Promethera Biosciences: Experience of a Belgian SME

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FAMHP Workshop:

National and EU scientific regulatory support mechanisms and initiatives for innovation in drug development

2 May 2016

PROMETHERA BIOSCIENCES

Presentation objectives

- Promethera Biosciences: a Belgian Biotech Company
- Product Development: HepaStem
- Regulatory challenges for a SME
- Assistance received from Regulatory bodies (EMA and national)
- Incentives and support

Promethera® Biosciences is a Belgian SME

Promethera® Biosciences is a Belgian pharmaceutical company, **spin-off of the Université Catholique de Louvain**, that develops innovative treatment based on allogeneic adult stem cell technology.

Promethera® Biosciences was founded in **2009** based on research discovery by Professor **Etienne Sokal's** (UCL, Brussels) **know-how** in hepatology and cell therapy.

- Located at Mont-Saint-Guibert in the Watson and Crick Hill (25 km South of Brussels)
- 350 m^2 facilites (clean rooms, QC and RD laboratories, stock, offices)
- Nine departments: Manufacturing and QC, QA, R&D, Clinical, RA, Business Development, Administration and IP.

Promethera® Biosciences is a Belgian SME

An experienced management team…

John Tchelingerian, PhD

Chairman and CEO

Prof. Etienne Sokal, MD, PhD

Founder and Chief Scientific Officer

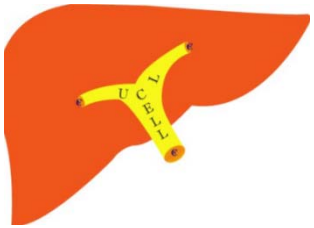
Frank Hazevoets

CFO and Head of Corporate Development

Patrick Stragier

VP Operations

…Dedicated staff



- **PEDI** (Pediatric Hepatology & Cell Therapy laboratory, UCL, Belgium). 20 scientists/technicians. Founding laboratory and close partner
- **Hepatocytes and hepatic stem cells banks** at Saint-Luc Hospital (Brussels, Belgium)

R&D and preclinical team
2 PhDs, 1 supervisor,
1 scientist, 2 research technicians

Production (10),
Quality Control (3) and
Quality Assurance (2)

IP manager (1PhD)
legal manager (1 Lawyer)
Project manager (1 PhD)

Clinical (2 CRA, 1MD, 1PhD)
Regulatory (2 PhDs)

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From Progenitor Cell Discovery to Cell Therapy Platform

ACADEMIC INNOVATION LEADING TO A SPIN-OFF…
Promethera Biosciences is a spin-off of the UCL (Brussels)

UCL

- **2005**: Discovery of the Liver Progenitor Cells named "HHALPC" by Prof Sokal's team
- **2005 to 2009**: Academic Proof of Concept (non-clinic)
- **2009 to 2011**: Clinical investigations (Hospital Exemptions)

Université catholique de Louvain UCL
Cliniques universitaires Saint-Luc

PROMETHERA BIOSCIENCES

PB

- **2009**: **CREATION OF PROMETHERA BIOSCIENCES**
- **From 2009 to 2014** : Since 2009, a total of 67M Euros has been invested through three rounds of financing.

HHALPC: Heterologous Human Adult Liver Progenitor Cells

- *Main investors : Vesalius Biocapital, Mitsui Global Investment, BI Venture Fund, Shire, ATMI and SRIW.*

Manufacturing Process of HepaStem

OFF-THE-SHELF ALLOGENIC PRODUCT

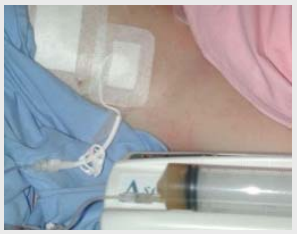
Tissue bank → **Promethera's Manufacturing cGMP plant** → **Transportation** → **Pharmacy/Hospital**

