EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

19 July 2012
EMA/882900/2011
Committee for Medicinal Products for Human Use (CHMP)

Assessment Report

Glybera

International Nonproprietary Name: **Alipogene tiparvovec**

Procedure No. EMEA/H/C/002145

Note

Assessment Report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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List of abbreviations

AAV	adeno-associated virus
AAV1	adeno-associated virus serotype 1
AAV2	adeno-associated virus serotype 2
AMT	Amsterdam Molecular Therapeutics
bp	base pairs
BVDV	Bovine viral diarrhoea virus,
BWP	Biotechnology Working Party
CAL	Cells at limit of or beyond the maximum level used for production
cap	capsid
CAT	Committee for Advanced Therapy Medicinal Products
CHMP	Committee for Human Medicinal Products
CM	chylomicrons
CMV	cytomegalovirus
CPK	creatine phosphokinase
CPV	Canine Parvovirus
CSA	ciclosporin A
CYP	cytochrome P450
DNA	deoxyribonucleic acid
DP	Drug Product
DS	Drug Substance
ELISA	Enzyme Linked Immunosorbant Assay
EMCV	Encephalomyocarditis Virus
EMEA/EMA	European Medicines Agency
ERA	Environmental Risk Assessment
gDNA	genomic DNA
gc	genome copies
GFP	Green Fluorescent Protein
GCP	Good Clinical Practice
GD	Gestation Day
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
GTWP	Gene Therapy Working Party
HBx	Hepatitis B Protein X
HDL	high-density lipoprotein
HDL-C	high-density lipoprotein cholesterol
HR	Homologous Repeats
ICH	International Conference on Harmonisation
ICU	intensive care unit
IM	intramuscular
INN	International Nonproprietary Name
ip	infectious particles
ITRs	inverted terminal repeats
IV	intravenous
LAM-PCR	Linear Amplification-Mediated PCR
LDL	Low Density Lipoproteins
LOD	limit of detection
LoI	List of outstanding issues
LOQ	limit of quantification
LoQ	List of questions
LPL	lipoprotein lipase gene
LPL	lipoprotein lipase
LPLD	lipoprotein lipase deficiency
LPL-/-	homozygous lipoprotein lipase deficient
LPL+/-	heterozygous lipoprotein lipase deficient
LTFU	Long-Term Follow Up
MCB	Master Cell Bank
MMF	mycophenolate mofetil
MOI	multiplicity of infection
MSV	Master Seed Virus
n	number
N/A	not applicable

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NGS	Next Generation Sequencing
NOAEL	non-observable-adverse-effect level
ORF	open reading frame
PBS	phosphate buffer solution
PETG	Polyethylene Terephthalate Copolyester
Ph. Eur.	European Pharmacopoeia
PP CM	post-prandial chylomicronemia
PRE	Post Transcriptional Regulatory Elements
PRV	Pseudorabies Virus
QC	quality control
Q-PCR	quantitative Polymerase Chain Reaction
QPPV	Qualified Person for Pharmacovigilance
rc	replication competent
rep	replicase
RMP	Risk Management Plan
SAEs	Serious Adverse Events
SmPC	Summary of Product Characteristics
SOP	Standard Operating Procedure
TC	total cholesterol
TG	triglycerides
VHH	Binding ligand from the immunoaffinity chromatography resin
VLDL	Very Low Density Lipoprotein
WCB	Working Cell Bank
WHV	Woodchuck Hepatitis Virus
WHx	Woodchuck Hepatitis Virus Protein X
WPRE	woodchuck hepatitis virus post transcriptional regulatory element
WSV	Working Seed Virus
wt	wild type

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1. Background information on the procedure

1.1. *Submission of the dossier*

The applicant Amsterdam Molecular Therapeutics (AMT) B.V) submitted on 23 December 2009 an application for Marketing Authorisation to the European Medicines Agency (EMA) for Glybera, through the centralised procedure falling within the Article 3(1) and point 4 of Annex of Regulation (EC) No 726/2004.

Glybera, was designated as an orphan medicinal product EU/3/04/194 on 08.03.2004. Glybera was designated as an orphan medicinal product in the following indication: treatment of lipoprotein lipase deficiency. The calculated prevalence of this condition was 0.02 per 10,000 EEA population.

Following the CHMP positive opinion on this marketing authorisation, the Committee for Orphan Medicinal Products (COMP) reviewed the designation of Glybera as an orphan medicinal product in the approved indication. The outcome of the COMP review can be found on the Agency's website ema.europa.eu/Find medicine/Rare disease designations.

The applicant applied for the following indication:

"Glybera is indicated for the long term correction of lipoprotein lipase deficiency, to control or abolish symptoms and prevent complications in adult patients clinically diagnosed with lipoprotein lipase deficiency (LPLD)".

The legal basis for this application refers to: Article 8.3 of Directive 2001/83/EC, as amended - complete and independent application.

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain test(s) or study(ies).

Information on Paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/119/2008 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP [P/119/2008] was not yet completed as some measures were deferred.

Information relating to Orphan Market Exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

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Applicant's request(s) for consideration

Marketing Authorisation under exceptional circumstances

The applicant requested consideration of its application for a Marketing Authorisation under exceptional circumstances in accordance with Article 14(8) of Regulation (EC) No 726/2004 based on the following claim(s):

The indication for which the product is intended is encountered so rarely that it has not been possible to provide a comprehensive data package in terms of clinical experience for a full application.

New active Substance status

The applicant requested the active substance, Alipogene tiparvovec, contained in the above medicinal product to be considered as a new active substance in itself.

Protocol Assistance

The applicant received Protocol Assistance from the CHMP on 25.05.2004, 29.05.2006 and 20.01.2009. The Protocol Assistance pertained to quality, non-clinical and clinical aspects of the dossier.

Licensing status

The product was not licensed in any country at the time of submission of the application.

1.2. *The Steps taken for the assessment of the product*

The Rapporteur and Co-Rapporteur appointed by the CHMP and the evaluation teams were:

CAT Rapporteur: Dr. Gopalan Narayanan CAT Co-Rapporteur : Dr. Egbert Flory

CHMP Coordinator(s): Dr. Ian Hudson, Dr. Christian Schneider

- The application was received by the EMA on 23 December 2009.
- The procedure started on 20 January 2010.
- The Rapporteur's first Assessment Report was circulated to all CAT members on 06 April 2010 . The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 09 April 2010.
- During the meeting on 12 May 2010, the CAT agreed on the consolidated List of Questions to be sent to the applicant. The final consolidated List of Questions was sent to the applicant on 19 May 2010.
- During a meeting of a SAG on 3 November 2010, experts were convened to address questions raised by the CHMP.
- The applicant submitted the responses to the CAT consolidated List of Questions on 22 November 2010.

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- The summary report of the GCP inspection carried out at the following site(s) Amsterdam Molecular Therapeutics B. V. (AMT), The Netherlands, and Centre d'Études Cliniques Écogène21, Canada, between 12-16 July 2010 and 9-13 August 2010 was issued on 15 October 2010.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Questions to all CAT members on 23 December 2010.
- During the CAT meeting on 14 January 2011, the CAT agreed on a list of outstanding issues to be addressed in writing and/or oral explanation by the applicant.
- The applicant submitted the responses to the CAT consolidated List of Outstanding Issues on 30 March 2011.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Outstanding Issues to all CAT members on 28 April 2011.
- During the CAT meeting on 12 May 2011, outstanding issues were addressed by the applicant during an oral explanation before the CAT.
- During the meeting on 16-17 June 2011, the CAT, in the light of the overall data submitted and the scientific discussion within the Committee, issued a negative draft opinion for granting a Marketing Authorisation under exceptional circumstances to Glybera on 17 June 2011.
- During the CHMP meeting on 20 June 2011, outstanding issues were addressed by the applicant during an oral explanation before the CHMP.
- During the meeting on 20-23 June 2011, the CHMP, in the light of the overall data submitted, based on the draft CAT opinion and the scientific discussion within the Committee, issued a negative opinion for granting a Marketing Authorisation under exceptional circumstances to Glybera on 23 June 2011.

1.3. *Steps taken for the re-examination procedure*

The Rapporteur and Co-Rapporteur appointed by the CHMP and the evaluation teams were:

CAT Rapporteur: Dr. Maria-Cristina Galli CAT Co-Rapporteur: Dr. Jānis Ancāns

CHMP Coordinator(s): Dr. Luca Pani, Dr. Juris Pokrotnieks

- The applicant submitted written notice to the EMA on 6 July 2011 to request a re-examination of Glybera CHMP opinion of 23 June 2011.
- During its meeting on 18-21 July 2011, the CHMP appointed Dr. Maria-Cristina Galli as CAT Rapporteur and Dr. Janis Ancans as CAT Co-Rapporteur.
- The applicant submitted the detailed grounds for the re-examination on 26 August 2011 (Appendix 2 of Final Opinion). The re-examination procedure started on 27 August 2011.
- The CAT Rapporteur's Assessment Report was circulated to all CAT and CHMP members on 21 September 2011. The CAT Co-Rapporteur's Assessment Report was circulated to all CAT and CHMP members on 21 September 2011.
- During a meeting of the Ad hoc Expert Group on 10 October 2011, experts were convened to consider the grounds for re-examination.

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- The CAT Rapporteurs circulated the Joint Assessment Report on the applicant's detailed grounds for re-examination to all CAT and CHMP members on 5 October 2011 and a revised Joint Assessment Report on 12. October 2011.
- During the CAT meeting on 13/14 October 2011, the detailed grounds for re-examination were addressed by the applicant during an oral explanation before the CAT.
- During the meeting on 13-14 October 2011, the CAT, in the light of the scientific data available and the scientific discussion within the Committee, the CAT re-examined its initial opinion and in its final opinion concluded that the application satisfied the criteria for authorisation and recommended by a majority of 18 out of 24 votes the granting of the marketing authorisation under exceptional circumstances.
- During the CHMP meeting on 17-20 October 2011, the detailed grounds for re-examination were addressed by the applicant during an oral explanation before the CHMP.
- During the CHMP on 17-20 October additional information was provided by the Applicant.
- During the meeting on 17-20 October 2011, taking into account the CAT draft opinion and in the light of the scientific data available and the scientific discussion within the Committee, the CHMP re-examined its initial opinion and in its final opinion concluded that the application did not satisfy the criteria for authorisation and did not recommend the granting of the marketing authorisation under exceptional circumstances.

1.5 Steps taken following the EC request for assessment of the benefit risk in patients with severe or multiple pancreatitis attacks

The Rapporteur and Co-Rapporteur appointed by the CHMP and the evaluation teams were:

CAT Rapporteur: Dr. Gopalan Narayanan CAT Co-Rapporteur: Dr. Paolo Gasparini

CHMP Coordinator(s): Dr. Ian Hudson, Dr. Luca Pani

- Following the Standing Committee meeting on 23 January 2012, the EC addressed a letter dated 30 January 2012 to the CHMP chair asking the CHMP to assess the benefit risk of Glybera in patients with severe or multiple pancreatitis attacks. The letter was received at EMA on 3 February 2012.
- During the CHMP meeting on 14-16 February 2012, the CHMP discussed the EC letter dated 30 January 2012 and adopted a List of Questions to the applicant.
- The applicant submitted the responses to the CHMP List of Questions on 8 March 2012.
- The CHMP Rapporteur's Assessment Report and Co-Rapporteur's Assessment Report were circulated to all CHMP/CAT members on 30 April 2012. During the CAT meeting on 12/13 April 2012, the CAT in the light of the scientific data available and the scientific discussion within the Committee, adopted on 13 April 2012 a summary of CAT discussion on the restricted indication for Glybera.
- During the CHMP meeting on 16-19 April 2012, and in the light of the scientific data available, taking into account the CAT summary of discussion and the scientific discussion within the Committee, the CHMP concluded that the application did not satisfy the criteria for authorisation and did not recommend the granting of the marketing authorisation under exceptional circumstances. Further to

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EMA legal scrutiny of the CHMP April 2012 opinion, it was identified that a formal CAT draft opinion should be adopted as basis for CHMP to re-adopt its opinion in order to address the EC request. Therefore the April 2012 CHMP opinion is considered void. During the CHMP meeting on 21-24 May 2012, a timetable was adopted for adoption the formal CAT opinion as basis for CHMP to re-adopt its opinion.

- The CAT Rapporteur's Assessment Report was circulated to all CHMP/CAT members on 01 June 2012. The CAT Co-Rapporteur's Assessment Report was circulated to all CHMP/CAT members on 01 June 2012.
- The Joint CAT Rapporteurs' Assessment Report was circulated to all CHMP/CAT members on 13 June 2012.
- During the CAT meeting on 14/15 June 2012, outstanding issues were addressed by the applicant during an oral explanation.
- During the meeting on 14/15 June 2012, the CAT, in the light of the overall data submitted, taking into account the argumentation provided by the Applicant in the Oral Explanation and the scientific discussion within the Committee on the benefit risk of Glybera in patients with severe or multiple pancreatitis attacks, issued a positive draft opinion for granting a Marketing Authorisation under exceptional circumstances to Glybera.
- During the June 2012 CHMP meeting, the CHMP discussed a List of Questions which was adopted by written procedure on 5 July 2012.
- On 12 July 2012, the EMA was informed about the change in applicant for the marketing authorisation application from Amsterdam Molecular Therapeutics (AMT) B.V. to uniQure biopharma B.V.
- During the CHMP meeting on 16-19 July 2012, outstanding issues were addressed by the applicant during an oral explanation.
- During the CHMP meeting on 16-19 July 2012, and in the light of the scientific data available, taking into account the CAT draft opinion, the argumentation provided by the applicant in the Oral Explanation and the scientific discussion within the Committee, the CHMP concluded that the application satisfied the criteria for authorisation and recommended the granting of the marketing authorisation under exceptional circumstances.

2. Scientific discussion

2.1. *Introduction*

Glybera is a gene therapy medicinal product intended for the treatment of lipoprotein lipase deficiency (LPLD), a rare autosomal recessive inherited condition caused by homozygosity or compound heterozygosity for mutations in the lipoprotein lipase (*LPL)* gene.

LPL is the key enzyme in the metabolism of circulating triglyceride-rich lipoproteins. LPL is responsible for efficient distribution of triglycerides to peripheral organs like skeletal muscle, adipose tissue, and cardiac muscle. It is primarily expressed in parenchymal cells including adipocytes, skeletal muscle cells, and cardiac muscle cells. After intracellular dimerisation, LPL is secreted and transported to the luminal side of

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the blood vessel where it is bound to the endothelium through heparan-sulphate proteoglycans. In the fasted state, LPL predominantly degrades liver-derived VLDL but in the fed state, LPL also clears triglyceride loaded chylomicrons (CM) that carry dietary lipid. For CM, LPL is the single most important degradation route, and its activity ensures that postprandial increase of CM in the circulation typically resolves within a few hours after meal consumption.

LPLD is a rare autosomal recessive inherited condition caused by homozygosity or compound heterozygosity for mutations in the *LPL* gene. The prevalence of LPLD is 0.02 per 10,000 individuals in the EU. To date, more than 70 *LPL* gene mutations have been described, most of them associated with loss of catalytic function. LPLD results in chylomicronemia and hence in extremely high levels of circulating triglyceride-rich lipoproteins. LPLD patients usually present with fasting plasma triglyceride values >11 mmol/l (1000 mg/dL) and those levels may exceed 113 mmol/l (10,000 mg/dL). Fasting triglyceride values of normal individuals range between 1 and 2.3 mmol/l.

The disease may present in infancy or childhood with severe abdominal pain, repetitive colicky pains, repeated episodes of pancreatitis, and often failure to thrive. On physical examination, eruptive xanthomas (accumulation of fat under the skin), lipaemia retinalis, and hepatosplenomegaly may be detected. The condition is often not diagnosed during childhood and may only become evident after several episodes of pancreatitis in adolescence or adulthood. Laboratory investigation reveals genuine lactescent plasma (lipemia) due to the increased CM concentrations. The severity of the symptoms is proportional to the degree of chylomicronemia.

The most severe complication associated with LPLD is pancreatitis. Pancreatitis in an LPLD subject may lead to admissions to an intensive care unit. In case of severe pancreatitis, subjects may develop chronic pancreatitis, ultimately resulting in endocrine and exocrine pancreatic insufficiency. Therefore, the risk of a pancreatitis episode should be minimized by maintaining fasting plasma triglyceride values below 10 mmol/l.

Treatment of LPLD patients currently consists of severe reductions in dietary fat to less than 20% of caloric intake. Compliance with this dietary regimen is very difficult, and even with good compliance, the diet is often ineffective at reducing chylomicronemia and triglyceride levels.

Hence, LPLD patients remain at increased risk for potentially lethal pancreatitis. Currently no triglyceride-lowering drug such as fibrates or statins or any specific therapy is available to modulate the course of the illness, so these patients are at high risk of morbidity and mortality. Enzyme replacement therapy is not expected to be effective, due to the short intravascular half-life of the LPL protein (approximately 15 minutes). Therefore, gene therapy was proposed as potential treatment for LPLD.

The therapeutic aim of Glybera is to control or abolish symptoms of LPLD, and to prevent complications in adult patients clinically diagnosed with LPLD. Transduction of part of the skeletal muscle mass is expected to restore a level of LPL activity which is sufficient to hydrolyse the triglyceride-rich lipoproteins, and influence lipid homoeostasis, and thus lead to clinical improvement or stabilisation.

The indication initially applied for was:

"Glybera is indicated for the long term correction of lipoprotein lipase deficiency, to control or abolish symptoms and prevent complications in adult patients clinically diagnosed with lipoprotein lipase deficiency (LPLD)".

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Orphan drug status was designated to Glybera in the EU in 2004. The applicant applied for marketing authorisation under exceptional circumstances for a product subject to medical prescription that may not be renewed.

2.2. *Quality aspects*

2.2.1. Introduction

Glybera (Alipogene tiparvovec) is a replication-deficient adeno-associated viral vector designed to deliver and express the human LPL gene variant LPLS447X.

Glybera drug substance (DS) is produced employing a baculovirus expression vector system. Insect cells are transduced with 3 different replicating baculovirus vectors either expressing the recombinant AAV vector genome carrying the LPL cassette, the AAV rep gene or the AAV cap gene. The baculovirus vectors replicating in insect cells are producing AAV components resulting in recombinant AAV particles. The AAV vectors are released from the cells by incubation in lysis buffer and are further purified, concentrated and filtered.

Glybera drug product (DP) is a sterile solution for injection presented as single use vials. Each vial contains 3×10^{12} genomic copies (gc) of alipogene tiparvovec (AAV1-LPL^{S447X}) in 1ml of a phosphate based formulation buffer containing 5% sucrose. Glybera is to be administered once at multiple sites intramuscularly at a dose of 1×10^{12} gc per kg body weight.

2.2.2. Active Substance

General Information

Nomenclature

The drug substance is Alipogene tiparvovec. The scientific name of the drug product is recombinant adeno-associated virus serotype 1 (AAV1) vector expressing the S447X variant of the human lipoprotein lipase (LPL) gene. The applicant uses two different company codes to differentiate between the current production system, AMT-011, versus the previous production system, which is referred to as AMT-010.

Structure

The structure of the active substance is sufficiently described. Alipogene tiparvovec is a recombinant adeno-associated viral particle with icosahedral symmetry and a diameter of approximately 25 nm (Figure below). It has a molecular mass of approximately 5×10^3 kDa and can be considered as a so called 'hybrid' vector, because the ITRs and the *rep* and *cap* genes are derived from AAV serotype 2 and the *cap* (protein coat) ORF is sourced from AAV serotype 1.

