GOBIERNO DE ESPAÑA
MINISTERIO DE SANIDAD, POLÍTICA SOCIAL E IGUALDAD

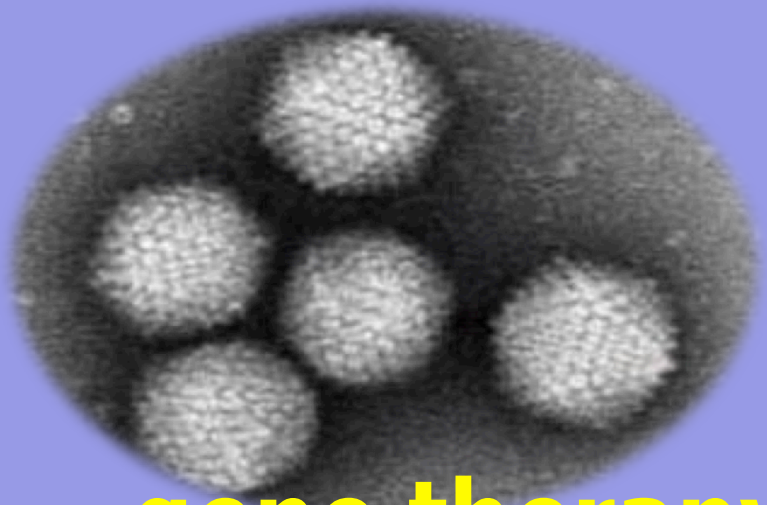
agencia española de medicamentos y productos sanitarios

advanced therapies in the EU

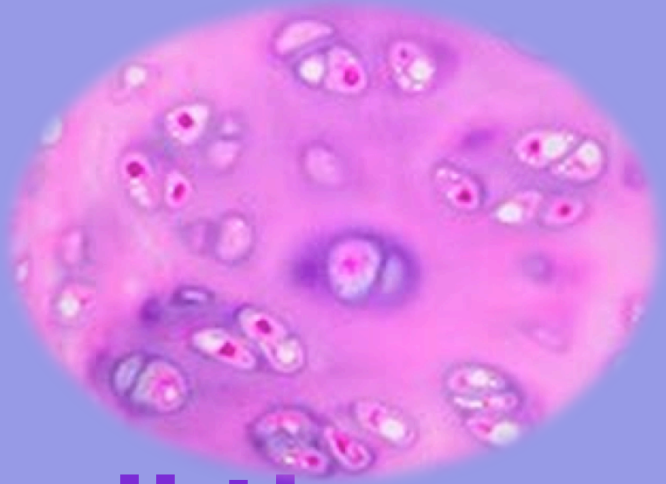
Sol Ruiz - AEMPS

New Developments in Drug Regulation- 10-10-2014

ATMP in the EU



gene therapy



cell therapy

tissue engineering

Regulation (EC) No 1394/2007

10.12.2007 EN Official Journal of the European Union L 324/121

REGULATION (EC) No 1394/2007 OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL

of 13 November 2007

on advanced therapy medicinal products and amending Directive 2001/83/EC and Regulation (EC) No 726/2004

(Text with EEA relevance)

Specific rules regarding the **authorization**
supervision
pharmacovigilance

of advanced therapy medicinal products (ATMPs)

COMMISSION DIRECTIVE 2009/120/EC

of 14 September 2009

amending Directive 2001/83/EC of the European Parliament and of the Council on the Community code relating to medicinal products for human use as regards advanced therapy medicinal products

(Text with EEA relevance)

Official Journal of the European Union

ANNEX

'PART IV

ADVANCED THERAPY MEDICINAL PRODUCTS

Directive 2009/120/EC

Gene therapy medicinal product

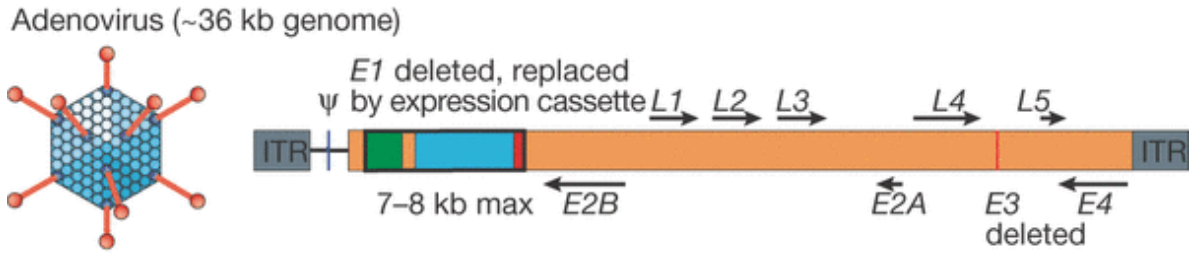
Gene therapy medicinal product means a biological medicinal product which has the following characteristics:

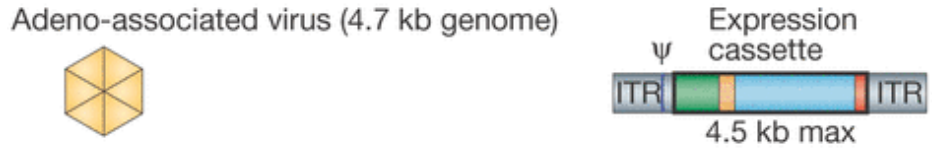
(a) it contains an active substance which contains or consists of a recombinant nucleic acid used in or administered to human beings with a view to regulating, repairing, replacing, adding or deleting a genetic sequence;

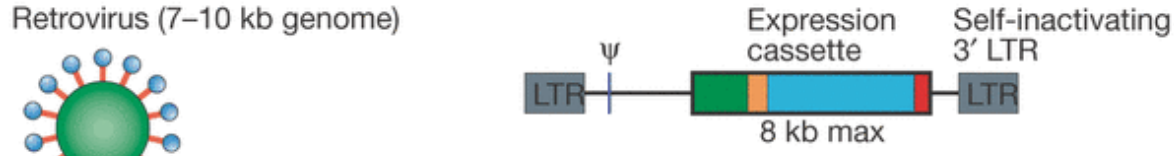
(b) its therapeutic, prophylactic or diagnostic effect relates directly to the recombinant nucleic acid sequence it contains, or to the product of genetic expression of this sequence.

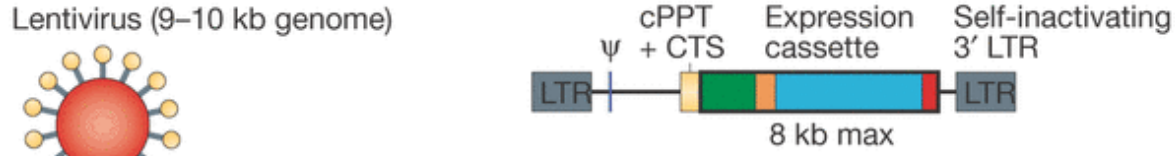
Gene therapy medicinal products shall not include vaccines against infectious diseases.

