1 ADMINISTRATIVE INFORMATION

EU CT number	2025-521283-35-00
Title of the study	Vasopressin and Steroids in addition to Adrenaline in cardiac arrest -a randomized clinical trial
Name of sponsor(s) *Note: if there is more than one sponsor the primary contact should be identified*	Tiohundra AB
Trial category *(as per EMA Appendix on disclosure rules: EMA/228383/2015 Endorsed)*	Category 1 Category 2 Category 3
Low intervention trial	Yes No
First in human Phase I II III IV	
Vulnerable population(s)	Yes No See Section 5.4.7
IMPs	Product name/EU MP number: Empressin 40 IE/2 ml koncentrat till infusionsvätska, lösning/PRD7094020 (Test) Substance (name/ code): ARGIPRESSIN/SUB05561MIG Strength: Argipressin 40I.U. / 2mL Pharmaceutical form: SOLUTION FOR INFUSION Route of administration: INTRAVENOUS Marketing authorisation status (MA number, MS where authorised etc): 55407 / SE Modified in relation to MA: No Max Dosage: IU international unit(s) Duration of use: Day Product name/EU MP number: Solu-Medrol 40 mg pulver och vätska till injektionsvätska, lösning/PRD547753 (Test) Substance (name/ code): METHYLPREDNISOLONE/SUB08872MIG Strength: Methylprednisolone 40mg Pharmaceutical form: SOLUTION FOR INJECTION Route of administration: INTRAVENOUS Marketing authorisation status (MA number, MS where authorised etc): 09408 / SE Modified in relation to MA: No Max Dosage: mg milligram(s) Duration of use: Day Product name/EU MP number: Adrenalin Aguettant 0,1 mg/ml, injektionsvätska, lösning i förfylld spruta/PRD8364439 (Test) Substance (name/ code): EPINEPHRINE/SUB06568MIG Strength: Epinephrine 0.1mg Pharmaceutical form: SOLUTION FOR INJECTION Route of administration: INTRAVENOUS Marketing authorisation status (MA number, MS where authorised etc): 52213 / SE Modified in relation to MA: No

	Max Dosage: mg milligram(s) Duration of use: Day Product name/EU MP number: Solu-Cortef 100 mg pulver och vätska till injektionsvätska, lösning./PRD566975 (Test) Substance (name/ code): HYDROCORTISONE/SUB08065MIG Strength: Hydrocortisone 50mg Pharmaceutical form: SOLUTION FOR INJECTION Route of administration: INTRAVENOUS Marketing authorisation status (MA number, MS where authorised etc): 05561 / SE Modified in relation to MA: No Max Dosage: mg milligram(s) Duration of use: Day
Placebo	
AMP(s)	Yes No See Section 5.4.9.2
Medical device(s)	Yes No See Section 5.4.9.3
Scientific Advice	Yes No If yes, CHMP NCA If yes, Date(s): -No Documents provided
PIP	Yes No -No Documents provided
Resubmission	Yes No If yes, provide details of previous submission(s):
EudraCT number(s) of other CT application(s) by the sponsor for the IMP(s)	2022-500137-89-00

2 INFORMATION ON THE PROCEDURE

Reporting Member State	Name of RMS and contact details: Sweden, kp.central@lakemedelsverket.se
Other Member States concerned	
Draft AR ☐ Revised Draft AR ☐ Final AR ☒	Date: Date: Date: 2026-02-03

SM 1 ☐ (see Section 14)	Date:	Protocol ☐	IMPD ☐	IB ☐	EU form ☐	Other ☐
SM 2 ☐ (see Section 15 etc)	Date:	Protocol ☐	IMPD ☐	IB ☐	EU form ☐	Other ☐
(repeat for each subsequent SM e.g. SM3, SM4)	Date:	Protocol ☐	IMPD ☐	IB ☐	EU form ☐	Other ☐

