



Associazione Farmaceutici Industria
Società Scientifica

L'EVOLUZIONE DEL REGOLATORIO NELLE TERAPIE AVANZATE

WEBINAR

**MERCOLEDÌ 9 APRILE 2025
14:30 - 18:00**

Holoclar: Authorization Process and Key Challenges

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QC Manager, QP



HOLOSTEM



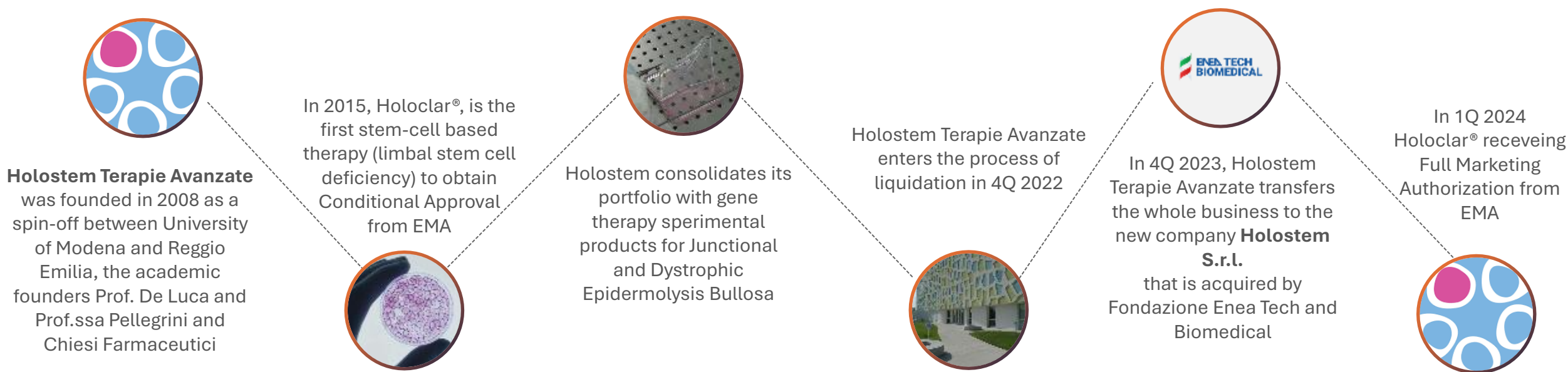
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MISSION AND HISTORY OF HOLOSTEM S.r.l.

Holostem is a biotechnology company entirely devoted to research, development, manufacture, registration and distribution of Advanced Therapies Medicinal Products (ATMPs) based on cultures of epithelial stem cells both for cell and gene therapy.

MISSION

DELIVER LIFE CHANGING ADVANCED THERAPIES FOR ALL IN NEED, TOGETHER!





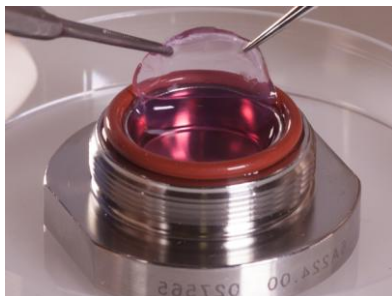
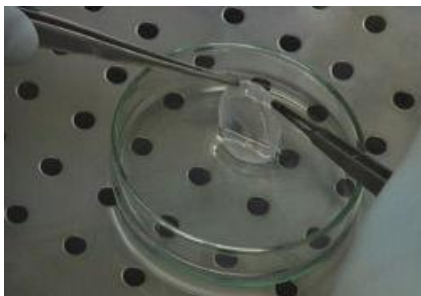
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HOLOCLAR®: the first stem cell based ATMP classified as tissue engineered product (TEP)

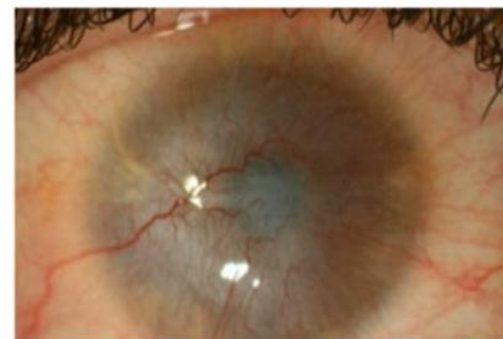
Holoclar is a Stem Cells (SCc)-based treatment used to replace damaged cells on the surface of the cornea

