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COMMISSION ON HUMAN MEDICINES

Minutes of the Extraordinary Meeting held on Thursday 18th September 2025 at 9:30 via MS Teams Videoconference

Commissioners Participated

Professor Sir Munir Pirmohamed (Chair)
Professor J Coleman
Mrs J Cons
Mr D Crundwell
Professor S Cunningham (Vice-Chair)
Professor D Dockrell
Professor R FitzGerald
Professor D Hunt
Professor D Moore
Dr G Mortimore
Professor P M Patel
Professor R Providencia
Professor H Wallace
Professor C Weir

Apologised for absence

Professor A Adler
Professor P Dargan
Professor Y Perrie
Professor V Raymont
Professor C Stewart
Professor M Turner
Professor A Williams
Dr M Wilson

Invited Experts

[redacted]

Legal Government Team

[redacted][1]

[1] Available to join online if requested

MHRA Professional Staff Attendees

[redacted]

Secretariat

[redacted]

[redacted]

17th December 2025

[redacted]

1. Announcements and Apologies

1.1 The Chair reminded Commissioners, Invited Experts and Observer(s) that the papers and proceedings are confidential and should not be disclosed and reminded all those participating online to mute their microphones when they are not speaking.

1.2 The Chair reminded Commissioners, Invited Experts and Observer(s) to declare their personal non-specific, non-personal specific, non-personal non-specific and other relevant interests in the agenda items. Commissioners were also reminded to declare any other matters which could reasonably be perceived as affecting their impartiality.

Commissioners were reminded that they are not permitted to hold any personal interests in the pharmaceutical industry, in line with the Code of Practice.

1.3 Interests of the items declared by Commissioners, Invited Experts and Observer(s) are recorded at **Annex A** to the minutes.

1.4 Due to the business needs of other commitments, Professors Adler, Dargan, Perrie, Raymont, Stewart, Turner, Williams, and Dr Wilson apologised for their absence at the meeting today.

1.5 The Chair welcomed the following new Commissioner, whose terms of appointment started from 08/09/2025 for four years:

> **Professor Richard FitzGerald** MD MBChB PhD FRCP
> CRF Director - NIHR Royal Liverpool and Broadgreen Clinical Research Facility; Consultant Physician, Clinical Pharmacology & Therapeutics/ General Medicine; Honorary Senior Lecturer, University of Liverpool

1.6 The Chair welcomed the following invited experts, who joined the meeting for item 3.1 - PATHWAYS TRIAL:

[redacted]

2. Matters Arising

2.1 None

3. Clinical Trial Application

3.1 CTA 14523/0296/001-0001; IRAS 1011645 PATHWAYS TRIAL King's College London

3.1.1 The Commission agreed with the non-clinical Grounds for Non-Acceptance (GNAs) raised by the MHRA. The Commission suggested that publicly available genotoxicity information for Zoladex should be highlighted to Investigators, to address the lack of genotoxicity information provided in the SmPC. Considering that Zoladex is not indicated for use in children, the Commission questioned its use as an alternative treatment option. The Commission supported the need for further information to support the proposed use of Zoladex in the proposed patient population.

3.1.2 The Commission discussed in detail the main clinical aspects of the study design, risk-mitigation measures and the overall acceptability of the risk/benefit balance. The Commission endorsed the majority of the clinical GNAs raised by the MHRA, recommended modifications to some of the points, and proposed the addition of some new points. The following is a summary of the most relevant recommendations:

3.1.2.1 Agreement that Tanner stage 2 should remain the primary entry criterion regardless of chronological age. Minimum age restrictions risk biasing randomisation and reducing generalisability.

3.1.2.2 Recommended that the protocol should have clear inclusion criteria, for example suggested replacing “exhausting” with “completing” or “delivering” in the eligibility criteria.

3.1.2.3 As the subgroup under 13 years is expected to be small; the minimisation based on age was not considered necessary.

3.1.2.4 Physical examination needs to be conducted by medical professionals, though this adds cost and inconvenience. It should occur at equal frequency across treatment arms, with allowance for nurse-led or remote visits where examination is not required.

