Research Square

Preprints are preliminary reports that have not undergone peer review. They should not be considered conclusive, used to inform clinical practice, or referenced by the media as validated information.

WITHDRAWN: Proxalutamide (GT0918) Reduces the Rate of Hospitalization and Death in COVID-19 Male Patients: A Randomized Double-Blinded Placebo-Controlled Trial.

John McCoy
Applied Biology Inc., Irvine, CA, USA
Andy Goren
Applied Biology Inc., Irvine, CA, USA
Flavio Adsuara Cadegiani
flavio.cadegiani@unifesp.br

Federal University of São Paulo, São Paulo, Brazil https://orcid.org/0000-0002-2699-4344
Sergio Vaño-Galván
Dermatology Department, Ramón y Cajal Hospital, Madrid, Spain.
Maja Kovacevic
Department of Dermatology and Venereology, University Hospital Center “Sestre milosrdnice”, Zagreb, Croatia.
Daniel Fonseca
Samel Hospital, Manaus, Brazil
Edinete Dorner
Samel Hospital, Manaus, Brazil
Dirce Costa Onety
Samel Hospital, Manaus, Brazil
Ricardo Ariel Zimerman
Hospital da Brigada Militar, Porto Alegre, Brazil
Carlos Gustavo Wambier
Department of Dermatology, Alpert Medical School of Brown University

---

Research Article

Keywords: COVID-19, SARS-CoV-2, androgen receptor, androgenetic alopecia, anti-androgen therapy, transmembrane protease serine 2, TMPRSS2, Proxalutamide

Posted Date: June 17th, 2021

DOI: https://doi.org/10.21203/rs.3.rs-135303/v2

License: This work is licensed under a Creative Commons Attribution 4.0 International License.
Read Full License

Version of Record: A version of this preprint was published at Frontiers in Medicine on July 19th, 2021. See the published version at https://doi.org/10.3389/fmed.2021.668698.

EDITORIAL NOTE:

The full text of this preprint has been withdrawn by the authors while they make corrections to the work. Therefore, the authors do not wish this work to be cited as a reference. Questions should be directed to the corresponding author.

Abstract

Background: Antiandrogens have demonstrated a protective effect for COVOD-19 patients in observational and interventional studies. The goal of this study was to determine if proxalutamide, an androgen receptor antagonist, could be an effective treatment for men with COVID-19 in an outpatient setting.

Study design and methods: A randomized, double-blinded, placebo-controlled clinical trial was conducted at two outpatient centers (Brasilia, Brazil). Patients were recruited from October 21 to December 24, 2020 (ClinicalTrials.gov number, NCT04446429). Male patients with confirmed COVID-19 but not requiring hospitalization (COVID-19 8-point ordinal scale <3) were administered proxalutamide 200mg/day or placebo for up to 7 days. The primary endpoint was hospitalization rate at 30 days post-randomization.

Results: A total of 268 men were randomized in a 1:1 ratio. 134 patients receiving proxalutamide and 134 receiving placebo were included in the intention-to-treat analysis. The 30-day hospitalization rate was 2.2% in men taking proxalutamide compared to 26% in placebo, P<0.001. The 30-day hospitalization risk ratio was 0.09; 95% confidence interval (CI) 0.03 to 0.27. Patients in the proxalutamide arm more frequently reported gastrointestinal adverse events, however, no patient discontinued treatment. In placebo group, 6 patients were lost to follow-up, and 2 patients died from acute respiratory distress syndrome.

Conclusion: The hospitalization rate in proxalutamide treated men was reduced by 91% compared to usual care.

Trial Registration: NCT04446429

Introduction

Androgen signaling plays a central role in SARS-CoV-2 infectivity. SARS-CoV-2 cell entry is mediated by priming of viral spike proteins by the androgen-promoted enzyme, transmembrane protease, serine 2 (TMPRSS2). Structural modification of viral spike proteins enhances binding of SARS-CoV-2 to angiotensin converting enzyme 2 (ACE2) and facilitates viral entry into cells. Thus, targeting the transcription of TMPRSS2 with antiandrogens can affect viral cell entry. [3,4] It has been demonstrated that ACE2 and TMPRSS2 levels in lung and cardiac cells are reduced by antiandrogens.[1,2] Conversely, patients with androgen sensitive phenotypes have been shown to have increased COVID-19 disease burden. The androgen-mediated phenotype androgenetic alopecia (AGA) has been associated with greater COVID-19 disease severity[5–7]. Further, the progression of AGA in hospitalized men showed a direct correlated with COVID-19 disease severity; men with more advanced AGA were more likely to require intensive care or die. [5,8]

