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Sponsor

Novartis Pharmaceuticals

Generic Drug Name

Not Applicable

Trial Indication(s)

Acute Kidney Injury Due to Sepsis

Protocol Number

CTIN816B12201

Protocol Title

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

Clinical Trial Phase

Phase 2

Phase of Drug Development

Phase 2

Study Start/End Dates

Study Start Date: November 22, 2022 (Actual)

Primary Completion Date: April 25, 2024 (Actual)
Study Completion Date: April 25, 2024 (Actual)

Reason for Termination (If applicable)

Not Applicable

Study Design/Methodology

This was a multi-center, participant and investigator-blinded, randomized, placebo-controlled, parallel group study to characterize PK/PD profile and to evaluate safety and efficacy of TIN816 in hospitalized adult participants with diagnosis of sepsis and acute kidney injury (AKI). The study aimed to enroll 20 participants and randomized to receive either TIN816 or placebo in a ratio of approximately 3:1.

Eligible participants received a single administration of TIN8161 at the dose of 2.0 mg/kg on Day 1 (Treatment period) and were followed for a period of 90 days.

The study consisted of a screening period (up to 48 hours), treatment period (Day 1), and post-treatment period (Day 2 to 90).

Centers

7 centers in 5 countries: Belgium(2), Hungary(1), France(2), Spain(1), Germany(1)

Objectives:

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 SA-AKI.

The secondary objective was to assess the safety and tolerability of TIN816 vs placebo.

Test Product (s), Dose(s), and Mode(s) of Administration

The investigational treatment was TIN816, administered at a dose of 2.0 mg/kg as a one-time IV infusion over approximately 2 hours. Placebo was 0.9% saline solution.

Statistical Methods

The pharmacokinetic (PK) set and Safety Set comprised of all participants who received any investigational drug. The PK analysis set included all participants who survived Day 7 with at least one available valid PK concentration measurement.

No inferential statistical analysis was conducted.

Descriptive summary statistics for TIN816 PK parameters have been provided. Summary statistics included means (arithmetic and geometric), standard deviation (SD), CV (arithmetic and geometric), median, minimum and maximum. An exception to this was Tmax where median, minimum, and maximum were presented.

Study Population: Key Inclusion/Exclusion Criteria

Inclusion Criteria:

1. Signed informed consent must be obtained prior to participation in the study.

2. ≥ 18 and ≤ 85 years of age.

3. Admitted to ICU or intermediate/HDU.

4. Diagnosis of sepsis according to criteria defined by The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3) based on:

Suspected or confirmed infection
SOFA score of 2 or more (excluding renal component)

5. Diagnosis of AKI Stage 1 or greater per the following criterion at randomization :

An absolute increase in serum or plasma creatinine (CR) by ≥0.3 mg/dL (≥26.5 µmol/L) within 48 hours or presumed to have occurred in the previous 48 hours as compared to the reference creatinine baseline.

For hospital-acquired AKI, a stable serum creatinine obtained in the hospital prior to AKI should be used as reference baseline, otherwise, baseline serum creatinine in the following order of preference:

Median value within 3 months of the hospital admission. If not available:
Median value between 3 and 6 months prior to hospital admission. If not available:
At hospital admission.

Exclusion criteria

1. Not expected to survive for 24 hours.

2. Not expected to survive for 30 days due to medical conditions other than SA-AKI.

3. History of CKD with a documented estimated GFR <45 ml/min prior to development of AKI.

4. Receiving RRT or a decision has been made to initiate RRT within 24 hours of admission.

5. Weight is less than 40 kg or more than 125 kg .

6. Has life support limitations (eg, do not resuscitate, do not dialyze, do not intubate).

7. AKI diagnosis according to the AKI inclusion criteria for a period longer than 48 hours prior to study drug administration.

8. Presence of AKI for a period longer than 48 hours prior to study drug administration as suggested by clinical manifestations, e.g., prolonged oliguria or severe renal dysfunction (eg, serum creatinine > 4 mg/dL) on admission without a history of CKD.

9. Evidence of recovery from AKI based on the investigator's clinical judgement prior to randomization.

10. AKI is most likely attributable to causes other than sepsis such as nephrotoxic drugs (Non-steroidal anti-inflammatory drugs (NSAIDs), contrast, aminoglycosides), other medical conditions (e.g. heart failure, liver failure, acute abdominal aortic aneurysm, dissection, renal artery stenosis) or urinary obstruction.

