Welén et al. Trials (2021) 22:209
https://doi.org/10.1186/s13063-021-05137-4

Trials

LETTER Open Access

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[1*], Anna K Överby[2,3], Clas Ahlm[4], Eva Freyhult[5], David Robinsson[6], Anna Jonsson Henningsson[7,8], Johan Stranne[1], Daniel Bremell[9], Martin Angelin[4], Elisabeth Lindquist[4], Robert Buckland[10,11], Camilla Thellenberg Carlsson[12], Karlis Pauksens[13], Anna Bill-Axelsson[14], Olof Akre[15], Cecilia Ryden[16], Magnus Wagenius[17], Anders Bjartell[17], Anna C. Nilsson[18], Johan Styrke[10], Johanna Repo[4], Åse Östholm Balkhed[8], Katarina Niward[8], Magnus Gisslén[9,19] and Andreas Josefsson[1,10,11*]

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)

* Correspondence: karin.welen@gu.se; Andreas.josefsson@umu.se
[1]Department of Urology/Sahlgrenska Center for Cancer Research, Institute of Clinical Sciences, Sahlgrenska Academy, University of Gothenburg, 405 30 Gothenburg, Sweden
Full list of author information is available at the end of the article

(Continued from previous 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 breast-feeding 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: Eudract 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

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s13063-021-05137-4.

Additional file 1:. Full study protocol.

Acknowledgements

Support, project management and facilities to conduct the study were provided by Clinical Research Center, Umeå University Hospital. Thanks to the clinical trial unit in Umeå: Marja-Liisa Lammi Tavelin, Lisette Marjavaara, Emma Wede, Kristina Öjbrant, Ida Lundström and Anna Ramnemark for excellent ongoing help with the startup and continued work with the trial, thanks also to the Centre for Clinical Cancer studies at Karolinska Institute for skillful help (Sanna Nyström and Susanne Wallberg). We also thank Fredrik Granström at ITS (ICT Services and System Development at Umeå University) for helping us create the electronic Clinical Report Form, and also thanks to Sonja Huldén, judge of appeal, for legal support.
Thanks also to all research personnel with all the work with starting up the trial at respective sites and for feedback to help us improve the trial: Frida Samuelsson, Jennie Bobeck, Mia Mickelsson, Helena Gisslén, Jenny Holm Fernström, Ann Carlstrand, Elisabeth Bengtsson, Kristina From, Sofia Sjöberg, Jennifer Amidi, Annika Löfgren, Suzy Lindberg, Malin Karlström, Mathias Cortés Rico, Malin Lindell, Beatrice Backman Lönn, Maria Casserdahl, Kerstin Almroth, Britt-Inger Dahlin, Ester Fridenström, Malin Hellgren, Rebecka Sundén , Ann-Charlotte Borgefeldt, Yvonne Pantzar, Cecilia Magnusson
We thank the Data Safety and Monitoring board for taking on the responsibility of this important and crucial work to externally review the ongoing trial: Associate Professor Martin Eklund, Professor Annika Bergquist, Associate Professor Jan Adolfsson, Professor Lars Hagberg, Professor Jan-Erik Damber, and Senior Medical Advisor Helén Seeman-Lodding
Thanks also to statistician Professor Marie Eriksson (Umeå Univerisity) for help with the randomization process.
We also acknowledge the work from the biobanks in the different regions: Biobank West, Biobank North, Uppsala Biobank, Biobank facility at Malmö, Sundsvall, Linköping and Jönköping.
The authors are grateful for the unconditional support received from Astellas Pharma Europe®. The trial is also funded by the Knut and Alice Wallenberg foundation (Andreas Josefsson)

Authors' contributions

AJ – PI, concept and design of the study, including protocol writing and management. KW – co-PI, concept and design of the study, including protocol writing and management. EF-Statistician. CA, MG, AB and AN- consultation for protocol concept, design and conduct. CTK – consultation of design and safety evaluation. AÖW– preclinical studies for rationale of the

trial, virology expertise. RB- trial management board. JStr, DB, JSty, JR, ÅÖB, KN, DR, AJH, 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 Umea 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
[1]Department of Urology/Sahlgrenska Center for Cancer Research, Institute of Clinical Sciences, Sahlgrenska Academy, University of Gothenburg, 405 30 Gothenburg, Sweden. [2]Department of Clinical Microbiology, Section of Virology, Umeå University, Umeå, Sweden. [3]Molecular Infection Medicine Sweden, Umeå University, Umeå, Sweden. [4]Department of Clinical Microbiology, Section of Infection and Immunology, Umeå University, Umeå, Sweden. [5]Department of Medical Sciences, National Bioinformatics Infrastructure Sweden, Science for Life Laboratory, Uppsala University, Uppsala, Sweden. [6]Department of Urology, Region of Jönköping, Jönköping, Sweden. [7]Department of Biomedical and Clinical Sciences, Linköping University, Linköping, Sweden. [8]Department of Clinical Microbiology, Region Jönköping County, Jönköping, Sweden. [9]Department of Infectious Diseases, Institute of Biomedicine, Sahlgrenska Academy, University of Gothenburg, Gothenburg, Sweden. [10]Department of Surgical and Perioperative Sciences, Urology & Andrology, Umeå University, 901 87 Umeå, Sweden. [11]Wallenberg Center for Molecular Medicine, Umeå University, Umeå, Sweden. [12]Department of Radiation Sciences, Oncology, Umeå University, Umeå, Sweden. [13]Department of Infectious Diseases, Uppsala University Hospital, Uppsala, Sweden. [14]Department of Surgical Sciences, Uppsala University, Uppsala, Sweden. [15]Department of Molecular Medicine and Surgery, Karolinska Institutet, Stockholm, Sweden. [16]Division of Infection Medicine, Department of Clinical Sciences, Lund University, Lund, Sweden. [17]Division of Urological Cancers, Department of Translational Medicine, Lund University, Malmö, Sweden. [18]Department of Translational Medicine, Infectious Diseases Research Unit, Lund University, Malmö, Sweden. [19]Department 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