3.1.2.5 Regarding prohibited concomitant medications, caution on corticosteroid use was recommended. It was advised that intermittent or short-term corticosteroid use may be permitted, while continuous long-term use could be considered a reasonable exclusion. Clarification on anticonvulsant restrictions was also required.

3.1.2.6 Concern was raised over protocol statement that efficacy is not being assessed. It was recommended performing annual Tanner staging by trained clinicians to document pubertal progression in line with patient expectations.

3.1.2.7 Serum magnesium should be added to the biochemistry profile and measured at every visit due to QT prolongation risk. Full safety blood panel should be

performed at all visits and not only limited to hormone and liver function markers. The current discontinuation criteria were considered too lenient and should be tightened.

3.1.2.8 Concern was raised that participants may obtain puberty blockers outside the trial. It was suggested that direct questioning in the study questionnaires could be considered, with clinician Tanner staging serving as an additional indicator.

3.1.2.9 Calcium and vitamin D supplementation should be considered for bone health safety monitoring.

3.1.2.10 The Commission concurred that adequate long-term follow-up is necessary, as reflected in the CHM public report, which outlines recommendations for the proposed use of GnRH agonists in children and young people under 18 years of age. Members agreed that a 20-year follow-up is desirable but acknowledged that funding could be a limiting factor. The Commission recommended that the wording of the GNA addressing this point should emphasise the importance of appropriate long-term follow-up without hindering the feasibility of conducting the study.

3.1.2.11 The dose rationale GNA wording should avoid suggesting that a separate dose-finding study is mandated.

3.1.2.12 The risk of Idiopathic intracranial hypertension (pseudotumor cerebri) should be adequately monitored and this should be specified in the protocol.

3.1.2.13 No pharmaceutical GNAs were raised.

3.1.3 The Commission's detailed advice is at **Annex 1** to the minutes.

4. Any Other Business

None.

5. Date and Time of Next Meeting

5.1 The next scheduled meeting will take place on Thursday 25th September 2025 at 10:00 and Friday 26th September 2025 at 09:30.

The meeting today started at 09:37 and ended at 10:52.

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Declaration of Interest **Annex A**

Members, Co-opted Member(s) appointed as Member for the day, Invited Experts and Observers adhere to the Code of Practice. They should submit declarations of interest at each meeting. The following list of declarations have been submitted specifically for the meetings held on **18th September 2025**. These were handled in accordance with the Code of Practice. A full annual declaration of interests submitted by members (between January-December) can be found at Human Medicines Regulations 2012 Advisory Bodies Annual Report 2024 - GOV.UK. The annual report is published around July. The difference between the two declarations (annual / meeting specific declarations) are due to the time period of the publication of the annual report. Product names listed have been withheld in line with Section 43(2) of the Freedom of Information Act 2000.

Key: PS = Personal Specific, PNS = Personal Non-Specific, NPNS = Non-Personal Non-Specific, NPS = Non-Personal Specific, Other relevant interests

Commissioners	Interest Type and Company/ Organisation/Sponsor	Nature of Interest	Related Agenda Item (to be deleted before publishing)
Professor Sir Munir Pirmohamed (Chair)	NPNS - AstraZeneca (AZ)	AZ are part of the MRC Medicines Development Fellowship Scheme (with MRC) with funding going to Universities of Liverpool, Manchester, Glasgow and Queen Mary (London).	PATHWAYS TRIAL
	Decision: The declared interests did not debar Professor Sir Munir Pirmohamed from Chairing the proceedings, in line with the Code of Practice.		
Professor Amanda Adler	Apologised for absence at the meeting today.		
Professor Jamie Coleman	None		
Mrs Julia Cons	None		
Mr David Crundwell	None		
Professor Steve Cunningham	None		
Professor Paul Dargan	Apologised for absence at the meeting today.		
Professor David Dockrell	NPNS – AstraZeneca (AZ)	The Commissioner is an advisor on a research project and have reviewed and been included on a research publication-not yet published. Compounds involved in assays - Idelalisib, Anakinra and Tofacitinib. No financial benefit. Historical link but papers not yet published if company even decide to publish.	PATHWAYS TRIAL
	Decision: The declared interest did not debar Professor Dockrell from taking part in the discussion, in line with the Code of Practice.		

