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How did the field of ATMPs evolve over time: The perspectives from the former CAT Chairs

Scientific Symposium on Advanced Therapy Medicinal Products: 'Contribution, evolution, revolution'

European Medicines Agency, Amsterdam

October 2014

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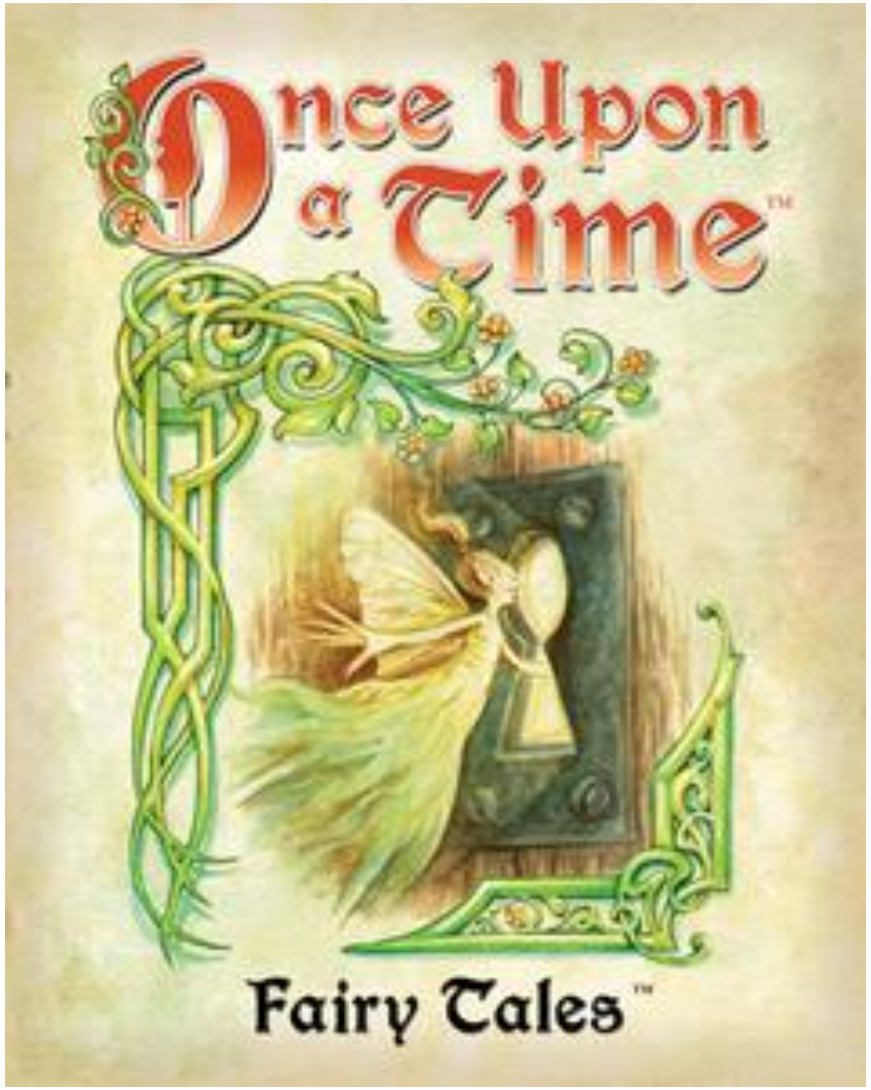
Disclaimer

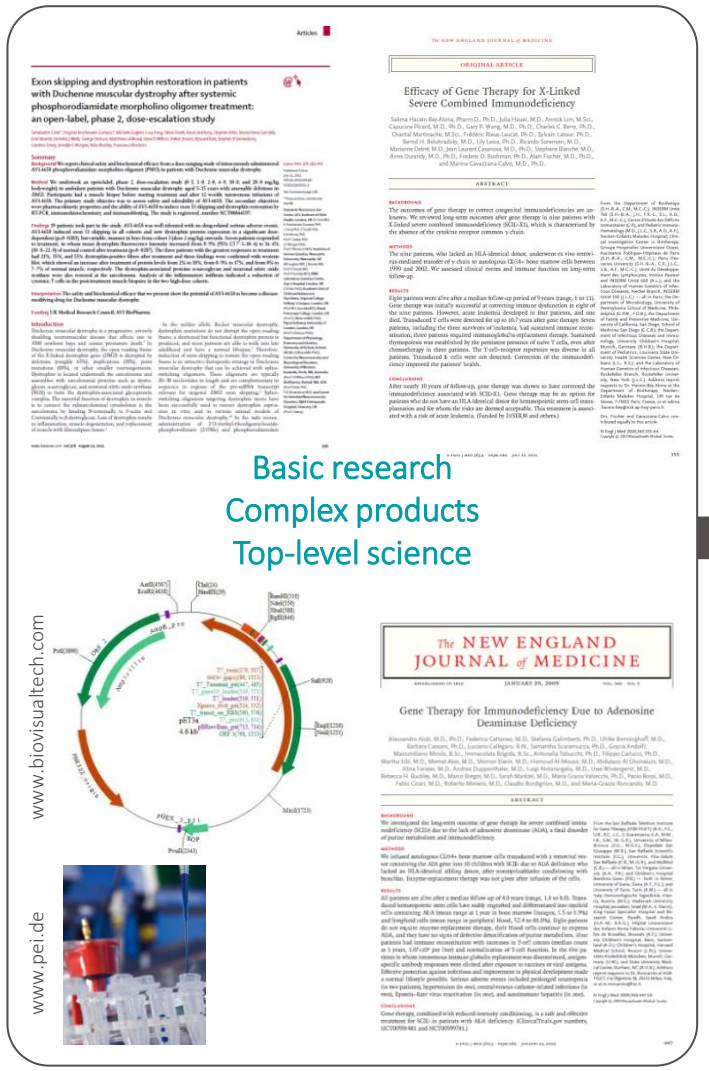


Regulatory archaeology!

… in 2009 and after…

Disclaimer: These are all my own views and memories, as a regulatory archaeologist!

“The Committee with no products”



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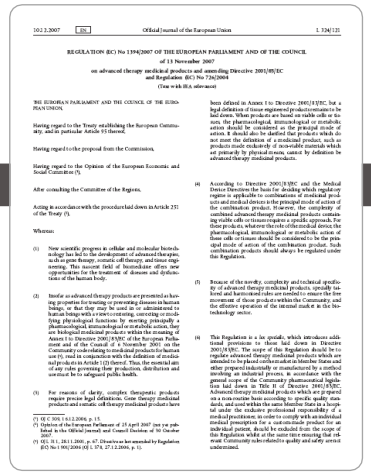

Regulation 1394/2007
(„ATMP regulation“)

Directive 2009/120/EC
amending Directive 2001/83/EC
(”Annex I”)

Marketing authorisation

Translation into a medicinal product (”translational medicine”)

The early days were not easy!

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

20 October 2011
EMA/CHMP/845661/2011
EMEA/H/C/002145

Questions and answers

Refusal of the marketing authorisation for Glybera (alipogene tiparvovec)

Outcome of re-e

On 23 June 2011, the
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The applicant request
this request, the CHM
Glybera should not be

What is Glybera

Glybera is a medicine
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What was Glybe

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SCIENCE MEDICINES HEALTH

20 July 2012
EMA/CHMP/474664/2012
Press Office

Press release

European Medicines Agency recommends first gene therapy for approval

Glybera offers new medical treatment for patients with severe or multiple pancreatitis attacks due to lipoprotein lipase deficiency

The European Medicines Agency's Committee for Medicinal Products for Human Use (CHMP) has recommended the authorisation of Glybera (alipogene tiparvovec) for marketing in the European Union. It is intended to treat lipoprotein lipase (LPL) deficiency in patients with severe or multiple

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doi:10.1038/mt.2012.194

Molecular Therapy

Endgame: Glybera Finally Recommended for Approval as the First Gene Therapy Drug in the European Union

available.

"The evaluation of this application has been
restricted indication than initially applied for
for treatment, and additional analyses by th
the robustness of the data provided and allc
greater than its known risks", said Dr Toma
ways of assessing the benefits and risks of

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doi:10.1038/mt.2012.14

Molecular Therapy

The Need for Increased Clarity and Transparency in the Regulatory Pathway for Gene Medicines in the European Union

Agency defies advice and rejects gene therapy for third time

For the third time, the European Medicines Agency (EMA) recommended that Glybera, a treatment for the inherited disorder lipoprotein lipase deficiency (LPL), should not be approved. The refusal on April 20 means there's still no approved gene therapy in a regulated Western market. It was bad news for suffers of the ultra-rare disorder and amplified the fault lines that the review of the product has opened up, both between different expert committees of the EMA, and between the agency and its masters at the European Commission.

Indeed, EMA's Committee for Medicinal Products for Human Use (CHMP) only got to vote on the

The EMA in London gives a thumbs down to AMT's gene therapy in May.

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Monday, 1 October 2012 09:25 GMT

EMA's Rasi defends CHMP/CAT interaction in face of marketing authorisation delay

by Nick Smith

LONDON, Oct 1 (APM) - The head of the European Medicines Agency has defended the relationship between its CHMP and its advanced technology CAT committee, saying the existing hierarchy will continue despite the tortuous nature of the final approval of Europe's first gene therapy.

Despite what some outside observers first saw as friction or problems between the CHMP and the CAT over gene therapy Glybera, EMA executive director Guido Rasi told APM in an interview the relationship had been proven rather than brought into question.

EDITORIAL

nature biotechnology

Will the floodgates open for gene therapy?

In a matter of days, a momentous event will occur: a gene therapy will, for the first time anywhere in the Western hemisphere, be available commercially with full marketing approval.

Commendations for *Nature* News & Comment in the 2012 Online Media Awards

NATURE | NEWS

Europe nears first approval for gene therapy

Treatment for rare fat-processing disease gains approval from medicines regulator.

Daniel Cressey

20 July 2012

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WEDNESDAY MARCH 7, 2012 — THE GLOBAL BIOTECHNOLOGY REPORT — WEDNESDAY MAY 2, 2012

Rasi Breaks EMA's Silence on Glybera, Transparency Issues

By Cormac Sheridan
Staff Writer

The month of May could prove to be an important milestone in the evolution of drug regulation in Europe. Around then, Amsterdam Molecular Therapeutics (AMT)

Seeking Greater Coordination, EMA Forms Another Committee

By Cormac Sheridan
Staff Writer

Faced with an increasingly complex system of committees, which threatens to undermine the coherence of pharmaceutical regulation in Europe, the European Medicines Agency (EMA) has come up with the perfect bureaucratic response: establish another committee.

SCRIP SCRIP

Hope yet for European approval of Glybera but delays continue

31 January 2012
Pial Ganguli

Amsterdam Molecular Therapeutics may yet see light at the long-running struggle to secure European approval for its gene deficiency, Glybera (alipogene tiparvovec), but is still facing Commission said it would delay a decision on the product information from its Committee for Human Medicinal Products (C

CORRESPONDENCE

Nature Reviews Drug Discovery | AOP, published online 10 April 2012; doi:10.1038/nrd3572

Glybera and the future of gene therapy in the European Union

Norman Miller

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The EMA's Shambolic Handling of Glybera

May 7, 2012 – 2:58 pm | By Nuala Moran | No comments yet

If you can't see the wood for the trees the common sense response is to do a little thinning and let the light shine through.

But for the bogged-down-in-bureaucracy European Medicines Agency (EMA), the response last week to the need to increase transparency and streamline its procedures was to set up an expert committee to investigate the activities and operations of its expert committees.

Erste Gentherapie vor der Zulassung

Medikament mit veränderten Zellen soll gegen seltene Fettstoffwechsel-Krankheit helfen

VON U. V. LESZCZYNSKI (dpa)

Eine Gentherapie kann ein Segen für Menschen mit unheilbaren Krankheiten sein. Rückschläge mit Todesfällen haben aber auch große Vorbehalte gegen diese Behandlung geweckt. Nun steht in Deutschland das erste Gen-Medikament vor der Zulassung.

BERLIN – Die Gentherapie soll gegen die seltene Fettstoffwechsel-Krankheit Lipoproteinlipase-Defizienz (LPLD) helfen, die maximal zwei unter einer Million Menschen trifft. Noch ist allerdings der komplizierte EU-Verfahrensweg nicht ganz beschritten. Zwar hat das Medikament „Glybera" (Alipogen Tiparvovec) die größte Hürde genommen und am 19. Juli den Ausschuss für Humanarzneimittel (CHMP) bei der EU-Arzneimittelbehörde EMA nach langen Beratungen überzeugt.

Mit Vertretern aus allen EU-Staaten besetzt, empfiehlt er nun eine Marktzulassung. Die Entscheidung über diese Zulassung aber fällt innerhalb von maximal drei Monaten die EU-Kommission. In der Regel richtet sie sich nach den Empfehlungen.

