Written evidence submitted by Cell and Gene Therapy Catapult (RES0033)

1 Introduction

This written submission, from Cell and Gene Therapy Catapult (CGT) as Sponsors of the INSPIRE trial, is in response to questions raised by the Chair of the Select Committee hearing on 21st Nov 2017.

The INSPIRE trial is a Phase I open-label study to assess the safety, tolerability and potential for efficacy of a novel tracheal replacement consisting of a tissue-engineered decellularised tracheal scaffold with seeded autologous Mesenchymal Stromal Cells (MSC) in subjects with severe tracheal stenosis or malacia. The product is made, under Good Manufacturing Practice (GMP), from a cadaveric trachea decellularised using proprietary technologies of UK SME Videregen Ltd (industrial lead for the INSPIRE and TETRA projects) and recellularised with the patient’s autologous MSC at the Centre for Cell Gene & Tissue Therapeutics (CCGTT) at the Royal Free Hospital, London. The Principal Investigator is Professor Martin Birchall and CGT are the sponsor. As sponsor, CGT are responsible for the initiation and management of the clinical trial, which includes ensuring the trial is authorised by the Medicines and Healthcare products Regulatory Agency (MHRA) (as competent authority), has received favourable ethics committee opinion, is run in accordance with Good Clinical Practice and Pharmacovigilance requirements and is manufactured and labelled to the appropriate standard.

No patients have been recruited or treated on the trial. In light of the emergence of new information from investigation of Prof Macchiarini’s clinical cases, discussions with the UCL group and the UCL Special Inquiry, CGT suspended the commencement of the recruitment of patients in order to allow a thorough risk assessment of relevant pre-clinical and clinical literature, including reviews of clinical case studies of tracheal grafts. This was discussed with the MHRA and a suspension of site initiation and patient recruitment was agreed with them on 2nd December 2016.

A risk assessment aiming to objectively and comprehensively further appraise the available pre-clinical and clinical literature to ascertain specific risks of the proposed study was completed after the conclusion of the UCL Special Inquiry. In order to provide as robust an assessment as possible, this risk assessment will also be shared with key opinion leaders (KOL) in the field, the Chair of the Data Safety Monitoring Board (DSMB, also a KOL in the field), and a multidisciplinary team (established to review subject suitability for trial entry to protect the ethical and safety interests of subjects). Following their input CGT will review the risks and make any changes required to the trial design and/or documentation. These documents will then be shared with the CGT Board for their review and input. They will also be submitted as a part of a Substantial Amendment to the MHRA and the Ethics Committee, with approval required before commencement of any clinical activities. If, following this review of all data (past and new), there are continuing concerns then the risk/benefit will be re-examined for the proposed clinical indication and patient group and further data gathered and/or a change of indication pursued if found necessary.

There is also a further tracheal project funded by EU H2020 grant to support a manufacturing development and a follow-on EU pivotal clinical trial in the same indication (TETRA). This trial will only commence if the INSPIRE clinical trial shows satisfactory evidence of safety and potential efficacy as reviewed by the European Medicines Agency (EMA).

3 Design of the INSPIRE Phase I clinical trial

A retrospective survey of three UK clinical centres was conducted in 2014-2015 to provide insights into the demographic and clinical features of patients with tracheal disorders who may be eligible for a tissue-engineered tracheal transplant and to inform the design of the Phase I clinical trial. The baseline data collated (41 patients) indicated that initial clinical trials should prioritise subjects presenting with the most severe clinical profile, including patients with tracheostomy dependence, repeat stenting or increasing number of hospital stays and interventions. Based on the patient survey a Phase I open-label study to assess the safety, tolerability and potential efficacy in patients with severe tracheal stenosis or malacia was devised.
4 Regulatory and ethics approvals and interactions

4.1 UK

The UK MHRA approved the use of the product in a first-in-human clinical trial (EudraCT 2015-002108-10) on 2nd October 2015. Ethics approval was confirmed on 7th January 2016. No patients have been enrolled in this trial and site initiation has not yet been performed.