11. Documented (biopsy proven) or suspected history of acute or sub-acute kidney diseases such as rapidly progressive glomerular nephritis (RPGN) and acute interstitial nephritis (AIN).

12. Patients who are post-nephrectomy.

13. Patients who are on dual antiplatelet therapy.

14. Patients who are thrombocytopenic at screening (Platelet count <100,000 microliter) or other high risk for bleeding in the opinion of the investigator.

15. Immunosuppressed patients:

History of immunodeficiency diseases or known HIV test positive.
Is receiving immunosuppressant treatment or is on chronic high doses (high-dose therapy exceeding 2 weeks of treatment) of steroids equivalent to prednisone/prednisolone 0.5 mg/kg/day, including solid organ transplant patients. Patients with septic shock treated with hydrocortisone (e.g., 3 × 100 mg) can be included.

16. Active hepatitis (defined as (a) abnormal liver enzymes (Alanine aminotransferase (ALT), Gamma-glutamyl transferase (GGT), ALP > 3x Upper Limit of Normal (ULN) or (b)) for active hepatitis B or C infection, a positive Hepatitis B Virus (HBV) or Hepatitis C Virus (HCV) serology or patients with advanced chronic liver disease, confirmed by a Child-Pugh score of 10–15 (Class C).

17. Acute pancreatitis with no established source of infection.

18. Active hematological malignancy (previous hematological malignancies that are not actively treated are allowable).

19. Burns requiring ICU treatment.

20. Sepsis attributed to confirmed COVID-19.

21. Use of other investigational drugs within 5 half-lives of enrollment within 30 days (e.g., small molecules) / or until the expected pharmacodynamic effect has returned to baseline (e.g., biologics), whichever is longer; or longer if required by local regulations.

22. History of hypersensitivity to the study treatment or its excipients or to drugs of similar chemical classes.

23. Any medical conditions that could significantly increase risk of participants' safety by participating in this study according to investigator's judgement.

24. Women with a positive pregnancy test, pregnancy or breast feeding.

25. Women of child-bearing potential

Participant Flow Table

Overall Study

	TIN816	Placebo	Total
Arm/Group Description	TIN816 2 mg/kg intravenous dose on Day 1.	Placebo intravenous dose on Day 1	
Started	16	4	20
Completed	12	3	15
Not Completed	4	1	5
Withdrawal by Subject	1	1	2
Death	3	0	3

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Baseline Characteristics

	TIN816	Placebo	Total
Arm/Group Description	TIN816 2 mg/kg intravenous dose on Day 1.	Placebo intravenous dose on Day 1	
Number of Participants [units: participants]	16	4	20
Baseline Analysis Population Description			
Age Continuous (units: years) Analysis Population Type: Mean ± Standard Deviation			
	66.25±12.250	68.0±19.950	66.60±13.484
Sex: Female, Male (units: participants) Analysis Population Type: Participants Count of Participants (Not Applicable)			
Female	3	1	4
Male	13	3	16
Race/Ethnicity, Customized (units: participants) Analysis Population Type: Participants Count of Participants (Not Applicable)			
White	2	1	3
Not Reported	14	3	17

Primary Outcome Result(s)

Maximum serum concentration (Cmax) of TIN816

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.
Time Frame	Day 1 (Pre-dose and 2 hours), Day 2, Day 3, Day 5, Day 8, Day 14, Day 30, Day 60 and Day 90
Analysis Population Description	The pharmacokinetic (PK) analysis set included all participants who survived Day 7 with at least one available valid (i.e., not flagged for exclusion) PK concentration measurement, who received complete study drug regardless of infusion duration.

	TIN816
Arm/Group Description	TIN816 2 mg/kg intravenous dose on Day 1.
Number of Participants Analyzed [units: participants]	16
Maximum serum concentration (Cmax) of TIN816 (units: ug/mL)	**Geometric Mean (Geometric Coefficient of Variation)**
	40.8 (36.7%)

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

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.
Time Frame	Day 1 (Pre-dose and 2 hours), Day 2, Day 3, Day 5, Day 8, Day 14, Day 30, Day 60 and Day 90
Analysis Population Description	The PK analysis set included all participants who survived Day 7 with at least one available valid (i.e., not flagged for exclusion) PK concentration measurement, who received complete study drug regardless of infusion duration.