In a large population based study of COVID-19 patients in northern Italy, it was reported that prostate cancer patients undergoing androgen depravation therapy (ADT) had lower SARS-CoV-2 infection rates

compared to prostate cancer patients not receiving ADT (OR 4.05; 95% CI 1.55-10.59).[9] Similarly, we have reported the protective effect of 5-alpha-reductase inhibitors (5ARi) for men with COVID-19 in two observational studies.[10,11] 5ARis such as finasteride and dutasteride block the conversion of testosterone to a more potent intracellular androgen, dihydrotestosterone.[2] In a study of 77 men hospitalized with COVID-19 we found that among chronic antiandrogen users (primarily dutasteride) 8% were admitted to the ICU, compared to 58% of men not taking antiandrogens (p=0.0015).[10] Moreover, the frequency of COVID-19 symptoms among men with AGA was drastically reduced in users of 5ARis in an outpatient setting. A statistically significant reduction in the frequency of 20 of 29 clinical symptoms was observed in 5ARi users compared to non-users. For example, 38% and 2% of men presented with low-grade fever, 60% and 6% with dry cough, and 88% and 15% reported anosmia in the non-5ARi and 5ARi groups, respectively.[11] In a randomized, placebo-controlled trial, early antiandrogen therapy with dutasteride resulted in faster recovery from symptoms, improvement in inflammatory markers, and reduced detection rates of SARS-CoV-2 in nasopharyngeal swabs after 7 days compared to placebo (35.7% versus 88.2%, p=0.0094).[12] Similarly, in a randomized clinical trial that enrolled 80 hospitalized men, the use of finasteride (a 5ARi with a shorter half-life than dutasteride) was associated with improvement in oxygen saturation by day 5, and a 75% lower mortality rate.[13]

Proxalutamide is a potent second-generation nonsteroidal androgen receptor (AR) antagonist.[14] AR antagonist competitively inhibit androgen hormones from binding to the AR, which prevents AR dimerization and binding of AR dimers to DNA.[15] We have previously reported our preliminary analysis of the effects of proxalutamide 200mg per day in COVID-19 patients, which showed an overall 74% reduction in nasopharyngeal detection of SARS-CoV-2 on the 7th day of treatment.[16] The objective of this study was to evaluate the efficacy of proxalutamide in preventing hospitalization in males diagnosed with COVID-19 in an outpatient setting.

Methods

Study Design and Oversight

This was double-blinded, randomized, placebo-controlled clinical trial of proxalutamide for the treatment of male outpatients with COVID-19 (NCT04446429). The study was approved by the Brazilian National Ethics Committee: #4.282.108; process number (CAAE) 36703320.8.0000.0023 of the Comitê de Ética em Pesquisa (CEP), Comitê Nacional de Ética em Pesquisa (CONEP), Ministry of Health (Ministério da Saúde (MS)) (CEP/CONEP/MS). All patients were volunteers and received no financial compensation. All patients gave informed consent.

Study Population and Covariates

Patients were recruited through social media or by referral from primary care physicians. Potential study patients presented one of two outpatient centers (Centro Clínico Advance and Exame Imagem e Laboratorio, Brasilia, Brazil). Self-referred patients that contacted the study sites for participation

underwent a medical screening visit prior to randomization. Nasopharyngeal swabs were collected from all potential patients by trained medical personal. SARS-CoV-2 status was confirmed by real-time reverse transcription polymerase reaction (rtPCR) testing following the Cobas rtPCR kit protocol (Automatized Platform, Roche, USA).

The inclusion criteria were: males with mild COVID-19 disease (COVID-19 8-point ordinal scale <3), positive rtPCR for SARS-CoV2 within seven days of randomization, initiation of symptoms seven days prior to randomization, creatinine below 1.5 times the upper limit of normalily (ULN), alanine transferase (ALT) below 3.0 times the ULN, total bilirubin below 2.0 times the ULN, and International Normalized Ratio of Prothrombin Time below 1.5 times the ULN, and age 18 years or older. The exclusion criteria included: signs of severe COVID-19 including respiratory rate >30 breaths/min, tachycardia >120 beats per minute, systolic and diastolic arterial blood pressure <90mmHg and <60mmHg, respectively, criteria for hospitalization at the time of randomization, uncontrolled types 1 or 2 diabetes mellitus or hypertension, congestive heart failure (CHF) grades 3 or 4 (New York Heart Association), or left ventricle ejection rate below 50%, rate corrected Q-T interval above 450mm in the electrocardiogram, HIV, active hepatitis B or C, active syphilis, cancer diagnosed in the past five years (except for skin and thyroid cancer), and refusal to use condom in the 90 days following treatment.

Baseline characteristics, comorbidities, test results, and medications used were recorded. For each patient, the age, frequency and duration of medication used and the following pre-existing conditions were recorded: type 2 diabetes, hypertension, obesity (defined as body mass index >30 kg/cm^2), and chronic obstructive pulmonary disease. Pre-existing conditions were chosen based on previous drug trials in COVID-19.

Procedures

Patients were randomized to receive either proxalutamide 200 mg/day for up to 7 days or placebo. Proxalutamide 200mg and placebo were manufactured to appear identical (Kintor Pharmaceuticals Ltd., Suzhou, China). A blocked randomization list was created with block size of 10 and the sequence of dispensing was followed throughout the trial. The group assignment was known only to the study monitor. The patients and doctors directly managing patient care were blinded to the study group allocation until the close of the study. Patients were instructed to take one tablet once a day. The telephone contact and clinical follow-up were independently performed by study assistants that were blinded to group assignments. No changes in the randomization process occurred during the trial.