Isolation of liver cell suspension from healthy cadaveric human liver donor

Purification & expansion, Filling in vials & cryopreservation

Transportation on dry ice

Reconstitution & Infusion to patients



Sokal, Transplantation 2003

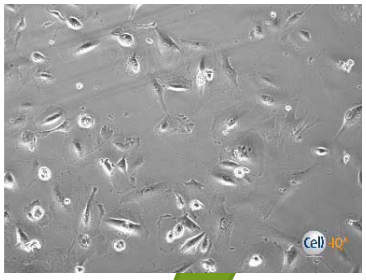
1 liver → **N patients**

Maximisation of the process and COGS control

PROMETHERA BIOSCIENCES

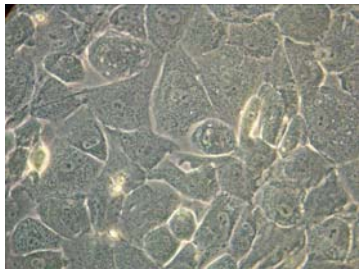
From Progenitor Cell Discovery to Cell Therapy Platform

HEPASTEM IS A LIVING MEDICINAL PRODUCT



Morphological differentiation

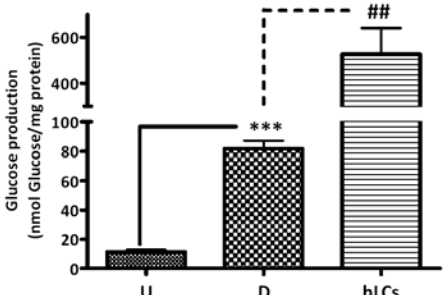
Differentiated Hepatocyte



Morphological differentiation

Markers	
Mesenchymal	CD73, CD44, CD29, CD90
Hepatic	Albumin Vimentin ASMA HNF4 G6-P MRP2 Cytochrome P450 2B6, 3A4
HLA	HLA-ABC **+**, HLA-DR **-**

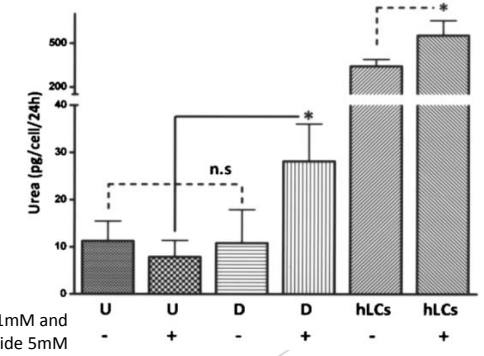
Gluconeogenesis Pathway Activity



Khuu *et al.*, 2011

De novo glucose production from lactate & pyruvate

Urea Synthesis

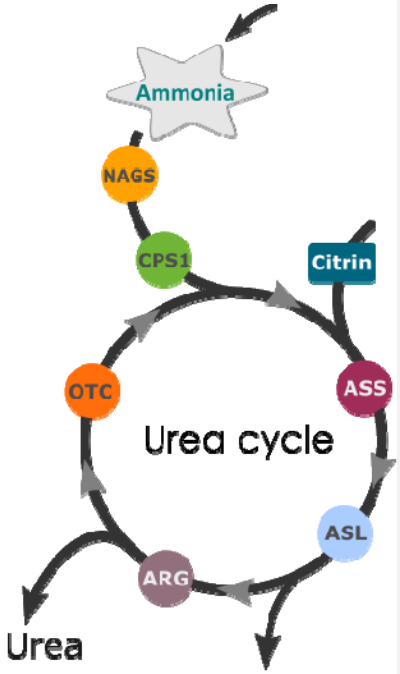


Ornithine 1mM and
Ammonium chloride 5mM

Khuu *et al.*, 2011

PROMETHERA BIOSCIENCES

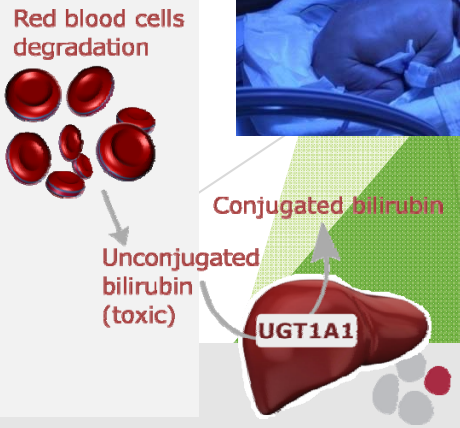
HepaStem Cell Therapy for the Treatment inborn errors of metabolism of the liver