Holoclar consists of a transparent circular sheet of 300,000–1,200,000 viable autologous human corneal epithelial cells. This medicinal product is the result of an industrial process consisting of amplifying the SCs *ex vivo* from a biopsy sample of 1–2 mm² of healthy limbal tissue from the patient who will receive the cellular sheet

A cultured sheet of corneal epithelium (Holoclar®)



Before Holoclar



Pre-surgery:

- Chemical burn, 3 years from the accident
- No previous surgery
- Neovascularization in 4 quadrants with central corneal involvement

After Holoclar



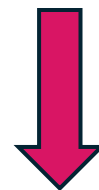
1 year post Holoclar implant:

- Avascular corneal surface with regular and stable epithelium
- Best corrected visual acuity: 0.9

Rama P, Matuska S, Paganoni G, et al. Limbal stem-cell therapy and long-term corneal regeneration. N Engl J Med. 2010;363(2):147-55.

HOLOCLAR® COMMERCIALIZZATION

MARKET ACCESS AND PRICE NEGOTIATION



Starting from 2015 Holoclar® has been distributed and reimbursed by national healthcare systems in 8 EU and UK countries



Holoclar Price Tag:
ITA € 95.000/eye
UK £ 80.000/eye



HOLOCLAR® REGULATORY JOURNEY: 2 STEPS

1. Holoclar registration – EMA Conditional Approval



2. Holoclar full marketing authorization

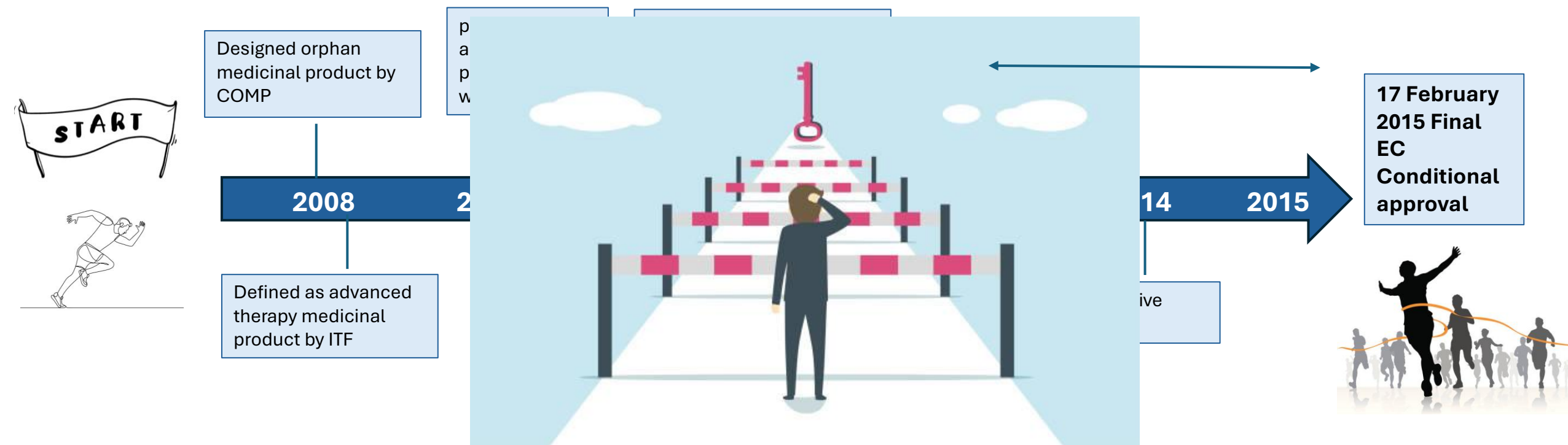




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STEP 1. The long and complex authorization process for Holoclar: conditional marketing approval in the EU in 2015

Protocol Assistance procedure and Submission included two retrospective clinical studies: HLSTM01 and HLSTM02



CAT, Committee for Advanced Therapies; **CHMP**, Committee for Medicinal Product for Human use; **COMP**, Committee for Orphan Medicinal Products; **EC**, European Commission; **EMA**, European Medicines Agency; **ITF**, Innovation Task Force; **NRG**, Name Review Group; **PDCO**, Paediatric Committee; **PEI**, Paul Erlich Institute; **PIP**, Pediatric Investigation Plan



