Medicines & Healthcare products Regulatory Agency

MHRA

MHRA
10 South Colonnade
Canary Wharf
London
E14 4PU
United Kingdom

gov.uk/mhra

[redacted]
KING'S HEALTH PARTNERS
CLINICAL TRIALS OFFICE, 16TH FLOOR TOWER WING,
GUY'S HOSPITAL, GREAT MAZE POND
LONDON
SE1 9RT
UNITED KINGDOM

22/09/2025

Dear [redacted]

THE MEDICINES FOR HUMAN USE (CLINICAL TRIALS) REGULATIONS 2004 S.I. 2004/1031 (as amended)(the 'Regulations')

Our Reference:	CTA 14523/0296/001-0001
IRAS ID:	1011645
Product:	Decapeptyl, Decapeptyl, Prostap, Gonapeptyl, Zoladex
Protocol number:	3646-PATHWAYS

NOTICE OF GROUNDS FOR NON-ACCEPTANCE AND RIGHT TO AMEND REQUEST

I refer to your request for a clinical trial authorisation (CTA), with effective received date of 25/08/2025. The Licensing Authority, having reviewed your application in collaboration with the Research Ethics Committee, has carefully considered your request in accordance with regulations 18-20 of the Regulations, but has decided that it is not acceptable at this point on the following grounds:

Grounds for Non-Acceptance:
COMBINED REVIEW MEDICAL - GNA Remarks: **MHRA Clinical Grounds for Non-acceptance:

An amended protocol must be submitted to address the following points (a commitment to submit an amended protocol before dosing the first trial participant will not be acceptable). A tracked changes version as well as a clean version, ideally signed, are required:

1. The language used in inclusion criteria #2 and #6 are open to variable interpretation, could permit premature pharmacological intervention and may allow inconsistency across sites or among investigators. The criteria must be amended as follows:

Inclusion criteria #2 - The CYP wants puberty suppression for their gender incongruence and this care preference persists after "completing all" other care deemed appropriate from the CYPGS and other sources.

Inclusion criteria #6 - The clinician in the CYPGS leading on care for an individual patient believes that they have participated sufficiently for their holistic health and well-being, "completing all" other forms of "psychosocial/psychological interventions" for puberty suppression to be considered, in line with NMDT recommendations.

Additionally, the criteria used to define the term "participated sufficiently" must be clearly detailed in the protocol.

2. The inclusion criterion #5 is vague and open to subjective interpretation. Terms such as "possibility", "may benefit" and "might be achieved" do not provide sufficient clarity to ensure consistent eligibility determination. In accordance with ICH E11(R1), eligibility criteria must be specific enough to define the study population. The inclusion criterion must therefore be revised as follows:

- The clinician in the CYPGS leading on care for that CYP believes "the CYP, with persistent gender incongruence despite other appropriate care, is likely to" benefit from GnRHa for puberty suppression. This benefit "is expected to" be achieved in relation to quality-of-life parameters (e.g., confidence in peer and family relations, participation in school and/or leisure activities, improved sense of well-being), mental or physical health.

3. The following clinical inclusion criteria must be added in line with GCP requirements:

- Willingness of the CYP and parent(s)/guardian(s) to be randomized into either study arm, documented by signed informed consent (parent/guardian) and assent (CYP).

4. The following clinical exclusion criteria must be added:

- Hypersensitivity to GnRH (gonadotropin releasing hormone), its analogues or to any of the excipients

- QTc interval > 450 milliseconds at screening.

- Known QT prolongation or family history of long QT syndrome.

5. The protocol currently states that longer term follow-up - "in the first instance will be for the life of the funding (total period 5.5 Years)."

While it is acknowledged that funding constraints may not be fully within the sponsor's control, this follow-up duration is inadequate to assess the long-term benefits and risks of the IMPs in the study participants. Identified risks include but not limited to, effect on fertility preservation, bone mineral accrual, fracture risk, cognitive development and sexual function which requires monitoring. Many of these outcomes will only become measurable in adulthood. Therefore, a follow-up for a period of up to 20 years or until the participant reaches the end of physical maturation (whichever is shorter) is deemed necessary.

