NAME OF SPONSOR: Universitätsklinikum Erlangen **NAME OF FINISHED PRODUCT:** IMPs defined by active substance **NAME OF ACTIVE SUBSTANCE:** IMP1: Pethidine hydrochloride IMP2: Buspirone hydrochloride	Individual Study Table Referring to Part of the Dossier	*(For National Authority Use Only)*

SYNOPSIS for study EuroHYP-1

TITLE OF STUDY

EuroHPY-1: European multicentre, randomized, phase III clinical trial of therapeutic hypothermia plus best medical treatment versus best medical treatment alone for acute ischaemic stroke

STUDY CENTRES / INVESTIGATORS

Subjects were treated at 23 sites in 8 EU countries; for further details see appendix 2.

PUBLICATION (REFERENCES)

1. H. Bart van der Worp, Malcolm R. Macleod, Philip M. W. Bath, Bridget Colam, Charlotte Cordonnier, Jacques Demotes, Isabelle Durand-Zaleski, Bernd Gebhardt, Christian Gluud, Rainer Kollmar, Derk W. Krieger, Kennedy R. Lees, Carlos Molina, Joan Montaner, Risto O. Roine, Jesper Petersson, Nikola Sprigg, Dimitre Staykov, Istvan Szabo, Joanna M. Wardlaw, Stefan Schwab, and on behalf of the EuroHYP-1 investigators: Therapeutic hypothermia for acute ischaemic stroke. Results of a European multicentre, randomised, phase III clinical trial. European Stroke Journal, accepted for publication.

2. Winkel P, Bath PM, Gluud C, Lindschou J, van der Worp HB, Macleod MR, Szabo I, Durand-Zaleski I, Schwab S; EuroHYP-1 trial investigators: Statistical analysis plan for the EuroHYP-1 trial: European multicentre, randomised, phase III clinical trial of the therapeutic hypothermia plus best medical treatment versus best medical treatment alone for acute ischaemic stroke. Trials. 2017 Nov 29;18(1):573.

3. van der Worp HB, Macleod MR, Bath PM, Demotes J, Durand-Zaleski I, Gebhardt B, Gluud C, Kollmar R, Krieger DW, Lees KR, Molina C, Montaner J, Roine RO, Petersson J, Staykov D, Szabo I, Wardlaw JM, Schwab S; EuroHYP-1 investigators: EuroHYP-1: European multicenter, randomized, phase III clinical trial of therapeutic hypothermia plus best medical treatment vs. best medical treatment alone for acute ischemic stroke. Int J Stroke. 2014 Jul;9(5):642-5.

STUDIED PERIOD

Date of first enrolment: 05.11.2013
Date of last completed: 09.05.2018

PHASE OF DEVELOPMENT

Phase III

OBJECTIVES

Primary objective:
To determine whether systemic cooling to a target body temperature between 34.0 and 35.0°C, started within 6 hours of symptom onset and maintained for 12 or 24 hours, improves functional outcome at 3 months in patients with acute ischaemic stroke.

Secondary objectives:
To assess the effect of systemic cooling to a target body temperature between 34.0 and 35.0°C, started within 6 hours of symptom onset maintained for 12 or 24 hours, in patients with acute ischaemic stroke on

- Mortality at 3 months
- Neurological outcome at 3 months
- Quality of life at 3 months
- Cerebral infarct size at 48±24 hours

To determine the safety and tolerability of systemic cooling in patients with acute ischaemic stroke

Other objectives:
To assess the effect of systemic cooling to a target body temperature between 34.0 and 35.0°C, started within 6 hours of symptom onset maintained for 12 hours, in patients with acute ischaemic stroke on

- selected biomarkers.
- other imaging parameters.
- cost-effectiveness parameters.