Einfach ist die Entscheidung trotzdem nicht. Da LPLD so selten ist, konnte die Therapie bisher in drei klinischen Prüfungen nur an 27 Menschen getestet werden. Sie sei dabei gut vertragen worden, berichtet der niederländische Hersteller „uniQure". Über den Preis ist noch nichts bekannt – außer, dass er wegen der Entwicklungskosten hoch sein wird.

„Menschen mit LPLD fehlt ein Enzym. Deshalb können Fette aus der Nahrung nicht richtig verarbeitet werden", erläutert Hildegard Büning, Präsidentin der Deutschen Gesellschaft für Gentherapie. Patienten litten an Bauchschmerzen, Einlagerung von Fett in die Haut (Xanthome) und Entzündungen der Bauchspeicheldrüse.

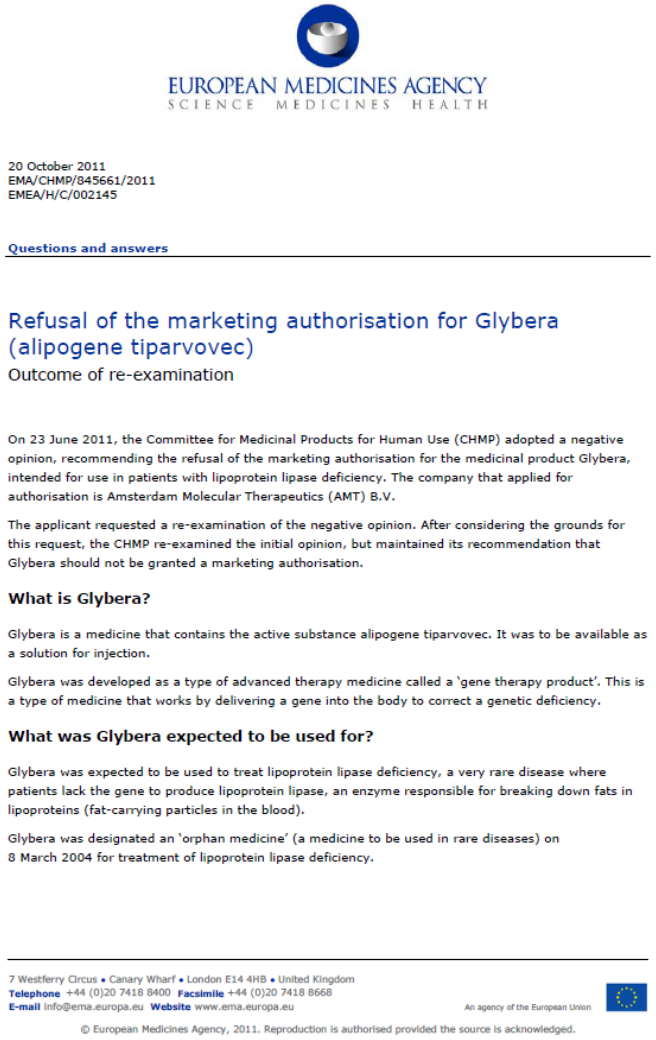
Die Patienten müssen Diät halten, aber eine fettfreie Ernährung ist fast nicht möglich. „Das ist eine sehr ernsthafte Erkrankung", meint Hildegard Büning. Gentherapien können Körperzellen mit Fehlfunktionen durch das Einschleusen „korrekter" Gen-Einheiten dauerhaft helfen. Nach diesem Grundprinzip arbeitet auch das neue Medikament „Glybera". Es beruht auf einem entschärften Virus, das statt seiner eigenen Erbinformation nun die Information für die korrekte Version des Lipoproteinlipase-Gens in Zellen von Patienten einbringt.

Mehrere Organe versagten

Die Rückschläge bei früheren Gentherapien macht das nicht vergessen. 1999 starb in den USA der 18-jährige Jesse Gelsinger, der an einer Harnstoffzyklus-Störung litt, nach der Gabe eines ähnlichen Gentaxis. Vermutlich versagten mehrere Organe aufgrund einer Immunreaktion.

Genau das ist der Zwiespalt, in dem sich Forscher immer noch sehen. Da es erst wenig Erfahrungen mit Gentherapien gibt, weiß niemand, ob die eingeschleusten Gene nicht auch Zellen in einer Weise verändern, die nicht beabsichtigt ist – und damit beispielsweise Krebs Vorschub leisten.

Regulatory history



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Outcome of re-examination

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The applicant requested a re-examination of the negative opinion. After considering the grounds for this request, the CHMP re-examined the initial opinion, but maintained its recommendation that Glybera should not be granted a marketing authorisation.

What is Glybera?

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- Assessment history:

  Primary marketing authorisation application:
  - June 2011: Negative CAT opinion (by consensus)
  - June 2011: Negative CHMP opinion (by majority)

  Re-examination:
  - October 2011: Positive CAT opinion (by majority)
  - October 2011: Negative CHMP opinion

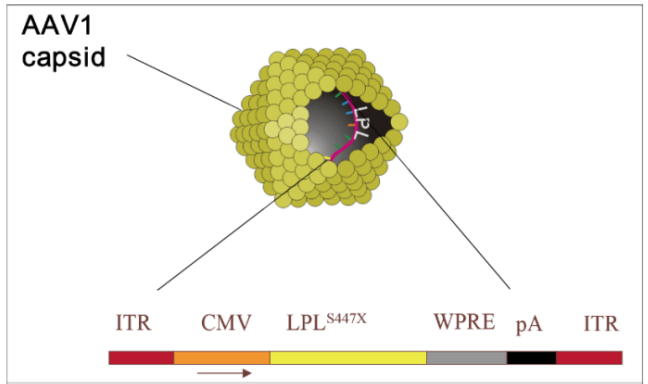
  Re-evaluation by CHMP following EC request:
  - April 2012: CAT consultation
  - April 2012: Negative CHMP opinion*)
    *) 16 positive, 15 negative votes
  - May 2012: CHMP opinion void, since required CAT opinion
  - June 2012: Another CAT oral explanation
    Positive CAT opinion (by majority)
  - July 2012: Another CHMP oral explanation
    Positive CHMP opinion (by majority)

=> Approval under exceptional circumstances

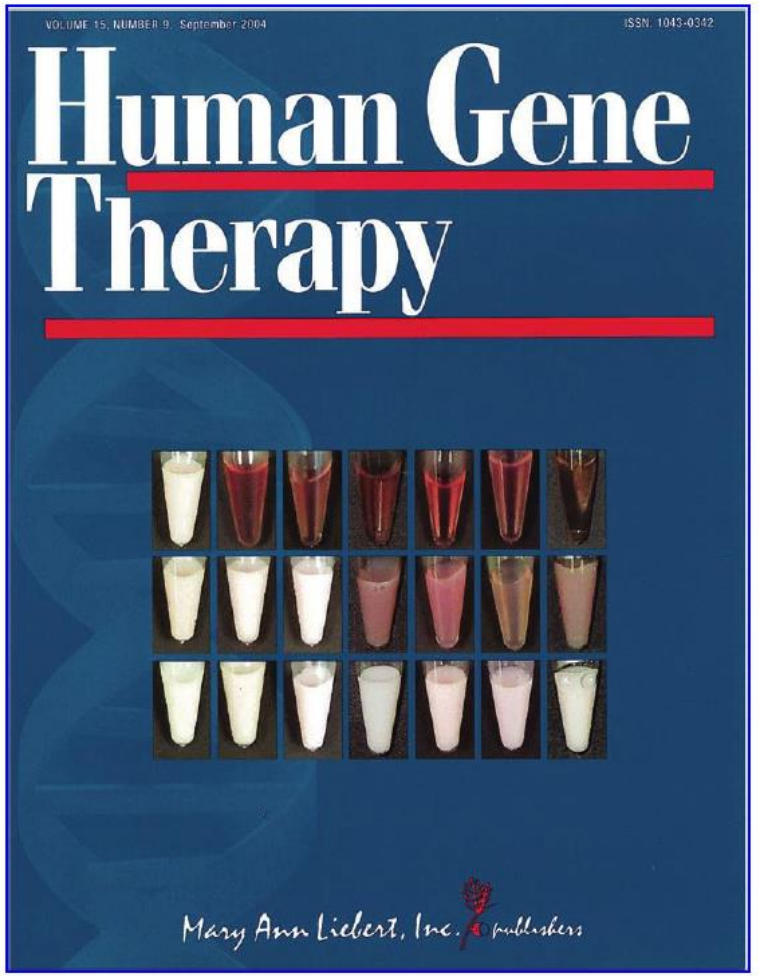
Sources: All information in the public domain, to be found in the CAT Monthly Report June 2011; CHMP Monthly Report June 2011; CAT Monthly Report October 2011; Q&A on re-examination October 2011; Q&A on re-evaluation by CHMP April 2012; AMT homepage: http://www.amtbiopharma.com/news/150/182/Amsterdam-Molecular-Therapeutics-Receives-Further-Opinion-on-Glybera-Marketing-Authorisation-Application.html

Glybera

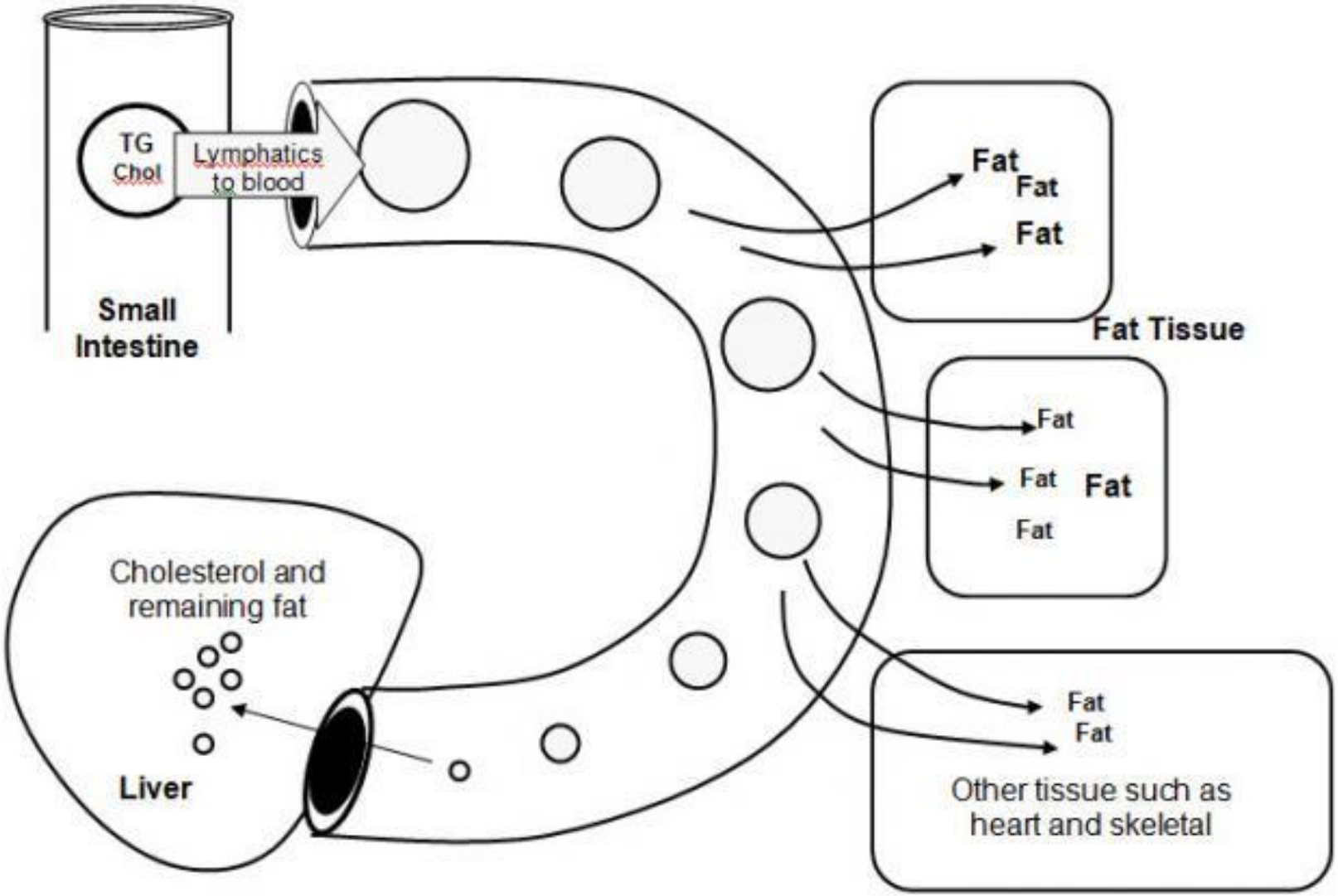
- Alipogene tiparvovec (gene therapy medicinal product)
- Treatment of lipoprotein lipase deficiency
- rare autosomal recessive inherited condition caused by homozygosity or compound heterozygosity for mutations in the LPL gene
- Prevalence: 0.02 per 10,000
- (i.e., 2 per 1 million inhabitants).
- Alipogene tiparvovec: replication-deficient adeno-associated viral vector designed to deliver and express the human LPL gene variant LPLS447X



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.



