CLINUVEL

A Proof of Concept, Phase IIa, Open Label Study to Evaluate the Safety of Afamelanotide in Patients with acute Arterial Ischaemic Stroke (AIS) due to Distal [M2 segment and beyond] Arterial Large Vessel Occlusion (LVO) or Perforator Occlusion and who are ineligible for Intravenous Thrombolysis (IVT) or Endovascular Thrombectomy (EVT)

[*Short Title: Phase IIa Stroke Study*]

Protocol No: CUV801

Final Version 3: 04 May 2021
PROTOCOL AMENDMENT

SPONSOR
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This study will be conducted in compliance with Good Clinical Practices (GCP) and ICH guidelines, and all patient study documents will be archived by CLINUVEL PHARMACEUTICALS LIMITED.

CONFIDENTIAL
Part or all of the information in this protocol may be unpublished material. Accordingly, this protocol is to be treated as confidential and restricted to its intended use. If any portion of this material is required for purposes of publication, authorization must be obtained from CLINUVEL PHARMACEUTICALS LIMITED and must not be disclosed or used except as authorized in writing by CLINUVEL PHARMACEUTICALS LIMITED. This material is the property of CLINUVEL PHARMACEUTICALS LIMITED and must not be disclosed or used except as authorized in writing by CLINUVEL PHARMACEUTICALS LIMITED.

[redacted]

SIGNATURES OF AGREEMENT FOR PROTOCOL AND AMENDMENTS

A Proof of Concept, Phase IIa, Open Label Study to Evaluate the Safety of Afamelanotide in Patients with Arterial Ischaemic Stroke (AIS) due to Distal [M2 segment and beyond] Arterial Large Vessel Occlusion (LVO) or Perforator Occlusion and who are ineligible for Intravenous Thrombolysis (IVT) or Endovascular Thrombectomy (EVT)

[*Short Title: Phase IIa Stroke Study*]

Protocol Final Version 3.0: 04 May 2021
Principal Investigator (PI): I have read this protocol and agree to conduct the study as outlined herein, complying with the obligations and requirements of clinical investigators and ICH Guidelines. Name of Principal Investigator (PI): Prof Geoffrey Cloud Investigational Site Name: Department of Neurology Alfred Hospital Melbourne Investigational Site Address: 99 Commercial Road Melbourne, 3000 VIC Signature: Date:
Study Director, Sponsor: Name of Sponsor Representative: Dr Dennis Wright Title of Sponsor Representative: Chief Scientific Officer Signature: Date:

PROTOCOL SYNOPSIS

Name of company: CLINUVEL Pharmaceuticals Ltd.	**Name of finished product:** SCENESSE®	**Name of active ingredient:** Afamelanotide 16mg
Title of study: A Proof of Concept, Phase IIa, Open Label Study to Evaluate the Safety of Afamelanotide in Patients with acute Arterial Ischaemic Stroke (AIS) due to Distal [M2 segment and beyond] Arterial Large Vessel Occlusion (LVO) or Perforator Occlusion and who are ineligible for Intravenous Thrombolysis (IVT) or Endovascular Thrombectomy (EVT).		
Study number: CUV801	**Phase of development:** IIa	
Principal investigators: Dr Geoffrey Cloud	**Study centers:** Alfred Hospital Melbourne	
Study period: 6 weeks		

Objectives:

The primary clinical objectives are to

(i) ***evaluate the safety of afamelanotide in acute Arterial Ischaemic Stroke (AIS), and***

The secondary objectives are to

(ii) ***identify changes in reperfusion of the ischaemic penumbra in AIS patients, specifically the ischaemic core and or the penumbral ischaemic zone (salvageable tissue).***

(iii) ***assess neurological functions and activities of daily living in AIS patients.***

Methodology:

This is an open label study of 42 days duration in patients with confirmed acute Arterial Ischaemic Stroke (AIS) (stroke) due to distal [M2 segment and beyond] large vessel occlusion (LVO) or perforator occlusion and who are ineligible to receive intravenous thrombolysis (IVT) or endovascular thrombectomy (EVT).

To determine eligibility for entry into the study, patients will undergo a screening evaluation on the day of admission following the AIS, Day 0. [redacted]

[redacted] Neurological functions will be assessed on Days 0, 1, 2, 3, 4, 7, 8 and 42 using the National Institutes of Health Stroke Scale (NIHSS). The modified Rankin Scale (mRS) will be used on Day 7 and Day 42 to compare to Day 0.

Assessments of adverse events (AEs) will be carried on Days 0, 1, 2, 3, 4, 7, 8 and 42. Efficacy analysis will be undertaken upon completion of the study; exploratory statistical analyses will be performed; $\alpha \leq 0.05$ (two-sided) will be considered as significant.
No. of participants planned: ➢ **Six (6) acute AIS patients with distal [M2 segment and beyond] arterial LVO or perforator occlusion.** **Open label study:** six (6) patients receiving afamelanotide.
Treatment: Afamelanotide [redacted]

Diagnosis and main criteria for entry:

To be eligible to enter the study, patients must meet the following ***inclusion criteria***:

- Male or female subjects with a diagnosis of first AIS due to distal [M2 segment and beyond] occlusion or perforator occlusion
- [redacted]
- Mild to moderate stroke severity [redacted]
- [redacted]
- Aged 18- 85 years
- Written informed consent obtained from patient and/or medical treatment decision maker prior to study-start (upon admission).

To be eligible to enter the study, patients must not meet any of the following ***exclusion criteria***:

- Administration of intravenous thrombolytic therapy in distal occlusion as etiology of AIS
- Intervention by endovascular thrombectomy (EVT)
- [redacted]
- Any evidence of hepatic (defined as three times standard range) or [redacted]
- [redacted]

Test product:
Afamelanotide [redacted]

Dose: [redacted]

Mode of administration: Subcutaneous administration

Reference therapy:
None

Study Endpoints:

Primary Endpoints

(i) Evaluate the safety of afamelanotide by monitoring and recording treatment-emergent adverse events (TEAEs) (on all days of administration and up to day 42).

Secondary Endpoints

(i) Evaluate changes in reperfusion of the ischaemic core and the penumbral ischaemic zone (salvageable tissue)

(ii) Evaluate neurological functions, cognitive functions, daily activities

Statistical Methods (exploratory):

Primary Endpoints

Safety Analyses:

The number of participants with TEAEs will be summarized by Medical Dictionary for Regulatory Activities (MedDRA) preferred term and body system. TEAEs will be further summarized by intensity, seriousness, outcome and relationship to study drug. Participants who prematurely terminate treatment due to AEs related to study medication will be summarized.

Secondary Endpoints

An evaluation will be made of c*hanges in the reperfusion of the ischaemic core and the penumbral ischaemic zone* (salvageable tissue) [redacted]

In this exploratory analysis, the null hypothesis is formulated as:

H_0: there is no change to the ischaemic core and or penumbral ischaemic zone following the administration of afamelanotide 16mg.

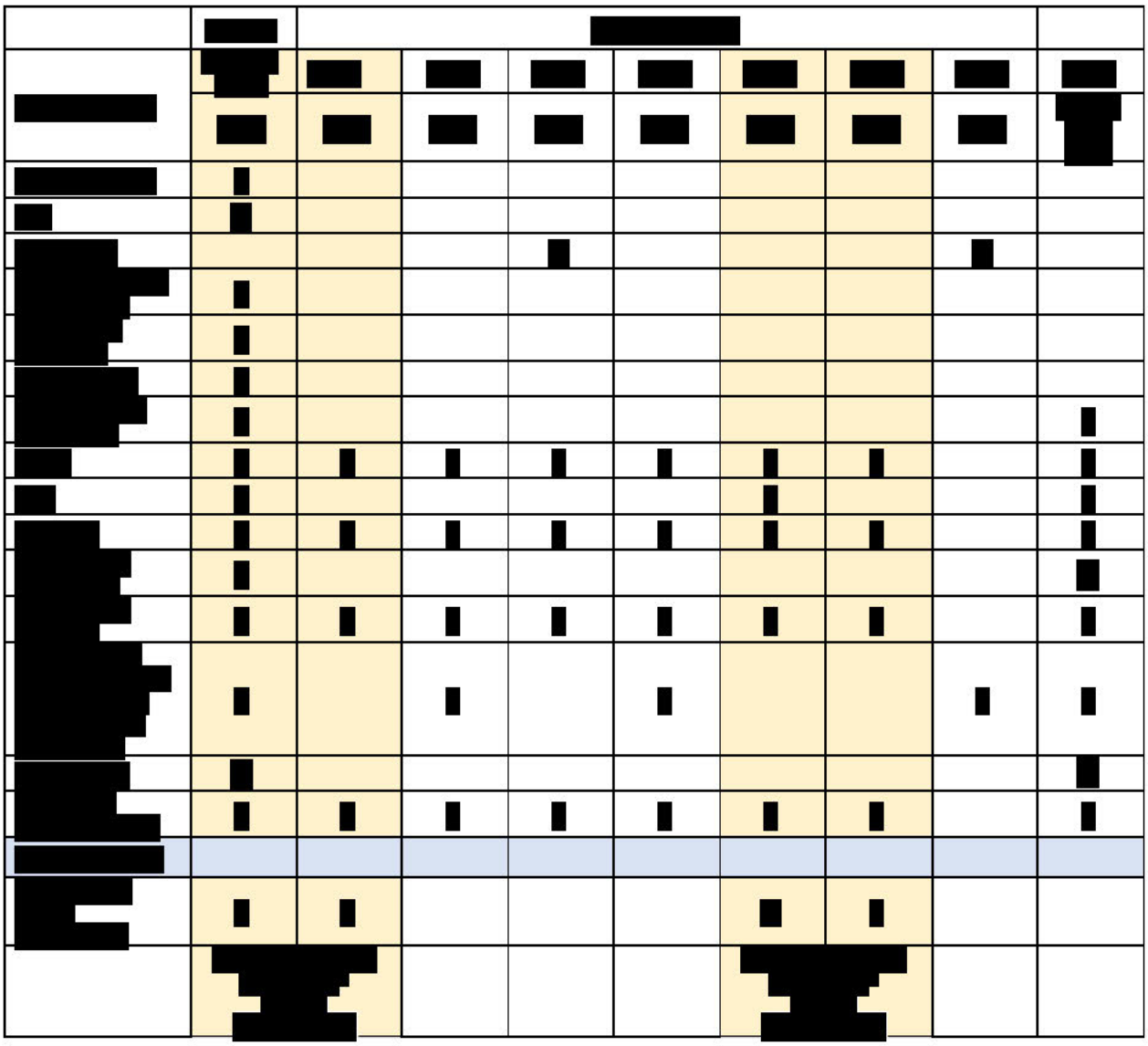
Following changes observed from cerebral imaging, standard clinical outcomes will be monitored.