	TIN816
Arm/Group Description	TIN816 2 mg/kg intravenous dose on Day 1.
Number of Participants Analyzed [units: participants]	16
Area under serum concentration-time curve from time zero to the last measurable concentration sampling time (AUClast) of TIN816 (units: day*ug/mL)	**Geometric Mean** **(Geometric Coefficient of Variation)**
	99.9 (49.0%)

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

Description	The AUC from time zero to infinity (mass x time x volume-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.
Time Frame	Day 1 (Pre-dose and 2 hours), Day 2, Day 3, Day 5, Day 8, Day 14, Day 30, Day 60 and Day 90
Analysis Population Description	Patients in the PK analysis set with an available value for the outcome measure. The PK analysis set included all participants who survived Day 7 with at least one available valid (i.e., not flagged for exclusion) PK concentration measurement, who received complete study drug regardless of infusion duration.

	TIN816
Arm/Group Description	TIN816 2 mg/kg intravenous dose on Day 1.
Number of Participants Analyzed [units: participants]	13
Area under the serum concentration-time curve from time zero extrapolated to infinity (AUC[0-inf]) of TIN816 (units: day*ug/mL)	**Geometric Mean** **(Geometric Coefficient of Variation)**
	104 (47.7%)

Time to reach maximum serum concentration (Tmax) of TIN816

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.
Time Frame	Day 1 (Pre-dose and 2 hours), Day 2, Day 3, Day 5, Day 8, Day 14, Day 30, Day 60 and Day 90
Analysis Population Description	The PK analysis set included all participants who survived Day 7 with at least one available valid (i.e., not flagged for exclusion) PK concentration measurement, who received complete study drug regardless of infusion duration.

	TIN816
Arm/Group Description	TIN816 2 mg/kg intravenous dose on Day 1.
Number of Participants Analyzed [units: participants]	16
Time to reach maximum serum concentration (Tmax) of TIN816 (units: Day)	**Median (Full Range)**
	0.0868 (0.0597 to 0.163)

Terminal elimination half-life (T1/2) of TIN816

Description	T1/2 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.
Time Frame	Day 1 (Pre-dose and 2 hours), Day 2, Day 3, Day 5, Day 8, Day 14, Day 30, Day 60 and Day 90
Analysis Population Description	Patients in the PK analysis set with an available value for the outcome measure. The PK analysis set included all participants who survived Day 7 with at least one available valid (i.e., not flagged for exclusion) PK concentration measurement, who received complete study drug regardless of infusion duration.

	TIN816
Arm/Group Description	TIN816 2 mg/kg intravenous dose on Day 1.

Number of Participants Analyzed [units: participants]	13
Terminal elimination half-life (T1/2) of TIN816 (units: Day)	**Geometric Mean (Geometric Coefficient of Variation)**
	5.70 (14.8%)

Total body clearance (CL) of TIN816

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.
Time Frame	Day 1 (Pre-dose and 2 hours), Day 2, Day 3, Day 5, Day 8, Day 14, Day 30, Day 60 and Day 90
Analysis Population Description	Patients in the PK analysis set with an available value for the outcome measure. The PK analysis set included all participants who survived Day 7 with at least one available valid (i.e., not flagged for exclusion) PK concentration measurement, who received complete study drug regardless of infusion duration.

	TIN816
Arm/Group Description	TIN816 2 mg/kg intravenous dose on Day 1.
Number of Participants Analyzed [units: participants]	13
Total body clearance (CL) of TIN816 (units: Liter/day/kg)	**Geometric Mean (Geometric Coefficient of Variation)**
	0.0189 (24.7%)

The apparent volume of distribution (Vz) of TIN816

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

Analysis Population Description	Patients in the PK analysis set with an available value for the outcome measure. The PK analysis set included all participants who survived Day 7 with at least one available valid (i.e., not flagged for exclusion) PK concentration measurement, who received complete study drug regardless of infusion duration.

	TIN816
Arm/Group Description	TIN816 2 mg/kg intravenous dose on Day 1.
Number of Participants Analyzed [units: participants]	13
The apparent volume of distribution (Vz) of TIN816 (units: Liter/kg)	**Geometric Mean (Geometric Coefficient of Variation)**
	0.155 (31.7%)

Secondary Outcome Result(s)

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

Description	Number of participants with treatment emergent AEs (any AE regardless of seriousness) and SAEs.
Time Frame	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.
Analysis Population Description	The safety analysis set (SAF) included all participants who received one dose of study treatment. Participants were analyzed according to the study treatment received, where treatment received was defined as the participants took at least one dose of that study treatment regardless treatment group randomized to.