viral vectors

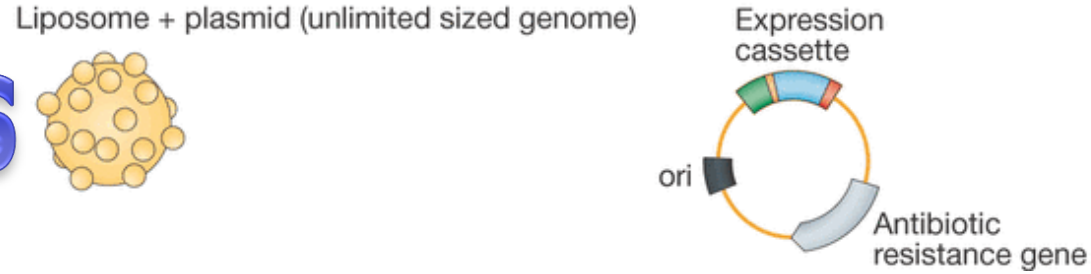


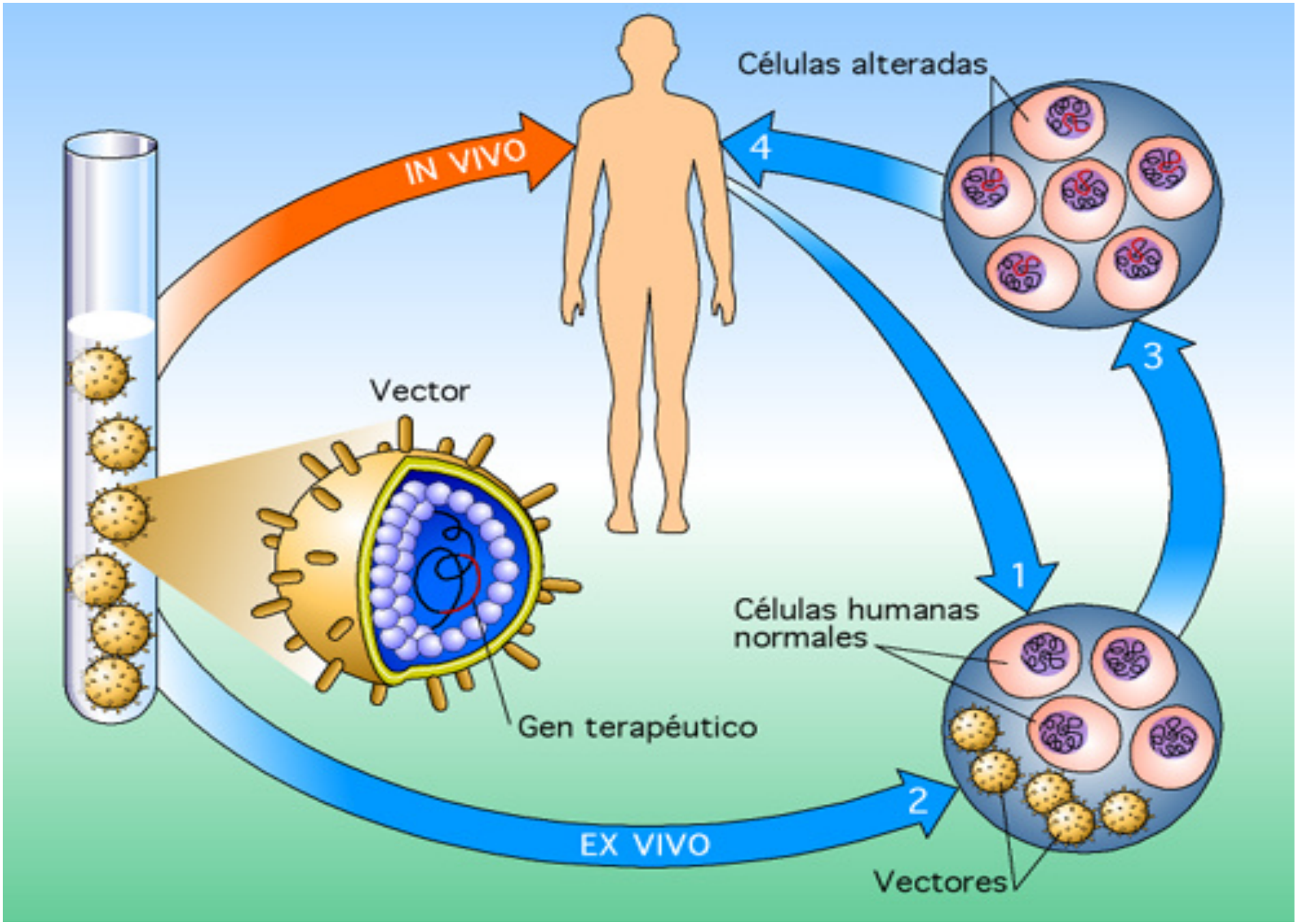


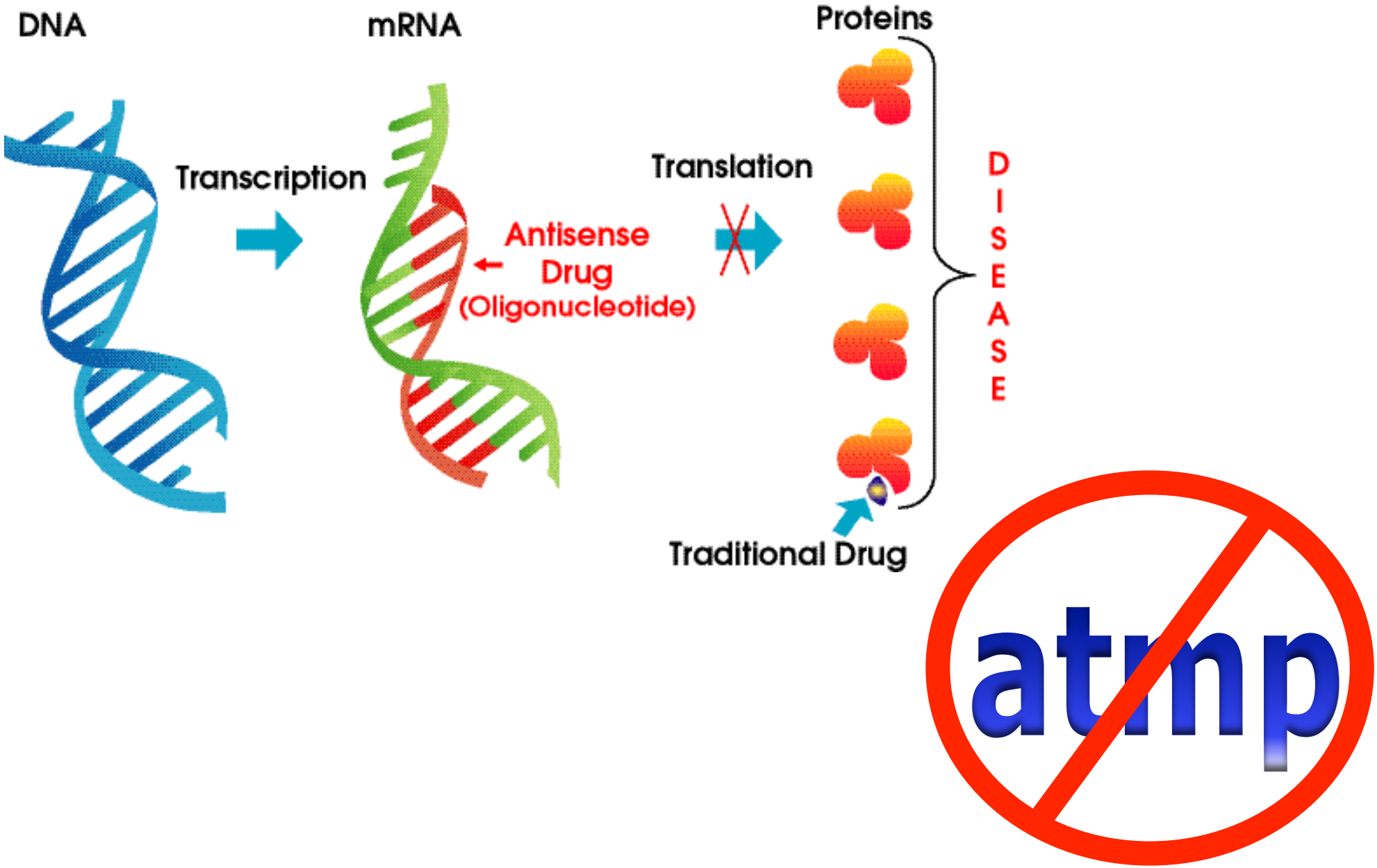


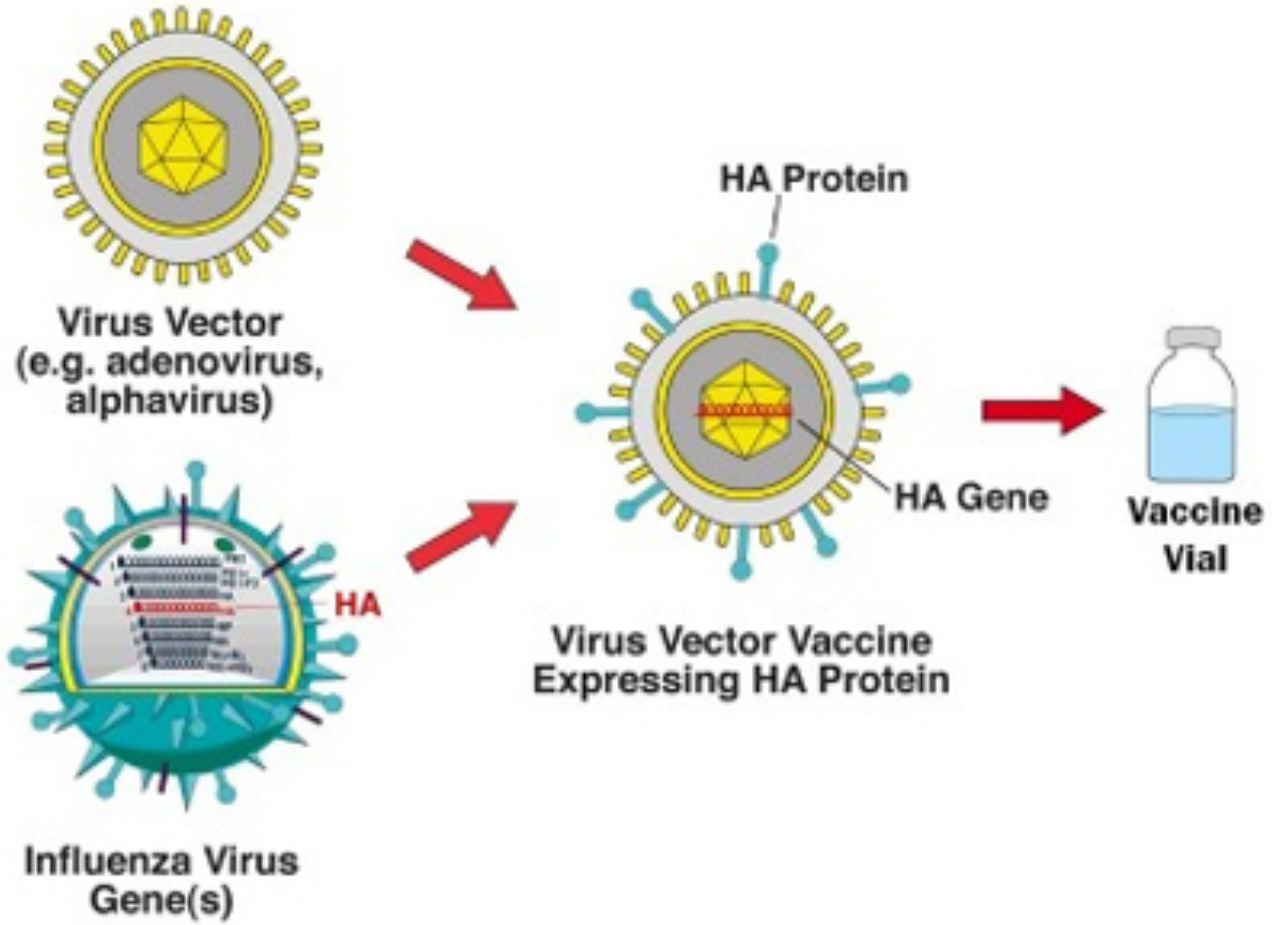


non-viral vectors

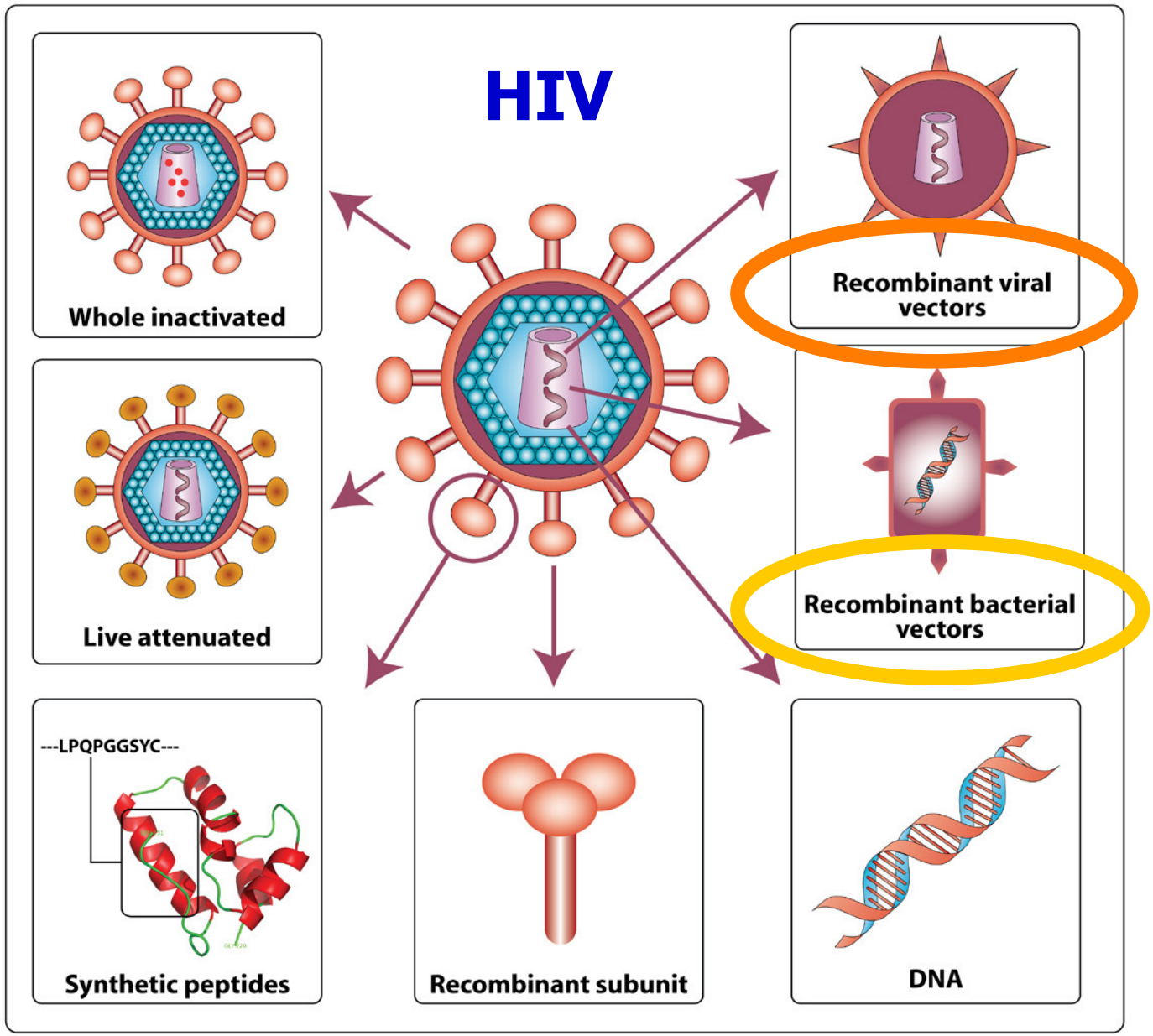



Células alteradas
IN VIVO
4
Vector
3
1
Células humanas
normales
Gen terapéutico
2
EX VIVO
Vectores


DNA
mRNA
Proteins
Transcription
Translation
Antisense
Drug
(Oligonucleotide)
DISEASE
Traditional Drug
atnp


Virus Vector
(e.g. adenovirus,
alphavirus)
HA
Influenza Virus
Gene(s)
HA Protein
HA Gene
Virus Vector Vaccine
Expressing HA Protein
Vaccine
Vial


atnp


HIV
Whole inactivated
Live attenuated
---LPQPGGSYC---
Synthetic peptides
Recombinant subunit
Recombinant viral vectors
Recombinant bacterial vectors
DNA


atnp

Directive 2009/120/EC

Somatic cell therapy medicinal product

Somatic cell therapy medicinal product means a biological medicinal product which has the following characteristics:

(a) contains or consists of cells or tissues that have been subject to substantial manipulation so that biological characteristics, physiological functions or structural properties relevant for the intended clinical use have been altered, or of cells or tissues that are not intended to be used for the same essential function(s) in the recipient and the donor;

(b) is presented as having properties for, or is used in or administered to human beings with a view to treating, preventing or diagnosing a disease through the pharmacological, immunological or metabolic action of its cells or tissues.

For the purposes of point (a), the manipulations listed in Annex I to Regulation (EC) No 1394/2007, in particular, shall not be considered as substantial manipulations.

Annex I

— cutting,

— grinding,

— shaping,

— centrifugation,

— soaking in antibiotic or antimicrobial solutions,

— sterilization,

— irradiation,

— cell separation, concentration or purification,

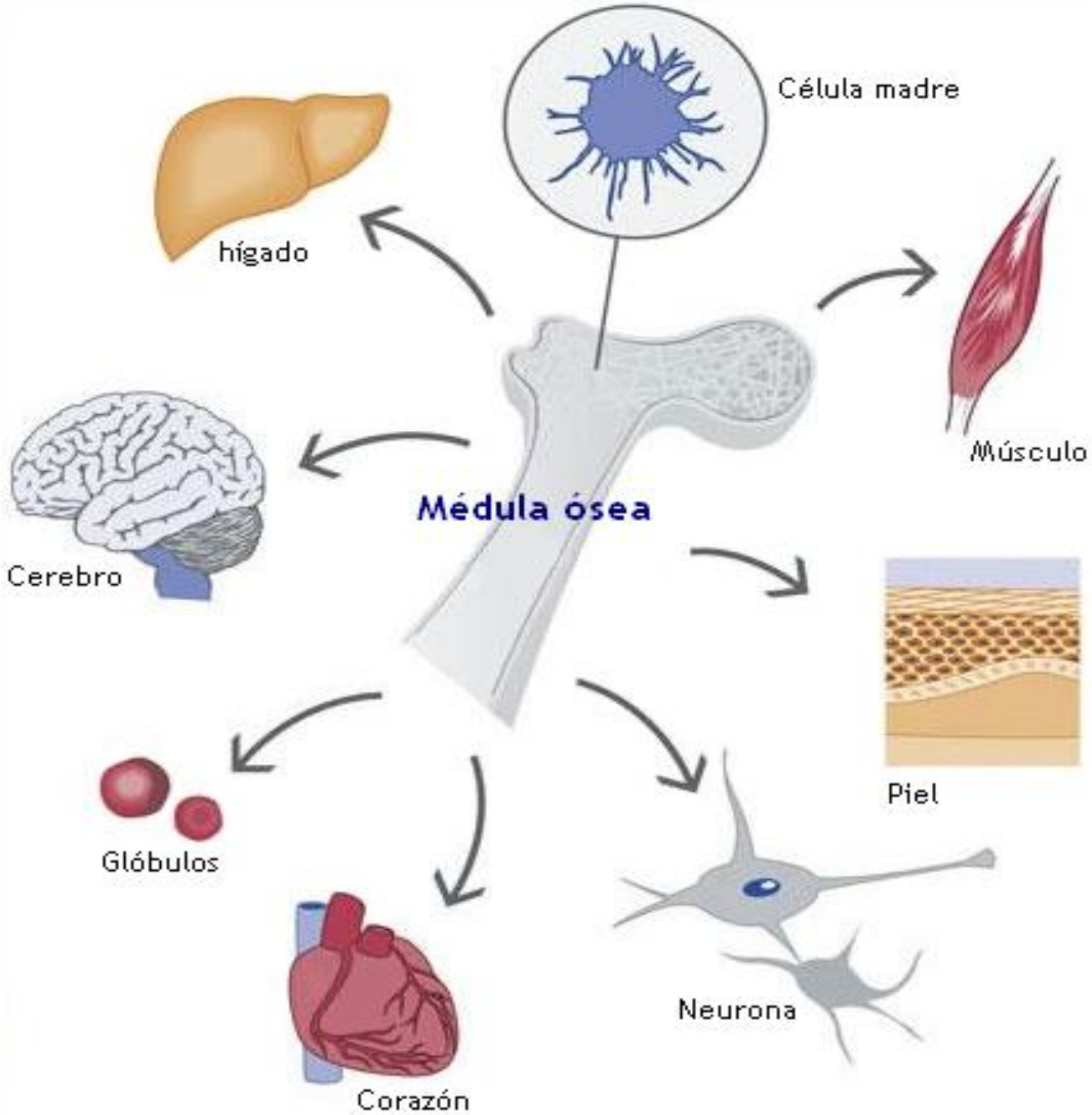
— filtering,

— lyophilization,

— freezing,

— cryopreservation,

— vitrification.


Célula madre
hígado
Músculo
Médula ósea
Cerebro
Piel
Glóbulos
Neurona
Corazón

Regulation (EC) No 1394/2007

Tissue engineered product means a product that:

— contains or consists of engineered cells or tissues, and

— is presented as having properties for, or is used in or administered to human beings with a view to regenerating, repairing or replacing a human tissue

Directive 2009/120/EC

Somatic cell therapy medicinal product

Somatic cell therapy medicinal product means a biological medicinal product which has the following characteristics:

engineered cells or tissues

(a) contains or consists of cells or tissues that have been subject to substantial manipulation so that biological characteristics, physiological functions or structural properties relevant for the intended clinical use have been altered, or of cells or tissues that are not intended to be used for the same essential function(s) in the recipient and the donor;

(b) is presented as having properties for, or is used in or administered to human beings with a view to treating, preventing or diagnosing a disease through the pharmacological, immunological or metabolic action of its cells or tissues.

For the purposes of point (a), the manipulations listed in Annex I to Regulation (EC) No 1394/2007, in particular, shall not be considered as substantial manipulations.

Article 2. Definitions

e.g. cell culture

or

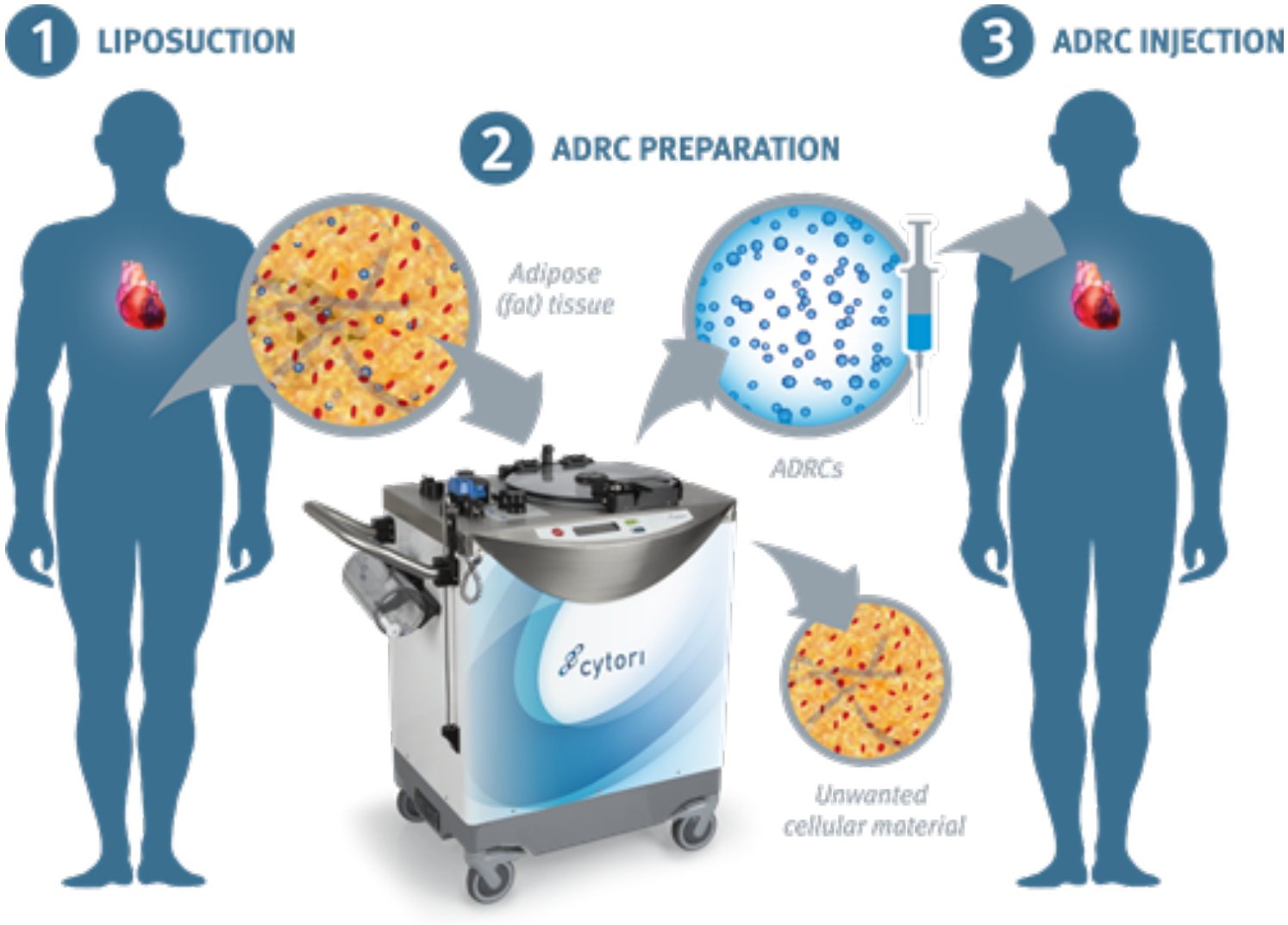
e.g. different location

Cells or tissues shall be considered 'engineered' if they fulfil at least one of the following conditions:

— the cells or tissues have been subject to substantial manipulation, so that biological characteristics, physiological functions or structural properties relevant for the intended regeneration, repair or replacement are achieved. The manipulations listed in Annex I, in particular, shall not be considered as substantial manipulations,

— the cells or tissues are not intended to be used for the same essential function or functions in the recipient as in the donor.

atmp


1 LIPOSUCTION
2 ADRC PREPARATION
3 ADRC INJECTION
Adipose (fat) tissue
ADRCs
cytori
Unwanted cellular material

Regulation (EC) No 1394/2007

(d) 'Combined advanced therapy medicinal product' means an advanced therapy medicinal product that fulfils the following conditions:

— it must incorporate, as an integral part of the product, one or more medical devices within the meaning of Article 1(2)(a) of Directive 93/42/EEC or one or more active implantable medical devices within the meaning of Article 1(2)(c) of Directive 90/385/EEC, and

— its cellular or tissue part must contain viable cells or tissues, or

— its cellular or tissue part containing non-viable cells or tissues must be liable to act upon the human body with action that can be considered as primary to that of the devices referred to.

advanced therapy medicinal products

SHOULD COMPLY WITH THE LEGISLATION FOR MED PROD

- their use needs to be **authorized**: marketing authorization, clinical study, compassionate use…
- **quality, safety and efficacy**
- **GMP** (production & control), **GLP** (non-clinical) and **GCP** (clinical studies) apply

aemps

- clinical studies, compassionate use
- *hospital exemption*

ema

MA in the EU
(centralized procedure)

Key points of the Regulation

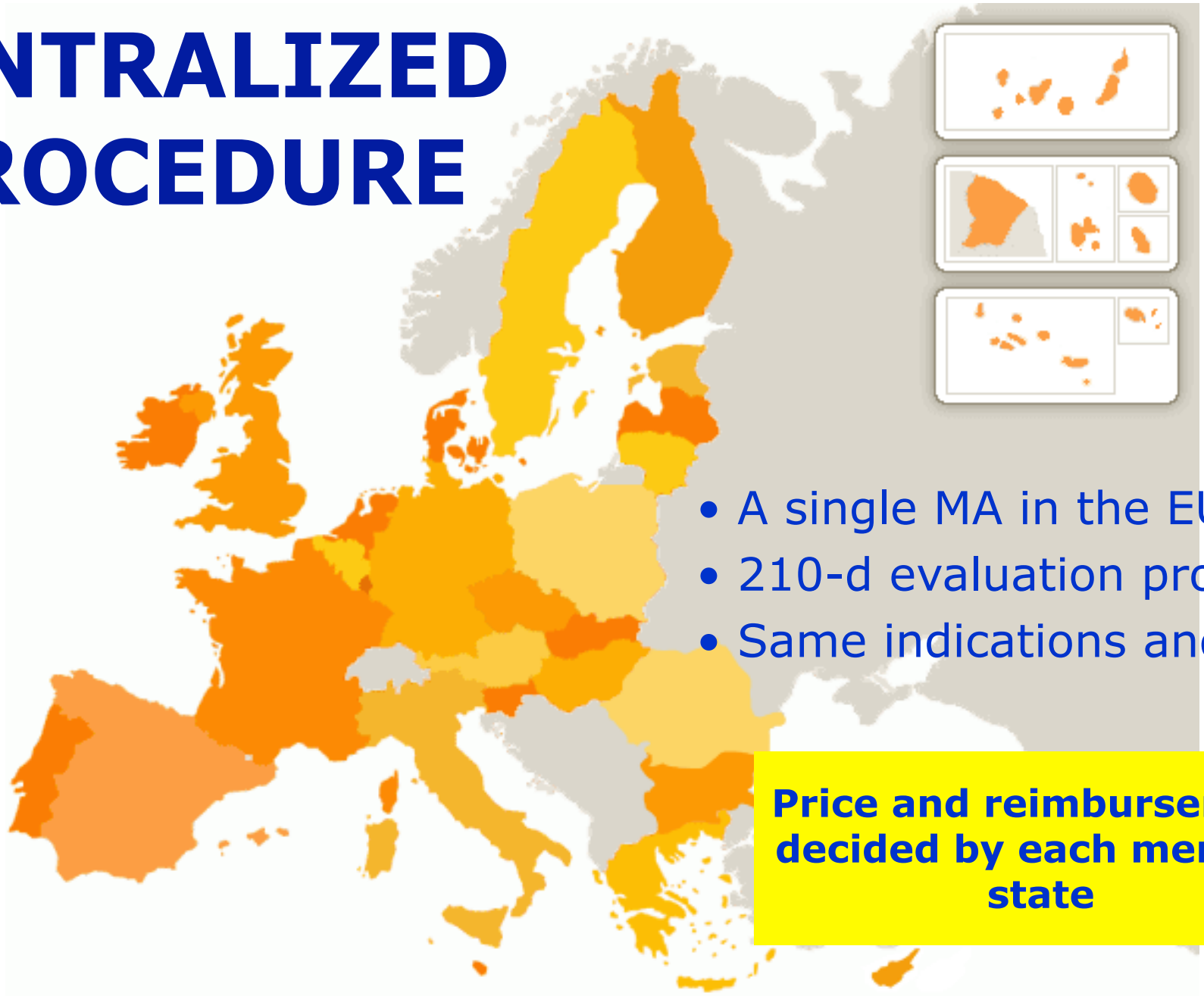
- Marketing authorisation required
- Demonstration of Quality, Safety & Efficacy
- Post-authorisation vigilance of **S & E**
- Centralised procedure mandatory

european medicines agency

EMA new premises

30 Churchill Place
London E14 5EU

CENTRALIZED PROCEDURE



- A single MA in the EU
- 210-d evaluation process
- Same indications and SPC

Price and reimbursement decided by each member state

Which products *must* be centrally authorised?

