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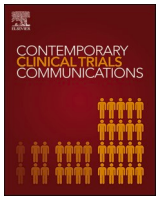

Novel approach for oligospermia (NAPO) - Protocol for a randomized controlled trial

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ABSTRACT

Background: Infertility affects millions of couples globally, with up to 40–50 % of cases linked to impaired semen quality. Insemination or in vitro fertilization are used frequently, regardless of the cause of infertility due to the lack of specific medical interventions for male infertility. Denosumab, an antibody blocking RANKL signaling, may enhance semen quality in infertile men. This randomized controlled trial evaluates if denosumab improves spermatogenesis in men with severely impaired semen quality identified by serum AMH levels as a predictive marker.

Methods: NAPO is a single-center, sponsor-investigator-initiated, placebo-controlled, double-blinded randomized trial. Subjects will be randomized in a 2:1 fashion to receive either denosumab 60 mg subcutaneously or a placebo. The study will be carried out at the Division of Translational Endocrinology, Copenhagen University Hospital, Herlev, Denmark. The primary outcome of the study is defined as the difference in sperm concentration (millions/mL) at one spermatogenesis (80 days) after inclusion.

Discussion: An important step in addressing infertility is establishing a viable treatment option for male infertility. With this study, we describe the protocol for a planned RCT aimed at evaluating whether treatment with denosumab can improve sperm concentration in men with severely impaired semen quality. The results of this study will provide evidence crucial for future treatment in a patient group where treatment options are minimal at best.

Trial registration: Clinical Trials: NCT06300229. Registered on March 12, 2024. Clinical Trials Information System (CTIS): 2023-508325-27-00. Approved on December 19, 2023.

1. Introduction

1.1. Background

Globally, infertility poses a substantial health burden impacting more than 15 % of couples worldwide [1]. Male infertility contributes to around half of the cases and is the only etiology in up to 30 % of all infertile cases [2–4]. As it stands today, there are no treatment options for the vast majority of infertile men [4], except when it is specific conditions like varicocele that can be removed surgically [5], or hypogonadotropic hypogonadism [6] that can be treated effectively with hormone medication. The remaining 90 % of infertile men receive no treatment even though they are the root cause of the infertility. Instead, the female counterparts are treated in fertility clinics with treatments ranging from mild intrauterine insemination (IUI) to more invasive assisted reproductive technologies (ART) such as in vitro fertilization (IVF) and intracytoplasmic sperm injection (ICSI) [7]. This is both expensive and associated with multiple side effects for the female

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partner who is undergoing it.

In response to this, there is a need to explore and understand regulators of male fertility for demographic health. Therefore, the research in this field has been extensive in the past 20 years, but without breakthroughs in identifying new treatment options for the male partner. However, recent studies have shown that Sertoli cells in the testes express receptor activator of nuclear factor kappa-B ligand (RANKL) that signals to its receptor RANK in spermatogonia and spermatocytes in both mice and humans [8,9]. The RANKL system is well-known for its role in the regulation of bone metabolism and treatment of osteoporosis, where the binding of RANKL to RANK on osteoclast precursor cells induces osteoclast maturation and activation leading to bone resorption [10], and influence cell proliferation, differentiation, and apoptosis [10,11]. However, with the presence of the RANKL system in the testis this indicates a possible direct effect on spermatogenesis. Moreover, treatment with denosumab, a RANKL inhibitor used to treat osteoporosis, could potentially stimulate sperm production in infertile men, and be a medical treatment option for low sperm concentration [8].

1.2. Our research

In light of this, our research group has investigated the effect of denosumab in human testicular germ cell lines as well as in human testicular tissue *ex vivo* "hanging drop" cultures [8]. Treatment with denosumab did in both cases increase the proliferation and reduced apoptosis in the germ cells, which is an indicator for denosumab treatment having a potential beneficial effect on sperm production. This led to a pilot intervention study of 12 infertile men who were overall healthy and without comorbidities. The men were treated with a single-dose of 60 mg of denosumab subcutaneous (s.c.). The study showed that the response to RANKL inhibition on sperm production was either bad or highly beneficial. This was an interesting finding and indicates that only some infertile men should be offered denosumab treatment and this fraction of beneficial responders should ideally be identified based on an easily accessible biomarker before initiation of treatment.