ABBREVIATIONS

AE	**Adverse event**
AR	**Adverse reaction**
AR	**Assessment report**
CA	**Competent authority**
GCP	**Good Clinical Practice**
IB	**Investigators brochure**
ICF	**Informed consent form**
ICH	**International Conference on Harmonisation**
IEC	**Independent Ethics Committee**
IMP	**Investigational medicinal products**
IMPD	**Investigational medicinal product dossier**
NA	**Not applicable**
NIMP	**Non-investigational medicinal products**
SAE	**Serious adverse event**
SAR	**Serious adverse reaction**
SmPC	**Summary of product characteristics**
SOP	**Standard operating procedure**
SUSAR	**Suspected unexpected serious adverse reaction**
QP	**Qualified Person**

8 CONCLUSION OF THE RMS

Is the overall benefit/risk ratio acceptable for approval and considered as positive for the individual subject participating in the clinical trial (from quality, non-clinical, clinical, statistical and regulatory perspectives)?	Yes ☐ No ☐
Workspace:	
Assessor's comment on benefit/risk:	

The clinical trial is approvable

Yes ☐

No ☐ as requests for additional information exist that need to be resolved

9 DRAFT LIST OF REQUESTS FOR ADDITIONAL INFORMATION PROPOSED BY THE REPORTING MEMBER STATE

QUALITY

NON-CLINICAL

CLINICAL

STATISTICS

REGULATORY

10 CONSIDERATIONS FROM OTHER MEMBER STATES CONCERNED

QUALITY

NON-CLINICAL

CLINICAL

STATISTICS

REGULATORY

11 FINAL LIST OF REQUESTS FOR ADDITIONAL INFORMATION (AFTER CONSOLIDATION)

QUALITY (to be redacted):
NON-CLINICAL CLINICAL STATISTICS REGULATORY

12 RMS's ASSESSMENT OF ADDITIONAL INFORMATION SUBMITTED BY THE SPONSOR

QUALITY (to be redacted):
NON-CLINICAL CLINICAL STATISTICS REGULATORY

13 FINAL OVERALL CONCLUSION OF THE RMS (as per Art 6(3) of the Regulation)

The Investigator's brochure is complete and adequate	Yes ☐ No ☐
For low-interventional trials only: The clinical trial fulfils the conditions for a low-intervention trial	Yes ☐ No ☐
The conduct of the clinical trial is acceptable in view of the requirements set out in this Regulation	☐
The conduct of the clinical trial is acceptable in view of the requirements set out in the Regulation, but subject to compliance with specific conditions which shall be specifically listed in that conclusion	☐
The conduct of the clinical trial is not acceptable in view of the requirements set out in this Regulation	☐
The wording of conditions or rejection as proposed by the RMS:	
The final agreed wording of conditions or rejects to be sent to sponsor:	

Final document versions approved:

<table>
<tr><td>Date/version/number of the protocol(s)</td><td colspan="2">Protocol(s)

Document Name: VASTA Studyprotocol Version 7 20220730 - Submission date: 2025-02-19 - Manual version: 1 - System version: 1.00</td></tr>
<tr><td rowspan="3">Date/version/number of IMPD(s) (subsection)</td><td>Subsection</td><td>Date/version</td></tr>
<tr><td>Quality</td><td></td></tr>
<tr><td>Safety and Efficacy</td><td></td></tr>
<tr><td>Date/version/number of the IB(s)</td><td colspan="2">Investigator Brochure

Role: Test - Empressin
Submission date: 2025-02-19 - Manual version: 1 - System version: 1.00

Adrenalin
Submission date: 2025-02-19 - Manual version: 1 - System version: 1.00

Solu-Medrol
Submission date: 2025-02-19 - Manual version: 1 - System version: 1.00

Solu-Cortef
Submission date: 2025-02-19 - Manual version: 1 - System version: 1.00

Role: Test - Solu-Medrol
Submission date: 2025-02-19 - Manual version: 1 - System version: 1.00

Adrenalin
Submission date: 2025-02-19 - Manual version: 1 - System version: 1.00

Empressin
Submission date: 2025-02-19 - Manual version: 1 - System version: 1.00

Solu-Cortef
Submission date: 2025-02-19 - Manual version: 1 - System version: 1.00

Role: Test - Empressin
Submission date: 2025-02-19 - Manual version: 1 - System version: 1.00

Solu-Cortef
Submission date: 2025-02-19 - Manual version: 1 - System version: 1.00

