# Ptcl-01373 - A double blind, randomized, placebo-controlled, parallel group, multicenter Phase 3 pivotal study to assess the safety and efficacy of 1mg/kg/day intravenous DP-b99 over 4 consecutive days versus placebo when initiated within nine hours of acute ischemic stroke onset

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| **Ethical review** | Approved WMO |
| **Status** | Recruitment stopped |
| **Health condition type** | Arteriosclerosis, stenosis, vascular insufficiency and necrosis |
| **Study type** | Interventional |

## Summary

### ID

NL-OMON34979

**Source**
ToetsingOnline

**Brief title**
MACSI

### Condition

- Arteriosclerosis, stenosis, vascular insufficiency and necrosis

**Synonym**
acute ischemic stroke

**Research involving**
Human

## Sponsors and support

**Primary sponsor:** D-Pharm Ltd
**Source(s) of monetary or material Support:** D-pharm LTD

## Intervention

**Keyword:** acute, DP-b99, ischemic stroke

## Outcome measures

### Primary outcome

To compare the clinical therapeutic effects of intravenous DP-b99 at a dose of

1.0 mg/kg initiated within 9 hours of stroke onset and administered daily over

2 hours for 4 consecutive days versus placebo

### Secondary outcome

To compare the safety and tolerability, as well as post-stroke recovery at day

90, in subjects treated with DP-b99 versus placebo

# Study description

### Background summary

Disorders such as acute stroke and myocardial infarction are associated with ischemic cell injury and cell death. These processes may be mediated via necrosis or mechanisms of programmed cell death (apoptosis). There is a growing body of evidence indicating that cation-mediated processes in ischemic neurons are important steps in the cascade leading to neuronal cell death. It has been postulated that attenuation of these processes may preserve the marginally viable ischemic penumbra and thus prevent expansion of the size of irreversibly damaged tissue and enable the recovery of the surrounding tissue.
DP-b99 is a membrane-activated chelator of divalent metal ions such as zinc and

calcium, currently under clinical development (phase 2 completed) by D-Pharm as a potential agent for the treatment of acute ischeamic stroke. Extensive nonclinical pharmacology and pharmacokinetic studies have demonstrated that DP-b99 influences a number of divalent metal ion-dependent processes implicated in the neurodegenerative and inflammatory cascades following stroke. Clinical studies provide evidence that DP-b99 while being safe is more effective than placebo in the treatment of acute stroke.
The clinical study proposed in this application is a phase 3 study planned to support a future Marketing Authorisation Application. This proposed study is planned to evaluate the efficacy and safety of DP-b99 in treating moderately severe acute ischeamic stroke when administered daily for 4 days beginning within nine hours after stroke onset.

**Study objective**

"The primary objective of this study is to compare the clinical therapeutic effects of intravenous DP-b99 at a
dose of 1.0 mg/kg initiated within nine hours of stroke onset and administered daily over 2 hours for 4
consecutive days versus placebo in subjects with moderately severe, acute ischemic stroke through the analysis
across the whole distribution of scores of the primary efficacy endpoint of mRS 90 days (or on last rating) after
the stroke".

The secondary objectives of this study are to compare the safety and tolerability,
as well as post-stroke recovery at Day 90, in subjects treated with DP-b99 versus
placebo.

**Study design**

This will be a randomized, double-blind, placebo controlled, multicenter, multi-national, parallel-arm, pivotal study, comparing a placebo group to a DP-b99 group treated with intravenous 1.0 mg/kg/d for 4 consecutive days, in acute ischemic stroke patients with an entry NIHSS score of 10-16 and a clinical syndrome that includes at least 1 of the following: visual, best language or extinction and inattention (formerly Neglect). An interim analysis for futility will be performed after day 90 primary endpoint data have been collected on 50% of subjects planned to be enrolled. Enrollment will be stratified on a one to one basis into two time-to-treatment tiers: 0- 4,5 hours and > 4,5-9 hours after stroke onset.
Clinical trial material (CTM) will be administered within 9 hours after the onset of acute ischemic stroke symptoms. Subjects will be randomized at a ratio of 1:1 to receive either DP-b99 or placebo.

