



## Clinical trial results:

**A participant and investigator-blinded, randomized, placebo-controlled Phase 2a study to investigate the pharmacokinetics, pharmacodynamics, safety and tolerability of TIN816 in patients with sepsis-associated acute kidney injury**

### Summary

EudraCT number	2022-000887-23
Trial protocol	ES FR DE BE HU
Global end of trial date	25 April 2024

### Results information

Result version number	v1 (current)
This version publication date	30 April 2025
First version publication date	30 April 2025

### Trial information

#### Trial identification

Sponsor protocol code	CTIN816B12201
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#### Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT05507437
WHO universal trial number (UTN)	-

Notes:

### Sponsors

Sponsor organisation name	Novartis Pharmaceuticals
Sponsor organisation address	Novartis Campus, Basel, Switzerland,
Public contact	Novartis Pharma AG, Clinical Disclosure Office, 41 613241111, novartis.email@novartis.com
Scientific contact	Novartis Pharma AG, Clinical Disclosure Office, 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	25 April 2024
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	25 April 2024
Was the trial ended prematurely?	No

Notes:

## General information about the trial

Main objective of the trial:

The primary objective was to assess the pharmacokinetics (PK) of TIN816 with a single dose of intravenous (IV) infusion in hospitalized adult participants with diagnosis of sepsis-associated acute kidney injury.

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	22 November 2022
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	Belgium: 8
Country: Number of subjects enrolled	Hungary: 1
Country: Number of subjects enrolled	France: 9
Country: Number of subjects enrolled	Spain: 1
Country: Number of subjects enrolled	Germany: 1
Worldwide total number of subjects	20
EEA total number of subjects	20

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)	7
From 65 to 84 years	12
85 years and over	1

## Subject disposition

### Recruitment

Recruitment details:

Participants took part in 7 investigative sites in 5 countries.

### Pre-assignment

Screening details:

The study consisted of a screening period up to 48 hours.

### Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Carer

### Arms

Are arms mutually exclusive?	Yes
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<b>Arm title</b>	TIN816
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Arm description:

TIN816 2 mg/kg intravenous dose on Day 1.

Arm type	Experimental
Investigational medicinal product name	TIN816
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Single i.v. infusion of TIN816 administered at a dose of 2 mg/kg.

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

Placebo intravenous dose on Day 1

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Single i.v. infusion of placebo.

<b>Number of subjects in period 1</b>	TIN816	Placebo
Started	16	4
Completed	12	3
Not completed	4	1
Consent withdrawn by subject	1	1

Adverse event	3	-
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## Baseline characteristics

### Reporting groups

Reporting group title	TIN816
Reporting group description: TIN816 2 mg/kg intravenous dose on Day 1.	
Reporting group title	Placebo
Reporting group description: Placebo intravenous dose on Day 1	

Reporting group values	TIN816	Placebo	Total
Number of subjects	16	4	20
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)	6	1	7
From 65-84 years	10	2	12
85 years and over	0	1	1
Age Continuous Units: years			
arithmetic mean	66.25	68.0	-
standard deviation	± 12.250	± 19.950	-
Sex: Female, Male Units: participants			
Female	3	1	4
Male	13	3	16
Race/Ethnicity, Customized Units: Subjects			
White	2	1	3
Not Reported	14	3	17

## End points

### End points reporting groups

Reporting group title	TIN816
Reporting group description:	TIN816 2 mg/kg intravenous dose on Day 1.
Reporting group title	Placebo
Reporting group description:	Placebo intravenous dose on Day 1

### Primary: Area under serum concentration-time curve from time zero to the last measurable concentration sampling time (AUClast) of TIN816

End point title	Area under serum concentration-time curve from time zero to the last measurable concentration sampling time (AUClast) of TIN816 <sup>[1][2]</sup>
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End point description:

AUClast is the area under the serum concentration-time curve from time zero to the time of last quantifiable concentration (tlast) of TIN816. TIN816 serum concentrations were determined using the actual recorded sampling times and non-compartmental method with Phoenix WinNonlin (Version 8.3). TIN816 concentrations were determined by a validated ligand binding assay with a lower limit of quantification (LLOQ) of 10 ng/mL.