METHODOLOGY

This was an international, multicentre, prospective, randomized, open-label, blinded endpoint, parallel-group, phase III clinical trial in adult subjects with acute ischaemic stroke and a NIHSS score ≥6. Patients were allocated to hypothermia plus standard care or to standard care alone. Randomization was performed through a web-based allocation service and involved stratification by country and minimization on: intention to give alteplase, intended method of cooling, sex, stroke severity, age, visibility of a relevant ischemic lesion on the first brain imaging, and time since symptom onset. In patients randomized to hypothermia (HT), cooling to a target body temperature of 34-35°C must have been started within six hours after symptom onset with rapid i.v. infusion of refrigerated saline ± a surface cooling technique and maintained for 24h with a surface or endovascular technique. To increase the feasibility of cooling, the duration of active cooling was reduced to 12 hours after inclusion of the first 50 patients. All cooling devices used in this study bear the CE marking and were used in strict adherence to their intended use. To prevent shivering and discomfort, HT patients received i.v. pethidine (maximum dose: 500mg/24h) and oral buspirone (maximum dose: 30mg/24h). Both drugs were used off-label in this trial.

The total duration of subject participation in the study was approximately 3 months consisting of a screening period (90 min), a treatment period (24/12 hours cooling with subsequent rewarming) and

a follow-up period (approx. 3 months). Primary outcome was the modified Rankin score (mRS) at day 91±14 days. To mitigate any potential for bias, the physicians assessing the mRS were blinded to participant treatment allocation.

NUMBER OF PATIENTS (PLANNED AND ANALYSED)

Planned: 1500 subjects, decreased to 800 after enrolment of 50 subjects (see appendix 2)
Enrolled: 98
Analysed: 94
Hypothermia group (HT): 48
Control group (C): 46

DIAGNOSIS AND MAIN INCLUSION CRITERIA

Patients of both sexes aged ≥18 years, with acute ischaemic stroke and a NIHSS score of at least 6 at screening; subjects were required to start HT:
a) within 6 hours after stroke onset and
b) within 150 min after start of endovascular treatment (if administered) and
c) within 150 min after start of thrombolysis (if administered) or
within 150 min after admission to trial site in patients not receiving thrombolysis

TEST PRODUCTS, DOSE AND MODE OF ADMINISTRATION

IMP 1: Pethidine hydrochloride (trade name/MAH not indicated in the protocol)
In the HT group, a bolus of 50mg pethidine hydrochloride was injected over 2 min prior to induction of cooling. Further boli of 25mg i.v. might have been administered as long as an interval of at least 30 min was respected and a maximum dose of 500mg/24h was not exceeded.

IMP 2: Buspirone hydrochloride (trade name/MAH not indicated in the protocol)
Buspirone 10mg p.o. was administered to HT patients prior to induction of cooling. Repeat doses of 10mg p.o. might have been administered as long as a maximum dose of 30mg/24h was observed.

DURATION OF TREATMENT

24/12 hours of active cooling followed by controlled rewarming (0.2°C/h until 36°C)

REFERENCE THERAPY

Best medical treatment (including thrombolysis and endovascular treatment)

CRITERIA FOR EVALUATION:

Primary outcome measure:
The primary outcome was the degree of disability post stroke as determined by the mRS score at day 91±14 days.

Secondary efficacy outcome measures were:

- NIHSS score at day 91±14 days
- Death or dependency (mRS >2) at day 91±14 days
- Death at day 91±14 days
- Brain infarct size as determined by cCT or MRI at hour 48±24 hours
- EQ-5D-5L score at day 91±14 days

- WHODAS 2.0 score at day 91±14 days

Safety outcome measure**:**
- Occurrence of SAE until day 91±14 days

Health economic measure:
- Cost utility ratio

Biomarker measures:
- Change in biomarker concentrations from baseline to assessment 2 (end of hour 24±2), and to assessment 5 (hour 72±4).

STATISTICAL METHODS

Sample size: Originally, it was planned to demonstrate or reject an absolute difference of 7% between the intervention groups (equivalent to an odds ratio of 0,74%) and allowing for a 3% loss to follow up in a sample size of 1500 randomised patients with a type-1-error risk of 5% and a type-2 error risk of 10%. Due to slow enrolment, this target was no longer realistic. Accordingly, the sample size was downgraded to 800.