Throughout 2016 there was considerable controversy relating to the prior case series of Professor Paolo Macchiarini who undertook a number of tracheal replacements with synthetic tracheal grafts. The technology of these synthetic tracheal grafts bears no relation to the decellularised cadaveric grafts seeded with autologous MSCs that are proposed to be implanted into patients within the INSPIRE trial. However, given the severity and poor outcomes of these cases that has now come to light and the amount of media coverage, the INSPIRE consortium decided to conduct an assessment of further risk mitigation which may be of value before commencing recruitment into the INSPIRE trial. We undertook this assessment to ensure due diligence and ensure complete satisfaction of the robustness and completeness of the supporting data prior to embarking on the recruitment of patients into a recognised high risk clinical trial. In view of the plans for risk re-assessment, CGT informed the MHRA on 2nd December 2016 that they would not proceed with site initiation and patient recruitment. A substantial amendment approval is required prior to restart of the trial.

4.2 EU

A positive opinion on EU orphan designation for the treatment of tracheal stenosis was given by the Committee for Orphan Medicinal Products (COMP) (application number EMA/OD/069/16) and then adopted by the European Commission on 29th October 2017 (application number EU/3/16/1717).

The product was classified as a Tissue Engineered ATMP according to Article 17 of Regulation (EC) 1394/2007 by EMA’s Committee for Advanced Therapies (CAT) on 9th November 2015 (Doc. Ref. EMA/CAT/650083/2015). However, the EMA have subsequently recommended a reclassification to a “combined ATMP” and this will be addressed in due course.

The INSPIRE and TETRA trials have been discussed with the regulators in the following meetings:

**MHRA Innovation Office 20th May 2014**

Advice was sought from the MHRA Innovation Office regarding the proposed quality and non-clinical packages and clinical trial design in preparation for the INSPIRE CTA application.

**EMA Committee for Orphan Medicinal Products (COMP) 12th July 2016**

An application was made in March 2016 to EMA COMP for orphan designation of the tissue engineered tracheal replacement. A meeting was held with COMP on 12th July 2016 to discuss the background data package supporting the clinical plausibility of the product. At the meeting COMP interrogated the background non-clinical data package and justification to support the clinical plausibility of the tracheal replacement product. During the meeting the historic clinical use of allografts, recent tissue engineered tracheal replacements and the clinical case series treated by Prof. Macchiarini (both synthetic and biologic grafts) were discussed. The COMP accepted the presented data package and explanations, leading to successful award of the orphan designation.

**EMA Innovation Task Force Meeting 20th January 2016**

Advice was sought from the EMA Innovation Task Force (ITF) on quality, non-clinical, clinical and broader product development topics. Advice on the non-clinical and clinical advice was largely deferred to a formal scientific advice procedure. The ITF outlined some of the key quality issues that should be discussed in scientific advice.
EMA Protocol Assistance Meeting with the Scientific Advice Working Party (SAWP) 11th January 2017

Formal scientific advice was received from the EMA SAWP on quality and non-clinical aspects of product development. Advice on quality and non-clinical aspects was received from the EMA. Of relevance to this Select Committee the CHMP stated that additional non-clinical studies are not required since they believed that further studies were likely to have similar outcomes and were supported by the clinical profile with case series of allografts with similar IMP (but not identical) known at the time.

In summary, quality and non-clinical development proposals to support a future Marketing Authorisation Application (MAA) to EMA was agreed, providing clinical trial data from INSPIRE and TETRA is supportive and additional recommendations have been implemented or if not, a justification provided.

A timeline of main regulatory interactions is provided in Figure 1 below.