An evaluation will be made of

(1) changes of neurological function as measured by NIHSS on Days 1, 2, 7 and 42 compared to baseline

(2) changes of daily activities as measured by mRS on Days 7 and 42 compared to baseline.

STUDY FLOW CHART



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[redacted]

LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

AE	Adverse event
[redacted]	[redacted]
AIS	Arterial ischaemic stroke
[redacted]	[redacted]
CFR	Code of Federal Regulations
[redacted]	[redacted]
CRA	Clinical research associate
CRF	Case report form
CS	Clinical specialist
CT	Computed tomography
CTB	Computed tomography brain
CTP	Computed tomography perfusion
[redacted]	[redacted]
FPI	First-patient-in
GCP	Good Clinical Practice
[redacted]	[redacted]
β-HCG	β-Human chorionic gonadotrophin
[redacted]	[redacted]
HREC	Human research ethics committee
IB	Investigator's Brochure
ICH	International Committee on Harmonization
[redacted]	[redacted]
ITT	Intention-to-treat
IVT	Intravenous thrombolysis

[redacted]	[redacted]
LPI	Last-patient-in
LPLV	Last-patient-last-visit
[redacted]	[redacted]
MedDRA	Medical Dictionary for Regulatory Activities
[redacted]	[redacted]
Mg	Milligram
Mm	Millimeter
[redacted]	[redacted]
mRS	Modified Rankin Scale
MRI	Magnetic resonance imaging
[redacted]	[redacted]
NIHSS	National Institutional Health Stroke Scale
PI	Principal Investigator
[redacted]	[redacted]
SOM	Study operating manual
[redacted]	[redacted]

1.0 ETHICS

1.1 Human Research Ethics Committee (HREC)

An appropriate HREC will approve the protocol and the Informed Consent Form before the study is initiated at the study center. Documentation of this approval will be provided to the Sponsor and/ or the Sponsor's designee. The Investigator(s) will have the following responsibilities:

[redacted]

1.2 Ethical Conduct of the Study

This study will be conducted in accordance with the Declaration of Helsinki (see Appendix 1), its revisions and ICH guidelines for Good Clinical Practice (GCP) governing the conduct of studies, and all applicable local regulations including the National Statement on Ethical Conduct in Human Research of the NHMRC. [redacted]

1.3 Participant Information and Informed Consent Form

Prior to any study specific screening procedures, the Investigator will explain to each participant or medical treatment decision maker the nature of the study, its purpose, procedures to be performed, the necessity for withdrawal of prohibited medication, expected duration, and the benefits and risks of study participation. After this explanation and before any study specific procedures are performed, the subject or medical treatment decision maker must voluntarily sign an informed consent statement

in the presence of a witness, if applicable (see Appendix 2). The inclusion and exclusion criteria will be reviewed at Day 0 prior to study medication administration.

1.4 Protocol Amendments

Changes in any portion of this protocol will be documented in the form of a protocol amendment and signed revision, signed by the appropriate CLINUVEL PHARMACEUTICALS LIMITED personnel and the Investigator.

Depending on the requirements of the study center's HREC and the relevant Competent Authority, where applicable, protocol amendment(s) will either need to be submitted for approval or advised by notification. Where formal approval is required, the revision(s) will not be implemented until approval has been obtained.

1.5 Confidentiality

All information provided to the Investigator by the Sponsor, including clinical observations at the study center, are held strictly confidential and confined to the clinical personnel involved in conducting the study, under the supervision of the Investigator. [redacted]

2.0 STUDY PERSONNEL AND STUDY ADMINISTRATION

3.0 INTRODUCTION AND STUDY RATIONALE

Stroke is the second commonest cause of death globally and the leading cause of adult neurological disability[1]. Acute arterial ischaemic stroke (AIS), due to arterial occlusion, accounts for 85% of all acute strokes whilst 15% of acute strokes are caused by an acute hemorrhage[2].

The outcome of AIS, both in terms of disability and survival, can be improved by reperfusion therapy using intravenous thrombolysis[3] (IVT) and, or thrombectomy[4] (mechanical endovascular removal of thrombus), in selected patients, where occlusion involves a proximal vessel of the circle of Willis. Both treatments are time dependent[5] and at best only a significant minority of patients with AIS, [redacted] are eligible for reperfusion treatments. [redacted] Perfusion brain imaging, with computed tomography (CT) or Magnetic resonance imaging (MRI), has become the cornerstone of selecting AIS patients for reperfusion therapy and as such individualized patient treatment by using imaging as a surrogate for a 'brain tissue clock,' as opposed to arbitrary time since last seen well, in treatment decision paradigms[6–9].

Stroke unit care has been shown to reduce mortality and dependence in AIS [redacted]

More than ever, effective neuroprotection – that may either facilitate more patients being suitable for timely reperfusion therapy by slowing the conversion of penumbra to core, or intrinsically attenuate the size of a threatened area of cerebral infarction is needed to aid assist in treating the global burden of disease due to AIS.

BLOOD BRAIN BARRIER (BBB)

It is well published that after a cerebrovascular accident (stroke) the damage to the blood-brain-barrier (BBB) includes decreased expression and altered organization of tight junction constituent proteins but also modulation of functional expression of endogenous BBB transporters.

Several hallmarks of pathology following ischaemic stroke is breakdown of the BBB, resulting in increased paracellular solute leak, modulation of transport proteins and endocytotic transport mechanisms, and inflammatory damage. Such barrier breakdown leads to a significant increase in paracellular permeability at the level of the cerebral microvasculature. These pathological derangements variably result in cognitive and motor impairments.

One of the most significant contributors to BBB breakdown in stroke is activation of proteinases such as matrix metalloproteinases (MMPs). This includes MMPs that are activated by hypoxia-inducible factor-1α (HIF-1α)-dependent mechanisms (i.e., MMP-2) and MMPs whose activation is triggered by cytokines (i.e., TNF-α, IL-1β) such as MMP-3 and MMP-9.

Integrins, transmembrane glycoprotein receptors for the extracellular matrix, also play a significant role in BBB breakdown. Physiologically, integrins interact with constituents of the basement membrane (i.e., collagen IV, fibronectin, laminin, heparin sulfate proteoglycans such as perlecan) to regulate BBB permeability and transport. In ischaemic stroke, integrins are rapidly degraded, which leads to BBB breakdown and subsequent edema, inflammation, and exacerbation of stroke injury.

[redacted]

[redacted]

In 111 patients a longitudinal study showed that the effect of early plasma α-MSH on stroke outcome was more than a reflection of the stress response related to stroke severity and that maintenance of plasma α-MSH after stroke onset could be protective. Furthermore, a growing body of experimental data has shown that exogenous administration of α-MSH decreases infarct volume and improves stroke outcome[16]. There are numerous mechanisms by which α-MSH (and related neuropeptides) could improve stroke outcome, and these effects are mediated through 5 different melanocortin receptors (MCRs). Potent antipyretic properties of α-MSH, which could potentially be capitalized on in the treatment of stroke, are mediated through the MCR3/MCR4 receptor complex in the brain.

OBJECTIVES

The objective of this pilot study is to evaluate the safety of afamelanotide, identify changes in reperfusion in AIS patients, specifically the ischaemic core and/or the penumbral ischaemic zone (salvageable tissue) and assess neurological functions and activities of daily living in AIS patients.

SCIENTIFIC HYPOTHESIS

The scientific hypothesis is that the pharmacologic intervention with afamelanotide would positively affect the infarcted area in patients with AIS [redacted]

Afamelanotide is a potent synthetic analogue of the naturally occurring hormone, alpha melanocyte stimulating hormone (α-MSH).