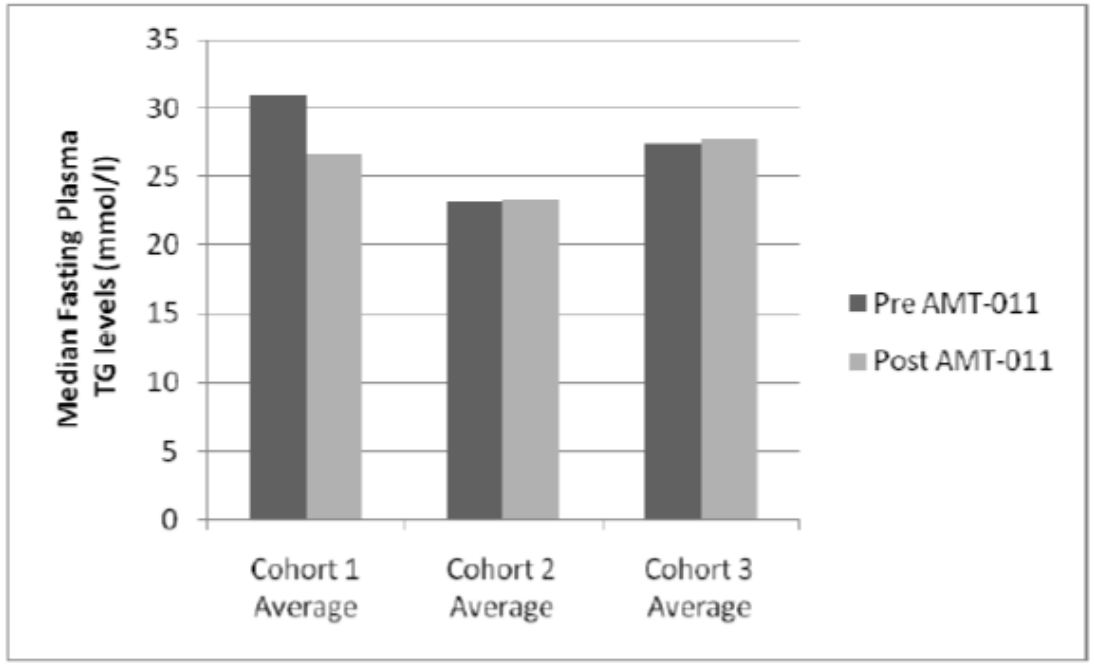
Chylomicron metabolism



http://www.thenutritiondr.com/files/CarbsProFat-ChylomicronMetabolism.jpg

Glybera: Efficacy

Figure 9: Median fasting plasma TG levels per cohort for the period 19-26W post-administration of AMT-011.



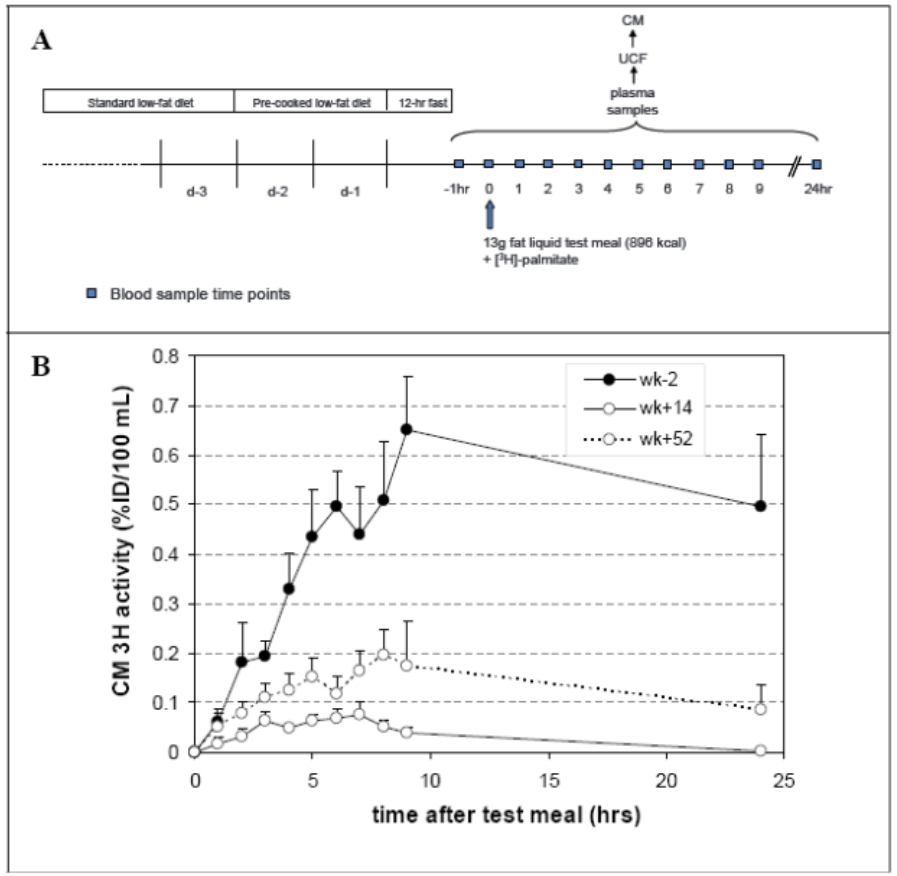
The study population was to be divided into 3 cohorts according to given treatments:

- LPLD subjects who received 3 x 1011 gc/kg (cohort 1);
- LPLD subjects who received 3 x 1011 gc/kg of AMT-011 with immunosuppressants (cohort 2);
- LPL D subjects who received 1 x 1012 gc/kg of AMT-011 with immunosuppressants (cohort 3).

https://www.ema.europa.eu/en/documents/assessment-report/glybera-epar-public-assessment-report_en.pdf

The CAT needed to look at the details: The **totality of evidence**

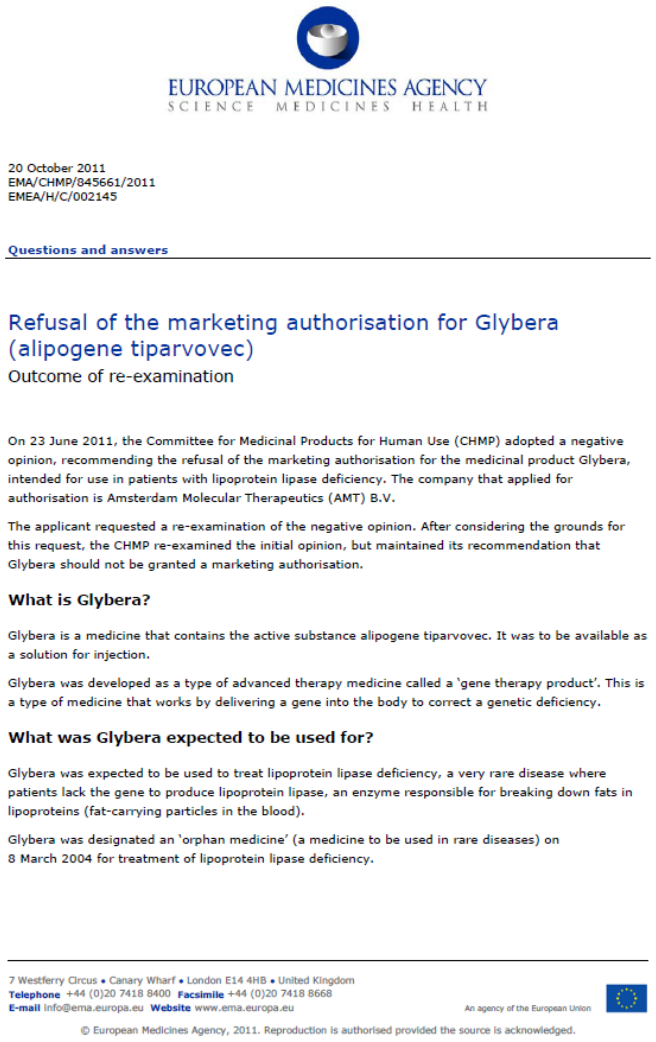
Lipid response



(A) LPLD subjects enrolled in CT-AMT-011-02 were subjected to a postprandial test. Following an overnight fast, subjects were given a low-fat liquid test meal supplemented with [3H]-palmitate tracer (at t=0). The [3H]-palmitate tracer is incorporated into the chylomicron (CM) particles as core TG; following their formation in the enterocytes of the gut, nascent (newly-formed, large/buoyant) [3H]-labeled CM are secreted into the blood circulation. Blood samples were taken over 24 hours following the meal, and a CM fraction was isolated using ultracentrifugation (UCF). (B) [3H]-activity in this CM fraction was determined by scintillation counting. Results are in level of [3H]- tracer measured in the CM fraction, expressed as % of ingested dose (ID) per 100 mL of plasma, and are displayed as a mean ± SEM (n=5 for wk-2 and wk+14; n=3 for wk+52).

https://www.ema.europa.eu/en/documents/assessment-report/glybera-epar-public-assessment-report_en.pdf

Glybera



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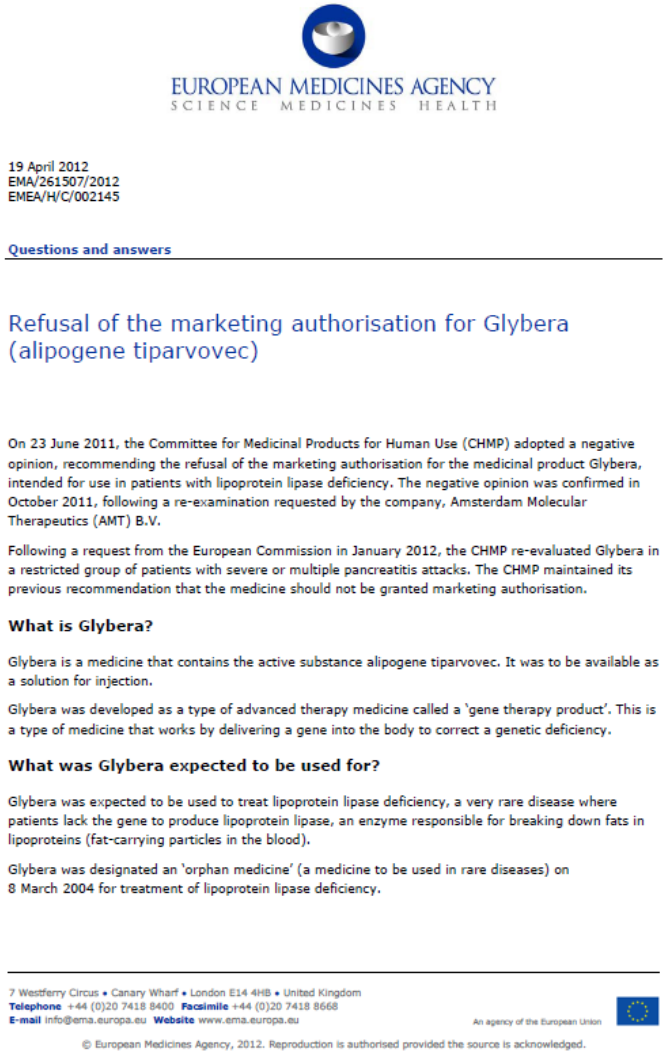
October 2011 (re-examination opinion)

- *"There was (..) insufficient evidence of a reduction in the rate of pancreatitis (inflammation of the pancreas), which is a major complication of lipoprotein lipase deficiency."*
- *"During the re-examination, the CAT concluded that these concerns could be addressed with additional post-marketing studies."*
- *"Whilst the CHMP still considers Glybera to be potentially valuable in the treatment of this very rare disease, it took a different view."*

Glybera



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Following a request from the European Commission in January 2012, the CHMP re-evaluated Glybera in a restricted group of patients with severe or multiple pancreatitis attacks. The CHMP maintained its previous recommendation that the medicine should not be granted marketing authorisation.