STEP 1. HOLOCLAR® WAS APPROVED BY RETROSPECTIVE CLINICAL STUDIES

More than 200 patients has been treated (1998-2007)

STUDY HLSTM-01

About 100 patients

2 Hospital centers involved

Aim: to evaluate product Safety and Efficacy

STUDY HLSTM-02 (GCP STUDY)

About 30 patients

More than 10 Hospital centers involved

Aim: to evaluate product Safety

Regulatory Challenges: new European regulation (EC Regulation 1394/2007; Directive 2009/120/CE)



The **manufacturing of corneal tissue** and the related clinical study were done **before regulatory changes** categorized this stem cell therapy as an advanced therapy in the same group as chemical drugs



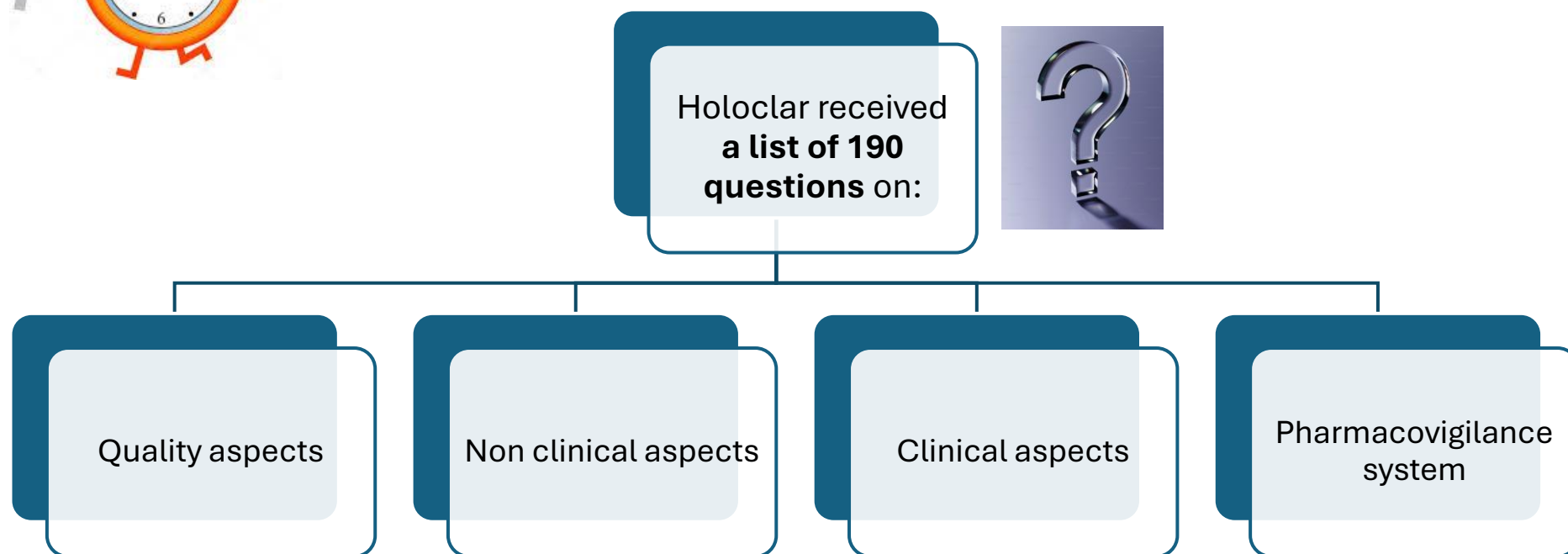
The **subsequent regulatory changes** had a significant impact not only on the definition and classification of stem cells as a therapeutic product but also on the **production and approval processes**

STEP 1. 2013: HOLOCLAR® DOSSIER SUBMISSION to EMA



Clock-stop: This first evaluation lasts up to 120 days

CHMP sent to Holostem “the Day 120 List of Questions”



Quality Challenges: How Holostem® Overcame Them



Requirement for GMP-Grade Raw Materials

- using GMP-grade raw materials in cell cultures, including stem cells, is essential for regulatory compliance and product quality.
- non-GMP components, such as animal- or human-derived serum, culture media, and growth factors, should be replaced with GMP alternatives where available.

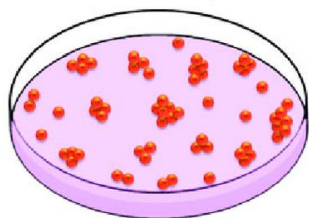
Mitigating risks through controls on raw materials, validation, and adherence to GMP standards is crucial.