The vector genome contains the transgene expression cassette containing the cytomegalovirus (CMV) immediate early promoter, the cDNA sequence of human lipoprotein lipase variant S447X (LPLS447X), the bovine growth hormone polyadenylation site, and a woodchuck hepatitis virus post transcriptional regulatory element (WPRE) which is required to improve LPL gene expression. The applicant is using the WPRE of WHV in the vector genome without destroying the X-open reading frame present in this region. Due to the putative tumorigenic potential of the X-gene product the applicant was asked to clarify whether

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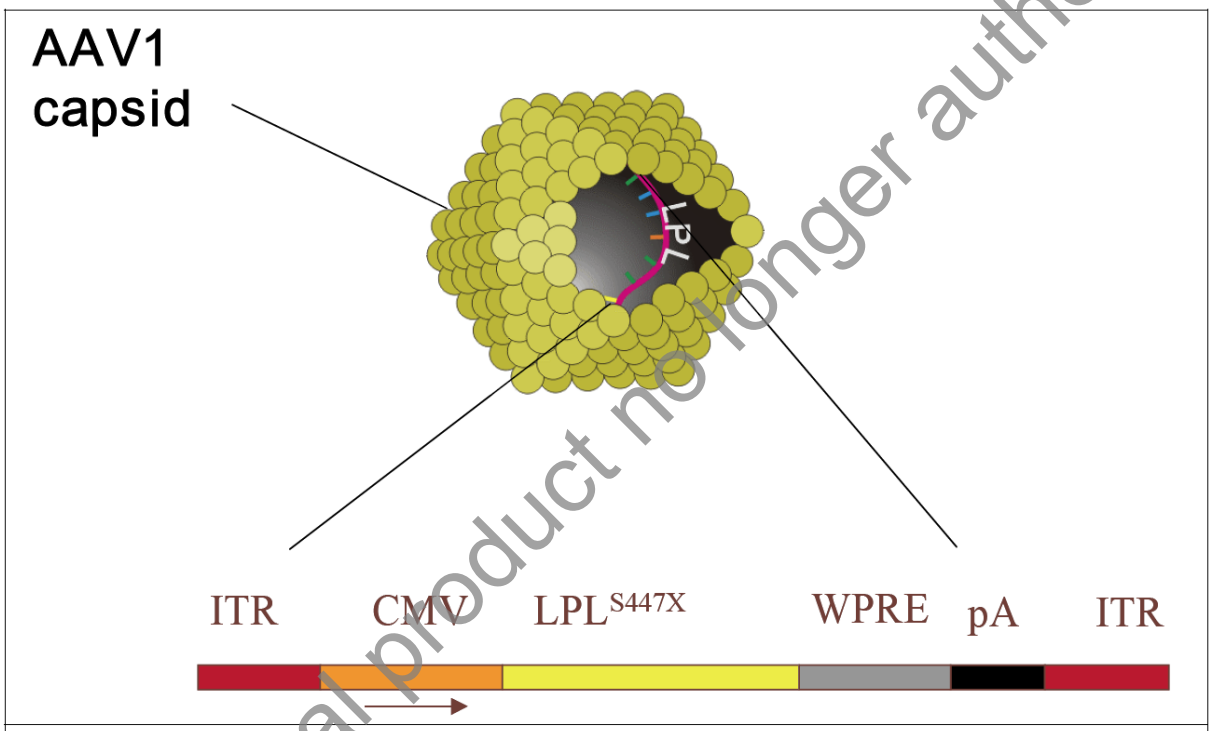
the present X-protein sequences give rise to tumorigenic potential. This was raised as major objection 1 in the LoQ and is considered to be resolved at the time of opinion (see discussion).

The expression cassette is flanked by two inverted terminal repeats (ITRs) derived from AAV serotype 2 (AAV2). Small intervening non-functional DNA sequences are derived in the process of assembling the genetic elements through standard recombinant DNA techniques.

The total length of the vector genome is 3.6 kb. The vector genome, either – or + strand, is pseudotyped with AAV serotype 1 capsids which are composed of 60 subunits formed by three viral proteins, VP1, VP2, and VP3, in a relative stoichiometry of 1:1:10. The major capsid protein is VP3, estimated to represent about 80% of the total mass.

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.

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Manufacture

Manufacturer

The name and address of the manufacturer responsible for manufacturing, release and stability testing of the drug substance alipogene tiparvovec were provided.

Cell bank and baculovirus seed bank vials are stored off-site.

A copy of the GMP certification issued by the Dutch Authorities has been provided (dated June 2008). AMT holds also the necessary Biosafety Authorisation for handling genetically modified organisms (GMOs) IG-00-095, issued by the Ministerie van VROM, The Netherlands. All production steps are conducted at a Biological Safety Level 2.

Some control tests performed for release testing of the drug substance are contracted out.

Manufacture and release testing of drug substance are under the control of the Qualified Person responsible for batch release of the final product, as such confirmation of GMP compliance of the contract laboratory is not required; nonetheless the applicant has provided a GMP certificate for this site (dated Jan 2008).

Manufacturing process development

The original manufacturing process (AMT-010) used a plasmid based system. The plasmids were then transfected into HEK293 in order to rescue the recombinant AAV. Scientific advice had been sought in relation to the comparability assessment of the DS derived from this process and the baculovirus production system (AMT-011) introduced for commercial production. On the whole the applicant has complied with the advice given. Some other concerns were raised which were considered as sufficiently addressed by the applicant's response to the LoQ.

During the development of the AMT-011 process a number of changes have been made during scale up.

A comparability assessment of product from these process stages has been undertaken, and of critical importance is the comparability between the process used for the clinical studies and the commercial process. The results indicate that the product purity has improved throughout the development of this manufacturing process. In most analyses the commercial process quality is comparable if not better than the clinically used process, except for significantly higher carry over of baculovirus DNA.

Overall the consistency in product quality throughout development has been shown.

The applicant did not consider the evaluation of comparability of the two products in terms of potency necessary as AMT011 has been qualified independently of AMT-010 on the basis of non-clinical studies. This is considered acceptable as toxicology and pharmacology studies were repeated with AMT-011.

Manufacturing process, control of critical steps and validation

On the whole the manufacturing process is well described. A two-tiered system has been established for commercial DS production based on a Master and Working Cell Bank (MCB, WCB) and Master and Working Viral Seed Stock (MSV, WSV).

The current manufacturing process of DS is starting with material from WCB and WSV and is divided into 9 steps.

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Most of the equipment is either single use or disposable therefore there are no concerns related to product carryover and cleaning validation.

However, the applicant was quite minimalistic in terms of process controls that are considered critical. As requested with the LoQ the applicant provided justification where controls are not considered critical or introduced appropriate in-process controls and acceptance limits.

Overall the approach taken to validate the manufacturing process for the DS is considered acceptable, however there are some additional data that were submitted on request to ensure the overall consistency of each of the manufacturing steps with regard to removal of process and product-related impurities.

Characterisation

The product has been characterised quite extensively using 3 consecutive drug product batches (commercial process) and one batch that was used in clinical investigations.

Parameters investigated were composition (genome integrity and size, protein analysis and molecular mass, stoicometry of capsid proteins), physical properties (particle size, glycosylation state of the virus particle), primary structure (sequence confirmation, protein identification), higher order structure (TEM and analytical ultracentrifugation to determine mass, density and distribution profiles); biological activity was addressed by the infectious particle assay, ratio of full:infectious virus particles and potency.

The impurity profile in terms of process- and product-related impurities was also covered. Overall, process and product related impurities were consistently low, and the limits of detection of the assays used are considered satisfactory.

Of major concern however, was the carry over of baculovirus DNA. Residual baculovirus DNA was not measured in the three clinical lots administered in the first clinical AMT-011 trial. Residual baculovirus DNA varied in the 6 lots of the commercial process raising the question of whether these baculovirus sequences can be transcribed and corresponding proteins translated. The applicant was requested to investigate further whether this was possible. It was observed that following administration the recombinant virus is distributed to many different tissues and organs, as such the diversity of cell lines to be used in this evaluation needed to be carefully justified. A detailed risk assessment regarding the clinical consequences of administering significant amounts of baculovirus sequence, and the subsequent expression of proteins (even if theoretical), was also requested. The applicant was asked to take into consideration the fact that the virus is likely to remain in the patient for a considerable amount of time, and so therefore, will the baculovirus sequences.

It was also noted, that the extent of co-packaged baculovirus DNA sequences could be underestimated due to the design of residual DNA assay.

These points were raised as major objection 2 in the LoQ and, following the subsequent responses of the applicant they were considered resolved at time of opinion (see discussion).

Specification

In general the proposed release tests comply with the Ph. Eur. general chapter (5.4). There are some deviations from the recommendations, but these are either justified, or simply the testing has been moved from DS to drug product (DP). On the whole this is acceptable.

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The applicant justified omitting replication competent (rc) AAV testing on the DS. As discussed this was not accepted and the applicant reintroduced this assay in the specification as requested during the evaluation procedure (major objection; see DP and discussion).

There was also a concern raised concerning the residual infectious baculovirus assay. This is also discussed further in relation to the viral safety and impurity profile of the product (see below and section 2.2.5).

Specifications for other release parameters are fully justified based on the manufacturing experience and the quality of the lots that have been used to generate DP used in clinical studies. The specification for ratio total:full particles was revised based on DS batches as requested.

Finally, the specification for potency was not acceptable and was revised as requested.

Stability

The stability data presented are supportive of the proposed DS shelf life for up to 8 weeks at -20 ± 5ºC.

Stress studies under elevated temperatures or increased number of freeze/thaw cycles provided additional information on the stability of the active substance. The stress studies suggest that temperatures of 25-50°C impact the biological activity of the product.

2.2.3. Finished Medicinal Product

Description and composition of the Finished Product

Glybera is a sterile solution for injection (3 x 10^{12} genome copies per 1mL), intended for intramuscular administration. The components of the DP formulation and their function are described and justified. All excipients are of Ph.Eur. grade.

Pharmaceutical Development

The choice of the formulation buffer is sufficiently justified. The same formulation buffer was used throughout the whole non-clinical and clinical development programme.

The Ph. Eur. test for sub-visible particles was introduced during clinical development. Considerable levels of particles (≥10µm and 25µm/vial) were observed, which resulted from repeated freeze/thawing and reoccurred after removal of particles by filtration. The Ph. Eur. release test and corresponding specifications for parenterals were therefore implemented.

Adventitious agents

The control of starting materials and raw materials is sufficient to ensure their viral and microbial safety. Cell banks and MSV used for Glybera production were extensively screened on extraneous virus contamination, following the principles of Ph. Eur. 5.1.4 and 2.6.16. Testing of WSV according to the principles of Ph. Eur. 2.6.16 has been addressed as requested in the LoQ and LoI. The routine testing of unprocessed bulk harvest for extraneous viruses is considered adequate. Process controls are also adequate to control adventitious microbial ingress during purification/manufacture. Overall, the testing for mycoplasma, bacteria and fungi is in agreement with Ph. Eur. requirements and thus acceptable.

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Enveloped viruses are efficiently inactivated during down-stream manufacture. The processing has been indicated to remove moderately a panel of enveloped and non-enveloped model viruses (PRV, BVDV, EMCV, and CPV). In summary, safety with regard to adventitious virus contamination seems adequately demonstrated.

High concentrations of replication competent helper baculoviruses are found in the production culture at the production stage before cell lysis. Significant inactivation/removal of baculoviruses can be assumed during down-stream processing. However, as these reduction factors are not sufficient to guarantee complete freedom of the final bulk with respect to infectious baculovirus particles, the applicant introduced the residual infectious baculovirus assay for quality control. The applicant presented a deterministic risk assessment considering the starting virus loads and the virus reduction capacity.

As the administration of single residual infectious particles to patients cannot be totally excluded, the applicant quoted many studies and in-vitro investigations cited in the literature which suggest that unless very high doses (>10^9 iu) are systemically administered, there is little evidence that baculoviruses are detrimental to human health. Although baculoviruses can enter mammalian cells, there is no evidence for virus replication or significant expression of virus genes. Nevertheless, it was proposed in a former EMA scientific advice to increase the safety margin by introducing an additional virus reduction step (e.g a virus filter) in the manufacturing process. As the applicant has not followed this advice prior to MAA this should be implemented in the future development of Glybera or other products manufactured with the same technology (see section 2.2.5).

Manufacture of the product

Manufacturer

The name and address of the manufacturer responsible for manufacturing, control, batch release and packaging of the finished product were provided.

Certain quality control tests are contracted out to appropriate third party contract laboratories to perform.

All relevant sites underwent GMP inspections by EEA/MRA authorities with a satisfactory outcome within the last 3 years. Hence, no GMP inspections deem necessary within the scope of this MAA evaluation procedure. Manufacturing licenses and/or GMP certifications are provided.

Manufacture, process control and validation

The process is relatively straightforward and adequately described. Critical controls are defined. Reprocessing is not permitted.

In general, validation of the manufacturing process demonstrated reproducibility and consistency of the process. As the scale of manufacture is small compared to other biological/biotechnology products, and given the variability in batch size, it is considered acceptable that the production lots used in the process validation studies may not reflect the full range of batch sizes that could potentially be prepared.

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Product Specification

On the whole the specification conforms to the recommendations made in the Ph. Eur (for GTMP's and parenterals) with the limitations discussed below. Furthermore, the applicant tightened as requested the acceptance criteria for some parameters.

Impurity profile

The assays used to measure residual cellular DNA and protein did not have particularly low LOD, and given the amount of product that is used during treatment (up to 30 ml for a 90Kg individual), specifications were considered unacceptably high.

Given the volume of product that is administered, the associated impurity profile in terms of cellular DNA and protein, baculovirus DNA – and probably baculovirus protein, though confirmatory data on the extent of this contamination were pending - was considered unacceptably high at the time of initial assessment and was raised as major objection in the LoQ. Muscle toxicity at the proposed dose has been observed in animal models as well as in clinical studies, and it was unclear whether this may, in part, be due to the high levels of these impurities. It was concluded that either the analytical assays used to test impurities are not sensitive enough (based on the declared LOD's), or the current purification strategy is not robust enough to remove these impurities to an acceptable level. Therefore, the applicant was asked to improve the process for example by introducing additional chromatography / diafiltration steps in order to generate product with significantly less process related impurities i.e. cellular and baculovirus DNA and protein; and/or develop more sensitive impurity assays. The provision of a validated baculovirus protein assay, and retrospective batch/comparability data was also required during the evaluation process. The issues were considered sufficiently addressed with the responses provided. Nevertheless, remaining aspects of quality issue were considered to require further investigation. (see discussion and section 2.2.5).

In addition it was unclear to what extent residual infectious baculovirus were administered to the patients as the LOD of this assay had not been experimentally confirmed. This made the assessment of the associated risks of administration of these particles to the patient impossible to evaluate. The company was therefore requested to confirm the LOD of the assay experimentally and revise the risk assessment presented in the MAA as necessary (see above section on adventitious agents, discussion and section 2.2.5).

Replication competent AAV assay

In the initial application, the amount of replication competent AAV was not specified. As absence of replication competent AAV had been shown in all drug substance batches the applicant did not intend to perform this test for batch release. This approach was not acceptable as a quantitative test for replication competent AAV in the drug product is recommended according to Ph. Eur. 5.14.

The point was raised as major objection and the applicant was asked to develop and validate a sufficiently sensitive test for the detection of rcAAV using an appropriate positive control and to include the detection of rcAAV as specification of the drug product with a reliable and justified upper limit, based on the retrospective batch analysis of rcAAV levels using the revised assay. The applicant's responses were considered sufficient to resolve the major objection besides a remaining aspect of this quality issue that was considered to require further investigation (see discussion and section 2.2.5).

Infectious vector titre

The design of the assay for quantification of the infectious vector titre was questioned in the LOQ as it may detect abundant amounts of DNA from non-infectious AAV particles present in the inoculum as well as

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infectious particles, leading to an over-estimation of the infectious particle titre. Thus, the suitability of the assay was not endorsed. The point was raised as major objection and sufficiently addressed at time of opinion (see discussion).

Stability of the product

Overall the stability data support the proposed storage conditions and shelf life. The revisions made to the release specifications during the evaluation procedure have also been extrapolated to the stability acceptance criteria. The assessment of the stability data using the revised limits indicate that the product is stable as proposed.

In-use stability evaluation was presented in the pharmaceutical development section and is supportive of the proposed time period for administration.

Acceptable shipping validation data were enclosed in the response to the LoQ to support the shipping conditions as specified in the SmPC.

2.2.4. Discussion on chemical, pharmaceutical and biological aspects

The following discussion focuses on the six major quality objections raised during the evaluation procedure. In addition, there were a high number of other quality concerns raised. Overall, these were satisfactorily resolved by the applicant with the responses to the LoQ and LOI as described for some above. The evaluation of the responses to some quality concerns resulted in recommendations for the further development of the product.

Structure

A major objection was raised concerning the inclusion of the WPRE element within the LPL expression cassette, which is required to improve LPL gene expression. This element contains an ORF for the expression of protein X which, it has been suggested, is pivotal to the generation of liver cancers associated with infection by hepadnaviruses (hepatitis B virus for man; woodchuck hepatitis virus for woodchucks). In the responses to the LoQ the applicant has provided a comprehensive literature review in relation to the oncogenic potential of the enhancer region of the WPRE located in the WPRE region and protein X, in relation to the PRE regions of HBV and HBx. Based on this data, it is accepted that the enhancer sequences contained within the WPRE in Glybera (We1) are unlikely to be linked to an oncogenic risk. Equally, the ability of WHx per-se to be directly carcinogenic seems unlikely, but this area of research is still heavily debated, and there is insufficient information against which to make firm conclusions.

Overall this major objection is considered resolved.

Residual baculovirus DNA

The second major objection was raised in relation to the characterisation of the genetic sequences encapsidated in the virus. The applicant provided data that suggested there are intact ORF within these contaminating baculovirus DNA sequences, however inconclusive data on whether or not proteins are expressed was presented. Thus it was unclear if there is the potential for baculovirus protein expression in cells transduced with AMT-011. The applicant had not provided an exhaustive risk assessment addressing

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the fact that non-therapeutic DNA sequences will almost certainly be administered to, and may persist in, the patients treated or the theoretical risks associated with any subsequent protein expression from those sequences.

There was also a concern that the assay used to measure baculovirus DNA contamination may well be underestimating the extent of this problem given the distance of baculovirus specific primers from the LPL expression cassette as data suggested that baculovirus sequences adjacent to the LPL cassette appear to be preferentially packaged. In addition, the batch data provided suggested that the product manufactured using the commercial process could potentially contain more than twice as much baculovirus DNA, compared to the one batch that has been measured and was used in clinical study, thus the proposed specification was not considered suitably justified.

The applicant was requested to carry out more extensive investigations to determine whether or not baculovirus proteins were expressed and to propose appropriate specifications to ensure consistency in the extent of baculovirus DNA co-packaged with the product. Furthermore, a risk assessment on the inclusion of these sequences in relation to public health was required.

In the responses to the LOQ the applicant provided data which gives assurance that neither baculovirus message or protein is likely to be expressed from the contaminating baculovirus sequences co-delivered with the product. They also provided next generation sequencing (NGS) data which indicates that the distribution profile of baculovirus sequences are comparable between the batches manufactured. In the responses to the LOI the applicant provided additional NGS data for batches covering the different manufacturing processes. These data indeed support the consistency in the frequency of the baculovirus DNA sequences co-packaged (i.e. those sequences in proximity to the ITR are over represented compared to those distal such as the HR3 region).

Furthermore, data, based on average baculovirus counts, was provided evaluating the extent of the underestimation of the residual baculovirus DNA assay focussing on the HR3 region, and confirming that indeed the assay is underestimating. These results support the applicant's position that the results of the HR region are consistent between lots and are relative to the overall baculovirus content in the product. Thus any observed increase in content as measured using this assay can be considered representative of an increase in the overall distribution of the baculovirus DNA impurity. It was agreed therefore that for the time being the current assay can be used for release purposes, pending the development of an additional release assay with a read out measuring the ratio of baculovirus sequences proximal to the ITR relative to that in the HR region. Furthermore the applicant has redefined the acceptance limits for baculovirus DNA content in the final product to reflect that which has been administered during clinical trials. Thus assurance is given that only product with a comparable content of this impurity to that used during clinical investigation will be released for commercial supply.