	TIN816	Placebo
Arm/Group Description	TIN816 2 mg/kg intravenous dose on Day 1.	Placebo intravenous dose on Day 1
Number of Participants Analyzed [units: participants]	16	4

Number of participants with treatment emergent adverse events (AEs) and serious adverse events (SAEs) (units: Participants)	**Count of Participants (Not Applicable)**	**Count of Participants (Not Applicable)**
Adverse events	14 (87.5%)	4 (100%)
Serious Adverse events	11 (68.75%)	1 (25%)

Safety Results

Time Frame	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.
Source Vocabulary for Table Default	MedDRA (27.0)
Collection Approach for Table Default	Systematic Assessment

All-Cause Mortality

	TIN816 N = 16	**Placebo N = 4**	**All Patients N = 20**
Arm/Group Description	TIN816 2 mg/kg intravenous dose on Day 1.	Placebo intravenous dose on Day 1	All Patients
Total Number Affected	3	0	3
Total Number At Risk	16	4	20

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Serious Adverse Events

	TIN816 N = 16	Placebo N = 4	All Patients N = 20
Arm/Group Description	TIN816 2 mg/kg intravenous dose on Day 1.	Placebo intravenous dose on Day 1	All Patients
Total # Affected by any Serious Adverse Event	11	1	12
Total # at Risk by any Serious Adverse Event	16	4	20
Blood and lymphatic system disorders			
Anaemia	1 (6.25%)	0 (0.00%)	1 (5.00%)
Disseminated intravascular coagulation	1 (6.25%)	0 (0.00%)	1 (5.00%)
Neutropenia	1 (6.25%)	0 (0.00%)	1 (5.00%)
Cardiac disorders			
Atrial fibrillation	1 (6.25%)	0 (0.00%)	1 (5.00%)
Cardio-respiratory arrest	1 (6.25%)	0 (0.00%)	1 (5.00%)
Gastrointestinal disorders			
Pancreatitis	1 (6.25%)	0 (0.00%)	1 (5.00%)
Infections and infestations			
Infectious pleural effusion	1 (6.25%)	0 (0.00%)	1 (5.00%)
Peritonitis	0 (0.00%)	1 (25.00%)	1 (5.00%)
Pneumonia	2 (12.50%)	0 (0.00%)	2 (10.00%)
Sepsis	0 (0.00%)	1 (25.00%)	1 (5.00%)
Septic shock	2 (12.50%)	0 (0.00%)	2 (10.00%)
Urinary tract infection	1 (6.25%)	0 (0.00%)	1 (5.00%)

Nervous system disorders			
Cerebral haematoma	1 (6.25%)	0 (0.00%)	1 (5.00%)
Renal and urinary disorders			
Acute kidney injury	2 (12.50%)	0 (0.00%)	2 (10.00%)
Renal tubular necrosis	1 (6.25%)	0 (0.00%)	1 (5.00%)
Urinary retention	1 (6.25%)	0 (0.00%)	1 (5.00%)
Respiratory, thoracic and mediastinal disorders			
Acute respiratory distress syndrome	1 (6.25%)	0 (0.00%)	1 (5.00%)
Acute respiratory failure	1 (6.25%)	0 (0.00%)	1 (5.00%)
Lung disorder	1 (6.25%)	0 (0.00%)	1 (5.00%)
Pulmonary embolism	1 (6.25%)	0 (0.00%)	1 (5.00%)
Skin and subcutaneous tissue disorders			
Toxic epidermal necrolysis	1 (6.25%)	0 (0.00%)	1 (5.00%)
Vascular disorders			
Distributive shock	1 (6.25%)	0 (0.00%)	1 (5.00%)

Other (Not Including Serious) Adverse Events

Frequent Event Reporting Threshold	5%

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	TIN816 N = 16	Placebo N = 4	All Patients N = 20
Arm/Group Description	TIN816 2 mg/kg intravenous dose on Day 1.	Placebo intravenous dose on Day 1	All Patients
Total # Affected by any Other Adverse Event	14	4	18
Total # at Risk by any Other Adverse Event	16	4	20
Blood and lymphatic system disorders			
Anaemia	3 (18.75%)	2 (50.00%)	5 (25.00%)
Lymphopenia	1 (6.25%)	0 (0.00%)	1 (5.00%)
Thrombocytopenia	2 (12.50%)	0 (0.00%)	2 (10.00%)
Cardiac disorders			
Atrial fibrillation	2 (12.50%)	0 (0.00%)	2 (10.00%)
Atrioventricular block first degree	1 (6.25%)	0 (0.00%)	1 (5.00%)
Stress cardiomyopathy	1 (6.25%)	0 (0.00%)	1 (5.00%)
Ear and labyrinth disorders			
Ear haemorrhage	1 (6.25%)	0 (0.00%)	1 (5.00%)
Eye disorders			
Phlyctenular keratoconjunctivitis	1 (6.25%)	0 (0.00%)	1 (5.00%)
Gastrointestinal disorders			
Abdominal pain	0 (0.00%)	1 (25.00%)	1 (5.00%)
Constipation	3 (18.75%)	0 (0.00%)	3 (15.00%)
Diarrhoea	1 (6.25%)	2 (50.00%)	3 (15.00%)
Faecaloma	2 (12.50%)	0 (0.00%)	2 (10.00%)
Gastrointestinal haemorrhage	1 (6.25%)	0 (0.00%)	1 (5.00%)