In the search for a valid biomarker to identify good responders to denosumab, a placebo-controlled randomized controlled trial (RCT) was conducted in 100 infertile men with severe male infertility (ClinicalTrials.gov NCT03030196). Here, active treatment with a single-dose of 60 mg denosumab s.c. was compared to placebo treatment. Data from the RCT showed that serum anti-Müllerian hormone (AMH) could serve as a biomarker to distinguish the good responders from the bad responders of denosumab treatment (data not published yet). In general, serum AMH is not generally included in the andrological evaluation of the infertile man but has for many years been routinely measured in women in their fertility evaluation. It is a helpful tool in the process of diagnosing polycystic ovarian syndrome (PCOS) and premature ovarian failure [12]. In men, AMH is synthesized by Sertoli cells, and the production of AMH is to some extent regulated by follicle-stimulating hormone (FSH) and Sertoli cell function [13]. Newer studies indicate that serum AMH can be used as a marker of Sertoli cell function, and since the beneficial effect of denosumab on germ cell number and sperm count is dependent on the preserved Sertoli function, it is plausible that a beneficial effect of denosumab on an infertile man could be predicted by measuring serum AMH before initiating treatment. Based on this knowledge, we are currently conducting a randomized controlled trial, FITMI (First In Treating Male Infertility) [14], to explore whether treatment with denosumab can improve semen quality in infertile men with moderate oligospermia who are selected by serum AMH, and have a sperm concentration of at least 2 million/mL. This is an important study, but unfortunately, it leaves out a solution for those with sperm concentration below 2 million/mL, who are the most vulnerable in this regard. Therefore, there is a need for an RCT that addresses the specific concerns of individuals with sperm concentrations below 2 million/mL to provide a viable treatment option. Moreover, denosumab also stimulates sperm motility in infertile men [8], which indicates an improved sperm function, and this may be of importance even if the man still needs in vitro fertilization. In NAPO, the inclusion criteria still include a high serum AMH concentration based on previous studies [14] but includes a criterion for average testicular size to be $\leq$ 17 mL, which allows a leniency in AMH concentrations (>28 pmol/L).

Importantly, we have not experienced any serious adverse reactions, severe side effects, increased DNA fragmentation index or an increased abortion rate in the female partners of the patients. Parallel to this, we have also conducted safety studies and shown both in tissue cultures [15] and a nationwide cohort study [16], that denosumab is not associated with cancer and therefore is seems safe to use as a single-dose in healthy young men.

1.3. Objective of NAPO

This RCT aims to assess whether treatment with denosumab can improve semen quality in infertile men selected by serum AMH as a positive predictive biomarker, and with severely impaired semen quality (Concentrations between 0.01 million/mL to 2 million/mL). This paper describes the background, rationale, and design of the study.

2. Methods

2.1. Trial design and setting

NAPO is a single-center, sponsor-investigator-initiated, placebo-controlled, double-blinded randomized trial. Following successful completion of screening procedures, subjects will be randomized in a 2:1 fashion to receive either denosumab 60 mg s.c. or placebo. The study will be carried out at the Division of Translational Endocrinology, Copenhagen University Hospital, Herlev, Denmark. The SPIRIT reporting guidelines have been used for reporting [17] and a CONSORT diagram outlining the trial has been shown in Fig. 1.

2.2. Inclusion criteria

Eligible participants will be infertile men $\geq$18 years and <60 years of age with a sperm concentration $\leq$2 million/mL and serum AMH levels $\geq$28 pmol/L.