It was the agency's position at time of LOI that the data provided suggests product safety is likely to be unaffected by the co-packaging of the baculovirus DNA impurities and this major objection can be considered resolved. However, this material represents a significant impurity. Therefore, for further development of Glybera or other products using the same manufacturing technology it is considered important that the applicant continues to characterise and investigate the longevity of these sequences. A program of work has been provided by the applicant to address these recommendations. Overall the response given to this major objection is acceptable and it can be considered resolved.

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Potency

The third major objection related to the potency specification of the DS. The proposed lower limit did not reflect the potency of DS lots that have been satisfactorily formulated into the DP. The applicant has now proposed a revised potency specification which is considered acceptable as such this major objection is now resolved.

Impurity profile

The fourth major objection was in relation to the extent of impurities that are co-administered with Glybera. It was accepted that the proposed specification in many instances was the defined limit of detection of the assays, but these limits were very high, given the volume of product that is administered. In addition, it was unclear to what extent these impurities would have played a role in the muscle damage observed in animal models at the proposed dose ($1x10^{12}$ gc/kg), and similar observations, with one serious adverse event, observed in the clinical evaluation of the product.

In relation to assay sensitivity of the impurity assays, the applicant provided an update of work that is currently on going to improve the assay sensitivities in the responses to the LoQ. A further update on the development programme and timelines for validation of the assays for residual cellular DNA and residual cellular and baculovirus protein was submitted in the responses to the LOI. It was concluded that the applicant could finalise the improvement of the impurity assays post opinion (see section 2.2.5). Under this perspective this major objection was considered resolved.

In addition, it was unclear to what extent infectious baculovirus is co-administered. The amount of infectious baculovirus introduced into the process may be in excess of the validated virus inactivation/removal potential of the process. A release test for infectious baculovirus had been introduced in the DS specification, however, with a theoretically determined LOD. Experimental confirmation of the LOD of this assay was therefore requested, and if necessary the revision of the risk analysis in relation to the extent of infectious baculovirus that may be present. The risk to the patient in terms of the potential to deliver such a low level of baculovirus also appears minimal based on the extensive literature review presented. However, it is not considered acceptable that the manufacturing process does not have any redundancy in terms of virus inactivation, given the fact that infectious viruses are used for production. To improve the virus safety profile of Glybera the applicant should develop an additional manufacturing step that can be validated to ensure that the process can effectively inactivate/remove the maximum recombinant baculovirus load used for production (see section 2.2.5).

In conclusion the applicant's response was considered adequate to resolve this outstanding issue. However, the introduction of an additional virus inactivation/removal manufacturing step and the validation of the LOD were considered to require further investigation (see section 2.2.5).

Replication competent AAV

The fifth major objection concerned the lack of testing for replication competent AAV (rcAAV). In the initial application the applicant did not intend to test the occurrence of replication competent AAV at release, since i) they estimated the formation of rcAAV as unlikely due to the low sequence overlap between the 3 vector components, and ii) no rcAAV have been detected in all batches tested. However, it was considered that as sequence overlaps between the 3 AAV coding vectors exist the formation of rcAAV could be expected, although at low levels. The high LOD of the assay used previously would result in $7x10^5$ rcAAV per dose remaining undetected, which was considered unacceptable. The applicant was asked to develop

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and validate a sufficiently sensitive test for the detection of rcAAV using an appropriate positive control and to include the detection of rcAAV as specification of the drug product with a reliable and justified upper limit, based on the retrospective batch analysis of rcAAV levels using the revised assay. In the response to the LOQ the applicant agreed to reintroduce the rcAAV assay for routine product release, and in the response to the LOI an overview of the development of a revised assay was submitted. The data provided suggests that the new assay has significantly improved sensitivity. The applicant is planning to test all commercial batches using this improved assay. Therefore, it was concluded that the applicant could finalise the validation of the rcAAV assay post opinion and that the major objection is resolved (see section 2.2.5).

Infectious titre

The sixth major objection related to the assay for infectious vector. It was unclear how this assay could discriminate between infectious and non-infectious particles. The dosage of Glybera was based on the number of genome copies which reflects the number of total full particles, whereas the potency is dependent on the number of infectious particles. Therefore, it was considered that the ratio of total to infectious particles (which is part of release specification) should be properly determined. The efforts made by the applicant to determine the different types of AAV vectors present in the final product, in particular the amount of total vector particles, genome containing vector particles and infectious vector particles, provided in the response package is acknowledged. The applicant also presented data on a statistically significant correlation of the amount of infectious particles and the level of biological activity of the produced therapeutic protein, as suggested during the clarification meeting. Correlation, although not rather good, of vector titre to potency was shown. The applicant states that for both types of analyses validated test methods have been employed, as such this correlation is considered acceptable.

In conclusion the quality outstanding major objections and other concerns raised during the evaluation procedure are considered resolved with some remaining quality issues identified for further investigation.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

In general, the different aspects of the chemical, pharmaceutical and biological documentation comply with relevant guidelines and the Ph.Eur. general chapter on Gene Transfer Medicinal Products for Human Use (5.14). Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way. Data has been presented to give assurance on viral/TSE safety. The major objections concerning the quality information have been addressed satisfactorily and no quality issue would have precluded granting of a marketing authorisation under exceptional circumstances. Nevertheless, the following remaining quality issues would have had to be further addressed by the applicant:

- Improvement of the sensitivity of the impurity assays, the validation of the release assays for cellular DNA, SF+ protein or a combined SF+/Baculovirus protein assay, residual Rep and Cap genes and rcAAV should be completed, and the drug product release specifications.
- To complete the validation of the residual infectious baculovirus assay, the LOD should be experimentally confirmed. In addition, the presented risk assessment should be revised taking into account the experimentally determined LOD.

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- To improve the virus safety profile of the product, an additional manufacturing process step should be developed and validated to ensure that the process is capable of inactivating or removing at least the maximal baculovirus load used in production. Ideally some redundancy should be incorporated into the process.

2.2.6. Recommendation(s) for future quality development

The CAT/CHMP recommends points for investigation for the further development of Glybera.

2.3. *Non-clinical aspects*

2.3.1. Introduction

Good Laboratory Practice is expected for pivotal preclinical safety studies and the applicant claimed GLP compliance for relevant studies. No specific concerns are raised in relation to GLP compliance.

Different batches of AMT-010 (plasmid derived) were used and the applicant intended to compare AMT-010 and AMT-011 (baculovirus derived) in non clinical bridging studies.

Pharmacology studies were investigated in LPL deficient models, pharmacokinetic was investigated in cats, mice and rabbits animal studies. General toxicity studies were conducted in mice. There were no carcinogeniticty studies. Issues related to genotoxicity and carcinogenicity were investigated in specific studies aim to identify risk of insertion and potential of mutagenicity. Furthermore, literature data was further analysed.

2.3.2. Pharmacology

Primary pharmacodynamic studies

Proof of principle for the treatment of LPLD with AMT-010 (plasmid derived) has been analysed in two studies using LPL deficient (LPL-/-) mice and cats, respectively. In general, sustained hypertriglyceridemia is accompanied by increased total cholesterol (TC) and low levels of HDL-C which has also been observed in LPL-/- mice. However, LPL-/- mice do not develop acute pancreatitis, which is the most severe complication observed in humans suffering from LPLD. The second animal model used to study the pharmacology of AMT-010 is a naturally occurring LPLD cat strain. Comparable to humans, LPL-/- cats develop xantomas, lipemia retinalis and controversally discussed pancreatitis.

The underlying mechanism leading to recurrent pancreatitis in LPLD patients is not completely understood. However, it is evident that reduction of plasma chylomicrons and triglycerides are required to reduce the risk for occurrence of this life-threatening complication. Thus, a sustained reduction of plasma TG is accepted as a non-clinical surrogate marker to analyse non-clinical efficiency of Glybera.

Reduction in plasma triglycerides in the plasma of treated animals was the primary pharmacodynamic measure used to show activity. Proof of pharmacodynamic activity was presented from studies in lipoprotein lipase deficient mice and cats, who, as in humans, have plasma that can be seen to be

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abnormally milky. There is a colony of domestic cats who have a phenotype resembling human LPL deficiency, with lactescent plasma, xanthomata and lipaemia retinalis and they have abnormally high plasma triglyceride concentrations. In these cats AMT-010 corrected severe triglyceridaemia and lipaemia, acting within 3-4 days and it was concluded that a dose needed for this effect was potentially achievable in humans. Immune responses, possibly from trans-species reactions, resulted in loss of this effect; immunosuppression could delay the loss of response.

In contrast to humans and cats, LPL -/- mice do not survive beyond age 24 hours, probably in association with starting to suckle with resulting hypertriglyceridaemia. However, the treatment of LPL -/- mice with adenovirus resulting in expression of human LPL enable mice to survive well beyond this initial period. This method of 'rescue' of transgenic mice was applied in experiments with LPL-/- mice and has the consequence that human LPL can be detected even in control mice not treated with Glybera. LPL -/- mice were not naïve for LPL protein since they were treated shortly after birth with an LPL-expressing adenoviral vector.

Antibody formation against LPL was not observed in these mice on treatment with AMT-010, indicating that local overexpression does not break immunological tolerance to LPL.

Since most patients do express LPL, but in inactive mutant forms, a similar situation of immune tolerance to Glybera-derived LPL is expected in humans.

Experiments were conducted in purpose bred LPL -/- mice, 'rescued' with adenoviral human LPL soon after birth, with the intent of determining an active dose of AMT-010 and using the measurement of plasma triglyceride as the primary proof of activity, with additional measurement of human LPL in plasma and in tissue samples.

The use of AAV2 vector, and of AAV2 vector with AAV1 capsids were investigated. Dose ranging experiments were conducted and the duration of action was investigated. In these investigations, test products were given as intramuscular injections on one occasion, except in one test which had the purpose of assessing effects on readministration.

The effects were compared with those in LPL +/- mice.

Different batches of AMT-010 were compared and the applicant intended to compare AMT-010 and AMT-011 in bridging studies, but as so few mice were used in each test, the conclusions from these tests very limited.

In study 411-002, results from mice given active treatment showed that plasma LPL concentrations at week 52 were comparable to those in the untreated group, but at the same time, complete and persistent resolution of visible lipaemia was observed.

The applicant argues that the residual protein expression and activity found at 52 weeks post treatment is still sufficient to reduce plasma trigylcerides. However, comparable baseline concentrations of LPL expression and activity are detectable in young untreated LPL-/- mice.

From these experiments the following findings were reported:

- treated mice exhibited a fall in plasma triglyceride concentration, ranging up to 99.2%;
- treated mice exhibited quantifiable human LPL activity and protein content in plasma in a dose-related manner;

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- such expression was maintained and although there appeared to be a loss of activity over time, 52 weeks after dosing, plasma human LPL concentration was higher than in untreated mice;
- injected muscle tissue expressed quantifiable human LPL activity; a complete and persistent resolution of visible lipaemia was observed over a year;
- immunohistochemical analyses of injected muscles indicated that there was expression of human LPL at the outer surface of muscle; this is similar to natural expression of LPL in muscle;
- for a fixed dose, using either 4 or 36 injections, there was no difference in transgene expression; this indicates that a fairly limited degree of muscle tissue can provide sufficient transgene to clear the circulating pool of triglyceride-rich lipoprotein, at least in mice;
- when given an intravenous lipid challenge, LPL -/- mice respond with an increase in plasma triglyceride concentrations; in AMT-010-treated mice, recovery from this increase in plasma triglycerides was much improved, compared to untreated mice;
- on readministration, the second dose was not able to elicit a response, an effect attributable to formation of neutralising antibodies to AAV1 capsid.

Persisting antibody effects against AAV1 will likely prevent any successful expression of the transgene on readministration of the product, but the same issue arises where origin of AAV1 antibodies is a natural infection with wild type AAV1. Thus, the pre-existing humoral response to the AAV capsid (considering crossreactivity with other serotypes) should be characterised for all patients before AMT-011 treatment.

Toxic effects when 11-24-fold overexpression of LPL in muscle have been described in transgenic mice[1]. This finding was acknowledged by the applicant and considered in the toxicological evaluation of AMT-010 and AMT-011.

Over several studies (411-008, 411-009, 411-010) the applicant showed either comparable or slightly reduced LPL expression with AMT-011 compared to AMT-010 particularly in study 411-010. When given at higher doses the increased local expression of LPL does not further increase biological activity, but could influence the duration of effect. *In vitro*, up to 4-fold reduced LPL expression was also measured for all AMT-011 batches as compared to AMT-010.

Overall, the applicant showed relevant pharmacodynamic activity of AMT-010 and AMT-011 in LPL-/- mice and/or cats. A single dose was able to induce a long-lasting expression of transgene, human LPL, which was associated with a clear effect to reduce raised triglycerides very markedly. This is considered to be an acceptable pharmacological surrogate for efficacy. A dose-response relationship was defined and it was shown that immunosuppression did not ameliorate transgene expression. This is relevant as the clinical dosing strategy uses immunosuppression to inhibit antibodies to AAV infection and it is fairly common for humans to have antibodies to AAV.

The critical data are with AMT-011 in LPL-/- mice. Across multiple studies the applicant presented data that showed a major reduction in plasma triglyceride concentration indicating that proof of principle was established. Activity was demonstrated in the dose range 10^{11}-10^{13} gc/kg compared to the proposed human dose of $1x10^{12}$ gc/kg.

The principle has been demonstrated that AMT-011 can deliver biologically active human LPL.

[1] Levak-Frank S et al 1995. Muscle-specific overexpression of lipoprotein lipase causes a severe myopathy characterized by proliferation of mitochondria and peroxisomes in transgenic mice. J Clin Invest. 96(2); 976-86.

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Secondary pharmacodynamic studies

No secondary pharmacodynamic studies have been conducted. Taking into account the specificities of Glybera, the guideline for gene therapy medicinal products EMEA/CHMP/GTWP/587488/2007 and the guideline (EMEA/CHMP/GTWP/12459/2006, Guideline on the non-clinical studies required before first clinical use of gene therapy medicinal products, this is considered acceptable by the CAT and CHMP.

Pharmacodynamic drug interactions

A pharmacodynamic study was conducted to support use of AMT-011 with immunosuppressive treatment. This was discussed above.

2.3.3. Pharmacokinetics

Different qPCR methods were validated for the detection of AMT-011 in tissue samples from animal species and humans. More complete information on the validation of the Q-PCR on rabbit gDNA was requested during the procedure.

Absorption

Studies to investigate absorption have not been conducted. The product is given intramuscularly and the expectation is that Glybera expresses the transgene within the muscle.

Distribution

Five GLP-compliant distribution studies were conducted. In these, some control samples were positive which the applicant attributed to sample contamination at necropsy or during DNA preparation.

Biodistribution of vector was studied in cats, mice and rabbits. As reflected in guidance (EMEA/CHMP/GTWP/12459/2006, Guideline on the non-clinical studies required before first clinical use of gene therapy medicinal products), biodistribution, persistence, mobilisation and shedding should be assessed. Biodistribution and persistence were studied in animals. Shedding was addressed only by analyses of samples from patients in clinical trials and was not addressed in preclinical studies. The applicant contended that vector DNA was cleared within 10 weeks of dosing in humans. This is further addressed in the clinical section. Mobilisation (exit of vector from the target cell and its uptake by another tissue or cell) was not studied but the vector was detected in blood and tissues other than those injected.

The main tissues where vector DNA was detected were the injected muscle, liver, spleen and inguinal lymph nodes.

In cats, AMT-010 vector DNA was detected in testis, epididymis and motile sperm fraction indicating some dissemination of the vector to their gonads. In mice, a time course for loss of expression was evident and longer expression was evident with a higher dose. However, complete clearance was not confirmed over an observation period of up to 180 days. Injected muscle and, to a lesser extent, the inguinal lymph nodes retained expression.

Metabolism

Studies to investigate metabolism have not been conducted. Taking into account the specificities of Glybera, the guideline for gene therapy medicinal products EMEA/CHMP/GTWP/587488/2007 and the

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guideline on the non-clinical studies required before first clinical use of gene therapy medicinal products (EMEA/CHMP/GTWP/12459/2006), this is considered acceptable by the CAT and CHMP.

Excretion

Studies to investigate vector mobilisation and excretion have not been conducted. Shedding was studied in clinical trials. Presence in rabbit semen was investigated as described in the Distribution section.

Pharmacokinetic drug interactions

Studies to investigate pharmacokinetic drug interactions have not been conducted. Taking into account the specificities of Glybera, the guideline for gene therapy medicinal products EMEA/CHMP/GTWP/587488/2007 and the guideline on the non-clinical studies required before first clinical use of gene therapy medicinal products (EMEA/CHMP/GTWP/12459/200), this is considered acceptable by the CAT and CHMP.

2.3.4. Toxicology

All toxicity studies were performed in wild type mice in accordance with GLP. The use of a single species for toxicity evaluation is in accordance with the guideline for gene therapy medicinal products EMEA/CHMP/GTWP/587488/2007 and the guideline on the non-clinical studies required before first clinical use of gene therapy medicinal products (EMEA/CHMP/GTWP/12459/2006).

The non-clinical toxicology programme of Glybera included one single dose toxicity study performed with AMT-010 with a 90-day observation period, two single dose toxicity studies performed with AMT-011 with a 180-day and 105-day observation period, respectively, and a combined reproductive toxicology and breeding study performed with AMT-011.

Single dose toxicity

General toxicity studies were conducted in mice dosed by the intramuscular route on one occasion with varying periods of follow-up to day 180. Studies were conducted with AMT-010 (plasmid derived) and several different batches of AMT-011 (baculovirus derived) and doses ranged from $1x10^{11}$ – $1x10^{13}$ gc/kg.

The use of a single species for toxicity evaluation can be accepted for Glybera.

The single dose toxicity studies reflect the clinical dosing situation by addressing the toxic effects following either IM (clinical use) or IV (worst case scenario) administration of AMT-011 at a single occasion. The single dose toxicity studies included IM application of up to a 10-fold higher dose (1×10^{11}, 1×10^{12} and 1×10^{13} gc/kg) than the proposed clinical dose (1×10^{12} gc/kg). Moreover, the long-term expression of the therapeutic gene has been taken into account by including an extended follow-up period of 6 months in one of the single dose toxicity studies performed with AMT-011. In the second single dose toxicity study performed with AMT-011, mice were also treated with CSA and MMF following IM administration of AMT-011 to investigate whether the toxicity profile of AMT-011 is influenced by immunosuppression.

The single dose toxicity studies did not result in any treatment-related death, systemic toxicity, or overt necrosis. In addition, no significant and consistent changes in clinical signs, food consumption, clinical parameters, or organ weights were observed. A decrease in body weight gain was noted in the single dose toxicity study performed with AMT-010, as well as in mice receiving AMT-011 and immunosuppressive co-

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treatment. With AMT-010, a slightly increased incidence of minor lymphoid hyperplasia in the spleen was observed in the high-dose group as compared to control animals. This finding was reversed at 91 days. Moreover, a decrease in urea and creatine phosphokinase (CPK) was observed in the single dose toxicity study performed with AMT-010, but not in the toxicity studies performed with AMT-011.

At the injection sites, histopathological findings including myodegenerative changes and sub-acute inflammation were consistently found in all three single dose toxicity studies upon IM administration of either 1x 10^{12} or 1 x10^{13} gc/kg AMT-010 and AMT-011, respectively. Although myodegeneration as well as sub-acute inflammation of minimal severity can be observed in control animals with increasing age, a treatment related increased incidence and/or severity in myodegeneration in the mid- and the high-dose groups of both sexes were observed. In the study with 180 days of follow-up after exposure to AMT-011, there were histopathological changes in injected muscle consistent as discussed above and this was dose-dependent and of moderate severity, however regression of the muscle lesions was observed ; further, in mice, no functional effect was identified in general toxicity studies, although no dedicated muscle function tests were included.