All human medicines derived from biotechnology and other high-tech processes must be evaluated by the Agency via the centralised procedure. The same applies to all advanced-therapy medicines and medicinal products containing new active substances intended for the treatment of HIV/AIDS, cancer, diabetes, neurodegenerative diseases, auto-immune and other immune dysfunctions, and viral diseases, as well as to all designated orphan medicines intended for the treatment of rare diseases.

CHMP

- Chair & Vice-Chair
- 1 scientific expert member nominated by each MS (+1 alternate) - 28
- 1 scientific expert member from NO and ICE (+1 alternate) (observers)
- 5 co-opted members (experts in specific areas of interest for the CHMP)

Meeting highlights from the Committee for Medicinal Products for Human Use (CHMP) 22-25 September 2014

News

26/09/2014

Meeting highlights from the Committee for Medicinal Products for Human Use (CHMP) 22-25 September 2014

Fifteen new medicines and three extensions of indication recommended for approval

Fifteen new medicines have been recommended for approval at the September meeting of the European Medicines Agency's Committee for Medicinal Products for Human Use (CHMP).

The Committee recommended a marketing authorisation for **Harvoni** (sofosbuvir / ledipasvir) for the treatment of chronic hepatitis C in adults. Harvoni belongs to a new generation of antiviral products for chronic HCV infection that have high cure rates and have recently reshaped the treatment landscape for this disease. Please see the press release in the grid below for more information.

Ketoconazole HRA (ketoconazole) was recommended by the CHMP as a new treatment for patients with Cushing's syndrome. Pharmacological options for this condition remain very limited and there is an unmet medical need for additional medicines. Ketoconazole HRA has an orphan designation. Please see the press release in the grid below for more information.

Two medicines were recommended for approval by the CHMP for the treatment of cancer: **Vargatef** (nintedanib) for the treatment of non-small cell lung cancer and the orphan medicine **Cyramza** (ramucirumab) for the treatment of gastric cancer. The diagnostic agent **Lymphoseek** (tilmanocept)was also recommended for the delineation and localisation of sentinel lymph nodes.

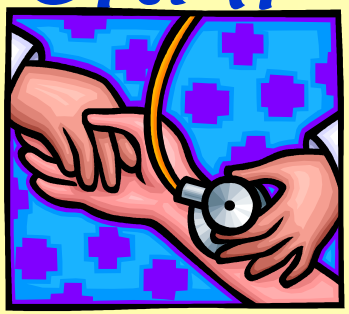
Related information

- Maci: EPAR
- Avastin: EPAR
- Javlor: EPAR
- Signifor: EPAR
- Valdoxan: EPAR
- Thymanax: EPAR
- Prezista: EPAR
- Budesonide/Formoterol Teva: Pending EC decision
- Vargatef: Pending EC decision
- Cyramza: Pending EC decision
- Duaklir Genuair: Pending EC decision
- Egranli: Pending EC decision
- Trulicity: Pending EC decision
- Tadalafil Mylan: Pending EC decision
- Signifor: Pending EC decision
- Harvoni: Pending EC decision
- Rezolsta: Pending EC decision
- Javlor: Pending EC decision
- Ketoconazole HRA: Pending EC decision
- Lymphoseek: Pending EC decision

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

SCIENTIFIC COMMITTEES

CHMP



Hu

CVMP

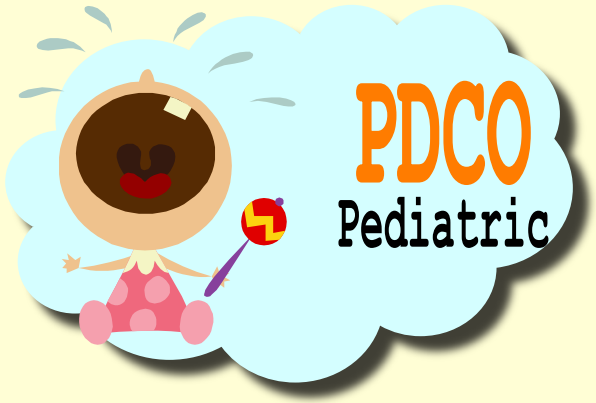
Vet

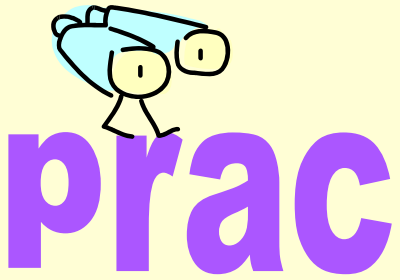
COMP

Orphan

HMPC

Herbal





Regulation (EC) No 1394/2007

CHAPTER 7

COMMITTEE FOR ADVANCED THERAPIES

Article 20

Committee for Advanced Therapies

1. A Committee for Advanced Therapies shall be established within the Agency.

2. Save where otherwise provided in this Regulation, Regulation (EC) No 726/2004 shall apply to the Committee for Advanced Therapies.

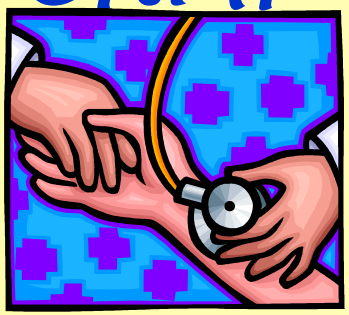
3. The Executive Director of the Agency shall ensure appropriate coordination between the Committee for Advanced Therapies and the other Committees of the Agency, in particular the Committee for Medicinal Products for Human Use and the Committee for Orphan Medicinal Products, their working parties and any other scientific advisory groups.

- **5** CHMP members with their alternates
- **1** M (1A) per MS (from MS not represented through CHMP)
- **2** M (2A) representing clinicians
- **2** M (2A) representing patients' associations
- At least 2 M (2A) with expertise in medical devices

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

atmp
centralized procedure

CHMP



Human Med

draft opinion

cat

final opinion

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

cHMP

Human Meds

FINAL opinion on medicines for human use

CHMP
PRAC
CVMP
COMP
HMPC
CAT
Overview
Members
Meetings
Agendas, minutes and reports
PDCO
Working parties and other groups

Committee for Advanced Therapies (CAT)

The Committee for Advanced Therapies (CAT) is the committee at the European Medicines Agency that is responsible for assessing the quality, safety and efficacy of advanced-therapy medicinal products (ATMPs) and following scientific developments in the field. It is a multidisciplinary committee, gathering together some of the best available experts in Europe.

It was established in accordance with Regulation (EC) No 1394/2007 on ATMPs.

- See the full overview of the CAT's role.

Composition

The members of the CAT are appointed for a renewable period of three years. The chair and vice-chair are elected from its members for a term of three years, which may be renewed once.

The CAT is composed of:

- five members or co-opted members of the Committee for Medicinal Products for Human Use (CHMP), with their alternates. These members are appointed by the CHMP itself;
- one member and one alternate appointed by each European Union (EU) Member State that is not represented by the members and alternates appointed by the CHMP;
- two members and two alternates appointed by the European Commission to represent clinicians;
- two members and two alternates appointed by the European Commission to represent patient associations.

Meeting calendar

- See full meeting plan for this year.

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

26 September 2014
EMA/CAT/581538/2014
Procedure Management and Business Support Division

CAT monthly report of application procedures, guidelines and related documents on advanced therapies

September 2014 meeting

The Committee for Advanced Therapies (CAT) held its 63rd CAT meeting on 18-19 September 2014.

The CAT Monthly Report includes statistical data on CAT scientific recommendations on Advanced Therapy Medicinal Product (ATMP) classification, certifications, initial evaluations, CAT contributions to Scientific Advice and Paediatric Investigation Plans, as well as variations, line extensions, renewals.

MACI: suspension of marketing authorisation

On 5 September 2014 the marketing authorisation holder closed the EU manufacturing site for MACI (matrix-applied characterised autologous cultured chondrocytes) and MACI will no longer be available in the EU. The closure of the site was due to commercial reasons and the benefit-risk balance of MACI remains positive.

Following the closure of the manufacturing site and because EU legislation requires authorised medicines to have a registered manufacturing site, a review was initiated at the request of the European Commission on 10 September 2014 (under Article 20 of Regulation (EC) No 726/2004) to determine whether the marketing authorisation for MACI should be suspended or revoked.

On 19 September 2014, CAT adopted a draft opinion recommending the suspension of the marketing authorisation of MACI until a new manufacturing site is registered in the EU. The draft CAT opinion was transmitted to the CHMP, who adopted on 25 September 2014 its final opinion recommending the suspension of the marketing authorisation for MACI. The final opinion will now be sent to the European Commission which will issue a legally binding decision.

Initial Evaluation of Marketing Authorisation Applications (MAA) for ATMP							
	2009	**2010**	**2011**	**2012**	**2013**	**2014**	**Total**
Submitted MAAs	3	1	2	3	2	2	13
Positive draft Opinion	1	0	1[i]	1[i]	2	0	5 Corresponding to 4 ATMPs
Withdrawals	1	1	0	0	2	0	4
Ongoing MAAs							5

[i] Same product (Glybera)

Variations (Type II) for authorised ATMP							
	2009	**2010**	**2011**	**2012**	**2013**	**2014**	**Total**
Positive draft Opinion	0	0	1	1	9	4	15

Scientific recommendation on advanced therapy classification							
	2009	**2010**	**2011**	**2012**	**2013**	**2014**	**Total**
Submitted	22	19	12	17	20	21	116
Adopted	12	27	12	14	23	20	110

Certification of quality and non-clinical data for small and medium-sized enterprises developing ATMPs							
	2009	2010	2011	2012	2013	2014	Total
Submitted	1	0	0	1	3	0	5
Adopted	0	1	0	1	1	2	5

Scientific advice procedures on ATMPs							
	2009	2010	2011	2012	2013	2014	Total
Discussed*	25	30	36	31	36	31	189

* Most scientific advices for ATMPs are discussed by the CAT at 2 time points during the SA procedure

Paediatric Investigation Plans (PIP) for ATMPs							
	2009	2010	2011	2012	2013	2014	Total
Discussed*	4	7	6	9	7	5	38

when the rubber

hits the road...

07/2007	**CEREPRO**	***AdV-HSVtk***. Withdrawn by the applicant
12/2008	**ADVEXIN**	***AdV-p53***. Withdrawn by the applicant
07/2009	**CHONDROCELECT**	***Autologous chondrocytes***
07/2012	**GLYBERA**	***AAV-LPL***
01/2013	**HYALOGRAFT C AUTOGRAFT**	***Autologous chondrocytes***. Withdrawn by the applicant
03/2013	**ORANERA**	***Autologous oral mucosal epithelial cells***. Withdrawn by the applicant
04/2013	**MACI**	***Matrix-induced autologous chondrocyte implantation***
06/2013	**PROVENGE**	***Autologous peripheral blood mononuclear cells activated with PAP-GM-CSF (sipuleucel-T)***

07/2007	**CEREPRO**	***AdV-HSVtk***. Withdrawn by the applicant
12/2008	**ADVEXIN**	***AdV-p53***. Withdrawn by the applicant
07/2009	**CHONDROCELECT**	***Autologous chondrocytes***
07/2012	**GLYBERA**	***AAV-LPL***
01/2013	**HYALOGRAFT C AUTOGRAFT**	***Autologous chondrocytes***. Withdrawn by the applicant
03/2013	**ORANERA**	***Autologous oral mucosal epithelial cells***. Withdrawn by the applicant
04/2013	**MACI**	***Matrix-induced autologous chondrocyte implantation.*** Now suspended
06/2013	**PROVENGE**	***Autologous peripheral blood mononuclear cells activated with PAP-GM-CSF (sipuleucel-T)***

ChondroCelect

2.1 General description

Characterised viable autologous cartilage cells expanded *ex vivo* expressing specific marker proteins.

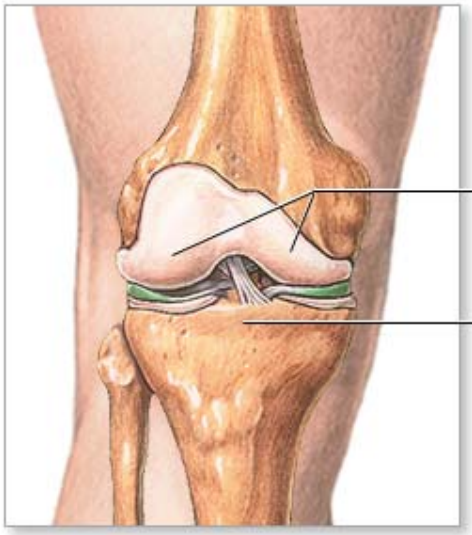
2.2 Qualitative and quantitative composition

Each vial of product contains 4 million autologous human cartilage cells in 0.4 ml cell suspension, corresponding to a concentration of 10,000 cells/microlitre.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

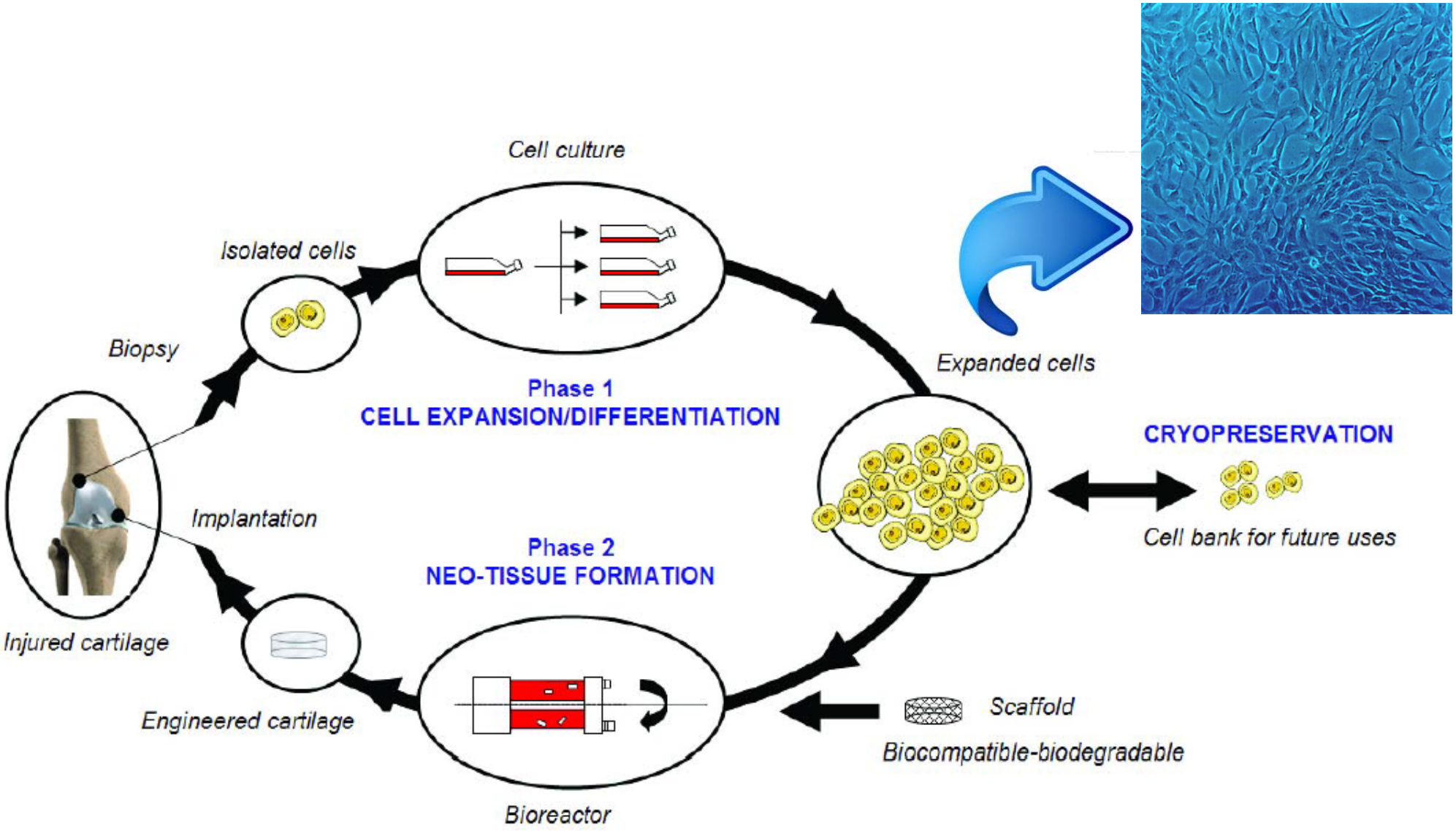
Implantation suspension
Before re-suspension the cells are settled to the bottom of the the excipient is a clear colourless liquid.