[redacted]

[redacted]

Afamelanotide 16mg has been shown to be effective in providing systemic photoprotection in EPP and has obtained marketing authorization in the European Union (October 2014) and the United States (October 2019) for the prevention of phototoxicity and endothelial damage incurred by adult EPP patients. The results of the clinical trials conducted by CLINUVEL, as well as of one long term observational study and the ongoing post-authorization pharmacovigilance activities, confirm the positive safety profile of afamelanotide to date[17–19]. [redacted]

[redacted]

[redacted]

It is proposed for AIS patients diagnosed with an acute stroke - and not eligible for intravenous thrombolysis (IVT) or endovascular thrombectomy (EVT) - originating from distal occlusion (M2 and beyond) of the large vessels be enrolled [redacted]

[redacted]

4.0 STUDY OBJECTIVES

4.1 Primary Objective

The objective of this pilot study is to evaluate the safety of afamelanotide in AIS patients.

4.2 Secondary Objectives

The secondary objectives of this pilot study CUV801 are to identify changes in reperfusion of the ischaemic core and ischaemic penumbra (salvageable tissue) in AIS patients with distal occlusion of the large vessels and who are ineligible to receive IVT or EVT, and to monitor changes in neurological function, cognitive functions and changes of daily activities in these patients.

5.0 INVESTIGATIONAL PLAN

5.1 Overall Design and Plan of the Study

This is an open label phase IIa pilot study to be conducted in six (6) patients with acute AIS during a 6-weeks period [redacted]

To determine eligibility for entry into the study, [redacted] Eligible patients will be enrolled and will be administered [redacted]

[redacted]

The results will be reviewed on the basis of a benefit: risk assessment. If the benefit: risk assessment is in favour of afamelanotide, in the opinion of the Investigator, [redacted]

Radiological evaluation by assessing the imaging from Computed Tomography Perfusion (CTP) [redacted]

Clinical evaluations will be performed by accredited study staff over the course of the study. The NIHSS will be performed at the Day of Admission (Day 0) and on Days 1, 2, 3, 4, 7, 8 and 42 or Premature Termination Visit (if applicable). The modified Rankin Scale (mRS) will be performed on Days 0, 7 and 42 or Premature Termination Visit (if applicable). [redacted]

Safety assessments (review of AEs and concomitant medications) will be carried out each day (each study visit from the Day of Admission to Day 8 and Day 42 or Premature Termination Visit). [redacted]

5.2 Selection of Study Population

The target population consists of male and female patients with AIS due to acute distal (M2 and beyond) large vessel occlusion (LVO) or perforator occlusion and who are ineligible to receive IVT or EVT. The following inclusion and exclusion criteria must be met by each patient before enrollment in the study.

5.2.1 Inclusion Criteria

The patients have to fulfill all of the following ***inclusion criteria*** for study participation:

- Male or female subjects with a diagnosis of first Arterial Ischaemic Stroke (AIS) due to distal [M2 segment and beyond] occlusion or perforator occlusion
- [redacted]
- Mild to moderate stroke [redacted]
- [redacted]
- Aged 18-85 years
- Written informed consent obtained from patient and/or medical treatment decision maker prior to study-start (upon admission).

5.2.2 Exclusion Criteria

Any of the following exclusion criteria will exclude the patient from the study:

- Administration of intravenous thrombolytic therapy in distal occlusion as etiology of AIS
- Intervention by endovascular thrombectomy (EVT)
- [redacted]
- Any evidence of hepatic (defined as three times standard range) or renal impairment (defined as [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]

5.2.3 Recruitment Management

[redacted] the patients will be recruited through the PI's acute stroke service.

5.2.4 Withdrawals and Replacement of Patients

A discontinuation occurs when a patient does not complete the study as required by the study protocol. Patients will be free to discontinue their participation in this trial at any time for any reason. In addition, patients may be withdrawn from the trial at the discretion of the Investigator or medically qualified nominee. A patient may be withdrawn for any of, but not limited to, the following reasons:

- Informed consent withdrawn by the patient or medical treatment decision maker;
- AE requiring study discontinuation;
- When the Investigator's or nominee's best professional judgment would indicate that it would be in the patient's best interest to be withdrawn;
- Violation of inclusion/exclusion requirements.

The reasons for withdrawal or discontinuation of a patient will be recorded in the patient's medical notes and CRF. If an AE is the reason for discontinuation, the event must be followed up and documented as described in the 5.5.3.2 Safety variables of the protocol. If the patient discontinued for any reason after the enrolment into the study, a study Premature Termination visit, as described in 5.5.1, should be performed at the time of study discontinuation, or as soon as possible after discontinuation. This visit will be documented in the patient's medical notes and CRF.

Any patient(s) withdrawn from the trial prior to their completion for any reason will not be replaced. Data compiled to the point of discontinuation will be used for 'intent to treat' (ITT) analysis. Patients violating any of the inclusion and exclusion criteria will be described as protocol deviators.

5.3 Study Medication

5.3.1 Description of Study Medication

[redacted] afamelanotide [redacted]

5.3.2 Treatment Groups

There is one treatment group in this study (Open-label study). As such, all patients who satisfy the inclusion/exclusion criteria will be allocated a study subject number and receive afamelanotide. Study subject number allocation will be detailed in the CUV801 Study Operating Manual (SOM).

[redacted]

The groups consist of:

- **Six (6) stroke patients with acute distal (M2 and beyond) LVO or perforator occlusion.**

Open label study: Six **(**6) patients receiving afamelanotide.

5.3.3 Dosage and Administration of Study Medication

Afamelanotide [redacted] will be administered [redacted] on the designated study days. [redacted]. Please refer to the CUV801 SOM for further details.

[redacted]

always within 24 hours of onset of symptoms or last seen well.

5.3.4 Packaging and Labeling of Study Medication

The implant formulation will be packaged in amber glass vials. The label will include information in compliance with the local regulatory requirements for clinical trials/investigational medicinal products.

5.3.5 Storage and Accountability

Study medication will be maintained in a safe and secure (locked, restricted access) location and kept at 2-8°C. The expiry or retest date for each afamelanotide vial will be printed on the label. The Investigator will agree not to supply study drug to any persons other than those enrolled in the study. Current and accurate drug receipts, inventory, accountability and dispensing records will be kept for all study drug in the Pharmacy/Investigator Site File(s), and upon study completion, a final inventory and reconciliation of all study drug will be compiled. [redacted]

5.3.6 Compliance

Data related to the administration of the study drug will be recorded on the CRF.

5.4 Prior and Concomitant Therapy

5.4.1 Prior Therapy

All subjects (or medical treatment decision makers) will be instructed to report to the Investigator any treatments, prescribed medicines, over-the-counter medications, dietary supplements or nutraceuticals that are being used. Use of any other prior and concomitant therapy which may interfere with the objective of the study, [redacted]

5.4.2 Concomitant Therapy

The Investigator must be informed as soon as possible about any medication taken from the time of screening (Day 0, Day of Admission) until the end of the study (Day 42) and these will be fully documented in the patients' medical records and CRF. In the event that a subject has taken a medication which has not been pre-approved, the Investigator will make a decision to continue or discontinue the subject, based on whether the medication may interfere with the objectives of the study.

For complete information, during the study, contraceptive therapy must not be changed.

5.5 Study Procedures

This will be an inpatient study (during hospital admission). [redacted] Patients may be discharged and will be asked to return to hospital for the rest of study visits. Patients will participate for a total of up to nine visits.

5.5.1 Description of Study Days

5.5.1.1 Screening Period

Screening Visit (Day 0) – Day of Admission

The Screening Visit and Admission Visit and related procedures on the Day 0 will only occur after the informed consent process is performed and a signed and dated informed consent form has been obtained from the patient (or medical treatment decision maker).

The Investigator will assess eligibility for the study after the following procedures are performed and information collected:

- [redacted]

5.5.1.2 Study Period

Visit 1 (Day 0)

Once all screening evaluations at Visit 1 (Day 0) have been completed and the Investigator has confirmed patient's eligibility, the following procedures will be performed:

[redacted]

[redacted]

5.5.2 Study Procedures Flowchart

Please refer to the section Study Flow Chart of the protocol.

5.5.3 Methods of Assessment

5.5.3.1 Efficacy Variables

The Efficacy of the treatment will be assessed by:

5.5.3.1.1 Evaluation of MRI imaging (CTP and DWI-FLAIR)

Background

For patients with acute arterial occlusion, [redacted]

[redacted]

MRI diffusion weighted imaging (DWI) is accurate in the identification of acutely infarcted tissue.

[redacted]

Imaging Protocol

Standard care multimodal computed tomography (CT) will be performed on Day 0. [redacted]

MRI will be performed at Days 3(±1) and 9(±1) [redacted]

Efficacy of treatment

[redacted]

[redacted]

[redacted]

[redacted]

5.5.3.1.2 Modified Rankin Scale (mRS)

The mRS (see Appendix A) indicates the degree of disability or dependence in the daily activities of patients who have suffered a stroke or other causes of neurological disability.

The mRS will be performed on Days 0, 7 and 42.

5.5.3.1.3 National Institutional Health Stroke Scale (NIHSS)

The validated NIHSS (see Appendix B) records the level of impairment caused by a stroke in 11 items.

A score assessed in 582 patients illustrated the distribution of mild, moderate and severe AIS.