No CD8+ve T cells were detected indicating that the cellular infiltrates that were detected do not represent cytotoxic T cells.

No neoplasia or specific liver toxicities were identified. Although liver hyperplasia was described, this was not at increased frequency than in the control group. The NOAEL dose assigned for this study when AMT-011 was given intramuscularly was 1x10^{11}gc/kg. The biodistribution component of this study indicated that the injected muscles, draining lymph nodes and liver showed the highest amounts of AMT-011. Apart from the liver, these tissues and the testes and epididymes showed higher amounts of AMT-011 injected intramuscularly than when it was injected intravenously.

Repeat-dose toxicity

Repeated dose toxicity studies were not conducted as Glybera will be administered once at multiple sites intramuscularly. In view of this intended clinical administration, it is acceptable that no repeated dose toxicity studies were performed. This is in accordance with the guideline for gene therapy medicinal products (CPMP/BWP/3088/99).

Genotoxicity

Standard genotoxicity studies, as applied to a conventional chemical drug, are not relevant for this type of product and were not performed. This is considered acceptable by the CAT and the CHMP and further addressed in the discussion.

Insertional mutagenesis and oncogenicity

The studies reported by the applicant do not indicate a hazard in term of insertional mutagenesis and oncogenicity but the method used was considered not fully adequate to identify an insertion event. Literature data contains many reports of the intramuscular use of rAAV and risks of insertional mutagenesis. The consensus view is that rAAV vector genomes remain episomal with minimal integration into the mammalian genome with no association with oncogenicity.

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The applicant initially conducted testing using a method described by Schnepp et al (2003), based on random amplification of DNA sequences (B1-PCR); however, due to unequal distribution of B1 sequences in the genome, it might result to an incomplete detection of genomic integrants. The repeat-anchored integration capture (RAIC) PCR method described by Wang et al (2004) which involves either vector to B1-, or, B1 to B1-PCR amplification using a biotinylated vector-primer for capture and subsequent nested PCR was further discussed as an alternative method. However, given that a negative result with B1-PCR RAIC may not necessarily mean that rAAV vector sequence integration has not occurred, it is judged that these methods have been sufficiently addressed by the applicant.

Considering that LAM-PCR was also not able to detect any integrated AMT-011 sequence from total DNA isolates, the applicant decided to use a non-restrictive (nr) LAM-PCR method combined with next-generation sequencing.

In vitro studies have been reported and the conclusion of the applicant is that these form a complete and appropriate means of assessing integration-related risk of cancer. In particular, data from the literature indicate that long term persistence of rAAV vectors is in the form of circular episomes. Studies using techniques to selectively digest genomic DNA showed that the majority (97%) of AMT-011 is not integrated into the genome, implying their presence episomally. Integration analysis did not identify any risky integration hotspots or clonal skewing that might indicate risk of mutagenesis on insertion of AMT-011 into the genome. Integration events were detectable (<2%) but were close to random in the genome.

Carcinogenicity

Carcinogenicity studies have not been conducted. The applicant argues that the studies conducted to assess integration are sufficient to address risk of carcinogenicity.

Inclusion of WPRE (woodchuck post-transcriptional regulatory element) and association with cancer

Glybera includes the woodchuck post-transcripitional regulatory element (WPRE) acting to amplify transgene expression and achieve sufficient levels of expression which could also lead to tumours, depending on what is amplified. WPRE is derived from woodchuck hepatitis virus (WHV). WPRE contains an element that promotes the WHV X protein which is being associated with the development of liver tumours in WHV-infected woodchucks.

The woodchuck posttranscriptional regulatory element (WPRE) is often essential to achieve sufficient levels of expression. Part of its sequence does overlap with that of the woodchuck hepatitis virus X (WVHx) which has been suspected of being implicated in the development of liver tumours but Glybera does not contain the We2 element, the second enhancer suspected of being involved in the initiation of tumours. As Glybera does not contain We2, the presence of WPRE in Glybera does not result in an increased oncogenic potential, in the applicant's view. The association of WVHx with liver tumours, in part, derives from the association between hepatitis B virus X protein (HBx). There is clear association with hepatitis B virus and development of hepatoceullar carcinoma and this is likely mediated by HBx, acting in conjunction with co-carcinogens. Evidence published by Dandri et al (1996) indicates that WHx protein is not present where animals had recovered from an acute infection with WHV, but is always present where there was persistent infection. Cell lines expressing WHx did not develop tumours spontaneously, but did do so when exposed to a carcinogen, indicating lack of ability to act as a carcinogen, but not excluding the possibility of tumour promoter potential.

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The WHx protein was not detected in two different cell lines after transfection. In toxicity studies with Glybera of 105 and 180 days' duration, no increase in tumour risk was identified either in the liver, nor in any other tissue. The applicant considered evidence in the literature of tumours reported in association with WPRE. The report of Kingsman et al (2005) and most other reports relate to use with a lentiviral vector whereas that of Embury et al (2008) related to its use with an adeno-associated virus and represents the only such instance to date. The latter did not indicate a specific liver tumour risk, despite dosing via the portal vein, as only 3 of 16 tumours mentioned were in the liver, with pulmonary and intestinal tumours reported and 4 tumours were reported in the same animal. The mechanism by which tumours are thought to have arisen relates to unexpected formation of a fusion protein between X-protein and a phenylalanine hydroxylase transgene (this being related to the intended therapeutic action in treating phenylketouria). The applicant has tested the crossreactivity of HBx and WHx with the monoclonal antibody used by Embury and concludes that it does crossreact with HBx but does not with WHx, and this finding therefore implies that the experiment described by Embury et al does not elicit WHx expression and therefore, it cannot be regarded as proof of the involvement in the tumours that, undoubtedly, were present.

Reproduction Toxicity

In female mice, treatment with AMT-011 four weeks prior to mating did not result in transmission of vector DNA to fetuses, indicating that germline transmission via the maternal line did not occur in this study. As the vector was detected in gonads of male mice, further studies investigating the presence of vector DNA in the germline cells and potential integration into the genome of these cells should be conducted. Persistent signals in gonads in cats, mice and rabbits triggered further testing in rabbits using cell fractionation methods to determine whether vector DNA is localised within sperm cells. Since a vector is found in both seminal fluid and sperm cells, the need for breeding studies to investigate whether the vector is transmitted to the F1 generation was discussed. Clinical testing also indicated positive signals in semen, indicating the relevance of requiring further animal testing.

Germline transmission via the male line was not tested and there was exposure to the gonads and the possibility of genomic integration has not been satisfactorily assessed.

Reproductive toxicity was studied in pregnant mice in whom no effects of female reproduction or fetal development were detected. It would nevertheless be prudent to avoid dosing during pregnancy.

Local tolerance

Local tolerance was assessed as part of general toxicity studies. There appears to be progressive and dose-related muscle toxicity at the recommended clinical dose. This has been shown to be reversible.

Other toxicity studies

A theoretical assessment of baculoviral DNA impurity-associated toxicity was presented. AMT-011 is made in insect cells intentionally infected with baculovirus. The applicant concluded from its pharmaceutical testing that baculoviral DNA content could result in a dose up to 3.3 iu baculoviral DNA/patient dose. The applicant conducted a literature review to identify risks associated with baculoviral DNA present at 10 particles/mammalian cell. Baculoviruses are viruses that infect insect cells which have been used as an

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insecticide for several decades and are not known to be pathogenic to humans. Intact baculovirus is susceptible to complement-mediated degradation and they are not known to have a specific cell-surface receptor and their binding to mammalian cells is thought to be relatively inefficient. Once inside the cell, they are susceptible to endosomic degradation and little nuclear penetration is expected. The applicant quantifies the probability of a baculovirus early promoter co-existing with an intact baculovirus gene at not higher than 11%, but to be functional, viral fragments need to integrate to each other or to the host genome, which the applicant quantifies as being a probability of $8x11^{-12}$%. As a consequence of this estimate, the applicant concludes there is no likelihood of risk associated with baculoviral content of the product.

2.3.5. Discussion on non-clinical aspects

Pharmacology studies indicated that treatment on a single occasion could result in long-lasting reduction of triglycerides with expression of the human transgene in animals.

There was a consistent finding of muscle damage on histopathological examination of animals with sub-acute inflammation and degenerative and regenerative changes. This may be linked to the expression of human LPL. The applicant was asked to consider these findings and determine whether this is reversible or permanent and further, to justify why, as regards a mechanism, no further experiments were conducted to distinguish whether the effect is due to local overexpression of LPL or whether these findings are due to immune reactions against AAV, as could be done for instance by comparing effects of a control AAV1 vector and those of Glybera.

According to the applicant, in the study with 180 days of follow-up after exposure to AMT-011, there is regression of the muscle lesions and in addition, in mice no functional effect was identified in general toxicity studies, although no dedicated muscle function tests were included for this exploration.

According to literature data, mice overexpressing LPL show these types of changes whereas this is not seen in transgenic rabbits that overexpress LPL. Therefore, according to the applicant, there are possible species differences, which could undermine the extrapolation of these findings in mice to humans.

This species difference could be impacted by biochemical differences between rabbits and mice in lipid metabolism and lipoprotein composition. The applicant considered that LPL overexpression resulting in excessive free fatty acid concentrations contribute probably to the muscle toxicity described with AMT-011 but they may not be the primary cause.

Histopathological changes in mice with changes in humans are considered comparable by the applicant: both changes are characterised by an ongoing degenerative process with regeneration and there is relatively few inflammatory cells.

The applicant considered that the combination of species differences in both immune responses to adeno-associated virus and in lipid metabolism make translation from findings in mice to the human situation uncertain.

The CAT did not fully agree with the applicant's justification for lack of further experimental evidence to compare the effect of a control adeno-associated virus and AMT-011 to study the significance of LPL overexpression. Such a study would however not remove the evidence of concern and therefore was finally not further requested and the issue considered solved.

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Pharmacokinetics addressed primarily the tissue distribution and duration of exposure. The injected muscle retains long term exposure in animals and tissues with significant exposure were the liver and lymph nodes. This exposure reduced over time. There was exposure to the gonads of both male and female animals but in pregnant mice, no fetal exposure was detected.

Upon request of the CAT, a breeding study in male CD-1 mice was carried out by the MAH showing that there was no paternal germ line transmission of AMT-011. The risk is therefore considered as being rather low.

In vivo carcinogenicity studies have not been conducted. The applicant argued that there is no existing study design that would be accepted as relevant to assess insertional mutagenesis and the risk of oncogenicity: the validity of any study design is questionable. The applicant discussed the literature on rAAV integration in vivo and hepatocellular carcinoma formation in mice in detail. Occurrence of hepatocellular carcinoma (Donsante et al., 2001; Donsante et al., 2007) was critically discussed and the applicant acknowledged that the model neonatal mouse has been recommended as possible alternative to the 2-year rodent model but questions its relevance as there is no similarity between rapidly dividing cells in the neonate and the adult muscle cell.

Overall, the CAT and CHMP finally agreed with the applicant that the data do not substantiate a concern for tumourigenicity. There are no further methods that are practical and able to assess the risk of tumourigenicity further and the available evidence suggests that the risk is either absent, or is likely to be very small. Theoretically, the product could integrate and cause a tumour, however, the CAT and CHMP agreed with the applicant that no further animal testing or experiments can usefully address these concerns.

2.3.6. Conclusion on the non-clinical aspects

Glybera contains two elements that may pose a tumourigenic hazard, these being the woodchuck post-transcriptional element and insertional mutagenesis. The applicant was asked to report its completed studies into these aspects and to present an integrated discussion and consider, if the data remain insufficient to draw a conclusion, to discuss further measures to evaluate this risk.

It is considered that although rAAV has potential integration risk, a consequent cancer is minimal and this is for the following reasons: 1– long term persistence of rAAV is mostly episomal; 2 – that integration events are not associated with cancer in studies in adult rodents, dogs or primates in the literature; 3 – pre-existing AAV-seropositivity in humans has not been associated with tumour formation. In the context of treating patients with this disease, these data suggest an acceptable safety profile.

Overall, the CAT and CHMP agreed that overall the data do not substantiate a concern for tumourigenicity. There are no further methods that are practical and able to assess the risk of tumourgenicity further and the available evidence suggests that the risk is either absent, or is likely to be very small. Theoretically, the product could integrate and cause a tumour, but the CAT agreed with the applicant that no further animal testing or experiments can usefully address these concerns. The applicant's data are acceptable and with no concern identified, the initial objections raised are considered solved.

The issue of risk of cancer in association with expression of WHx protein and in association with insertional mutagenesis is considered resolved.

There are no objections to the approval of Glybera, based on review of the non-clinical data.

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2.4. *Clinical aspects*

2.4.1. Introduction

Glybera is a gene therapy medicinal product intended for the treatment of lipoprotein lipase deficiency (LPLD).

LPLD is a rare autosomal recessive inherited condition caused by homozygosity or compound heterozygosity for mutations in the *LPL* gene. The prevalence of LPLD is 0.02 per 10'000 individuals in the EU.

The disease may present in infancy or childhood with severe abdominal pain, repetitive colicky pains, repeated episodes of pancreatitis, and often failure to thrive. On physical examination, eruptive xanthomas (accumulation of fat under the skin), lipaemia retinalis, and hepatosplenomegaly may be detected. The condition is often not diagnosed during childhood and may only become evident after several episodes of pancreatitis in adolescence or adulthood. The severity of the symptoms is proportional to the degree of chylomicronemia.

The most severe complication associated with LPLD is pancreatitis. Pancreatitis in an LPLD subject may lead to admissions to intensive care units. In case of severe pancreatitis, subjects may develop chronic pancreatitis, ultimately resulting in endocrine and exocrine pancreatic insufficiency. Therefore, the risk of a pancreatitis episode should be minimized by maintaining fasting plasma triglyceride values below 10 mmol/l.

GCP

The Clinical trials were performed in accordance with GCP as claimed by the applicant and a triggered GCP inspection found no critical findings.

The applicant has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

A triggered inspection was conducted at the sponsors' and investigator's site following a request from CHMP/CAT in connection with their evaluation of the MAA in order to verify whether the clinical trial CT-AMT-011-01 was conducted in compliance with Good Clinical Practice (GCP) and applicable regulations in particular where it has an impact on the validity of the data or the ethical conduct of the trials,.

There were no critical findings at either inspection site. clinical development programme consisted of three main open label uncontrolled studies. Studies CT-AMT-010-01 and CT-AMT-011-01 included observational non-interventional phases named Preparation 1 and Preparation-2, respectively. Total efficacy and safety data were available from 27 patients with heterozygous and homozygous mutations in LPL gene. Around 60% of all patients were individuals with homozygous P270L mutations mainly those patients living around Quebec (Canada) (founder effect).

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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

2.4.2. Pharmacokinetics

Conventional pharmacokinetic characterisation of the product is not possible and not expected from gene therapy products. However thorough analysis of the vector delivery into the target tissue, persistence of expression and the presence of the functional protein is required by the guideline for gene therapy medicinal products EMEA/CHMP/GTWP/587488/2007. The applicant has carried out an extensive characterisation work using quantitative PCR, immunocytochemistry and measurement of total and specific LPL activities in subsets of patients who consented for the muscle biopsy in CT-AMT-010-01, CT-AMT-011-01 and ongoing CT-AMT-011-02 studies.

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Study	Subject ID	Dose (gc/kg)	ISR	biopsy (weeks post)	QPCR (gc/µg gDNA) I	QPCR (gc/µg gDNA) C	LPL mass (ng/mg) I	LPL mass (ng/mg) C	LPL Activity (nmol FFA/min/mg) I	LPL Activity (nmol FFA/min/mg) 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.

In study CT-AMT-010-01 a product derived from an earlier manufacturing process was used. In this study, muscle biopsy was performed between week 10 and 36 post-administration in 8/8 patients. LPL mass expression in the muscle could be demonstrated for all patients enrolled. LPL activity could be observed in 7/ 8 patients.

In study CT-AMT-011-01 muscle biopsy was performed in 7 / 14 patients between week 25 and 26 post administration. LPL mass expression and LPL activity was observed in 3/7 patients; whereas in 4 patients neither LPL mass nor LPL activity was observed.

In study CT-AMT-011-02 all 5 enrolled patients agreed to muscle biopsy. Samples were taken between week 14 and 36, with an additional sample at week 52 for one patient. Between week 14 and 52 all patients showed evidence of LPL mass for at least at one time point. Interestingly one patient was negative for LPL mass and activity at 18 months; but a signal for both tests was detected at 52 month. For two other patients, although LPL mass was detected no LPL activity was seen at the same time point.

These results shed some doubts in the validity of the methods used.

In summary, in clinical studies performed with the product derived from the current manufacturing process in 8/13 samples LPL mass could be detected and in 6/13 samples LPL activity was observed. From these results, it can be concluded that the applicant failed to demonstrate a sustained expression and activity of LPL in the muscle.

In the clinical setting lipolytic activity is measured by measuring LPL activity in post-heparin plasma.

The applicant failed to demonstrate this serum LPL activity in treated patients consistently in the clinical studies.

The applicant claimed that the applied LPL activity assay used for the clinical studies (the same assay as used by centres around the world to diagnose LPLD) was found not to be sensitive enough to detect small

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increases. The applicant however presented non-clinical data to demonstrate LPL protein and activity in post-heparin plasma following IM administration of alipogene tiparvovec to wild type and LPL-/- mice.

The data in humans are however considered inconclusive; a methodological problem could be a possible explanation for the lack of demonstrable LPL activity in plasma; however, a true lack of LPL plasma activity could not be ruled out. Local LPL activity may not be expected to decrease plasma triglycerides in a clinically relevant manner.

The applicant's hypothesis that an improved chylomicron (CM) particle metabolism is linked to reduction in pancreatitis in patients with LPL deficiency needs to be further substantiated by clinical data and the post-hoc data provided during the procedure were not considered to have addressed this requirement sufficiently. It has to be borne in mind that in the muscle LPL mass and LPL activity could only demonstrated in a subset of patients; LPL plasma activity could not be consistently demonstrated and no sustained TG decrease could be observed. Additional information on post prandial chylomicron levels in 5 patients at week 14 and 3 patients at week 52 was provided. While the CM peak was lower for pre-treatment patients, the CM peak remained delayed (about 10 hrs) at 52 weeks, which is considered to reflect delayed CM clearance due to LPLD. The results are unexpected, though this may in part be due to the very small numbers and methodological problems. In conclusion, too limited data to elucidate the mode of action and substantiate the clinical benefit of Glybera have been provided and it is concluded that the applicant failed to adequately demonstrate pharmacokinetic and pharmacodynamic properties of Glybera in the clinical setting.

Biodistribution and shedding of Glybera has been evaluated as part of the clinical efficacy and safety studies CT-AMT-010 or CT-AMT-011-01 and the ongoing study CT-AMT-011-02. The highest vector DNA concentrations in serum were detected on day 1 or 2. The majority of subjects in all three trials had cleared vector DNA from their sera by week 8-12. Vector DNA concentrations in saliva increased after vector administration with a maximum value on day 2. Thereafter, the concentration of vector DNA decreased exponentially and was cleared from the saliva of all but one subject in each trial by week 3-4. AAV1-LPLS447X DNA was detected in the urine of several subjects; urine was the first body fluid to clear vector DNA beginning 1 week after AMT-010/AMT-011 administration. After 3-10 weeks, the urine was cleared of vector DNA in all subjects. In CT-AMT-010-01 study, very low AAV1-LPLS447X DNA concentrations were transiently detected in the semen of 2 subjects (at maximum 31 to 110 copies/µg DNA) up to week 2 after AAV1-LPLS447X dosing. For 2 male subjects, no semen samples were available. In CT-AMT-011-01, semen vector DNA concentrations decreased beyond detection limit between week 8 and week 10 in most subjects. In two subjects positive semen sample at week 12 and 26 respectively were detected with levels were at the limit of detection of 1.0 x 101 gc/kg DNA. In the ongoing CT-AMT-011-02 study, no AAV1-LPLS447X DNA was found in any of the analysed samples beyond week 3. Although limited and highly variable data on vector shedding, qPCR measurements and the level of local LPL expression based on biopsy sampling support the finding that alipogene tiparvovec becomes available systemically following injections, and some proportion of the vector results in local expression of the LPL enzyme.