The following sets were considered for analysis:

Intention-to-treat population (ITT): all evaluable subjects classified according to the intervention to which they were randomized. This population comprised 94 subjects (48 HT, 46 C, dead patients included).

Per protocol set (PP): all subjects without major protocol violations and classified according to the intervention to which they were randomized. Subjects randomized to hypothermia treatment must have had a body temperature ≤35.0°C for at least 6 hours during the active cooling period. This population comprised 61 subjects (15 HT, 46 C).

Primary, secondary, and other outcomes:
Primary and secondary efficacy outcomes were assessed in the ITT population. The primary efficacy variable, the mRS score at 91 days, was intended to be determined with ordinal logistic regression. Because the proportional odds assumptions of the ordinal regression analyses were not fulfilled, the two groups were also compared using von Elteren´s test stratified by nationality.
For secondary and exploratory outcomes frequencies and percentages per group as well as risk rations with 95% confidence intervals were reported for binary outcomes. Logistic regression for binary quantities, the general linear univariate model for continuous outcomes, and the Poisson distribution or negative binomial distribution for rate outcomes were used. If the assumptions of the Poisson or negative binomial distribution for rate outcomes were not fulfilled with reasonable approximation, a non-parametric method (van Elteren adjusted by nationality) was used. In case of outcomes planned to be measured at 91 ± 14 days but not measured because the patient had died, the worst possible value has been assigned. For economic analysis, the EQ 5D 5L scores were converted into utilities using the UK value set. For biomarker analyses, inter-group comparisons (Wilcoxon test) were performed.

Subgroup analysis:

The duration of cooling was reduced from 24 hours to 12 hours after the recruitment of the first 50 participants. Therefore, subgroup analyses for the primary and secondary outcomes were conducted to compare the participants who were included before the protocol change (subject 1-50) to the participants included after the change (subject 51-98). A subgroup indicator was calculated and its interaction with the intervention indicator was included in the analyses of the outcomes.

SUMMARY – CONCLUSIONS

The first patient was randomized on 05.11.2013. Patients were recruited from 23 sites in 8 European countries. Of 98 patients enrolled at the time, 49 were randomly assigned to the hypothermia group and 49 to the control group. Baseline characteristics are shown below (Table 1.2 and 4.1). 1 patient randomized to HT and 3 control patients were lost to follow up.

Disposition and Baseline Characteristics

Table 1: Disposition:

	Hypothermia (HT)	Control (C)
Subjects randomized	49	49
Lost to FU	1	3
Subjects analysed (ITT)	48	46
Subjects without major protocol deviations (PP)	15	46

Table 2: Baseline Characteristics

	HT	C
	n = 49	n = 49
Age – years mean (SD)	69.6 (11.8)	71.1 (12.9)
Male sex – no (%)	28 (57.1)	27 (55.1)
NIHSS score – median (IQR)	11 (7 – 17)	11 (8 – 17)
Visible acute ischaemic lesion on cCT – no (%)	22 (44.9)	22 (44.9)
Treatment with i.v. alteplase – no (%)	39 (79.6)	41 (83.7)
Time from symptom onset to randomization - min	203 (155 – 244)	220 (164 – 293)

Other baseline characteristics (body weight, height, body temperature, pre-stroke mRS score, or systolic and diastolic blood pressure) were balanced between the two groups.

Efficacy results

There was no difference between the groups in the mRS scores at 91 days in the ITT or PP sets. There were also no differences in the risks of death, death or dependency, the scores on the NIHSS or EQ-5D-5L at 91 days, or infarct volume at 48 hours in both data sets.