Previous prescriptions from referring medical doctors, initiated upon the diagnosis of COVID-19, were continued. Usual care consisted of various combinations of medications and was individualized to each patient's needs. Azithromycin 500mg q.d. (5 days) and nitazoxanide 500mg b.i.d. (6 days) were offered to all patients, while the following medications were prescribed as needed: dipyrone, paracetamol, ondansetron, dexamethasone, rivaroxaban, and enoxaparin. In cases of hospitalization, additional drugs

were prescribed according to the clinical judgement of the hospital staff. Treatment compliance was not evaluated during the trial.

Protocol Modifications

The initial protocol approved by the IRB proposed the use proxalutamide 200 mg per day for 3 days only (approval #4.282.108). However, after the first safety analysis conducted from Oct 30 to Nov 01 (35 patients randomized), the safety committee observed that 3 patients allocated in the same group experienced unexpected relapse of previous symptoms after a few days of interruption of the investigational product. The study director agreed to unblind the 3 patients, which were observed to be from the proxalutamide group. The protocol was amended to change the posology from one tablet per day for 3 days to 1 tablet per day for 7 days (IRB approval #4.513.428). Upon study closing, a total of 75 patients were randomized and given bottles with 3 tablets (38 received proxalutamide), and a total of 193 patients were randomized and given bottles with 7 tablets (96 received proxalutamide).

Study Outcomes

The primary outcome for the study was the percentage of patients hospitalized due to COVID-19. The COVID-19 8-point ordinal scale was used for screening as well as identifying patients as hospitalized. The 8-point ordinal scale is defined as: 8. Death; 7. Hospitalized, on invasive mechanical ventilation or ECMO; 6. Hospitalized, on non-invasive ventilation or high flow oxygen devices; 5. Hospitalized, requiring supplemental oxygen; 4. Hospitalized, not requiring supplemental oxygen- requiring ongoing medical care (COVID-19 related or otherwise); 3. Hospitalized, not requiring supplemental oxygen - no longer requires ongoing medical care; 2. Not hospitalized, limitation on activities; 1. Not hospitalized, no limitations on activities

Statistical Analysis

Sample size estimate was based on a report by Riccardo et al[17]. In the report it was shown that in Italy the hospitalization rate was as high as 20% among adults above the age of 65 tested positive for SARS-CoV-2. Further, Montopoli et al[9] reported that males represent 60% of hospitalized patients; therefore, we estimated that the 30-days rate of hospitalization of males over the age of 65, tested positive for SARS-CoV-2 would be approximately 30%. For the assumed efficacy of proxalutamide as a treatment for COVID-19, we estimated a 50% reduction in the hospitalization rate. 236 patients are required to have 80% chance of detecting, as significant at the 5% level, a reduction in hospitalization rate from 30% in the control group to 15% in the proxalutamide group. Adjusting for non-compliance/cross-over of 2.5% in each group, we estimated a total of 262 patients (131 in each arm). Hospitalization risk ratio was used as the measure of efficacy in the analysis of the primary outcome. Kaplan-Meier survival estimates were used to evaluate the differences of hospitalization rates throughout the 30-days post-randomization observation period. Under the intention-to-treat analysis, all patients that were randomized and had ongoing consent to be evaluated for outcomes were included. Chi-squared test for independent

proportions was adopted with statistical significance was set at $p<0.05$. Stata/SE 17.0 for Mac (StataCorp, TX, USA) was used to perform all statistical analysis.

Results

268 men were randomized to the study. 134 men were randomized to the proxalutamide arm and 134 men were assigned to placebo. Six patients in the placebo arm discontinued treatment and withdrew consent. A total of 134 patients from the proxalutamide group and 128 patients from the placebo group were followed throughout the study period. The six patients from the placebo arm that were not followed were assumed to be non-hospitalized (COVID-19 8-point ordinal scale 1) and were included in the intention-to-treat analysis. The flow chart of patients recruited into the study is shown in **Figure 1**. Baseline characteristics of the two study groups are displayed in **Table 1**. Concomitant treatments were difficult to assess owing to the outpatient nature of the sampled population and were not monitored.

During the 30-day post-randomization period, 3 patients (2.2%) in the proxalutamide group versus 35 (26.1%) in the placebo group were hospitalized (**Table 2**). The 30-day hospitalization risk ratio was 0.09 (95% confidence interval (CI), 0.03 to 0.27), i.e., the hospitalization rate in proxalutamide treated men was reduced by 91% compared to placebo. The risk difference was -0.24 (95%CI, -0.32 to -0.16).

A summary of the distribution of COVID-19 8-point ordinal scale scores at day 15 and day 30 post-randomization is included in **Table 2**. At day 30, 12 patients were still hospitalized in the placebo group, compared to zero in the proxalutamide arm. **Figure 2** shows the cumulative hospitalization rates over the follow-up period of 30-days post-randomization. The 3 patients that were hospitalized in the proxalutamide group had later hospitalizations compared to the placebo group, which showed a higher rate of hospitalizations in the first 10 days. After 10 days, the rate of hospitalization was similar between groups.