A score equal or less than 8	mild AIS	[19.8%]
A score between 9 and 15	moderate AIS	[30.3%]
A score equal or above 16	severe AIS	[49.9%]

Table 2. NIHSS scores

Score [3]	Stroke severity
0	No stroke symptoms
1–4	Minor stroke
5–15	Moderate stroke
16–20	Moderate to severe stroke

21–42	Severe stroke

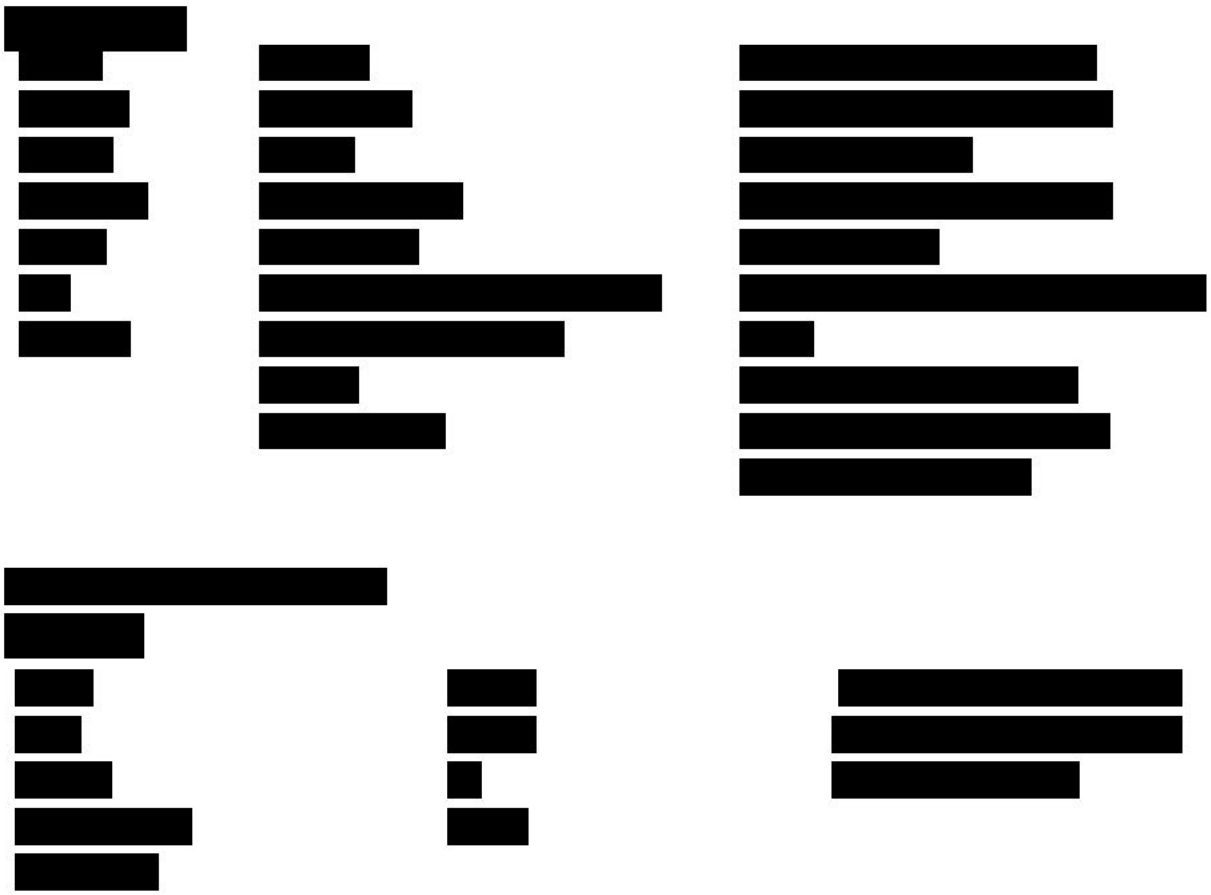
[redacted]

5.5.3.2 Safety Variables

The number of patients with treatment-emergent AEs (TEAEs) will be summarized by MedDRA preferred term and body system. TEAEs will be further summarized by intensity, seriousness, outcome and relationship to study drug. Patients who prematurely terminate treatment due to AEs related to study medication will be summarized.

5.5.3.2.1 Clinical Laboratory Evaluations

[redacted]



The Investigator will sign and date all laboratory reports and review all laboratory test results as soon as possible. The Investigator will evaluate the clinical significance of all values outside the reference range and will document within the laboratory report as well as in the patient's CRF. If a laboratory value is outside the reference range and felt to represent a clinically significant change from the baseline value, this will be reported as an AE in the patient's medical notes and on the AE CRF page. An assessment of this AE will be made by the Investigator, in particular regarding the relationship of the event to the study drug.

5.5.3.2.2 General Physical Examination

A general physical examination will be performed

Weight and Height

Weight in kilograms will be recorded [redacted]

5.5.3.2.3 Neurological examination

Neurological examination using a NIHSS will be conducted in a standardized manner [redacted]

5.5.3.2.4 Vital Signs Measurements

Vital signs (blood pressure, temperature and pulse rate) will be recorded [redacted]

5.5.3.2.5 Adverse Events

An adverse event (AE) is defined as any untoward medical event (clinical or laboratory) experienced by a patient during the course of a clinical trial, whether or not it is related to the investigational product. An AE may be a symptom, sign, or abnormal finding or test result. Whenever possible, the Investigator will group together into a single term, signs and symptoms that constitute a single diagnosis. For example, cough, rhinitis and sneezing might be grouped together as "upper respiratory tract infection".

The Investigator will monitor each patient closely for the development of AEs, and any adverse experience spontaneously reported by or elicited from the patient or observed by the Investigators (physician or study staff) will be recorded in the patient's medical notes and on the appropriate AE page of the CRF, when applicable. [redacted] It is the responsibility of any member of the study site staff to immediately report any suspected AE to the Investigator.

The Investigator will assess the AE(s) in the patient's medical notes and provide the date and time of onset, severity, seriousness, action taken, outcome, date of resolution (or comment that the event is still continuing) and relationship to study medication.

If a laboratory value is outside the normal range, the Investigator must comment on the findings in the laboratory report. For any clinical laboratory abnormality, the Investigator will make a judgment as to clinical significance. All clinically significant laboratory abnormalities will be recorded as an AE in the patient's medical notes and on the AE page of the CRF.

All AEs will be followed up in accordance with GCP. AEs will be graded for severity as defined below:

- **Mild** - The AE is transient and easily tolerated by the patient. Specific action is optional;
- **Moderate** - The AE causes the patient discomfort and interrupts the patient's usual activities;
- **Severe** - The AE causes considerable interference with the patient's usual activities and may be incapacitating or life-threatening.

Outcome of the event must be described as one of the following:

- Recovered without sequelae;
- Recovered with sequelae;
- Recovering;
- Not recovered;
- Death.

The Investigator will be asked to document his/her opinion of the relationship of the event to the study drug as follows:

- **Related** - There are facts or arguments to suggest a causal relationship, i.e. there is a reasonable possibility of a causal relationship between the drug and the AE(s);
- **Not Related** - There is not a reasonable possibility that the AE(s) is/are related to the drug – alternative aetiology, diagnosis, or explanations for the AE(s) exist, or the time from suspect drug intake make a relationship improbable;
- **Not Assessable** - Report suggesting an adverse reaction BUT cannot be judged because information is insufficient or contradictory OR cannot be supplemented or verified.

Serious Adverse Events (SAE)

A Serious Adverse Event (SAE) is any adverse event occurring at any dose that results in any of the following outcomes:

- Death (due to any cause);
- Is life-threatening;
- Requires a prolongation of an existing hospitalization.
- Results in a persistent or significant disability/incapacity;
- Is a congenital anomaly/birth defect;
- Important medical events that may not be immediately life threatening, result in death or require prolonged hospitalization but may be considered a SAE when, based upon appropriate medical judgment, they may jeopardize the patient or may require medical or surgical intervention to prevent one of the outcomes listed in the definition above.

Reporting: Any SAE, including death due to any cause, which occurs during this study, has to be reported to CLINUVEL **within 24 hours** of the Investigator or their delegate becoming aware of the event, even if only limited information regarding the event is available. The CLINUVEL safety team will follow up on any missing information or any other information needed and it is expected that the investigator responds to these queries as the information becomes available.

An SAE report form must be completed and sent to CLINUVEL Safety Team at [redacted] or sent by fax to the number provided in the form within 24 hours of the event occurring or within 24 hours of becoming aware of the event. In addition to completing the SAE report form (one form completed for each SAE), additional supporting information should be provided as appropriate, such as photocopies of pertinent test results and medical notes, trial records, consultant report(s), hospital discharge summary and autopsy report (if relevant and as soon as available to the Investigator). All SAEs will be recorded in the patient's medical notes and on the AE page of the CRF.

The Investigator will determine whether the seriousness of the event warrants removal of any patient from the study. The Investigator will institute appropriate diagnostic and therapeutic measures and keep the patient under observation for as long as is medically indicated.

Certain AEs and/or SAEs, including suspected unexpected serious adverse reactions (SUSARs), may warrant expediting to HRECs, according to the regulatory requirements for the individual countries or sites involved, either by the Investigator or the Sponsor. The modalities for reporting and filing relevant documentation will be detailed in the CUV801 SOM.

[redacted]

Pregnancy and/or Breastfeeding

The following situations must be reported to CLINUVEL **within 24 hours** of the Investigator or their delegate becoming aware of the event, even if only limited information regarding the event is available.