![Figure 1: A timeline of regulatory milestones](image)

**Independent Ethics Advisor Review**

An independent ethics advisor was appointed by Videregen Ltd to review ethical considerations and safeguards in place for INSPIRE that will follow through into the TETRA project. The ethics advisor was selected based on wide-ranging expertise across European projects in the areas of research integrity, biomedical ethics and clinical trials. In summary, the conclusions were that:

A. The patient facing documents reviewed are consistent with good ethical practices: the information given is complete and authentic, the presentation is understandable for any person of medium literacy and the fact that the risk of serious adverse effects occurring cannot be excluded is clearly underlined,
B. Prior to the trial authorisation the ethical permits were obtained from the Local and National Authorities,
C. The process of a two-stage screening process and a MDT review and recommendation is exemplary of a highly ethical, robust and objective process in order to ensure patients are selected appropriately and particularly vulnerable patients’ medical and psychological needs are fully reviewed within the selection process,

Overall, it appeared that whole procedures of research, including the application of the trial in very vulnerable patients, complied with the European guidelines and that there was no objection, from the ethical point of view, to the procedure adopted.

5 Additional safety measures for the trial

The trial has a fully independent Data Safety Monitoring Board. Also, in view of the severe clinical condition and vulnerability of potential patients a robust screening process has been designed for the INSPIRE clinical trial to ensure the most comprehensive and objective review of patients with tracheal stenosis and malacia being considered for the study.

A discussion will be held between the Surgeon and the patient specifically focussed on the patient’s initial interest in participating in the clinical trial. If a patient is interested in being considered for the trial they will then be referred for a two-stage pre-screen review process. The first pre-screen will be a patient profile review by the Sponsor Medical Monitor in collaboration with the Principal Investigator (PI). The profile submitted will include, but not be limited to, the patient’s medical history, diagnosis and previous treatments, location and extent of lesions, projected treatment plans including anticipated clinical benefit from continued standard of care options, and anticipated study-specific surgical complexities and techniques.

Following successful completion of the joint review the patient can progress into the second stage of the pre-screen review process. Prior to the patient being formally consented to enter the trial, his/her medical condition will be discussed within an on-site Multi-Disciplinary Team (MDT) meeting which will include health care professionals independent of the trial. The remit of the MDT is to objectively assess the referred patient’s suitability for the trial according to the eligibility criteria and the likely vulnerability of the patient to adverse outcomes and their ability to safely consent for a high risk clinical trial. There may be a second meeting of the MDT, if the preliminary MDT meeting fails to reach a consensus on patient suitability but where strong arguments remain for trial entry posed by the PI in concert with significant expressed interest from the patient. The PI may invite the patient to attend this second MDT meeting if both the PI and patient consider this attendance will provide additional medical considerations and personal opinion that is highly relevant to the MDT’s overall consideration of the patient’s suitability for the trial.

Upon documented agreement within the MDT of suitability, each patient will be provided the currently approved information sheet to review and given the opportunity to pose any further questions to the PI. Before signing consent to enter the study, the subject must additionally discuss the study with an appropriately qualified and senior physician/surgeon who is not involved in the trial to ensure all questions and any concerns regarding the clinical trial have been sufficiently addressed. After this discussion with the independent physician or surgeon, and once the subject is satisfied that they fully understand the overall risk benefit profile of the study for their individual condition and situation, they may then sign the study consent form in the presence of the PI. A separate consent form must be additionally signed by the patient in the presence of the independent physician or surgeon.

After signing an informed consent form, each subject will undergo a period of screening lasting up to 8 weeks to determine full eligibility for surgical implantation of IMP.
6 Conclusion

The risk assessment has been shared with KOL in the field, DSMB and the multidisciplinary team. Following their input, CGT will review the risks and make any changes required to the trial design and/or documentation, which will only proceed on satisfactory resolution of any outstanding issues. These documents will be submitted as a substantial amendment to the MHRA and the Ethics Committee for their review and approval prior to restart of the trial. If, following this review of all data (past and new), there are continuing concerns then the risk/benefit will be re-examined for the proposed clinical indication and patient group and further data gathered and/or a change of indication pursued.

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