LÆGEMIDDELSTYRELSEN
DANISH MEDICINES AGENCY

Attn.: Anæstesiologisk afd. Nina Christine Andersen-Ranberg
Sjællands Universitetshospital, Køge
Lykkebækvej 1
4600 Køge
Danmark

30 November 2017
Case No.: 2017101527
Reference:
Emilie Arnth Jørgensen
T +45 4488 91 23
E kf@dkma.dk

Agents Intervening against Delirium in Intensive Care Unit (AID-ICU), protocol no./code AID-ICU, EudraCT no. 2017-003829-15

Decision:

The Danish Medicines Agency (DKMA) hereby authorises the conduct of the above-mentioned clinical trial on medicinal products, cf. section 88(1) of the Danish Medicines Act.[1]

The authorisation is valid up to and including **01 March 2021**

The trial covers the following investigational medicinal products:

- Serenase
- Placebo

The authorisation is granted on the following Conditions:

1. The statement in the protocol regarding pregnancy testing is still not acceptable as it only indicates that a pregnancy test has been performed before the inclusion in the trial, but does not indicate where and when the pregnancy test has been done. Thus, the applicant has still not confirmed that the pregnancy test will be performed at the investigational site prior to inclusion.
   This should be added to the protocol before the trial can be approved.

The trial must not be initiated before we have received the required documents and have confirmed receipt. The documents should be sent to us **no later 30 December 2017.** Any changes in the documentation must be clearly presented i.e. with track changes.

It is a condition for the authorisation that we are **notified** of any of the following events:

- Trial duration is extended beyond the date in authorisation letter
- Addition of new investigator sites (incl. an updated xml-file)
- Changes of principal/coordinating investigator (incl. an updated xml-file)
- Changes of CRO/applicant
- National end of trial

On the webpage http://laegemiddelstyrelsen.dk/en/topics/side-effects-and-trials/clinical-trials/trials-in-humans/guideline-for-applications-for-authorisa---in-humans/amendments-to-clinical-trials-.aspx you will find a summary of the changes that we consider substantial and therefore must be approved by us.

[1] Danish act no. 1180 of 12 December 2005 on medicinal products as amended by act no. 538 of 8 June 2006 and act no. 1557 of 20 December 2006

Lægemiddelstyrelsen
Axel Heides Gade 1
2300 København S
Denmark
T +45 44 88 95 95
E dkma@dkma.dk
LMST.DK

The Danish Medicines Agency have based its assessment on the following:

Documents:

- Cover Letter, dated 10 October 2017
- Application Form, signed by Nina Christine Andersen-Ranberg on 13 November 2017 (pdf+xml)
- EudraCT Validation Form
- Protocol AID-ICU, version 3.4, dated 10 November 2017
- Danish Protocol Addendum, Version 2.0, dated 29 September 2017
- SmPC for Serenase (haloperidol), 5 mg/ml, solution for injection
- Placebo Content Documentation
- Labels
- Orientation Letter to Manufacturer
- Danish Subject Information Leaflet, for Guardian, version 2.3, dated 17 October 2017
- Danish Subject Information Leaflet, for Relatives, version 2.2, dated 17 October 2017
- Danish Subject Information Leaflet, for Subject, version 2.2, dated 17 October 2017
- Letter of Grounds for Non-Acceptance, dated 02 November 2017
- Response to Letter of Grounds for Non-Acceptance, dated 13 November 2017

Also, prior to initiation of the trial it has to be authorised by a research ethics committee.

Any complaint about this decision can be filed to the Ministry of Health, Holbergsgade 6, DK-1057 Copenhagen K, Denmark.

We kindly refer to the enclosed extract of the Danish legislation.

Kindly address any further questions to M.Sc. Emilie Arnth Jørgensen

T: + 45 44 88 96 39 **E: eaj@dkma.dk**

Best Regards

Mette Andersen

Copy: Research Ethics Committee, Region Zealand

Legal obligations related to the conduct of clinical trials on medicinal products

Good clinical practice (GCP)
Clinical trials on medicinal products must be conducted in accordance with good clinical practice, cf. section 88(2) of the Danish Medicines Act[2], and the Danish executive order on good clinical practice in clinical trials of medicinal products in humans[3].

Good manufacturing practice (GMP)
The medicinal products of clinical trials must comply with the current standards for good manufacturing practice, cf. section 92(1) of the Danish Medicines Act, and the Danish executive order on the manufacturing and import of medicinal products and intermediary products. Investigational medicinal products manufactured in or imported from a third country (a non EU/EEA country) must comply with good manufacturing standards (at least equivalent to EU GMP).
In order to ensure that the investigational products manufactured in a third country comply with EU GMP or similar requirements, it is the practice of the Danish Medicines Agency to require that documents in support thereof be made available on request. This could be in the form of a GMP certificate issued by an EU authority and/or an EU GMP audit report from a Qualified Person and/or other EU GMP report issued by a regulatory body. This also applies to sites that manufacture active biological substances. In the case of countries with mutual recognition agreements (Canada, Switzerland, Australia and new Zealand) the above documents may be replaced by a GMP certificate and/or manufacturing licence issued by a regulatory body in the concerned MRA country.

Good distribution practice (GDP)
Distribution of medicinal products to sites must be in accordance with GDP i.e. the Danish executive order on distribution of medicinal products. The Danish Medicines Agency must authorise wholesale or retail distribution of medicinal products, i.e. distribution of medicinal products, cf. section 39(1) of the Danish Medicines Act.

Free provision of test products
Investigational medicinal products and any devices used to administer investigational medicinal products must be supplied free of charge to trial subjects, cf. section 13 of the Danish executive order on good clinical practice in clinical trials of medicinal products in humans.

Amendments to clinical trials
Section 4 of the Danish executive order on clinical trials of medicinal products in humans establishes when amendments to a clinical trial require authorisation from the Danish Medicines Agency. Please also see 'Amendments to clinical trials' available on our website www.dkma.dk . Direct link: http://laegemiddelstyrelsen.dk/en/licensing/clinical-trials/trials-in-humans/guideline-for-applications-for-authorisation-of-clinical-trials-of-medicinal-products-in-humans/amendments-to-clinical-trials-

Reporting of adverse reactions occurring during the trial period
The sponsor must

- *immediately* inform the Danish Medicines Agency of any suspected unexpected serious adverse reactions that occur during the trial.
- once a year submit a list of all suspected serious adverse reactions that have occurred during the trial period as well as a report on the safety of the trial subjects, cf. section 89 (2) of the Danish Medicines Act.

Termination of a trial
The sponsor must

[2] Danish act no. 1180 of 12 December 2005 on medicinal products as amended by act no. 538 of 8 June 2006 and act no. 1557 of 20 December 2006

[3] Danish executive order no. 744 of 29 June 2006 on good clinical practice in clinical trials of medicinal products in humans (Danish title: Bekendtgørelse nr. 744 af 29. juni 2006 om god klinisk praksis i forbindelse med kliniske forsøg med lægemidler på mennesker).

- notify the Danish Medicines Agency when the trial has been completed (no later than 90 days thereafter),
- earlier than planned. The reasons for stopping the trial must be given cf. 89 of the Danish Medicines Act.

Study results

- Results should be reported to the EudraCT database as soon as possible and no later than one year after end of trial according to http://ec.europa.eu/health/files/eudralex/vol-10/2012_302-03/2012_302-03_en.pdf.
- The DKMA do not wish to be informed about this or receive the final study report. The DKMA will review the EudraCT database regarding study results.