- Pregnancy occurring in a female patient, when dose was administered less than three months after the last afamelanotide;
- Pregnancy occurring in the female partner of a male patient treated, when the start of the pregnancy is less than three months after the last afamelanotide dose was administered to the male patient;
- Female patient breastfeeding when less than three months after the last afamelanotide dose was administered;
- Birth of a child from a female patient, when the start of the pregnancy was less than three months after the last afamelanotide dose was administered;
- Birth of a child from the female partner of a male patient, when the start of the pregnancy is less than three months after the last afamelanotide dose was administered to the male patient.

[redacted] Report Form and/or a Pregnancy Outcome/Breastfeeding Report form will be completed and sent to the CLINUVEL Safety Team at [redacted] or faxed to the number provided in the forms within 24 hours of becoming aware of the event. All pregnancies will be followed from the date of pregnancy detection until pregnancy outcome and/or lactation (when applicable).

Female patients who become pregnant, give birth or begin breastfeeding during the treatment period will be withdrawn from treatment and complete the Premature Termination Visit.

For male patients of female partners who become pregnant, the responsible Investigator will determine whether the event warrants removal of any patient from the study.

5.6 Data Quality Assurance

[redacted]

[redacted]

5.6.2 Database Management and Quality Control

The study will be monitored by the Clinical Monitor, and/or representatives of CLINUVEL, or its delegated representative, as frequently as is necessary to determine that data recording and protocol adherence are satisfactory. [redacted]

The detailed procedures for data entry, data coding, cleaning and electronic data transfer will be provided in the Data Management Plan.

5.7 Statistical Methods, Exploratory Statistics

[redacted]

Descriptive and exploratory statistics (non-parametric analyses) will be performed [redacted]

5.7.2 Efficacy Assessment

5.7.2.1 Specification of Efficacy Endpoints

Primary Endpoints

(i) Evaluate the safety of afamelanotide by monitoring and recording TEAEs (on all days of administration and up to day 42).

TEAEs will be recorded and coded as MedDRA Preferred Terms.

Secondary Endpoints

(i) Evaluate changes in the reperfusion of the ischaemic core and the penumbral ischaemic zone (salvageable tissue) by quantitative analysis of hemodynamics:

[redacted]

Upon completion of the study, each patient will generate efficacy after comparing the DWI-FLAIR on Days 3(±1) and 9(±1) with the CTP on Day 0 (Day of Admission).

[redacted]

5.7.3 Safety Assessment

5.7.3.1 Specification of Safety Endpoint (Primary Endpoint)

The safety endpoint will be the incidence of TEAEs occurring during the study period, including clinically significant changes in laboratory parameters, will be listed by intensity, seriousness, outcome, and relationship to study drug.

5.7.4 Sample Size

While this is a phase IIa study of common indication, the sample size is based on availability of patients. A total of six (6) patients are planned to be enrolled in this study. This constitutes an open-label exploratory study.

5.7.5 Analysis Plan

5.7.5.1 Safety Population

The Safety Population will include all enrolled patients. Patients screened but not enrolled will be shown in separate listings.

5.7.5.2 ITT Population

The ITT population will include all treated patients, who provide at least one post dose efficacy assessment. This will be the main population for all efficacy analyses.

5.7.5.3 Handling of Missing and Incomplete Data

[redacted]

5.7.5.4 Per Protocol Analysis (PPA) Population

[redacted]

5.7.5.5 Demographic and Initial Characteristics

Demographic and baseline characteristics will be summarized using descriptive statistics.

5.7.5.6 Efficacy

Primary and secondary efficacy endpoints are described under section 5.5.3.1 Efficacy variables of the Study Protocol.

[redacted]

5.7.5.7 Safety

Descriptive methods will be used to summarize the safety data. These will be based upon the safety population.

5.7.5.8 Adverse Events

All AEs, including non-TEAEs, will be listed. A TEAE is defined as:

- An event that was not present prior to or on the day of the first study medication administration but was present after study medication was administered.
- An event that was present prior to first administration of study medication and continued to occur after the administration of the first dose at an increased level of severity.

- An event that was present prior to administration of study medication and was documented as completely resolved and re-emerged after the administration of the first dose.

The MedDRA AE dictionary will be used to map verbatim AE terms to preferred terms and body systems. The number of patients with TEAEs will be summarized by preferred term and body system. TEAEs will be further summarized by intensity, seriousness and relationship to study medication. The number of patients who terminate treatment early due to AEs related to study medication will be tabulated. Summaries of the incidence of toxicities will be prepared, as appropriate.

SAEs, SUSARs, and AEs of special interest will be listed individually. Any SAE that occurs prior to the first dose of the study medication, will be documented in the study report.

5.7.5.9 Clinical Laboratory Data

[redacted]

5.7.5.10 Other Clinical Data Analyses

[redacted]

5.7.5.11 Interim Evaluations

[redacted]

[redacted]

Safety assessments (review of AEs) will be carried out at each study visit and in between, if required for safety-related reasons, at the Investigator's discretion.

5.8 Premature Termination of the Study

The study may be terminated early if the Sponsor, Investigator or Clinical Monitor discovers conditions arising during the course of the study which indicate that the clinical investigation should be halted. The study may then be terminated after appropriate consultation and discussion.

Conditions that may warrant study termination include, but are not limited to, the discovery of a significant, unexpected, and unacceptable risk to the patients, failure of the Investigator to enroll patients at an acceptable rate, insufficient adherence to the protocol requirements, completion of study objectives or at the discretion of the Sponsor.

6.0 STUDY REPORT, PUBLICATION POLICY & ARCHIVING OF STUDY DOCUMENTATION

Investigators are required to maintain all study documentation, including copies of CRFs, Informed Consents, and adequate records for the receipt and disposition of study medications, for a period of 15 years following study close-out.

The Investigator will ensure to make all study data accessible to the Clinical Monitor, Sponsor, or other authorized representatives of the Sponsor and Regulatory Agencies during the conduct of the study as well as during the archiving period. A file for each patient will be maintained that includes the signed Informed Consent form and copies of all source documentation related to that patient. The Investigator will ensure the availability of the source documents from which the information on the CRF is derived (conform industry standards, patient details will be pseudonymized).

All information provided to the Investigator dealing with this study drug or the methodologies used in the protocol, as well as information obtained during the course of the study will be regarded as strictly confidential and proprietary to the Sponsor ("Proprietary Information"). The Investigator agrees not to disclose any information supplied by the Sponsor in any way without written permission as outlined in the Confidentiality section of this protocol. For the purposes of this section, "Investigator" includes, but is not limited to, the PI and/or his/her agents, designees, sub-investigators, or other individuals involved in the running, administration, or collection/handling of patients/data for this study.

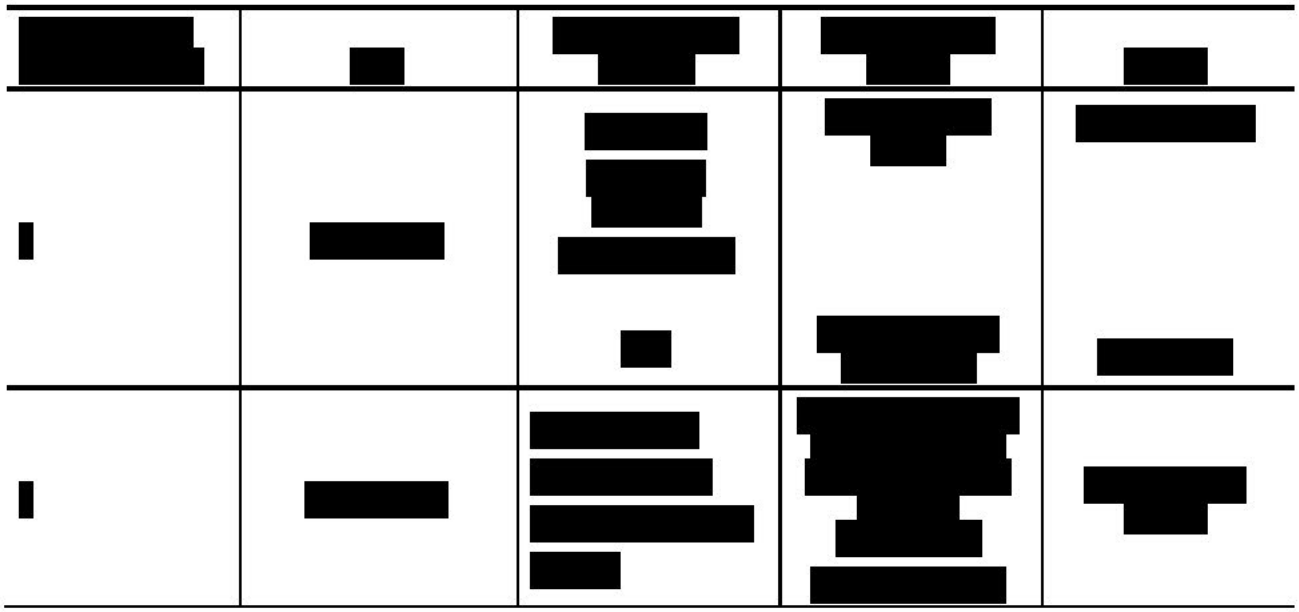
[redacted]

[redacted]

[redacted]

[redacted]

7.0 AMENDMENTS AND UPDATES



- Projected starting date (first-patient-in [FPI])* 1 June 2021
- Projected number of patients Six (6)
- Projected completion of patient accrual (last-patient-in [LPI])* December 2021
- Patient study end date (last-patient-last-visit [LPLV])* January 2022

* These are approximate timeframes which are dependent of regulatory and ethics approvals.