A summary of treatment emergent adverse events (TEAEs) is presented in **Table 3**. Gastrointestinal TEAEs were more frequent in the proxalutamide arm: diarrhea (21% proxalutamide versus 9% placebo), nausea (14% proxalutamide versus 6% placebo), abdominal pain (12% proxalutamide versus 5% placebo). Death within 30 days of enrollment in the study was reported for 2 patients (1.6%) in the placebo arm. No deaths were reported in the proxalutamide arm (**Table 3**). In the placebo arm, the primary cause of death was reported as acute respiratory distress syndrome (ARDS) resulting from progressive COVID-19 disease. The percentage of patients reported to have serious adverse events (SAEs) was 0% in proxalutamide arm and 29% in the placebo arm. The primary cause of SAEs in was due to progressive COVID-19.

Discussion

These results show the improvement of clinical outcomes in men with COVID-19 after the use of proxalutamide 200 mg per day. We have previously reported the protective effect of the 5-alpha-

reduactase inhibitor, dutasteride, in men with COVID-19, both in hospitalized patients and in an outpatient setting.[11,12,18] As dutasteride has a half-life of 5 weeks and carries a labeled contraindication for the use in women of childbearing age,[19] we were keen to explore an antiandrogen that could be applied more broadly. Proxalutamide has been evaluated for 28 days in Phase 1 safety studies for both men and women; furthermore, the pharmacokinetics clearance rate for proxalutamide is 22 hours.[20] As such, proxalutamide would be more suitable for application in men and women. We are currently completing a similar outpatient trial focused on female patients (NCT04853134). Additionally, we have completed a randomized, placebo-controlled trial of proxalutamide for male and female hospitalized COVID-19 patients (NCT04728802). Future trials should also explore other non-steroidal antiandrogens (NSAA) with proven safety data in the treatment of COVID-19, e.g., apalutamide, enzalutamide, darolutamide, bicalutamide, or flutamide.

The dosage used in this trial, 200mg for up to 7 days, was effective in reducing the hospitalization rates by 91%. It is still unknown if different posology could improve efficacy in the outpatient setting. However, higher dosages, higher initial loading dose, or a longer treatment course could be explored in future trials. For example, 300 mg per day has been used in hospitalized patients (NCT04728802). Additionally, a loading dosage 600 mg followed by 200 mg per day for 7 days has been reported in a case report.[21]

SARS-CoV-2 cell entry into type II pneumocytes is blocked by TMPRSS2 inhibitors[27,28] and TMPRSS2 transcription inhibitors (antiandrogens).[1,3] We expect an antiandrogen-class effect on protection from COVID-19, which may be explained by mechanisms distinct from the androgen-mediated SARS-COV-2 cell entry mechanism.[22] A non-immunosuppressive anti-inflammatory effect may occur, as the activation of the androgen receptor by dihydrotestosterone leads to increased IL-6 production in macrophages, delaying repair of injury.[24] Furthermore, NSAA use was associated with a reduction in plasma IL-6 and TNF post-trauma,[25] and reduction in inflammatory response induced by radiation.[26] Of note, the androgen receptor may be activated though the IL-6 STAT3 activation pathway.[1,23] More reseach is needed to elucidate the mechanism of NSAA on COVID-19.

We acknowledge that there are important limitations in the present study. Primarily, no direct monitoring of treatment compliance was conducted; this combined with the protocol change from a 3-day to a 7-day intervention schedule could have masked differences between treatment with placebo and proxalutamide, i.e., treatment with 3 days of proxalutamide may have been ineffectual. Nevertheless, proxalutamide retained its efficacy in intention-to-treat analysis. Second, owing to the open recruitment, data for the usual care medications was not analyzed. Finally, the six patients that withdrew from the study were all from the placebo arm. To account for this we assumed the greatest bias against the tested drug, and included all six patients as non-hospitalized in the intention-to-treat analysis.

Here we demonstrate that proxalutamide was a benefit to men with mild to moderate COVID-19. Male outpatients with SARS-CoV-2 were 91% less likely to be hospitalized versus those treated with placebo.

We hope the results of this study encourage more trials of proxalutamide and other antiandrogens for the treatment of COVID-19.

Conclusion

In COVID-19 male outpatients, treatment with proxalutamide reduced the rate of hospitalization by 91%. The results of the present study further elucidate the protective impact of early antiandrogen treatment for COVID-19 in the outpatient setting. Further studies of antiandrogen therapies in COVID-19 patients are needed.

Declarations

Funding sources: This investigator-initiated trial was supported by an unconditional research grant from Kintor Pharmaceuticals, Ltd. to Applied Biology, Inc., which provided study drugs at no cost. Kintor Pharmaceuticals, Ltd. had no role in the design of the study, data collection, analysis, interpretation of data, or in writing the manuscript, and provided no financial support to the hospitals, or to investigators. Applied Biology, Inc. funded study costs.