Gastrooesophageal reflux disease	2 (12.50%)	0 (0.00%)	2 (10.00%)
Impaired gastric emptying	0 (0.00%)	1 (25.00%)	1 (5.00%)
Nausea	0 (0.00%)	1 (25.00%)	1 (5.00%)
Oesophagitis	1 (6.25%)	0 (0.00%)	1 (5.00%)
Oral mucosal blistering	0 (0.00%)	1 (25.00%)	1 (5.00%)
Pancreatitis	0 (0.00%)	1 (25.00%)	1 (5.00%)
General disorders and administration site conditions			
Chest pain	1 (6.25%)	0 (0.00%)	1 (5.00%)
Hyperthermia	1 (6.25%)	0 (0.00%)	1 (5.00%)
Pyrexia	1 (6.25%)	0 (0.00%)	1 (5.00%)
Systemic inflammatory response syndrome	1 (6.25%)	0 (0.00%)	1 (5.00%)
Hepatobiliary disorders			
Cholecystitis acute	1 (6.25%)	0 (0.00%)	1 (5.00%)
Hepatic cytolysis	1 (6.25%)	0 (0.00%)	1 (5.00%)
Hyperbilirubinaemia	1 (6.25%)	0 (0.00%)	1 (5.00%)
Infections and infestations			
Bacteraemia	1 (6.25%)	0 (0.00%)	1 (5.00%)
Bronchitis	1 (6.25%)	0 (0.00%)	1 (5.00%)
Clostridium difficile infection	0 (0.00%)	1 (25.00%)	1 (5.00%)
COVID-19	1 (6.25%)	0 (0.00%)	1 (5.00%)
Endocarditis	1 (6.25%)	0 (0.00%)	1 (5.00%)
Herpes simplex reactivation	1 (6.25%)	0 (0.00%)	1 (5.00%)
Oral candidiasis	1 (6.25%)	0 (0.00%)	1 (5.00%)
Oral herpes	0 (0.00%)	1 (25.00%)	1 (5.00%)

Pneumonia	0 (0.00%)	1 (25.00%)	1 (5.00%)
Skin bacterial infection	1 (6.25%)	0 (0.00%)	1 (5.00%)
Systemic candida	1 (6.25%)	0 (0.00%)	1 (5.00%)
Urinary tract candidiasis	1 (6.25%)	0 (0.00%)	1 (5.00%)
Urinary tract infection	1 (6.25%)	0 (0.00%)	1 (5.00%)
Urosepsis	0 (0.00%)	1 (25.00%)	1 (5.00%)
Investigations			
Alanine aminotransferase increased	2 (12.50%)	0 (0.00%)	2 (10.00%)
Aspartate aminotransferase increased	2 (12.50%)	0 (0.00%)	2 (10.00%)
Metabolism and nutrition disorders			
Folate deficiency	0 (0.00%)	1 (25.00%)	1 (5.00%)
Hyperferritinaemia	0 (0.00%)	1 (25.00%)	1 (5.00%)
Hyperglycaemia	1 (6.25%)	0 (0.00%)	1 (5.00%)
Hyperkalaemia	1 (6.25%)	0 (0.00%)	1 (5.00%)
Hypernatraemia	3 (18.75%)	1 (25.00%)	4 (20.00%)
Hyperphosphataemia	1 (6.25%)	0 (0.00%)	1 (5.00%)
Hypertriglyceridaemia	3 (18.75%)	0 (0.00%)	3 (15.00%)
Hyperuricaemia	1 (6.25%)	0 (0.00%)	1 (5.00%)
Hypervolaemia	1 (6.25%)	0 (0.00%)	1 (5.00%)
Hypoalbuminaemia	1 (6.25%)	0 (0.00%)	1 (5.00%)
Hypocalcaemia	3 (18.75%)	0 (0.00%)	3 (15.00%)
Hypokalaemia	2 (12.50%)	1 (25.00%)	3 (15.00%)
Hypomagnesaemia	1 (6.25%)	0 (0.00%)	1 (5.00%)
Hypophosphataemia	3 (18.75%)	1 (25.00%)	4 (20.00%)
Malnutrition	1 (6.25%)	1 (25.00%)	2 (10.00%)