Implementation of a rapid sterility test which is suitable to deliver results prior to administration of Holoclar.

- essential for ensuring patient safety, regulatory compliance, and product quality prior to administration of Holoclar
- cell-based products added complexity to sterility testing

The rapid sterility test was successfully implemented, providing results within three days.



Implementing a method to quantify 3T3 feeder contaminant cells is crucial due to concerns about the risks of contamination, immunogenicity, and the transmission of infectious agents.

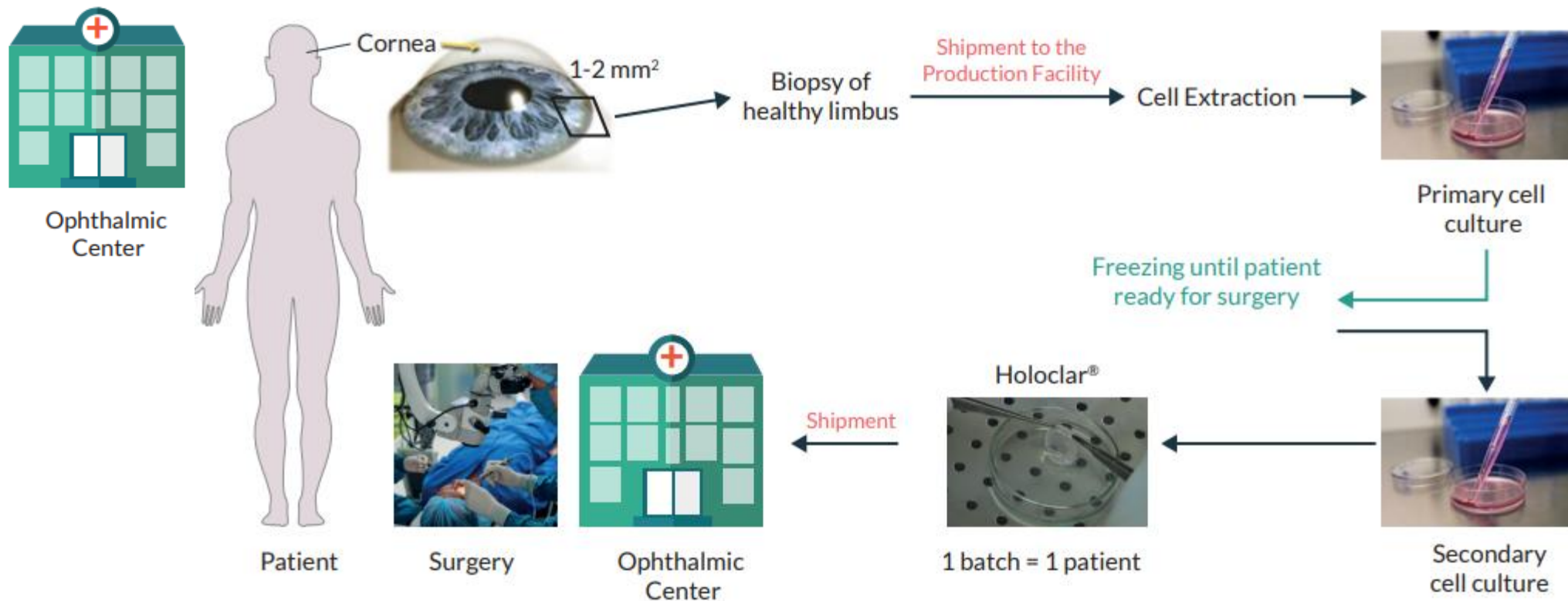
- the use of a feeder layer can complicate the consistency of the manufacturing process for products like Holoclar.
- detailed characterization of feeder cells, including their origin, growth conditions, and potential contaminants, is essential to evaluate the safety and efficacy of Holoclar

The method to quantify 3T3 feeder contaminant cells in both the drug substance (DS) and drug product (DP) has been successfully implemented.

Challenges in the Manufacture and Clinical Application of the Holoclar® Medicinal Product



The biopsy can be safely stored at -0.4-8°C for up to 29 hours



The graft can be stored at 15-25°C for 36 hours



Logistic Challenges of Holoclar®

The transportation and logistics of Holoclar require meticulous planning for several reasons:



Temperature Control:

Holoclar must be stored and transported at specific temperatures to maintain the viability of the limbal stem cells.