The sponsor is required to address the following:

5.1. The protocol must be amended to include the necessary long-term safety monitoring either by extending the formal follow-up period in this study, or through a separate safety long-term extension study. Alternatively,

the sponsor must provide a scientific rationale, supported by clinical data, to justify the lack of long-term safety monitoring.

5.2. References to study funding should be confined to section 15.5 (Funding) and removed from the sections on trial design, objectives, safety monitoring, and the schedule of events. Funding is an operational element of the study, and it should not be part of the scientific and methodological aspects of the protocol.

5.3. Section 3.5 (Informed Consent) of the protocol must clarify that participants will be informed of all the potential long-term risks of the IMPs and the requirement for long-term safety monitoring.

6. There is currently no clear rationale for the proposed dosing strategy in the protocol. The sponsor should provide justification for the selected doses of the IMP (and any alternate IMPs), the planned treatment duration, and the timing of treatment exposure. This justification should specifically address the safety of the proposed regimen and explain why the selected doses and schedules are considered appropriate for the study population.

7. QT prolongation is a recognised risk with GnRHa. However, there is no provision in the schedule of assessments for systematic cardiac monitoring. Specifically, the protocol does not mandate the collection of 12-lead ECGs at any timepoint.

The protocol schedule of events must be amended to include 12 lead ECG at screening, baseline and every 6 months including the final visit at Month 24 for immediate GnRHa treatment arm and screening, baseline, every 6 months starting from month 12 including the final visit at Month 24 for the participants in delayed GnRHa treatment arm.

8. The protocol currently defines the screening period as "Day –XX to Day 0" but does not specify a maximum permitted duration. As a result, there is potential for variability and extended delays between consent and randomisation. This could lead to situations where participants enrolled at the upper end of the eligible age range (e.g. 15 years and 10 months) are exposed to unnecessary delays in treatment initiation and may reach adulthood during the trial without clarity on re-consent requirements.

The protocol must be amended to specify a defined maximum screening window (e.g. $\leq$8 weeks), within which all eligibility procedures and baseline assessments are to be completed.

9. The current protocol specifies assessment of quality of life (QoL) using the KIDSCREEN-10 questionnaire at baseline, Month 12, and Month 24 only. This frequency is inadequate. For all participants in PATHWAYS TRIAL (both arms) the schedule of events (table 5 & 6) must be amended so that the KIDSCREEN-10 is administered at least every 6 months (i.e. baseline, Months 6, 12, 18, and 24).

10. The protocol currently specifies safety assessments based on a 6-monthly triptorelin regimen. However, alternate IMPs with 3-monthly or monthly dosing schedules may be used. In this scenario, the protocol does not ensure alignment of safety surveillance with each IMP administration.

The protocol must be amended to state that, if alternate IMPs with 3-monthly or monthly administration are used, a brief safety review will be conducted at each study medication administration visit. This review must include at a minimum:

• Vital signs

• Adverse event reporting

• Concomitant medication review

• Assessment of anxiety and depression symptoms (RCADS-25)

• Assessment of suicidality and self-harm risk (ASQ)

• Pregnancy test (POCBP only)

The sponsor is strongly advised to consider providing specific schedule of events for each alternate IMP.

11. The protocol must be amended to clearly specify prohibited concomitant medications for the entire duration of participant involvement in the trial.

• Medicinal products known to prolong the QT interval or associated with Torsade de pointes, including but not limited to class IA antiarrhythmics (e.g. quinidine, disopyramide), class III antiarrhythmics (e.g. amiodarone, sotalol, dofetilide, ibutilide), methadone, moxifloxacin, and antipsychotic agents.

• Prolonged use of medicinal products associated with clinically relevant bone mineral density loss, such as systemic glucocorticoids (for >14 days) and traditional anticonvulsants (e.g. phenytoin, phenobarbital, carbamazepine, valproic acid).