Metabolic acidosis	1 (6.25%)	1 (25.00%)	2 (10.00%)
Vitamin C deficiency	1 (6.25%)	0 (0.00%)	1 (5.00%)
Vitamin D deficiency	1 (6.25%)	1 (25.00%)	2 (10.00%)
Musculoskeletal and connective tissue disorders			
Back pain	1 (6.25%)	0 (0.00%)	1 (5.00%)
Gouty arthritis	0 (0.00%)	1 (25.00%)	1 (5.00%)
Musculoskeletal pain	2 (12.50%)	0 (0.00%)	2 (10.00%)
Rhabdomyolysis	1 (6.25%)	0 (0.00%)	1 (5.00%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Plasma cell myeloma	1 (6.25%)	0 (0.00%)	1 (5.00%)
Transitional cell carcinoma	0 (0.00%)	1 (25.00%)	1 (5.00%)
Nervous system disorders			
Extrapyramidal disorder	1 (6.25%)	0 (0.00%)	1 (5.00%)
Intensive care unit acquired weakness	0 (0.00%)	1 (25.00%)	1 (5.00%)
Myoclonus	1 (6.25%)	0 (0.00%)	1 (5.00%)
Psychiatric disorders			
Agitation	2 (12.50%)	0 (0.00%)	2 (10.00%)
Confusional state	1 (6.25%)	0 (0.00%)	1 (5.00%)
Delirium	2 (12.50%)	1 (25.00%)	3 (15.00%)
Insomnia	0 (0.00%)	1 (25.00%)	1 (5.00%)
Renal and urinary disorders			
Dysuria	0 (0.00%)	1 (25.00%)	1 (5.00%)
Renal failure	0 (0.00%)	1 (25.00%)	1 (5.00%)

Urinary retention	1 (6.25%)	0 (0.00%)	1 (5.00%)
Respiratory, thoracic and mediastinal disorders			
Acute respiratory distress syndrome	1 (6.25%)	0 (0.00%)	1 (5.00%)
Hypercapnia	1 (6.25%)	0 (0.00%)	1 (5.00%)
Pulmonary embolism	1 (6.25%)	0 (0.00%)	1 (5.00%)
Respiratory acidosis	1 (6.25%)	0 (0.00%)	1 (5.00%)
Respiratory distress	2 (12.50%)	0 (0.00%)	2 (10.00%)
Skin and subcutaneous tissue disorders			
Decubitus ulcer	1 (6.25%)	0 (0.00%)	1 (5.00%)
Pruritus	0 (0.00%)	1 (25.00%)	1 (5.00%)
Rash	1 (6.25%)	0 (0.00%)	1 (5.00%)
Vascular disorders			
Deep vein thrombosis	1 (6.25%)	1 (25.00%)	2 (10.00%)
Haemodynamic instability	1 (6.25%)	0 (0.00%)	1 (5.00%)
Haemorrhage	1 (6.25%)	0 (0.00%)	1 (5.00%)
Hypertension	1 (6.25%)	1 (25.00%)	2 (10.00%)
Hypotension	2 (12.50%)	0 (0.00%)	2 (10.00%)
Jugular vein thrombosis	1 (6.25%)	0 (0.00%)	1 (5.00%)
Pelvic venous thrombosis	0 (0.00%)	1 (25.00%)	1 (5.00%)
Shock haemorrhagic	1 (6.25%)	0 (0.00%)	1 (5.00%)

Conclusion:

The observed low values for total body clearance and volume of distribution led for TIN816 to a median terminal half-life of approximately 6 days, thereby providing exposure of TIN816 in SA-AKI patients as expected (i.e., adequate levels, time-course and variability) after a single dose treatment of nominally 2.0 mg/kg. The inter-patient coefficient of variation was ≤ 25.2% for both exposure parameters Cmax and AUC. PK characteristics therefore provide a characterization of the PK profile within ICU SA-AKI patient population and support the dosing strategy in the current Phase 2b study.

Single IV dose of TIN816 as administered was generally safe and well tolerated in SA-AKI patients.

Date of Clinical Trial Report

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