COVIDENZA - A prospective, multicenter, randomized PHASE II clinical trial of enzalutamide treatment to decrease the morbidity in patients with Corona virus disease 2019 (COVID-19): a structured summary of a study protocol for a randomised controlled trial

Karin Welén*, Anna K Överby, Clas Ahlm, Eva Freyhult, David Robinsson, Anna Jonsson Henningsson, Johan Stranne, Daniel Bremeli, Martin Angelin, Elisabeth Lindquist, Robert Buckland, Camilla Thellenberg Carlsson, Karlis Pauksens, Anna Bill-Axelsson, Olof Akre, Cecilia Ryden, Magnus Wagenius, Anders Bjartell, Anna C. Nilsson, Johan Styrke, Johanna Repo, Åse Östholm Balkhed, Katarina Niward, Magnus Gisslén and Andreas Josefsson

Abstract

Objectives: The main goal of the COVIDENZA trial is to evaluate if inhibition of testosterone signalling by enzalutamide can improve the outcome of patients hospitalised for COVID-19. The hypothesis is based on the observation that the majority of patients in need of intensive care are male, and the connection between androgen receptor signalling and expression of TMPRSS2, an enzyme important for SARS-CoV-2 host cell internalization.

Trial design: Hospitalised COVID-19 patients will be randomised (2:1) to enzalutamide plus standard of care vs. standard of care designed to identify superiority.

(Continued on next page)
Participants: Included participants, men or women above 50 years of age, must be hospitalised for PCR confirmed COVID-19 symptoms and not in need of immediate mechanical ventilation. Major exclusion criteria are breastfeeding or pregnant women, hormonal treatment for prostate or breast cancer, treatment with immunosuppressive drugs, current symptomatic unstable cardiovascular disease (see Additional file 1 for further details). The trial is registered at Umeå University Hospital, Region Västerbotten, Sweden and 8 hospitals are approved for inclusion in Sweden.

Intervention and comparator: Patients randomised to the treatment arm will be treated orally with 160 mg (4x40 mg) enzalutamide (Xtandi®) daily, for five consecutive days. The study is not placebo controlled. The comparator is standard of care treatment for patients hospitalised with COVID-19.

Main outcomes: The primary endpoints of the study are (time to) need of mechanical ventilation or discharge from hospital as assessed by a clinical 7-point ordinal scale (up to 30 days after inclusion).

Randomisation: Randomisation was stratified by center and sex. Each strata was randomized separately with block size six with a 2:1 allocation ratio (enzalutamide + "standard of care": "standard of care"). The randomisation list, with consecutive subject numbers, was generated by an independent statistician using the PROC PLAN procedure of SAS version 9.4 software (SAS Institute, Inc, Cary, North Carolina)

Blinding (masking): This is an open-label trial.

Numbers to be randomised (sample size): The trial is designed to have three phases. The first, an exploration phase of 45 participants (30 treatment and 15 control) will focus on safety and includes a more extensive laboratory assessment as well as more frequent safety evaluation. The second prolongation phase, includes the first 100 participants followed by an interim analysis to define the power of the study. The third phase is the continuation of the study up to maximum 600 participants included in total.

Trial Status: The current protocol version is COVIDENZA v2.0 as of September 10, 2020. Recruitment started July 29, 2020 and is presently in safety pause after the first exploration phase. Recruitment is anticipated to be complete by 31 December 2021.

Trial registration: Eudracit number 2020-002027-10
ClinicalTrials.gov Identifier: NCT04475601, registered June 8, 2020

Full protocol: The full protocol is attached as an additional file, accessible from the Trials website (Additional file 1). In the interest in expediting dissemination of this material, the familiar formatting has been eliminated; this Letter serves as a summary of the key elements of the full protocol.

Keywords: COVID-19, Randomised controlled trial, multicentre, protocol, enzalutamide, androgen signalling, TMPRSS2, antiandrogen
trial, virology expertise. RB- trial management board. JStr, DB, JSty, ÅÖB, KN, DR, AHI, KP, AB-A, OA, CR, MW, MA and EL - Investigators at sites. All have participated in the review of this paper. The author(s) read and approved the final manuscript.

Authors’ information
This is an academic trial and AJ and KW are independent researchers at Umeå and Gothenburg University.

Funding
This investigator initiated trial is supported by an unconditional research grant from Astellas Pharma Ltd. Astellas Pharma had no role in the design of the study and has no role in data collection, nor analysis, nor interpretation of data, nor in writing any manuscript. Open Access funding provided by Umeå University. Knut and Alice Wallenberg foundation (Andreas Josefsson).

Availability of data and materials
The trial board will have access to the final trial and no contractual agreements limit the access to the dataset.

Declarations
Ethics approval and consent to participate
The trial with reference number 2020-02122 was approved by the Swedish Ethical Review Authority May 13, 2020. Due to special requirements to limit virus spread, local variations in the procedures for obtaining informed consent were allowed. However, all participants were informed and understood the consequences of the trial, before signing the informed consent form.

Consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing interests.

Author details
1Department of Urology/Sahlgrenska Center for Cancer Research, Institute of Clinical Sciences, Sahlgrenska Academy, University of Gothenburg, 405 30 Gothenburg, Sweden. 2Department of Clinical Microbiology, Section of Virology, Umeå University, Umeå, Sweden. 3Molecular Infection Medicine Sweden, Umeå University, Umeå, Sweden. 4Department of Clinical Microbiology, Section of Infection and Immunology, Umeå University, Umeå, Sweden. 5Department of Medical Sciences, National Bioinformatics Infrastructure Sweden, Science for Life Laboratory, Uppsala University, Uppsala, Sweden. 6Department of Urology, Region of Jönköping, Jönköping, Sweden. 7Department of Biomedical and Clinical Sciences, Linköping University, Linköping, Sweden. 8Department of Clinical Microbiology, Region Jönköping County, Jönköping, Sweden. 9Department of Infectious Diseases, Institute of Biomedicine, Sahlgrenska Academy, University of Gothenburg, Gothenburg, Sweden. 10Department of Surgical and Perioperative Sciences, Urology & Andrology, Umeå University, 901 87 Umeå, Sweden. 11Wallenberg Center for Molecular Medicine, Umeå University, Umeå, Sweden. 12Department of Radiation Sciences, Oncology, Umeå University, Umeå, Sweden. 13Department of Infectious Diseases, Uppsala University Hospital, Uppsala, Sweden. 14Department of Surgical Sciences, Uppsala University, Uppsala, Sweden. 15Department of Molecular Medicine and Surgery, Karolinska Institutet, Stockholm, Sweden. 16Division of Infection Medicine, Department of Clinical Sciences, Lund University, Lund, Sweden. 17Division of Urological Cancers, Department of Translational Medicine, Lund University, Malmö, Sweden. 18Department of Translational Medicine, Infectious Diseases Research Unit, Lund University, Malmö, Sweden. 19Department of Infectious Diseases, Sahlgrenska University Hospital, Region Västra Götaland, Gothenburg, Sweden.

Received: 15 February 2021 Accepted: 18 February 2021
Published online: 16 March 2021

Publisher’s Note
Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.