2.3. Exclusion criteria

Participants will as a part of the screening process be excluded from any of the following reasons: Chronic diseases, defined as diagnosis where signs, symptoms, and treatment imply an expected long duration and lack of a cure, such as diabetes mellitus, thyroid disorders, autoimmune diseases such as arthritis, vasculitis or inflammatory bowel disease and osteoporosis. A sperm concentration <0.01 million/mL, serum FSH <3 IU/L, BMI $\geq$35 kg/m^2, or testis size >17 mL. Also, men with current or previous malignancies, or men who are referred to a testicular biopsy after baseline examination and ultrasound will be excluded. Furthermore, men with hypocalcemia, vitamin D deficiency, or impaired kidney function at baseline, defined as albumin-corrected calcium <2.17 mmol/L or total calcium <2.14 mmol/L, serum vitamin D (25OHD) level <25 nmol/L or eGFR <60 mL/min/1,73 m^2 will also be excluded. Finally, insufficient dental status, vasectomy, semen volume <0.9 mL, or hypersensitivity to latex, denosumab, or any of the excipients (acetic acid, sodium hydroxide, Sorbitol (E420), Polysorbate 20) will be excluded.

2.4. Withdrawal

Besides the mentioned exclusion criteria, a participant can still be withdrawn from the study after randomization. This will happen with the occurrence of a malignancy, calcium disorder, parathyroid disorder,

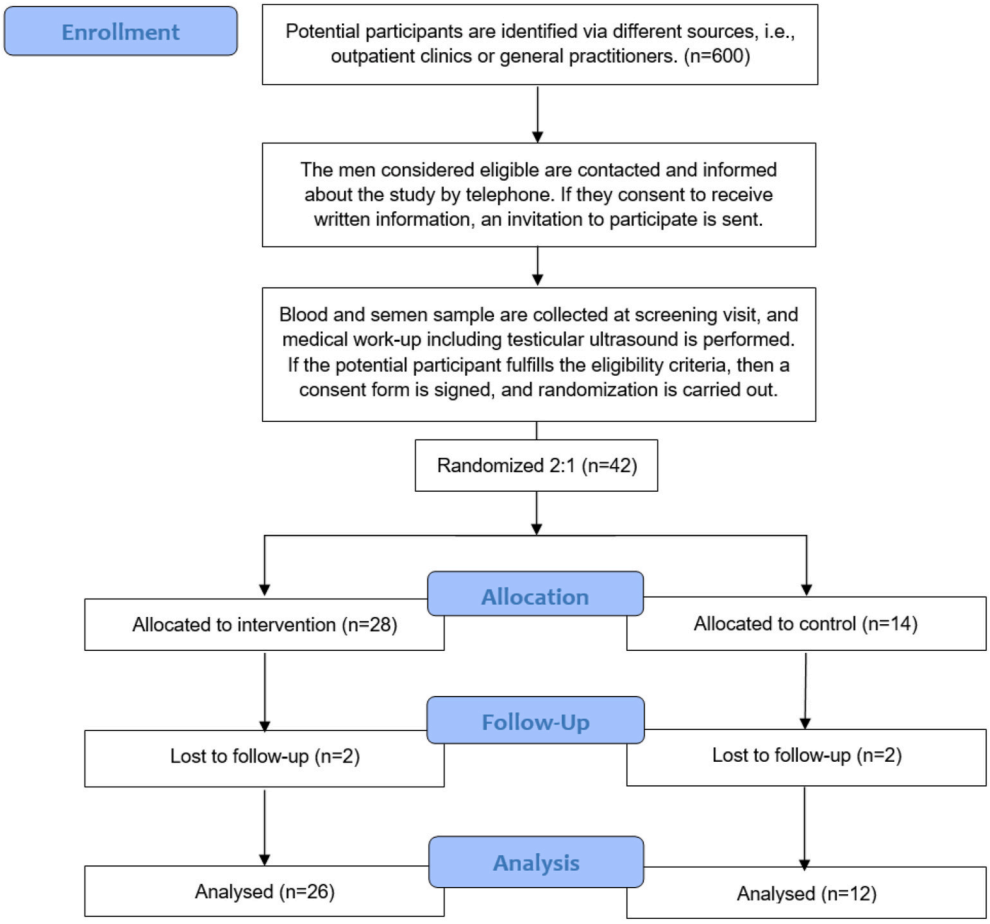

Fig. 1. The expected flow diagram of the progress through the study (CONSORT)
Figure legend: An expected CONSORT diagram showing the expected flow of NAPO.

or thyroid disorder, diabetes, or other endocrine disorders that would require hormone treatment. Also, treatment with drugs such as chemotherapies, diuretics, calcium channel blockers, Salazopyrines, Corticosteroids, TNF-alpha blockers, Cellcept, Imurel, Protopic, or Methotrexate. Also, if a testicular biopsy or other genital surgery is performed during the trial period or if the patient is admitted with temporary or permanent organ failure of either liver, heart, kidney, lung, gastrointestinal system, or urogenital system. Lastly, if participant changes his mind and withdraws consent, or there is a breach of the blinding, the subject will be withdrawn.