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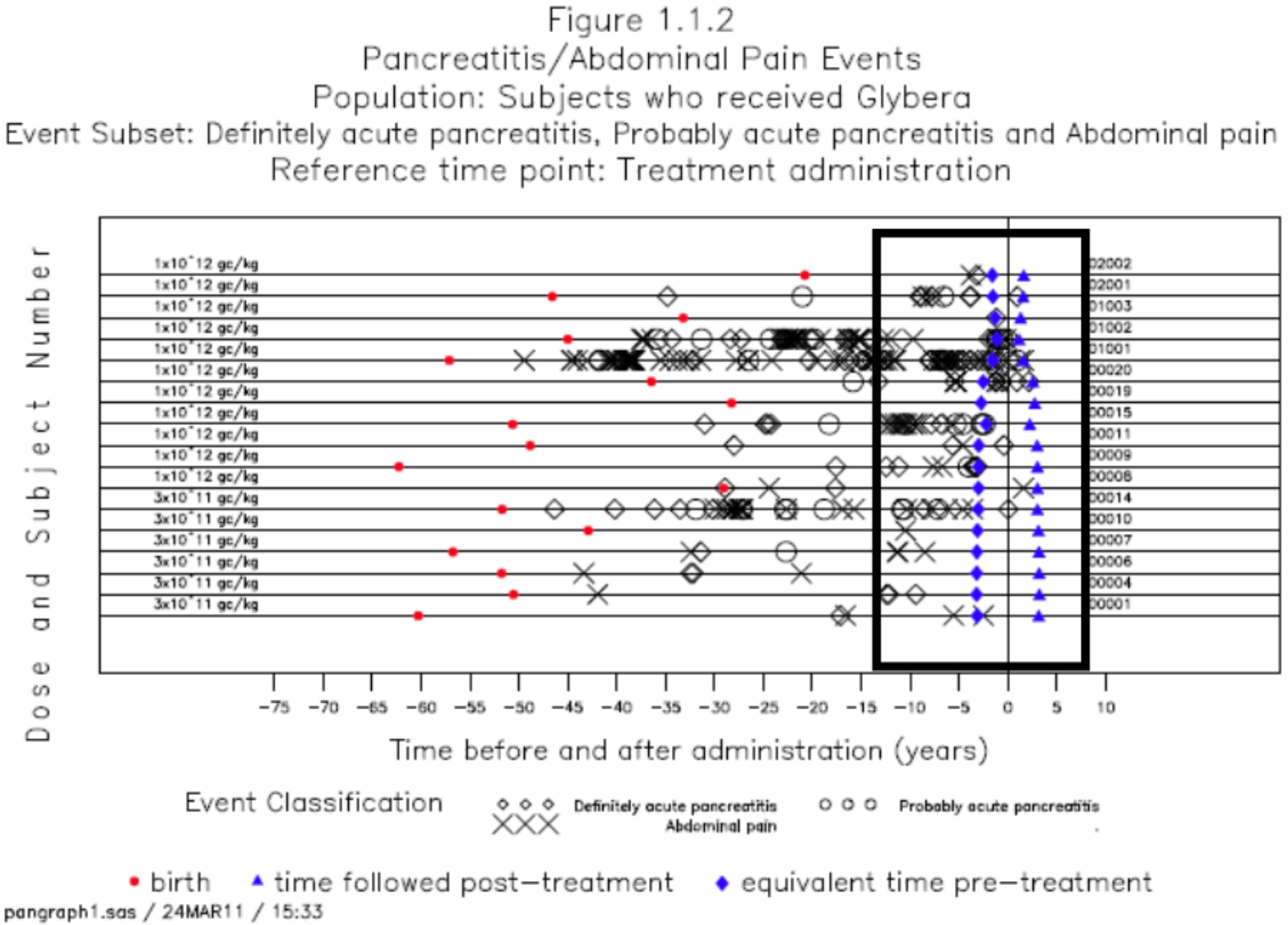
April 2012 (CHMP re-evaluation following EC request)

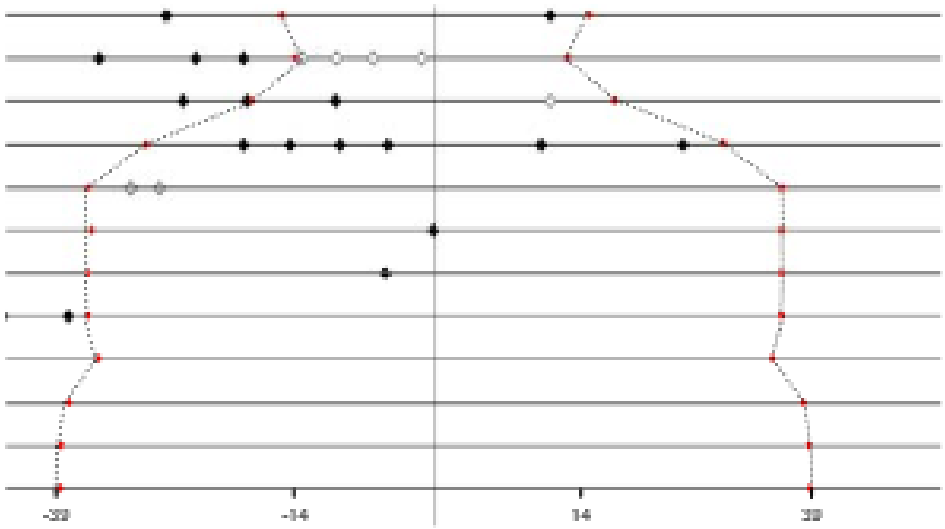
- *"When evaluating Glybera in patients with severe or multiple pancreatitis attacks, the CHMP found that the evidence of efficacy from the small number of patients assessed (data from only 12 patients were available) was not sufficiently convincing."*
- *"In addition, the reduced risk of pancreatitis seen in a few of the patients could have been due to other factors (such as changes in lifestyle and diet, and the natural course of the disease)."*
- *"In its discussions, the Committee [CHMP] recognized the difficulty of obtaining data in this rare disease and took this into account while assessing the data."*

Glybera: Pancreatitis as clinically relevant event



https://www.ema.europa.eu/en/documents/assessment-report/glybera-epar-public-assessment-report_en.pdf

Glybera: Comparable periods before and after treatment



Month from Glybera treatment

◆ Definite
◇ Probable
● ± FU period from Glybera

https://www.ema.europa.eu/en/documents/assessment-report/glybera-epar-public-assessment-report_en.pdf

Glybera: ”Pharmacodynamic effects”

Study	Subject ID	Dose (gc/kg)	ISR	biopsy (weeks post)	QPCR (gc/µg gDNA) I	QPCR C	LPL mass (ng/mg) I	LPL mass C	LPL Activity (nmol FFA/min/mg) I	LPL Activity C	LPL IHC I	LPL IHC C	Oil Red O I	Oil Red O C
CT-AMT-010-01		1.00E+11	N	36	62474	7	2.50	1.60	0.00	0.70	++	-	+++	-
		1.00E+11	N	32	4091	23	0.30	0.70	1.70	0.30	-	-	+	-
		1.00E+11	N	28	178114	31	5.50	1.00	0.50	1.00	+	-	++	-
		1.00E+11	N	ND										
		3.00E+11	N	10	188964	NA	10.70	NA	1.50	NA	-	-	++	-
		3.00E+11	N	32	932020	ND	140.20	5.20	5.60	0.00	+++	-	+++	-
		3.00E+11	N	26	2378945	323	658.40	2.20	33.90	0.00	+++	-	+++	-
		3.00E+11	N	27	3	ND	0.60	2.10	0.30	0.00	-	-	-	-
CT-AMT-011-01		3.00E+11	N	26	170000	110	24.06	0.00	5.91	0.00	++	-	++	-
		3.00E+11	N	25	22000	30	0.00	0.00	0.00	0.00	-	-	+	-
		3.00E+11	Y	27	900	0	0.00	0.00	0.00	0.00	-	-	-	-
		3.00E+11	Y	ND										
		3.00E+11	Y	25	110000	30	0.00	0.00	0.00	0.00	+	-	++	-
		3.00E+11	Y	ND										
		1.00E+12	Y	no biopsy										
		1.00E+12	Y	26	77000	0	85.75	0.00	23.29	0.00	++	-	+++	-
		1.00E+12	Y	25	630000	0	182.76	0.00	77.52	0.00	+++	-	+++	-
		1.00E+12	Y	26	13000	30	0.00	0.00	0.00	0.00	-	-	-	-
		1.00E+12	Y	ND										
		1.00E+12	Y	ND										
		1.00E+12	Y	ND										
		1.00E+12	Y	ND										
CT-AMT-011-02		1.00E+12	Y	18	130	13	0.00	0.20	0.00	0.00	-	-	-	-
		second biopsy		52	1100000	0	188.30	0.00	54.10	0.00	+++	-	+	-
		1.00E+12	Y	30	7800	13	4.50	0.00	0.00	0.00	+	-	+	-
		1.00E+12	Y	14	730000	2400	49.00	1.90	13.00	0.00	+	-	+	-
		1.00E+12	Y	36	2500000	0	76.50	0.50	16.40	0.00	++	-	+	-
		1.00E+12	Y	14	770	290	0.50	0.00	0.00	0.00	-	-	-	-

I: injected muscle; C: non-injected muscle; ISR: immunosuppressive regimen; LPL IHC: detection of LPL by immunohistochemistry; Oil Red O: muscle sections stained for (intracellular) neutral lipid; ND: not done, biopsy not obtained.

https://www.ema.europa.eu/en/documents/assessment-report/glybera-epar-public-assessment-report_en.pdf

Glybera: Supportive clinical data

Table 2: Duration of hospitalization

Event		pre treatment (N=17)	post treatment (N=17)	untreated (N=5)
definite pancreatitis	Subjects with a hospitalization	14	3	4
	Median (min-max)	28.0 (0-1119)	0.0 (0-19)	53.0 (0-610)
probable pancreatitis	Subjects with a hospitalization	8	1	3
	Median (min-max)	0.0 (0-96)	0.0 (0-4)	7.0 (0-77)
abdominal pain	Subjects with a hospitalization	10	1	4
	Median (min-max)	3.0 (0-367)	0.0 (0-5)	8.0 (0-212)
other	Subjects with a hospitalization	13	0	3
	Median (min-max)	12.0 (0-95)	0.0 (0-0)	7.0 (0-20)

For subjects with no events the duration of hospitalization is set to 0 days; Sources: CSR 011-03 Table 8

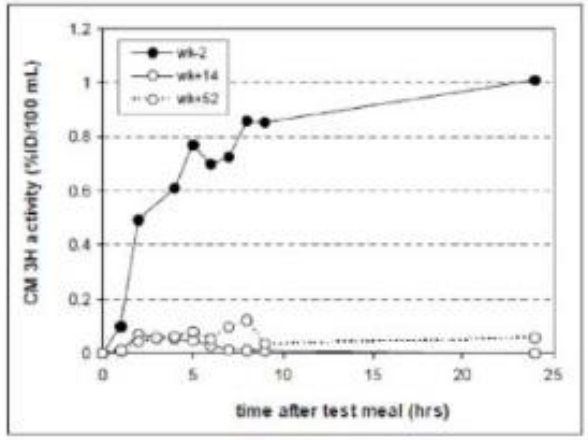
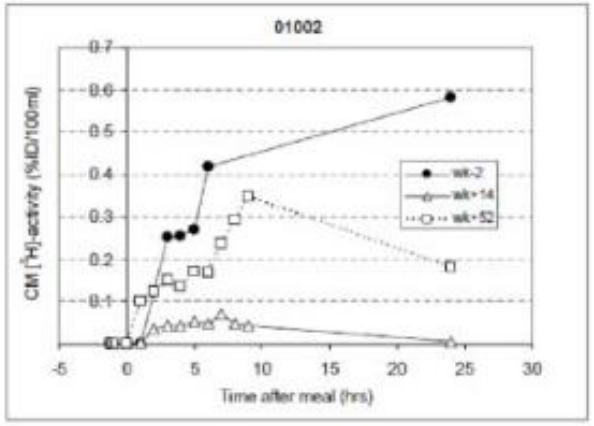
Table 3: Duration of ICU stay

Event		pre treatment (N=17)	post treatment (N=17)	untreated (N=5)
definite pancreatitis	Subjects with ICU stay	7	0	2
	Median (min-max)	0.0 (0-35)	0.0 (0-0)	0.0 (0-10)
probable pancreatitis	Subjects with ICU stay	2	0	1
	mean (SD)	0.2 (0.73)	0.0 (0.00)	0.0 (0.00)
	Median (min-max)	0.0 (0-3)	0.0 (0-0)	0.0 (0-0)
abdominal pain	Subjects with ICU stay	3	0	1
	Median (min-max)	0.0 (0-5)	0.0 (0-0)	0.0 (0-0)
other	Subjects with ICU stay	2	0	0
	Median (min-max)	0.0 (0-4)	0.0 (0-0)	0.0 (0-0)

For subjects with no events the duration of ICU stay is set to 0 days Sources: Table 4.3.3

https://www.ema.europa.eu/en/documents/assessment-report/glybera-epar-public-assessment-report_en.pdf

