Clinical trial results:
Prospective, randomized, multi-center, double-blind, controlled, two-period, two-treatment,
crossover, phase II trial to evaluate the safety and efficacy of PD-protec® in peritoneal
dialysis in patients with chronic renal failure

Summary

EudraCT number	2013-000400-42
Trial protocol	AT
Global end of trial date	10 November 2016

Results information

Result version number	v1 (current)
This version publication date	17 December 2021
First version publication date	17 December 2021

Trial information

Trial identification

Sponsor protocol code	ZP_PDProtec-201

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Zytoprotec GmbH
Sponsor organisation address	Mariannengasse 28/2, Vienna, Austria, 1090
Public contact	Bernd Seibel, Zytoprotec GmbH, 0043 14062002, office@zytoprotec.com
Scientific contact	Bernd Seibel, Zytoprotec GmbH, 0043 14062002, office@zytoprotec.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	10 November 2016
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	10 November 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of the trial was to examine if PD-protec provides benefits for peritoneal health by measuring cancer antigen 125 (CA-125) appearance rate and ex vivo stimulated interleukin (IL)-6 release in 1 hour PD effluent.

Protection of trial subjects:

All study participants were required to read and sign an Informed Consent Form.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	26 June 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	Austria: 50
Worldwide total number of subjects	50
EEA total number of subjects	50

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)	33
From 65 to 84 years	17
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

First patient in: 26-Jun-2014
Last patient out: 10-Nov-2016
Recruitment Duration: 24 months
Countries: Austria
Number of centers: 8

Pre-assignment

Screening details:

Screening tests have been conducted within 35 days prior to the beginning of the treatment I period.

Period 1

Period 1 title	Run-in
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Carer

Arms

Are arms mutually exclusive?	Yes
Arm title	Sequence A-B

Arm description:

Screening Tests have been conducted within 35 days prior to the beginning of Treatment Period I.

Arm type	Sequence A-B
Investigational medicinal product name	Physioneal 40
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for peritoneal dialysis
Routes of administration	Intraperitoneal use

Dosage and administration details:

A: Physioneal 40 Glucose 1.36%, 2.27% and 3.86% (as DCB).
Dose: volume of PDF will vary with patient’s body weight and based on patient’s pre-randomization PD prescription by physician

Arm title	Sequence B-A

Arm description:

Screening Tests have been conducted within 35 days prior to the beginning of Treatment Period I.

Arm type	Sequence B-A
Investigational medicinal product name	Physioneal 40 with added Placebo (Aqua bidest)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for peritoneal dialysis
Routes of administration	Intraperitoneal use

Dosage and administration details:

A: Physioneal 40 Glucose 1.36%, 2.27% and 3.86% (as DCB).
Dose: volume of PDF will vary with patient’s body weight and based on patient’s pre-randomization PD prescription by physician

Number of subjects in period 1	Sequence A-B	Sequence B-A
Started	25	25
Completed	24	23
Not completed	1	2
Consent withdrawn by subject	1	1
Adverse event, non-fatal	-	1

Period 2	
Period 2 title	Treatment period 1
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Carer

Arms

Are arms mutually exclusive?	Yes
Arm title	Treatment period 1 Sequence A-B

Arm description:

Physioneal 40 with added Placebo (Aqua bidest)

Arm type	Sequence A-B
Investigational medicinal product name	Physioneal 40 with added Placebo (Aqua bidest)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for peritoneal dialysis
Routes of administration	Intraperitoneal use

Dosage and administration details:

A: Physioneal 40 Glucose 1.36%, 2.27% and 3.86% (as DCB) with an added placebo (Aqua bidest®: water for injection)
Dose: volume of PDF will vary with patient’s body weight and based on patient’s pre-randomization PD prescription by physician

Arm title	Treatment period 1 Sequence B-A

Arm description:

Sequence A-B: Physioneal40 (Reference Product) - PD-protec (IMP)

Arm type	Sequence B-A
Investigational medicinal product name	PD-protec DCB 8.0
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for peritoneal dialysis
Routes of administration	Intraperitoneal use

Dosage and administration details:

Dipeptiven (N(2)-Alanyl-L-Glutamine 200 mg/mL) added to Physioneal 40 Glucose 1.36%, 2.27% and 3.86% to a final concentration of 8 mM (1.74 g/L).
Dose: amount of AGD per liter PDF is constant (8 mM); volume of PDF will vary with patient’s body weight and individual PD prescription by physician.