Urea Cycle Disorders

- Genetic diseases
- Overall incidence of UCD in Europe: 1:8,000-1:44,000
- Acute/Chronic Ammonium Intoxication > Sudden decompensation at any age
- Mortality up to 50% for neonatal onset and 28% for late onset
- Low IQ < 50 for neonatal onset, neurologic and psychiatric problems in all forms.
- **Unmet Medical need !**

Crigler-Najjar syndrome



- Genetic syndrome
- Incidence: 1/1,000,000 births
- Poor quality of life (phototherapy)
- Sudden brain damage may occur at any age
- Long term progressive fibrosis and cirrhosis
- Soon or later transplanted
- **Unmet Medical need !**

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HepaStem Cell Therapy for the Treatment inborn errors of metabolism of the liver

HepaStem

- Innovative Medicinal Product to treat liver diseases (Advanced Therapy Medicinal Product)
- Treatment of Orphan indications like Crigler-Najjar Syndrome (CN) and Urea Cycle Disorders (UCD)
- Treatment of paediatric populations

Regulatory Status relative to HepaStem

DATE	HEPASTEM STATUS
July 2007	Eligibility as **Medicinal Product**
May 2008	**Orphan Designation** for the treatment of Ornithine Transcarbamylase Deficiency (OTCD)
June 2008	**Orphan Designation** for the treatment of Crigler-Najjar Syndrome (CN)
May 2011	Classification of a **Somatic Cell based-Medicinal Product**
June 2013	**Orphan Designation** for the treatment of other types of UCD (7 forms)
Nov 2013	Agreement on **Paediatric Investigational Plan** (PIP)

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Challenges of Promethera Biosciences Being a SME

MEDICINAL PRODUCT
HEPASTEM

Objectives in line with conducting a first clinical trial

HepaStem

- To demonstrate Safety and Proof of concept in representative animal models
- To get GMP accreditation to manufacture clinical batches
- To receive approval from Competent Authorities and EC in two indications
- To conduct a Paediatric clinical study in Orphan indications (PIP)
- Monitoring of Urea Cycle Disorders patients present huge difficulties
- To deliver living cells within a limited shelf life all over Europe

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Assistance received from EMA and other Regulatory Bodies

Scientific Advice (SA) with EMA

DATE	Protocol Assistance to:
March 2009	Preclinical development program
July 2010	Quality Development Program
May 2012	Preclinical development program (follow-up)
March 2013	Preclinical development program (follow-up)
July 2015	EMA/HTA SA - Clinical development program (Phase II)

Scientific Advice (SA) with National Competent Authorities

DATE	AGENCY	OBJECTIVE
June 2010	FAMHP	Quality aspects for approval of Phase I/II
January 2011	PEI	Clinical development program of Phase I/II
Feb 2011	FAMHP	Preclinical development program of Phase I/II
July 2011	MHRA	Clinical development program of Phase I/II
July 2011	FAMHP	Preclinical development program of Phase I/II
April 2016	FAMHP	Quality aspects (planned)

SA experience with EMA

- ✓ Scope of the Protocol Assistance

To get advice on quality data of the product in order to safely enter in phase I/II

Contact: Scientific Advice Secretariat of EMA

- ✓ Overall process timeline: 6 months

1) Letter of intent : Feb 2010

2) Submission of the draft briefing document: 6 April 2010

3) Submission of the final Briefing document: 19 April 2010

4) Meeting with EMA: 24 June 2010

5) Final Meeting Minutes: 22 July 2010

- ✓ Questions:

Does CHMP agree with the proposed validation plan relating to potency testing? Does CHMP agree that the bioproducts used for the manufacturing do not raise safety issues? Acceptability of the karyotyping method and related batch release specification

- ✓ Key message:

Very instructive meeting allowing the Company to present product development and receive clear recommendations from CHMP in line with the quality program.

SA experiences with FAMHP (Belgium)

✓ Scope of the Scientific advices

1) The purpose of the first SA with **FAMHP** was to validate that the preclinical development program was relevant to start with Phase I/II clinical trial

2) The purpose of the second SA with **FAMHP** was to validate that the characterization, QC and the stability testing approaches of the product were acceptable to start with Phase I/II clinical trial

3) The objective of the third SA with **FAMHP** was follow-up of non-clinical program

✓ Overall process timeline:

	Non-clinical SA	**Quality SA**	**Non-clinical SA**
Submission of Briefing document	17 March 2010	04 Jan 2011	22 June 2011
Meeting with Agency	11 June 2010	15 Feb 2011	18 July 2011
Meeting minutes	09 July 2010	05 April 2011	14 Sept 2011

✓ Key messages

Thanks to subsequent SA with FAMHP, CTA was consolidated according to recommendations provided by Agency. The process to get CTA approval was accelerated as major issues were discussed during SA.