Conflicts of Interest: Kintor Pharmaceuticals, Ltd. manufactures and plans to market proxalutamide, and has an investigational new drug (IND) application under United States Food and Drugs Administration to conduct a Phase 3 study for proxalutamide for COVID-19. Applied Biology, Inc. has patents pending regarding antiandrogen therapy for COVID-19. Dr. Goren and Dr. McCoy are employees of Applied Biology, Inc. Dr. Cadegiani has served as a clinical director for Applied Biology, Inc. Dr. Wambier has served as an advisor to Applied Biology, Inc. The other authors have no conflict of interest to declare.

IRB approval status: The study was approved by an ethics committee and registered with clinicaltrials.gov (NCT04446429), and also approved by Brazilian National Ethics Committee (Approval number #4.282.108; CAAE:36703320.8.0000.0023; Comitê de Ética em Pesquisa (CEP) of the Comitê Nacional de Ética em Pesquisa (CONEP) of the Ministry of Health (MS)) (CEP/CONEP/MS).

References

1. Samuel RM, Majd H, Richter MN, et al. Androgen Signaling Regulates SARS-CoV-2 Receptor Levels and Is Associated with Severe COVID-19 Symptoms in Men. *Cell Stem Cell*. 2020;27(6):876-889.e12. doi:10.1016/j.stem.2020.11.009

2. Wambier CG, Goren A. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection is likely to be androgen mediated. *J Am Acad Dermatol*. 2020;83(1):308-309. doi:10.1016/j.jaad.2020.04.032

3. Qiao Y, Wang XM, Mannan R, et al. Targeting transcriptional regulation of SARS-CoV-2 entry factors ACE2 and TMPRSS2. *Proc Natl Acad Sci U S A*. 2020;118(1). doi:10.1073/pnas.2021450118

4. Ou T, Mou H, Zhang L, Ojha A, Choe H, Farzan M. Hydroxychloroquine-mediated inhibition of SARS-CoV-2 entry is attenuated by TMPRSS2. *PLOS Pathog*. 2021;17(1):e1009212. doi:10.1371/journal.ppat.1009212

5. Wambier CG, Vaño-Galván S, McCoy J, Pai S, Dhurat R, Goren A. Androgenetic alopecia in COVID-19: compared to age-matched epidemiologic studies and hospital outcomes with or without the Gabrin sign. *J Am Acad Dermatol*. July 2020. doi:10.1016/j.jaad.2020.07.099

6. Lee J, Yousaf A, Fang W, Kolodney M. Male Balding is a Major Risk Factor for Severe COVID-19. *J Am Acad Dermatol*. July 2020. doi:10.1016/j.jaad.2020.07.062

7. Ramos PM, Ianhez M, Miot HA. Alopecia and Gray Hair Are Associated with COVID-19 Severity. *Exp Dermatol*. October 2020:exd.14220. doi:10.1111/exd.14220

8. Salazar Arenas MÁ, Muñoz Del Carpio-Toia A, Aybar Galdos J, Rodriguez-Morales AJ. Alopecia and severity of COVID-19: a cross-sectional study in Peru. *Le Infez Med*. 2021;29(1):37-45. http://www.ncbi.nlm.nih.gov/pubmed/33664171.

9. Montopoli M, Zumerle S, Vettor R, et al. Androgen-deprivation therapies for prostate cancer and risk of infection by SARS-CoV-2: a population-based study (N = 4532). *Ann Oncol*. May 2020. doi:10.1016/j.annonc.2020.04.479

10. Goren A, Wambier CG, Herrera S, et al. Anti-androgens may protect against severe COVID-19 outcomes: results from a prospective cohort study of 77 hospitalized men. *J Eur Acad Dermatology Venereol*. 2021;35(1):e13-e15. doi:10.1111/jdv.16953

11. McCoy J, Cadegiani FA, Wambier CG, et al. 5-alpha-reductase inhibitors are associated with reduced frequency of COVID-19 symptoms in males with androgenetic alopecia. *J Eur Acad Dermatol Venereol*. 2021;35(4):e243-e246. doi:10.1111/jdv.17021

12. Cadegiani FA, McCoy J, Gustavo Wambier C, Goren A. Early Antiandrogen Therapy With Dutasteride Reduces Viral Shedding, Inflammatory Responses, and Time-to-Remission in Males With COVID-19: A Randomized, Double-Blind, Placebo-Controlled Interventional Trial (EAT-DUTA AndroCoV Trial – Biochemical). *Cureus*. February 2021. doi:10.7759/cureus.13047

13. Zarehoseinzade E, Allami A, Ahmadi M, Bijani B, Mohammadi N. Finasteride in hospitalized adult males with COVID-19: A risk factor for severity of the disease or an adjunct treatment: A randomized controlled clinical trial TT -. *MJIRI*. 2021;35(1):232-237. doi:10.34171/mjiri.35.30