## Intervention

Assessments completed during the screening/ baseline period will include recording of medical history, physical examination with body weight evaluation and performance of vital signs and ECG. Laboratory assessments including haematology, coagulation for patients on anticoagulants (excluding patients administered low molecular weight heparin) chemistry, urinanlysis will be collected and analyzed.
Immediately after randomization and within 9 hours of stroke onset, subjects will be given a 2 hour infusion of DP-b99 or placebo. Subsequent doses will be given at 24± 3 hours intervals. Subjects will be hospitalized for the entire 4 day treatment period. The NIHSS score will be assessed daily during the treatment period. Patients will remain hospitalized for observation for at least 24 hours after the last dose. Subjects will be further evaluated for efficacy and safety during the 90- day post-treatment period. On day 12 ambulatory visit, laboratory assessments will be performed. Neurological function and disability scales (NIHSS and mRS) will be administered at day 30 and day 90 along with safety assessments. Vital signs and ECGs will be recorded and physical examination and clinical laboratory tests will be performed at various time points.

## Study burden and risks

Assessments completed during the screening/ baseline period will include recording of medical history, physical examination with body weight evaluation and performance of vital signs and ECG. Laboratory assessments including haematology, coagulation for patients on anticoagulants (excluding patients administered low molecular weight heparin) chemistry, urinanlysis will be collected and analyzed.
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The most frequent adverse events in humans were local reactions to the study drug such as inflammation, redness, tenderness of the injection site and inflammation of the vein with blood clot formation inside the vein. Other events include high or low blood pressure, mild elevation of liver enzymes,

anemia, nausea, vomiting, constipation, abdominal discomfort, dizziness, muscle pain, tiredness, problems with sleeping, drug intolerance, headache and fever.
Most of these events were mild and reversible.
Drawing blood from the arm may cause pain, bruising, lightheadedness, and, on rare occasions, infection.

# Contacts

**Public**
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IL
**Scientific**
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# Trial sites

## Listed location countries

Netherlands

# Eligibility criteria

**Age**
Adults (18-64 years)
Elderly (65 years and older)

## Inclusion criteria

Patients may be considered eligible for enrollment in this study if they meet the inclusion criteria listed
below:
1. Males or females 18 to 85 years of age, inclusive
2. Have suffered an acute hemispheric ischemic stroke, defined as acute, focal, neurological

deficit(s),
secondary to a presumed vascular event, which must include at least one of the following components (as
reflected by at least 1 point on any of the corresponding items of the NIHSS: 3, 9 or 11):
- Visual
- Best Language
- Extinction and Inattention (formerly Neglect)
3. Have suffered the onset of an acute ischemic stroke that can be evaluated and treatment initiated within 9
hours after the onset of acute ischemic stroke symptoms. (Onset is defined as the time that the subject
was last seen in a normal state, or bedtime for un-witnessed strokes occurring during sleep.)
4. Have at screening a NIHSS score of 10 to 16, inclusive
5. Have readily accessible peripheral venous access for clinical trial material (CTM) administration and
blood sampling
6. Have the ability to understand the requirements of the study and be willing to provide written informed
consent (IC) (as evidenced by signature on an informed consent document approved by an institutional
review board (IRB) or independent ethics committee (IEC), and agree to abide by the study restrictions
and return for the required assessments (In the event of incapacitated subjects, informed consent will be
sought from a legally acceptable representative or by any other means as approved by the IRB or IEC).
7. Have provided written authorization for use and disclosure of protected health information (PHI) in
accordance with the Health Insurance Portability and Accountability Act (HIPAA) in the United States
and the Personal Information Protection and Electronic Documents Act (PIPEDA) in Canada

## Exclusion criteria

To be eligible for entry into the study, the subject must not meet any of the exclusion criteria listed below:
1. Have an intracerebral or subarachnoid hemorrhage per screening/baseline computerized tomography
(CT) scan or susceptibility-weighted magnetic resonance imaging (MRI)
2. Be a candidate for thrombolytic therapy or have been treated with thrombolytic therapy for the current
stroke
3. Be delirious, comatose or stuporous (a score of *2 on item 1.a of the NIHSS) or demented, or having a
mental impairment that in the investigator*s opinion renders the subject incapable to