End point type	Primary
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End point timeframe:

Day 1 (Pre-dose and 2 hours), Day 2, Day 3, Day 5, Day 8, Day 14, Day 30, Day 60 and Day 90

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: only analyzed descriptively.

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

Justification: PK Endpoint not analyzed for participants on placebo

End point values	TIN816			
Subject group type	Reporting group			
Number of subjects analysed	16			
Units: day*ug/mL				
geometric mean (geometric coefficient of variation)	99.9 (± 49.0)			

### Statistical analyses

No statistical analyses for this end point

### Primary: Maximum serum concentration (Cmax) of TIN816

End point title	Maximum serum concentration (Cmax) of TIN816 <sup>[3][4]</sup>
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End point description:

Cmax is defined as the maximum (peak) observed concentration following a dose. TIN816 serum concentrations were determined using the actual recorded sampling times and non-compartmental method with Phoenix WinNonlin (Version 8.3). TIN816 concentrations were determined by a validated

ligand binding assay with a lower limit of quantification (LLOQ) of 10 ng/mL.

End point type	Primary
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End point timeframe:

Day 1 (Pre-dose and 2 hours), Day 2, Day 3, Day 5, Day 8, Day 14, Day 30, Day 60 and Day 90

Notes:

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

Justification: only analyzed descriptively.

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

Justification: PK Endpoint not analyzed for participants on placebo

<b>End point values</b>	TIN816			
Subject group type	Reporting group			
Number of subjects analysed	16			
Units: ug/mL				
geometric mean (geometric coefficient of variation)	40.8 (± 36.7)			

## Statistical analyses

No statistical analyses for this end point

### Primary: Terminal elimination half-life (T<sub>1/2</sub>) of TIN816

End point title	Terminal elimination half-life (T <sub>1/2</sub> ) of TIN816 <sup>[5][6]</sup>
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End point description:

T<sub>1/2</sub> is the elimination half-life associated with the terminal slope. TIN816 serum concentrations were determined using the actual recorded sampling times and non-compartmental method with Phoenix WinNonlin (Version 8.3). TIN816 concentrations were determined by a validated ligand binding assay with a lower limit of quantification (LLOQ) of 10 ng/mL.

End point type	Primary
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End point timeframe:

Day 1 (Pre-dose and 2 hours), Day 2, Day 3, Day 5, Day 8, Day 14, Day 30, Day 60 and Day 90

Notes:

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

Justification: only analyzed descriptively.

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

Justification: PK Endpoint not analyzed for participants on placebo

<b>End point values</b>	TIN816			
Subject group type	Reporting group			
Number of subjects analysed	13			
Units: Day				
geometric mean (geometric coefficient of variation)	5.70 (± 14.8)			

## Statistical analyses

No statistical analyses for this end point

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**Primary: Total body clearance (CL) of TIN816**

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End point title	Total body clearance (CL) of TIN816 <sup>[7][8]</sup>
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End point description:

CL is the total body clearance of TIN816 from the serum following intravenous administration (volume x time-1). TIN816 serum concentrations were determined using the actual recorded sampling times and non-compartmental method with Phoenix WinNonlin (Version 8.3). TIN816 concentrations were determined by a validated ligand binding assay with a lower limit of quantification (LLOQ) of 10 ng/mL.

End point type	Primary
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End point timeframe:

Day 1 (Pre-dose and 2 hours), Day 2, Day 3, Day 5, Day 8, Day 14, Day 30, Day 60 and Day 90

Notes:

[7] - 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: only analyzed descriptively.

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

Justification: PK Endpoint not analyzed for participants on placebo

End point values	TIN816			
Subject group type	Reporting group			
Number of subjects analysed	13			
Units: Liter/day/kg				
geometric mean (geometric coefficient of variation)	0.0189 ( $\pm$ 24.7)			

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**Statistical analyses**

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No statistical analyses for this end point

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**Primary: The apparent volume of distribution (Vz) of TIN816**

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End point title	The apparent volume of distribution (Vz) of TIN816 <sup>[9][10]</sup>
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End point description:

Vz is the apparent volume of distribution during terminal phase following intravenous administration. TIN816 serum concentrations were determined using the actual recorded sampling times and non-compartmental method with Phoenix WinNonlin (Version 8.3). TIN816 concentrations were determined by a validated ligand binding assay with a lower limit of quantification (LLOQ) of 10 ng/mL.