Glybera: Looking at (selected) individual patients

Subject	Pancreatitis prior to Glybera administration	Date of administration of Glybera/ Pancreatitis after Glybera	24-hour time course for [3H]-tracer within the postprandial chylomicron (CM) fraction, 2 weeks before and 14 and 52 weeks after Glybera administration.	LPL expression and activity
	14 (10 definite and 4 probable)	Glybera adm.:5 May-09 **1** probable pancreatitis (27 Apr 2010)		Table 3: LPL expression and activity in Injected (I) and Control, non-injected (C) muscle Subject No. / Sample / Visit / LPL Protein (ng/mg) / LPL Activity (nmol/mg/min) / Lipid Deposits (Oil Red O) / LPL Protein (ICH) / Glybera DNA (gc/mg DNA) [redacted] / I[1] / Wk14 / 0.0 / 0.0 / - / - / 130 C[1] / 0.2 / 0.0 / - / - / 13 I / Wk52 / 188.3 / 54.1 / 1+ / 3+ / 1100000 C / 0.0 / 0.0 / - / - / 0
	25 (16 definite, 8 probable, 1 probable occurred in the run-in period)	Glybera adm.: 27 Oct 2009 **0** pancreatitis		30 weeks post Glybera administration Table 3. Vector DNA and LPL expression and activity in muscle of subject 01002 previously administered Glybera. QPCR (gc/mg g DNA) I: 7800, C: 13 / LPL mass (ng/mg) I: 4.50, C: 0.00 / LPL Activity (nmol FFA/min/mg) I: 0.00, C: 0.00 / LPL IHC I: +, C: - / Oil Red O I: +, C: -

https://www.ema.europa.eu/en/documents/assessment-report/glybera-epar-public-assessment-report_en.pdf

A scientific approach to ultra-orphan drugs

CORRESPONDENCE

LINK TO ORIGINAL ARTICLE

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Regulatory evaluation of Glybera in Europe — two committees, one mission

Daniela Melchiorri, Luca Pani, Paolo Gasparini, Giulio Cossu, Janis Ancans, John Joseph Borg, Catherine Drai, Piotr Fiedor, Egbert Flory, Ian Hudson, Hubert G. Leufkens, Jan Müller-Berghaus, Gopalan Narayanan, Brigitte Neugebauer, Juris Pokrotnieks, Jean-Louis Robert, Tomas Salmonson, and Christian K. Schneider

Representing the first gene therapy to be approved in the Western world, alipogene tiparvovec (Glybera; Uniqure) has recently been said to have had a "substantial impact from a regulatory perspective" (*Nature Rev. Drug Discov.* **11**, 664; 2012)[1]. The therapy was granted marketing authorization in the European Union for the treatment of lipoprotein lipase deficiency, which results in a clinically heterogeneous condition with a risk of potentially life-threatening pancreatitis[2], at the end of 2012. The decision followed a positive opinion by the European Medicines Agency (EMA)'s Committee for Medicinal Products for Human Use (CHMP)[3], and a previous recommendation of the EMA's Committee for Advanced Therapies (CAT)[4,5].

The approval process for Glybera was extensively discussed in the scientific community, sometimes critically[6–12]. During the process, the opinions of the CHMP and the CAT differed: although the opinion of both committees was originally negative, in a "re-examination procedure" the opinion of the CAT became positive[5], whereas the CHMP maintained its negative opinion[13]. However, both committees finally recommended approval of the medicine. As regulators who have been involved in this approval process, we would like to provide insight into why the Glybera procedure was challenging, and give assurance to the scientific community regarding confidence in both orphan drug and gene therapy regulation in Europe.

The approval process for Glybera

In Europe, gene therapies undergo a centralized approval procedure via the EMA. For advanced therapy medicinal products (ATMPs), which include gene therapies, the CAT as an expert committee first performs a scientific assessment of the application dossier and prepares a draft opinion on its approvability for a final decision by the CHMP, a committee with considerable long-term expertise, which also ensures consistency in the opinions.

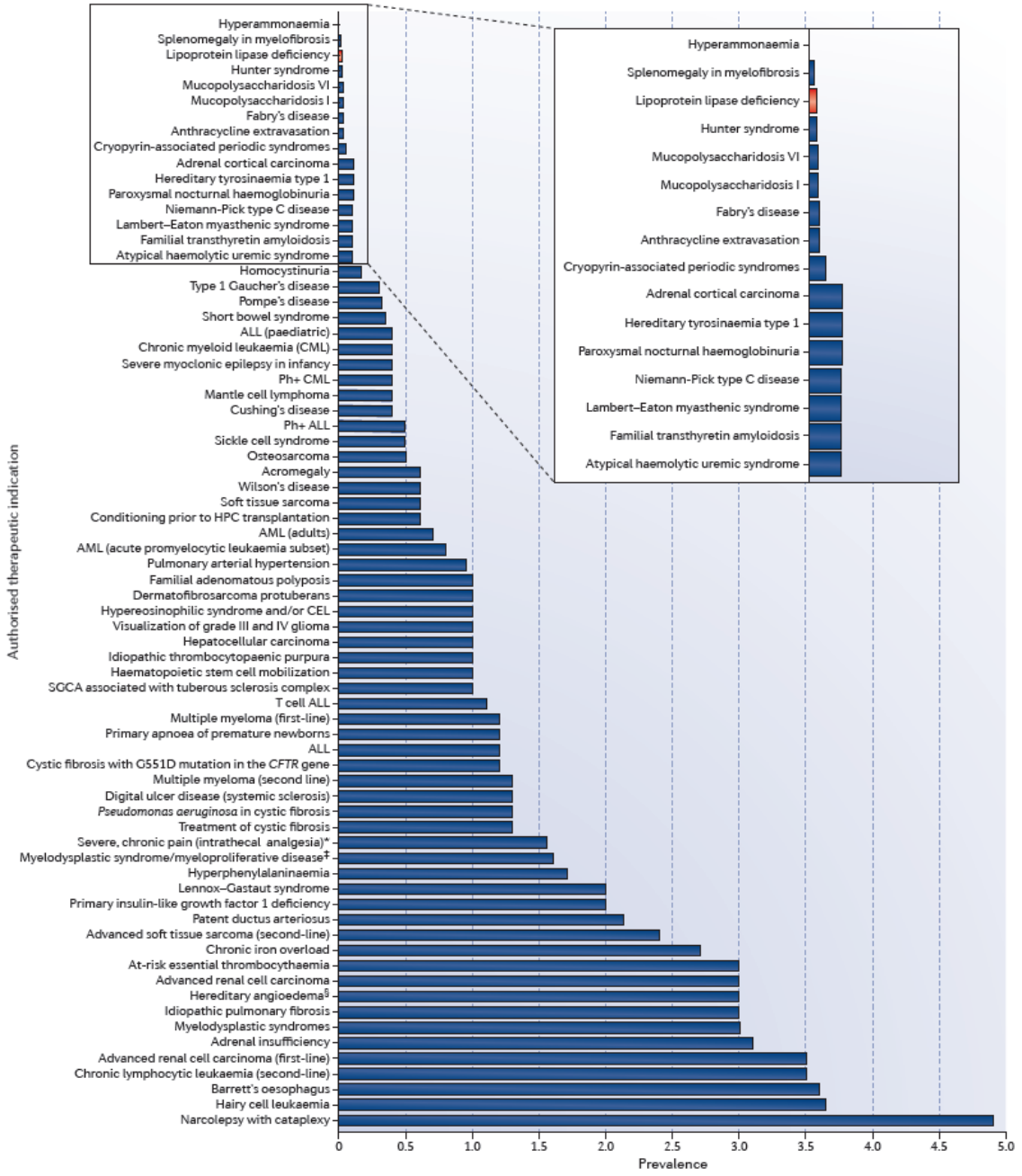
The assessment process for Glybera was long and complex owing to multiple reasons. These included the complexity of the product class for which there was little previous regulatory experience (this was the first procedure for a gene therapy to correct a genetic deficiency); the long product development time, during which science evolved and specific regulatory requirements were about to be established; the complex disease scenario (a very rare disease) with a fluctuating clinical outcome (pancreatitis); and the fact that the company was small with academic origins (as usually also seen for other ATMPs)[14].

The applicant's total clinical programme included 27 patients with lipoprotein lipase deficiency on a low-fat diet[2]. At first, the main measure of efficacy was based on a reduction in blood triglyceride levels. However, this was later changed to postprandial chylomicrons, as this biomarker was thought to more specifically address the pharmacodynamic effect of Glybera, whereas the effect on triglyceride levels was only short-lived. This raised additional issues during the scientific review: were the data robust enough for a previously non-validated biomarker (postprandial chylomicrons) in the presence of more inconclusive clinical evidence (pancreatitis)? Should data from that biomarker be accepted as pivotal evidence for activity, as it was scientifically better fitted to measure the treatment effect (as recommended by an *ad hoc* scientific advisory group to the CAT and CHMP) than the one originally defined in the protocol (triglyceride levels)? Or should one rather focus on that (formally failed) primary end point? There were only a handful of patients from the study population for whom such data on the newly proposed biomarker were available, and even fewer for a sustained period.

Although different opinions were issued by the two committees during the procedure, both committees were consistent in their scientific judgement when the details were considered. The CHMP acknowledged the promising nature of the data by an almost unprecedented "positive tone" when drafting its initial negative opinion, so as to demonstrate that it would be prepared to reconsider the case once more specific and supportive data had been collected (and here the vast majority of the CHMP agreed). The CHMP was clearly of the view that development should continue. We consider that both committees had already, at that time, taken major steps towards finding a way for ATMPs to be used for the treatment of very rare diseases, by considering all data rather than single outcome measures. Both committees considered that evolution of scientific knowledge can make the appreciation of an emerging, biologically more plausible biomarker necessary, if well justified and supported by data. Both committees were well aware that the acceptance of a limited data set was a double-edged sword, as it could be perceived as lowering the standards. However, this was not the case: both committees agreed that the limited clinical efficacy and safety data set needed to be supplemented by additional data.

The opinion of the two committees differed on the stage at which such additional data should be submitted: before approval (as initially preferred by the CHMP) or after approval (as recommended by the CAT). It is important to note that the final positive outcome was, to a major extent, also driven by an appreciation of the specific clinical scenario of lipoprotein lipase deficiency. Assessing orphan drugs in 'ultra-rare' conditions (here defined as a prevalence of less than 1 in 100,000) was not new to the CHMP; several drugs are already licensed for conditions with such low prevalence (FIG. 1). However, all of these conditions follow either a continuously progressive course of deterioration or a very active disease course if left untreated (TABLE 1). The effect of a therapeutic intervention for such conditions is therefore easier to measure within a relatively short timeframe.

Furthermore, surrogate markers for clinical outcome existed for these conditions (TABLE 1). By contrast, lipoprotein lipase deficiency results in pancreatitis in otherwise often phenotypically healthy individuals — a complication that is not



Need for a wider perspective

„Ultra-orphan drugs“:
Could be defined as prevalence of the disease of equal to or less than 0.1 in 10,000.

Melchiorri D et al: Regulatory evaluation of Glybera in Europe - two committees, one mission.
Nat Rev Drug Discov. 2013 Sep;12(9):719.