14. Qu F, Gu Y, Wang Q, et al. Metabolomic profiling to evaluate the efficacy of proxalutamide, a novel androgen receptor antagonist, in prostate cancer cells. *Invest New Drugs*. 2020;38(5):1292-1302. doi:10.1007/s10637-020-00901-w

15. Tran C, Ouk S, Clegg NJ, et al. Development of a second-generation antiandrogen for treatment of advanced prostate cancer. *Science*. 2009;324(5928):787-790. doi:10.1126/science.1168175

16. Cadegiani FA, McCoy J, Gustavo Wambier C, et al. Proxalutamide Significantly Accelerates Viral Clearance and Reduces Time to Clinical Remission in Patients with Mild to Moderate COVID-19: Results from a Randomized, Double-Blinded, Placebo-Controlled Trial. *Cureus*. February 2021. doi:10.7759/cureus.13492

17. Riccardo F, Ajelli M, Andrianou XD, et al. Epidemiological characteristics of COVID-19 cases in Italy and estimates of the reproductive numbers one month into the epidemic. *medRxiv*. January 2020:2020.04.08.20056861. doi:10.1101/2020.04.08.20056861

18. Goren A, Wambier CG, Herrera S, et al. Anti-androgens may protect against severe COVID-19 outcomes: results from a prospective cohort study of 77 hospitalized men. *J Eur Acad Dermatology Venereol*. 2020. doi:10.1111/jdv.16953

19. Wambier CG, Pereira CS, Prado Júnior BDPA, Foss NT. Brazilian blood donation eligibility criteria for dermatologic patients. *An Bras Dermatol*. 2012;87(4):590-595. doi:10.1590/S0365-05962012000400012

20. Zhou T, Xu W, Zhang W, et al. Preclinical profile and phase I clinical trial of a novel androgen receptor antagonist GT0918 in castration-resistant prostate cancer. *Eur J Cancer*. 2020;134:29-40. doi:10.1016/j.ejca.2020.04.013

21. Cadegiani F, Lin EM, Goren A, Wambier CG. Potential risk for developing severe COVID-19 disease among anabolic steroid users. *BMJ Case Rep*. 2021;14(2). doi:10.1136/bcr-2021-241572

22. Li F, Han M, Dai P, et al. Distinct mechanisms for TMPRSS2 expression explain organ-specific inhibition of SARS-CoV-2 infection by enzalutamide. *Nat Commun*. 2021;12(1):866. doi:10.1038/s41467-021-21171-x

23. Culig Z. Interleukin-6 Function and Targeting in Prostate Cancer. *Adv Exp Med Biol*. 2021;1290:1-8. doi:10.1007/978-3-030-55617-4_1

24. Gilliver SC, Ashworth JJ, Mills SJ, Hardman MJ, Ashcroft GS. Androgens modulate the inflammatory response during acute wound healing. *J Cell Sci*. 2006;119(4):722-732. doi:10.1242/jcs.02786

25. Kan WH, Hsieh CH, Schwacha MG, et al. Flutamide protects against trauma-hemorrhage-induced liver injury via attenuation of the inflammatory response, oxidative stress, and apopotosis. *J Appl Physiol*. 2008;105(2):595-602. doi:10.1152/japplphysiol.00012.2008

26. Wu C-T, Chen W-C, Lin P-Y, Liao S-K, Chen M-F. Androgen deprivation modulates the inflammatory response induced by irradiation. *BMC Cancer*. 2009;9(1):92. doi:10.1186/1471-2407-9-92

27. Hoffmann M, Kleine-Weber H, Schroeder S, et al. SARS-CoV-2 Cell Entry Depends on ACE2 and TMPRSS2 and Is Blocked by a Clinically Proven Protease Inhibitor. *Cell*. 2020;181(2):271-280.e8. doi:10.1016/j.cell.2020.02.052

28. Olaleye OA, Kaur M, Onyenaka CC. Ambroxol Hydrochloride Inhibits the Interaction between Severe Acute Respiratory Syndrome Coronavirus 2 Spike Protein's Receptor Binding Domain and Recombinant Human ACE2. *bioRxiv Prepr Serv Biol*. September 2020. doi:10.1101/2020.09.13.295691

Tables

Table 1. Baseline characteristics of the study arms.

Characteristics	Overall N=268	Proxalutamide N=134	Placebo N=134
Age (years), median (IQR)	45 (17)	45 (19)	46 (15)
Coexisting conditions, no. (%)			
Type 2 diabetes	21 (8)	11 (8)	10 (7)
Hypertension	55 (21)	33 (25)	22 (16)
Chronic Obstructive Pulmonary Disease	1 (0)	1 (0)	0 (0)
BMI > 30 kg/m^2	43 (16)	22 (16)	21 (16)
No. of coexisting conditions, no. (%)			
0	158 (59)	74 (55)	84 (63)
1	49 (18)	29 (22)	20 (15)
2+	55 (21)	31 (23)	24 (18)
Baseline 8-point ordinal scale score			
1	160 (60)	63 (47)	97 (72)
2	108 (40)	71 (53)	37 (28)