SA experience with MHRA (United Kingdom)

✓ Scope of the Scientific Advices

The scope of the request of the SA with **MHRA** was to validate that the preclinical development program and clinical protocol were in line with Phase I/II authorization.

Contact: Pre-Application Scientific Advice for Human Products from the Medicines and Healthcare products Regulatory Agency.

✓ Overall Process Timeline:

1) Submission of LoI and briefing document: 6 April 2010

3) Meeting with MHRA: 1 July 2011

5) Final Meeting Minutes: 5 August 2011

✓ Key Messages

Clear answers and recommendations provided by MHRA

Very helpful in consolidating the CTA

MHRA advised PB to apply for Paediatric Investigation Plan (PIP)

SA experience with Paul Ehrlich Institute (PEI – Germany)

✓ Scope of the Scientific Advices

The purpose of the SA with *Paul Ehrlich Institute* (**PEI**) was to discuss on the clinical development (Phase I/II and Phase II/III).

Contact: Innovation Office

✓ Overall Process Timeline:

1) Letter of intent : 6 Oct 2010

3) Submission of the Briefing document: 9 Nov 2010

4) Meeting with PEI: 18 Jan 2011

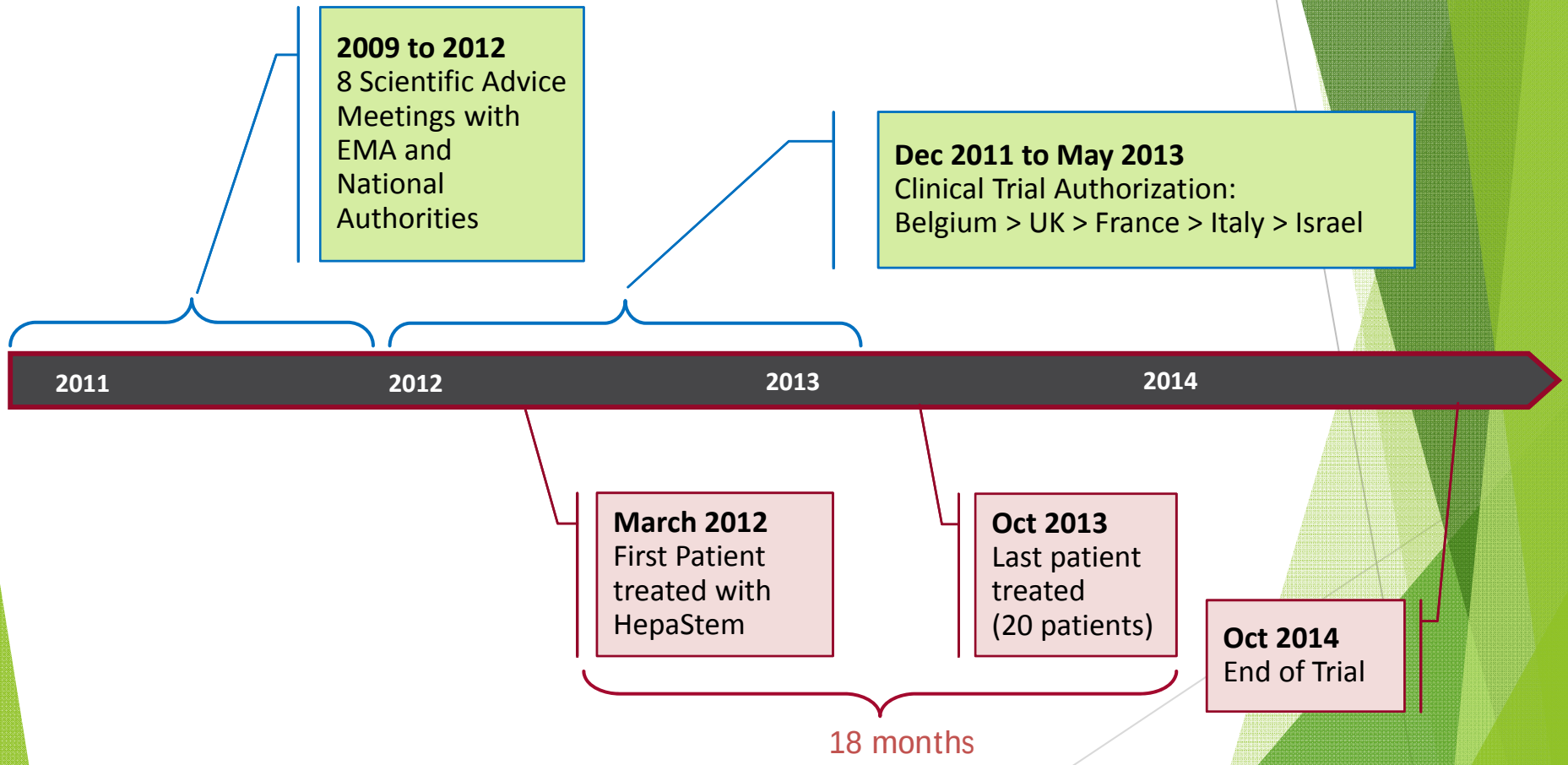
5) Final Meeting Minutes: 11 April 2011

✓ Key Messages

For all questions in accordance to Phase I/II appropriateness, we received complete advice.
For questions linked to MAA, PEI proposed to discuss with EMA at a later stage.

Scientific Advices and Clinical trial process

Multicentric Phase I/II clinical trial (completed)



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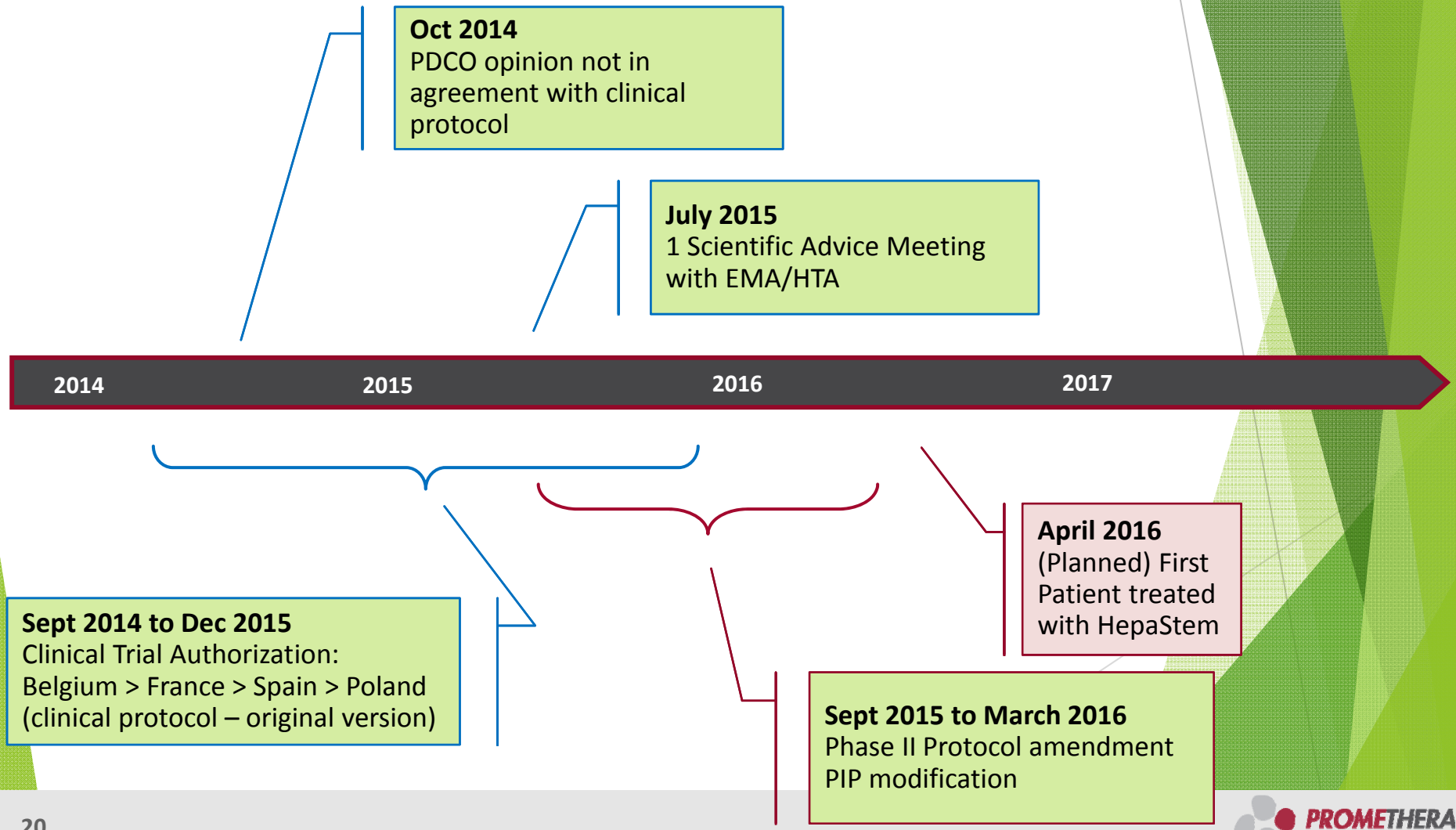
Scientific Advices and Clinical trial process