2.5. Recruitment, screening, and enrollment

The recruitment of participants will be done via different sources, but mainly through the fertility clinic at Herlev Hospital. In addition, we will contact and visit other both public and private fertility clinics, endocrinology departments, and private practices in Copenhagen and encourage sites to refer patients directly to our study. At this moment in time, fertility is a very current issue raised in the Danish media, and we fully expect potential participants will also contact our site self-motivated. Regardless of the point of contact, a telephone interview will be the initial screening where the participant will be briefly informed about the study and offered to receive detailed material. As a starting point, we will only invite infertile men with a sperm concentration that is expected to meet the eligibility criteria to the screening visit. The enrollment will made by a trained clinician. At the screening visit, the trial and process are explained in detail and if the candidate is still interested and agrees to participate, informed consent will be signed. Also, at the screening visit, the participant will be measured for height and weight and must produce a semen sample and have a blood sample taken where we measure serum AMH, FSH, vitamin D, calcium, and creatinine. The participants must have a time of abstinence of at least two days, which includes intercourse and masturbation. At the visit, a testicular ultrasound will also be performed to exclude potential testicular tumors and describe degree of varicocele in combination with palpation. To ensure adherence to the trial, and minimize the loss to follow-up, automated messages are sent as reminders before each visit. Furthermore, to ensure all reports of severe adverse effects are reported properly, automated messages will be sent to the trial investigators if a participant is admitted to a hospital.

2.6. Randomization and blinding process

Since we wish to ensure a wide distribution in the range of the eligibility criteria, participants will be divided into two groups based on their sperm concentration. Separation thresholds will be sperm concentration at 0.7 million/mL. In this way, two groups will consist of participants with sperm concentration 0.7–2.0 million/mL (Group A, n = 21), and sperm concentration 0.01–0.7 million/mL (Group B, n = 21). The blinding of the treatment from the placebo arm will be prepared centrally by an independent pharmacy (Glostrup Apotek), who uses https://www.sealedenvelope.com/for the allocation sequence. The medicine will arrive in closed boxes with labels on the outside, indicating each unique randomization number. At the inclusion day, a trained clinician will initially prepare the injection but will not have any contact with the participant. Another clinician will pick up the prepared syringe and thus be blinded and inject the participant with the medicine (denosumab or placebo). This means the allocated trial medication will

be blinded to the participant, the clinical staff caring for the participant, the investigators, and the outcome assessors. The empty packaging will be put back in the box, which is sealed with tape and stored in a locked room. This ensures that should an individual breach of code be required, the box with the associated unique randomization number can be found and opened.

2.7. Outcome measures

The primary outcome of the study is defined as the difference in sperm concentration (million/mL) between the denosumab and placebo arm. For this purpose, it will be average sperm concentration of two semen samples delivered on day 80 and day 83 after inclusion that is used. The sperm concentration is measured both manually and on SCA® CASA System for semen analysis, which allows the accurate, repetitive, and automatic assessment of sperm concentration. Secondary endpoints include the difference in semen quality (total sperm count, total number of motile sperm, percentage of motile sperm, total number of progressive motile sperm and percentage of progressive motile sperm, total number of morphologically normal sperm, and percentage of morphologically normal sperm) between the denosumab and placebo arm. Also, differences in pregnancies achieved spontaneously or IUI before day 180. Furthermore, the difference in the number of miscarriages throughout the trial period, and the difference in serum levels of reproductive hormones (FSH, LH, AMH, and Inhibin B) on day 80 and changes within groups. As exploratory endpoints, we will look at the difference in expression of the cation channels of sperm (CatSper and RANKL) and RANKL concentration in seminal fluid on day 80 and changes within groups.