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9.0 REFERENCES

1. Strong, K., Mathers, C. & Bonita, R. Preventing stroke: saving lives around the world. *The Lancet Neurology* **6**, 182–187 (2007).
2. Benjamin Emelia J. *et al.* Heart Disease and Stroke Statistics—2019 Update: A Report From the American Heart Association. *Circulation* **139**, e56–e528 (2019).
3. Wardlaw, J. M., Murray, V., Berge, E. & del Zoppo, G. J. Thrombolysis for acute ischaemic stroke. *Cochrane Database of Systematic Reviews* (2014) doi:10.1002/14651858.CD000213.pub3.
4. Goyal, M. *et al.* Endovascular thrombectomy after large-vessel ischaemic stroke: a meta-analysis of individual patient data from five randomised trials. *The Lancet* **387**, 1723–1731 (2016).
5. Emberson, J. *et al.* Effect of treatment delay, age, and stroke severity on the effects of intravenous thrombolysis with alteplase for acute ischaemic stroke: a meta-analysis of individual patient data from randomised trials. *The Lancet* **384**, 1929–1935 (2014).
6. Hill, M. D. & Goyal, M. Treat fast but abandon time from ischaemic stroke onset as a criterion for treatment: The DAWN and DEFUSE-3 trials. *International Journal of Stroke* **13**, 344–347 (2018).
7. Román, L. S. *et al.* Imaging features and safety and efficacy of endovascular stroke treatment: a meta-analysis of individual patient-level data. *The Lancet Neurology* **17**, 895–904 (2018).
8. Campbell, B. C. V. *et al.* Penumbral imaging and functional outcome in patients with anterior circulation ischaemic stroke treated with endovascular thrombectomy versus medical therapy: a meta-analysis of individual patient-level data. *The Lancet Neurology* **18**, 46–55 (2019).
9. Ma, H. *et al.* Thrombolysis Guided by Perfusion Imaging up to 9 Hours after Onset of Stroke. *N Engl J Med* **380**, 1795–1803 (2019).

10. Cheatwood, J. L., Emerick, A. J. & Kartje, G. L. Neuronal Plasticity and Functional Recovery After Ischaemic Stroke. *Topics in Stroke Rehabilitation* **15**, 42–50 (2008).
11. Wu, X. *et al.* NDP-MSH binding melanocortin-1 receptor ameliorates neuroinflammation and BBB disruption through CREB/Nr4a1/NF-κB pathway after intracerebral hemorrhage in mice. *Journal of Neuroinflammation* **16**, 192 (2019).
12. Rinne, P. *et al.* α-Melanocyte-stimulating hormone regulates vascular NO availability and protects against endothelial dysfunction. *Cardiovascular Research* **97**, 360–368 (2013).
13. Giuliani, D. *et al.* Broad therapeutic treatment window of [Nle4, D-Phe7]α-melanocyte-stimulating hormone for long-lasting protection against ischaemic stroke, in Mongolian gerbils. *European Journal of Pharmacology* **538**, 48–56 (2006).
14. Chen, G. *et al.* Reduction of ischaemic stroke in rat brain by alpha melanocyte stimulating hormone. *Neuropeptides* **42**, 331–338 (2008).
15. Bitto, A. *et al.* Protective effects of melanocortins on short-term changes in a rat model of traumatic brain injury*. *Crit. Care Med.* **40**, 945–951 (2012).
16. Zierath, D., Tanzi, P., Cain, K., Shibata, D. & Becker, K. Plasma α-melanocyte stimulating hormone predicts outcome in ischaemic stroke. *Stroke* **42**, 3415–3420 (2011).
17. Minder, E. I. Afamelanotide. *Drugs of the Future* **35**, 365 (2010).
18. Langendonk, J. G. *et al.* Afamelanotide for Erythropoietic Protoporphyria. *N. Engl. J. Med.* **373**, 48–59 (2015).
19. Biolcati, G. *et al.* Long-term observational study of afamelanotide in 115 patients with erythropoietic protoporphyria. *Br. J. Dermatol.* **172**, 1601–1612 (2015).

10.0 APPENDICES

APPENDIX 1: WORLD MEDICAL ASSOCIATION DECLARATION OF HELSINKI

Ethical Principles for Medical Research Involving Human Subjects

Adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964, and amended by the:
29th WMA General Assembly, Tokyo, Japan, October 1975
35th WMA General Assembly, Venice, Italy, October 1983
41st WMA General Assembly, Hong Kong, September 1989
48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996
52nd WMA General Assembly, Edinburgh, Scotland, October 2000
53th WMA General Assembly, Washington 2002 (Note of Clarification on paragraph 29 added)
55th WMA General Assembly, Tokyo 2004 (Note of Clarification on Paragraph 30 added)
59th WMA General Assembly, Seoul, October 2008
64th WMA General Assembly, Fortaleza, Brazil, October 2013

Preamble

1. The World Medical Association (WMA) has developed the Declaration of Helsinki as a statement of ethical principles for medical research involving human subjects, including research on identifiable human material and data.

The Declaration is intended to be read as a whole and each of its constituent paragraphs should be applied with consideration of all other relevant paragraphs.

2. Consistent with the mandate of the WMA, the Declaration is addressed primarily to physicians. The WMA encourages others who are involved in medical research involving human subjects to adopt these principles.

General Principles

3. The Declaration of Geneva of the WMA binds the physician with the words, "The health of my patient will be my first consideration," and the International Code of Medical Ethics declares that, "A physician shall act in the patient's best interest when providing medical care."

4. It is the duty of the physician to promote and safeguard the health, well-being and rights of patients, including those who are involved in medical research. The physician's knowledge and conscience are dedicated to the fulfilment of this duty.

5. Medical progress is based on research that ultimately must include studies involving human subjects.

6. The primary purpose of medical research involving human subjects is to understand the causes, development and effects of diseases and improve preventive, diagnostic and therapeutic interventions (methods, procedures and treatments). Even the best proven interventions must be evaluated continually through research for their safety, effectiveness, efficiency, accessibility and quality.

7. Medical research is subject to ethical standards that promote and ensure respect for all human subjects and protect their health and rights.

8. While the primary purpose of medical research is to generate new knowledge, this goal can never take precedence over the rights and interests of individual research subjects.

9. It is the duty of physicians who are involved in medical research to protect the life, health, dignity, integrity, right to self-determination, privacy, and confidentiality of personal information of research subjects. The responsibility for the protection of research subjects must always rest with the

physician or other health care professionals and never with the research subjects, even though they have given consent.

10. Physicians must consider the ethical, legal and regulatory norms and standards for research involving human subjects in their own countries as well as applicable international norms and standards. No national or international ethical, legal or regulatory requirement should reduce or eliminate any of the protections for research subjects set forth in this Declaration.

11. Medical research should be conducted in a manner that minimises possible harm to the environment.

12. Medical research involving human subjects must be conducted only by individuals with the appropriate ethics and scientific education, training and qualifications. Research on patients or healthy volunteers requires the supervision of a competent and appropriately qualified physician or other health care professional.

13. Groups that are underrepresented in medical research should be provided appropriate access to participation in research.

14. Physicians who combine medical research with medical care should involve their patients in research only to the extent that this is justified by its potential preventive, diagnostic or therapeutic value and if the physician has good reason to believe that participation in the research study will not adversely affect the health of the patients who serve as research subjects.

15. Appropriate compensation and treatment for subjects who are harmed as a result of participating in research must be ensured.

Risks, Burdens and Benefits

16. In medical practice and in medical research, most interventions involve risks and burdens.

Medical research involving human subjects may only be conducted if the importance of the objective outweighs the risks and burdens to the research subjects.

17. All medical research involving human subjects must be preceded by careful assessment of predictable risks and burdens to the individuals and groups involved in the research in comparison with foreseeable benefits to them and to other individuals or groups affected by the condition under investigation.

Measures to minimise the risks must be implemented. The risks must be continuously monitored, assessed and documented by the researcher.

18. Physicians may not be involved in a research study involving human subjects unless they are confident that the risks have been adequately assessed and can be satisfactorily managed.

When the risks are found to outweigh the potential benefits or when there is conclusive proof of definitive outcomes, physicians must assess whether to continue, modify or immediately stop the study.

Vulnerable Groups and Individuals

19. Some groups and individuals are particularly vulnerable and may have an increased likelihood of being wronged or of incurring additional harm.

All vulnerable groups and individuals should receive specifically considered protection.

20. Medical research with a vulnerable group is only justified if the research is responsive to the health needs or priorities of this group and the research cannot be carried out in a non-vulnerable group. In addition, this group should stand to benefit from the knowledge, practices or interventions that result from the research.

Scientific Requirements and Research Protocols

21. Medical research involving human subjects must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and adequate laboratory and, as appropriate, animal experimentation. The welfare of animals used for research must be respected.

22. The design and performance of each research study involving human subjects must be clearly described and justified in a research protocol.