Pivotal data for ultra-orphan drugs

Authorised therapeutic indication	Prevalence (per 10,000)	Medicinal product	Date of Marketing Authorisation	Endpoints used	pivotal study duration	pivotal study(ies) size (patients)	Disease characteristics
Hyperammonaemia	0,001	**Carbaglu®**	24-01-2003	Biochemical and clinical course, incl. growth and survival	N/A	20	progressive disease (metabolical)
Splenomegaly in myelofibrosis	0,01	**Jakavi®**	23-08-2012	Number of patients with ≥ 35% spleen volume reduction at Week 24	24 weeks	219	progressive disease (haematological)
LPLD (lipoprotein lipase deficiency)	0,02	**Glybera®**	25-10-2012	reduction in fasting plasma triglyceride levels; additonal enpoints included chylomicron-related endpoints 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 (metabolical)
Hunter syndrome	0,02	**Elaprase®**	08-01-2007	6-minute walk test, % predicted FVC (baseline to week 53)	12 months	96	progressive disease (organ impairment)
Mucopolysaccharidosis VI	0,024	**Naglazyme®**	24-01-2006	12-minute walk test over time (week 6, 12, 18, 24)	24 weeks	39	progressive disease (organ impairment)
Mucopolysaccharidosis I	0,025	**Aldurazyme®**	10-06-2003	6-minute walk test, % predicted FVC (baseline to week 26)	26 weeks	45	progressive disease (organ impairment)
Fabry disease	0,027	**Fabrazyme®**	03/08/2001 (expired 07/08/2011)	Reduction of GL-3 accumulation from the capillary endothelium of the kidney to score 0 at week 20	20 weeks	58	progressive disease (organ impairment)
Fabry disease	0,027	**Replagal®**	03-08-2001	brief pain inventory BPI (study TKT003) and cardiac Gb3 levels as determined from cardiac biopsy samples (study TKT005)	24 weeks	26 and 15	progressive disease (organ impairment)
Anthracycline extravasation	0,03	**Savene®**	28-07-2006	proportion of patients undergoing surgical intervention	<28 days	23 and 57	acute condition
Cryopyrin-Associated Periodic Syndromes	0,05	**Ilaris®**	23-10-2009	proportion of patients with disease flare in part II (randomized withdrawal)	48 weeks (three parts)	35	active inflammatory clinical course
Cryopyrin-Associated Periodic Syndromes	0,05	**Rilonacept Regeneron®**	23-10-2009	mean change from baseline to endpoint in the mean key symptom score (both parts of study)	48 weeks	47	active inflammatory clinical course
Adrenal cortical carcinoma	0,1	**Lysodren®**	28-04-2004	Bibliographical evidence (220 articles) with various endpoints including survival, remission time, tumour size reduction	N/A (variable)	N/A (ca. 500 patients overall)	progressive disease (cancer)
Hereditary tyrosinemia type 1	0,1	**Orfadin®**	21-02-2005	Data from a compassionate use programme including survival, survival without transplantation, death due to liver failure, transplantation due to liver failure and hepatocellular carcinoma.	N/A (variable)	ca. 207	progressive disease (metabolical)
Paroxysmal nocturnal haemoglobinuria	0,1	**Soliris®**	20-06-2007	haemoglobin stabilization and units of PRBCs transfused during the treatment phase	26 weeks	88	active disease requiring regular intervention
Niemann-Pick type C disease	0,1	**Zavesca®**	26-01-2009	mean change from baseline to Month 12 for Horizontal saccadic eye movements	12 months	29	progressive disease (neurological)
Lambert-Eaton myasthenic syndrome	0,1	**Firdapse®**	23-12-2009	Bibliographical evidence with two main studies; endpoint measurements included various neurological scores including measurements of neurological disability score, muscle strength, electrophysiological measurements, or the quantitative myasthenia gravis score	15 days and 6 days	12 and 26	progressive disease (neurological)
Familial transthyretin amyloidosis	0,1	**Vyndaqel®**	16-11-2011	Co-primary endpoint: (1) improvement or stabilization in the Neurologic Impairment Score–Lower Limb score; (2) Change from Baseline in the Total Quality of Life Norfolk QOL-DN score	18 months	128	progressive disease (neurological)
Atypical haemolytic uremic syndrome (aHUS)	0,1	**Soliris®**	24-11-2011	Platelet change from baseline and haematologic normalisation (study 1), and TMA Event-Free status and haematologic normalization from baseline (study 2)	26 weeks	17 and 20	progressive disease (organ impairment)

Melchiorri D et al: Regulatory evaluation of Glybera in Europe - two committees, one mission. Nat Rev Drug Discov. 2013 Sep;12(9):719.

The CAT as a scientific player

OPINION

Challenges with advanced therapy medicinal products and how to meet them

The Committee for Advanced Therapies (CAT) and the CAT Scientific Secretariat

Abstract | Advanced therapy medicinal products (ATMPs), which include gene therapy medicinal products, somatic cell therapy medicinal products and tissue-engineered products, are at the cutting edge of innovation and offer a major hope for various diseases for which there are limited or no therapeutic options. They have therefore been subject to considerable interest and debate. Following the European regulation on ATMPs, a consolidated regulatory framework for these innovative medicines has recently been established. Central to this framework is the Committee for Advanced Therapies (CAT) at the European Medicines Agency (EMA), comprising a multidisciplinary scientific expert committee, representing all EU member states and European Free Trade Association countries, as well as patient and medical associations. In this article, the CAT discusses some of the typical issues raised by developers of ATMPs, and highlights the opportunities for such companies and research groups to approach the EMA and the CAT as a regulatory advisor during development.

Advanced therapy medicinal products (ATMPs) comprise gene therapy medicinal products (GTMPs), somatic cell therapy medicinal products and tissue-engineered products (for legal definitions see BOX 1 and REFS 1,2). They are at the forefront of innovation, offering potential treatment opportunities for diseases that currently have limited or no effective therapeutic options. ATMPs have therefore been subject to considerable interest, but have generated both positive and negative outcomes.

For example, recent publications have suggested that gene therapy for monogenetic diseases could result in long-term beneficial results and may prove to be an effective treatment strategy[3–5]. In addition, cell-based skin substitutes and cartilage products have already been used for more than a decade, and upcoming somatic cell therapy medicinal products and tissue-engineered products might also become efficacious treatment modalities. However, despite their promise and the progress made, ATMPs have sometimes caused clinical problems, which have led to reports in the lay press. For example, although rare, fatalities following gene therapy have been reported, including a lethal systemic inflammatory immune reaction and leukaemia due to insertional oncogenesis[6,7]. Recently, fetal stem cells were reported to cause a brain tumour, suggesting that cell-based medicinal products (CBMPs) also have intrinsic risks that need to be addressed[8].

With the new European regulation on ATMPs[1], a consolidated regulatory framework for these innovative medicines has recently been assembled. Central to this new legislation is the establishment of the Committee for Advanced Therapies (CAT) at the European Medicines Agency (EMA) in London, UK. The CAT is a multidisciplinary scientific committee of experts representing all member states of the European Union and countries from the European Economic Area and the European Free Trade Association (Iceland and Norway are currently represented in the CAT), as well as representatives from patient and medical associations (BOX 2). This independent committee, with a high degree of expertise in both the scientific and regulatory aspects of ATMPs, started its work in January 2009. The CAT gathers dedicated European experts to review the quality, safety and efficacy of ATMPs according to standards established by regulatory authorities, and to debate scientific developments in the field. Information on the declared scientific expertise of the CAT members and alternates (reflecting the expertise required by the regulation on ATMPs) can be found in FIG. 1.

The CAT is responsible for the primary evaluation of ATMP marketing authorization applications (MAAs) for the EMA's Committee for Medicinal Products for Human Use (CHMP). The CAT operates two new regulatory procedures for companies developing ATMPs — the classification procedure and the certification procedure — which are both discussed further below. The CAT aims to foster innovative medicines while maintaining a high standard of regulatory responsibility. Guidance had already been developed by various EMA and CHMP regulatory groups (for example, the Biologics Working Party, the Gene Therapy Working Party or the Cell-based Products Working Party) before the establishment of the CAT, and through the Scientific Advice Working Party. However, the CAT now combines and complements these activities within a single committee to support the development of ATMPs in Europe.

Marketing authorization of ATMPs requires, as for all medicinal products, that the applicant demonstrates that the product is consistently manufactured to a predefined quality, and that it is safe and efficacious in patients. The CAT recognizes that some ATMPs will require new strategies for their development and scientific assessment. For example, the clinical performance of many types of CBMPs strongly depends on the final performance of the cell preparation administered. Success depends on the rigorous control of the manufacturing process and specifications, which has

PERSPECTIVES

Box 2 | **The European Committee for Advanced Therapies**

Members and their alternates, as of February 2010, of the European Committee for Advanced Therapies (CAT) are outlined below. Full details of each member, including contact details, are available from the European Medicines Agency website (see Further information).

- CAT Chairman: Christian K. Schneider
- CAT Vice-Chairperson: Paula Salmikangas
- European Commission representative: María-Angeles Figuerola-Santos
- European Medicines Agency and CAT Scientific Secretariat: Lucia D'Apote
- European Medicines Agency and CAT Secretariat: Olga Oliver-Diaz
- Paul-Ehrlich-Institut and CAT Scientific Secretariat: Isabel Büttel
- European Medicines Agency and CAT Scientific Secretariat: Patrick Celis

Country/Organization	Representative	Alternate
Members nominated from within the Committee for Medicinal Products for Human Use		
Lithuania	Romaldas Mačiulaitis	Jolanta Gulbinovic
Luxembourg	Jean-Louis Robert	Guy Berchem
Portugal	Beatriz Silva Lima	Margarida Menezes-Ferreira
Spain	Sol Ruiz	Marcos Timón
Members nominated by member states		
Austria	Bernd Jilma	Ilona G. Reischl
Belgium	Bruno Flamion	Claire Beuneu
Bulgaria	Lyubina Racheva Todorova	Rosen Georgiev
Cyprus	Anna Paphitou	Maria Vassiliou
Czech Republic	Ivana Haunerova	Alena Pychova
Denmark	Awaiting nomination	Mette Clausen
Estonia	Toivo Maimets	Awaiting nomination
Finland	Paula Salmikangas	Taina Methuen
France	Jean-Hugues Trouvin	Sophie Lucas
Germany	Egbert Flory	Martina Schüssler-Lenz
Greece	Asterios Tsiftsoglou	Vasileios Kokkas
Hungary	Balázs Sarkadi	Zsuzsanna Buzás
Iceland	Kolbeinn Gudmundsson	Awaiting nomination
Ireland	Maura O'Donovan	Niall MacAleenan
Italy	Giovanni Migliaccio	Maria Cristina Galli
Latvia	Jānis Ancāns	Aija Linē
Malta	Anthony Samuel	Awaiting nomination
Netherlands	Johannes H. Ovelgönne	Awaiting nomination
Norway	Marit Hystad	Awaiting nomination
Poland	Andrzej Mariusz Fal	Mariusz Frączek
Romania	Anca Stela Moraru	Nela Vilceanu
Slovakia	Peter Turčáni	Mikuláš Hrubiško
Slovenia	Robert Zorec	Petra Marinko
Sweden	Lennart Åkerblom	Wing Cheng
United Kingdom	Gopalan Narayanan	George Andrew Crosbie
Members representing patient organizations		
EGAN	Alastair Kent	Nick Meade
EURORDIS	Fabrizia Bignami	Michelino Lipucci di Paola
Members representing clinicians		
ESGCT	J. George Dickson	Thierry VandenDriessche
EBMT	Dietger Niederwieser	Per Ljungman

EBMT, European Group for Blood and Marrow Transplantation; EGAN, European Genetic Alliances' Network; ESGCT, European Society of Gene and Cell Therapy; EURORDIS, European Organisation for Rare Diseases.

considerations might have to be used to specifically measure toxicity, potentially at a low dose. In addition, a surgical explantation and *in vitro* propagation of cells might lead to bacterial or viral contaminations, which cannot be eliminated by sterilization. Consequently, this warrants the development of new safety methods and improved testing for potential contaminants.

One of the major clinical hurdles to overcome is the definition of the clinical target dose, as classical dose-finding strategies — that is, by selecting a dose for a confirmatory study from several tested doses in exploratory studies — may be problematic and raise the need for alternative approaches to define at least a minimally effective dose. In the field of regenerative medicine, suitable comparator treatments or products may not always be available, and a double-blind design might not be possible. Acceptable end points that were originally established for other product types may sometimes have to be adapted for a cell-based product[13]. For example, initial tumour swelling for cancer immunotherapies due to T-cell influx that would, in a common definition, represent a progression of disease owing to an increase in tumour diameter.

Certainly, such challenges are common in the development of ATMPs, and early dialogue with regulators should prove to be useful. The development concept, characterization programme and complementation by non-clinical and clinical testing are issues frequently discussed in scientific advice procedures in which the CAT is actively involved. Considering the aforementioned diversity of products and a risk-based approach, a central milestone document has already been developed by the Cell-based Products Working Party[14].

Gene therapy medicinal products

GTMPs aim at delivering a gene with the intention to obtain, through its expression, a therapeutic effect in a patient (for a legal definition see BOX 1 and REF. 2). This gene may encode a protein that is either absent or dysfunctional, or a protein that inhibits or modulates the function of a given effector structure associated with the underlying pathology. A GTMP typically functions as a sequence of different components. That is, the vector and the inserted sequence(s), the target cells modified by the vector, and finally the protein encoded by the vector and expressed upon successful gene transfer. Each of these components can contribute to either desired effects or untoward side effects[15]. This adds to the complexity of GTMPs as compared

The CAT took a stance

Special Report: International

The murky ethics of stem-cell tourism

A recent case of adverse outcomes from an unproven stem-cell treatment has exposed an ethical grey area. Fears that the improper use of stem-cell therapies could have serious adverse consequences were confirmed recently, after it was reported that an Israeli boy developed benign tumours in the brain and spinal cord after being injected with fetal neural cells at a Moscow clinic in Russia. The case was described in the Feb 17, 2009, issue of *PLoS Medicine*.

The authors of the report, who are based at the Sheba Medical Center in Tel Aviv, Israel, point out that this is the first example of donor-derived brain tumours developing after fetal neural cell transplantation. They call the case "worrying" and urge more research to assess the safety of this therapy.