End point type	Primary
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End point timeframe:

Day 1 (Pre-dose and 2 hours), Day 2, Day 3, Day 5, Day 8, Day 14, Day 30, Day 60 and Day 90

Notes:

[9] - 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: only analyzed descriptively.

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

Justification: PK Endpoint not analyzed for participants on placebo

<b>End point values</b>	TIN816			
Subject group type	Reporting group			
Number of subjects analysed	13			
Units: Liter/kg				
geometric mean (geometric coefficient of variation)	0.155 (± 31.7)			

## Statistical analyses

No statistical analyses for this end point

### Primary: Time to reach maximum serum concentration (Tmax) of TIN816

End point title	Time to reach maximum serum concentration (Tmax) of TIN816 <sup>[11][12]</sup>
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End point description:

Tmax is the time to reach maximum (peak) drug concentration after single-dose administration (time). TIN816 serum concentrations were determined using the actual recorded sampling times and non-compartmental method with Phoenix WinNonlin (Version 8.3). TIN816 concentrations were determined by a validated ligand binding assay with a lower limit of quantification (LLOQ) of 10 ng/mL.

End point type	Primary
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End point timeframe:

Day 1 (Pre-dose and 2 hours), Day 2, Day 3, Day 5, Day 8, Day 14, Day 30, Day 60 and Day 90

Notes:

[11] - 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: only analyzed descriptively.

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

Justification: PK Endpoint not analyzed for participants on placebo

<b>End point values</b>	TIN816			
Subject group type	Reporting group			
Number of subjects analysed	16			
Units: Day				
median (full range (min-max))	0.0868 (0.0597 to 0.163)			

## Statistical analyses

No statistical analyses for this end point

### Primary: Area under the serum concentration-time curve from time zero extrapolated to infinity (AUC[0-inf]) of TIN816

End point title	Area under the serum concentration-time curve from time zero extrapolated to infinity (AUC[0-inf]) of TIN816 <sup>[13][14]</sup>
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End point description:

The AUC from time zero to infinity (mass x time x volume<sup>-1</sup>). TIN816 serum concentrations were determined using the actual recorded sampling times and non-compartmental method with Phoenix

WinNonlin (Version 8.3). TIN816 concentrations were determined by a validated ligand binding assay with a lower limit of quantification (LLOQ) of 10 ng/mL.

End point type	Primary
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End point timeframe:

Day 1 (Pre-dose and 2 hours), Day 2, Day 3, Day 5, Day 8, Day 14, Day 30, Day 60 and Day 90

Notes:

[13] - 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: only analyzed descriptively.

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

Justification: PK Endpoint not analyzed for participants on placebo

<b>End point values</b>	TIN816			
Subject group type	Reporting group			
Number of subjects analysed	13			
Units: day*ug/mL				
geometric mean (geometric coefficient of variation)	104 (± 47.7)			

## Statistical analyses

No statistical analyses for this end point

## Secondary: Number of participants with treatment emergent adverse events (AEs) and serious adverse events (SAEs)

End point title	Number of participants with treatment emergent adverse events (AEs) and serious adverse events (SAEs)
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End point description:

Number of participants with treatment emergent AEs (any AE regardless of seriousness) and SAEs.

End point type	Secondary
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End point timeframe:

Adverse events were reported from first dose of study treatment until end of study treatment plus follow up period, up to a maximum duration of approximately 90 days.

<b>End point values</b>	TIN816	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	16	4		
Units: Participants				
Adverse events	14	4		
Serious Adverse events	11	1		

## Statistical analyses

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No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Adverse events were reported from first dose of study treatment until end of study treatment plus follow up period, up to a maximum duration of approximately 90 days.