Regulatory Compliance:

Adhering to regulatory guidelines for the transport of biological materials is crucial to ensure safety and compliance.



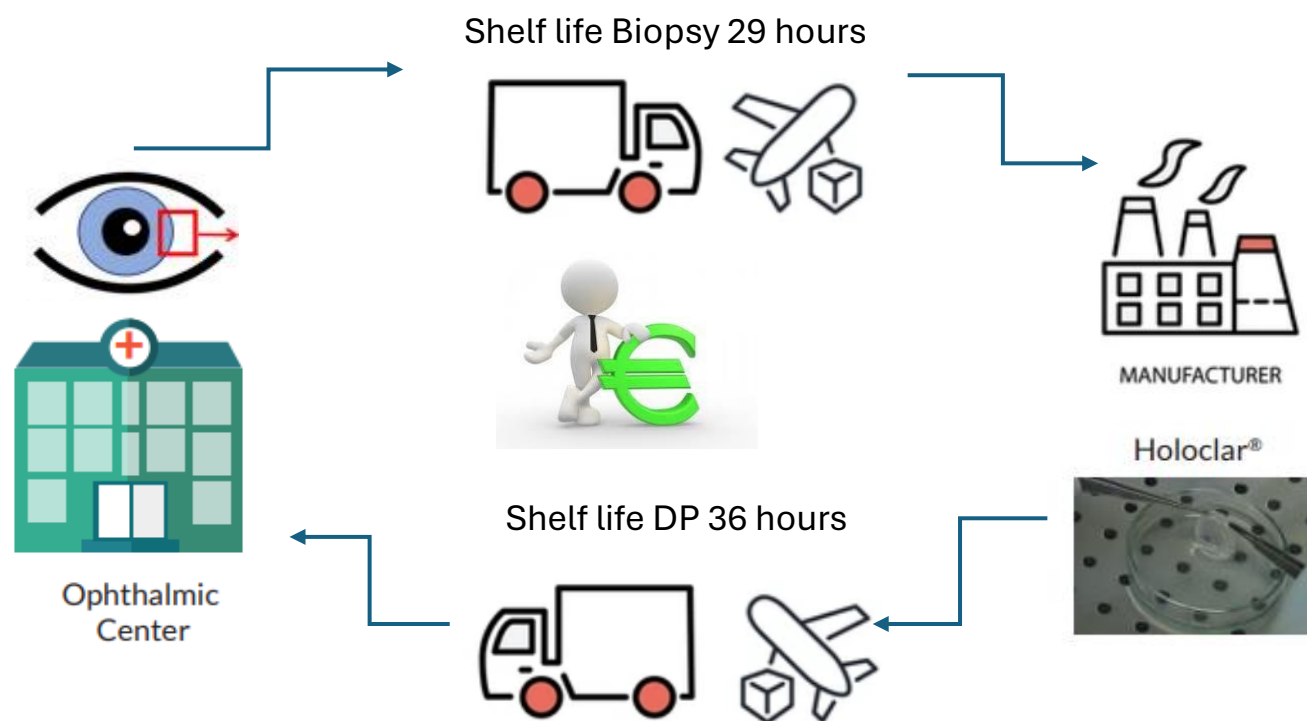
Communication: Clear communication between all parties involved- manufacturers, transporters, and healthcare providers



Time Sensitivity: The biopsy and the drug product have a limited shelf life, making timely transportation critical.