participate in the
study
4. Have seizure(s) anytime from stroke onset to screening/baseline NIHSS evaluation
5. Have neurological or non-neurological comorbidities that in the investigator*s opinion may lead,
independent of the current stroke, to further deterioration in the subject*s neurological status during the
trial period, or may render the study*s neurological assessments inconclusive for the purpose of
evaluating solely the stroke*s effects (e.g., metabolic encephalopathies, hemiplegic migraine, multiple
sclerosis, central nervous system tumor, convulsive disorder, monocular blindness)
6. Be likely to undergo a procedure involving cardiopulmonary bypass during the study period
7. Have suffered a myocardial infarction in the last 90 days
8. Have any medical condition that in the investigator*s opinion may threaten the subject*s ability to
complete the study (e.g., concurrent significant or life-threatening diseases, such as malignancies or end
stage organ failure)
9. Have rapid spontaneous improvement of neurological signs during screening/baseline assessments
10. Have premorbid neurological deficits and functional limitations assessed by a pre-stroke Modified
Rankin Scale score of > 1
11. Have suffered a stroke within 90 days of the screening/baseline assessments that is either diagnostically
confirmed or assumed to be in the same cerebral territory as is the current acute stroke
12. Have either severe hypertension (systolic blood pressure (BP) >220 mm Hg or diastolic BP >120 mm
Hg) or hypotension (systolic BP <90 mm Hg), as measured by at least 2 consecutive supine measurements taken 10 minutes apart immediately prior to first drug administration.
13. Have significant current renal or hepatic disease(s): a serum creatinine concentration of >2.5 mg/dL;
alanine aminotransferase (ALT), aspartate aminotransferase (AST), or gamma-glutamyl transferase
(GGT) values that are three times greater the upper limit of normal (ULN)
14. Have a platelet count of <100,000/mm3 or, for patients on oral anticoagulants at study entry, INR of >4
15. Be a female of childbearing potential (less than 2 years* postmenopausal or not surgically sterilized) who
is not willing to use adequate and effective birth control measures for the duration of the trial. Effective
birth control measures include hormonal contraception, a barrier method such as a diaphragm,
intrauterine device (IUD) and/or condom with spermicide (IUD, diaphragm, condoms alone or the

rhythm method are not considered reliable methods)
16. Have a positive urine pregnancy test at screening/baseline or be a lactating female
17. Be currently dependent on, or abusing, alcohol or one or more of the following: sympathomimetic
amines (amphetamine-like), cannabis, cocaine, hallucinogens, inhalants, opioids, phencyclidine,
sedatives and hypnotics
18. Have received an investigational drug or product or participated in an investigational drug study within a
period of 30 days prior to receiving study medication or have previously participated in a clinical trial
involving DP-b99

# Study design

## Design

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| Study phase: | 3 |
| Study type: | Interventional |
| Intervention model: | Parallel |
| Allocation: | Randomized controlled trial |
| Masking: | Double blinded (masking used) |
| Control: | Placebo |
| Primary purpose: | Treatment |

## Recruitment

NL

| | |
|---|---|
| Recruitment status: | Recruitment stopped |
| Start date (anticipated): | 21-07-2010 |
| Enrollment: | 36 |
| Type: | Actual |

## Medical products/devices used

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|---|---|
| Product type: | Medicine |
| Brand name: | DP-b99 |
| Generic name: | DP-b99 |

# Ethics review

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| Approved WMO Date: | 06-04-2010 |
| Application type: | First submission |
| Review commission: | METC Z: Zuyderland-Zuyd (Heerlen) |
| Approved WMO Date: | 25-06-2010 |
| Application type: | First submission |
| Review commission: | METC Z: Zuyderland-Zuyd (Heerlen) |
| Approved WMO Date: | 24-01-2011 |
| Application type: | Amendment |
| Review commission: | METC Z: Zuyderland-Zuyd (Heerlen) |
| Approved WMO Date: | 21-10-2011 |
| Application type: | Amendment |
| Review commission: | METC Z: Zuyderland-Zuyd (Heerlen) |

# Study registrations

## Followed up by the following (possibly more current) registration

No registrations found.

## Other (possibly less up-to-date) registrations in this register

No registrations found.

## In other registers

| Register | ID |
|---|---|
| EudraCT | EUCTR2009-012025-11-NL |
| ClinicalTrials.gov | NCT00893867 |
| CCMO | NL31087.096.10 |