Assessment type	Systematic
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### Dictionary used

Dictionary name	MedDRA
Dictionary version	27.0

### Reporting groups

Reporting group title	TIN816
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Reporting group description:

TIN816

Reporting group title	All Patients
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Reporting group description:

All Patients

Reporting group title	Placebo
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Reporting group description:

Placebo

<b>Serious adverse events</b>	TIN816	All Patients	Placebo
<b>Total subjects affected by serious adverse events</b>			
subjects affected / exposed	11 / 16 (68.75%)	12 / 20 (60.00%)	1 / 4 (25.00%)
number of deaths (all causes)	3	3	0
number of deaths resulting from adverse events	0	0	0
<b>Vascular disorders</b>			
Distributive shock			
subjects affected / exposed	1 / 16 (6.25%)	1 / 20 (5.00%)	0 / 4 (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
<b>Cardiac disorders</b>			
Atrial fibrillation			
subjects affected / exposed	1 / 16 (6.25%)	1 / 20 (5.00%)	0 / 4 (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
Cardio-respiratory arrest			
subjects affected / exposed	1 / 16 (6.25%)	1 / 20 (5.00%)	0 / 4 (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			
Cerebral haematoma			
subjects affected / exposed	1 / 16 (6.25%)	1 / 20 (5.00%)	0 / 4 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 1	0 / 0
Blood and lymphatic system disorders			
Neutropenia			
subjects affected / exposed	1 / 16 (6.25%)	1 / 20 (5.00%)	0 / 4 (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
Disseminated intravascular coagulation			
subjects affected / exposed	1 / 16 (6.25%)	1 / 20 (5.00%)	0 / 4 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 1	0 / 0
Anaemia			
subjects affected / exposed	1 / 16 (6.25%)	1 / 20 (5.00%)	0 / 4 (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
Gastrointestinal disorders			
Pancreatitis			
subjects affected / exposed	1 / 16 (6.25%)	1 / 20 (5.00%)	0 / 4 (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			
Pulmonary embolism			
subjects affected / exposed	1 / 16 (6.25%)	1 / 20 (5.00%)	0 / 4 (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
Lung disorder			
subjects affected / exposed	1 / 16 (6.25%)	1 / 20 (5.00%)	0 / 4 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 1	0 / 0
Acute respiratory failure			

subjects affected / exposed	1 / 16 (6.25%)	1 / 20 (5.00%)	0 / 4 (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
Acute respiratory distress syndrome			
subjects affected / exposed	1 / 16 (6.25%)	1 / 20 (5.00%)	0 / 4 (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
Skin and subcutaneous tissue disorders			
Toxic epidermal necrolysis			
subjects affected / exposed	1 / 16 (6.25%)	1 / 20 (5.00%)	0 / 4 (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
Renal and urinary disorders			
Urinary retention			
subjects affected / exposed	1 / 16 (6.25%)	1 / 20 (5.00%)	0 / 4 (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
Renal tubular necrosis			
subjects affected / exposed	1 / 16 (6.25%)	1 / 20 (5.00%)	0 / 4 (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
Acute kidney injury			
subjects affected / exposed	2 / 16 (12.50%)	2 / 20 (10.00%)	0 / 4 (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
Infections and infestations			
Sepsis			
subjects affected / exposed	0 / 16 (0.00%)	1 / 20 (5.00%)	1 / 4 (25.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	2 / 16 (12.50%)	2 / 20 (10.00%)	0 / 4 (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

Peritonitis			
subjects affected / exposed	0 / 16 (0.00%)	1 / 20 (5.00%)	1 / 4 (25.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infectious pleural effusion			
subjects affected / exposed	1 / 16 (6.25%)	1 / 20 (5.00%)	0 / 4 (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	2 / 16 (12.50%)	2 / 20 (10.00%)	0 / 4 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract infection			
subjects affected / exposed	1 / 16 (6.25%)	1 / 20 (5.00%)	0 / 4 (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

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

<b>Non-serious adverse events</b>	TIN816	All Patients	Placebo
Total subjects affected by non-serious adverse events			
subjects affected / exposed	14 / 16 (87.50%)	18 / 20 (90.00%)	4 / 4 (100.00%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Plasma cell myeloma			
subjects affected / exposed	1 / 16 (6.25%)	1 / 20 (5.00%)	0 / 4 (0.00%)
occurrences (all)	1	1	0
Transitional cell carcinoma			
subjects affected / exposed	0 / 16 (0.00%)	1 / 20 (5.00%)	1 / 4 (25.00%)
occurrences (all)	0	1	1
Vascular disorders			
Hypertension			
subjects affected / exposed	1 / 16 (6.25%)	2 / 20 (10.00%)	1 / 4 (25.00%)
occurrences (all)	1	2	1
Haemorrhage			