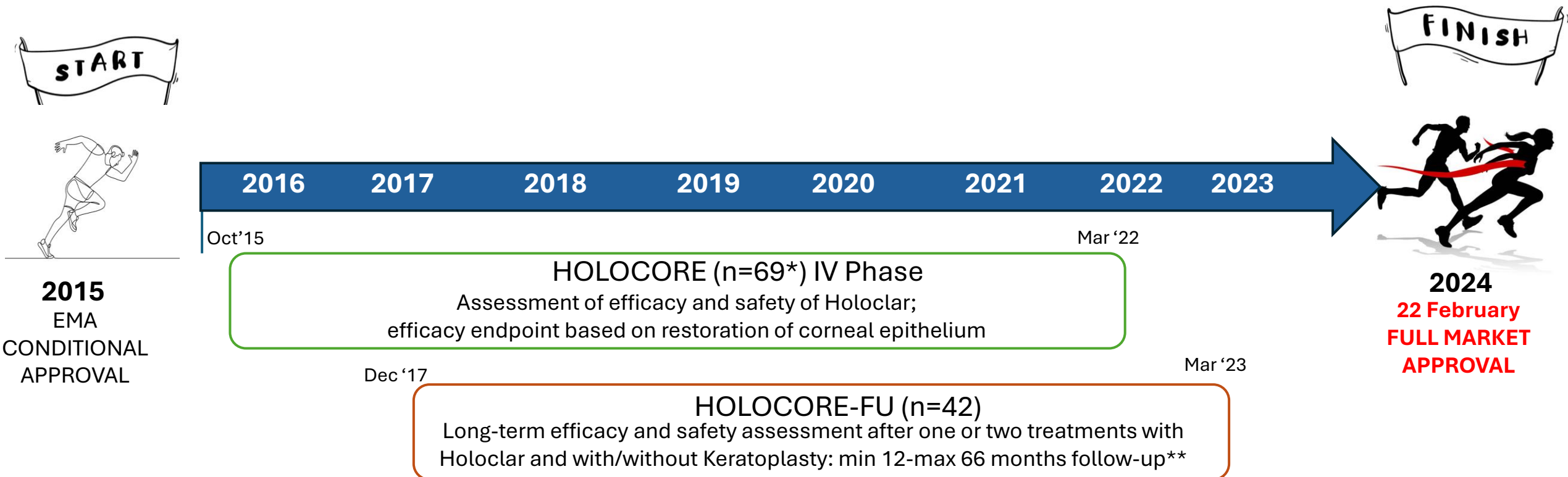
Qualification of Transporter: The transporter must be qualified based on their ability to comply with specific regulations.





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STEP 2. Holoclar®: The regulatory process for Full Market Approval in 2024