Adrenalin
Submission date: 2025-02-19 - Manual version: 1 - System version: 1.00</td></tr>
</table>

	Solu-Medrol Submission date: 2025-02-19 - Manual version: 1 - System version: 1.00 Role: Test - Solu-Cortef Submission date: 2025-02-19 - Manual version: 1 - System version: 1.00 Adrenalin Submission date: 2025-02-19 - Manual version: 1 - System version: 1.00 Solu-Medrol Submission date: 2025-02-19 - Manual version: 1 - System version: 1.00 Empressin Submission date: 2025-02-19 - Manual version: 1 - System version: 1.00

14 ASSESSMENT OF SUBSTANTIAL MODIFICATION SM-01

Note: Copy section 14 for each subsequent substantial modification and renumber appropriately (e.g. SM2 will be Section 15)

14.1 The proposed changes are in relation to the following parts of the dossier:

Study protocol	☒
IMPD	☐
Investigator's brochure	☐
EU Application form	☐
Other	☐

14.2 Description and assessment of the proposed changes

Sponsorns beskrivning av ändringarna (ur följebrevet)

1. I stället för att ha dubbel-blindat både för patient och behandlande personal kommer vi nu att driva studien vid randomiseringen oblindat (open label). Tidigare hade vi en fristående person som drog upp läkemedel och sträckte över sprutan med interventionsläkemedlet alternativt placebo till behandlande personal som då gav läkemedel blindat. Nu kommer vi i stället ha att behandlande personal själva drar upp läkemedel och ger efter randomisering. Kontrollgruppen kommer inte att få placebo utan enbart standardbehandling efter riktlinjer.

Bedömning: Acceptabelt och rent praktiskt en förbättring.

2. Vi har nu möjlighet att ha vasopressinet (argipressin) i 1 ml ampuller, se bilaga SmPC. Tidigare hade vi 2 ml ampuller men gav bara 1 ml (20 IU) åt gången. Upprepades upp till 5 gånger. Nu kan vi dra upp hela ampullen, 1ml= 20 IU och ge allt vid varje cykel upp till 5 gånger. Dettas minskar risken för ojämn administrering.

Bedömning: Kliniskt OK (förbättring)

3. Vi kommer inte att randomisera patienter som får hjärtstopp under pågående operation eller under kranskärlsintervention. Detta för att nya riktlinjer rekommenderar att man ger adrenalin i mindre doser under dessa förutsättningar. Införs som exklusionskriterium inför randomisering.

Bedömning: Kliniskt OK (förbättring)

4. Vi har även uppdaterat vår powerberäkning efter nya körningar mot svenska hjärtstoppsregistret. Dessutom kommer vi att göra minst 1 interimanalys, första efter 274 patienter.

Bedömning: Bedöms i första hand av statistiker.

Statistisk bedömning:

Storleken på studien räknas om baserat på första delen och ny data från andra studier. Detta är godtagbart. En interim ska göras efter ca 35% av patienterna har enrollerats. I 7.1.2 står att det är en interim för effekt. Det är inte godtagbart framförallt på grund av att detta är en öppen studie. Läkemedelverkets bedömare tolkar dock interimavsnittet 7.2 som att det snarare handlar om en interim för futilitet och kanske ännu en omräkning av storleken. Det kan godtas (även om det ur statistiskt synvinkel hade varit bättre utan en interim). Protokollet 7.1.2 bör uppdateras för att undvika missförstånd.

Provide a short description of the proposed changes and an assessment of these changes. The table should include the version/number of the Protocol/IMPD/IB proposed for this SM.

Date/version/number of the protocol(s)		
Date/version/number of IMPD(s) (subsection)	Subsection	Date/version
Date/version/number of the IB(s)		
Workspace:		

14.3 Final overall conclusion on the substantial modification

For low-interventional trials only: The clinical trial fulfils the conditions for a low-intervention trial.	Yes ☐ No ☐
The proposed changes are acceptable	☒
The proposed changes are not acceptable	☐
The proposed changes are acceptable subject to conditions	☐

The wording of conditions or rejection as proposed by the RMS:
The final agreed wording of conditions or rejection to be sent to the sponsor: