SUMMARY NOTIFICATION INFORMATION FORMAT (SNIF)

For the Deliberate Release of a Genetically Modified Organism (GMO)
(Directive 2001/18/EC)

A. General Information

1. **EU CT-number:** 2024-519320-24-00
2. **Date of Notification:** 10 March 2025
3. **Notifying Party:**
    - **Name:** Oslo University Hospital
    - **Address:** Sognsvannsveien 20, 0372 Oslo, Norway
    - **Contact Person:** Jochen Büchner
    - **Telephone:** +47 23074560
    - **Email:** jocbuc@ous-hf.no
4. **Project Title:** A Phase I/IIa study to assess the safety and biological activity of TdT-3, an autologous TCR T-cell therapy targeting TdT, in HLA-A*02:01+ patients aged ≥1 year with relapsed or refractory TdT^+ acute leukemia or lymphoblastic lymphoma.
5. **Type of Notification:** ☑ First-time release ☐ Renewal

B. Characteristics of the GMO

1. **Identity of the GMO:**
    - **Species name:** Homo sapiens (human) autologous T cells
    - **Common name:** TdT-3 (=T-cell receptor engineered T cells)
    - **Modified traits:** Expression of a Terminal deoxynucleotidyl transferase (TdT)-specific chimeric T-cell receptor (TCR)
2. **Genetic Modification Details:**
    - **Method used for transformation:** Retroviral vector transduction with a self-inactivating (SIN) vector
    - **Inserted genetic material:**
        - *Chimeric TCR specific for a terminal deoxynucleotidyl transferase (TdT)-derived peptide presented on HLA-A*02:01*

- *Murine constant alpha and beta domain of TCR*
- *Human variable alpha and beta domain of TCR (defines specificity of introduced TCR)*

3. **Intended Function of the Modification:**
    - **Purpose of genetic modification:**
        - TCR-T cells are engineered to recognize and destroy TdT-expressing B-/T-cell acute leukemia or lymphoblastic lymphoma cells.
    - **Expected benefits:**
        - Enhanced efficacy in treating relapsed or refractory TdT^+ acute leukemia or lymphoblastic lymphoma.
4. **Host Range:**
    - **Target organisms:** Human B and T cells expressing TdT.
    - **Potential for gene transfer to other organisms:**
        - The inserted genetic material is integrated into the T-cell genome and is not capable of further horizontal transfer to other human cells or environmental organisms.

C. Information on the Release

1. **Purpose of the Release:**
    - Clinical trial administration of TdT-3 (investigational medicinal product) to evaluate safety and efficacy in patients with relapsed or refractory TdT^+ acute leukemia or lymphoblastic lymphoma.
2. **Location of Release:**
    - **Country and region:** Norway
    - **Clinical trial sites:** University Hospital Oslo (Norway)
3. **Size and Scale of Release:**
    - **Number of patients to be treated:** 15
    - **Total number of modified cells per patient:**
        - Patients ≤50 kg body weight: 0.80×10^6 - 14.40×10^6 transduced $CD8^+$ T cells/kg body weight
        - Patients >50 kg body weight: 0.40×10^8 - 7.20×10^8 transduced $CD8^+$ T cells
    - **Expected duration:** 5 years study period

4. **Environmental Conditions at Release Site:**
    - **Clinical setting:** TCR-T cell infusion is performed in a controlled hospital environment with strict biosafety protocols (incl. use of protective equipment, such as gowns and gloves, and guidelines for cases of accidental spilling or accidental self-administration). TdT-3 administration in a closed system (via participant's IV catheter), the risk of spills or accidental self-administration is almost zero.
5. **Risk Management Strategies:**
    - **Containment measures:**
        - Cells are manufactured, cryopreserved and stored in certified Good Manufacturing Practice (GMP) laboratories.
        - Infusion occurs under strict medical supervision.
    - **Monitoring plan:**
        - Regular blood monitoring for persistence and clearance of TCR-T cells.
        - Assessment of potential adverse effects such as cytokine release syndrome (CRS).
    - **Emergency response plan:**
        - Availability of tocilizumab and corticosteroids for CRS management.
        - Immediate reporting and intervention in case of adverse events.

D. Interactions with the Environment

1. **Potential for Survival and Multiplication in the Environment:**
    - **Reproductive ability/ dispersal mechanisms:** TCR-T cells do not divide outside the human body. The cells cannot survive outside controlled conditions and degrade rapidly upon exposure to environmental factors.
2. **Potential Effects on Target and Non-Target Organisms:**
    - **Effects on biodiversity:** Minimal, as TCR T cells are patient-specific and do not persist outside the host.
    - **Impact on pollinators or other organisms:** None, as the release is confined to human administration in clinical settings.
3. **Potential for Gene Transfer:**
    - **Horizontal gene transfer:**

- Extremely low risk; gamma-retroviral vector is replication-deficient (SIN vector design; absence of replication-competent retrovirus demonstrated on virus batch and end-of-production cells) and does not produce infectious particles.

- **Stability of inserted genes:**
  - The TCR construct is stably integrated into the T-cell genome and is not transmitted to offspring.

E. Monitoring and Risk Assessment

1. **Monitoring Plan:**
   - **Clinical monitoring:** Regular blood tests to assess TCR-T cell persistence.
   - **Environmental monitoring:** No environmental release; thus, no external monitoring required.
2. **Risk Management Measures:**
   - **Containment strategies:** TdT-3 cells are administered under strict medical protocols and remain within the patient's body. Empty TdT-3 bags are disposed of in a biohazard waste-bin. Equipment being used in the administration of the TdT-3 will also be disposed of in biohazard waste, according to local guidelines.
   - **Mitigation plans:** If unexpected persistence or toxicity occurs, patients may receive immunosuppressive or lymphotoxic therapy to deplete TdT-3 cells.

F. Additional Information

1. **Previous Approvals:**
   - Similar therapies (TCR-T therapy: Tecelra: CAR-T therapies: e.g., Kymriah, Yescarta) have been approved by the European Medicines Agency (EMA) and U.S. Food and Drug Administration (FDA).
2. **Confidential Business Information (if applicable):**
   - Retroviral vector production details are considered confidential
3. **Public Consultation (if applicable):**
   - Not required for this clinical trial but stakeholder engagement has been conducted with patient advocacy groups.

Signature:

Jochen Büchner
10 March 2025
Oslo University Hospital