2.8. Timeline of study

Table 1 shows the timeline for the participants of the trial. As mentioned before, if the participant fulfills the eligibility criteria at the screening visit, he is invited to the day 1 visit. Here he will provide another semen sample, have a blood sample drawn, and finally receive a subcutaneous injection of either denosumab 60 mg or placebo. The participants will also be handed out supplementation containing 180 tablets of 10 μg vitamin D and 400 mg of calcium. On day 80, another semen sample is provided, another blood sample is drawn, and a questionnaire is answered by the participant. Three days later on day 83, the participant delivers the final semen sample. This is the last physical visit for the participant. On day 180, the participants will receive an electronic questionnaire focusing on pregnancies and adverse events. If they do not respond to this form, they will be contacted by telephone. If they have achieved pregnancy before day 180, they will be sent an additional electronic questionnaire on day 450 regarding pregnancy complications, birth complications as well as data on the child (gender, birth weight, birth length, and whether the child is healthy).

Table 1
The expected timeline flow for patients participating in the trial.

	STUDY PERIOD					
	Enrollment	Allocation	Post-allocation			
TIMEPOINTS	*Day -30*	*Day 1*	*80*	*83*	*180*	*450*
ENROLLMENT:						
Eligibility screen	X					
Informed consent	X					
Semen and blood sample	X	X				
Testicular ultrasound	X					
Allocation		X				
INTERVENTIONS:						
Denosumab 60 mg		X	←	—	→	
ASSESSMENTS:						
Semen sample			X	X		
Blood sample			X			
Interview			X			
Questionnaire					X	
Pregnancies, birth, and child health						X

Table legend: A SPIRIT figure showing the expected timeline for patients included in NAPO.

2.9. Ethical considerations

The trial will be conducted following the principles of the Declaration of Helsinki and compliance with the protocol approved by the competent authority and Ethics Committee, and according to GCP standards [18]. This ensures that all participants will be informed of potential adverse effects, and that they withdraw from the trial at any point without any consequences. Denosumab is a drug that has been traded since 2008 (approved by both the FDA and EMA) and has proven to be safe in several randomized studies. We have seen no effect on sperm DNA fragmentation index (DFI) or abortions in the first two clinical trials performed by our research group, so we have no safety concerns in that regard. Furthermore, in general, there is currently no medical treatment to improve male fecundity which makes ARTs the primary option for infertile couples. This is a treatment where women must undergo fertility treatment and often receive several hormonal drugs and a surgical intervention associated with side effects. This is a significant ethical issue that in our view fully justifies the mild potential side effects caused by denosumab.

3. Data analysis and management

3.1. Population analysis

Data will be analyzed using the intention-to-treat (ITT) principles. Therefore, all randomized participants will be analyzed in the groups to which they were originally allocated, regardless of whether a protocol violation or protocol deviation occurred. Participants who withdraw consent for the use of their data will not be included in any analysis and withdrawal of consent will be reported.

3.2. Sample size

With the power to avoid a type II error set to 80 % (1-β) at a two-sided 5 % significance level, 42 men allocated 2:1 in each of the investigation arms (28 vs. 14) are needed to detect a difference in sperm concentration of 100 % between intervention and placebo group in the primary outcome. This is based on the Minimum Clinically Important Difference (MCID), as improvement from 1 million/mL to 2 million/mL, which have clinical implications as that is the threshold from ICSI treatment compared to other ARTs such as IVF. We estimate to screen 600 infertile men as around 10 % will meet the eligibility criteria and around 80 % will in the end agree to participate in the trial. The calculations are based on the intra-individual variation in sperm concentration when including infertile men with sperm concentrations between 0.01 and 2 million/mL. We expect that the placebo group will have a post-trial sperm concentration of 1 million/mL while the denosumab group will have 2 million/mL with a maximum SD of 1.1.