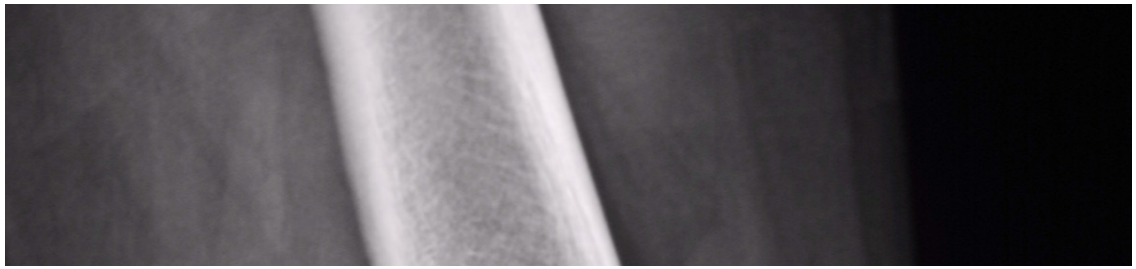


4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Repair of single symptomatic cartilage defects of the femoral condyle of the knee (International Cartilage Repair Society [ICRS] grade III or IV) in adults. Concomitant asymptomatic cartilage lesions (ICRS grade I or II) might be present. Demonstration of efficacy is based on a randomised controlled trial evaluating the efficacy of Chondrocelect in patients with lesions between 1-5cm².

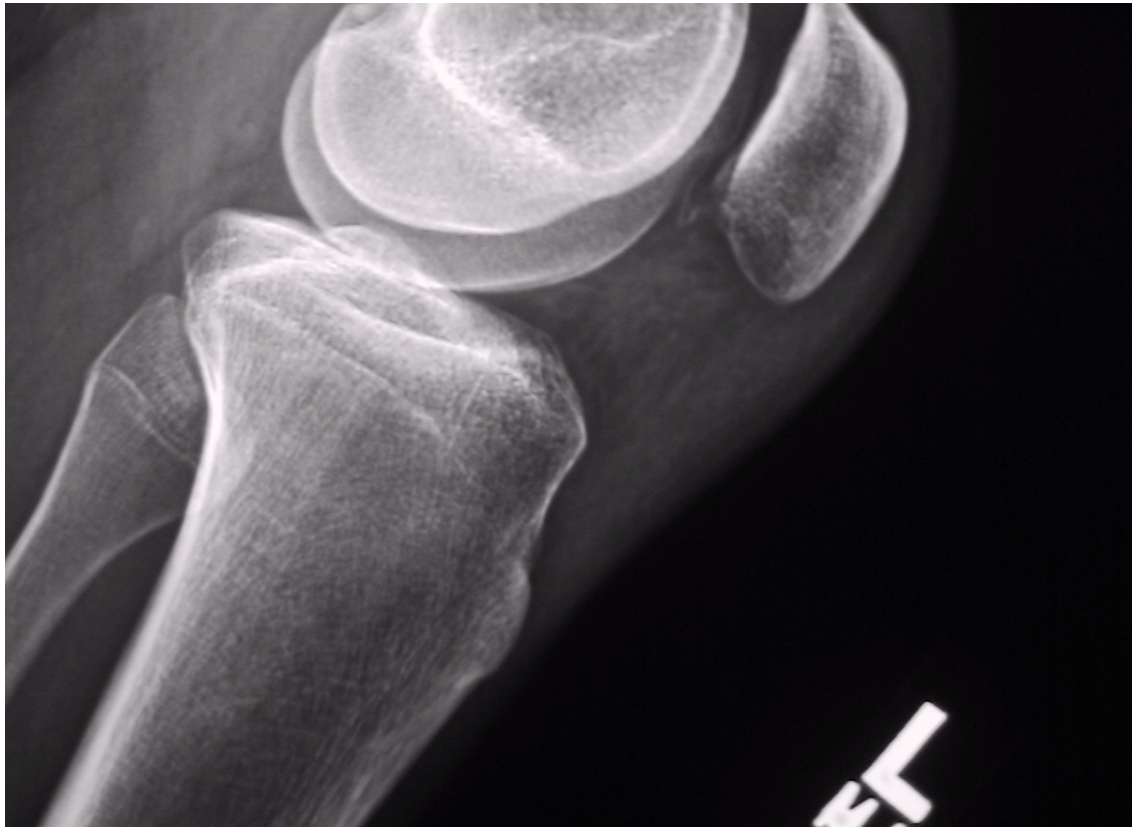

Cell culture
Isolated cells
Biopsy
Injured cartilage
Implantation
Engineered cartilage
Bioreactor
Phase 1
CELL EXPANSION/DIFFERENTIATION
Phase 2
NEO-TISSUE FORMATION
Expanded cells
CRYOPRESERVATION
Cell bank for future uses
Scaffold
Biocompatible-biodegradable



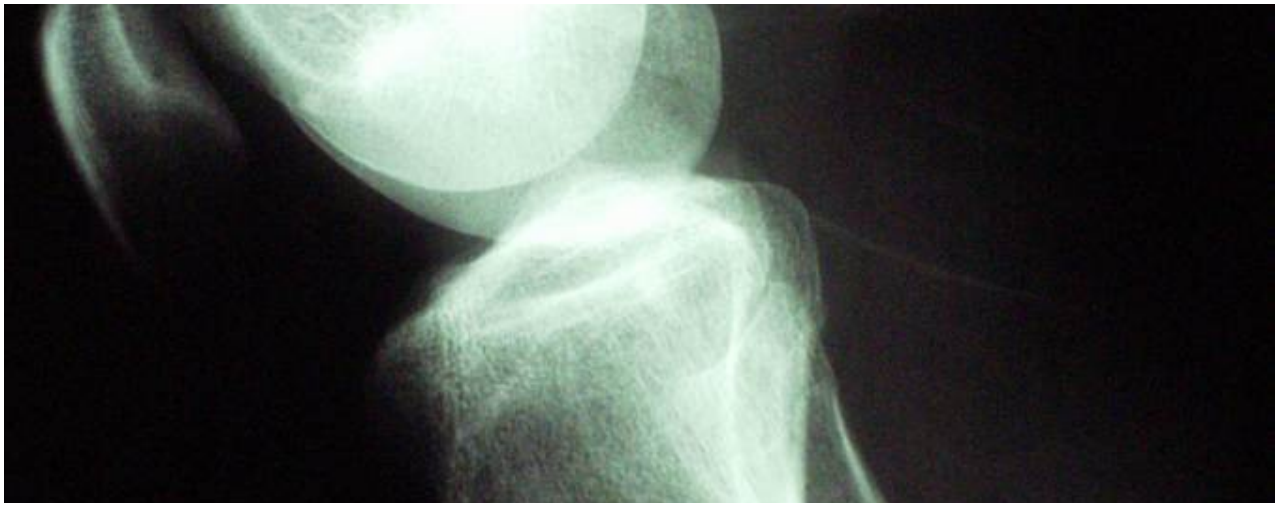
Clinical efficacy

- Dose response study(ies)

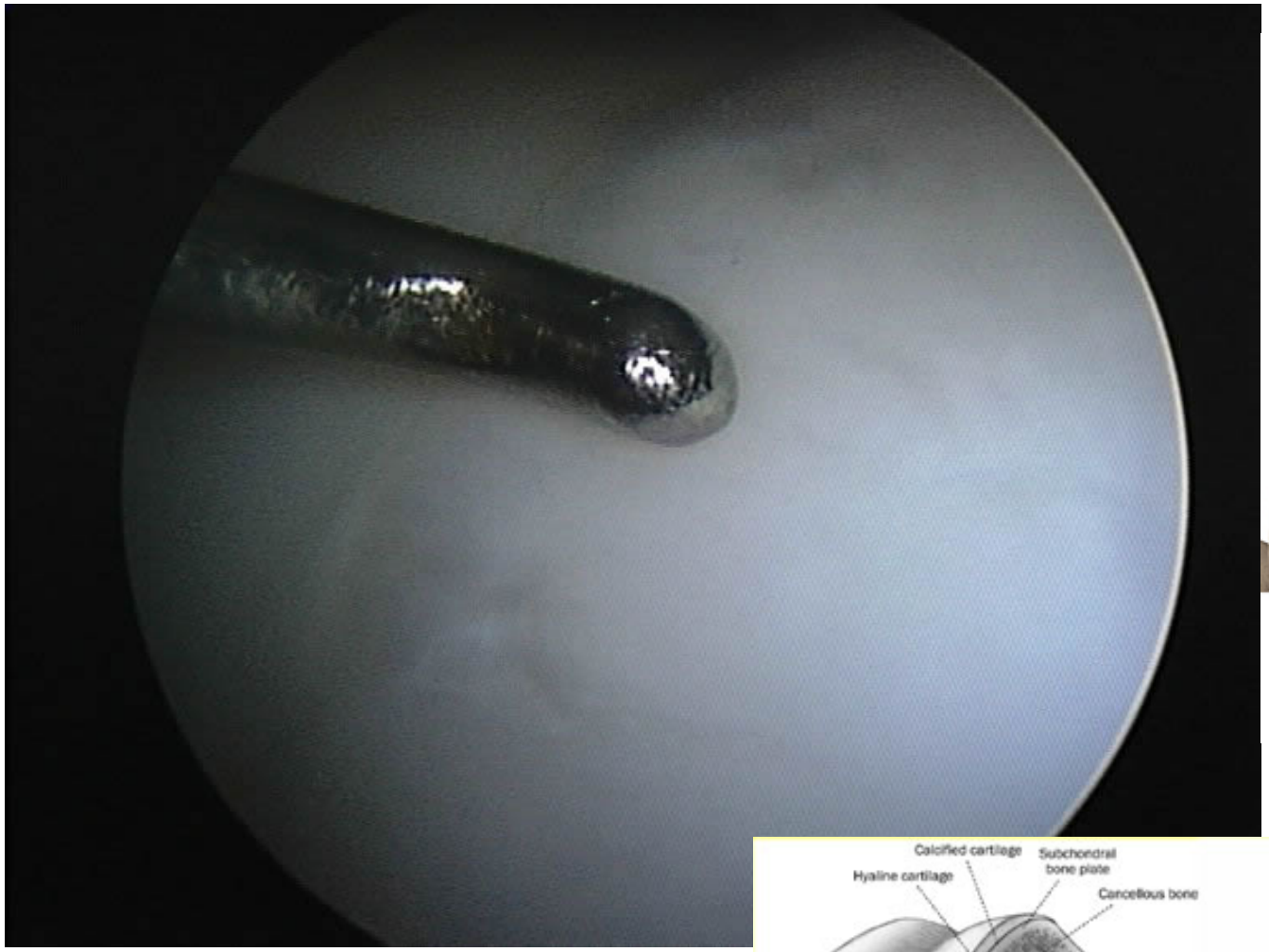
No dose-response studies have been performed. The dose selection was based on a combination of animal studies conducted by TiGenix, published literature and experience in humans with ACI. On the basis of this information the dose of between 0.8 and 1 × 10^6 cells/cm^2 was used.

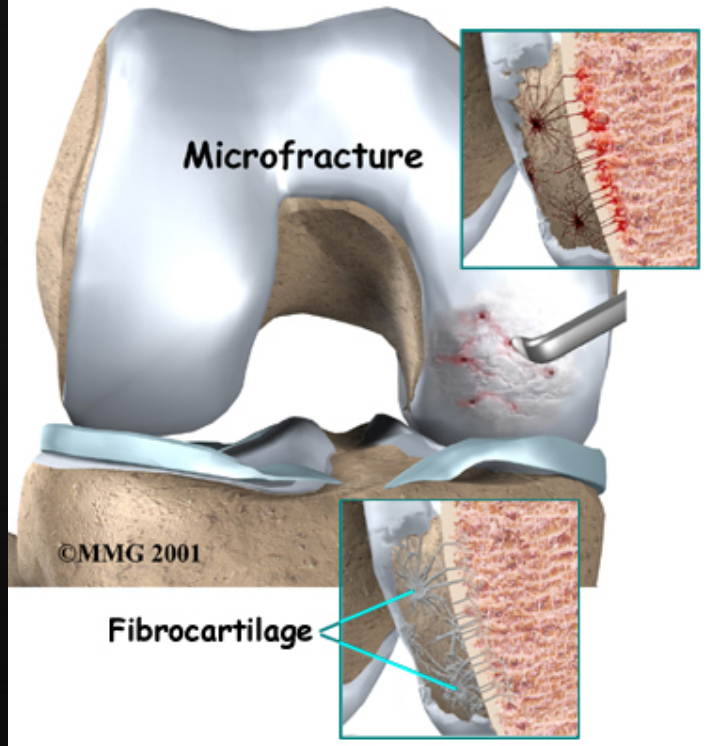


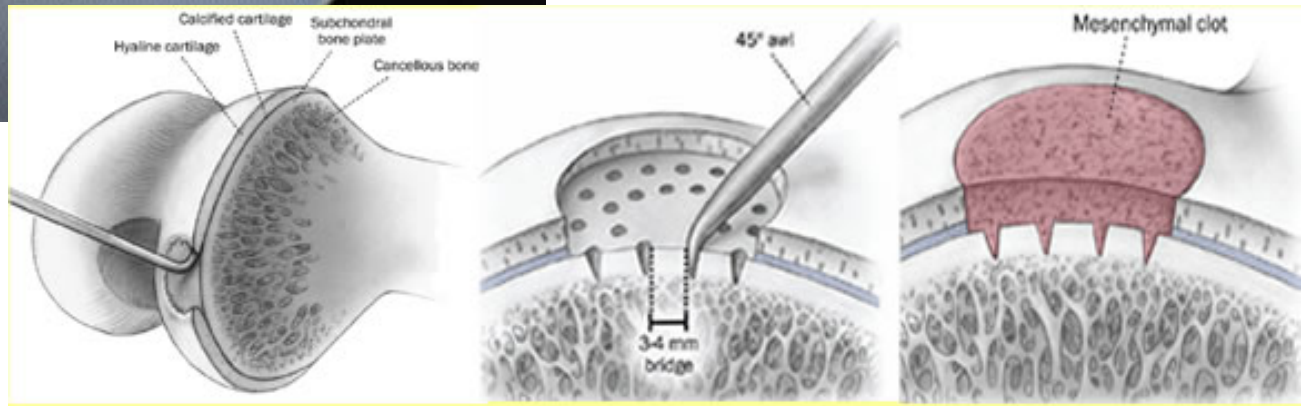
The modified **primary objectives** of the study included the following structural and clinical objectives: To show an advantage of ChondroCelect compared with microfracture in the treatment of symptomatic cartilaginous defects of the femoral condyle of the knee by demonstrating superiority on the structural repair (histology) endpoint at 12 months and non-inferiority on the clinical endpoint (change from baseline in KOOS) for the average of the 12- to 18-months follow-up data. Due, firstly, to the more complex nature of ACI compared with microfracture and associated safety issues, secondly, due to the fact that very limited data exists on the efficacy of MF, in particular in the long term setting, and thirdly, due to the fact that the relevance, both short term and long term, of the structural findings has not been established, CHMP Scientific advice (EMEA/151996/2006) recommended that it is of importance to establish the superiority of ACI.



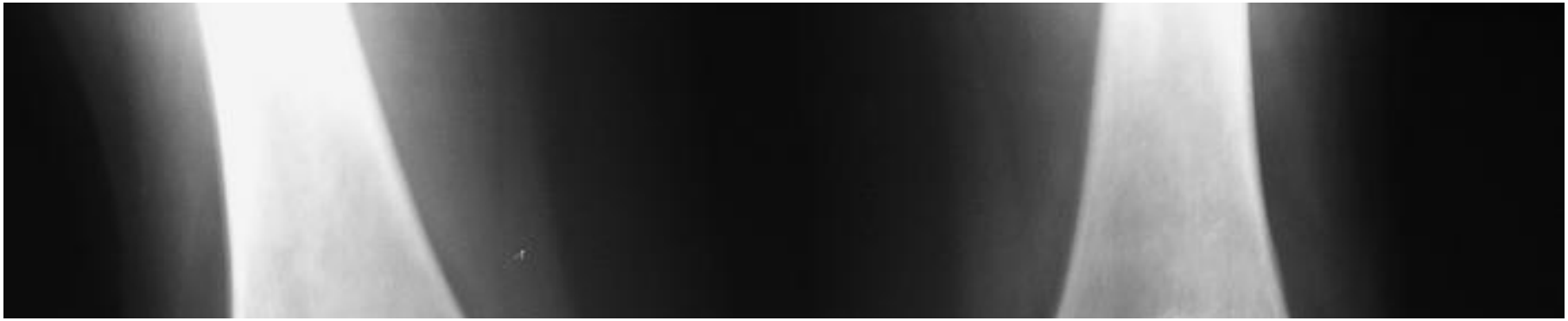
meaningful primary endpoint should be used. Therefore, the Applicant decided to follow CHMP Scientific Advice and to select overall KOOS (The Knee Injury and Osteoarthritis Outcome Score, 1998) for the second primary efficacy endpoint. This questionnaire-based endpoint has five separately scored subscales: 1) pain; 2) other symptoms such as swelling, restricted range of motion and mechanical restrictions; 3) function in daily living; 4) function in sport and recreation; 5) knee-related Quality of Life. At the ad-hoc expert group that was convened on 13th of October 2008, the experts