The report has intensified concerns regarding the unregulated use of therapies involving various types of stem cells to treat conditions ranging from cancer to Parkinson's disease. It has focused attention on a phenomenon known as stem-cell tourism, in which desperately ill patients and their families go to clinics all over the world in the hope of finding at least an improvement in their condition, if not a cure. One Chinese clinic claims to have treated more than 5000 patients from different countries. Reports of people mortgaging their homes to finance these journeys are not unusual.

The patient involved in the *PLoS Medicine* paper traveled to Moscow with his parents for treatment of his ataxia telangiectasia. Between 2001 and 2003, he received several injections of fetal neural tissue into his brain and cerebrospinal fluid. In 2005, when he was 13 years old, he began complaining of recurrent headaches. MRI studies done at the Sheba Medical Center showed abnormal growths in his brain and spinal cord, which turned out to be benign. Doctors at Sheba removed the spinal cord tumour in 2006, but were unable to remove the brain growth. The spinal tissue resembled a glioneuronal tumour and contained both male and female cells. HLA typing suggested that the fetal cells came from at least two different donors, one of whom was female. Unfortunately, the treatment yielded "no detectable benefit for the patient", said Gideon Rechavi, head of the Sheba Cancer Research Center, and Ninette Amariglio, head of the Hematological Oncology Research Laboratory at Sheba Medical Center.

Other observers were more outspoken. D Eugene Redmond Jr, professor of psychiatry and neurosurgery at Yale University (New Haven, CT, USA), was one of a team of western physicians who examined the Moscow clinic, which had reported good results treating several patients with ataxia telangiectasia. "Our findings were quite negative", he recalled. "We could not see any evidence of real clinical benefit, although the families and the doctors seemed desperate to find one. There were no control procedures, except that the videotapes could be viewed and evaluated by other experts. They did not show us any evidence that the cells that they were injecting were anything other than primary fetal brain cells that had been in culture—no evidence that they were in fact stem cells of any type." All in all, he said, "the whole effort was sufficiently poorly controlled that it is impossible to gain any useful scientific data from these tragic cases".

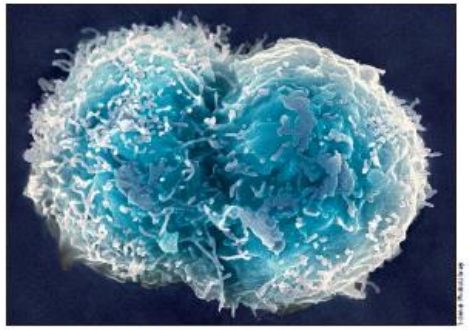
Evan Snyder, director of the Program in Stem Cells and Regenerative Biology at the Burnham Institute (La Jolla, CA, USA), has also visited the hospital in question and analysed the cells used in a similar case. "We demonstrated that these were not neural stem cells. What these patients are getting is essentially fetal brain put in a blender. It has no implications for proper stem cell biology. It's closer to fetal tissue transplantation, but it's not even good fetal tissue transplantation."

Desperately ill people and their loved ones will snatch at any glimmer of hope, so it is easy to fathom the appeal of these clinics to the public. They claim to use embryonic, adult, and haematopoietic stem cells as well as cord blood cells, and advertise

For more on **the Moscow clinic case** see *PLoS Med* 2009; published online Feb 17; DOI:10.1371/journal.pmed.1000029

For more on **the follow-up of Hongyun Huang's patients** see *Neurorehabil Neural Repair* 2006; 20: 5–13

For the **Guidelines for the Clinical Translation of Stem Cells** see *Cell Stem Cell* 2008; 3: 607–09



Stem cells raise new hopes and new questions

Ouagadougou, Burkina Faso (AO); and University of Newcastle, Newcastle, UK (SC)

1 Kok M, de Souza DK. Young Voices demand health research goals. *Lancet* 2010; **375:** 1416–17.
2 Anon. Declaration of the International Students' Meeting on Public Health (ISMOPH). April 27, 2009; Istanbul, Turkey. http://www.t-hasak.org/english/word%20congres/ismoph.pdf (accessed July 27, 2010).

Use of unregulated stem-cell based medicinal products

Advanced-therapy medicinal products (ATMPs) include stem cells, gene therapy, or engineered tissues, and hold promise for a large number of currently incurable diseases. Yet no marketing authorisation has been granted for any stem-cell medicinal products in the European Union.

ATMPs are complex and their evaluation requires specific expertise. For this reason, the Committee for Advanced Therapies (CAT) was established in the European Medicines Agency. The CAT is responsible, among other tasks, for preparing a draft opinion on the quality, safety, and efficacy of ATMPs that follow the centralised marketing authorisation procedure.[1]

The CAT is concerned about a phenomenon known as stem-cell tourism in which severely ill patients travel to clinics around the world where unauthorised stem-cell-based treatments are offered in the absence of rigorous scientific and ethical requirements. Some clinics offer these unauthorised therapies to desperate patients with incurable diseases at a high cost without ethics approval from independent bodies and potentially without documentation of adequate quality standards necessary for the protection of patients' safety.

There are serious concerns about the safety and efficacy of such experimental treatments that use poorly defined stem-cell preparations from a variety of sources. These preparations are often inadequately characterised[2] and they can lack pharmacological or toxicological data from non-clinical studies to establish reasonable evidence of safety and efficacy.[2,3] Generally, there are no peer-reviewed publications to demonstrate their efficacy. The retrospective data analyses that are sometimes found on the clinics' websites lack transparency; hence, such data cannot be properly assessed. However, there are already well documented cases of where so-called stem-cell therapy has resulted in serious adverse effects, including brain tumours,[2] meningitis, or other life-threatening infections.[3]

The CAT strongly encourages high-quality research leading to the development of stem-cell-based medicinal products in approved programmes of research and development. Before clinical use, rigorous non-clinical studies should be done to establish the safety and effectiveness.[4]

To ensure the safety of patients involved in clinical research, development of stem cells should comply with the highest standards, as for any investigational medicinal product, under the supervision of statutory regulatory bodies. Those planning the development of such treatments are encouraged to engage in dialogue with the CAT at an early stage of this process.

We declare that we have no conflicts of interest.

For members of the **Committee for Advanced Therapies** and the **CAT Scientific Secretariat** see webappendix

Committee for Advanced Therapies and CAT Scientific Secretariat
advancedtherapies@ema.europa.eu
European Medicines Agency, London E14 4HB, UK

1 European Union. 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. http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2007:324:0121:0137:en:PDF (accessed July 21, 2010).
2 Regenberg AC, Hutchinson LA, Schanker B, Mathews DJ. Medicine on the fringe: stem cell-based interventions in advance of evidence. *Stem Cells* 2009; **27:** 2312–19.
3 Barclay E. Stem-cell experts raise concerns about medical tourism. *Lancet* 2009; **373:** 883–84.
4 Committee for Advanced Therapies. Reflection paper on stem cell-based medicinal products. http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2010/03/WC500079932.pdf (accessed July 27, 2010).

Patients' information sheets and multicentre studies

Service Users Research Endeavour (SURE) is a patients' representative group at the Liverpool Heart and Chest Hospital, UK. One of our main functions is to check the clarity of patients' information sheets. We would like to bring to your attention what we find to be a lack of consistency in the information sheets that accompany commercial multicentre studies.

Patients' information sheets should give a fully comprehensive idea of what the study means and what is expected from participating individuals. But they should also be concise and in a language easily understood by patients and laypeople. In May, 2008, the UK's National Research Ethics Service introduced the requirement for a lay summary with each new clinical research application, but there does not seem to be any way of enforcing this requirement. In our experience, when dealing with commercial multicentre studies with a central site responsible for drafting and circulating patients' information sheets, the lay summary is often missing from the submitted documentation.

Our experience with one study led us to write directly to the sponsoring pharmaceutical company. In this case, the patients' information sheet was 18 pages long and written in complicated language that was not very meaningful to a layperson and even less so to a sick patient. The company then produced a one-page lay summary that was clear and informative and very welcome to the SURE group members.

In general terms, lay groups might feel that there is a lack of cooperation from big pharmaceutical companies in the production of lay summaries, but our experience shows that direct communication can have the desired result. However, a direct approach should not be necessary if companies

Our environment was (is) different than for conventional medicines

commentary

Clinical Development of Advanced Therapy Medicinal Products in Europe: Evidence That Regulators Must Be Proactive

Romaldas Maciulaitis[1,2], Lucia D'Apote[3], Andrew Buchanan[3], Laura Pioppo[3,4] and Christian K Schneider[1,5,6]

doi:10.1038/mt.2012.13

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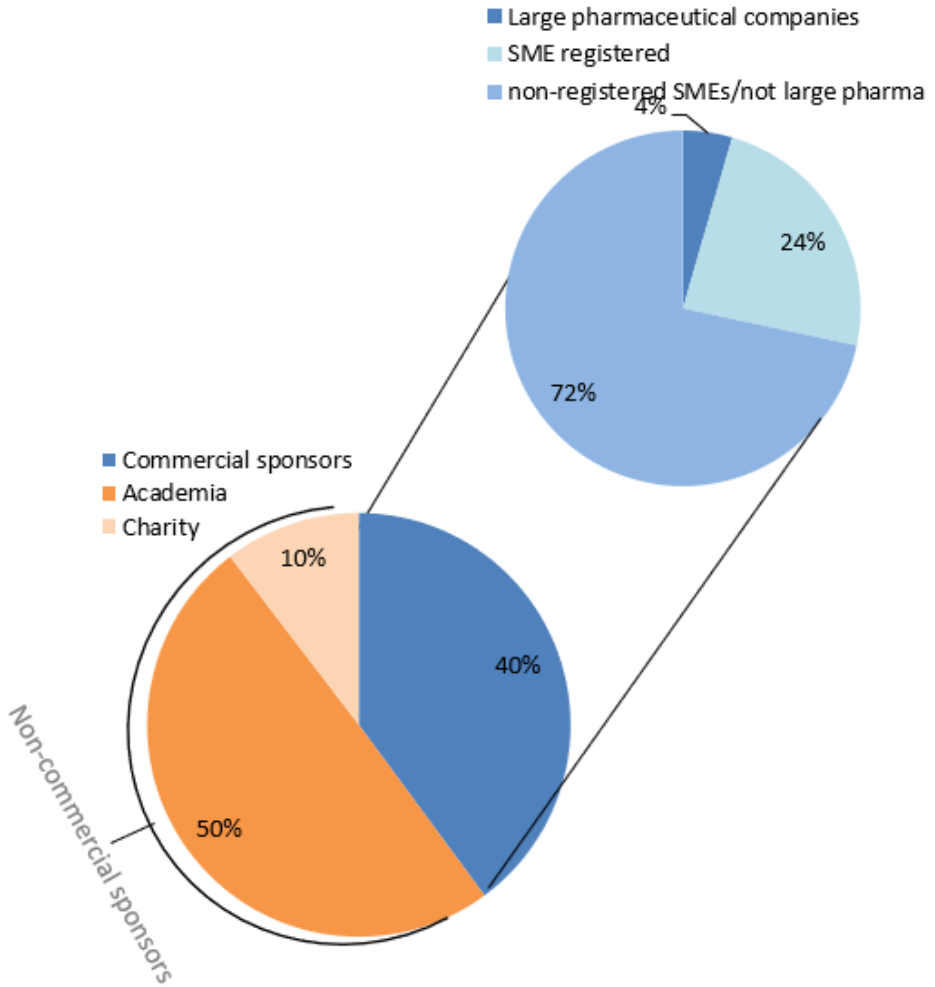
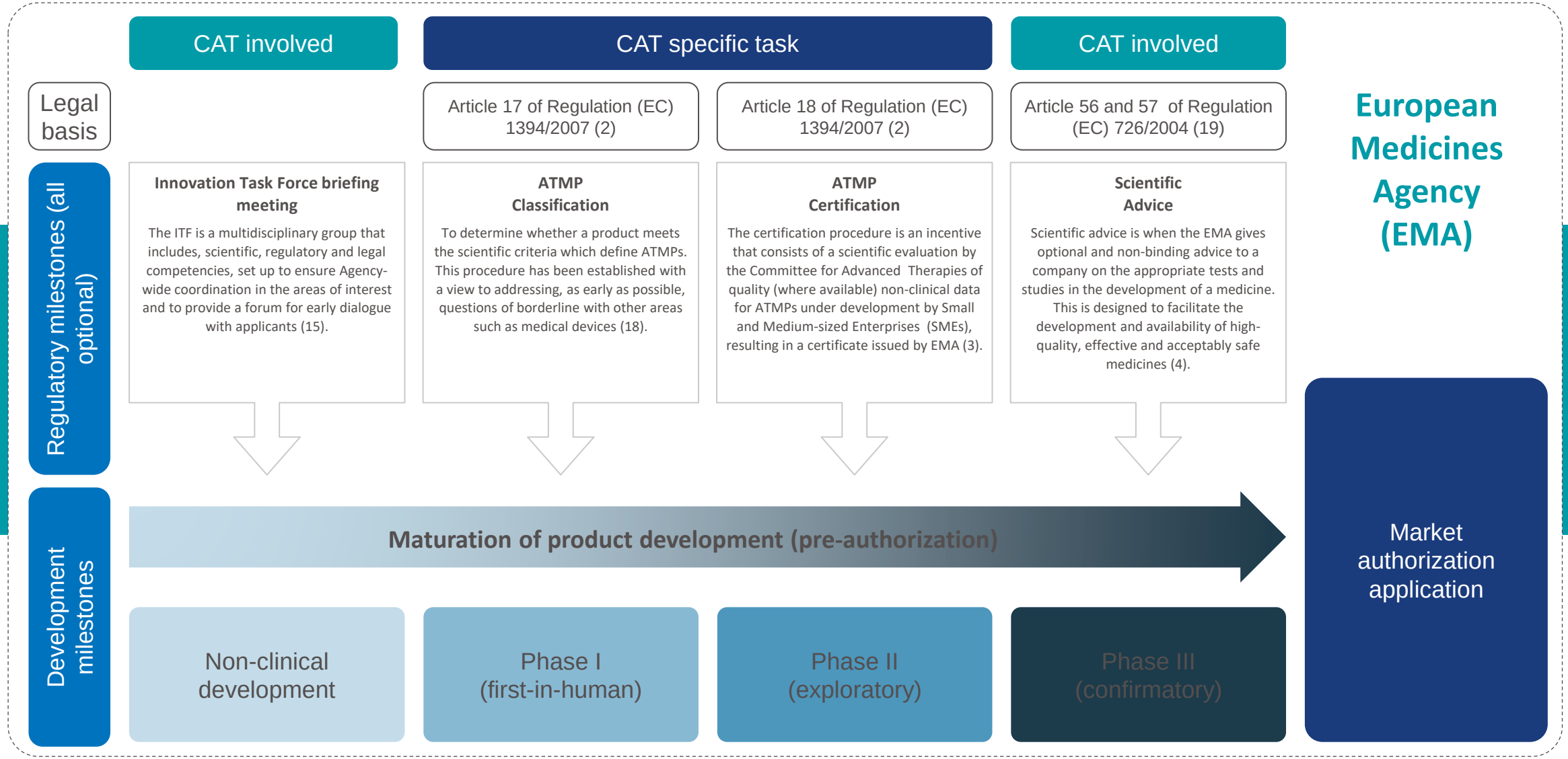