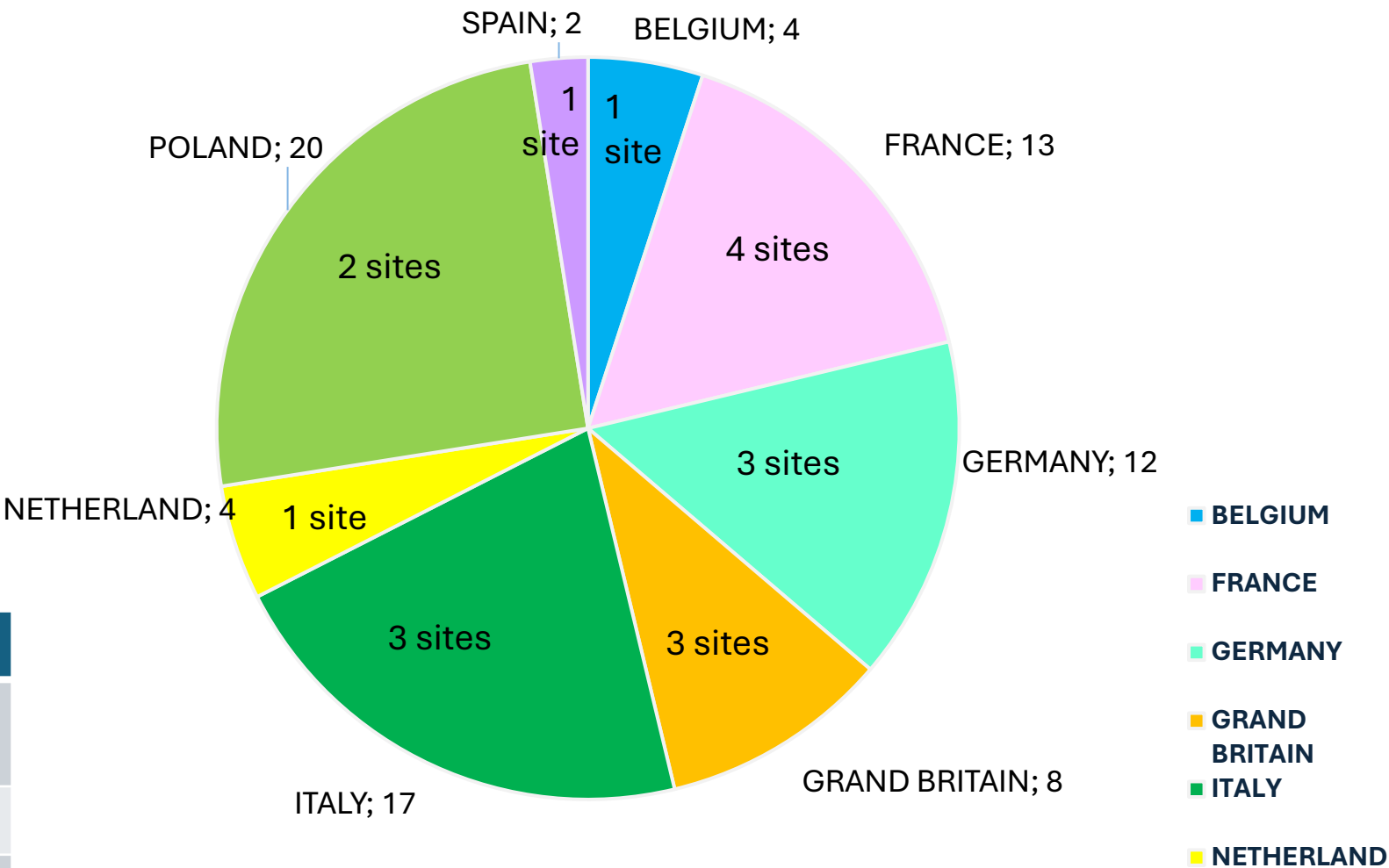


* 69 adults + 4 minor 6-17 treated in HOLOCORE; **since inclusion in Follow-up study (+12-m after Holoclar implantation)



Holocore: Enrolled patients by Country

Phase IV interventional study to confirm Holoclar efficacy and safety



TIMELINES	
First Site Initiated and First Patient First Visit	28 October 2015
First Patient Last Visit	11 March 2022
Final Clinical Study Report	20 March 2023

About 80 patients enrolled, 18 Hospital Centers, 8 countries (EU and UK)