2.4.3. Pharmacodynamics

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. The key

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expected pharmacodynamic read-out of Glybera activity encompasses the ability of the gene-therapy to restore enzymatic activity attributed to the functional LPL, which thus results in a reduction of TG-rich lipoproteins such as chylomicrons (CM) and very low density lipoproteins (VLDL).

During the clinical development it became clear that changes in TG in LPLD patients were not linked to therapy as was expected. The effect of gene-therapy on fasting TG was measured as a primary efficacy endpoint in all conducted studies and results are detailed in the section on Efficacy. It became clear that the reduction in fasting TG levels could be achieved only in a small proportion of patients at W12 and was accompanied with significant variability of median values. The TG-lowering effect was transient and ceased to exist in a majority of patients beyond 1 year. The applicant now considers that fasting TG cannot serve a reliable role in predicting the efficacy of Glybera in LPLD patients. Instead, the role of Glybera in reduction of post-prandial CM was proposed as a surrogate marker of efficacy by the applicant. Assays to characterise CM particles (o.a. CM-specific ApoB48 assays), two methods of lipoprotein profiling and post-prandial CM and lipid/carbohydrate metabolism tracer studies were initiated but only during the last study CT-AMT-011-02 (3 patients out of 5 showed some reduction in post-prandial CM up to week 52), whereas only 1 patient showed fasting TG response at week 12. Results obtained in these additional evaluations were largely exploratory, not accompanied with sufficient data on pancreatitis and failed to yield any reliable associations with fasting TGs. The applicant proposed to elucidate post-prandial CM response in all patients included in the Glybera clinical programme. Such data is considered essential in the appraisal of currently unvalidated, but potentially acceptable exploratory endpoint especially following failure to achieve a reliable PD read-out (fasting TGs using criteria <10 mmol/L and ≥40% reduction). The potential validity and clinical utility of post-prandial CM response should be further substantiated before any attempt to change the diagnostic and monitoring paradigm of LPLD is made.

2.4.4. Discussion on clinical pharmacology

No conventional PK/PD studies were carried out, which is considered acceptable by the CAT for a gene-therapy product and rare orphan condition. The study programme to evaluate biodistribution / shedding was adequate.

The key pharmacodynamic read-out for the Glybera treatment is based on an attempt to restore deficient LPL function via transfer of extra copies of over-functional LPL gene into muscles cells of patients with LPLD in order to normalise levels of TG/CM. There was a clear lack of fasting TG response beyond 12 weeks. Adenoviral vector based Glybera is inherently incapable of permanently curing the LPLD since the vector expression is only maintained episomally and solely shared between rarely divided cells or intercellular communications. Since the expression of transgene cannot be constitutively expressed life-long, a complete abolishing of disease complications is not feasible unless further repeat treatment is applied. Normally LPL enzyme is never expressed in endothelial cells but rather produced in muscle or parenchymatous cells and subsequently transported onto the luminal surface of endothelium to render a direct contact with large circulating CM particles. Muscle biopsies taken between weeks 25-27 indicated a certain proportion of patients with intracellular staining for LPL and intracellular lipid accumulation. However local transgene expression has not been accompanied with any marginal increase in systemic LPL levels and did not correlate with TG response measured at week 12.

In contrast, signs of local muscle degeneration and regeneration, with some cellular infiltration, seemingly dose related, were observed in injected muscles up to approximately half a year post study drug administration. A role of the persistent local LPL activity in the development of this effect cannot be ruled

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out. Furthermore, an inhibitory mechanism for triglyceride hydrolysis as present in the endothelial system is lacking. Consequently local triglyceride hydrolysis is resulting in uninhibited local increase of free fatty acids. The increase of free fatty acids eventually may result in damage of the muscle cells. It might well be that these histological findings become more apparent after cessation of the immunosuppressive therapy.

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. *Clinical efficacy*

The clinical development programme for Glybera consisted of two observational studies (Preparation-01 and Preparation-02) and three uncontrolled, open-label, interventional studies: CT-AMT-010-01, CT-AMT-011-01 and CT-AMT-011-02. The latter study was initially planned as a controlled study, however it was subsequently amended to recruit only 1/3 of the originally planned study population into an uncontrolled study due to difficulties in identifying patients with high baseline risk of pancreatitis. It is acknowledged that a controlled study could be a challenge due to the rarity of LPLD-associated mutations.

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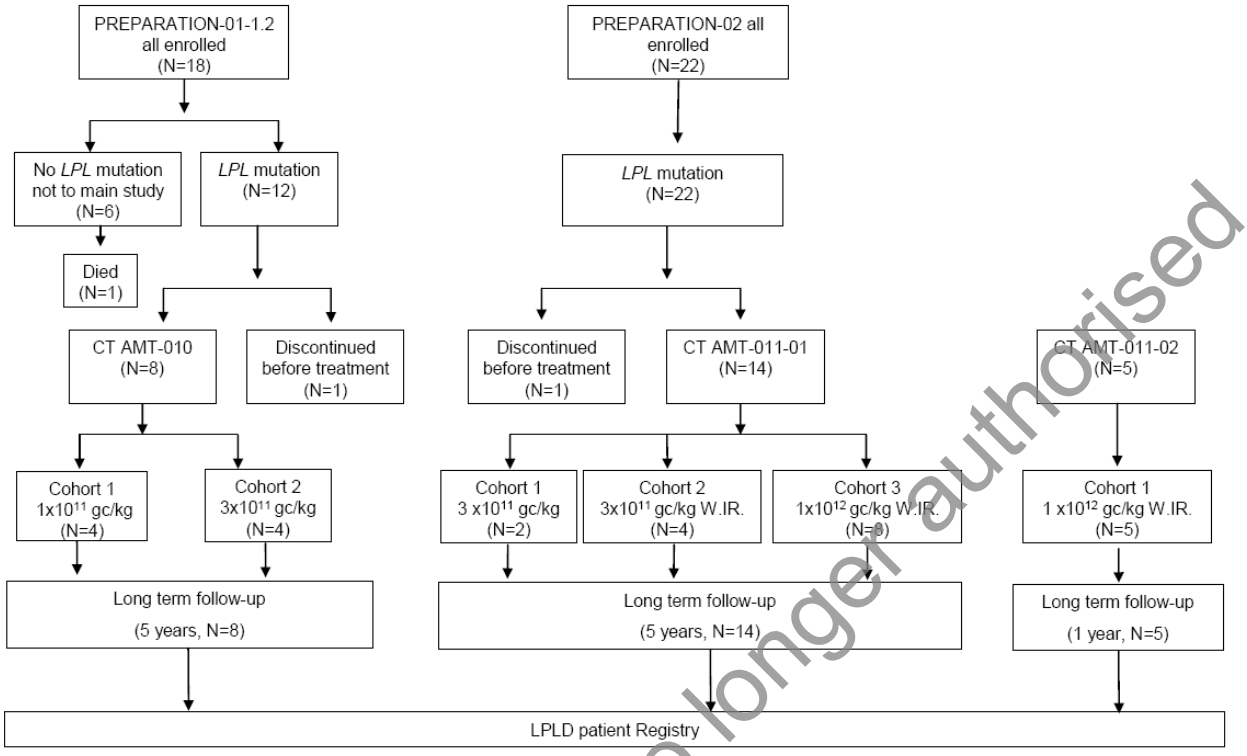
Figure 1: Flow diagram of treated patients in the clinical development programme of Glybera



Dose-response studies and main clinical studies

Three different dose regimens were evaluated in CT-AMT-010-01, CT-AMT-011-01, and CT-AMT-011-02, as indicated in Figure 1 above. The latter 2 studies also included immunosuppressive regimen. In study CT-AMT-011-01, Glybera was combined with a modified immunosuppressant regimen consisting of 12 weeks of ciclosporin A (3 mg/kg/day) and mycophenolate mofetil (2 g/day) post dosing. This regimen was further modified in study CT-AMT-011-02: ciclosporin A and mycophenolate mofetil treatment was started 3 days prior to AMT-011 administration and continued for 12 weeks post dosing, and a single bolus of methylprednisolone (single IV bolus 1 mg/kg) was given half an hour before AMT-011 administration.

2.5.1. Preparation-01 study (supportive study for CT-AMT-010-01)

The clinical programme was started from the observational study Preparation-01.

PREPARATION-01study

Pre-monitoring LPL-deficient Patient Analysis Prior to Trial Enrolment in Triglyceride lowering *LPL*

Gene Therapy **CT-AMT-010-01**

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- **Methods / Study participants:**

The preparation 01 study was conducted in Netherlands and enrolled a total of 18 LPL-deficient patients ≥18 year old diagnosed with type I hyperchylomicronaemia with post-heparin LPL activity <25% of normal level, plasma concentrations of TG >95th percentile for age and gender.

Exclusion criteria concerned patients with apolipoprotein CII deficiency, BMI>35 kg/m2, history of serious physical or mental illness (including malignant neoplasm), and acute infection. All patients entered the study were instructed to follow 20-25% fat restrictive diet. Individual diet counselling was performed by a dedicated dietician and patients were required to fill out daily food diary. Subjects were followed at minimum 3 months and at maximum 17 months. During the follow-up, adverse events, including pancreatitis were recorded in the case report form. Subjects with median triglyceride concentrations >10 mmol/L, despite compliance to dietary restrictions, were to be enrolled in subsequent gene therapy study CT-AMT-010-01.

- **Treatments**

No treatments were allowed and lipid-lowering therapies were discontinued at the study beginning.

- **Objectives/endpoints**

Measurement of the amount of fasting triglycerides in LPL-deficient subjects at a consecutive time points to obtain further insight in the fasting plasma triglyceride concentrations in LPL-deficient subjects during a low-fat dietary regimen.The outcome of the study was to monitor fasting plasma TG level variations in the plasma. The incidence of pancreatic events were monitored in the context of the safety evaluation.

- **Sample size / Descriptive statistics**

The study was open non-randomised observational in nature. The protocol was planned for 30 patients. The study population was divided into 3 groups:

1. Subjects proven to be homozygous or compound heterozygous for LPL mutations who continued to the main study CT-AMT-010-01

2. Subjects proven to be homozygous or compound heterozygous for LPL mutations who were not subsequently enrolled into the subsequent LPL gene therapy study CT-AMT-010-01

3. Subjects in whom LPL mutations could not be identified and who did not continue to the CT-AMT-010-01 study

Subjects with a median triglyceride level ≥10 mmol/L were to be included in the main study CT-AMT-010-01.

Results

- **Participant flow**

A total of 18 subjects were enrolled in the Preparation-01 study and divided into 2 groups based on *LPL* mutation status. Of those with the *LPL* gene mutation, 9 progressed to study CT-AMT-010-01, and 8 received treatment with AMT-010. Of the 18 subjects enrolled, 17 subjects completed the study and 1 subject died of a cardiac arrest.

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- **Baseline data**

Subjects ranged in age from 18 to 70 years with a median of 45 years, 78% of the population was male, and BMI ranged from 21.9 to 29.4 kg/m2. 72.2% were Caucasians and 27.8% belonged to "Other" ethnic groups. With the exception of 2 subjects (neither of whom continued to the main study), all had experienced episodes of potentially lethal pancreatitis. Triglycerides at baseline in the Preparation-01 study were >10 mmol/L, as expected for LPL-deficient subjects. 66.7% (6) patients enrolled into the subsequent study were on lipid-lowering medication. These included: 33.3% (3) patients on fibrates; 44.4% (4) on HMG reductase inhibitors, and 22.2% (2) on nicotinic acid and derivatives.

- **Outcomes and estimation**

Large variations were observed between subjects but also between visits for the same subject. Median triglyceride level varied throughout the observation period between 21 and 35 mmol/L with no apparent trend, indicating that dietary counselling and the food diary were not efficient in lowering triglycerides in LPLD subjects. Five significant and serious clinical events occurred in 4 subjects which were all related to the underlying disease condition. Pancreatitis occurred 5 times in 4 subjects during this study. Another subject suffered an episode of pancreatitis during the interim period between the end of the PREP-01 study and the initiation of the 010-01 study. Thus, there were a total of 6 episodes of pancreatitis that developed in five subjects prior to initiation of CT-AMT-010-01. Three of the subjects with LPLD (one with a homozygous mutation and two with a compound heterozygous mutation) continued to into CT-AMT-010-01. The other two subjects did not continue after the Preparation-01 study. By comparison, one subject (homozygous mutation) developed pancreatitis episode ~1.7 years following AMT-010 administration in CT-AMT-010-01 and another subject experienced a series of pancreatitis incidents between 0.9 and 2.5 years after injection.

Discussion

The Preparation-01 study allowed to enrol patients with and without mutations in LPL gene and therefore resulted in increased heterogeneity of observational results. There was high level of missing data on fat-restrictive diet in main subpopulation included in subsequent study. The range of fat(%) intake varied between 13-45% with medians of around 21.0-33.0%. This indicated that despite strict dietary recommendations, to maintain strict compliance with fat restriction and achieve maintenance of intake to <20% was extremely difficult. Levels of TG and CM levels are highly variable and the past incidence of pancreatitis was highly variable between different subgroups. It is remarkable that patients with LPL mutations continued to the main study CT-AMT-010-01 (N=9) had a range of yearly incidence of pancreatitis as 0.06-0.62 (mean 0.258, median 0.247) but patients with LPL mutations which did not continue to the main study (N=3) had the incidence in the range of: 0.00-2.24 (the analysis of pancreatitis was carried out in retrospective manner).

There was an incomprehensible number of missing values from week 0 to the last visit during week 35 which impacted the reliability and usefulness of the data. A high variability of values of TG despite the diet regimen was observed and median levels varied between 3.39-27.23 mmol/l.

The Preparation-01 study nevertheless was useful in understanding challenges associated with patient recruitment, maintenance of dietary restrictions and correlating lipid levels with clinical manifestation of the disease.

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From the data submitted, 4 patients out of 9 who were enrolled into PREP-01 and continued into CT-AMT-010-01 study did not experience any pancreatitis episodes within 1.5 year trial. The incidence of events can vary substantially from patient to patient and the presentation of cumulative rate of pancreatitis in such a heterogeneous group of patients can be misleading. Retrospective analysis of pancreatitis events requested by CAT (CT-AMT-011-03 study)

Further details on intervals between past events and appropriate time-to-event analysis were requested to the applicant. The overall data on pancreatitis events are presented and discussed later in the report under CT-AMT-011-03 study.

2.5.2. CT-AMT-010-01 study

CT-AMT-010-01:

A Study to Determine the Safety and Efficacy in Lipoprotein Lipase-Deficient Subjects after Intramuscular Administration of AMT-010, an Adeno-Associated Viral Vector Expressing Human Lipoprotein LipaseS447X

- **Methods**

8 Patients with confirmed homozygotic and compound heterozygotic LPL gene mutations enrolled in Preparation-01 study were recruited into the main open-label uncontrolled interventional study CT-AMT-010-01, which was conducted in a single centre in Netherlands.

- **Study participants**

Inclusion criteria included patients >18 years of age who were prepared to maintain contraception, who previously were enrolled in Preparation-01 study and had: (I) LPL activity levels in post heparin plasma ≤20% of normal; (II) Confirmed homozygocity or compound heterozygocity for mutations in the LPL gene; (III) Post heparin plasma LPL mass >5% of normal; and (IV) Median fasting plasma triglyceride concentrations >10 mmol/L, as determined during the pre-monitoring period.

Exclusion criteria concerned patients with apolipoprotein CII deficiency, inflammatory muscle disease (e.g., myositis, myopathies, or rhabdomyolysis), history of malignancy, active infectious disease; platelet count <100 x 10^9/L; anaemia, liver failure, creatine phosphokinase (CPK)>3 x ULN; creatinine >3 x ULN; coagulopathy, seropositivity for HIV, hepatitis C, or hepatitis B; severe obesity defined as BMI >30 kg/m^2; history of abuse of alcohol and substances abuse, concomitant treatment with immunosuppression and anticoagulants.

All patients were monitored in post-dose period up to 12 weeks with TG, total cholesterol, lipids, lipoprotein levels, anti-AAV, anti-LPL antibodies and other safety variables monitored weekly. T-cell response to AAV and LPL was measured at weeks 2, 4, 6, 8 and 12. Serum, saliva, and urine Q-PCR were carried out at day 2 and day 7 and semen Q-PCR at Day 7.

- **Treatments**

The single dose escalation regimen was employed with 4 patients dosed with AMT-010 (Human LPL*S447X* expressed using an Adeno-Associated Viral Vector) at the dose of 1 x 10^{11} (cohort 1) followed by 4 patients dosed with 3 x 10^{11} gc/kg (cohort 2). There were at least 2 weeks between dosing of subjects within one dose cohort, and 4 weeks between the dosing of the last subject in a dose cohort and the dosing of the first subject in the subsequent dose cohort, to allow review of the safety and efficacy

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endpoints, indicated below. AMT-010 was administered as a single dose by multiple injections into the upper and lower leg muscles. The third dose of AMT-010 was not administered because of lack of additional available trial subjects.

AMT-010 was to be administered in a special isolation unit. Total dose was to be calculated using the subject's body weight obtained at baseline screen. Volume per injection was not to exceed 0.5 mL. The muscle was to be visualized before injection using ultrasound to identify major vessels and was to be injected using a 27-gauge needle. Injections were to be spread evenly over the various selected muscle groups, and within each muscle. Skin above 2 injection sites was to be marked by a tattoo to facilitate localising of injection sites at a later time point.

- **Objectives**

Primary:

1. To assess the safety profile of AMT-010;

2. After administration of AMT-010, to achieve a reduction in individual median fasting plasma triglycerides to a level ≤10 mmol/L on top of diet, or to achieve a reduction in fasting plasma triglycerides such that the difference in individual median plasma triglycerides observed before and after administration represents a 40% reduction, in addition to diet.

Secondary:

1. To determine the biologic activity and expression of LPL, the transgene product (LPLS447X);

2. To evaluate potential immune responses against LPLS447X transgene product and the adeno-associated viral (AAV) vector;

3. To assess the shedding of AMT-010.

- **Outcomes/endpoints**

Primary endpoint: reduction in individual median fasting plasma triglyceride levels of ≤10 mmol/L concurrent with a low-fat diet, or 40% reduction, concurrent with a low-fat diet.

Safety: adverse events, vital signs, physical examination, immunogenic response, biologic activity, DNA shedding.

- **Sample size / Descriptive statistics**

The analysis of efficacy and safety variables was presented using descriptive statistics.

CT-AMT-010-01 study was open label study and the analysis of pancreatitis events was attempted in post-hoc way as was not pre-specified in the statistical analysis plan (SAP). For the long-term (3 year) observational period no separate protocol and SAP were available.

- **Results**

- **Participant flow**

Disposition:

Twelve subjects in the Preparation-01 study had LPL mutations identified. Nine subjects progressed to Study CT-AMT 010-01 and 3 subjects with LPL gene mutations did not (1 woman wanted to become

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pregnant, and 2 subjects were withdrawn due to difficult study logistics). Of the 9 subjects from the Preparation-01 study, 1 tested positive for hepatitis B surface antigen and was not randomised for study treatment. One subject was terminally ill (lung cancer) and only completed the 2-year follow-up visit. The last subject to have entered CT-AMT-010-01 was scheduled for a 3-year follow-up visit in the fourth quarter of 2009.

- **Baseline data**

With the exception of 1 subject, all were Caucasian, and had a similar weight and BMI. Subjects in cohort 2 tended to be older than those in cohort 1

Twelve subjects in the Preparation-01 study had LPL mutations identified. Nine subjects progressed to Study CT-AMT 010-01 and 3 subjects with LPL gene mutations did not.