• Use of puberty blockers outside this clinical trial.

• Any other investigational medicinal products (IMPs).

In addition, the sponsor must provide clear guidance to the investigators on how to manage concomitant use of antidepressants (SSRIs, TCAs) if clinically indicated, as there is risk of QT prolongation.

12. The proposed discontinuation criteria are not acceptable in their current form. While the listed risks are clinically relevant, the current reliance on a general reference to "values >2.5 SD outside the mean" is insufficiently precise and open to inconsistent interpretation.

Thus, the discontinuation criteria must be revised to add the following:

• Occurrence of any condition that, in the opinion of the Investigator, significantly jeopardizes the wellbeing and safety of the patient, including serious or intolerable AE that prevents the subject from continuing with study participation

• Change in compliance with any inclusion or exclusion criterion that is clinically relevant and affects subject safety, as determined by the Investigator.

• Use of prohibited concomitant medications

• QTc > 450ms

• Pregnancy

13. In addition to participant-level discontinuation criteria, the following trial-level stopping rules must be applied to ensure adequate protection of this vulnerable paediatric population:

• The occurrence of any serious adverse reaction (at least possibly related to IMP administration) in one subject.

• The occurrence of two severe adverse reactions (at least possibly related to IMP administration), independent of whether they occur within the same or different system of organ classes.

Also, the sponsor is required to include in the protocol that if the trial is halted due to safety concerns, or if the study stopping rules are triggered, the trial can only be re-started after regulatory authority approval via a substantial amendment.

14. The protocol does not provide an adequate plan for follow-up of participants who discontinue study treatment prematurely (for example, if they fulfil any of the discontinuation criteria per protocol). Simply encouraging participants to remain in the trial is not sufficient, particularly in cases where discontinuation is Investigator-initiated for safety reasons.

The protocol must be amended to state that all discontinued participants remain in follow-up according to their randomised arm's schedule of events till the end of the study unless they explicitly withdraw consent.

15. The protocol section 9 must be amended as follows:

- All Adverse Events and Serious Adverse events will be recorded from "the signing of the informed consent form" until 12 weeks following the final dose.

16. The schedule of events and section 4.14.2 states that tanner staging is optional for some of the study visits. This is not acceptable. The tanner staging assessment must be mandatory for participants in both treatment arms, performed by a qualified, adequately experienced physician at visits specified in the schedule of events. The protocol must be amended to make this clear.

17. The current protocol (Section 4.15.1.1, follow up visits) specifies that only FSH, LH, Oestradiol, Testosterone, and Liver Profile are required at each visit, with Full Blood Count, Prolactin, Renal, Lipid, and Bone Profiles performed only if clinically indicated at investigator discretion. This approach is inadequate for ensuring consistent and systematic safety monitoring across all participants.

The protocol must be amended to add the following mandatory laboratory tests at all follow-ups visits:

• Full Blood Count

• Prolactin

• Renal Profile

• Lipid Profile

• Bone Profile

• Magnesium

18. There is a possibility that the participants randomised to delayed arm may access puberty blocker therapy outside this clinical trial. The protocol must include details on how such use will be monitored along with clear guidance for the investigators on how to manage such cases.

19. Idiopathic intracranial hypertension (pseudotumor cerebri) has been reported in paediatric patients receiving the IMP. The protocol must be amended to state that participants should be warned for signs and symptoms of idiopathic intracranial hypertension, including severe or recurrent headache, vision disturbances and tinnitus.

*Remark:

A. The sponsor is reminded that any changes to a document other than those requested in this letter to address the grounds of non-acceptance (GNAs) are not permitted and may be a cause of rejection. Any other additional changes should be addressed via an appropriate amendment following MHRA authorisation, if granted.