subjects affected / exposed occurrences (all)	1 / 16 (6.25%) 1	1 / 20 (5.00%) 1	0 / 4 (0.00%) 0
Haemodynamic instability subjects affected / exposed occurrences (all)	1 / 16 (6.25%) 1	1 / 20 (5.00%) 1	0 / 4 (0.00%) 0
Deep vein thrombosis subjects affected / exposed occurrences (all)	1 / 16 (6.25%) 1	2 / 20 (10.00%) 2	1 / 4 (25.00%) 1
Pelvic venous thrombosis subjects affected / exposed occurrences (all)	0 / 16 (0.00%) 0	1 / 20 (5.00%) 1	1 / 4 (25.00%) 1
Jugular vein thrombosis subjects affected / exposed occurrences (all)	1 / 16 (6.25%) 1	1 / 20 (5.00%) 1	0 / 4 (0.00%) 0
Hypotension subjects affected / exposed occurrences (all)	2 / 16 (12.50%) 2	2 / 20 (10.00%) 2	0 / 4 (0.00%) 0
Shock haemorrhagic subjects affected / exposed occurrences (all)	1 / 16 (6.25%) 1	1 / 20 (5.00%) 1	0 / 4 (0.00%) 0
General disorders and administration site conditions			
Pyrexia subjects affected / exposed occurrences (all)	1 / 16 (6.25%) 1	1 / 20 (5.00%) 1	0 / 4 (0.00%) 0
Hyperthermia subjects affected / exposed occurrences (all)	1 / 16 (6.25%) 2	1 / 20 (5.00%) 2	0 / 4 (0.00%) 0
Chest pain subjects affected / exposed occurrences (all)	1 / 16 (6.25%) 1	1 / 20 (5.00%) 1	0 / 4 (0.00%) 0
Systemic inflammatory response syndrome subjects affected / exposed occurrences (all)	1 / 16 (6.25%) 1	1 / 20 (5.00%) 1	0 / 4 (0.00%) 0
Respiratory, thoracic and mediastinal disorders			

Respiratory distress subjects affected / exposed occurrences (all)	2 / 16 (12.50%) 2	2 / 20 (10.00%) 2	0 / 4 (0.00%) 0
Respiratory acidosis subjects affected / exposed occurrences (all)	1 / 16 (6.25%) 1	1 / 20 (5.00%) 1	0 / 4 (0.00%) 0
Pulmonary embolism subjects affected / exposed occurrences (all)	1 / 16 (6.25%) 1	1 / 20 (5.00%) 1	0 / 4 (0.00%) 0
Hypercapnia subjects affected / exposed occurrences (all)	1 / 16 (6.25%) 1	1 / 20 (5.00%) 1	0 / 4 (0.00%) 0
Acute respiratory distress syndrome subjects affected / exposed occurrences (all)	1 / 16 (6.25%) 1	1 / 20 (5.00%) 1	0 / 4 (0.00%) 0
Psychiatric disorders			
Agitation subjects affected / exposed occurrences (all)	2 / 16 (12.50%) 2	2 / 20 (10.00%) 2	0 / 4 (0.00%) 0
Confusional state subjects affected / exposed occurrences (all)	1 / 16 (6.25%) 1	1 / 20 (5.00%) 1	0 / 4 (0.00%) 0
Delirium subjects affected / exposed occurrences (all)	2 / 16 (12.50%) 2	3 / 20 (15.00%) 3	1 / 4 (25.00%) 1
Insomnia subjects affected / exposed occurrences (all)	0 / 16 (0.00%) 0	1 / 20 (5.00%) 1	1 / 4 (25.00%) 1
Investigations			
Aspartate aminotransferase increased subjects affected / exposed occurrences (all)	2 / 16 (12.50%) 2	2 / 20 (10.00%) 2	0 / 4 (0.00%) 0
Alanine aminotransferase increased subjects affected / exposed occurrences (all)	2 / 16 (12.50%) 2	2 / 20 (10.00%) 2	0 / 4 (0.00%) 0
Cardiac disorders			