Outcomes and estimation

Efficacy was assessed using data from the first 12 weeks after dosing. LTFU consisted of data collected over a period of 26 weeks to 3 years post dosing.

Lipid response

Over the first 12 weeks post dosing, all subjects showed a reduction in median triglyceride levels, and 3 subjects showed a reduction of greater than 40%. Percent reduction in triglyceride values ranged from 18.53% to 50.90% for the 1 x 10^{11} gc/kg-dose group and 24.99% to 47.06% for the 3 x 10^{11} gc/kg-dose group.

Based on assessment from 1 to 12 weeks post dosing, only 2 subjects met the primary endpoint, defined as median triglyceride level after injection <10 mmol/L, or a 40% reduction of the median compared with baseline value. The percent success was 2/8: 25% overall: reduction to 0% in subsequent period. Three years post dosing, all of the subjects showed triglyceride levels around or above baseline, indicating that the administration of the study drug had induced only a transient reduction of plasma triglyceride.

Rate of complications (pancreatitis events)

Based on the observation that only 1 subject experienced pancreatitis in 3 years of follow-up post dosing, the applicant elected to further explore the rate of pancreatitis in this population. During the CT-AMT-010-01 study 5 pancreatitis episodes were observed. This lower incidence resulted in a calculated rate of 0.18 episodes per year, which is about 70% lower than the rate observed during the observation period.

Discussion

Rate of complications (pancreatitis events)

Given that patients with LPL deficiency are prone to attacks of pancreatitis and that plasma TG concentrations above 10 mmol/l are critical levels for the development of pancreatitis and that at plasma TG levels below that threshold the risk of pancreatitis would be substantially reduced,the applicant decided to monitor the incidence of pancreatitis in the context of the safety evaluation and relating it to the patient's medical history. The incidence of pancreatitis events varied substantially from patient to patient and the presentation of cumulative rates of pancreatitis in a heterogeneous group of patients is misleading.

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While there was a trend in reduction of annualised rate of pancreatitis attacks, the past incidence of pancreatitis events varied substantially from patient to patient and from year to year in a given patient. A key pitfall of the study was that the protocol is lacking a definition of pancreatitis event and had not been accompanied with an appropriate diagnostic algorithm to ensure that the diagnosis of pancreatitis was being made reliably. In addition, some patients developed events following treatment. There were inconsistent effects on annualised rates between different dose cohorts.

Therefore the evidence provided by the applicant in support of reduced rate of pancreatitis is insufficient and does not follow any pattern. Any small trends observed within such a small trial could have been a chance finding.

Biologic activity of AMT-010

Analysis of muscle biopsies (10-36 month after injection) showed a variable degree of nonspecific muscle fibre degeneration and regeneration, lipid accumulation and inflammation in injected muscle. A dose-dependent but variable level of vector sequence was detected in injected muscle in all subjects but one. Immunohistochemistry confirmed the presence of increased levels of LPL protein. The applicant explained the absence of DNA in one patient by sampling error.

The correlation of DNA/LPL expression levels in muscle biopsy to the clinical efficacy results, namely with systemic lipid levels and incidence of pancreatitis events was not discussed by the applicant. Therefore, with regards to the company's main claim of preventing complications due to LPL deficiency, it is impossible to conclude that there was a plausible association between successful gene-transfer into the muscle tissue and the altered rate of pancreatitis.

2.5.3. Preparation-02 study (supportive study for CT-AMT-011-01)

The second main study consisted of two subsequent studies, observational non-interventional study Preparation-02 and uncontrolled open interventional CT-AMT-011-01, which were conducted in two centres in Canada selected because the prevalence of LPLD in eastern Quebec is probably the highest in the world at an estimated 1 per 10,000. The high prevalence is due to a founder population from the 1700's that was amplified by the isolated geography and consanguinity. The design and objectives were almost identical to studies Preparation-01 and CT-AMT-010-01, to allow comparison of outcomes with AMT-011 to those obtained with AMT-010.

Preparation 02 study

A single centre uncontrolled observation study designed to evaluate TG levels and disease complications in LPL deficient subjects on a low-fat diet, providing baseline assessments for the subsequent intervention gene therapy study in preparation of CT-AMT-011 study.

- **Methods/ Study Participants**

The design and objectives were almost identical to Preparation 01 study.

Preparation-02 enrolled 22 subjects with LPLD documented by genotyping, lipoprotein lipase activity ≤ 20 % of normal, LPL mass > 5 % of normal and fasting plasma TG concentrations > 10 mmol/l. Subjects were maintained on a low fat diet (55 gm fat, 2000 calories) with dietary consultation provided every 6 ± 2 weeks. Twenty subjects completed the study as two subjects withdrew from the study prior to the first

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evaluation visit. Thus, the data set for this study consists of 20 subjects. Fifteen of the 20 subjects were subsequently enrolled into CT-AMT-011-01.

- **Treatments**

No investigational product was administered.

- **Objectives/endpoints**

(i) To determine fasting plasma TG levels in LPLD subjects on a low-fat dietary regime and

(ii) To observe and measure the incidence of clinical complications, reflecting the morbidity of this disease in LPLD under severe diet restrictions.

- **Statistical methods / conduct**

The study planned to enrol 30 patients but was prematurely terminated after enrolment of 22 patients. Descriptive statistics were used to calculate lipid parameters. Some ancillary analyses on rate of complications (pancreatitis) were carried out as post-hoc analysis.

- **Results**

A total number of 22 subjects with hypertriglyceridemia were enrolled, of which 21 subjects showed reduced LPL activity, thus meeting the inclusion and exclusion criteria and are included in the analysis of this observational study. These 21 subjects were confirmed to be homozygous or compound heterozygous for mutations linked to loss-of-functions in the LPL gene. Fourteen subjects completed the PREP-02 study and rolled over into the subsequent gene therapy study CT-AMT-011-01, six subjects discontinued the PREP-02 study for various reasons and two subjects completed the PREP-02 study without roll over to CT-AMT-011-01.

Baseline data

The median age of the 20 subjects was 49.5 years (range: 27 to 63 years) with 9 males and 11 females. All of the subjects were Caucasian and their body mass index ranged from 14.4 to 27.8kg/m^2. The medical history was remarkable for prior hospitalization for acute pancreatitis in all 20 subjects (range: 1-11 prior episodes). Eight subjects were on lipid-lowering medication at baseline: seven subjects were receiving a fibrate and another subject was receiving a statin.

- **Outcomes and estimation**

Five of the observed clinical events were assessed by the investigator to be serious; two in 2 subjects who subsequently received study drug and three in 3 subjects who did not. The former two subjects developed pancreatitis and an aortic aneurysm during the study while two of the latter three subjects had pancreatitis while the other developed colitis. The three cases of pancreatitis were attributed by the investigator to the underlying LPLD.

The median TG level of the enrolled patients with a first assessment (n=20) was 20.7 mmol/l at baseline. It remained unchanged at 20.6 mmol/l at 6 weeks, increased to 26.0 mmol/l at 12 weeks, fell to 18.3 mmol/l at 18 weeks (n=19) and then increased again to 23.7 mmol/l at 24 weeks (n=14). Even though diet was strictly controlled and blood samples were taken after fasting, there was a large inter- and intra-subject variability of TG levels. TG levels varied as much as 5.5-fold between visits in an individual subject and over 10-fold between subjects. There was no difference in the TG levels between the 15 subjects who were subsequently enrolled into CT-AMT-011-01 and the five subjects who were not enrolled. These data

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suggest that dietary counselling was not effective in lowering TG in LPLD and many of the subjects were unable to comply with the low-fat diet. Approximately half (9/20) of the subjects managed to keep to a diet with total fat intake below 55 g /day during all of the PREP-02. This suggests that diet compliance and/or adherence to lipid lowering medications did not consistently reduce the TG levels.

Discussion

As with Preparation-01, the Preparation-02 study established that TG levels in patients with LPLD are characterised with significant inter- and intra-patient variability. Diet alone seems to be insufficient for maintaining desirable levels of <10 mmol/l due to issues of compliance and adherence in less than 40% of patients. Baseline medical history indicates the presence of pancreatitis events in all patients. However it was noted that a large proportion of patients also had past surgical interventions. Therefore, the presentation of abdominal pain resembling pancreatitis could have been due to abdominal pain of different origin, e.g. due to adhesions.

Retrospective analysis of pancreatitis events requested by CAT (CT-AMT-011-03 study)

Clarification was further requested on how investigators censored past acute pancreatitis events from past medical history and whether data on CT imaging, amylase and other blood tests were available. Periods for which patients remained in the study was relatively short with a very low proportion of pancreatitis events identified. Therefore intra-study comparisons between pre-treatment and post-treatment periods were not possible. (see additional discussion later in the report)

2.5.4. CT-AMT-011-01 study

A single centre, uncontrolled, open-label, dose-escalation study to investigate the safety and efficacy of AMT 011 over 12 weeks, for the treatment of subjects with Lipoprotein Lipase Deficiency (LPLD). Long term follow up (LTFU) until 5 years is recorded.

- **Methods/ study participants**

15 subjects from Preparation-02 were initially rolled-over into an open-label, single centre, dose escalation study (CT-AMT-011-01) to assess the safety and efficacy of gene therapy with AMT-011. The only difference in inclusion criteria between CT-AMT-011-01 and CT-AMT-010-01 was that the former study required patients to have a history of pancreatitis. One subject was withdrawn from the study; thus 14 subjects were enrolled in the study active phase. Thereafter, subjects entered the study long term follow up extending up to 5 years.

This was a 15 week study (3 week baseline and 12 week study period) with long term follow-up extending out to 5 years.

- **Treatments**

Due to a change in the manufacturing process as described earlier, the first cohort (n=2 subjects) was administered 3 x 10^{11} gc/kg of AMT-011. This served as a bridging arm to gauge similarity of the safety and efficacy of AMT-011 relative to AMT-010. Immunosuppression included a combination of cyclosporine A (3 mg/kg/day) and mycophenolate mofetil (2 g/day) which was given over 12 weeks. The combination of CSA and MMF was chosen because this combination had been extensively used to prevent allograft rejection. The doses selected for this study are consistent with those approved for transplantation. Finally,

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this regimen was selected, as according to the applicant, these two drugs do not affect plasma lipids or glucose.

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).

- **Objectives**

Primary Objectives:

1. To assess the safety profile of AMT-011;

2. To achieve a reduction in fasting plasma TG such that the difference in median plasma TG observed before administration of AMT-011, on top of a low-fat LPLD diet, and up to 12 weeks after administration, while maintaining a low-fat LPLD diet, represents approximately 40% reduction.

Secondary Objectives:

1. To achieve sustained efficacy, defined as approximately 40% reduction in fasting plasma TG up to 26 weeks after administration in LPL-deficient individuals following a low-fat LPLD diet. Note that this is an objective related to the long term follow up study (LTFU)

2. To achieve a reduction in fasting TG to a level equal to or less than 10.00 mmol/l on top of a low-fat LPLD diet at 12 weeks after administration.

3. To achieve sustained efficacy, defined as a reduction in fasting plasma TG at 26 weeks after administration to a level equal to or less than 10.00 mmol/l on top of a low-fat diet. Note that this is an objective related to the long term follow up study (LTFU).

4. To determine the biological activity and expression of the transgene product (LPLS447X).

5. To evaluate potential immune responses against the transgene product (LPLS447X) and the AAV vector.

6. To assess shedding of AMT-011.

- **Outcomes/endpoints**

Efficacy:

Primary: Reduction in fasting plasma TG (median of baseline vs median of week 3-12 post AMT-011) ≥ 40%.

Secondary: Decrease in fasting plasma TG ≤ 10.00 mmol/l between week 3-12 post AMT-011. Sustained efficacy: Reduction in fasting plasma TG (median of baseline vs median of week 3-26 post AMT-011) ≥ 40%, Yes/No, OR Decrease in fasting plasma TG ≤ 10.00 mmol/l between week 3-26 post AMT-011.

Other: relating to biological activity and expression of LPLS447X; reduction in frequency and/or severity of clinical signs and symptoms related to LPL deficiency including pancreatitis. -

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Safety:

AEs were assessed at each visit starting in the Prep-02 study. Any changes in safety profile in the main study, compared to baseline data from the Prep-02 study, were followed. Dose limiting toxicity (grade III or more or neurotoxicity grade II or more). No other formalised quantitative criteria defined. Adverse Events, and possible Immunogenicity (humoral, T-cellular) and vector DNA shedding, in urine, saliva and semen, and local muscle tolerance to the therapy were studied.

- **Sample size / Descriptive statistics**

A total number of 14 subjects were planned to be enrolled in the CT-AMT-011-01 study and 14 patients' data were analysed. For each study population, all data were described and summarised by means and standard deviations, medians, minimum and maximum, and/or number and percentages, where appropriate. There were no protocol amendments made to CT-AMT-011-01. The analysis of pancreatitis events was done in post-hoc manner.

Results

- **Participant flow**

Overall, 15 subjects (68%) were entered into the main gene therapy (CT-AMT-011-01) study, 1 subject completed the PREP-02 study. Of the 15 subjects enrolled and screened for entry into the gene therapy study (CT-AMT-011-01), one subject (# 3) declined to have a retest for a positive urine drug test during screening and withdrew consent prior to AMT-011 administration. Thus, fourteen subjects (93%) were allocated into dose cohorts in accordance with the pre-defined dose-escalation schedule. All 14 subjects received study drug (AMT-011).

All 14 subjects receiving AMT-011 completed the main study (week 12) and entered the long term follow up phase (5 years total). At time of submission, all subjects in cohort 1 and 2 have completed 1.5 years of follow up. In cohort 3, all 8 subjects have completed to week 39, at which point one subject withdrew consent due to stress generated through participation. Of the remaining 7 subjects in cohort 3, 7 (87.5%) have completed the 1 year follow-up and 3/8 subjects (37.5%) have completed the 1.5 years follow-up.

All available data to June 17, 2009 are included in the report. Serious adverse event data, including pancreatitis events, are included until July 23, 2009.

Of the 22 subjects enrolled into study PREP-02, 10 subjects (45.5%) recorded one protocol deviation each. The majority of protocol deviations were attributed to screening visits falling outside of pre-specified time. Out of the 22 subjects, 14 entered the long term follow up period in three separate cohorts.

- **Demographics and patients characteristics**

All subjects in the main CT-AMT-011-01 study were Caucasian. The majority of subjects were female (9 subjects, 64.3%), with no females in cohort one and an equal proportion (75%) in cohorts 2 and 3. Overall, the mean age was 45.6 years with a minimum age of 28 years and a maximum age of 62 years. Subjects in cohort 3 tended to be younger than those in cohort 1 and 2 (mean age 41.1 versus 50.5 and 52.3, respectively). Subjects in cohort 1 tended to be taller and heavier than those in cohort 2 and 3. The mean number of pancreatitis episodes per year (since first episode recorded in the medical history) was 0.27 per subject.

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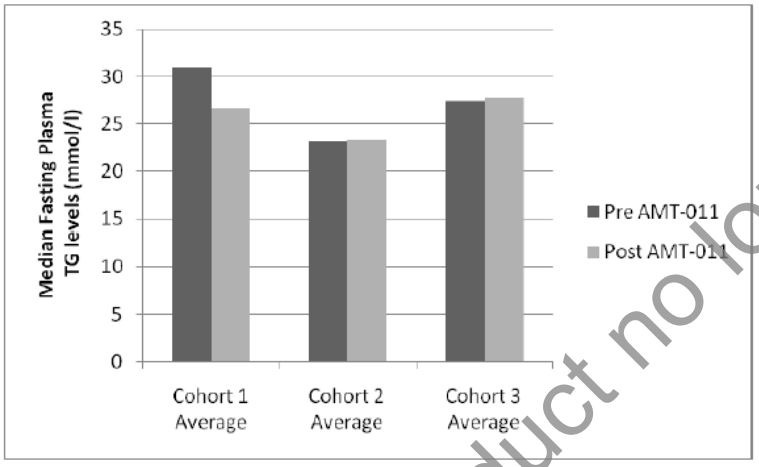
- **Outcomes and estimation**

Lipid response

7 out of the 14 subjects (50%) in CT-AMT-011-01 reached the primary endpoint of a 40% reduction of the median TG in week 3 until week 12 post-AMT-011 administration compared with baseline median TG value. One of 2 subjects (50%) in cohort 1, one of 4 subjects (25%) in cohort 2, and 5 out of 8 subjects in cohort 3 (63%) attained this endpoint. However the overall TG lowering effect was clearly transient and beyond week 12 levels gradually elevated until baseline levels were reached by 1 year.

Additional post-hoc analyses were performed in which the post-AMT-011 administration TG data from visits beyond week 12 were not collated with data from weeks 3-12. As can be seen from Figure 9 the TG values did not change much during W19-26 period.

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



Additional lipid parameters were measured at baseline and over the week 2-12 period post dosing. The collective data showed a trend for reduction in Tchol in patients with TG reduction. When studying this on a per patient basis the TG and Tchol profiles were very similar. Further measurement of cholesterol in VLDL, LDL and HDL fractions indicated a limited increase in the otherwise low levels (below the normal range) of LDL-cholesterol, in particular in those subjects who had the most TG reduction. The HDL-cholesterol data showed that the levels were below the normal range and were not affected by the treatment. The CM-cholesterol showed a reduction in the majority of subjects indicating clearance or partial clearance of CM in the week 2-12 time frame; the subjects with the most robust reduction in CM-cholesterol levels were also among the TG responders.

Total Cholesterol

Since CM particles contain cholesterol, the applicant was expecting to see an effect on cholesterol levels (Tchol) following AMT-011 treatment. Separation of CM containing plasma fractions from non-CM-containing plasma fractions could not be achieved completely with the method used. Hence, clear plasma used to determine HDL-, LDL- and especially VLDL-cholesterol was likely to be 'contaminated' by CM-cholesterol.

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Rate of complications

Pancreatitis events

Prior to dosing with AMT-011, subjects in the combined dose groups experienced pancreatitis episodes at a yearly rate of 0.22 episodes/subject since the first episode. During the PREP-02 study and the period until dosing of AMT-011, the pancreatitis incidence rate was 0.20 episodes/year. In this period 4 subjects were actually found to suffer from a pancreatitis episode.

According to the applicant, the first variable, annual pancreatitis frequency from birth is likely to be unreliable, and an underestimation, given the time lapse between taking the history and birth. The pancreatitis timing recorded in the more distant past of the subjects tended to be less precise, which also indicates that the event frequency in the past may be underestimated. As of the screening visit in PREP-02 events were recorded prospectively, hence as of that point in time, data and calculations are more reliable.

Based on observations from PREP-01 and CT-AMT-010-01 and on the observation that only 2 of the 14 dosed subjects experienced pancreatitis in 0.75-1.5 years of follow-up post dosing in CT-AMT-011-01, the applicant elected to further explore the rate of pancreatitis in the PREP-02 and CT-AMT-011-01 population using retrospective analysis (post-hoc).

Abdominal pain

Since no appropriate scales and tools were implemented, no conclusive findings were established.

Lipaemia retinalis

No improvement in lipaemia retinalis was shown.

Other disease complications

Organomegaly evaluated simply by physical examination (palpation). No obvious improvements were achieved in the presentation of organomegaly and xanthomata.

LPL gene expression in the muscle

To assess successful drug delivery to the target tissue and also study drug-derived LPL expression and biologic activity, open muscle biopsies were taken at 25-27 weeks after study drug dosing from both non-injected and injected muscle. Biopsies were obtained from 7 out of 14 subjects administered AMT-011 in CT-AMT-011-01. Taken together, the data show persistence of AMT-011 vector DNA sequence encoding the therapeutic transgene LPLS447X over the 26-week time frame between local AMT-011 administration and sampling of the injected muscle. Also, the data show that very little AMT-011 vector DNA sequence is distributed to other muscle groups; at best ~0.1% of the level found in injected muscle was detected in non-injected muscle of the same patient.