B. The following statistical remarks are for information only. No response is required.

i. The sponsor is advised that in study design use of too many stratification factors may be less successful at achieving balance.

ii. The sponsor is advised to consider the burden to participants when assessing a large number of outcomes, balancing the need for information versus completeness of data. Considerations should be given to ranking the various outcomes in terms of their importance to patients as well as to support regulatory decision making.

iii. Regarding analysis method, the sponsor is advised that use of a treatment policy strategy for handling death is not acceptable since data after death do not exist.

iv. The sponsor is reminded that intervals following Bayesian principles have a fundamentally different interpretation compared to the intervals described which follow a frequentist statistical approach. Results bases on frequentist approach will be required for regulatory decision making. Furthermore, Bayesian methods should be "calibrated" to have good frequentist properties in particular with regards to type I error control. Therefore, it is important to assess the operating characteristics of the Bayesian design (e.g. power and type I error rate)

If you require any clarification on these comments, please contact Clinical Trial Helpline on ctdhelpline@mhra.gov.uk

** REC Queries:

1. Please provide additional information around the current and previous standard of care treatments for this group of patients as well as what potential future standard of care may look like if the results of this application reveal that puberty blockers are not beneficial.

2. Provide additional information around the potential treatment options that will be made available to participants at the end of the study. This should include who will decide whether puberty blockers will continue

to be available and how continued access will be possible given the current restrictions around access. The potential options should also be clear in the information sheets.

3. Provide additional information around the long term follow up plan and how likely it will be to secure funding to support this as the Committee feel that this is a vital aspect of the study.

4. Please make the following changes to the protocol:

a. Create a clear process relating to serious adverse events including how and when they should be referred to the DMEC and regulatory authorities as per the HRA website Safety and progress reports (CTIMPs) procedural table - Health Research Authority.

b. State that part of the urine sample test is to monitor a participant's glucose level as diabetes is a potential side effect of the medication.

TOXICOLOGY - GNA Remarks: Non-clinical Grounds for Non-Acceptance

1. For Zoladex, no information on genotoxicity is provided in the SmPC. The Sponsor must discuss the potential for genotoxicity in the intended patient population. Supportive information may be available from safety data sheets or the US label/prescribing information.

2. For Zoladex, the SmPC states 'Zoladex LA is not indicated for use in children, as safety and efficacy have not been established in this patient group'. To include this medicinal product as an alternative regimen, the Sponsor must provide a scientific justification to support the administration of Zoladex in the proposed patient population which includes children. This justification must include a discussion of safety and efficacy, using all available non-clinical and clinical data, relevant to the proposed patient population. In addition, no information on posology for children is included in the SmPC for Zoladex. Therefore, the Sponsor must provide a scientific justification to support the proposed clinical dose of Zoladex in children. Alternatively, in the absence of supportive information, this treatment option must be removed from use in the trial.

3. An amended protocol (complete, signed document) must be submitted to address the following (a commitment to submit an amended protocol before dosing the first trial participant will not be acceptable):

The SmPCs for the investigational medicinal products state that non-hormonal methods of contraception should be employed during treatment until menses return. The list of effective methods of contraception for use in the trial must be updated to remove all hormonal methods of contraception. The duration of contraception, which is currently stated as 'at least three months after stopping GnRHa' must be updated, according to the requirements of the SmPCs, i.e. until menses return.

The Sponsor is reminded that any changes to the protocol other than those requested by the MHRA to address the grounds of non-acceptance (GNAs) are not permitted. Any other additional changes, however minor, should be submitted with a separate substantial amendment at a later date.

If you have a query on these comments, please contact the Clinical Trial Helpline at ctdhelpline@mhra.gov.uk

PART 2 - GNA Remarks: REC Queries

1. Provide additional information around the specialist team that will be discussing potential fertility options with potential participants and what experience they have of such a sensitive area with a vulnerable population. Also state what potential options, such as sperm donation and egg retrieval, will be given and how long they will be given to decide whether to take any of these options. This information should also be clear in the information sheets.

2. The Committee feel that providing vouchers to participants might be considered a financial inducement to participate. Please remove this aspect in the protocol and information sheets.

3. State how it will be ensured that participants completing questionnaires in conjunction with a translator will be appropriately supported due to the sensitive nature of the questionnaires.

4. Provide a rationale for the proposed blinding status of researchers as per section 6.3 of the protocol, including why the trial statistician will be initially blinded to complete the Statistical Analysis Plan and then unblinded to complete DMC reports.

5. The Committee was not assured that the current contraceptives proposal is suitable, but recognised that this would form part of the MHRA's review. Any request for action and/or information in this area which comes from the MHRA should be reflected in the protocol and all information sheets.

6. Make expenses available not only to patient participants but also parents/guardians. Update the protocol and information sheets to reflect this.

7. Please make the following changes to all information sheets:

a. Use only PATHWAYS and not its full definition so as not to imply that this study relates to transitioning.

b. Create a specific section titled 'Risks or possible risks of taking part in the study' and detail all potential risks as well as any mitigations taken by the research team and how a participant should react if they experience any side effects. This includes clearly relaying the potential impacts of the study drug on cognitive abilities, bone density and fertility.

c. Include the potential risks of MRI scans, including claustrophobia, and what steps the research team take to mitigate these.

d. Ensure that the frequency of injections given from the outset of treatment is clear.

e. State how a participant would go about withdrawing from the study if they chose to do so.

f. Some information sheets states that if scans reveal abnormalities then parents will be informed. This should be stated in all information sheets.

g. Explicitly state what will happen at the end of the study and the potential likelihoods. If it is not possible to know what will happen, this should be stated clearly.

h. Rephrase reference to the data monitoring and ethics committee to make it clear that this is not affiliated with the Research Ethics Committee that reviewed the study.

i. Any potential impacts on school attendance by participating in the study should be made clear.

j. The information sheets are inconsistent in terms of doctor, clinician and researcher. For instance, one flowchart refers to questionnaires being delivered by a doctor whereas another states it will be delivered by a researcher. Please review and ensure consistency.

8. Please make the following changes to the under 16 assent form:

a. Include a clause relating stating outright that they understand the potential impacts of puberty blockers, i.e. potential reduction in bone density, potential fertility impacts and potential cognitive impacts.

b. Add a short explanation of the phrase 'chaperone'.

9. Please make the following change to the APCTSS Parent document:

a. Replace 'mad' with 'angry' in question 4.

10. Please make the following changes to the BISGS Body image screen:

a. The directions state that answers should be 'checked'. Replace with 'ticked'.

b. Question 33 refers to stature. Please add a short explanation of this phrase in brackets.

11. Please make the following changes to the SCOFF for parents:

a. Add a metric equivalent to stones and pounds.

b. Change " 'you' are too thin " to " 'you are too thin' ".

12. Please make the following change to the Scoff for young people:

a. Add a metric equivalent to stones and pounds.

Note only

1. Please note that any additional recruitment materials, including documents designed to support participant understanding of the recruitment process, need to be submitted for review by the Committee either as part of a response or via an amendment.

Assessment Queries

1. Please adopt the HRA's recommended transparency wording in all information sheets verbatim with no additional wording. The wording can be found at: GDPR transparency wording for all sponsors - Health Research Authority

2. Please remove reference to REC having access to participant data from all information sheets as this is not correct.

3. Please review section 1.2.1 figure 1 in the protocol as it currently refers to 2000-2017 however the actual figure shows 2009-2021.

4. Please provide a copy of the insurance policy and confirm that there no exclusions related to minors

5. The IRAS form states 'Only after a CYP has been confirmed as clinically eligible for GnRHa will they be referred to the PATHWAYS research team. At this point, the research team will be provided with limited identifiable information (e.g. name, date of birth, contact details) solely for the purpose of discussing potential participation in the study' Please confirm that the identifiable data will only be passed to the research team with the consent of the individual.

You may respond to the grounds identified in this letter within the timescales set out in regulations 18-20 of The Medicines for Human Use (Clinical Trials) Regulations 2004, as amended. This amended request should cover all the issues raised in this letter, and only these issues.

Medicines & Healthcare products
Regulatory Agency

MHRA

Yours sincerely,

Clinical Trials Unit
MHRA