Multicentric Phase II clinical trial (ongoing)



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SA experience with EMA and HTA

- ✓ Scope of the Parallel SA with EMA and European Health Technology Assessment Bodies (HTA) :
- ❑ **Regulatory authorities and HTA authorities basically have different perspectives:**

Regulatory perspective	HTA perspective
Efficacy Safety	Clinical effectiveness Cost effectiveness

The same evidence can lead to different requirements

- ❑ **Why did Promethera Biosciences seek for parallel EMA/HTA advice?**

To understand what shapes additional therapeutic benefit in the eyes of the patients.

To understand the related evidence requirements, and modify our plans accordingly, if feasible

To assess the value of information (additional data / studies / analyses to demonstrate relative effectiveness) versus additional investments in terms of time and costs for product development in a permanently changing environment

To reduce the risks linked to investment in drug development.

SA experience with EMA and HTA

✓ Scope of the Parallel SA with EMA and European Health Technology Assessment Bodies (HTA) :

To seek advice in parallel from the Scientific Advice Working Party and some European Health Technology Assessment Bodies to confirm the adequacy and robustness of the clinical program for Marketing Authorisation and HTA evaluations in Urea Cycle Disorders.

✓ Overall process timeline: 5 months

	EMA procedure	Promethera's experience
Pre-notification phase	1 to 2 months	1 month
Pre-validation phase	45 days	24 days
Validation phase	2 months	40 days
Meeting minutes (separate EMA and HTA)	/	1 month

✓ Key messages

Clear feedback received from EMA and HTA on the clinical program with UCD. EMA and HTA provided independent conclusions. EMA and HTA SA allowed to re-discuss overall clinical program with members of PDCO.

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Incentives and Support

- **Administrative and procedural assistance** from the SME office

- **Attendance to SME meetings**

- **Fee reductions for procedures in the pre-** and post-marketing-authorisation phases, including scientific advice, inspections, line extensions and variations;

- Fee exemptions for certain administrative services of the Agency;

- Deferral of the fee payable for an application for marketing authorisation or related inspection;

- Conditional fee exemption where scientific advice is followed and a marketing authorisation application is not successful;

- Assistance with translations of the product information documents submitted in the application for marketing authorisation;

- Waiver of the MedDRA licensing fee when registering with EudraVigilance.

- **Inclusion in the public** SME register

Concluding Remarks

Promethera, as ATMP manufacturer, benefited from strong EMA ATMP expertise on quality, clinical and non-clinical aspects and of valuable input throughout the process

Promethera valued the early opportunity of getting joint feedback/input from relevant EMA Committees and EU representatives

Promethera strongly valued the assistance received from EMA and National HA

Early interactions with EMA and National HA constituted an important learning opportunity in order to get a better understanding of the relevant processes and requirements


Thank you!
Promethera Biosciences SA
www.promethera.com