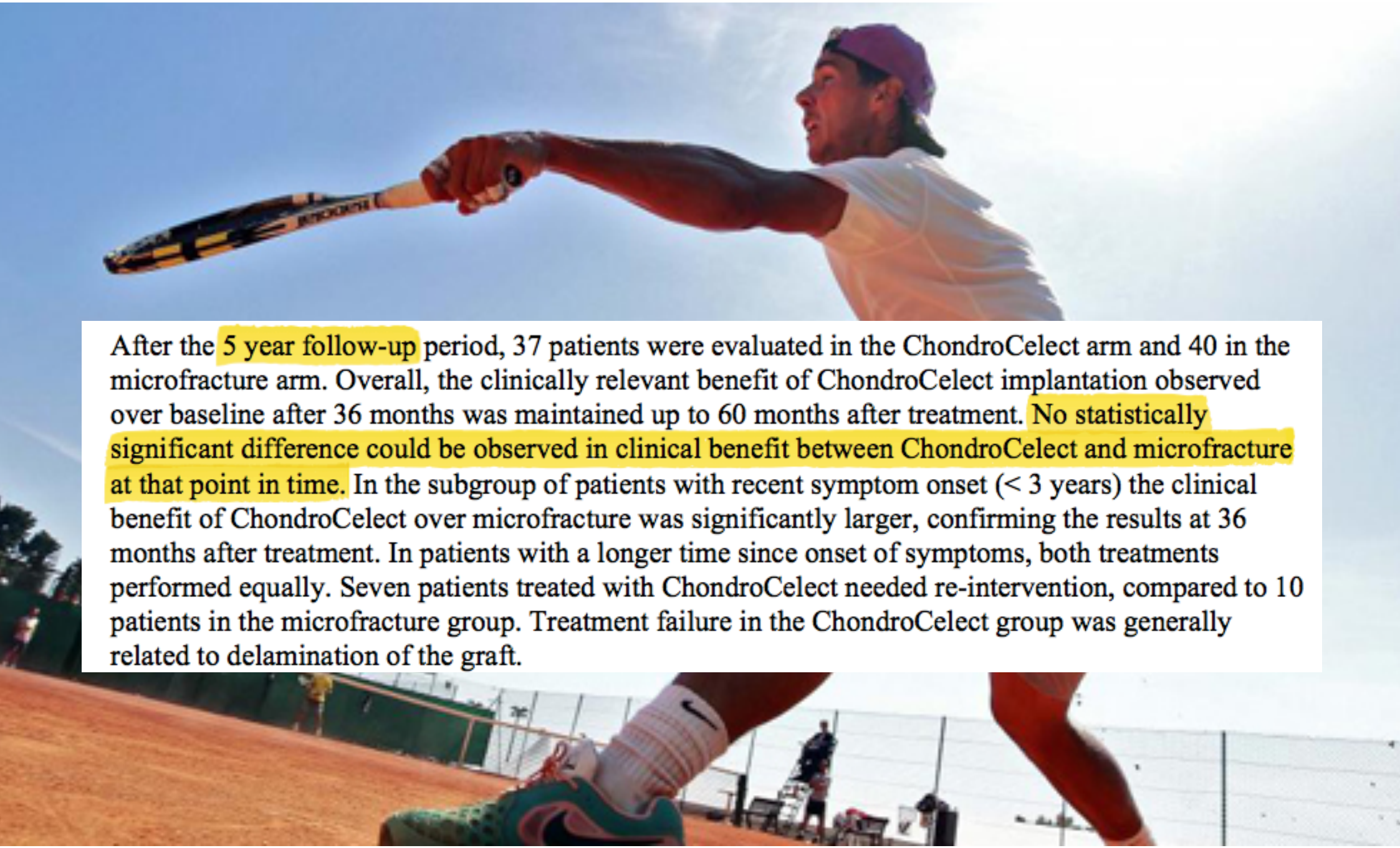
Microfracture - The defect is scraped clean. Small holes are punched in the exposed bone. Clot forms in the defect and matures into new joint lining



Clinical efficacy

The efficacy of ChondroCelect was studied in a phase III, multicenter, randomized, controlled trial (TIG/ACT/01/2000) and the first two years of its 4-years extension phase (TIG/ACT/01/2000EXT). ChondroCelect was compared to the procedure of microfracture in the repair of symptomatic single cartilage lesions of the femoral condyles of the knee. 51 patients were treated with ChondroCelect, 61 patients were treated with microfracture. Patients aged between 18 and 50 years, who had a single symptomatic cartilage lesion between 1 and 5 cm^2 of the femoral condyles met the inclusion criteria. Patients could be treatment-naïve or might have undergone previous arthroscopic or other surgical repair procedure(s). Patients with patellofemoral cartilage lesion, OCD, depth of lesion >0.5 cm, prior meniscal transplant, prior mosaicplasty and prior microfracture within the last 12 month were excluded. Patients had to agree to actively participate in a strict rehabilitation protocol and follow-up program.

Histological examination of the repair biopsy at 12 months showed superior structural repair in the ChondroCelect arm compared to the microfracture arm. There was continuous improvement up to 36 months in the clinical outcome measure KOOS (the Knee Injury and Osteoarthritis Outcome Score) in both treatment arms. The estimated benefit was larger in the ChondroCelect group but the results did not reach statistical significance. At this time point 41 patients were evaluated in the ChondroCelect arm and 49 were evaluated in the microfracture arm. Patients with less than 3 years since onset of symptoms (n=27 in the ChondroCelect arm and n=32 in the microfracture arm) benefited most from ChondroCelect. For the group with a longer time since onset of symptoms there were no apparent differences between the 2 groups. Re-intervention on the treated lesion for graft delamination or periost loosening occurred in 2 of 51 patients within 36 months after ChondroCelect implantation, compared to 7 of 61 patients treated with microfracture having generally insufficient or inadequate cartilage repair.



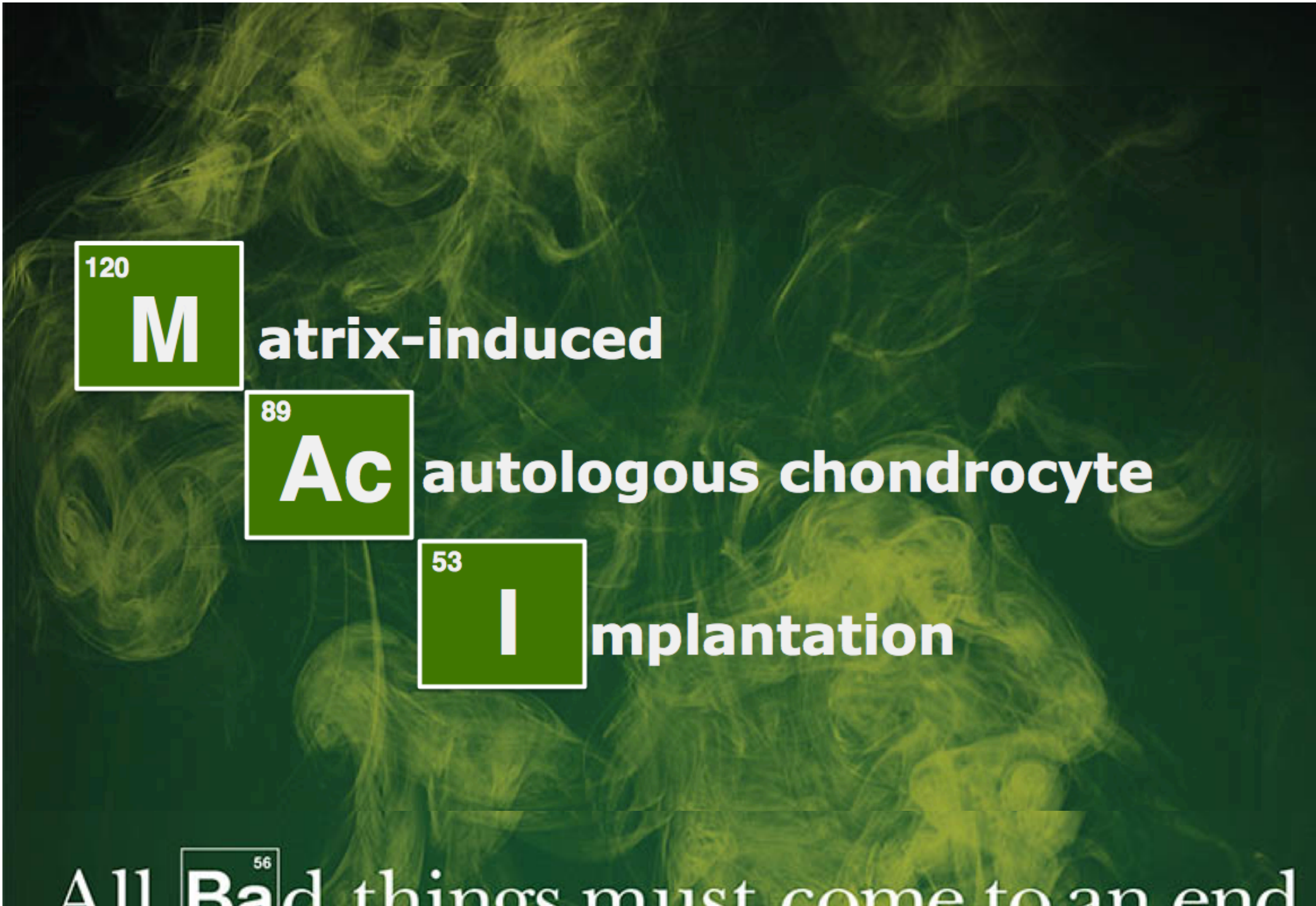
After the 5 year follow-up period, 37 patients were evaluated in the ChondroCelect arm and 40 in the microfracture arm. Overall, the clinically relevant benefit of ChondroCelect implantation observed over baseline after 36 months was maintained up to 60 months after treatment. No statistically significant difference could be observed in clinical benefit between ChondroCelect and microfracture at that point in time. In the subgroup of patients with recent symptom onset (< 3 years) the clinical benefit of ChondroCelect over microfracture was significantly larger, confirming the results at 36 months after treatment. In patients with a longer time since onset of symptoms, both treatments performed equally. Seven patients treated with ChondroCelect needed re-intervention, compared to 10 patients in the microfracture group. Treatment failure in the ChondroCelect group was generally related to delamination of the graft.

Safety

The overall safety summary shows that the main difference in treatment related adverse events compared to microfracture is related to the open knee surgery (arthrotomy) which causes an increase in joint swelling and possible joint effusion. Cartilage hypertrophy can be reduced by using a biomembrane to cover the lesion, and will therefore not pose a major safety concern in future applications of ChondroCelect. However, a higher number of patients in the microfracture arm have a treatment failure and require a subsequent surgical intervention. Therefore the short and long term complication rate is not higher for ChondroCelect compared to microfracture.
The Applicant has presented an acceptable RMP including a proposal for a confirmatory randomized controlled trial and an observational follow-up study.

In the Risk Management Plan, the MAH commits to confirm and extend the pivotal clinical study data with an appropriately designed trial. The design should be subject to EMEA Scientific Advice, and agreed with the CAT.

In the Risk Management Plan, the MAH also commits to further study efficacy and safety of ChondroCelect in large lesions. The design of such a study should be subject to EMEA Scientific Advice, and agreed with the CAT.


120
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d things must come to an end

1. NAME OF THE MEDICINAL PRODUCT

MACI 500,000 to 1,000,000 cells/cm^2 implantation matrix

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each implant contains matrix applied characterised autologous cultured chondrocytes.

2.1 General description

Characterised viable autologous chondrocytes expanded *ex vivo* expressing chondrocyte-specific marker genes, seeded onto a CE marked porcine derived Type I/III collagen membrane.

2.2 Qualitative and quantitative composition

Each implantation matrix consists of characterised autologous chondrocytes on a 14.5 cm^2 Type I/III collagen membrane, at a density of 500,000 to 1,000,000 cells per cm^2, to be trimmed by the surgeon to the size and shape of the defect.

4.1 Therapeutic indications

MACI is indicated for the repair of symptomatic, full-thickness cartilage defects of the knee (grade III and IV of the Modified Outerbridge Scale) of 3-20 cm^2 in skeletally mature adult patients.

MACI has been investigated in a parallel, randomised, open-label trial in 144 patients with Outerbridge Grade III or IV focal cartilage defects of the knee of 3-20 cm^2 (median 4 cm^2). Seventy-two patients received MACI, and 72 were treated with microfracture. The median age of patients was 34 to 35 years (age range: 18 to 54), and the mean body mass index was 26. The majority of patients had undergone at least 1 prior orthopaedic knee surgery. MACI was superior compared to microfracture regarding the improvement of pain and function according to the KOOS scale (Knee Injury and Osteoarthritis Outcome Score). See responder rates in Table 1 below.

Four patients were treatment failures in the microfracture treatment arm, versus one in the MACI treatment arm. There were no significant differences observed in the structural markers of cartilage repair between both treatments, as assessed by International Cartilage Repair Society (ICRS) II overall assessment histology scores of biopsies, and MRI defect fill scores.

Table 1: KOOS Response Rate*: Full Analysis Set

n (%)	MACI N=72	Microfracture N=72	p-value
Visit 10 (Week 104) Stratified by centre			
Responded	63 (87.50)	49 (68.06)	0.016
Not Responded	9 (12.50)	20 (27.78)	
Missing	0	3 (4.17)	
Visit 10 (Week 104) Unstratified			
Responded	62 (86.11)	48 (66.67)	0.011
Not Responded	7 (9.72)	18 (25.00)	
Missing	3 (4.17)	6 (8.33)	

* KOOS Response Rate: Responder is defined as an improvement of the Knee Injury and Osteoarthritis Outcome Score from baseline of minimal 10 points of a scale of 100.

It was noted by the Committees that MACI and microfracture treatment did not show statistically significant differences with regard to the structural endpoints, infill of defects as assessed by MRI and the quality of repair tissue as assessed by the histology score. The hypothesis that MACI leads to superior quality of hyaline cartilage repair compared to non-transplantation techniques like microfracture has thus not been established. There is generally no consensus on whether structural repair as measured by MRI or histology scoring systems is able to distinguish the true functional repair of cartilage defects, and hence be a meaningful surrogate for clinical outcomes. Consequently, in the view of the Committees improvements in the clinical outcomes of pain and function, as observed in the study, remain the most clinically valid endpoints in cartilage repair studies.

Two types of important unfavourable effects were identified, those related to the MACI implant and those related to peri-operative complications. In the main clinical study, fewer patients treated with MACI reported treatment-emergent (serious) adverse events than those treated with microfracture, despite MACI requiring two surgical procedures. The difference in incidence of treatment-emergent serious adverse events was mainly due to more serious cases of treatment failure, cartilage injury and arthralgia in the microfracture group compared with MACI. The results of the SUMMIT study are consistent with the known safety profile for MACI, including the safety information reported in the published literature. Overall, based on the exposure of more than 6,000 patients to MACI, the two main risks related to MACI are symptomatic graft hypertrophy and graft delamination (complete or partial, possibly leading to loose bodies in the joint or graft failure). No case of graft hypertrophy was seen with MACI in this study while one case of delamination was observed. The risks related to peri-operative complications of surgical intervention of the knee are haemarthrosis, arthrofibrosis, localised surgical site inflammation, localised surgical site infection or thromboembolic events. The SmPC

Results and Analysis			
Analysis description	**Primary Analysis**		
Analysis population and time point description	Full analysis set 2years		
Descriptive statistics and estimate variability	Treatment group	MACI	MF
	Number of subject	72	72
	Co-Primary endpoint - Pain - Function Means At week 104	 82.45 60.9	 70.85 48.71
	SD	16.18 27.84	24.22 30.33
	Histology Overall score Week 104	64.3	64.5
	SD	22.34	22.78
	MRI Degree of defect fill 76-100% Week 104	35	41
	SD	48.6	58.9

Effect estimate per comparison	Co-Primary endpoint	Comparison groups	MACI vs MF
		Difference LS means - Pain - Function	 11.76 11.41
		P-value	0.001
	Secondary endpoint: Histology	Comparison groups	MACI vs MF
		Difference LS means	1.52
		P-value	0.717
	Secondary endpoint: MRI	Comparison groups	MACI vs MF
		Weighted kappa	0.571
		95% CI	0.421, 0.722
		P-value	0.920

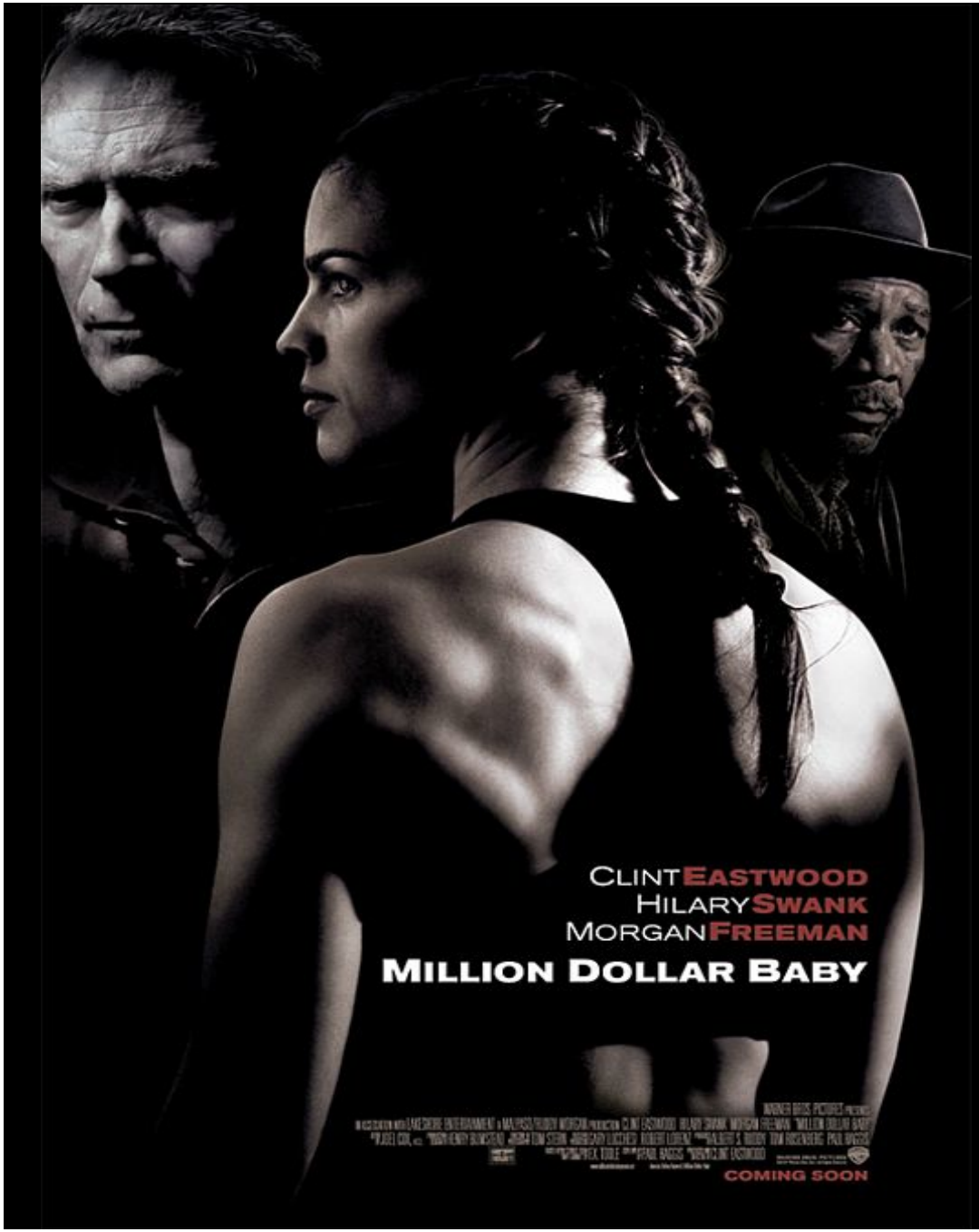
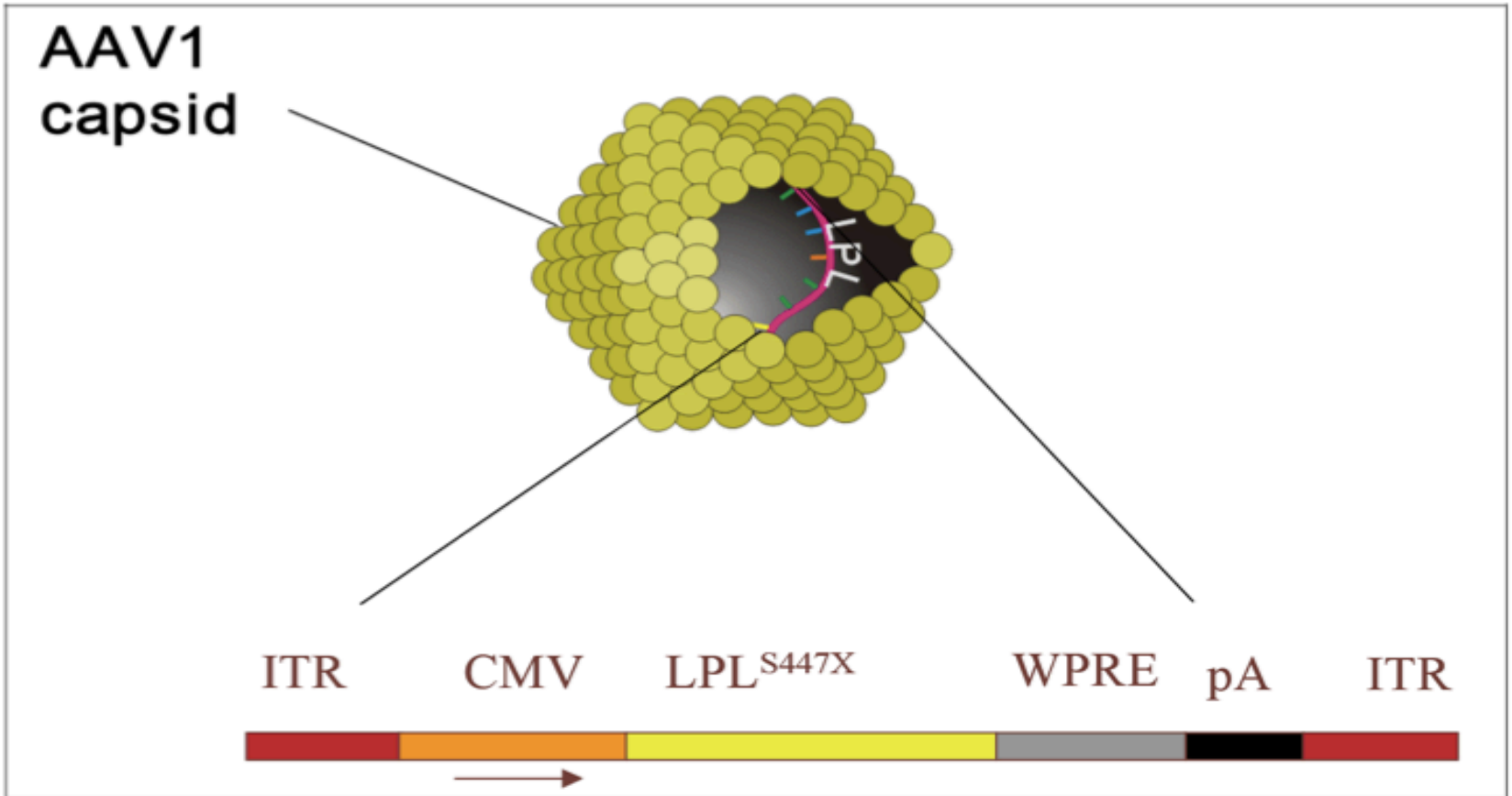

