LÆGEMIDDELSTYRELSEN
DANISH MEDICINES AGENCY

Aalborg Universitetshospital
Att: Klinik Akut Anæstesi - Bodil Steen Rasmussen
Hobrovej 18-22
9100 Aalborg
Danmark

31 May 2017
Case no 2017021858
Reference:
Agnete Lindequist Debois
T 44 88 91 23
E kf@dkma.dk

Handling oxygenation targets in adults with acute hypoxaemic respiratory failure in the intensive care unit: A randomised clinical trial of a lower versus a higher oxygenation target, protocol no./code AAUH-ICU-01, EudraCT no. 2017-000632-34

The Danish Medicines Agency (DKMA) acknowledges receipt of your letter of 25 May 2017 in response to DKMA's conditional approval letter of 25 April 2017.

Receipt is also acknowledged of the following attachments to your above letter:

- Protocol, Version 1.2, 24 May 2017
- EudraCT Application Form (pdf+xml), dated 24 May 2017
- Approval letter from the Research Ethics Committee dated the 22th of May 2017

DKMA has no comments to your response, and the specified conditions are considered met.

Kind regards

Mette Andersen

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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 June 2020**

The trial covers the following investigational medicinal products:

- 100 % oxygen

The authorisation is granted on the following

Conditions:

1. Recording of all AEs
   It does not appear from the protocol that all AEs will be recorded in the patient journal. Please update the adverse event section in the protocol with this information. Furthermore it should be considered to include information about the fact that the patients are acute and very critically ill and that this is the reason for that most of the AEs will be recorded in the patient journal and not in the eCRF. Please also consider highlighting which events you record in the eCRF and why.

2. Definition and recording of SARs and assessment of the relationship to the IMP (oxygen)
   The first three lines in the section "Serious Adverse Reaction (SAR)" on page 35 in the protocol are ok, but in the following lines recording of SARs is still associated with side effects in the SPC, which is not correct.
   In a clinical trial SARs should be understood as all serious events that are considered to be related to the IMP and in principle, the investigator (and sponsor) should assess all events both serious and non-serious with regards to relationship to the IMP. This assessment is based on knowledge of the properties of the IMP and known side effects of the IMP and the patient's underlying disease, general condition and other medication. This

[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

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means that SARs are not exclusively the same as the side effects in the SPC.
Please consider revising and updating the section “Serious Adverse Reaction (SAR)” and only describe the definition of a SAR in this section. Recording of SARs could be mentioned as part of the section mentioned in question nr. 1.
Furthermore you should consider updating the adverse event section in general with information about how you will assess relationship to the IMP. Often is relationship assessment categorized as : not related, likely related, possible related or probably related or just not related/related. You should consider updating the adverse event section in the protocol with a similar categorization scale for assessment of relationship between the event and the IMP.

3. Assessment and recording of SUSARs
   It is still not clear how you will detect a SUSAR and how it will be recorded. A SUSAR is a serious event assumed to be related to the IMP (oxygen), but not expected and it is not a known side effect to the IMP (oxygen). As it is not clear how you in general will assess whether an event is related to the IMP or not, it is neither clear how you will detect a SUSAR. This should be clarified.

4. Comment about the final report
   It is no longer a requirement that the final report should be submitted to The Danish Medicines Agency. The results from the clinical trial including important AEs must instead be recorded on EudraCT/clinicaltrialregister.eu. The sponsor is responsible for evaluating whether an AE is important or not and whether it should be recorded on EudraCT/clinicaltrialregister.eu.

5. EudraCT form
   Thank you for the corrected EudraCT form, please also submit the xml-file.

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 than 25 May 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.

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

Documents:

- Cover Letter, Signed 13 January 2017
- EudraCT Application form, PDF, dated 11 April 2017
- Protocol AAUH-ICU-01, Version 1.1, 10 April 2017

- Protocol Résumé (Danish), Version 1.0, 30 January 2017
- Danish Subject Information Leaflet / Informed Consent Form, Version 1.0, 30 January 2017 (for Patient) - (received in DKMA 24 February 2017)
- Danish Subject Information Leaflet / Informed Consent Form, Version 1.0, 30 January 2017 (for Relatives) - (received in DKMA 24 February 2017)
- Danish Subject Information Leaflet / Informed Consent Form, Version 1.0, 30 January 2017 (First and Second Legal Guardian for Clinical Trial) - (received in DKMA 24 February 2017)
- Procedure for the Oral Submission of Subject Information, Version 1.0, 30 January 2017
- Obtaining Informed Consent in the HOT-ICU trial, Version 1.0, 30 January 2017
- SmPC for:
- Medical Oxygen “Air Liquide” 100 %, medical gas, Cryogen
- Orientation Letter to Manufacturers
- Letter of Grounds for Non-Acceptance, dated 29 March 2017
- Response to Letter of Grounds for Non-Acceptance, dated 11 April 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.Pharm Agnete Lindequist Debois
T: + 45 93596487 E: agld@dkma.dk

Kind regards

Mette Andersen

Copy: Research ethics committee, Region Nordjylland

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

- 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

[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).

- 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.