3.3. Statistics and underlying assumptions

After the trial, baseline data as well as follow-up data will be presented for all the trial participants and stratified into the treatment groups. This includes unadjusted baseline and follow-up averages for the entire study population, as well as baseline and follow-up averages for the two subgroups mentioned earlier. The primary analysis will be a covariance analysis in which day 80 measurements are analyzed, initially as crude values but also adjusted on baseline. The baseline is defined as the average of day −30 and day 1, and day 80 is defined as the average of day 80 and day 83 unless abstinence time is < 2 days or high fever which will result in the exclusion of data. In both cases, data will be transformed as necessary to meet model assumptions. When reporting a potentially relevant clinically significant effect, due diligence will be exercised because of the risk of type I errors when performing multiple tests. Missing data will be minimized by performing repeated monitoring of data entry into electronic case report forms (our eCRFs). In this way, we will be able to monitor the extent of missing data and intervene if necessary. Hence, we do not anticipate that there will be any significant number of missing values.

3.4. Software and data handling

All data will be entered as an electronic database in REDcap. REDcap is a worldwide online system developed specifically for non-commercial clinical research to significantly reduce data entry and study management errors to improve data fidelity. Regarding GDPR, the study has been registered and approved by Privacy, which is the entity that approves the data handling of the capital region of Denmark. The law on the processing of personal data will be complied with. After completion of the trial, data will be anonymized and shared with 'XY Therapeutics' who can use the data for possible approval by the EMA and FDA authorities. The sharing of data with 'XY Therapeutics' will be reflected in participant information and informed consent so that it is clear to the participants.

3.5. Monitoring

The trial will be externally monitored by the national Good Clinical Practice (GCP) unit at Frederiksberg Hospital, Copenhagen, Denmark. The frequency of onsite monitoring will depend on compliance with the protocol, the number of enrolled participants, and the quality of data handling. The GCP will monitor inclusion and exclusion criteria, consent obtained in all subjects according to legislation, and data included in the eCRF. All personal information about potential and enrolled participants is collected in the eCRF and only accessible by relevant users which secures confidentiality before, during, and after the trial.

3.6. Safety

In general, our safety concerns for denosumab are at a minimum. This is due to several factors. First of all, as mentioned earlier denosumab is a drug already used in millions of patients worldwide. The common adverse effects associated with denosumab are abdominal pain, constipation, musculoskeletal pain, skin rash, and mild infection. Rare adverse effects are symptomatic hypocalcemia, osteonecrosis of the jaw, atypical femoral fracture, and anaphylaxis [19]. The side effect profile is better than most competing drug treatments used to treat osteoporosis, and denosumab is well tolerated by patients with competing diseases such as kidney disease, in contrast to i.e. zoledronic acid. In the NAPO trial, we will register the adverse events (AE), serious adverse events (SAEs), serious adverse reactions (SARs), and suspected unexpected serious adverse reactions (SUSARs) in the intervention period and will be reported to the relevant authorities according to guidelines from GCP and the Danish Medicines Agency. NAPO will be the fourth clinical trial we are conducting with denosumab 60 mg s.c. injection, and we have yet to see serious reactions caused by the drug. Furthermore, to avoid symptomatic hypocalcemia participants with vitamin D deficiency and/or hypocalcemia are excluded and concomitant supplementation with 10 μg vitamin D and 400 mg calcium is given to all participants for 180 days. Furthermore, to ensure that the handling of safety is independent of the sponsor and investigators, a safety committee will be set up. The members of the safety committee will be four senior medical doctors who are leading experts in bone diseases and reproductive diseases in men. All serious incidents or adverse reactions will be referred to the safety committee within 72 hours and they will independently decide on the need for code breaches. All this, alongside our previously mentioned safety studies [15,16] minimizes our worries about the use of denosumab in a group of healthy young men.

3.7. Dissemination plans

The results of the trial will be submitted for publication in international peer-reviewed journals and submitted for presentation at international conferences. Authors SKY and MJJ will be shared first authors, MBJ will be the last author, and other researchers contributing will be listed as co-authors.

4. Discussion

Infertility affects millions of individuals globally, with male factor issues like impaired semen quality contributing significantly to nearly half of all cases [20,21]. Despite its widespread occurrence, there's a noticeable absence of medical treatments aimed at enhancing semen quality for most infertile men [22,23]. This gap underlines a pressing need for advancements in reproductive medicine. Only by exploring and finding new treatment options for male infertility, new opportunities to couples with fertility challenges worldwide can be offered. As it stands today, most treatments are solely targeted at the woman, as she must undergo hormonal treatment to optimize conditions for various types of ART. These treatments are often associated with many side effects including serious side effects and a high economic cost for the couple and/or the health care system. In brief, we are treating females for a male disease.