Stress cardiomyopathy subjects affected / exposed occurrences (all)	1 / 16 (6.25%) 1	1 / 20 (5.00%) 1	0 / 4 (0.00%) 0
Atrioventricular block first degree subjects affected / exposed occurrences (all)	1 / 16 (6.25%) 1	1 / 20 (5.00%) 1	0 / 4 (0.00%) 0
Atrial fibrillation subjects affected / exposed occurrences (all)	2 / 16 (12.50%) 2	2 / 20 (10.00%) 2	0 / 4 (0.00%) 0
Nervous system disorders Extrapyramidal disorder subjects affected / exposed occurrences (all)	1 / 16 (6.25%) 1	1 / 20 (5.00%) 1	0 / 4 (0.00%) 0
Intensive care unit acquired weakness subjects affected / exposed occurrences (all)	0 / 16 (0.00%) 0	1 / 20 (5.00%) 1	1 / 4 (25.00%) 1
Myoclonus subjects affected / exposed occurrences (all)	1 / 16 (6.25%) 1	1 / 20 (5.00%) 1	0 / 4 (0.00%) 0
Blood and lymphatic system disorders Anaemia subjects affected / exposed occurrences (all)	3 / 16 (18.75%) 4	5 / 20 (25.00%) 6	2 / 4 (50.00%) 2
Lymphopenia subjects affected / exposed occurrences (all)	1 / 16 (6.25%) 1	1 / 20 (5.00%) 1	0 / 4 (0.00%) 0
Thrombocytopenia subjects affected / exposed occurrences (all)	2 / 16 (12.50%) 2	2 / 20 (10.00%) 2	0 / 4 (0.00%) 0
Ear and labyrinth disorders Ear haemorrhage subjects affected / exposed occurrences (all)	1 / 16 (6.25%) 1	1 / 20 (5.00%) 1	0 / 4 (0.00%) 0
Eye disorders Phlyctenular keratoconjunctivitis			

subjects affected / exposed occurrences (all)	1 / 16 (6.25%) 1	1 / 20 (5.00%) 1	0 / 4 (0.00%) 0
<b>Gastrointestinal disorders</b>			
Abdominal pain subjects affected / exposed occurrences (all)	0 / 16 (0.00%) 0	1 / 20 (5.00%) 1	1 / 4 (25.00%) 1
Constipation subjects affected / exposed occurrences (all)	3 / 16 (18.75%) 3	3 / 20 (15.00%) 3	0 / 4 (0.00%) 0
Diarrhoea subjects affected / exposed occurrences (all)	1 / 16 (6.25%) 1	3 / 20 (15.00%) 3	2 / 4 (50.00%) 2
Faecaloma subjects affected / exposed occurrences (all)	2 / 16 (12.50%) 2	2 / 20 (10.00%) 2	0 / 4 (0.00%) 0
Gastrointestinal haemorrhage subjects affected / exposed occurrences (all)	1 / 16 (6.25%) 1	1 / 20 (5.00%) 1	0 / 4 (0.00%) 0
Gastrooesophageal reflux disease subjects affected / exposed occurrences (all)	2 / 16 (12.50%) 2	2 / 20 (10.00%) 2	0 / 4 (0.00%) 0
Impaired gastric emptying subjects affected / exposed occurrences (all)	0 / 16 (0.00%) 0	1 / 20 (5.00%) 1	1 / 4 (25.00%) 1
Nausea subjects affected / exposed occurrences (all)	0 / 16 (0.00%) 0	1 / 20 (5.00%) 1	1 / 4 (25.00%) 1
Oesophagitis subjects affected / exposed occurrences (all)	1 / 16 (6.25%) 1	1 / 20 (5.00%) 1	0 / 4 (0.00%) 0
Oral mucosal blistering subjects affected / exposed occurrences (all)	0 / 16 (0.00%) 0	1 / 20 (5.00%) 1	1 / 4 (25.00%) 1
Pancreatitis subjects affected / exposed occurrences (all)	0 / 16 (0.00%) 0	1 / 20 (5.00%) 1	1 / 4 (25.00%) 1