Table 3: Primary Outcome: mRS score at day 91±14 days

Set	Group	mRS								OR (95% CI)	p
		0	1	2	3	4	5	6			
		n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n		
ITT	HT	3	7	14	5	4	10	5	48	1.01 (0.48-2.13)	0.97
	C	1	6	11	9	12	3	4	46		0.5*

PP	HT	1	1	4	2	1	5	1	15	1.07 (0.35-3.32)	0.91
	C	1	6	11	9	12	3	4	46		0.86*

*Second p value originate from the van Elteren´s test stratified by nationality

Table 4a: Secondary Outcome Measures at day 91±14 days (ITT)

Outcome	HT	C	RR (95% CI)	p
	n = 48	n = 46		
Death – n (%)	5 (10.2)	4 (8.2)	1.25 (0.34–3.81)	0.73
Death or dependency – n (%)	24 (50.0)	28 (60.9)	0.82 (0.5-1.14)	0.29

Table 4b: Secondary Outcome Measures at day 91±14 days (ITT)

	HT	C	Diff of least square mean (95%CI)*	p
NIHSS score – median (IQR)	3 (1-11)	3 (1-8)	-2.2 (-7.26-2.86)	0.39
EQ-5D-5L – median (IQR)	70 (50-90)	67 (50-80)	-4.1 (-14.8-6.62)	0.45
WHODAS 2.0 – median (IQR)	53.5 (5.8-86.5)	38.0 (12.0-74.0)	-16.9 (-37.6-3.75)	0.11
Infarct size/ml at 48 ±24 hours – mean (95% CI)	37.5 (13.0-102.8)	34.3 (10.5-65.5)	-14.7 (-64.2-34.8)	0.55

*Control minus Hypothermia

Safety results

The overall incidence of AEs and SAEs was higher in the hypothermia group compared to control (Table 5). The majority of events were of mild or moderate intensity (86.2 % HT, 91.0% C). The most commonly reported AEs for subjects randomized to the hypothermia group (i.e., those occurring in 5 or more HT subjects) compared to controls are listed below (Table 6).

18 subjects (38%) in the hypothermia group and 14 controls (29%) experienced at least one SAE (relative risk 1.22; 95% CI 0.65-1.94; p=0.52). The most commonly reported SAEs for subjects randomized to the hypothermia group were pneumonia (incl. pneumonia aspiration), other infections, intracranial haemorrhage and malignant infarction. 5 subjects in the hypothermia group and 4 controls died due to SAEs (Tables 7 and 8).

Table 5: Total number of AEs/ARs

	HT	C
All AEs	225	111
All related AEs	32	-
Drug-related AEs	21	-
AEs related to the devices/procedure	21	-

Table 6: Most frequent AEs (n ≥ 5, any grade), relationship to IMP/IMD/procedure

Type of event (PT)	HT			C
	All causality	Drug-related AEs	AEs rel. to IMDs /procedure	
Constipation	8	1	1	7
Urinary tract infection	8	-	1	3
Pneumonia aspiration	7	1	1	1

Pneumonia	5	2	3	2
Fall	6	-	-	-
Haemorrhagic transformation stroke	6	-	1	1
Hypokalaemia	6	-	-	1
Pyrexia	6	-	-	4
Delirium	5	1	-	2
Hypotension	5	2	1	-
Nausea	5	3	1	1
Vomiting	5	2	2	2
Atrial fibrillation	4	-	-	5

Table 7: Total number of SAEs/SARs, and number of subjects with at least one SAE

	HT	C	RR (95% CI)	p
All SAEs	32	16		
Subjects with at least 1 event	18	14	0.82 (0.52-2.41)	0.52
Mortality	5	4		
All related SAEs	13	-		
Drug-related SAEs	7	-		
SAEs related to the devices/procedure	12	-		

Table 8: Type of event

Type of event (PT)	HT			C
	All causality	Drug-related SAEs	SAEs rel. to IMD /procedure	
Pneumonia and Pneumonia aspiration	9 (1 †)	4 (1 †)	4 (1 †)	2 (2 †)
Infection other than pneumonia	4	2	2	1
Intracranial haemorrhage	4 (1 †)	1 (1 †)	3 (1 †)	2
Progression to malignant infarction	4 (2 †)	-	1 (1 †)	1
Seizures	1	-	-	-
Other	10 (1 †)	-	2	10 (2 †)