Number of subjects in period 2	Treatment period 1 Sequence A-B	Treatment period 1 Sequence B-A
Started	24	23
Completed	20	21
Not completed	4	2
Adverse event, non-fatal	2	2
Transplantation	2	-

Period 3	
Period 3 title	Treatment period 2
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Carer

Arms

Are arms mutually exclusive?	Yes
Arm title	Treatment period 2 Sequence A-B

Arm description:

Sequence A-B: Physioneal40 (Reference Product) - PD-protec (IMP)

Arm type	Sequence A-B
Investigational medicinal product name	PD-protec DCB 8.0
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for peritoneal dialysis
Routes of administration	Intraperitoneal use

Dosage and administration details:

Dipeptiven (N(2)-Alanyl-L-Glutamine 200 mg/mL) added to Physioneal 40 Glucose 1.36%, 2.27% and 3.86% to a final concentration of 8 mM (1.74 g/L).
Dose: amount of AGD per liter PDF is constant (8 mM); volume of PDF will vary with patient’s body weight and individual PD prescription by physician.

Arm title	Treatment period 2 Sequence B-A

Arm description:

Physioneal 40 with added Placebo (Aqua bidest)

Arm type	Sequence B-A
Investigational medicinal product name	Physioneal 40 with added Placebo (Aqua bidest)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for peritoneal dialysis
Routes of administration	Intraperitoneal use

Dosage and administration details:

A: Physioneal 40 Glucose 1.36%, 2.27% and 3.86% (as DCB) with an added placebo (Aqua bidest®: water for injection)
Dose: volume of PDF will vary with patient’s body weight and based on patient’s pre-randomization

Number of subjects in period 3	Treatment period 2 Sequence A-B	Treatment period 2 Sequence B-A
Started	20	21
Completed	19	18
Not completed	1	3
Adverse event, non-fatal	1	2
Transplantation	-	1

Baseline characteristics

Reporting groups	
Reporting group title	Sequence A-B
Reporting group description:	
Screening Tests have been conducted within 35 days prior to the beginning of Treatment Period I.	
Reporting group title	Sequence B-A
Reporting group description:	
Screening Tests have been conducted within 35 days prior to the beginning of Treatment Period I.	

Reporting group values	Sequence A-B	Sequence B-A	Total
Number of subjects	25	25	50
Age categorical			
Age was categorized as <65 years and ≥65 years.			
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)	16	17	33
From 65-84 years	9	8	17
85 years and over	0	0	0
Gender categorical Units: Subjects			
Female	7	10	17
Male	18	15	33

End points

End points reporting groups

Reporting group title	Sequence A-B
Reporting group description:	
Screening Tests have been conducted within 35 days prior to the beginning of Treatment Period I.	
Reporting group title	Sequence B-A
Reporting group description:	
Screening Tests have been conducted within 35 days prior to the beginning of Treatment Period I.	
Reporting group title	Treatment period 1 Sequence A-B
Reporting group description:	
Physioneal 40 with added Placebo (Aqua bidest)	
Reporting group title	Treatment period 1 Sequence B-A
Reporting group description:	
Sequence A-B: Physioneal40 (Reference Product) - PD-protec (IMP)	
Reporting group title	Treatment period 2 Sequence A-B
Reporting group description:	
Sequence A-B: Physioneal40 (Reference Product) - PD-protec (IMP)	
Reporting group title	Treatment period 2 Sequence B-A
Reporting group description:	
Physioneal 40 with added Placebo (Aqua bidest)	
Subject analysis set title	Physioneal
Subject analysis set type	Full analysis
Subject analysis set description:	
CA-125: concentration at 4-hour PDE; volume alone: concentration (4-hour) – concentration(0-hour); and (concentration (4-hour) – concentration (0-hour))*volume / time • IL-6 release: IL-6 release at 1-hour PDE / basal IL-6 release at 4-hour PDE	
Subject analysis set title	PD-Protec
Subject analysis set type	Full analysis
Subject analysis set description:	
CA-125: concentration at 4-hour PDE; volume alone: concentration (4-hour) – concentration(0-hour); and (concentration (4-hour) – concentration (0-hour))*volume / time • IL-6 release: IL-6 release at 1-hour PDE / basal IL-6 release at 4-hour PDE	

Primary: CA-125 apperance rate (U/min), FAS

End point title	CA-125 apperance rate (U/min), FAS
End point description:	
End point type	Primary
End point timeframe:	
CA-125: concentration at 4-hour PDE; volume alone: concentration (4-hour) – concentration(0-hour); and (concentration (4-hour) – concentration (0-hour))*volume / time • IL-6 release: IL-6 release at 1-hour PDE / basal IL-6 release at 4-hour PDE	

End point values	Physioneal	PD-Protec		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	41	41		
Units: U/min				
median (standard deviation)	253.9 (± 103.1)	302.3 (± 141.7)		

Statistical analyses

Statistical analysis title	Primary

Statistical analysis description:

The sample size calculation was based on the effect on the CA-125 concentration using data from the previous first-in-man trial.18 Sample sizes between 32 and 36 patients would result in power values between 89% and 92% assuming a difference in means of 7 units and a crossover analysis of variance root mean square error of 8.5 using a 1-sided 2-group t-test. An effect of 7 units in concentration would translate to mean difference of approximately 58 U/min in the CA-125 appearance rate.

Comparison groups	Physioneal v PD-Protec
Number of subjects included in analysis	82
Analysis specification	Post-hoc
Analysis type	superiority
P-value	= 0.0001
Method	Log-transformed

Primary: stimulated IL-6 release (1 h) ([log10] pg/ml), FAS

End point title	stimulated IL-6 release (1 h) ([log10] pg/ml), FAS

End point description:

End point type	Primary

End point timeframe:

CA-125: concentration at 4-hour PDE; volume alone: concentration (4-hour) – concentration(0-hour); and (concentration (4-hour) – concentration (0-hour))*volume / time
• IL-6 release: IL-6 release at 1-hour PDE / basal IL-6 release at 4-hour PDE

End point values	Physioneal	PD-Protec		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	41	41		
Units: pg/ml				
arithmetic mean (standard deviation)	1.36 (± 0.55)	1.52 (± 0.48)		

Statistical analyses

Statistical analysis title	Primary

Statistical analysis description:

The sample size calculation was based on the effect on the CA-125 concentration using data from the previous first-in-man trial.18 Sample sizes between 32 and 36 patients would result in power values between 89% and 92% assuming a difference in means of 7 units and a crossover analysis of variance root mean square error of 8.5 using a 1-sided 2-group t-test. An effect of 7 units in concentration would translate to mean difference of approximately 58 U/min in the CA-125 appearance rate.

Comparison groups	Physioneal v PD-Protec
Number of subjects included in analysis	82
Analysis specification	Post-hoc
Analysis type	superiority
P-value	= 0.004
Method	Log-transformed

Adverse events

Adverse events information[1]	
Timeframe for reporting adverse events:	
From signing of the informed consent until the end of the study (end of study visit).	
Adverse event reporting additional description:	
Safety population: All patients treated at least once with the study medication. All patients were analyzed according to the treatment they received.	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	19.1

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

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: No serious AE was related to the study treatment, less than 5% of the non serious AEs were assessed as at least possibly related to study treatment

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
18 March 2014	Version 1.2 In addition to a number of minor changes, relevant changes included: • Change in inclusion criteria no. 4 ("Extraneal allowed; Nutrineal not allowed" was deleted) and no. 5 (text was added "in CAPD patients or, in the case of APD, during nightly cycler treatment [additional exchange with Extraneal allowed; Nutrineal not allowed]) • Clarifications with respect to the following were added: i) IMP handling manual will be provided to patients: ii) up to 3-month data for some PD parameters will be acceptable to be documented at baseline, III) performance of PET procedure at Visit 1
24 June 2014	Version 1.3 The following changes were implemented in the protocol: • Study medication (IMP and reference product) was to be mixed by a study nurse at patient's home within 72 hours prior to drug administration. • In case of an infection, the PET could be delayed for additional 7 days.
06 March 2015	Version 1.4 Study will not be conducted in Hungary, as initially planned, but only in Austria. This resulted in a number of changes in the protocol, including: • Total number of centers and patients to be enrolled were reduced • One stratification factor (SCB) was excluded • Re-estimation of sample size • Implementation of a complementary randomization schedule and additional emergency envelops with additional 48 randomization numbers stratified by peritonitis status
05 November 2015	Version 1.5 In addition to few minor changes, relevant changes included: • Change in inclusion criteria no. 5 (text added is shown in bold"…in CAPD patients or, in the case of APD, during nightly cycler treatment on at least 5 out of 7 days per week [additional exchange with Extraneal allowed; Nutrineal not allowed]) • Randomization was to performed after screening, and not at baseline (Visit 1)
08 April 2016	Version 1.6 Major changes in the study design were implemented with this protocol amendment. Relevant changes included: • Change in study title ("adaptive design" was excluded from the title) • Re-estimation of sample size and study power • Cancelation of interim analysis and related changes in the primary analysis • Cancelation of data monitoring committee involvement • Modification of the stratification by previous peritonitis (yes/no), aiming for 1:1 ratio if a sufficient number of patients with positive peritonitis could be enrolled

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

http://www.ncbi.nlm.nih.gov/pubmed/30360960