The protocol should contain a statement of the ethical considerations involved and should indicate how the principles in this Declaration have been addressed. The protocol should include information regarding funding, sponsors, institutional affiliations, potential conflicts of interest, incentives for subjects and information regarding provisions for treating and/or compensating subjects who are harmed as a consequence of participation in the research study.

In clinical trials, the protocol must also describe appropriate arrangements for post-trial provisions.

Research Ethics Committees

23. The research protocol must be submitted for consideration, comment, guidance and approval to the concerned research ethics committee before the study begins. This committee must be transparent in its functioning, must be independent of the researcher, the sponsor and any other undue influence and must be duly qualified. It must take into consideration the laws and regulations of the country or countries in which the research is to be performed as well as applicable international norms and standards but these must not be allowed to reduce or eliminate any of the protections for research subjects set forth in this Declaration.

The committee must have the right to monitor ongoing studies. The researcher must provide monitoring information to the committee, especially information about any serious adverse events (SAE). No amendment to the protocol may be made without consideration and approval by the committee. After the end of the study, the researchers must submit a final report to the committee containing a summary of the study's findings and conclusions.

Privacy and Confidentiality

24. Every precaution must be taken to protect the privacy of research subjects and the confidentiality of their personal information.

Informed Consent

25. Participation by individuals capable of giving informed consent as subjects in medical research must be voluntary. Although it may be appropriate to consult family members or community leaders, no individual capable of giving informed consent may be enrolled in a research study unless he or she freely agrees.

26. In medical research involving human subjects capable of giving informed consent, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail, post-study provisions and any other relevant aspects of the study. The potential subject must be informed of the right to refuse to participate in the study or to withdraw consent to participate at any time without reprisal. Special attention should be given to the specific information needs of individual potential subjects as well as to the methods used to deliver the information.

After ensuring that the potential subject has understood the information, the physician or another appropriately qualified individual must then seek the potential subject's freely-given informed

consent, preferably in writing. If the consent cannot be expressed in writing, the non-written consent must be formally documented and witnessed.

All medical research subjects should be given the option of being informed about the general outcome and results of the study.

27. When seeking informed consent for participation in a research study the physician must be particularly cautious if the potential subject is in a dependent relationship with the physician or may consent under duress. In such situations the informed consent must be sought by an appropriately qualified individual who is completely independent of this relationship.

28. For a potential research subject who is incapable of giving informed consent, the physician must seek informed consent from the legally authorised representative. These individuals must not be included in a research study that has no likelihood of benefit for them unless it is intended to promote the health of the group represented by the potential subject, the research cannot instead be performed with persons capable of providing informed consent, and the research entails only minimal risk and minimal burden.

29. When a potential research subject who is deemed incapable of giving informed consent is able to give assent to decisions about participation in research, the physician must seek that assent in addition to the consent of the legally authorised representative. The potential subject's dissent should be respected.

30. Research involving subjects who are physically or mentally incapable of giving consent, for example, unconscious patients, may be done only if the physical or mental condition that prevents giving informed consent is a necessary characteristic of the research group. In such circumstances the physician must seek informed consent from the legally authorised representative. If no such representative is available and if the research cannot be delayed, the study may proceed without informed consent provided that the specific reasons for involving subjects with a condition that renders them unable to give informed consent have been stated in the research protocol and the study has been approved by a research ethics committee. Consent to remain in the research must be obtained as soon as possible from the subject or a legally authorised representative.

31. The physician must fully inform the patient which aspects of their care are related to the research. The refusal of a patient to participate in a study or the patient's decision to withdraw from the study must never adversely affect the patient-physician relationship.

32. For medical research using identifiable human material or data, such as research on material or data contained in biobanks or similar repositories, physicians must seek informed consent for its collection, storage and/or reuse. There may be exceptional situations where consent would be impossible or impracticable to obtain for such research. In such situations the research may be done only after consideration and approval of a research ethics committee.

Use of Placebo

33. The benefits, risks, burdens and effectiveness of a new intervention must be tested against those of the best proven intervention(s), except in the following circumstances:

Where no proven intervention exists, the use of placebo, or no intervention, is acceptable; or

Where for compelling and scientifically sound methodological reasons the use of any intervention less effective than the best proven one, the use of placebo, or no intervention is necessary to determine the efficacy or safety of an intervention

and the patients who receive any intervention less effective than the best proven one, placebo, or no intervention will not be subject to additional risks of serious or irreversible harm as a result of not receiving the best proven intervention.

Extreme care must be taken to avoid abuse of this option.

Post-Trial Provisions

34. In advance of a clinical trial, sponsors, researchers and host country governments should make provisions for post-trial access for all participants who still need an intervention identified as beneficial in the trial. This information must also be disclosed to participants during the informed consent process.

Research Registration and Publication and Dissemination of Results

35. Every research study involving human subjects must be registered in a publicly accessible database before recruitment of the first subject.

36. Researchers, authors, sponsors, editors and publishers all have ethical obligations with regard to the publication and dissemination of the results of research. Researchers have a duty to make publicly available the results of their research on human subjects and are accountable for the completeness and accuracy of their reports. All parties should adhere to accepted guidelines for ethical reporting. Negative and inconclusive as well as positive results must be published or otherwise made publicly available. Sources of funding, institutional affiliations and conflicts of interest must be declared in the publication. Reports of research not in accordance with the principles of this Declaration should not be accepted for publication.

Unproven Interventions in Clinical Practice

37. In the treatment of an individual patient, where proven interventions do not exist or other known interventions have been ineffective, the physician, after seeking expert advice, with informed consent from the patient or a legally authorised representative, may use an unproven intervention if in the physician's judgement it offers hope of saving life, re-establishing health or alleviating suffering. This intervention should subsequently be made the object of research, designed to evaluate its safety and efficacy. In all cases, new information must be recorded and, where appropriate, made publicly available.

APPENDIX 2: ELEMENTS OF INFORMED CONSENT DOCUMENTATION

In seeking informed consent, the following information shall be provided to each patient:

1. A statement that the study involves research, an explanation of the purposes of the research and the expected duration of the patient's participation, a description of the procedures to be followed, and identification of any procedures which are experimental;
2. A description of any reasonably foreseeable risks or discomforts to the patient;
3. A description of any benefits to the patient or to others which may reasonably be expected from the research;
4. Disclosures of appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the patient;
5. A statement describing the extent, if any, to which confidentiality of records identifying the patient will be maintained; and,
6. An explanation of whom to contact for answers to pertinent questions about the research and participants' rights. It is the Sponsor's policy to reimburse an institution or Investigator for expenditures for the medical treatment of normal and patient volunteers who are injured as a direct result of their participation in the Sponsor's protocol as long as the Investigator has complied with the provisions of the protocol. Therefore, the consent form should reflect this in its explanation of the institution's policy. Further details on whom the volunteer should contact in case of injury should also be included.
7. An explanation of whom to contact for answers to pertinent questions about the research and research patient's rights and whom to contact in the event of a research-related injury to the patient.
8. A statement that participation is voluntary, that refusal to participate will involve no penalty or loss of benefits to which the patient is otherwise entitled, and that the patient may discontinue participation at any time without penalty or the loss of benefits to which the patient is otherwise entitled.

When appropriate, one or more of the following elements of information shall also be provided to each patient (required under ICH):

1. A statement that the particular treatment or procedure may involve risks to the patient (or to the embryo or foetus, if the patient is or may become pregnant) which are currently unforeseeable;
2. Anticipated circumstances under which the patient's participation may be terminated by the Investigator without regard to the patient's consent;
3. Any additional costs to the patient that may result from participation in the research;
4. The consequences of a patient's decision to withdraw from the research and the procedures for the orderly termination of participation by the patient;
5. A statement that significant new findings that develop during the course of the research which may relate to the patient's willingness to continue participation will be provided to the patient; and,
6. The approximate number of participants involved in the study.

[redacted] [redacted]

[redacted]

[redacted] [redacted]

[redacted]

[redacted] [redacted]

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NIH STROKE SCALE

[redacted]

[redacted]