(n †): number of events leading to death

Results from the health economic analysis:

QoL data was available for 81 subjects. Analysis on the total population of survivors found a mean utility of 0.45 with a SD of 0.43. The utility values ranged from 1 (full recovery) to -0.5 (worse than death). Health on the VAS rated between 0 and 100 had a mean of 61 with a SD of 24. The mean utility for HT subjects (n=39) was 0.59 (0.44) compared to 0.43 (0.42) in the control group (n=42), with a non-significant p value at 0.39. The mean for the VAS was 63 (25) for HT subjects vs 60 (50) in the control arm.

Results from the analysis of certain biomarkers:

Samples were obtained in 54 subjects, 27 subjects treated with HT and 27 controls. As a global interpretation, we did not see a major effect of hypothermia on the levels of MMPs, cardiac stress markers or brain damage biomarkers. However, levels of several inflammatory and immunity markers such as IL-6, CRP or PCT are elevated after 24 hours in the treatment group. The preliminary

and limited nature of the data makes it difficult to raise definitive conclusions and further analyses should be performed on the results, including by sub-groups of patients. However, the observed elevation of inflammatory markers in the treatment arm might be a future tool for hypothermia monitoring.

Subgroup analyses:

A subgroup indicator was calculated and the indicator and its interaction with the intervention indicator was included in the analyses of the outcomes. None of the interactions were significant (p values between 0.96 and 0.11). So, no significant effect of the protocol change could be discerned.

Conclusions

In this trial, cooling to a target temperature of 34°C to 35°C and maintaining this for 12 or 24 hours was not feasible in the majority of patients. There is no evidence that active cooling to a target of 34.0 to 35.0°C for 24/12 hours started within six hours after onset of ischaemic stroke has an impact on functional outcome at three months. However, with 98 subjects included the trial was substantially underpowered to detect any clinically relevant benefit or harm.

DATE OF REPORT

23.04.2019

Appendix 1: Overview of protocol amendments

Document	Date	
Clinical Trial Protocol v2.0 20-Dec-2012	20.12.2012	Original
Clinical Trial Protocol v3.0 24-Mar-2014	24.03.2014	Substantial Amendment 05
Clinical Trial Protocol v4.0 29-Jun-2015	29.06.2015	Substantial Amendment 08
Clinical Trial Protocol v5.0 24-Jun-2016	24.06.2016	Substantial Amendment 11

Description:

Substantial Amendment 05

Section 6.2 Inclusion criteria: Inclusion criterium 7 was updated to include patients who have received thrombolysis at a different site.

Section 7.2.1.4 Instructions for administration: Reference: 5-HT3RA for the prevention of opioid-induced nausea and vomiting need to be administered slowly due to QT interval prolongation

Section 8.1.1.4 Assessment of body temperature: Body temperature monitoring through bladder or rectal thermal probes is limited to the cooling/rewarming period. In all other cases body temperature might be assessed according to local standard clinical practice.

Section 8.1.1.6 Glasgow Coma Scale motor response subscale: GCS motor response need to be assessed in subjects undergoing therapeutic hypothermia prior to intended repeat pethidine injection only.

Sections 8.1.1.8 BSAS, 9.6.2 Vital signs, 9.6.3 Pulse oxymetry: The number of assessments was reduced.

Sections 15 References, 16 Appendices: SmPCs and questionnaires were updated

Substantial Amendment 08

Section 1 Synopsis: The number of planned trial sites was increased to 60.

Section 3.2.2.3.3 Time of onset and duration of cooling: The duration of hypothermia has been shortened from 24 to 12 hours. The interval between start of thrombolysis and start of hypothermia was increased to 150 minutes instead of 90 minutes due to feasibility reasons. Endovascular intervention before start of cooling was implemented.