CLINT EASTWOOD
HILARY SWANK
MORGAN FREEMAN
MILLION DOLLAR BABY
COMING SOON

Figure: Structure of Alipogene tiparvovec



ITR: inverted terminal repeat derived from AAV2

CMV: cytomegalovirus immediate early promoter

LPL^{S447X}: cDNA for lipoprotein lipase variant S447X

WPRE: Woodchuck hepatitis virus posttranscriptional regulatory element

pA: bovine growth hormone polyadenylation site.

1. NAME OF THE MEDICINAL PRODUCT

Glybera 3 × 10^{12} genome copies/ml solution for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

2.1 General description

Alipogene tiparvovec contains the human lipoprotein lipase (LPL) gene variant LPL^{S447X} in a vector. The vector comprises a protein shell derived from adeno-associated virus serotype 1 (AAV1), the Cytomegalovirus (CMV) promoter, a woodchuck hepatitis virus posttranscriptional regulatory element and AAV2 derived inverted terminal repeats. Alipogene tiparvovec is produced using insect cells and recombinant baculovirus technology.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Glybera is indicated for adult patients diagnosed with familial lipoprotein lipase deficiency (LPLD) and suffering from severe or multiple pancreatitis attacks despite dietary fat restrictions. The diagnosis of LPLD has to be confirmed by genetic testing. The indication is restricted to patients with detectable levels of LPL protein (see section 4.4).

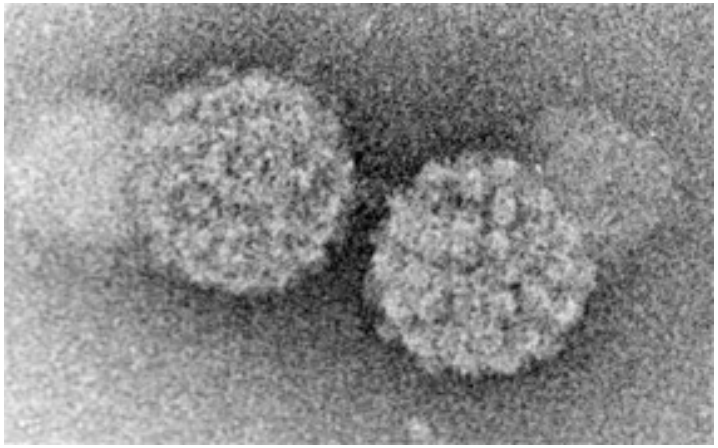
Tabular overview of clinical studies

Study number	Dose (gc/kg)	Number of patients	Duration of monitoring	Duration of follow-up	Status
PREPARATION-01	None	18	13 – 78 weeks	-	Completed
AMT-010-01	1×10^{11} 3×10^{11}	4 4	12 weeks	5 years	Active phase completed, follow-up ongoing
PREPARATION-02	None	22	2 – 83 weeks	-	Completed
AMT-011-01	3×10^{11} 1×10^{12}	6 8	12 weeks	5 years[a]	Active phase completed, follow-up ongoing
AMT-011-02	1×10^{12}	5	18 weeks (incl. 4 weeks run-in)	1 year	Completed

[a] plus 10 years of annual safety and efficacy monitoring through the LPLD registry

Table 1 | **Pivotal data for authorized treatments in ultra-rare conditions***

Authorized therapeutic indication	Prevalence (per 10,000)	Medicinal product (generic name)	Date of marketing authorization	End points used	Duration of pivotal study	Size of pivotal study or studies	Disease characteristics
Hyper-ammonaemia	0.001	Carbaglu (carglumic acid)	24/01/2003	Biochemical and clinical course, including growth and survival	N/A	20	Progressive disease (metabolic)
Splenomegaly in myelofibrosis	0.01	Jakavi (ruxolitinib)	23/08/2012	Number of patients with ≥ 35% spleen volume reduction at week 24	24 weeks	219	Progressive disease (haematological)
Lipoprotein lipase (LPL) deficiency	0.02	Glybera (alipogene tiparvovec)	25/10/2012	Reduction in fasting plasma triglyceride levels; additional end points included chylomicron-related end points and reduction in frequency and/or severity of clinical signs and symptoms related to LPL deficiency including pancreatitis	N/A (variable)	14 and 5	Fluctuating clinical course (metabolic)
Hunter syndrome	0.02	Elaprase (idursulfase)	08/01/2007	6-minute walk test, percentage predicted FVC (baseline to week 53)	12 months	96	Progressive disease (organ impairment)
Mucopolysaccha-ridosis VI	0.024	Naglazyme (galsulfase)	24/01/2006	12-minute walk test over time (week 6, 12, 18, 24)	24 weeks	39	Progressive disease (organ impairment)
Mucopolysaccha-ridosis I	0.025	Aldurazyme (laronidase)	10/06/2003	6-minute walk test, percentage predicted FVC (baseline to week 26)	26 weeks	45	Progressive disease (organ impairment)
Fabry disease	0.027	Fabrazyme (agalsidase beta)	03/08/2001	Reduction of GL3 accumulation from the capillary endothelium of the kidney to score 0 at week 20	20 weeks	58	Progressive disease (organ impairment)



2.4.5. Conclusions on clinical pharmacology

No specific pharmacodynamic studies were carried out. It is however expected that transgene expression will be accompanied by a reliably established relationship with at least one pharmacodynamic parameter, such as correlation with CM, fasting TG levels or change in the disposition of lipoprotein particles.

Evidence that the PK and PD effects of treatment are correlated at an individual subject level, such that individuals with increased LPL expression and increased LPL activity are also those who have a reduction in fasting TG and in post-prandial CM levels are required for interpretation of the clinical effects.

2.5.8. Conclusions on the clinical efficacy

Given the rarity of LPLD (prevalence in the EU: 2:1000000), the uncontrolled study design applied in all 3 clinical trials subjects as their own control, is accepted and in line with the scientific advice given.

The efficacy of Glybera has not been satisfactorily demonstrated. Plasma TG concentrations >10 mmol/l are critical levels for development of pancreatitis. Neither a sustained reduction in individual median fasting plasma triglycerides under this level i.e. to a level ≤10 mmol/l in addition to diet could be achieved. Furthermore, the reduction in fasting plasma triglycerides is not maintained over time.

Initially, fasting whole plasma triglyceride levels were chosen as the primary efficacy endpoint: initially a level of less than 10mol/l, and subsequently a reduction in fasting TGs of 40% from baseline. Neither of these proposed endpoints were met. The applicant then argued that the evaluation of fasting TG was no longer a reliable read-out of the Glybera efficacy and proposed an alternative surrogate marker of efficacy (post-prandial chylomicronemia). The CAT considered that a reduction in post prandial CM could be accepted as a surrogate marker for efficacy subject to clinical validation. However methodological issues, including the lack of controls were highlighted.

The limited data provided on post-prandial chylomicronemia (n=3 at 52 weeks) is insufficient, and data on all patients would be required. In addition a link or trend between the surrogate efficacy marker of post prandial CM and incidence of pancreatitis is required as post prandial CM is not a clinically validated surrogate endpoint at present. The interpretation of reported treatment effects on pancreatitis are hampered by several methodological deficiencies of the clinical development program. Reduction in Quality of Life in 60% patients in whom it was assessed following treatment with Glybera is also of major concern.

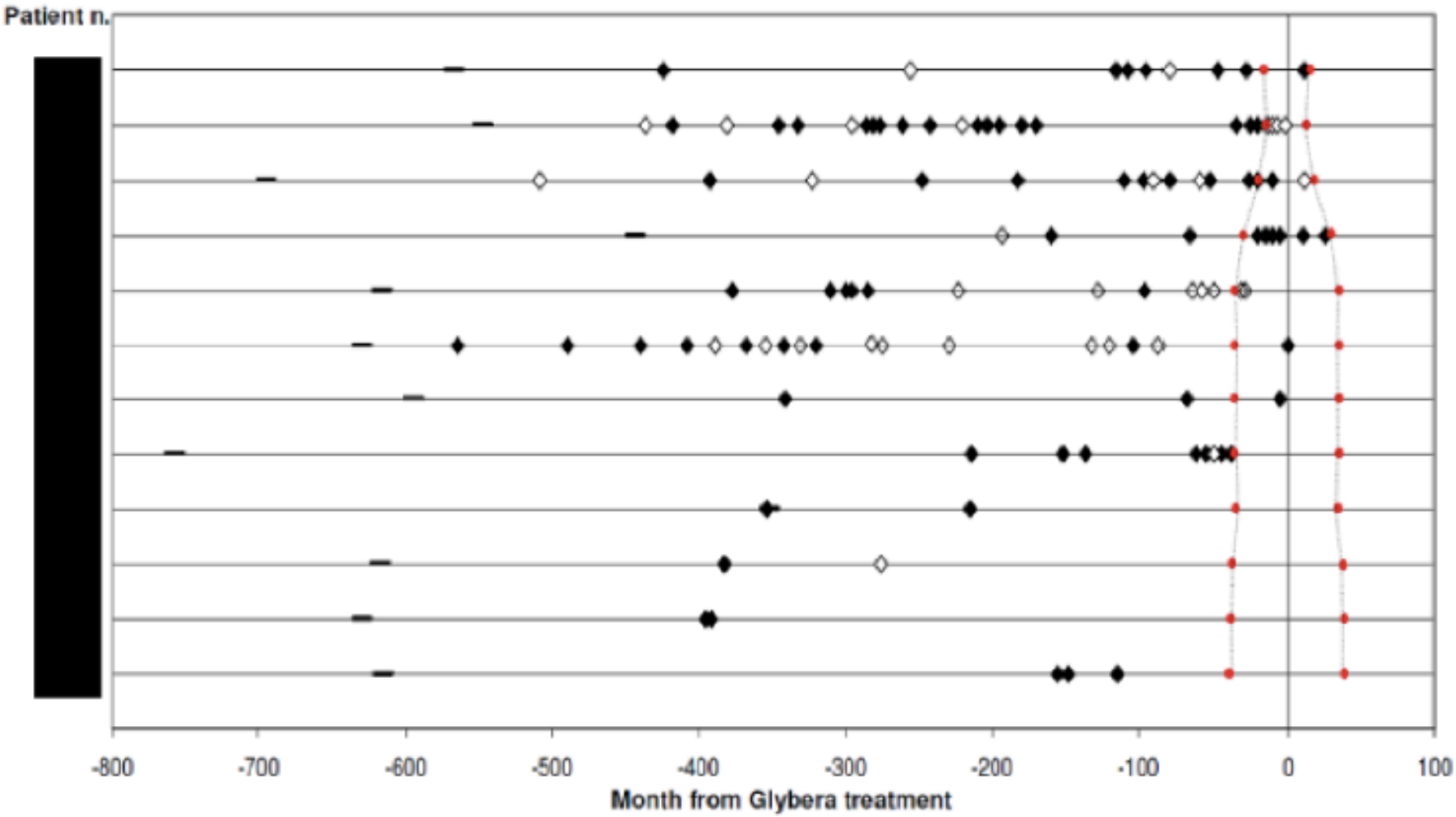
The effect of Glybera on fasting TG was short-term and gradually disappeared with fasting triglycerides reverting to baseline levels after 1 year. Glybera failed to show demonstration on a long term sustained effect for this chronic condition.

The limited data provided on three patients at 52 weeks on postprandial chylomicrons levels together with missing information on intra –inter patient variability inppCM measurement precludes any firm conclusion on this surrogate marker which is not clinically validated at present.

No correlation has been shown on reduction in post prandial chylomicrons with lipoprotein lipase activity or fasting triglycerides. No quality of life at 52 weeks was provided for these patients, which is considered an additional limitation.

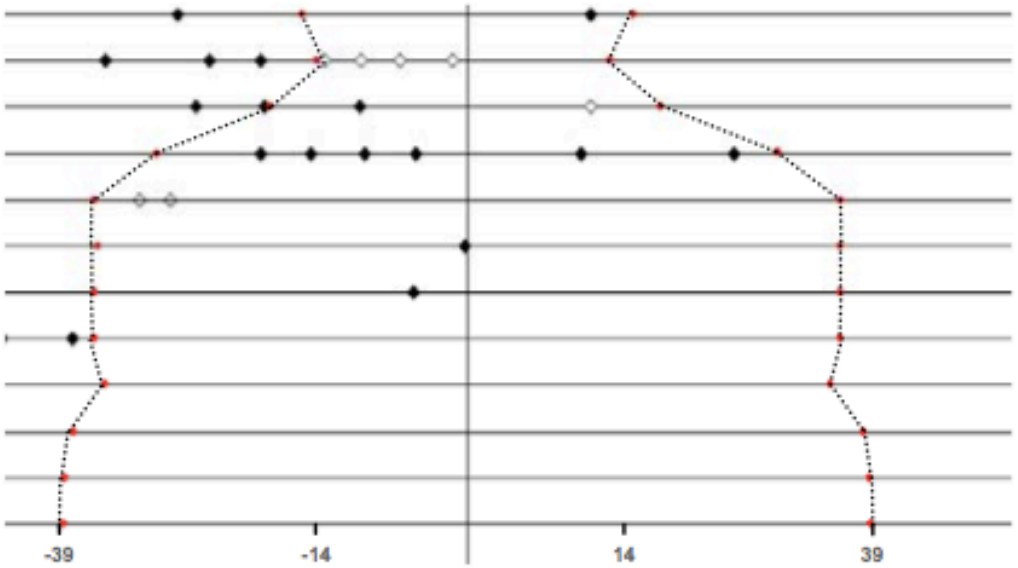
Furthermore, Glybera failed to show any clinically meaningful effect on organomegaly, lipaemia retinalis and xanthomata across all conducted studies.