Hepatobiliary disorders			
Hyperbilirubinaemia			
subjects affected / exposed	1 / 16 (6.25%)	1 / 20 (5.00%)	0 / 4 (0.00%)
occurrences (all)	1	1	0
Hepatic cytolysis			
subjects affected / exposed	1 / 16 (6.25%)	1 / 20 (5.00%)	0 / 4 (0.00%)
occurrences (all)	1	1	0
Cholecystitis acute			
subjects affected / exposed	1 / 16 (6.25%)	1 / 20 (5.00%)	0 / 4 (0.00%)
occurrences (all)	1	1	0
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	1 / 16 (6.25%)	1 / 20 (5.00%)	0 / 4 (0.00%)
occurrences (all)	1	1	0
Pruritus			
subjects affected / exposed	0 / 16 (0.00%)	1 / 20 (5.00%)	1 / 4 (25.00%)
occurrences (all)	0	1	1
Decubitus ulcer			
subjects affected / exposed	1 / 16 (6.25%)	1 / 20 (5.00%)	0 / 4 (0.00%)
occurrences (all)	1	1	0
Renal and urinary disorders			
Dysuria			
subjects affected / exposed	0 / 16 (0.00%)	1 / 20 (5.00%)	1 / 4 (25.00%)
occurrences (all)	0	1	1
Renal failure			
subjects affected / exposed	0 / 16 (0.00%)	1 / 20 (5.00%)	1 / 4 (25.00%)
occurrences (all)	0	1	1
Urinary retention			
subjects affected / exposed	1 / 16 (6.25%)	1 / 20 (5.00%)	0 / 4 (0.00%)
occurrences (all)	1	1	0
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	1 / 16 (6.25%)	1 / 20 (5.00%)	0 / 4 (0.00%)
occurrences (all)	1	1	0
Gouty arthritis			

subjects affected / exposed occurrences (all)	0 / 16 (0.00%) 0	1 / 20 (5.00%) 1	1 / 4 (25.00%) 1
Musculoskeletal pain subjects affected / exposed occurrences (all)	2 / 16 (12.50%) 2	2 / 20 (10.00%) 2	0 / 4 (0.00%) 0
Rhabdomyolysis subjects affected / exposed occurrences (all)	1 / 16 (6.25%) 1	1 / 20 (5.00%) 1	0 / 4 (0.00%) 0
<b>Infections and infestations</b>			
Bronchitis subjects affected / exposed occurrences (all)	1 / 16 (6.25%) 1	1 / 20 (5.00%) 1	0 / 4 (0.00%) 0
Bacteraemia subjects affected / exposed occurrences (all)	1 / 16 (6.25%) 1	1 / 20 (5.00%) 1	0 / 4 (0.00%) 0
COVID-19 subjects affected / exposed occurrences (all)	1 / 16 (6.25%) 1	1 / 20 (5.00%) 1	0 / 4 (0.00%) 0
Endocarditis subjects affected / exposed occurrences (all)	1 / 16 (6.25%) 1	1 / 20 (5.00%) 1	0 / 4 (0.00%) 0
Herpes simplex reactivation subjects affected / exposed occurrences (all)	1 / 16 (6.25%) 1	1 / 20 (5.00%) 1	0 / 4 (0.00%) 0
Oral candidiasis subjects affected / exposed occurrences (all)	1 / 16 (6.25%) 1	1 / 20 (5.00%) 1	0 / 4 (0.00%) 0
Oral herpes subjects affected / exposed occurrences (all)	0 / 16 (0.00%) 0	1 / 20 (5.00%) 1	1 / 4 (25.00%) 1
Pneumonia subjects affected / exposed occurrences (all)	0 / 16 (0.00%) 0	1 / 20 (5.00%) 1	1 / 4 (25.00%) 1
Skin bacterial infection subjects affected / exposed occurrences (all)	1 / 16 (6.25%) 1	1 / 20 (5.00%) 1	0 / 4 (0.00%) 0