Professor Richard FitzGerald	None		
Professor David Hunt	Other Interest	The Commissioner leads NHS multiple sclerosis services within the Anne Rowling Regenerative Neurology Clinic, University of Edinburgh. The Anne Rowling Clinic is supported by a philanthropic gift from JK Rowling to the University of Edinburgh.	PATHWAYS TRIAL
	Decision: The declared interest did not debar Professor Hunt from taking part in the discussion, in line with the Code of Practice.		
Professor David Moore	None		
Dr Gerri Mortimore	None		
Professor Poulam Patel	None		
Professor Yvonne Perrie	Apologised for absence at the meeting today.		
Professor Rui Providencia	None		
Professor Vanessa Raymont	Apologised for absence at the meeting today.		
Professor Claire Stewart	Apologised for absence at the meeting today.		
Professor Marc Turner	Apologised for absence at the meeting today.		
Professor Heather Wallace	None		
Professor Christopher Weir	NPNS – King's College London	The Commissioner has collaborated on research with colleagues from King's College London, unrelated to the agenda of this CHM meeting. These are non-personal, non-specific interests and relate to research led by his institution or an institution other than King's College London, which he has co-authored with a member of staff at King's College on a multi-author publication arising from the research.	PATHWAYS TRIAL
	Decision: The declared interest did not debar Professor Weir from taking part in the discussion, in line with the Code of Practice.		
Professor Anthony Williams	Apologised for absence at the meeting today.		
Dr Martin Wilson	Apologised for absence at the meeting today.		

Invited Expert (s)	Interest Type and Company/ Organisation/Sponsor	Nature of Interest	Related Agenda Item
[redacted]	NPNS – AstraZeneca	Research Grant Funding as part of an IMI consortium (TransQST) from 2017-2022, not for a specific product. The grant funding was to [redacted] University Department. Continuing collaboration with the AZ scientists to write a roadmap article on systems toxicology. PhD Studentship (2024-2028; not for a specific product). Co-Supervision with Uni Liverpool colleagues of a PhD to investigate cfDNA as a class of biomarker to inform on drug-induced liver injury; funding to [redacted] department	• PATHWAYS TRIAL
	Decision: The declared interest did not deba[redacted] from taking part in the discussion, in line with the Code of Practice.		
	None		

Back to top

ANNEX 1

COMMISSION ON HUMAN MEDICINES		FINAL ADVICE
DATE OF MEETING	:	18 September 2025
REFERENCE NUMBER(S)	:	1011645
COMPANY	:	King's College London
PRODUCT	:	Decapeptyl SR 22.5 mg (PR1), Decapeptyl SR 11.25 mg (PR2), PROSTAP ® 3 DCS 11.25 mg (PR3), Gonapeptyl Depot 3.75 mg (PR4) and Zoladex LA 10.8 mg (PR5)
ACTIVE CONSTITUENT	:	Triptorelin pamoate (PR1, PR2), leuprorelin acetate (PR3), triptorelin acetate (PR4) and goserelin acetate (PR5)
THERAPEUTIC CLASS	:	Gonadotropin-releasing hormone analogues (GnRHa)
KEY WORDS	:	Puberty Suppression, Gender incongruence

On the evidence before them, the CHM had reason to think that on grounds relating to safety they might be unable to advise the grant of a Clinical Trial Authorisation for this trial at present.

The CHM considered that the following additional information should be requested from the trial sponsor:

Pharmaceutical

Not applicable - no pharmaceutical questions raised.

Preclinical

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.

Clinical

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. ≤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.

*Clinical Remark:

The following statistical remarks are for information only. No response will be 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)

Back to top