Figure 1 - Definite and probable pancreatitis events per patient



Patients with multiple attacks

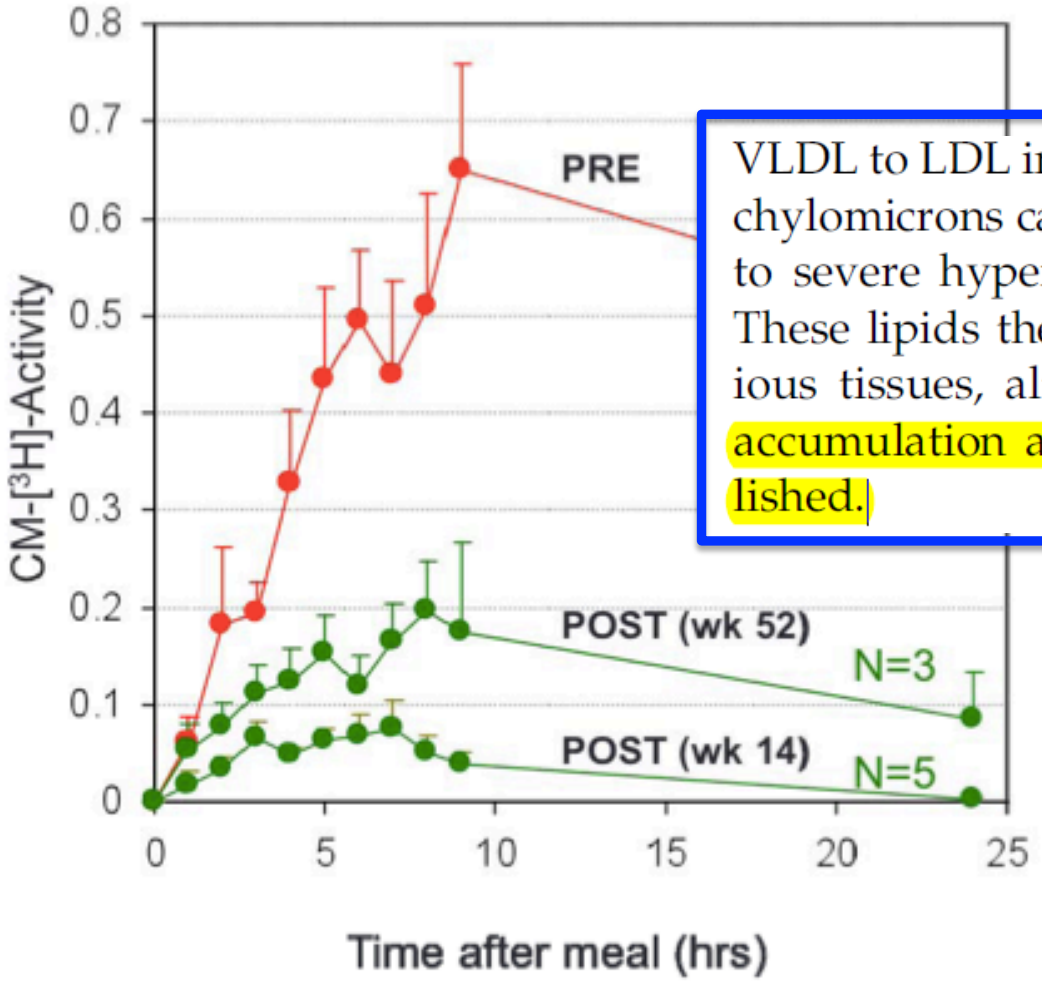
Definite and probable pancreatitis events per patient enlargement of the ± FU period area



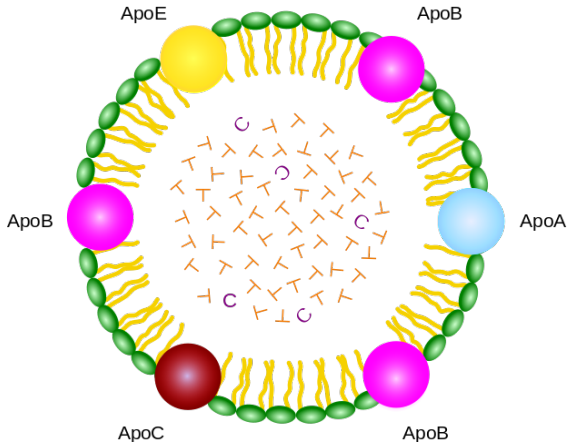
Month from Glybera treatment

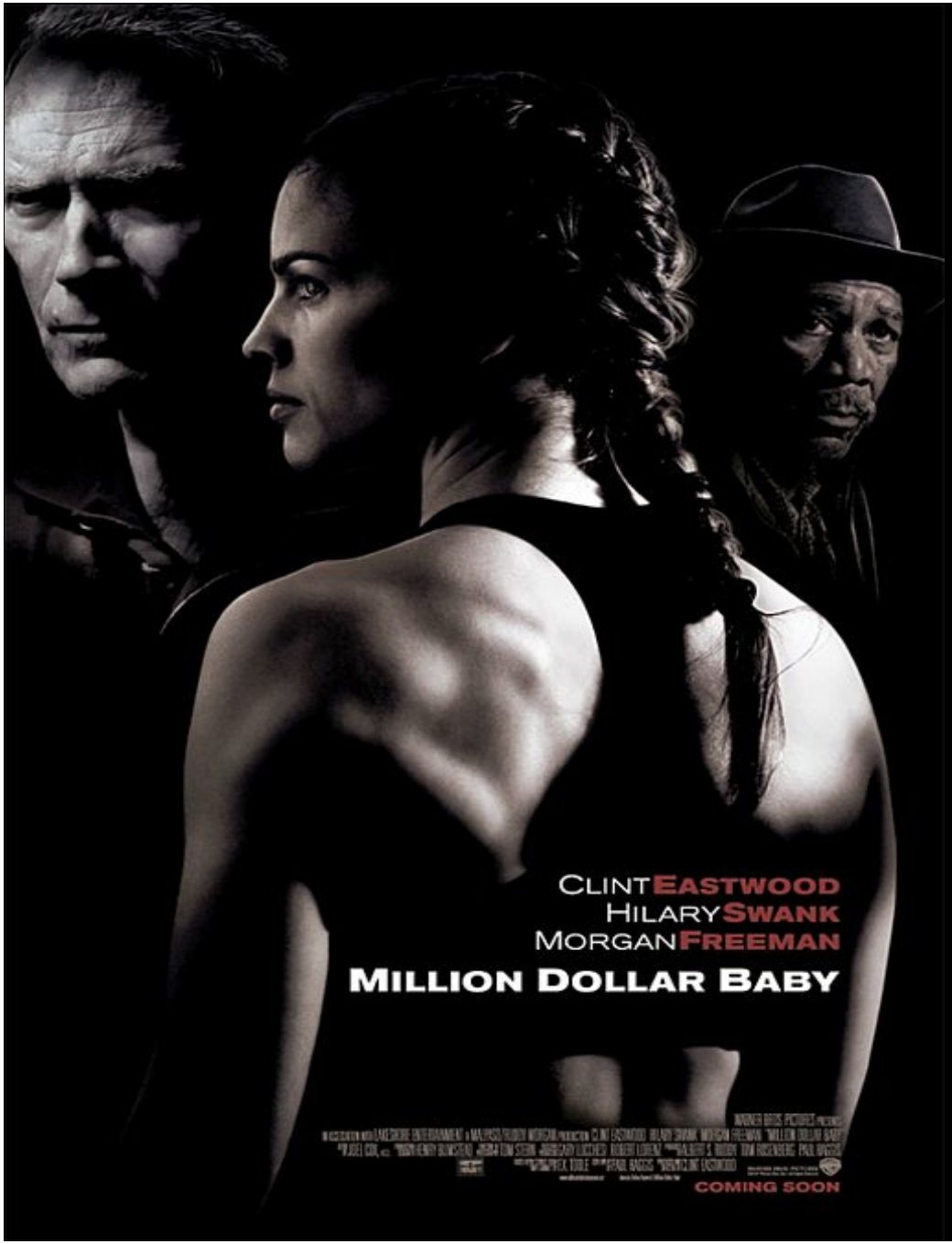
◆ Definite
◇ Probable
● ± FU period from Glybera

Figure 1: Postprandial Metabolism of Newly-formed Chylomicrons



VLDL to LDL in the plasma (Mead *et al.*, 2002). Without LPL, chylomicrons cannot be depleted of their dietary fats, leading to severe hypertriglyceridemia and hyperchylomicronemia. These lipids then accumulate and lead to pathology in various tissues, although the exact relationship between lipid accumulation and disease presentation has not been established.

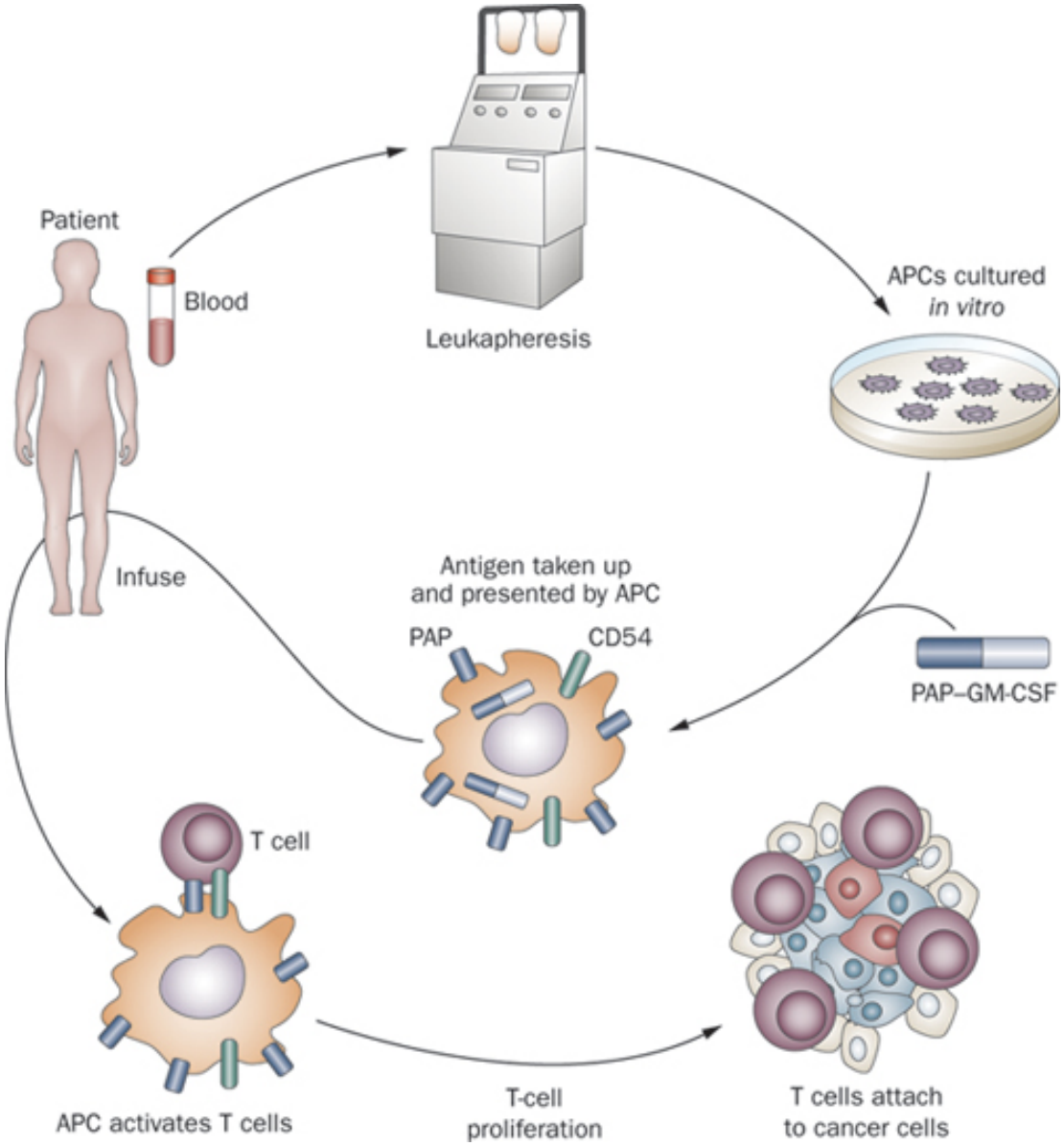




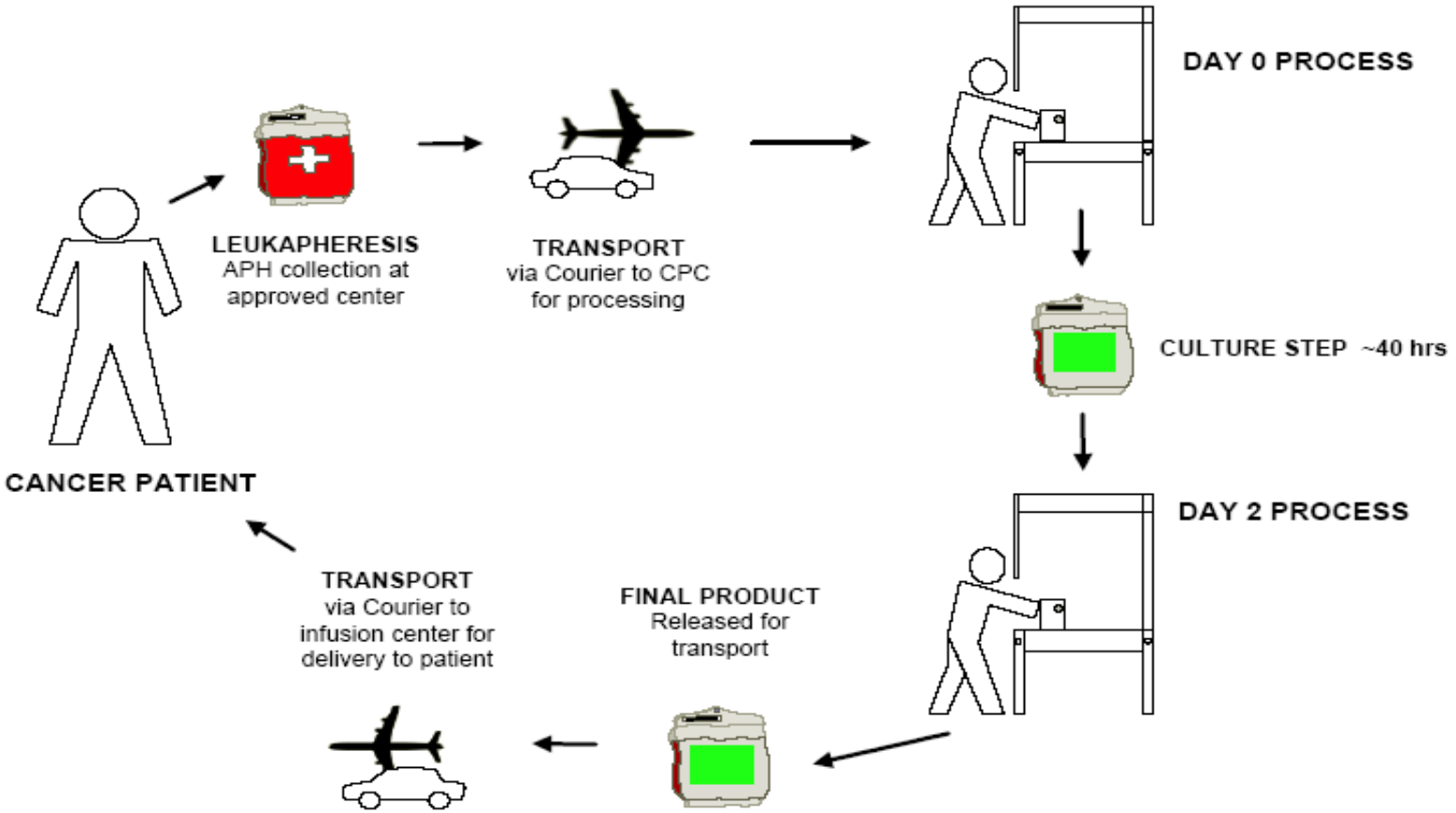
GLYBERA

The need for a single treatment marks a divide between Glybera and enzyme replacement therapies for similar inherited enzyme deficiency disorders, which must be administered on a chronic basis. Marketed enzyme replacement therapies cost between €150,000 and €450,000 per patient, per annum, and Aldag thinks the pricing for Glybera should be a multiple of some price in that range to reflect the fact that a one off-treatment with Glybera has an effect that lasts over years (BioWorld).

provenge


Patient
Blood
Leukapheresis
APCs cultured
in vitro
Infuse
Antigen taken up
and presented by APC
PAP
CD54
PAP–GM-CSF
T cell
APC activates T cells
T-cell
proliferation
T cells attach
to cancer cells

Provenge® manufacturing process



18 hr shelf life

A
PROVENGE®
FOR AUTOLOGOUS USE ONLY
A minimum of 50 million autologous CD54+ cells activated with PAP-GM-CSF/250 mL suspension for infusion.

27 June 2013
EMA/CHMP/363851/2013
Committee for Medicinal Products for Human Use (CHMP)

Summary of opinion[1] (initial authorisation)

Provenge

Autologous peripheral blood mononuclear cells activated with PAP-GM-CSF (sipuleucel-T)

On 27 June 2013, the Committee for Medicinal Products for Human Use (CHMP) adopted a positive opinion, recommending the granting of a marketing authorisation for the medicinal product Provenge to Dendreon UK Ltd. This recommendation will now be forwarded to the European Commission, which will issue a legally binding decision.

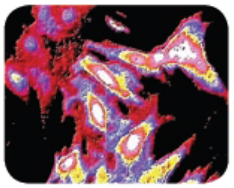
The indication recommended by the CHMP is as follows: *'Provenge is indicated for the treatment of asymptomatic or minimally symptomatic metastatic (non-visceral) castrate resistant prostate cancer in male adults in whom chemotherapy is not yet clinically indicated.'* Provenge should only be administered by physicians experienced in the treatment of prostate cancer and in an environment where resuscitation equipment is available.

The active substance of Provenge consists of autologous peripheral blood mononuclear cells activated with prostatic acid phosphatase fused with granulocyte-macrophage colony-stimulating factor (sipuleucel-T). Provenge is an immunotherapy designed to induce an immune response targeted against prostatic acid phosphatase (PAP), an antigen expressed in most prostate cancers.

Provenge will be available as a dispersion for infusion (50 x 10^6 $CD54^+$ cells/250 mL). The recommended course of treatment is 3 doses at approximately 2-week intervals. Each dose of Provenge is preceded by a standard leukapheresis procedure approximately 3 days prior to the scheduled infusion date.

IN this section

IL-1 blockers treat diabetic inflammation p533



Big suppliers sell stem cells as screening tools p535

Warning on weed resistance to glyphosate p537

Landmark approval for Dendreon's cancer vaccine

The April 29 approval of Seattle-based Dendreon's prostate cancer vaccine, Provenge (sipuleucel-T), is being hailed as a victory for cancer immunotherapy. For Dendreon, the US Food and Drug Administration's (FDA) go-ahead marks the end of a tortuous regulatory path, marked not only by missteps by the company but also by controversy at the FDA, not least the decision in 2007 by the Center for Biologics Evaluation and Research (CBER) to act against its advisory panel's positive recommendations. After the turmoil of ad campaigns critical of the agency, picketing and lobbying by patient groups, death threats, lawsuits and even calls for a Congressional investigation (*Nat. Biotechnol.* 26, 1, 2008), the FDA issued a complete response letter on the earlier trials and requested further clinical evidence of efficacy. Dendreon then soldiered on with a phase 3 placebo-controlled trial (Immunotherapy for Prostate Adenocarcinoma Treatment; IMPACT), the results of which were submitted to FDA last November. On the basis of these data, which have yet to be published in a peer-reviewed journal, the agency finally gave Provenge its imprimatur, approving the first therapeutic vaccine for use in individuals with asymptomatic, or minimally symptomatic hormone refractory metastatic

It remains unclear, however, whether Dendreon's decade-long struggle to pass regulatory muster has clarified the path of oversight for other cancer vaccines or even whether autologous cellular vaccines will rival the success of 'off-the-shelf' vaccines or other types of adjunct therapies, such as antibodies or small molecules. Therapeutic cancer vaccines are a diverse group of products; they can be cellular or acellular (peptides, proteins, DNA), be targeted against a single antigen or groups of antigens, use viruses or other scaffolds to present antigens or use patient cells or cell lines (*Nat. Biotechnol.* 27, 129–139, 2009).