Table 2. Summary of Outcomes

Characteristic, no. (%)	Proxalutamide N=134	Placebo N=134
Hospitalizations	3 (2)	35 (26)
Supplemental oxygen	2 (1)	33 (25)
Non-invasive ventilation	0 (0)	19 (14)
High flow oxygen devices	1 (1)	26 (19)
Invasive mechanical ventilation	0 (0)	17 (13)
Extracorporeal membrane oxygenation	0 (0)	6 (4)
Vasopressors	0 (0)	12 (9)
Death	0 (0)	2 (1)
Day 15 – 8-point ordinal scale score, no. (%)		
1	129 (96)	83 (62)
2	4 (3)	28 (21)
3	0 (0)	2 (1)
4	0 (0)	1 (1)
5	0 (0)	3 (2)
6	1 (1)	4 (3)
7	0 (0)	12 (9)
8	0 (0)	1 (1)
Day 30 – 8-point ordinal scale score, no. (%)		
1	132 (99)	104 (78)
2	2 (1)	17 (13)
3	0 (0)	0 (0)
4	0 (0)	4 (3)
5	0 (0)	4 (3)
6	0 (0)	0 (0)
7	0 (0)	3 (2)
8	0 (0)	2 (1)

Table 3. Summary of treatment emergent adverse events (TEAEs).

Characteristic	Proxalutamide N=134	Placebo N=128	P
1 or more TEAE, no. (%)	82 (61.2%)	116 (90.6%)	
General, no. (%)			
Disease progression	4 (3)	43 (34)	<0.001
Hypoxemia (>4% decrease or reaching SpO2 <92%)	3 (2)	36 (28)	<0.001
Tachycardia	6 (4)	45 (35)	<0.001
Fatigue	1 (1)	71 (55)	<0.001
Shortness of breath	4 (3)	40 (31)	<0.001
Fever	2 (1)	34 (27)	<0.001
Dehydration	20 (15)	51 (39)	<0.001
Increase in ALT or AST (over the ULN)	4 (3)	22 (17)	<0.001
Gastrointestinal, no. (%)			
Diarrhea	39 (28)	20 (16)	0.009
Dyspepsia or Heartburn	23 (17)	6 (5)	0.001
Abdominal pain or discomfort	22 (16)	18 (14)	0.596
Nausea	21 (16)	15 (12)	0.353
Vomiting	4 (3)	6 (5)	0.472
Nervous system, no. (%)			
Headache	1 (1)	12 (9)	0.001
Ageusia	13 (10)	23 (18)	0.052
Anosmia	14 (10)	26 (20)	0.026
Diffuse sweating	48 (36)	5 (4)	<0.001
Orthostatic dizziness	6 (4)	8 (6)	0.524
Musculoskeletal, no. (%)			
Arthralgia	5 (4)	22 (17)	<0.001
Muscle pain	3 (2)	39 (30)	<0.001
Lower back pain	11 (8)	24 (19)	0.012
Upper back pain	5 (4)	12 (9)	0.064
Pain in extremity	2 (1)	4 (3)	0.377
Skin and subcutaneous tissue, no. (%)			
Skin Lesions	10 (7)	7 (5)	0.512
Total TEAE, no.*	276	591	-

*Patients with multiple adverse events were counted more than once in the total TEAEs. ALT: alanine aminotransferase; AST: aspartate aminotransferase; ULN: Upper Limit of Normality.