Addressing male infertility requires a shift in societal perceptions and healthcare practices to ensure that men feel comfortable seeking help and participating actively in the fertility treatment process. This may involve raising awareness about male infertility, reducing stigma, and providing support and counseling services for men and couples facing fertility challenges. Establishing effective treatment options for male infertility involves a multifaceted approach. It includes advancing research to better understand the underlying causes of male infertility, developing targeted therapies to address specific issues such as sperm production, and improving diagnostic techniques to accurately identify male infertility factors early in the treatment process. An important step in this direction is to establish a treatment option for male infertility. However, some limitations must also be mentioned. In studies with semen quality as a main outcome, there are challenges in relation to a high intra-individual variation in semen parameters. Furthermore, the study drug itself is used at a dose (60 mg) because it is already on the market. However, this is a dose for another indication (osteoporosis) which may not be the optimal dose for infertile men to improve semen quality. One of the challenges in the use of denosumab lies in its repetitive usage in patients with osteoporosis or to prevent skeletal-related events in patients with bone metastasis. If the treatment were to be expanded from a one-time injection to a repetitive injection, there would be other adverse effects to take into account, e.g., accelerated bone loss after treatment. In contrary, if you would stick to a one-dose treatment, the effect would not be sustained after six months, which leaves a narrow interval for treatment effect.

Nevertheless, the NAPO study becomes highly relevant and is the next logical RCT to evaluate the effectiveness of denosumab as a

treatment for male infertility, as it includes men with severely impaired semen quality, and is selected based on a potential biomarker, serum AMH. Its predecessor, the FITMI study, excluded participants with sperm concentration under 2 million/mL, and the results of this present study will provide evidence crucial for future treatment in a patient group where treatment options are minimal at best. The clinical implications of improving semen quality can be significant. While men with severely impaired semen quality may still require assisted reproductive technologies (ARTs) such as IVF, enhancing semen quality can increase the chances of success. Higher sperm concentration and improved sperm function can lead to better outcomes in ART procedures, potentially making treatments more effective and increasing the likelihood of conception. Moreover, the explorative outcome on CatSper and RANKL expression will reveal whether denosumab in addition to an effect on sperm concentration also may improve sperm function.

4.1. Trial status

Participants are currently being recruited. The recruitment period is estimated to run from April 2024 to December 2024, with follow-up until June 2025. Further information will be available at clinicaltrial.gov (NCT06300229).

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Availability of data and materials

Data sharing does not apply to this article, because no datasets were generated or analyzed during the present study.

Consent for publication

Not applicable.

Ethics approval and consent to participate

The study will be carried out to include the protection of human subjects according to the 2008 Declaration of Helsinki and following Good Clinical Practice Guidelines. After verbal and written information is given to potential participants, informed consent will be obtained. All risk or safety issues will be reported to the principal investigators, who will take any necessary further steps. The study has been approved by the National Ethics Committees of the capital region of Denmark and the Danish Medicines Agency (CTIS no: 2023-508325-27-00) which qualified for registration in the ClinicalTrials.gov database (NCT06300229).

CRediT authorship contribution statement

Sam Kafai Yahyavi: Writing – original draft, Visualization, Project administration, Methodology, Data curation, Conceptualization. **Mads Joon Jorsal:** Writing – original draft, Visualization, Project administration, Methodology, Data curation, Conceptualization. **Rune Holt:** Writing – review & editing. **Bugge Nøhr:** Writing – review & editing. **Martin Blomberg Jensen:** Writing – review & editing, Validation, Supervision, Resources, Project administration, Funding acquisition, Conceptualization.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

Martin Blomberg Jensen is also the CEO of 'XY Therapeutics' a spin out company from the Hospital that have two patents on the use of RANKL inhibitors to treat male infertility.

Data availability

No data was used for the research described in the article.

Acknowledgments

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.conctc.2024.101352.

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