Section 6.2 Inclusion criteria: Inclusion criteria 6, 7 and 9 were updated. The upper boundary of 18 on the NIH Stroke Scale has been abandoned.

Section 7.1.4.2 Description of IMD: 2 accessories (ICY 3585 AE and ICY 3585 CO) were excluded from the range by the manufacturer Zoll and must therefore be deleted.

Section 11.1 Determination of sample size: The sample size was reduced from 1500 to 800.

Sections 15 References: SmPCs and user manuals were updated

Substantial Amendment 11

Sections 7.1.1, 7.1.3, 7.1.4, 7.1.6, and 7.1.8: BrainCool System and BrainCool cooling pads2, Quattro 4593 AE and Quattro 4593 CO catheters, and EMCOOLS Flex.Pad added

Section 7.2.1.3 Instructions for preparation: Instructions added for buspirone handling in countries where no commercialized buspirone is available.

Section 8.1.2.1 Clinical and research laboratory evaluations: Extension of the baseline biomarker sample collection timeframe

Appendix 2: List of study sites (≥ 1 patient)

Country	Clinical site institution name	Clinical site address
Belgium	AZ Sint Jan Brugge-Ostende AV	Ruddershove 10, 8000 Brugge, Belgium
	Centre Hospitalier Chrétien	Rue de Hesbaye 75, 4000 Liège, Belgium
Denmark	Bispebjerg Hospital	Bispebjerg Bakke 23, 2400 NV Copenhagen, Denmark
France	CHU Bordeaux Hopital Pellegrin	Place Amelie Raba Leon, 33076 Bordeaux, France
	CHRU Lille Service Neurologie vasculaire	Rue Emile laine, 59000 Lille, France
Germany	Klinikum Altenburger Land	Am Waldessaum 10, 04600 Altenburg, Germany
	Universitätsklinikum Carl Gustav Carus, Klinik für Neurologie	Fetscherstr. 74, 01307 Dresden, Germany
	Universitätsklinikum Erlangen, Neurologische Klinik	Schwabachanlage 6, 91054 Erlangen, Germany
	Universität Frankfurt, Zentrum der Neurologie	Schleusenweg 2-16, 60528 Frankfurt am Main, Germany
	Martin-Luther-Universität Halle-Wittenberg, Klinik für Neurologie	Ernst-Grube-Str. 40, 06120 Halle, Germany
	Universitätsklinikum Leipzig, Klinik für Neurologie	Liebigstr. 20, 04103 Leipzig, Germany
Italy	Azienda Ospedaliera Sant`Andrea	Via di Grottarossa 1035, 00189 Roma, Italy
Lithuania	Vilnius University Hospital Santaros klinikos	Santariskiu str. 2, LT-08661 Vilnius, Lithuania
Spain	Hospital Universitari Dr Josep Trueta	Avda. de Francia s/n, 17007 Girona, Spain
	Vall d´Hebron Barcelona Hospital	Avenida de la Vall d´Hebron, 08035 Barcelona, Spain
UK	Royal Liverpool University Hospital	Prescot Street, Liverpool L7 8XP, UK
	The Royal London Hospital	Whitechapel Road, London E1 1BB, UK
	University College Hospital	5 Gower Place, London WC1E 6BT, UK
	Royal Victoria Infirmary	Queen Victoria Road, Newcastle upon Tyne NE1 4LP, UK
	Northwick Park Hospital	Watford Road, Harrow/Middlesex HA1 3UJ, UK
	Nottingham University Hospital	Hucknall Road, Nottingham NG5 1PB, UK
	Royal Surrey County Hospital	Egerton Road, Guildford GU2 7XX, UK
	Royal Hallamshire Hospital	Glossop Road, Sheffield S10 2JF, UK

Signature page

I have read this Clinical Study Report Synopsis and approve its content.

Sponsor´s designee,
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