Figures

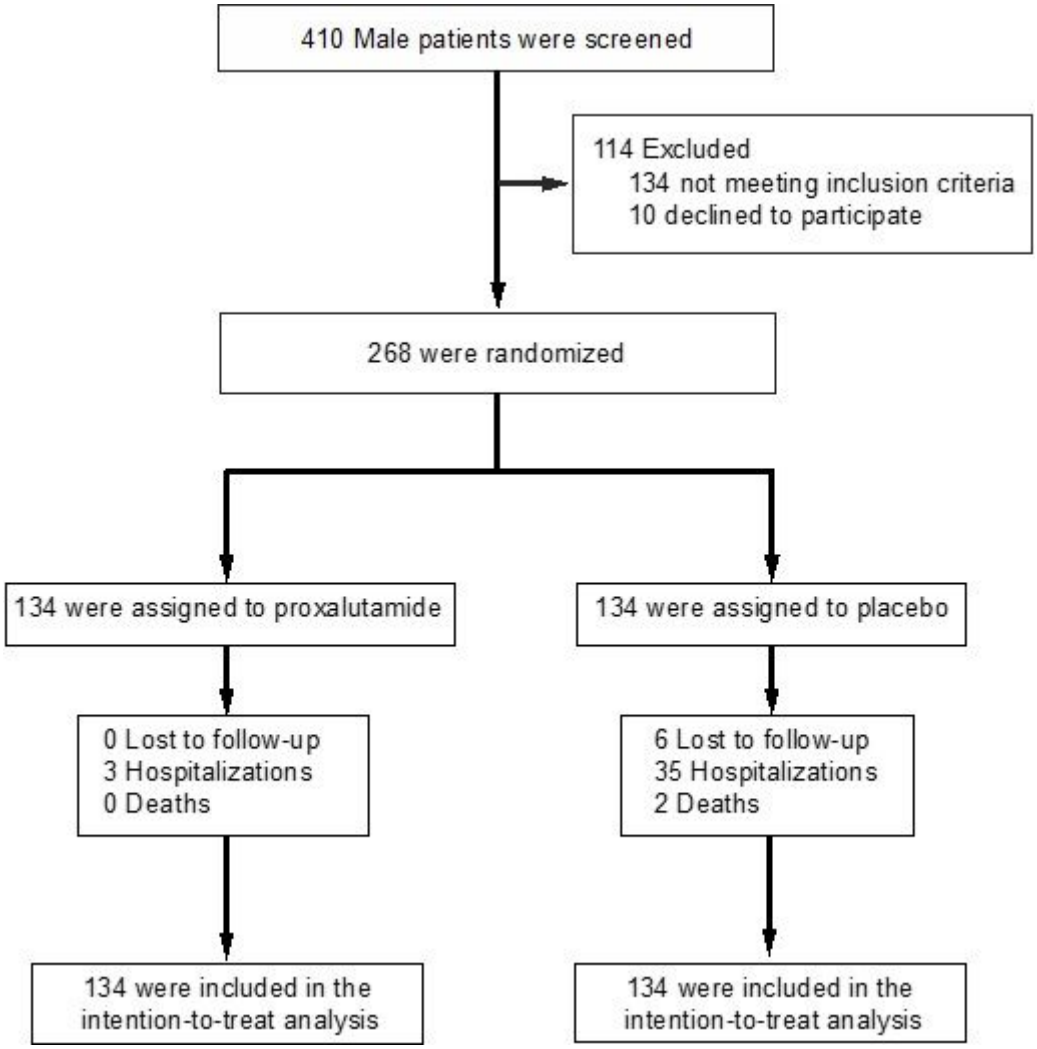

Figure 1

Enrollment and analyzed population.

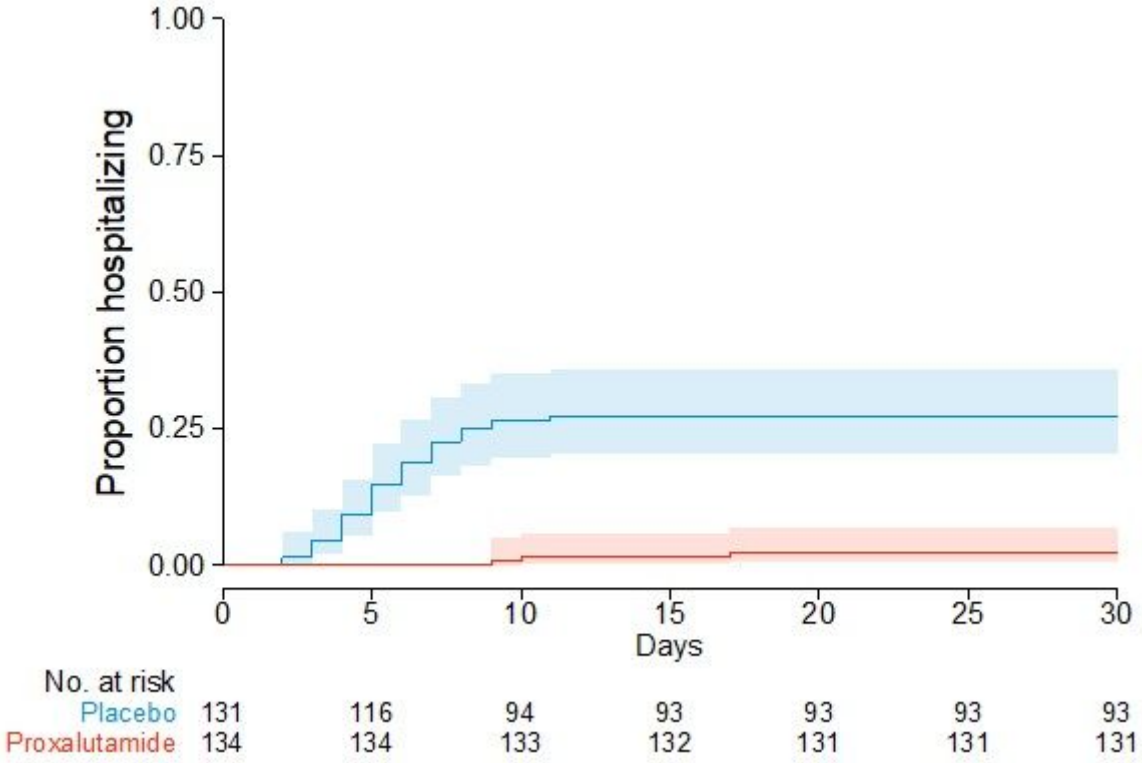

Figure 2

Kaplan-Meier estimates of proportion hospitalizing due to COVID-19 during the 30-day post-randomization follow-up.