Provenge, unique among cancer vaccines in late-stage clinical trials (**Table 1**), is an autologous, cell-based therapy created by incubating (activating) the patient's own antigen-presenting cells *ex vivo* with a fusion of prostatic acid phosphatase (an antigen specific to prostate tissue) and granulocyte macrophage colony-stimulating factor, which act to stimulate immune cell responses. This is a first-generation product, but it is both simpler (uses a single antigen) and more complex (works with a mélange of cells) than some of the other products under development.

Dendreon's clinical trial design and analysis of the human data have been dogged by controversy. Two early trials of Provenge showed a benefit in overall survival (OS) but not progression-free survival (PFS), which is unusual according to Don Berry, chairman of biostatistics at MD Anderson Hospital in Houston. "If something is effective in cancer, it inhibits or slows growth and this apparently does not," he says. Unfortunately for Dendreon, PFS was the primary endpoint in these early trials. The FDA refused to move the goalposts, and sent Dendreon back to gather more data, this time using OS as an endpoint in a large (512-patient) phase 3 trial, which was already underway.

Last October, Dendreon announced interim results, essentially priming the pump for investors, if not regulators. (The company raised $409.5 million in a stock offering the following month.) The release of interim results to the company by the data monitoring group was unusual, according to Susan Ellenberg of the University of Pennsylvania in Philadelphia, who led the team that wrote the guidance for placebo-controlled trials when she was at CBER. Apparently in this case it was done with the consent of the FDA. The interim data had not achieved statistical

As reported at the American Society of Clinical Oncology (ASCO) 2010 Genitourinary Cancers Symposium, held March 5–7 in San Francisco, three-year OS rates were 38% higher among men who received the drug than those who received placebo. Provenge showed a median OS benefit of 4.1 months compared with the placebo ($P = 0.032$).

On the basis of these results, the FDA declined to convene an advisory panel, although rumors circulated in March that one might take place. Dendreon's stock price took a hit, as investors tried to second-guess which way the winds were blowing at the agency. But

One further complication with the IMPACT data has had statisticians scratching their heads. This is the use of previously frozen Provenge—which some are calling Frovenge—as the salvage protocol for patients who progressed on the placebo arm. Those on the experimental arm whose disease progressed received chemotherapy with docetaxel. Offering progressors alternative therapies is common, but giving an unproven therapy, which on top of being unproven, is different from the product given to the experimental arm, introduces an uncontrolled variable and confounds analysis when the endpoint had yet to be met (death).

cated on the label. The $93,000 price tag for three infusions may also dictate who gets the treatment. According to Frohlich,

Interdisciplinary Critique of Sipuleucel-T as Immunotherapy in Castration-Resistant Prostate Cancer

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Sipuleucel-T was approved by the US Food and Drug Administration on April 29, 2010, as an immunotherapy for late-stage prostate cancer. To manufacture sipuleucel-T, mononuclear cells harvested from the patient are incubated with a recombinant prostatic acid phosphatase (PAP) antigen and reinfused. The manufacturer proposes that antigen-presenting cells exogenously activated by PAP induce endogenous T-cells to attack PAP-bearing prostate cancer cells. However, the lack of demonstrable tumor responses has prompted calls for scrutiny of the design of the trials in which sipuleucel-T demonstrated a 4-month survival benefit. Previously unpublished data from the sipuleucel-T trials show worse overall survival in older vs younger patients in the placebo groups, which have not been shown previously to be prognostic for survival in castration-resistant prostate cancer patients receiving chemotherapy. Because two-thirds of the cells harvested from placebo patients, but not from the sipuleucel-T arm, were frozen and not reinfused, a detrimental effect of this large repeated cell loss provides a potential alternative explanation for the survival "benefit." Patient safety depends on adequately addressing this alternative explanation for the trial results.

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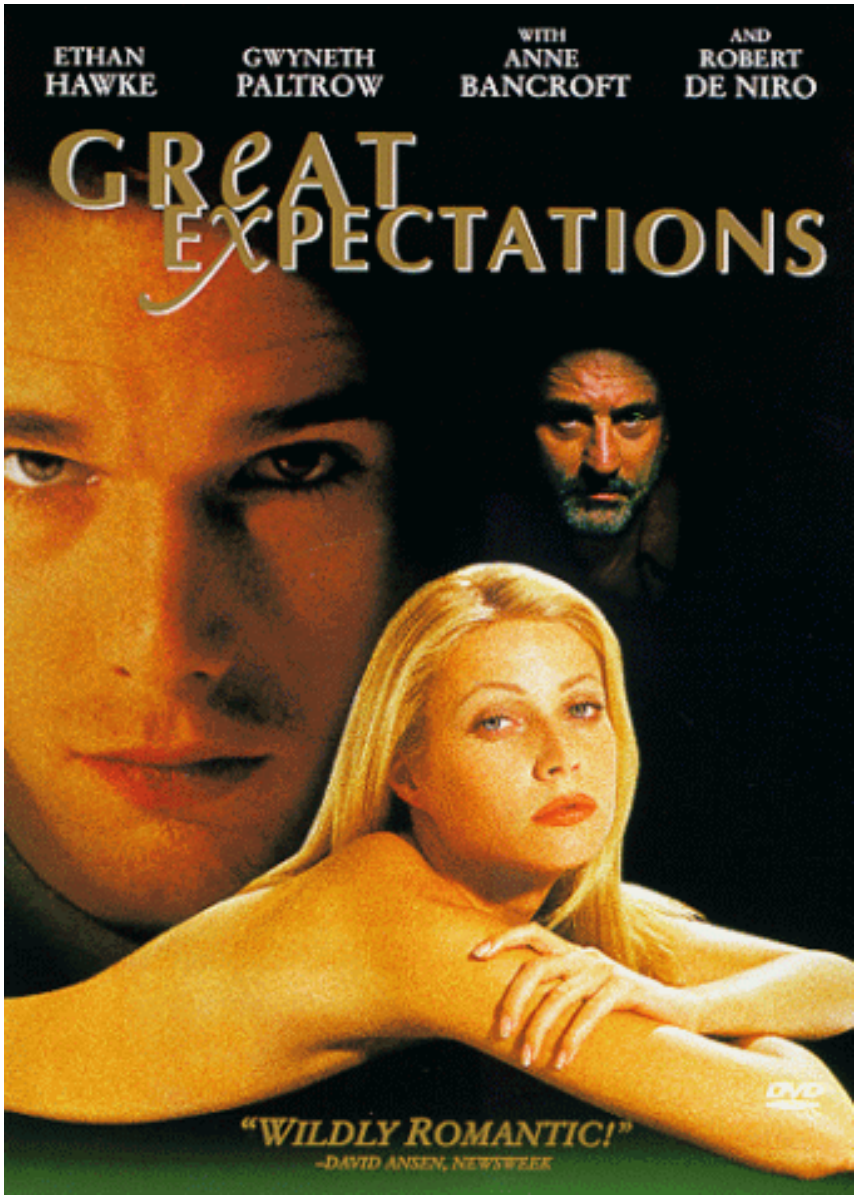

GREAT EXPECTATIONS

BY

CHARLES DICKENS.

IN THREE VOLUMES.

VOL. I.

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CLINICAL RESEARCH

Gene Therapists Celebrate a Decade of Progress

Some Gene Therapy Successes

Disorder	Disease type	Patients benefiting	First publication
X-SCID	Immunodeficiency	17/20	2000
ADA-SCID	Immunodeficiency	26/37	2002
Adrenoleukodystrophy	Neurologic	2/4*	2009
Leber's congenital amaurosis	Blindness	28/30	2008
Wiskott-Aldrich syndrome	Immunodeficiency	8/10	2010
β-thalassemia	Hemoglobinopathy	1/1	2010
Hemophilia	Coagulation	6/6	2011?

*Includes a patient treated too recently to see benefit

l needed for regula-
for treating adenos-
cy–SCID. Last year,
eal with pharmaceu-
Cline to commercial-
ven disorders. "Gene
: diseases is really a
thon Institute immu-
Roncarolo said at the

other success story.
"kind of biblical in
s, eyesight improved,
, in 28 of 30 patients
amaurosis, a type of
ness, after gene ther-
leno-associated virus
er a curative gene to
Children's Hospital of
HOP) plans to apply
U.S. Food and Drug
to conduct a phase
is treatment. Gene
for two other blind-
re under way. "In the
a half, there's going
d coming out," says
chief research officer
Fighting Blindness.
py is working for
eases, too. The San
thon Institute has
tients with a devas-
sorder called meta-

IUM, 26 SEPTEMBER, 2011; LANCET 374, 1597 (2009); NEJM 358, 2231 (2008); NATURE 467, 318 (2010)

Gene therapy matures in the clinic

To the Editor:

Gene therapy has promised much and delivered little for patients over many years, but a range of clinical projects are now showing clear signs of efficacy, giving considerable reassurance that technology from this field will soon enter into mainstream medicine. The studies showing clinical promise cover several different diseases and use a variety of vectors, ranging from simple oligonucleotides to replicating lytic viruses. However, one crucial unifying feature is that they all focus on realistic and achievable objectives, particularly in terms of effective delivery of the therapeutic agent to target cells, but also using levels and durations of transgene expression commensurate with the desired treatment outcome. Careful selection of disease targets on the basis of the vector systems available is an essential prerequisite to success. Here we highlight some of the more notable recent advances and try to put them into the context of the underpinning technological improvements; details of selected recent clinical studies are summarized in **Table 1**.

Gene therapies for genetic disease

Although integrating viral vectors are often used to mediate long-term stable gene expression, other viral vectors, such as those based on adeno-associated viruses (AAV), are being widely explored to mediate extended transgene expression in non-replicating cells, where they are thought to persist as non-integrated non-replicating episomes. However, all viral vectors are limited by their packaging capacity—in other words, by the size of the transgenic cassette, which may restrict capacity for incorporation of large genes or complex regulatory elements. Furthermore, very large-scale bio-production remains challenging for some viral vectors. Non-viral technologies based on different chemistries, targeting strategies and genetic constructs are being developed to remove some of these problems, and although efficiency has remained problematic, for some applications there are signs of genuine efficacy. Emerging successful strategies are therefore a 'best fit' based on knowledge of the target disease, the desired regulatory pattern of gene expression and the bioactivity of different vector systems.

Gene therapies for genetic disease

Recombinant AAV2 expressing RPE65 (the retinal pigment protein that is lost in LCA) under transcriptional control of its physiological promoter was administered to three patients (**Table 1**)[2]. Although none of the recipients showed any change in retinal responses measured by electroretinography in this trial, one patient had significant improvement in visual function measured by microperimetry and dark-adapted perimetry, and also showed improvement in a subjective test of visual mobility. In another study, each patient showed a modest improvement in measures of retinal function in subjective tests of visual acuity, although normal vision was not achieved[3]. Finally, a dose-escalation study of AAV2 expressing RPE65 under control of the chicken β-actin promoter produced sustained improvements in subjective and objective measurements of vision, with at least a 2-log-unit increase in pupillary light responses in all 12 patients. The greatest improvement was noted in children, all of whom gained ambulatory vision[3,4]. The fact that maximal benefit occurred in younger recipients indicates that regenerative therapies for this and many

Table 1 Some recent advances in clinical gene therapy

	Vector, dose range, and number and ages of patients	Transgene and promoter	Route of administration and cell target	Scientific and clinical outcomes	Reference
Gene therapy for genetic disease					
Leber's congenital amaurosis	AAV2; 1.5×10^{10} vg per patient; three patients (19–26 years old)	RPE65 under chicken β-actin promoter	Subretinal injection to retinal epithelial cells	All patients showed improved visual acuity and modest improvements in pupillary light reflexes.	3
	AAV2; 10^{11} vg per patient; three patients (17–23 years old)	RPE65 under cognate promoter	Subretinal injection to retinal epithelial cells	No change in visual acuity or retinal responses to flash or pattern electroretinography; microperimetry and dark-adapted perimetry showed no change in retinal function in patients 1 and 2 but showed improved retinal function in patient 3.	2
	AAV2; 1.5×10^{10}, 4.8×10^{10} or 1.5×10^{11} vg per patient; 12 patients (8–44 years old)	RPE65 under chicken β-actin promoter	Subretinal injection to retinal epithelial cells	All patients showed sustained improvement in subjective and objective measurements of vision (dark adaptometry, pupillometry, electroretinography, nystagmus and ambulatory behavior).	4
Hemophilia B	AAV8; 2×10^{11}, 6×10^{11} or 2×10^{12} vg per kg body weight; six patients (27–64 years old)	FIX gene, regulated by the human apolipoprotein hepatic control region and human α-1-antitrypsin promoter	Intravenous delivery targeting hepatocytes	Durable circulating FIX at 2–11% normal levels; decreased frequency (two of six patients) or cessation (four of six) of spontaneous hemorrhage	11
X-linked severe combined immunodeficiency (SCID-X1)	Gammaretrovirus; ten patients (4–36 months old); $CD34^+$ cells were infused (without conditioning) at doses of 60×10^6 to 207×10^6 cells per patient	Interleukin-2 receptor common γ-chain, retroviral LTR	*Ex vivo*, $CD34^+$ hematopoietic stem and progenitor cells	Functional polyclonal T-cell response restored in all patients; one patient developed acute T-cell lymphoblastic leukemia	23
	Gammaretrovirus; nine patients (1–11 months old); $CD34^+$ cells were infused (without conditioning) at doses of 1×10^6 to 22×10^6 cells per kg	Interleukin-2 receptor common γ-chain, retroviral LTR	*Ex vivo*, $CD34^+$ hematopoietic stem and progenitor cells	Functional T-cell numbers reached normal ranges. Transduced T cells were detected for up to 10.7 years after gene therapy. Four patients developed acute T cell lymphoblastic leukemia, one died.	24
Adenosine deaminase deficiency resulting in severe combined immunodeficiency (ADA-SCID)	Gammaretrovirus; six patients (6–39 months old); $CD34^+$ cells were infused (after non-myeloablative conditioning with melphalan (Alkeran), 140 mg per m^2 body surface area, or busulfan (Myleran), 4 mg per kg) at doses of $<0.5 \times 10^6$ to 5.8×10^6 cells per kg	Adenosine deaminase gene, retroviral LTR	*Ex vivo*, $CD34^+$ hematopoietic stem and progenitor cells	Restoration of immune function in four of six patients; three of six taken off enzyme-replacement therapy; four of six remain free of infection	25
	Gammaretrovirus; ten patients (1–5 months old); $CD34^+$ cells were infused (after non-myeloablative conditioning with busulfan, 4 mg per kg) at doses of 3.1×10^6 to 13.6×10^6 cells per kg	Adenosine deaminase gene, retroviral LTR	*Ex vivo*, $CD34^+$ hematopoietic stem and progenitor cells	Nine of ten patients had immune reconstitution with increases in T-cell counts (median count at 3 years, 1.07×10^9 l^{-1}) and normalization of T-cell function. Eight of ten patients do not require enzyme-replacement therapy.	26

Chronic granulomatous disorder	A range of studies, using gammaretrovirus vectors pseudotyped either with gibbon ape leukemia virus envelope or with an amphotrophic envelope; various non-myeloablative conditioning strategies	Gp91phox, retroviral LTR	*Ex vivo*, $CD34^+$ hematopoietic stem and progenitor cells	Twelve of twelve patients showed short-term functional correction of neutrophils with resolution of life-threatening infections. Three patients developed myeloproliferative disease.	27*
Wiskott-Aldrich syndrome	Gammaretrovirus; ten patients; $CD34^+$ cells were infused (after non-myeloablative conditioning with busulfan, 4 mg per kg)	WAS gene, retroviral LTR	*Ex vivo*, $CD34^+$ hematopoietic stem and progenitor cells	Nine of ten patients showed improvement of immunological function and platelet count. Two patients developed acute T-cell lymphoblastic leukemia.	28, 29
β-thalassemia	Self-inactivating HIV-1–derived lentivirus; one patient (18 years old) received fully myeloablative conditioning with busulfan; 3.9×10^6 $CD34^+$ cells per kg	Mutated adult β-globin ($\beta^{A(T87Q)}$) with anti-sickling properties, LCR control	*Ex vivo*, $CD34^+$ hematopoietic stem and progenitor cells	Patient has been transfusion independent for 21 months. Blood hemoglobin is maintained between 9 and 10 g dl^{-1}, of which one-third contains vector-encoded β-globin.	30
Adrenoleukodystrophy	Self-inactivating HIV-1–derived lentivirus; two patients (7 and 7.5 years old) received myeloablative conditioning with cyclophosphamide (Cytoxan) and busulfan; transduced $CD34^+$ cells, 4.6×10^6 and 7.2×10^6 cells per kilogram, respectively	Wild-type *ABCD1* cDNA under the control of the MND viral promoter	*Ex vivo*, $CD34^+$ hematopoietic stem and progenitor cells	9–14% of granulocytes, monocytes, and T and B lymphocytes expressing the ALD protein; beginning 14–16 months after infusion of the genetically corrected cells, progressive cerebral demyelination in the two patients attenuated.	8

(continued)

SCOPE

Advanced therapy medicinal products which are intended to be placed **on the market in Member States** and either **prepared industrially** or manufactured by a method involving an industrial process (Title II of Directive 2001/83).

SCOPE

EXCLUDED from the scope of this Regulation:

advanced therapy medicinal products which are prepared on

- a non-routine basis according to specific quality standards,
- used within the same Member State in a hospital
- under the exclusive professional responsibility of a medical practitioner in order to comply with an individual medical prescription for a custom-made product for an individual patient

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in accordance with Article 25 of Regulation (EC) No 1394/2007 of the European Parliament and of the Council on advanced therapy medicinal products and amending Directive 2001/83/EC and Regulation (EC) No 726/2004

5. CONCLUSIONS

Advanced therapies have the potential to bring major benefits to patients. However, there are still many unknowns and it is therefore important to put in place adequate controls to prevent detrimental consequences for public health.

The ATMP Regulation protects patients by requiring that an independent review of the ATMP is done by the best available experts in the EU according to high standards of quality, efficacy and safety before the product is made available to

- clarification of the scope of the ATMP Regulation by fine-tuning the current definitions of ATMPs and by reflecting on the appropriate regulatory framework for new innovative products that many not be captured by existing provisions;
- considering measures to avoid disparities in the classification of ATMPs in the EU;
- clarification of the conditions for the application of the hospital exemption, as well as the role of data obtained therefrom in the context of marketing authorisation procedures;
- revising the requirements for the authorisation of ATMPs with a view to ensure that applicable requirements are proportionate and well-adapted to the specific characteristics thereof, having specific consideration to autologous products;
- streamlining the marketing authorisation procedures;

- extending the certification procedure and clarification of the link between the certification and the marketing authorisation procedure;
- creating a more favourable environment for ATMP developers working in an academic or non-for-profit setting, including by promoting early contacts with the authorities through the application of the fee reduction for scientific advice and by extending the certification scheme to these developers;
- considering possible fee incentives to reduce the financial impact of post-marketing obligations.


Thank U
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