Discussion

CT-AMT-011-01 is the most pertinent pivotal study in the submission due to following reasons:

(1) AMT-011 is a product intended for marketing purposes;

(2) The number of analysed patients was 14 (compared to 8 in CT-AMT-010-01 study), therefore, efficacy and safety data are slightly larger.

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Following CHMP advice on Protocol assistance given in 2006, it was agreed that despite the fact that an uncontrolled study would be able to separate the effect of various confounding factors, such as fat-restrictive diet and changes in the life style, a controlled study in such a rare orphan indication is not feasible. Therefore the applicant was recommended to carry out an uncontrolled study and attempt to collect all possible clinically meaningful variables.

A number of issues emerged from the interpretation of the CT-AMT-011-01 study results. First of all, despite the fact that the study was uncontrolled and open in nature, procedures could have been put in place to ensure the assessment of at least some efficacy variables in more objective manner (e.g. impact on lipaemia retinalis, organomegaly, etc.). No QALY assessments were pre-defined and collected in this study which is a major deficiency. The applicant has been constantly evaluating all incoming data and making respective changes along the study. When it became clear that no relevant, durable and clinically important changes in lipid levels were possible to achieve, the applicant started to explore the effect of Glybera on other secondary events, for which the study has not been designed. A number of variables and time-points were implemented post-hoc and the analysis of previous pancreatitis events was conducted retrospectively in study CT-AMT-011-01. Therefore, there is concern as to how relevant patient data on incidences of pancreatitis events were collected at the entry into the study, how the event of pancreatitis was defined and how the severity of individual events was interpreted in an objective and independent manner

Apart from various post-hoc changes in procedures and algorithms for analysis, the imputation of missing values raised an additional concern for the CAT. Missing covariate data were imputed by using the population median value for a continuous covariate. No sensitivity analyses were carried out using more a conservative treatment of missing values. The applicant stated that in principle all data will be included in the analysis however extreme values might be excluded with the caveat that they are infrequent and are randomly distributed in order to avoid outlying values influencing the model analysis disproportionally. However, there is no information provided by the applicant on outlying values which were excluded and how they have been interpreted. Therefore, beyond the usual concerns on the validity of open uncontrolled interventional studies, the CAT considered that this raised additional concern over the validity of some of the applicant's conclusions and interpretations.

Similarly to the results of CT-AMT-010-01 study, the inter- and intra-patient variability in fasting TG levels was very high in the CT-AMT-011-01 study. The primary efficacy endpoint in terms of ≥ 40% reduction in fasting TG levels was achieved in 50% of completed patients with some dose-dependent trend seen amongst patients from 3rd cohort. However the overall TG lowering effect was clearly transient and beyond week 12 levels gradually increased until baseline levels were reached at 1 year. The trend for TG elevation was more pronounced amongst patients who received the highest dose regimen with the immunosuppression. This indicates that most likely a single treatment as currently proposed by current posology is unlikely to be acceptable on the premise of transiency of the effect and presence of some rebound phenomenon. The DNA/LPL expression level identified at the injected muscle had no impact on systemic levels of LPL following gene therapy.

When considering the pancreatitis data it must be remembered that there is substantial bias as the decision to look at pancreatitis was made retrospectively. Therefore any result seen may be a chance finding. Similarly to the CT-AMT-010-01 study, the applicant stated that the comparison of the total mean annualised rate of pancreatitis events collected from the birth was unlikely to be reliable. It was evident that there was no apparent difference between mean rates found in pre-treatment life-long period (0.1)

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and those after treatment (in 1.5 year observational period) (0.11). Comparing rates of events collected during 1.5 year in post-treatment period, there was a numerical advantage of the treatment with overlapping confidence intervals (0.11 vs 0.22).

The hazard ratio for the risk of pancreatitis comparing the medical history/run in to the main study/long-term follow-up period was 0.272, representing a 73% reduction in risk. The confidence interval ranged from 0.032 to 2.235, reflecting the small number of observations involved, and showing that a more than doubling of the risk was still compatible with the data – this before the bias from the retrospective analysis is taken into account. With this context, it is difficult to conclude that an effect on pancreatitis had been demonstrated.

Also the rate of events was extremely high just before treatment and in immediate period after treatment. There was no observational period consistently applied to all patients in order to detect a background rate of pancreatitis in a more reliable manner. The monitoring of pancreatitis events has not been pre-specified and neither of the conducted studies was designed for this purpose.

In similar fashion to CT-AMT-010-01, using individual frequency data, it is possible to see that the frequency per year was highly variable in some patients and there was a trend for reduction of rate after Glybera in some patients with previously high rates of pancreatitis. However, even relying on past medical history, the frequency of events was highly variable between patients and in some patients individual events were separated by relatively long periods of time (in some cases several years). It should be noted that the pancreatitis episode reported post-AMT-011 administration in one subject occurred within one week of dosing and the event in another subject happened 10 months post AMT-011 administration. The latter two patients are failures. The weight of this evidence of trend for reduction of pancreatitis events is entirely based on the collection of past pancreatitis events. Therefore, the way how each event was defined and diagnosed is crucial and prognostic and diagnostic features and criteria used to define the type of patients with regards to pancreatitis events have not been established. No attempt was made to explain the physiological nature of potential pancreatitis response to Glybera induced LPL production The duration of post-treatment follow-up of 1.5 years is deemed insufficiently long to establish the durability of the Glybera effect on pancreatitis-associated complications. The analysis is fundamentally flawed because it lacks an appropriate algorithm and the definition of individual pancreatitis events, and without it events are not considered as reliably censored. These events might be merely a representation of abdominal pain rather then pancreatitis attacks in some cases and therefore interpretation of this data is not possible.

Claims that reported in the post-treatment period events were milder in nature and were accompanied by less severe abdominal pains are subjective and difficult to interpret since no details on character and severity of past events were reported or discussed. Due to the limited size of biopsy data it is impossible to draw any parallels between muscular LPL expression and the level of response in terms of TG reduction.

2.5.5. CT-AMT-011-02 study

CT-AMT-011-02: A dual-centre, uncontrolled, open-label, single-dose study to investigate the safety and efficacy of AMT 011 over 12 weeks, for the treatment of subjects with Lipoprotein Lipase Deficiency (LPLD).

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- **Methods/ study participants**

The study was originally planned as a Canadian multi-center, randomized, open label, controlled study. The study initially was aimed for 16 subjects to be randomized to receive either no treatment or AMT-011 (1 x 10^{12} gc/kg) and immunosuppression. However, the applicant could not identify patients with documented history of pancreatitis in past medical notes. Therefore the study design was amended to an open-label, uncontrolled study currently undergoing at two centers in Canada. A total number of 8 subjects were planned to be enrolled in the CT-AMT-011-02 study. The first patient was enrolled on 9/04/09. Two subjects had completed the 14-week study while interim data are presented for the other three subjects at time of submission.

Inclusion/exclusion criteria were similar to those in the CT-AMT-011-01 study and required patients to have a history of pancreatitis. The study constitutes an 18 week study with a 4-week baseline period and a 14 week study period with a follow-up period of 1 year.

- **Treatments**

In CT-AMT-011-02, all subjects were administered with the same dosage of AMT-011 (1 x 10^{12} gc/kg) with immunosuppressants. From day -3 through the last visit at week 12, subjects received a daily oral dose of 3 mg/kg/day ciclosporin and 2 gram/day mycophenolate mofetil. Dose of immunosuppressive medication was adjusted for safety and efficacy. Additionally, an intravenous steroid bolus was given 30 min before AMT-011 injection.

- **Objectives**

Primary Objective: To achieve a 40 % reduction of median fasting TG concentrations 12 weeks after treatment with AMT-011.

Secondary Objectives: (i) To achieve a reduction of fasting median chylomicrons and/or chylomicron-TG ratio 12 weeks after treatment with AMT-011; ii) To achieve an improved clearance of post-prandial chylomicrons and/or a reduced chylomicron-TG ration 14 weeks after treatment with AMT-011; (iii) To achieve a reduction of median fasting TG to a value equal or below 10 mmol/L 12 weeks after treatment with AMT-011; (iv) To explore the effect of AMT-011 on lipoprotein fractions and lipid profiles 14 weeks after treatment with AMT-011; (v) To determine the biological activity and expression of the lipoprotein lipase (LPLS447X) transgene product; (vi) To achieve a reduction in frequency and/or severity of clinical signs and symptoms related to LPL deficiency (i.e eruptive xanthomas, lipaemia retinalis, pancreatitis, episodes of abdominal pain, plasma lactescence, lack of energy/fatigue and QoL and diabetes management.

- **Sample size / Descriptive statistics**

The study was planned to enrol 8 subjects. The statistical analysis of the data are descriptive.

Results

- **Participant flow**

5 study participants were identified and enrolled from a database of LPLD subjects present at the sites participating in the study.

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- **Demographics and Baseline Characteristics**

5 subjects entered Study CT-AMT-011-02, all of which were Caucasian. 75 % of subjects were male and 25 % were female. The mean age of subjects was 41.8 years with a minimum age of 20 years and a maximum of 57 years. The weight of subjects varied between 56.8-74.6 kg, with the mean weight of 62.83 kg (at day 0). The average height of subjects was 1.67 m, ranging between 1.62-1.72 m. The BMI of subjects ranged from 20.5-25.4 kg/m2, with the mean value 22.44 kg/m2. All subjects were homozygous for the P207L mutation in the LPL gene.

- **Outcomes and estimation**

Despite the study enrolling only 5 patients, somehow 14 patients were discussed, although subsequently only 5 patients were mentioned again. There were a number of other inconsistencies and errors in the clinical documentation throughout the clinical efficacy summary and CT-AMT-011-02 study report.

Only 1/5 (20%) patient responded to Glybera at week 12 in terms of fasting TG reduction of <10 mmol/l. The data on fasting TG at week 52 were not provided. A new exploratory endpoint in reduction of post-prandial CMs has been introduced showing response at week 12 and up to week 52. A response noted in 3/5 patients (60%).

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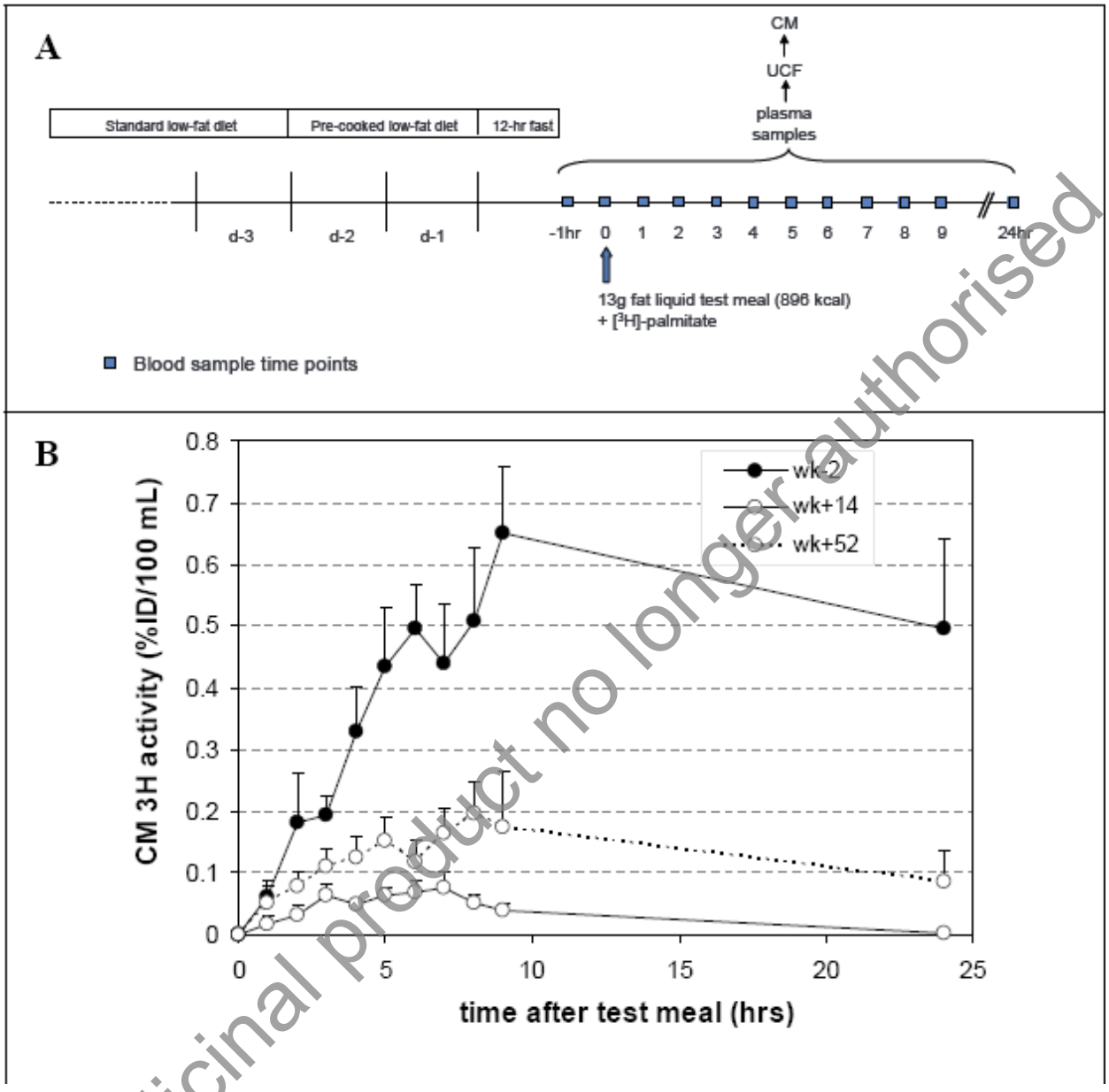
Lipid response



(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).

The data provided from the post-prandial CM at week 14 and week 52 is compared with subjects who were tested 2 weeks before treatment. There are unexplained findings regarding the data. In subjects with normal LPL activity the post-prandial peak of CM is at ~3 hours. As seen in the figure above, subjects who were tested at week -2 had a peak which was very delayed at 10 hours. This is likely to be due to delayed clearance and accumulation of CM in LPL deficiency. While it is not clear that the same patients were used

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for the week -2 and the week 52 data, it can still be seen that the timing of the peak is still delayed at ~10 hours at week 52. It would be expected that if the LPL activity was increased that the peak in PP CM would be earlier as this should reflect lack of accumulation of CM following absorption as a result of LPL activity.

While post-prandial CM could be accepted as a surrogate marker of efficacy (subject to validation), the small number of subjects for whom data is available (n=3 at 52 weeks) and the uncertainties relating to the robustness of the assay in these cases combine to make the data insufficient to support efficacy. In addition the reduction in QoL for 3/5 at week 14 and the absence of any further QoL measurements at later time points further weakens the data in terms of efficacy.

The claim of long-term correction of LPL deficiency is not supported by existing clinical data. While sufficient reduction of TG levels for a sustained period (at least 6 months) has not been demonstrated neither is sufficient evidence of a clear reduction in PP CM in the same patients before and after treatment evident. Too few patients have been studied for this newly revised endpoint to be considered as sufficient evidence of efficacy.

Rate of complications

Pancreatitis

Remarkable variability in the incidence of past pancreatitis events was identified in CT-AMT-011-02 study. The past rate of pancreatitis was especially high amongst 3 patients from CT-AMT-011-02 study (up to 11-41 events). Paradoxically, each of remaining 2 patients had only 1 event in the past. At least three patients reported numerous abdominal pains following treatment with Glybera.

Lipaemia retinalis

No improvement in lipaemia retinalis was shown.

Other disease complications

No improvement in organomegaly and xanthomata were shown.

Quality of Life

It is of major concern that 3/5 patients treated with Glybera in the last study CT-AMT-011-02 reported reduced SF36 scores both due to physical and metal functioning. The applicant has justified the reduction in SF36 scores to the temporal proximity of evaluations at 14 weeks to the effect of immunosuppression, muscle biopsy, frequent intervention procedures and a number of long-lasting health problems due to SAEs in two affected patients. It is agreed that this might be plausible. However no further QoL data on the same 5 patients at later time points following treatment (6-12 months) were provided, and so the reduction in QoL remains a concern.

2.5.6. CT-AMT-011-03 study (Pooled analysis of all pancreatitis data further to CAT request)

CT-AMT-011-03 study was performed as a case note review study to provide data on the occurrence and the nature of pancreatitis in (untreated) LPLD patients, and to compare pre- and post-treatment situations in LPLD patients to establish the effect of treatment with Glybera.

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The analysed data did not refer to the results of the post prandial CM levels or the fasting TG levels in individual patients. The company reviewed the dataset using appropriate algorithms developed for the study CT-AMT-011-03. Patients involved in the CT-AMT-011-01 and 011-02 studies and untreated LPLD patients from Preparation-02, were invited to consent to enrol in this case note review study and in total 22/ 26 eligible patients consented to participate. 17 of the 22 patients had received treatment with Glybera and statistical analysis was performed on these 17 cases. No information was provided on the other 5 patients.

The outcome of hazard ratio analysis with regard to definite pancreatitis was calculated for different lengths of the historic control periods with 1 year increments up to 10 years. Starting with inclusion of a period of 3 years and up to a period of 10 years before the initiation of the prep/run-in studies, the result are all consistent regarding the estimate of a Hazard Ratio (between 0.41 and 0.49), p-values ranging from 0.032 to 0.087.

If the historic control is limited to the prep/run-in period, the prep/run-in+1 year period or the prep/run-in+2years period, treatment effect is not a significant explanatory factor in the statistical model.

This reflects the small numbers and inherent variability in pancreatitis rates between individuals.

The data on the 17 patients before and after treatment with Glybera is shown in the figure below. As can be seen the number of events of pancreatitis (definite/probable) and abdominal pain are shown for 17 subjects from birth.

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Figure: Pancreatitis and Abdominal Pain Events (Source: Figure 1.1.2)

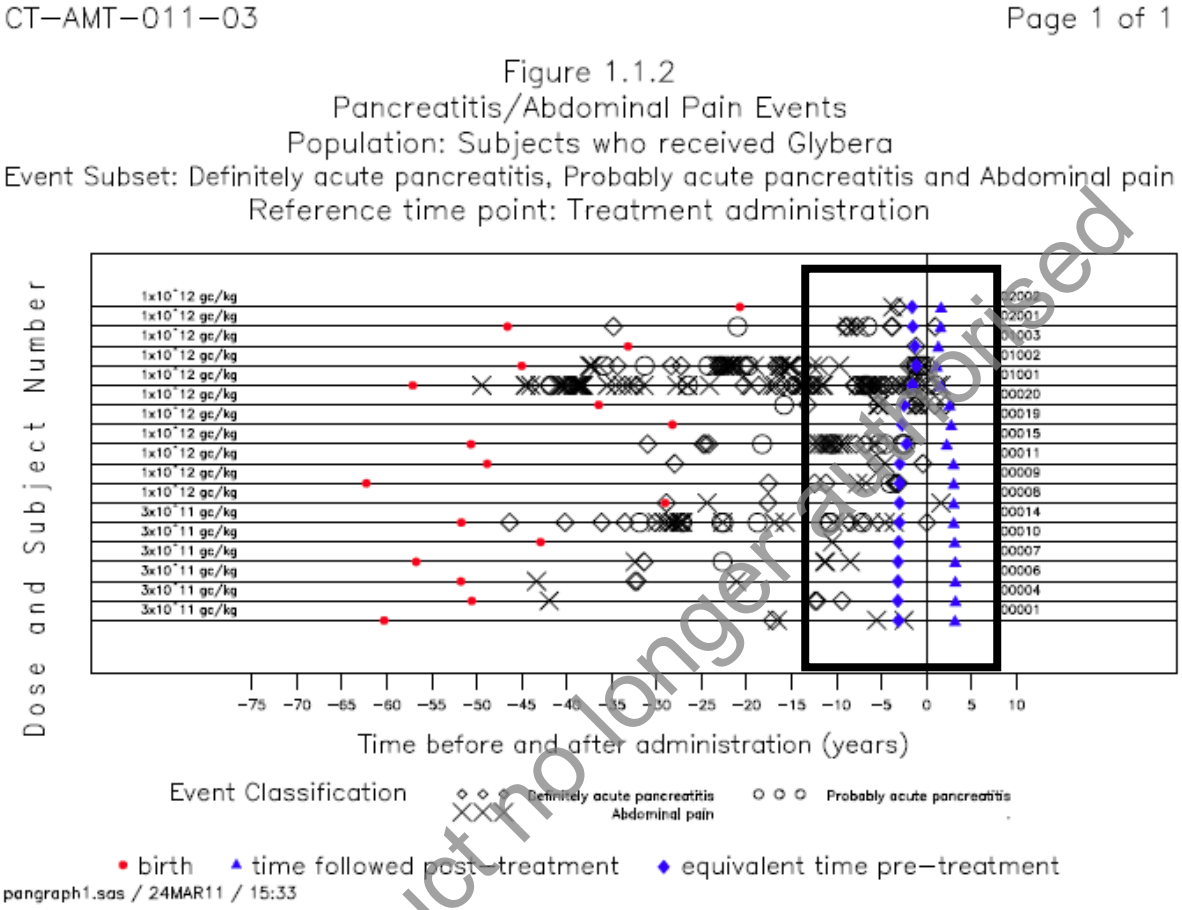

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Figure. Enlargement of section in figure 1 above of pancreatitis/abdominal pain events within the equivalent times period pre- and post- treatment.