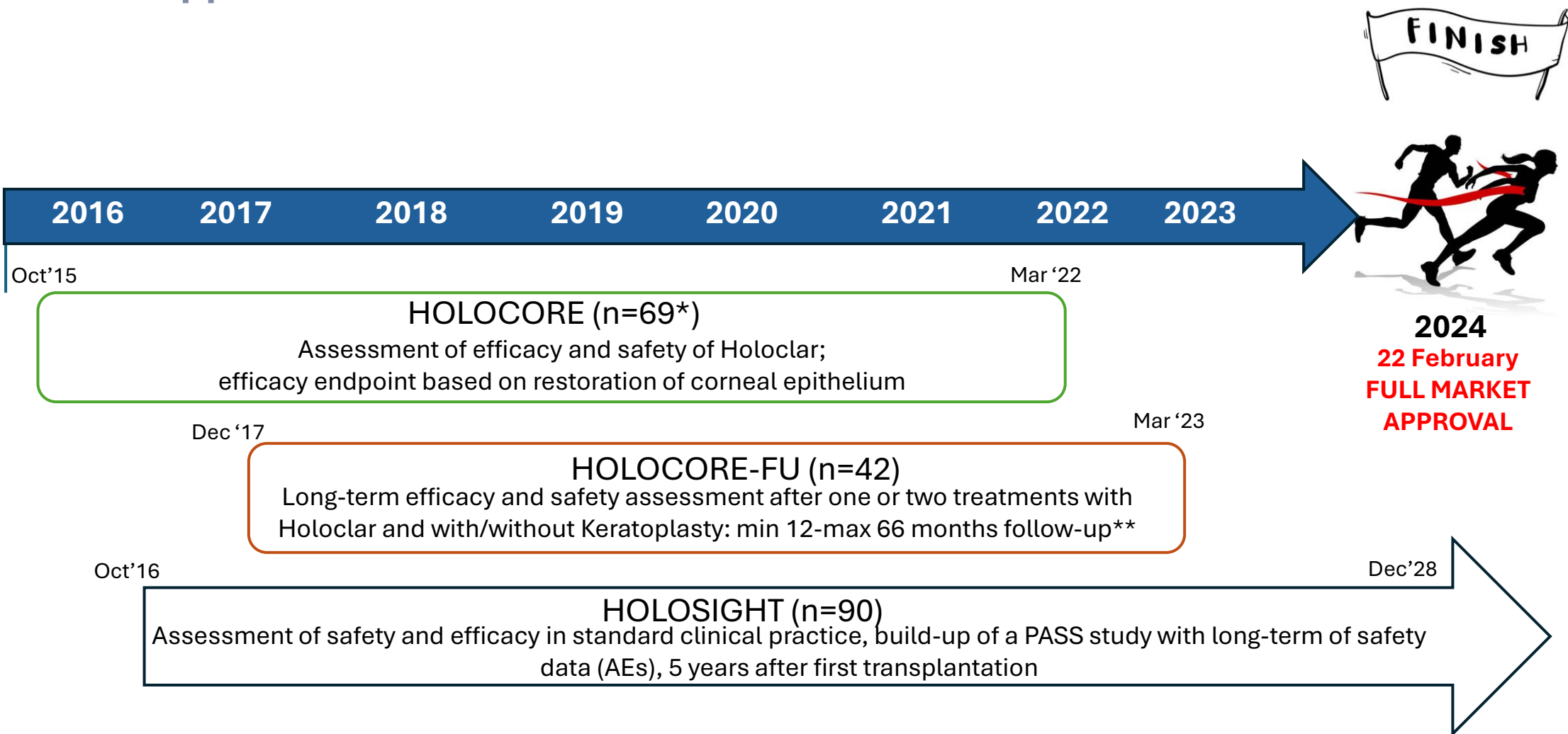


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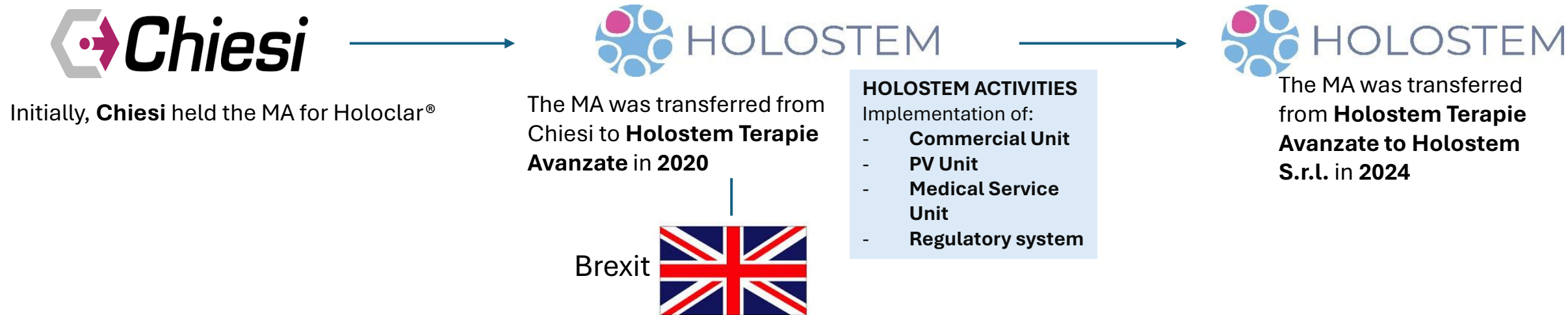


2015
EMA
CONDITIONAL
APPROVAL



* 69 adults + 4 minor 6-17 treated in HOLOCORE; **since inclusion in Follow-up study (+12-m after Holoclar implantation)

Challenges to Transfer the HOLOCLAR® marketing authorization (MA)



Following the UK's exit from the EU (Brexit), Holostem Terapie Avanzate also navigated the regulatory changes to maintain its market presence in the UK. This involved applying for a new marketing authorization specific to the UK regulatory framework, ensuring compliance with local regulations.

Take home messages



The relationship with the regulatory authorities from the first development phase is mandatory



Monitor every stage of the supply chain to ensure that all raw materials, reagents, product components, and manufacturing equipment comply with the required standards



Early product development should prioritize GMP-grade raw materials and, when possible, animal-free alternatives, while ensuring researchers are trained on regulatory rules from the start of their education



Achieving the long-term sustainability of ATMPs requires a unified effort from all stakeholders including manufacturers, healthcare providers and regulators, to address challenges in production, accessibility and regulatory frameworks



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Ringrazio

Tutto il personale di Holostem:

- Produzione
- Controllo Qualità
- Quality Assurance
- Regolatorio
- BD
- Clinica
- Cleaning
- Risorse Umane
- Amministrazione



CEO: Alessandro
Padova



... e GRAZIE a tutti voi per l'attenzione!