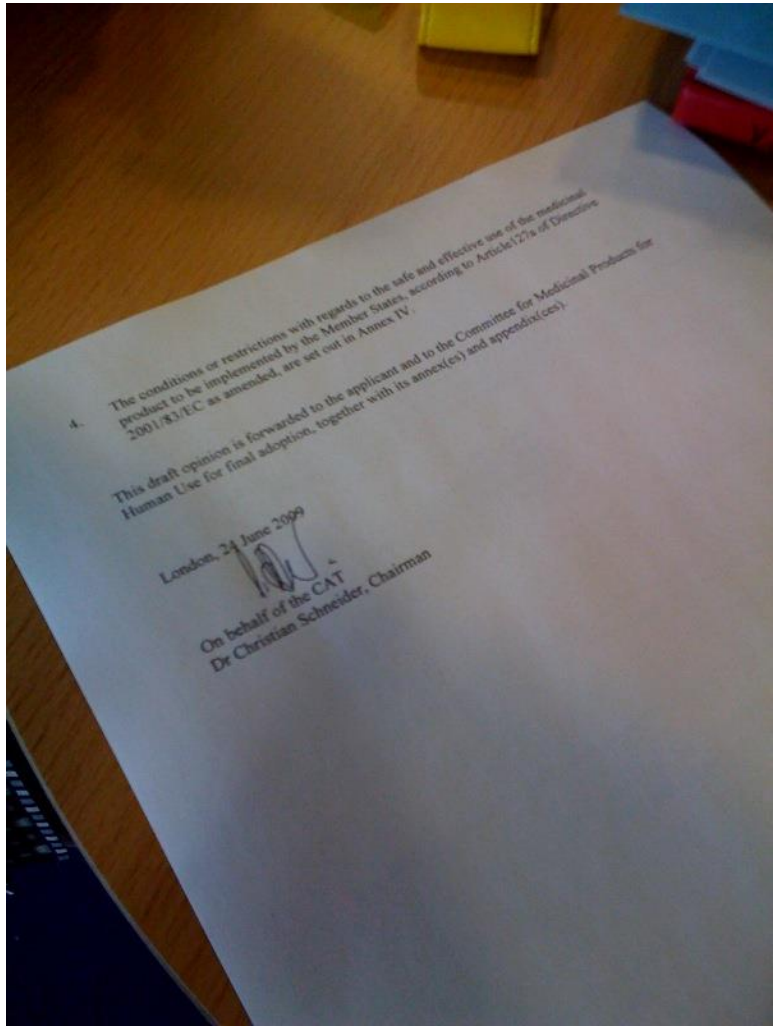
Analysis of the EudraCT database (2004-2010):
318 trials with ATMPs

We filled a powerhouse of innovation with life!



The figure shows the usual sequence on when the procedures are requested by Applicants.
Note that all procedures can be requested at any time during development

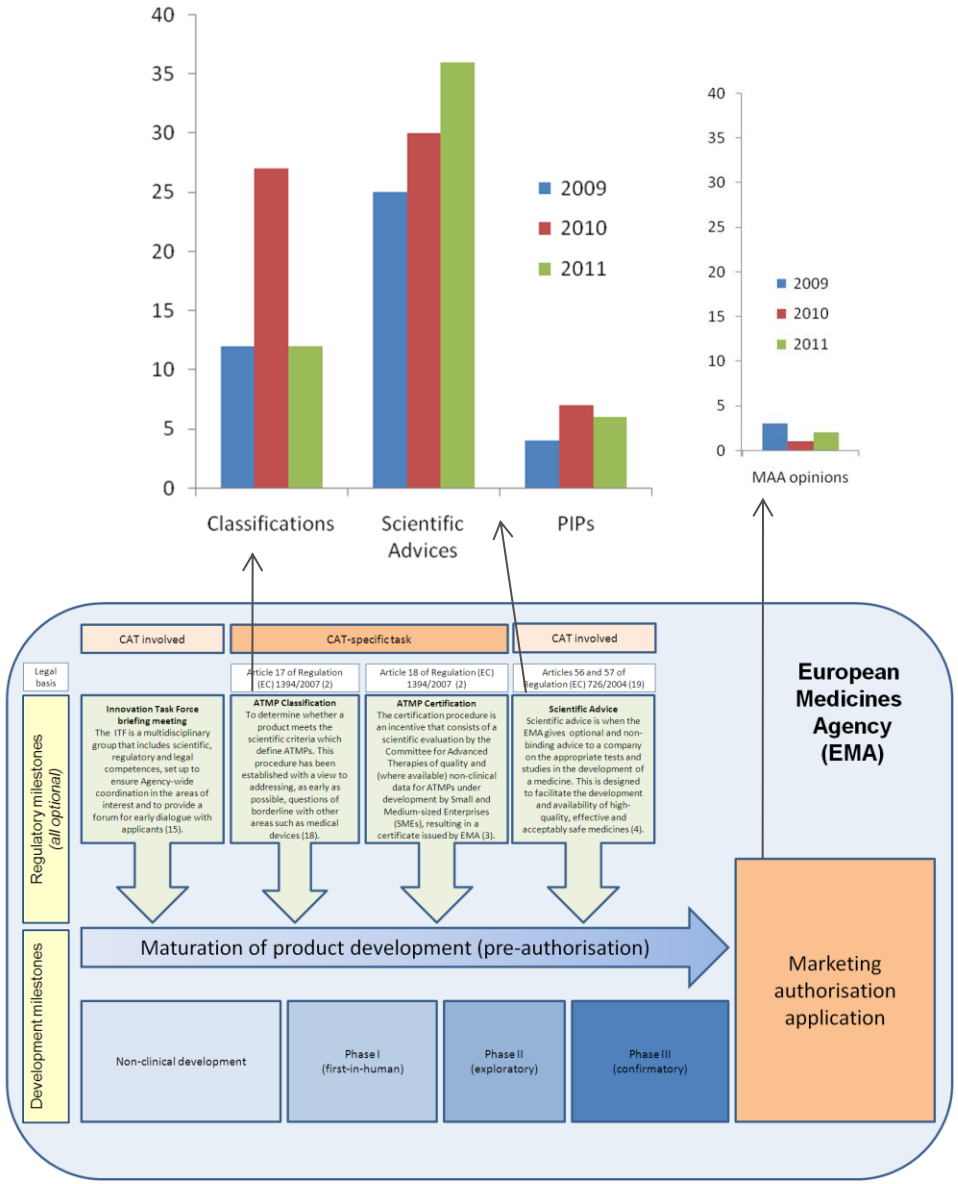
Our scientific approach led to…
…the first authorized ATMP in the EU (ChondroCelect®!



Where were we after the first term (3 years)?

- First ATMP licensed
- Several ones under review
- First certification issued
- Two papers published
  (Nature Reviews Drug Discovery, The Lancet)
- Framework further defined
  (Guidelines, Reflection Papers)
- Work programme adopted
- Interaction with stakeholders intensified
- Gaps identified
  (Hospital exemption, minimally manipulated ATMPs, borderline classifications, lack of incentives for academia,…)

”The Committee with only two products”?

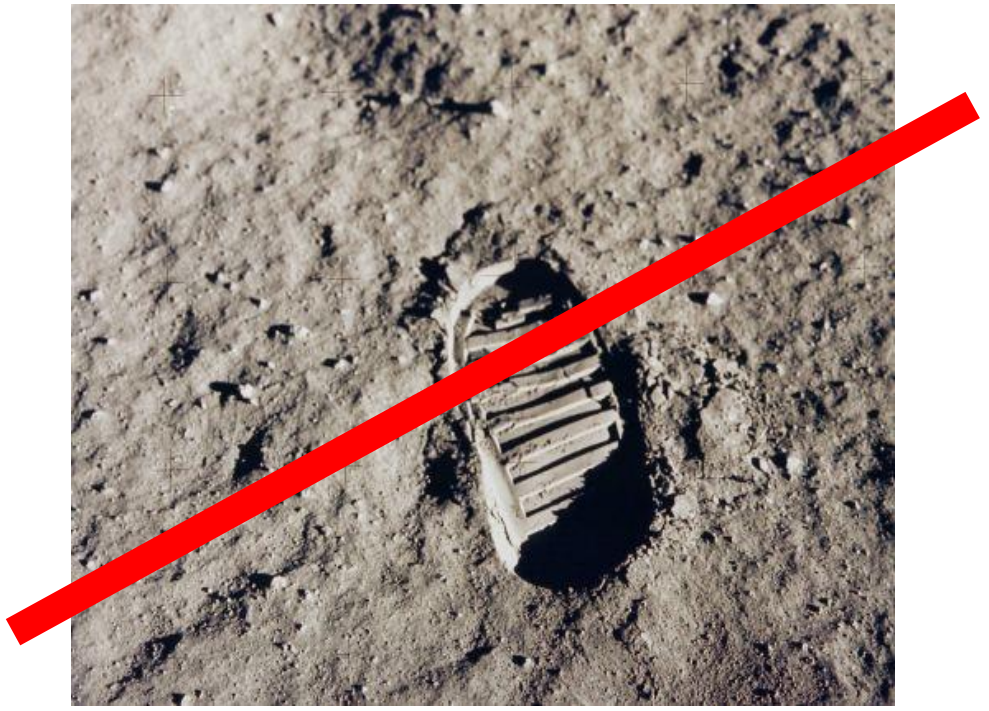


Source: CAT monthly report, EMA website

What made (and makes) the CAT so special?

- Multidisciplinary committee – this was (is) vital
  - CMC discussions, for example, can impact clinical debates, and clinical experts can be important to put CMC and non-clinical findings into perspective
  - We sometimes found solutions to problems at hand which we had not thought of in our individual disciplines
- The CAT had decent time to discuss items in-depth which was an important aspect, at least in the early days
  - It was a time where not only Pharmaceutical Companies with new developments, but also the Regulators had to bring the field forward
- These discussions trained members, assessors and others involved, beyond their core disciplines – a true forum of scientific excellence.
- Every member was active and involved – a true European undertaking.

We became:
The Committee with the large pipeline



That's one small step for a man,
but one giant step for mankind…
…but I am not going to take it,
because it's too risky.

Neil Armstrong

Thank you!

Dr Christian K Schneider, M.D.

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