Instructions	Scale Definition	Score
1a. Level of Consciousness: The investigator must choose a response if a full evaluation is prevented by such obstacles as an endotracheal tube, language barrier, orotracheal trauma/bandages. A 3 is scored only if the patient makes no movement (other than reflexive posturing) in response to noxious stimulation.	0 = **Alert**; keenly responsive. 1 = **Not alert**; but arousable by minor stimulation to obey, answer, or respond. 2 = **Not alert**; requires repeated stimulation to attend, or is obtunded and requires strong or painful stimulation to make movements (not stereotyped). 3 = Responds only with reflex motor or autonomic effects or totally unresponsive, flaccid, and areflexic.	_____
1b. LOC Questions: The patient is asked the month and his/her age. The answer must be correct - there is no partial credit for being close. Aphasic and stuporous patients who do not comprehend the questions will score 2. Patients unable to speak because of endotracheal intubation, orotracheal trauma, severe dysarthria from any cause, language barrier, or any other problem not secondary to aphasia are given a 1. It is important that only the initial answer be graded and that the examiner not "help" the patient with verbal or non-verbal cues.	0 = **Answers** both questions correctly. 1 = **Answers** one question correctly. 2 = **Answers** neither question correctly.	_____
1c. LOC Commands: The patient is asked to open and close the eyes and then to grip and release the non-paretic hand. Substitute another one step command if the hands cannot be used. Credit is given if an unequivocal attempt is made but not completed due to weakness. If the patient does not respond to command, the task should be demonstrated to him or her (pantomime), and the result scored (i.e., follows none, one or two commands). Patients with trauma, amputation, or other physical impediments should be given suitable one-step commands. Only the first attempt is scored.	0 = **Performs** both tasks correctly. 1 = **Performs** one task correctly. 2 = **Performs** neither task correctly.	_____
2. Best Gaze: Only horizontal eye movements will be tested. Voluntary or reflexive (oculocephalic) eye movements will be scored, but caloric testing is not done. If the patient has a conjugate deviation of the eyes that can be overcome by voluntary or reflexive activity, the score will be 1. If a patient has an isolated peripheral nerve paresis (CN III, IV or VI), score a 1. Gaze is testable in all aphasic patients. Patients with ocular trauma, bandages, pre-existing blindness, or other disorder of visual acuity or fields should be tested with reflexive movements, and a choice made by the investigator. Establishing eye contact and then moving about the patient from side to side will occasionally clarify the presence of a partial gaze palsy.	0 = **Normal.** 1 = **Partial gaze palsy;** gaze is abnormal in one or both eyes, but forced deviation or total gaze paresis is not present. 2 = **Forced deviation,** or total gaze paresis not overcome by the oculocephalic manoeuvre.	_____

[redacted]

NIH STROKE SCALE

3. Visual: Visual fields (upper and lower quadrants) are tested by confrontation, using finger counting or visual threat, as appropriate. Patients may be encouraged, but if they look at the side of the moving fingers appropriately, this can be scored as normal. If there is unilateral blindness or enucleation, visual fields in the remaining eye are scored. Score 1 only if a clear-cut asymmetry, including quadrantanopia, is found. If patient is blind from any cause, score 3. Double simultaneous stimulation is performed at this point. If there is extinction, patient receives a 1, and the results are used to respond to item 11.	0 = **No visual loss.** 1 = **Partial hemianopia.** 2 = **Complete hemianopia.** 3 = **Bilateral hemianopia** (blind including cortical blindness).	_____
4. Facial Palsy: Ask – or use pantomime to encourage – the patient to show teeth or raise eyebrows and close eyes. Score symmetry of grimace in response to noxious stimuli in the poorly responsive or non-comprehending patient. If facial trauma/bandages, orotracheal tube, tape or other physical barriers obscure the face, these should be removed to the extent poss ble.	0 = **Normal** symmetrical movements. 1 = **Minor paralysis** (flattened nasolabial fold, asymmetry on smiling). 2 = **Partial paralysis** (total or near-total paralysis of lower face). 3 = **Complete paralysis** of one or both sides (absence of facial movement in the upper and lower face).	_____
5. Motor Arm: The limb is placed in the appropriate position: extend the arms (palms down) 90 degrees (if sitting) or 45 degrees (if supine). Drift is scored if the arm falls before 10 seconds. The aphasic patient is encouraged using urgency in the voice and pantomime, but not noxious stimulation. Each limb is tested in turn, beginning with the non-paretic arm. Only in the case of amputation or joint fusion at the shoulder, the examiner should record the score as untestable (UN), and clearly write the explanation for this choice.	0 = **No drift;** limb holds 90 (or 45) degrees for full 10 seconds. 1 = **Drift;** limb holds 90 (or 45) degrees, but drifts down before full 10 seconds; does not hit bed or other support. 2 = **Some effort against gravity;** limb cannot get to or maintain (if cued) 90 (or 45) degrees, drifts down to bed, but has some effort against gravity. 3 = **No effort against gravity;** limb falls. 4 = **No movement.** UN = **Amputation** or joint fusion, explain: _____ **5a. Left Arm** **5b. Right Arm**	5a_____ 5b _____
6. Motor Leg: The limb is placed in the appropriate position: hold the leg at 30 degrees (always tested supine). Drift is scored if the leg falls before 5 seconds. The aphasic patient is encouraged using urgency in the voice and pantomime, but not noxious stimulation. Each limb is tested in turn, beginning with the non-paretic leg. Only in the case of amputation or joint fusion at the hip, the examiner should record the score as untestable (UN), and clearly write the explanation for this choice.	0 = **No drift;** leg holds 30-degree position for full 5 seconds. 1 = **Drift;** leg falls by the end of the 5-second period but does not hit bed. 2 = **Some effort against gravity;** leg falls to bed by 5 seconds, but has some effort against gravity. 3 = **No effort against gravity;** leg falls to bed immediately. 4 = **No movement.** UN = **Amputation** or joint fusion, explain: _____ **6a. Left Leg** **6b. Right Leg**	6a_____ 6b _____

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NIH STROKE SCALE

7. Limb Ataxia: This item is aimed at finding evidence of a unilateral cerebellar lesion. Test with eyes open. In case of visual defect, ensure testing is done in intact visual field. The finger-nose-finger and heel-shin tests are performed on both sides, and ataxia is scored only if present out of proportion to weakness. Ataxia is absent in the patient who cannot understand or is paralysed. Only in the case of amputation or joint fusion, the examiner should record the score as untestable (UN), and clearly write the explanation for this choice. In case of blindness, test by having the patient touch nose from extended arm position.	0 = **Absent.** 1 = **Present in one limb.** 2 = **Present in two limbs.** UN = **Amputation** or joint fusion, explain: _____	_____
8. Sensory: Sensation or grimace to pinprick when tested, or withdrawal from noxious stimulus in the obtunded or aphasic patient. Only sensory loss attributed to stroke is scored as abnormal and the examiner should test as many body areas (arms [not hands], legs, trunk, face) as needed to accurately check for hemisensory loss. A score of 2, "severe or total sensory loss," should only be given when a severe or total loss of sensation can be clearly demonstrated. Stuporous and aphasic patients will, therefore, probably score 1 or 0. The patient with brainstem stroke who has bilateral loss of sensation is scored 2. If the patient does not respond and is quadriplegic, score 2. Patients in a coma (item 1a=3) are automatically given a 2 on this item.	0 = **Normal;** no sensory loss. 1 = **Mild-to-moderate sensory loss;** patient feels pinprick is less sharp or is dull on the affected side; or there is a loss of superficial pain with pinprick, but patient is aware of being touched. 2 = **Severe to total sensory loss;** patient is not aware of being touched in the face, arm, and leg.	_____
9. Best Language: A great deal of information about comprehension will be obtained during the preceding sections of the examination. For this scale item, the patient is asked to describe what is happening in the attached picture, to name the items on the attached naming sheet and to read from the attached list of sentences. Comprehension is judged from responses here, as well as to all of the commands in the preceding general neurological exam. If visual loss interferes with the tests, ask the patient to identify objects placed in the hand, repeat, and produce speech. The intubated patient should be asked to write. The patient in a coma (item 1a=3) will automatically score 3 on this item. The examiner must choose a score for the patient with stupor or limited cooperation, but a score of 3 should be used only if the patient is mute and follows no one-step commands.	0 = **No aphasia;** normal. 1 = **Mild-to-moderate aphasia;** some obvious loss of fluency or facility of comprehension, without significant limitation on ideas expressed or form of expression. Reduction of speech and/or comprehension, however, makes conversation about provided materials difficult or impossible. For example, in conversation about provided materials, examiner can identify picture or naming card content from patient's response. 2 = **Severe aphasia;** all communication is through fragmentary expression; great need for inference, questioning, and guessing by the listener. Range of information that can be exchanged is limited; listener carries burden of communication. Examiner cannot identify materials provided from patient response. 3 = **Mute, global aphasia;** no usable speech or auditory comprehension.	_____
10. Dysarthria: If patient is thought to be normal, an adequate sample of speech must be obtained by asking patient to read or repeat words from the attached list. If the patient has severe aphasia, the clarity of articulation of spontaneous speech can be rated. Only if the patient is intubated or has other physical barriers to producing speech, the examiner should record the score as untestable (UN), and clearly write an explanation for this choice. Do not tell the patient why he or she is being tested.	0 = **Normal.** 1 = **Mild-to-moderate dysarthria;** patient slurs at least some words and, at worst, can be understood with some difficulty. 2 = **Severe dysarthria;** patient's speech is so slurred as to be unintelligible in the absence of or out of proportion to any dysphasia, or is mute/anarthric. UN = **Intubated** or other physical barrier, explain:_____	_____
11. Extinction and Inattention (formerly Neglect): Sufficient information to identify neglect may be obtained during the prior testing. If the patient has a severe visual loss preventing visual double simultaneous stimulation, and the cutaneous stimuli are normal, the score is normal. If the patient has aphasia but does appear to attend to both sides, the score is normal. The presence of visual spatial neglect or anosognosia may also be taken as evidence of abnormality. Since the abnormality is scored only if present, the item is never untestable.	0 = **No abnormality.** 1 = **Visual, tactile, auditory, spatial, or personal inattention** or extinction to bilateral simultaneous stimulation in one of the sensory modalities. 2 = **Profound hemi-inattention or extinction to more than one modality;** does not recognise own hand or orients to only one side of space.	_____

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[redacted]

You know how.

Down to earth.

I got home from work.

Near the table in the dining room.

They heard him speak on the radio last night.

[redacted]

[redacted]