Systemic candida			
subjects affected / exposed	1 / 16 (6.25%)	1 / 20 (5.00%)	0 / 4 (0.00%)
occurrences (all)	1	1	0
Urinary tract candidiasis			
subjects affected / exposed	1 / 16 (6.25%)	1 / 20 (5.00%)	0 / 4 (0.00%)
occurrences (all)	1	1	0
Urinary tract infection			
subjects affected / exposed	1 / 16 (6.25%)	1 / 20 (5.00%)	0 / 4 (0.00%)
occurrences (all)	2	2	0
Urosepsis			
subjects affected / exposed	0 / 16 (0.00%)	1 / 20 (5.00%)	1 / 4 (25.00%)
occurrences (all)	0	1	1
Clostridium difficile infection			
subjects affected / exposed	0 / 16 (0.00%)	1 / 20 (5.00%)	1 / 4 (25.00%)
occurrences (all)	0	1	1
Metabolism and nutrition disorders			
Hyperkalaemia			
subjects affected / exposed	1 / 16 (6.25%)	1 / 20 (5.00%)	0 / 4 (0.00%)
occurrences (all)	1	1	0
Hyperglycaemia			
subjects affected / exposed	1 / 16 (6.25%)	1 / 20 (5.00%)	0 / 4 (0.00%)
occurrences (all)	1	1	0
Hyperferritinaemia			
subjects affected / exposed	0 / 16 (0.00%)	1 / 20 (5.00%)	1 / 4 (25.00%)
occurrences (all)	0	1	1
Folate deficiency			
subjects affected / exposed	0 / 16 (0.00%)	1 / 20 (5.00%)	1 / 4 (25.00%)
occurrences (all)	0	1	1
Hypernatraemia			
subjects affected / exposed	3 / 16 (18.75%)	4 / 20 (20.00%)	1 / 4 (25.00%)
occurrences (all)	3	4	1
Hyperphosphataemia			
subjects affected / exposed	1 / 16 (6.25%)	1 / 20 (5.00%)	0 / 4 (0.00%)
occurrences (all)	1	1	0
Hypertriglyceridaemia			

subjects affected / exposed	3 / 16 (18.75%)	3 / 20 (15.00%)	0 / 4 (0.00%)
occurrences (all)	3	3	0
<b>Hyperuricaemia</b>			
subjects affected / exposed	1 / 16 (6.25%)	1 / 20 (5.00%)	0 / 4 (0.00%)
occurrences (all)	1	1	0
<b>Hypervolaemia</b>			
subjects affected / exposed	1 / 16 (6.25%)	1 / 20 (5.00%)	0 / 4 (0.00%)
occurrences (all)	1	1	0
<b>Hypoalbuminaemia</b>			
subjects affected / exposed	1 / 16 (6.25%)	1 / 20 (5.00%)	0 / 4 (0.00%)
occurrences (all)	1	1	0
<b>Hypocalcaemia</b>			
subjects affected / exposed	3 / 16 (18.75%)	3 / 20 (15.00%)	0 / 4 (0.00%)
occurrences (all)	3	3	0
<b>Hypokalaemia</b>			
subjects affected / exposed	2 / 16 (12.50%)	3 / 20 (15.00%)	1 / 4 (25.00%)
occurrences (all)	2	4	2
<b>Hypomagnesaemia</b>			
subjects affected / exposed	1 / 16 (6.25%)	1 / 20 (5.00%)	0 / 4 (0.00%)
occurrences (all)	1	1	0
<b>Hypophosphataemia</b>			
subjects affected / exposed	3 / 16 (18.75%)	4 / 20 (20.00%)	1 / 4 (25.00%)
occurrences (all)	3	4	1
<b>Malnutrition</b>			
subjects affected / exposed	1 / 16 (6.25%)	2 / 20 (10.00%)	1 / 4 (25.00%)
occurrences (all)	1	2	1
<b>Metabolic acidosis</b>			
subjects affected / exposed	1 / 16 (6.25%)	2 / 20 (10.00%)	1 / 4 (25.00%)
occurrences (all)	1	2	1
<b>Vitamin C deficiency</b>			
subjects affected / exposed	1 / 16 (6.25%)	1 / 20 (5.00%)	0 / 4 (0.00%)
occurrences (all)	1	1	0
<b>Vitamin D deficiency</b>			
subjects affected / exposed	1 / 16 (6.25%)	2 / 20 (10.00%)	1 / 4 (25.00%)
occurrences (all)	1	2	1



## **More information**

### **Substantial protocol amendments (globally)**

Were there any global substantial amendments to the protocol? No

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### **Interruptions (globally)**

Were there any global interruptions to the trial? No

### **Limitations and caveats**

None reported