 / 95 (1.05%)	5 / 116 (4.31%)	4 / 21 (19.05%)
occurrences (all)	1	5	4
Blood alkaline phosphatase increased			
subjects affected / exposed	3 / 95 (3.16%)	6 / 116 (5.17%)	3 / 21 (14.29%)
occurrences (all)	3	6	3
Gamma-glutamyltransferase increased			
subjects affected / exposed	6 / 95 (6.32%)	9 / 116 (7.76%)	3 / 21 (14.29%)
occurrences (all)	6	9	3
Lipase increased			
subjects affected / exposed	6 / 95 (6.32%)	7 / 116 (6.03%)	1 / 21 (4.76%)
occurrences (all)	7	8	1
Weight decreased			
subjects affected / exposed	9 / 95 (9.47%)	10 / 116 (8.62%)	1 / 21 (4.76%)
occurrences (all)	10	11	1
Weight increased			
subjects affected / exposed	4 / 95 (4.21%)	6 / 116 (5.17%)	2 / 21 (9.52%)
occurrences (all)	5	7	2
Nervous system disorders			

Headache subjects affected / exposed occurrences (all)	8 / 95 (8.42%) 8	9 / 116 (7.76%) 9	1 / 21 (4.76%) 1
Blood and lymphatic system disorders Anaemia subjects affected / exposed occurrences (all)	18 / 95 (18.95%) 21	21 / 116 (18.10%) 24	3 / 21 (14.29%) 3
Gastrointestinal disorders Abdominal distension subjects affected / exposed occurrences (all)	5 / 95 (5.26%) 7	7 / 116 (6.03%) 9	2 / 21 (9.52%) 2
Abdominal pain subjects affected / exposed occurrences (all)	17 / 95 (17.89%) 21	18 / 116 (15.52%) 22	1 / 21 (4.76%) 1
Abdominal pain upper subjects affected / exposed occurrences (all)	7 / 95 (7.37%) 9	7 / 116 (6.03%) 9	0 / 21 (0.00%) 0
Constipation subjects affected / exposed occurrences (all)	19 / 95 (20.00%) 24	22 / 116 (18.97%) 27	3 / 21 (14.29%) 3
Diarrhoea subjects affected / exposed occurrences (all)	26 / 95 (27.37%) 35	30 / 116 (25.86%) 40	4 / 21 (19.05%) 5
Dry mouth subjects affected / exposed occurrences (all)	5 / 95 (5.26%) 6	5 / 116 (4.31%) 6	0 / 21 (0.00%) 0
Gastrooesophageal reflux disease subjects affected / exposed occurrences (all)	2 / 95 (2.11%) 2	4 / 116 (3.45%) 4	2 / 21 (9.52%) 2
Nausea subjects affected / exposed occurrences (all)	20 / 95 (21.05%) 20	25 / 116 (21.55%) 25	5 / 21 (23.81%) 5
Vomiting subjects affected / exposed occurrences (all)	11 / 95 (11.58%) 15	14 / 116 (12.07%) 19	3 / 21 (14.29%) 4
Skin and subcutaneous tissue disorders			

Pruritus			
subjects affected / exposed	8 / 95 (8.42%)	9 / 116 (7.76%)	1 / 21 (4.76%)
occurrences (all)	10	11	1
Rash			
subjects affected / exposed	10 / 95 (10.53%)	12 / 116 (10.34%)	2 / 21 (9.52%)
occurrences (all)	12	14	2
Renal and urinary disorders			
Proteinuria			
subjects affected / exposed	6 / 95 (6.32%)	7 / 116 (6.03%)	1 / 21 (4.76%)
occurrences (all)	9	10	1
Endocrine disorders			
Hypothyroidism			
subjects affected / exposed	7 / 95 (7.37%)	7 / 116 (6.03%)	0 / 21 (0.00%)
occurrences (all)	7	7	0
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	8 / 95 (8.42%)	8 / 116 (6.90%)	0 / 21 (0.00%)
occurrences (all)	11	11	0
Back pain			
subjects affected / exposed	12 / 95 (12.63%)	14 / 116 (12.07%)	2 / 21 (9.52%)
occurrences (all)	15	17	2
Muscular weakness			
subjects affected / exposed	6 / 95 (6.32%)	6 / 116 (5.17%)	0 / 21 (0.00%)
occurrences (all)	8	8	0
Pain in extremity			
subjects affected / exposed	7 / 95 (7.37%)	7 / 116 (6.03%)	0 / 21 (0.00%)
occurrences (all)	7	7	0
Infections and infestations			
Infection			
subjects affected / exposed	0 / 95 (0.00%)	2 / 116 (1.72%)	2 / 21 (9.52%)
occurrences (all)	0	3	3
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	15 / 95 (15.79%)	18 / 116 (15.52%)	3 / 21 (14.29%)
occurrences (all)	21	24	3
Hyperglycaemia			

subjects affected / exposed	7 / 95 (7.37%)	8 / 116 (6.90%)	1 / 21 (4.76%)
occurrences (all)	12	13	1
Hypoalbuminaemia			
subjects affected / exposed	8 / 95 (8.42%)	8 / 116 (6.90%)	0 / 21 (0.00%)
occurrences (all)	8	8	0
Hypoglycaemia			
subjects affected / exposed	5 / 95 (5.26%)	5 / 116 (4.31%)	0 / 21 (0.00%)
occurrences (all)	5	5	0
Hyponatraemia			
subjects affected / exposed	5 / 95 (5.26%)	5 / 116 (4.31%)	0 / 21 (0.00%)
occurrences (all)	5	5	0

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
27 April 2017	The main purpose of this amendment was to add a group of approximately 20 patients with advanced or metastatic, poorly-differentiated gastroenteropancreatic neuroendocrine carcinoma (GEP-NEC). This cohort was added because of the following reasons: 1) biological rationale supporting the potential efficacy of immunotherapy; 2) no approved treatment and no consensus on the standard of care upon progression on 1st line chemotherapy. Moreover, the possibility of stopping the study early for futility at the time of the protocol defined interim analysis and the maximum treatment duration of 24 months was removed. Several inclusion/ exclusion criteria were modified.
12 January 2018	This amendment included the following modifications: 1) Inclusion of Part 2 (Expansion part) aiming to further characterize the efficacy and safety of PDR001 single agent in any of the well-differentiated NET cohorts if antitumor activity was observed in Part 1; 2) Possibility to implement the PDR001 liquid formulation for patients treated in Study Part 2 (expansion part); 3) Addition of an inclusion criterion regarding life expectancy of at least 3 months for patients treated in Study Part 2 in order to decrease the occurrence of deaths during the screening period and before the first tumor assessment scheduled 8 weeks after the first treatment dose.
24 May 2018	The major rationale for this amendment was to remove the possibility to expand the study to Part 2 when at least 20% overall response rate (ORR) per RECIST 1.1 by central radiology review was observed in any of the cohorts of the well-differentiated NET group. While the results of the additional efficacy analysis demonstrated an ORR of 20% in the thoracic cohort of the well-differentiated NET group and met the criterion for starting Part 2, no overwhelming supportive evidence of strong efficacy was observed on other endpoints. Moreover, all other cohorts showed ORR below 10%. Based on this, there was a change in the clinical development strategy for PDR001, which was no longer developed as a single agent immunotherapy in NET, and the study was not expanded into Part 2. Importantly, this change was not due to safety concerns.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported