Dear [redacted] and Team,

CONFIDENTIAL

Subject: Invitation to discuss proposed amendments to Clinical Trial Protocol

1. I write further to the MHRA's letter of 7th November 2025. As you are aware, there is a great deal of public and professional interest in this trial. MHRA keeps under review all of the representations that have been made. I write now to discuss potential amendments that we believe will strengthen the trial protocol.

Implementation of a minimum age restriction

2. We would like to discuss the inclusion of a minimum age for participation in the trial, given the known effects of this agent and the fact that the duration-exposure element of these drugs is significant (adding to the unknown effect of duration-exposure on various stages of Tanner development). Since potentially significant and, as yet, unquantified risk of long-term biological harms is present to participants and biological safety has not been definitively demonstrated in this proposed cohort, at the very least, there should be a graded/stepwise approach starting with those aged 14 as the lower limit of eligibility. Future trials may consider lowering the threshold depending on the findings of the initial trial. From the description of the trial involvement, that for those participants who complete the trial after 2 years but are below the age of 16, it is likely that further GnRHa treatment could be needed for many years (particularly if participants are significantly below the age of 16 at trial completion) as a bridging measure as cross-sex hormones are only prescribable from the age of 16.

3. There is a risk that broad Tanner stage inclusion introduces heterogeneity that the study is not powered to address.

4. Another factor is that the expected effects of the drugs include the sterilising effect of puberty blockers followed by cross sex hormones and that gamete retrieval to preserve fertility is not possible at the stage when puberty blockers are given (Tanner stage 2) as neither sperm nor ova have matured. The technology does not currently exist to remove ova and mature them in vitro and there are potential impacts on participants' human rights.

5. Furthermore, one of the proposed secondary endpoints is to assess patient choice post 2 years of GnRHa between no further treatment, further GNRHa or cross-sex hormone therapy. This would be moot for the very young as cross-sex hormones are not prescribable anyway until 16. The CHM report to

the Secretary of State on the proposed permanent order to restrict the sale and supply of GNRHa in CYP<18 years (dated 13 November 2024) Recommendation 7 states : "*A clear exit strategy needs to be put into place for continuation of GnRH agonists when exiting the trial if this is the pathway agreed with the patient and/or parents or carers. This should be accompanied by data collection on the efficacy and safety of the GnRH agonists*." For children recruited to the Trial below 14 years of age there will be potentially many years of therapy to bridge to the point of age 16. Therefore, a minimum age of 14 might be a way to avoid a long bridge and will allow any participant in the trial to have all options available to them after the 2 years trial. Ensuring the full suite of options are available will also allow the trial to assess fully the extent to which participants choose different options and how they are impacted by them.

Suggested Amendment to the Trial Protocol

Inclusion criteria 4

4. 14 years or older at the time of consent.

Safety monitoring and withdrawal criteria

6. The MHRA recognises that this CTIMP is already being used in precocious puberty. However, unlike patients with precocious puberty, the proposed cohort in this trial have normal biological hormonal and sexual development but a psychological condition of gender dysphoria. This of itself would not preclude an off-label use within the confines of a trial. However, the MHRA would like to explore the inclusion of much more detailed physiological safety assessment for this biologically healthy cohort. The statistically powered primary endpoint being presented is the KIDSCREEN10 QOL questionnaire. However, in this situation, the physiological and adverse pharmacological impacts may long outlast and outweigh any QoL detected differences:

   (a) Bone effects- It is recognised that short-term bone effects of triptorelin may sometimes be reversible. However, available data suggests treatment with triptorelin beyond 12 months will result in persistent and potentially permanent bone structural change. The involvement of the patients for 24 months means that patients may demonstrate irreversible harm at the 12-month scan. It would be helpful if you could clarify whether participants with **any** reduction in bone density after 12 months (a clear deviation from normal physiology) be removed from the trial and provided with bone protection therapy to prevent further harm? We would also like to discuss potential clarification to the withdrawal

criteria at 12 months if this point is not already clear. See MHRA recommendation below.

(b) Vaginal bleeding- There is a risk of flare-up effects in very young children who may not be able to report these developments; this is another reason why we suggest a minimum age limit should be introduced. In any event, for all participants we would like to discuss the provision of haematological monitoring, particularly if it persists beyond 2 weeks, as is sometimes seen when this agent is used in endometriosis treatment. Regular haematological monitoring in cases of bleeding beyond 2 weeks is suggested.

(c) Potential loss of fertility- It is widely understood that reduction in gametogenesis will very likely cause infertility in these young people. These are medically consequential effects for a future adult individual that may involve infertility treatment and significant medical interventions. In light of the long term fertility consequences, Gillick Competence for consent as per RCPCH and the Academy of Medical Sciences Guidelines (academy_of_medical_royal_colleges_statement_on_gillick_competency_final_003.pdf) guidance on consent in children under 16 years of age should be sought. We suggest that this should be assessed and documented before consent is obtained using tools such as Gillick Competency checklist (Microsoft Word - Gillick Competence 2016 update.doc). Given the suggested changes, we would expect that an amendment would be submitted to HRA and the REC would want to look again at whether their decision that the consent process is acceptable still stands.

(d) Cognitive effects- We recommend that advice from independent clinical experts in neurocognition and brain imaging should be sought to advise what degree of adverse BOLD fMRI signal change between scans would necessitate withdrawal from the study. We would like to discuss this as a key safety assessment measure at 12 months.

Recommended Amendments to Individual Participant Withdrawal Criteria

7. We would like to discuss the following potential amendments to the withdrawal criteria:

- The IMP to be discontinued in any participant who meets one or more of the following criteria at 12-month DEXA scan:

- Progressive clinically significant BMD decline or confirmed osteopenia on DEXA.
- Significant reduction in height velocity or emerging growth failure.
- Any vertebral fracture (low-trauma or asymptomatic).
- Any low-trauma long bone fracture suggesting systemic bone fragility.

- Persistent Vaginal bleeding beyond 2 weeks could be considered as discontinuation criteria and to additionally require close follow-up with Haematological monitoring (FBC).

- Cognitive effects – Withdrawal criteria if adverse functional MRI changes detected at any time point could be added. Advice to be sought by research team from experts in neuroimaging to clarify degree of adverse signal that would necessitate participant withdrawal at any scan but crucially at the 12 month point if an adverse signal of change from baseline is detected in order to prevent further harm to participants.

We suggest that a meeting should be set to discuss the above matters, to include the Sponsor team, the MHRA and the HRA.

As you will know, there is also potential legal action in relation to this trial which we are in the process of considering to determine whether, in our view, there are any further matters which impinge upon safety or efficacy that should also be considered alongside the issues set out above. If so, we will write to you as soon as possible.

Please let us know your availability for a meeting next week.

Yours sincerely

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