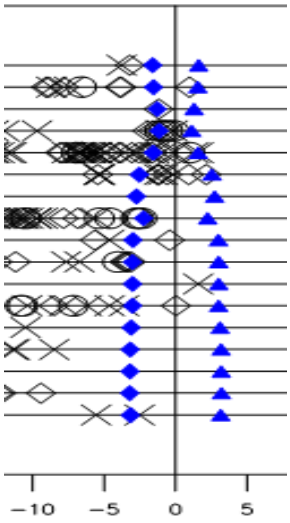

Figure 2 is the section of the figure 1 where the interval before and after treatment is equivalent and enlarged. Here it can be seen that many subjects (8/17) had no events during the equivalent time period before (marked with a blue diamond) and after (marked with a blue triangle) treatment. The open diamonds represent definite pancreatitis and probable pancreatitis is represented by an open circle. Pain is marked as an X.

From Figure 2 it can be seen that the actual number of events was very limited within the time frame shown where pre- and post-treatment intervals were equivalent. The majority of events are in 3 subjects. Robust statistical conclusion from this data cannot be considered to provide robust evidence of efficacy in terms of reduction of pancreatitis rates after Glybera treatment.

In general a retrospective analysis comparing pre and post-treatment data is not ideal. However, this approach was accepted by CAT, subject to an objective evaluation of these data. On review of the incidence of pancreatitis events pre- and post- treatment the number of events are very limited and are insufficient to provide evidence of efficacy for a reduction in the rate of pancreatitis.

In view of the methodological limitations with study CT-AMT-011-03, the limited data available from a historical review, the retrospective nature of the analysis, the limited number of events and the paucity of data for post prandial CM levels, no firm conclusions on efficacy can be made. Data on post-prandial CM response accompanied with reliable pancreatitis analysis using an entire dataset employed in the clinical program is required to make any reliable and robust conclusions on the efficacy of Glybera on lipid levels and pancreatitis rates.

Clinical studies in special populations

No studies were carried out. There is no clinical data available on effect of Glybera on fertility, pregnancy outcomes, and lactation.

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2.5.7. Discussion on clinical efficacy

Results of main studies:

Due to the limited subset of patients available in Glybera clinical development programme a summary table is provided which illustrates all key demographic features, efficacy, muscle biopsy and immunogenicity results for all individually treated patients.

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Table summary of all clinical variables established during Glybera clinical development program

CT-AMT-010-01												
Gender/	LPL mutation	Dose (gc/kg)	Median TG at baseline (mmol/L)	Median TG at W12 (mmol/L) response to <10 mmol/L / 40% reduction	Median TG at 6-12 M (mmol/L) response to <10 mmol/L / 40% reduction	Median TG at 1.5-2Y (mmol/L, response to <10 mmol/L / 40% reduction	Median TG at 3.0 Y mmol/L, response to <10 mmol/L / 40% reduction	Annualised pancreatitis incidence in past medical history	Annualised pancreatitis incidence during preparation–1/2 study (RUN-IN phase)	Annualised pancreatitis incidence in post-treatment period	Quality of Life evaluations / Muscular toxicity findings (signs of de/regeneration)	Serious adverse events
M	D250N/ S251C	$1X10^{11}$	15.48	7.60 Yes/ Yes	10.45 No/No	17.10 No/No	10.62 No/No	0.12	0	0	- Mild, non-specific	+
M	V69L/ G188E	$1X10^{11}$	17.97	14.64 No/ No	22.96 No/No	14.75 No/ No	15.26 No/ No	0.62	1.63	0	- some	++
M	V69L/ G188E	$1X10^{11}$	12.77	10.16 No/ No	8.92 No/(Yes)*	11.54 No/No	15.48 No/No	0.1	1.43	0	- -	N/a
F	G154S/ G154S	$3X10^{11}$	15.14	12.21 No/ No	15.55 No/ No	16.75 No/ No	18.08 No/ No	0.15	2.63	0	- extensive	+++
M	R243H/ R243H	$3X10^{11}$	42.30	31.73 No/ No	40.85 No/ No	43.97 No/ No	19.66 No/ (Yes)*	0.41	0	0	- some	++
M	G154S/ G154S	$3X10^{11}$	19.73	10.45 No/Yes	12.25 No/No	19.03 No/No	32.43 No/ No	0.3	0	0.3	- extensive	+++
M	G154S/ G154S	$3X10^{11}$	10.40	5.89 Yes/ Yes	24.97 No/ No	19.44 No/ No	-	0.25	0	0	- extensive	Death due to malignancy/ +++
M	DI56G/ DI56G	$3X10^{11}$	28.56	19.50 No/No	40.45 No/No	20.17 No/No	0	0.06	0	1.48	- Slight non specific	0

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Fasting TG levels and response rates for all patients *average from median values: Response <10 mmol/l; Response >40% reduction	20.29*	14.02 25% 25%	22.05 12.5% 0%	20.34 0% 0%	18.59 No 12.5%			25% response		
			* rather by chance, than product related		* rather by chance, than product related				Physio test. Panel: 6 min walking and time to get up: slight decrease at week 12	

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CT-AMT-011-01											
Gender	LPL mut-ation	Median TG at baseline (mmol/L)	Median TG at W12 (mmol/), response to <10 mmol/L / 40% reduction	Median TG at W26 (mmol/L), response to <10 mmol/L / 40% reduction	Median TG at W52 (mmol/L, response to <10 mmol/L / 40% reduction	Median TG at 1.5–3.0 YR, mmol/L, response to <10 mmol/L / 40% reduction	Annualised pancreatitis incidence in past medical history	Annualised pancreatitis incidence during preparation–1/2 study (RUN-IN phase)	Annualised pancreatitis incidence in post-treatment period	Quality of Life evaluations / Muscular toxicity findings	Serious adverse events
F	P207L/ P207L	22.6	21.39, No/No	39.9, No /No	19.41, No/No	16.90, No /No	0.91	0	0	No	
M	P207L/ P207L	49.1	30.41, No/No	43.75, No/No	40.35, No/No	23.12, No/No	0.26	0	0	No	++
M	P207L/ P207L	15.9	4.37, Yes/Yes	9.56, Yes/Yes	9.42, Yes/Yes	14.69, No/No	0.03	0	0	No	+
F	P207L/ P207L	23.3	6.73, Yes/Yes	9.04, Yes/Yes	26.77, No/yes	26.65, No/No	0.16	0	0	No	No biopsy
M	P207L/ D9N	21.9	29.01, No/No	20.32, No/No	18.87, No/No	22.31, No/No	0.1	0	0	No	++
F	P207L/ P207L	22.4	14.76, No/No	23.97, No/No	18.05, No/No	15.27, No/No	0.55	0	0.58	No	N/a
M	P207L/ P207L	22.9	18.72, No/No	19.34, No/No	29.23, No/No	18.94, No/No	0.07	0	0	No	N/a
F	P207L/ G188E	23.8	5.38, Yes/Yes	14.83, No/No	23.76, No/Yes	16.00, No/No	0.32	0	0	No	Not provided
F	P207L/ P207L	28.4	24.44, No/No	24.85, No/No	33.58, No /No	52.83, No/No	0.11	1.13	0	No	+++

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F	P207L/ G188E	34.2	10.17, No/Yes	22.06, No/Yes	21.02, No/Yes	21.02 No/No	0.39	1.09	0	No	0
F	P207L/ P207L	65.5	29.17, No/Yes	29.38, No/Yes	51.05, No/No	51.05 No/No	0.36	0	0	No	Died suddenly on 14/03/10 No autopsy
M	P207L/ P207L	16.5	9.56, Yes/Yes	16.94, No/No	18.39, No/No	18.39 No/No	0.28	0	0	No	N/a
F	P207L/ P207L	13.0	13.95, No/No	17.03, No/No	15.04, No/No	15.04 No/No	0.07	0	0	No	N/a
F	P207L/ P207L	21.4	10.99, No/Yes	31.06, No /Yes	26.58, No/No	26.58 No/No	0.59	0	1.03	No	N/a
Fasting TG levels and response rates for all patients *average from median values: Response <10 mmol/l; Response >40% reduction		27.2	28.6% 50%	14.3% 43%	7.1% 28.6%	0% 0%			85.7% response		

Dose (gc/kg): $1X10^{12}$
Immunosuppression : CyA+ MMF

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CT-AMT-011-02											
Gender	LPL mut-ation	Median TG at baseline (mmol/L)	Median TG at W3-12 (mmol/L), response to <10 mmol/L / 40% reduction	Median TG at W26-39 (mmol/L), response to <10 mmol/L / 40% reduction	Median TG at W52 (mmol/L, response to <10 mmol/L / 40% reduction	Median TG at 1.5–3.0 YR, mmol/L, response to <10 mmol/L / 40% reduction	Annualised pancreatitis incidence in past medical history	Annualised pancreatitis incidence during preparation–1/2 study (RUN-IN phase)	Annualised pancreatitis incidence in post-treatment period	Quality of Life evaluations / Muscular toxicity findings	Serious adverse events
M	P207L/ P207L	52.2	21.3 No/Yes	40.42 No/No	23.21 Yes No		Not available	Not available	Not available	No change	Not available
F	P207L/ P207L	37.9	39.9 No/No	41.93 No/No	Not available		1 episode of abdominal pain after treatment	Not available	Not available	SF36 score reduction at W14	2 acute pancreatitis/ myositis with CPK of 750 /not available
F	P207L/ P207L	13.3	5.62 Yes/Yes	8.26 Yes/No	Not available		2 episodes of abdominal pain after treatment	Not available	Not available	No change	Not available
M	P207L/ P207L	24.3	19.35 No/No	28.35 No/No	Not available		4 episodes of abdominal pain after treatment	Not available	Not available	SF36 score reduction at W14	Pulmonary embolism/ not available
M	P207L/ P207L	45.9	42.55 No/No	79.92 No/No	Not available		Not available	Not available	Not available	SF36 score reduction at W14	Not available
Response <10 mmol/l; Response >40% reduction							20% 40%	20% 0%	Not available		

Dose (gc/kg): $1X10^{12}$
Immunosuppression : CyA+ MMF+ IVMP

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The current submission is based on data derived from 27 patients with different homozygous and compounds mutations resulting in LPLD. The development was hampered by difficulties in recruitment of sufficient numbers of patients and therefore the initial study was started in NL with subsequent studies conducted in Canada.

The rationale for LPL gene therapy is based on the strategy of adding extra-copies of functionally potent enzyme into muscle tissue of patients with homozygous or heterozygous "loss-of-function" mutations. However the enzyme has a property of being ectopically expressed on the luminal surface of the endothelial cells in both liver and extra-hepatic compartments (muscle) to ensure direct contact with CM particles. The approach taken by the applicant was to administer large quantities of the vector via multiple intramuscular injections. Muscular biopsies showed DNA/LPL expression, ICH staining and intracellular accumulation of lipids in muscle cells. However it is unclear how muscular enzyme would have a systemic role unless it would have a more intimate contact with the vasculature and circulating CMs.

A profound muscular degeneration and scarring were identified at week 25-27 in some biopsies thus suggesting that Glybera-delivered LPL may have even more localised expression without significant systemic impact on circulating TG. The applicant has not discussed the relevance of endothelial LPL and the proportion of expected vascular expression of the enzyme following intramuscular injections.

Issues discussed at the Scientific Advisory Group meeting

The some issues identified by the CAT were also discussed at a Scientific Advisory Group (SAG) meeting during the procedure and are summarised as follows:

- *Change of efficacy endpoints and relevance of endpoints*

Following SAG recommendation, it was considered acceptable to the CAT to consider as primary endpoints the proportion of patients with <40% reduction of the fasting TG levels AND/OR postprandial levels of triglycerides (defined as postprandial peak of the CM OR postprandial area under curve of the CM catabolism) at week 12. However, the need for long term data at 6 months and 1 year was also considered necessary. It was felt that the postprandial peak of the triglycerides could be considered as a particularly valid endpoint in view of the risk of pancreatitis.

- *Number of injections*

It was considered that the need of 60 injections would be justified providing the medicinal product would show the efficacy for at least 6 months in at least 50% of patients. In this respect, demonstration of efficacy only at 12 weeks would not be sufficient to balance the inconvenience related to the injections.

- *Impact on diet and concomittant treatments*

Considering that a durable compliance to low fat diet can not be realistically expected, the current trial design can not provide reassurance that the TG level reduction is primarily attributable to Glybera rather then the diet or concurrent treatment. However, as the conventional lipid lowering treatment does not have any effect on TG levels in this population of patients from the available literature, the TG level reduction could very likely be attributed to Glybera.

- *Recommendations for additional data to be collected*

Further data on patients characteristics (weight changes over time, alcohol consumption, physical activity patterns, the prevalence and treatment efficacy (HbA1c, glucose) of the diabetes mellitus, apo

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E genotypes,) and the prevalence and treatment efficacy of pancreatic exocrine failure in the population of patients would be considered helpful to improve the level of reassurance and understand the reasons for pancreatitis.

Recommendation to collect also data on quality of life before and on treatment with Glybera was made by the Experts. The CAT agreed with these recommendations and requested further information from the applicant.

Assessment of pancreatitis events

The SAG considered that it is not possible to exclude completely the hypothesis that the reduction in the incidence of pancreatitis in some patients is due to the inherent temporal rarity of pancreatitis events. The usefulness of the analysis of the annual incidence of pancreatitis in particular in years prior to the treatment was acknowledged by the SAG as there were limitations of the historical analysis. The methodology for adjudication of the suspected pancreatitis events by the independent experts' panel for study CT-AMT-011-03 was acknowledged by the SAG and agreed upon by CAT, as capabale of providing a more reliable retrospective analysis of the events of pancreatitis than was available from the earlier trials. However issues inherent to retrospective data assessment in comparison to prospective data were highlighted by the CAT.

Immunosuppression regimen

Based on current efficacy and safety data the role of escalating immunosuppression has not been adequately justified. Furthermore, regardless of immunosuppression, the magnitude of the effects, immunogenicity responses and histological findings in injected muscle were similar. Therefore, the addition of immunosuppression has not been sufficiently justified and raised as major concern.

Xanthomata, organomegaly and lipaemia retinalis

The effect on other LPLD associated complications, such as xanthomas, lipaemia retinalis and organomegaly were not measured in a masked and objective manner. In conclusion, Glybera has failed to show any effect on organomegaly, lipaemia retinalis and xanthomata across all conducted studies.

Mutational status

Despite that the dataset is very limited to allow any conclusive association with mutational status of patients or other co-variates, it is of interest that the presence of diabetes and heterozygocity tended to be associated with lower rates of pancreatitis events.

Diet

Although it is accepted that compliance with the diet is difficult for a number of patients, it was of concern to note that Glybera could not assist in reducing pancreatitis in those patients who find it difficult or unable to comply with the diet as "dietary transgressions" are likely to precipitate further events even after treatment.

Weight changes

The results of the analyses of weight dynamics across 3 studies illustrated that Glybera has no appreciable effect on post-treatment weight improvement except for 2 patients. The weight curves fluctuated throughout the time with some dips around the treatment period and some decrease in weight prior to treatment in some patients. It has not been supported by any patient reported questionnaires or outcomes.

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Quality of life

The reduction in SF36 scores (those from both the physical functioning and mental domains) in 3 out of 5 patients from CT-AMT-011-02 study at week 14 following treatment is of major concern. The applicant has explained the QoL reduction by adverse events and immunosuppression. However the data on Quality of Life data from later time-points (up to week 52) and from all other studies conducted with Glybera are not available.

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.

Overall the totality of evidence derived from CT-AMT-010-01, CT-AMT-011-01 and CT-AMT-011-02 studies indicated that AMT-011 may temporarily reduce median fasting TG levels following administration of the vector, but any conclusions on the rate of pancreatitis following treatment can not be made with the data available However the proposed single treatment is insufficient to provide a durable and measurable effect on TGs. The duration of the post-treatment observation period is insufficient to conclude on whether any change in the rate of pancreatitis events occurred following Glybera therapy compared to similar periods pre-treatment. Confounding factors, such as temporal rarity of events in some patients, the inherent variability in event rates over time for each patients and the imposed fat-restrictive diet would also be expected to affect the rate of pancreatitis events.

Furthermore from the statistical analysis provided by the company which supported a reduction in rate of pancreatitis post-treatment compared to more distant (>3 years previously) historical yearly rates of pancreatitis, this result could have been (i) a chance finding, (ii)the endpoint was selected for investigation retrospectively after the results had been seen and the results are thus subject to severe bias and (ii) the confidence interval for the hazard ratio was very wide and did not exclude the possibility of a doubling of risk (i.e. that Glybera could have a detrimental effect). Theses points all

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contribute to the conclusion that efficacy in terms of a reduction in rate of pancreatitis has not been demonstrated following Glybera therapy.

2.6. *Clinical safety*

In the clinical development programme for Glybera, 27 LPLD subjects have been exposed to study drug.

Patient exposure

	Gender		Age		Ethnicity
CT-AMT-010-01[a]	Male	Female	> 18 - 65 years	> 65 years	
	7	1	5	3	Caucasian
CT-AMT-011-01[b]	5	9	14	0	Caucasian
CT-AMT-011-02 (Ongoing)	3	2	5	0	Caucasian

a 14 subjects entered PREPARATION-01, 8 went on to receive AMT-011.
b 22 subjects entered PREPARATION-02, 14 went to receive AMT-011.

Adverse events

All studies were uncontrolled in nature which makes it impossible to compare rates of adverse events in concurrent manner. The applicant attempted to compare rate of adverse reactions between run-in and interventional phases of relevant studies. A significant number of "background" events, involving all organ classes and including episodes of acute pancreatitis, lipaemia retinalis and eruptive xanthomas, abdominal pain episodes, and multiple surgery, among others, were apparent on review of the participants' medical history and in particular in relation to LPLD.

All 27 (100%) patients who received the drug had adverse events. The most frequent adverse reactions in the period immediately following Glybera administration consisted mainly of local injection reactions or adverse response to epidural anaesthesia. Local pain, myalgia, bruising were commonly seen a few days after study drug administration. Local reactions were mild to moderate. Headache, nausea and less commonly dizziness, hypoaesthesia, burning sensation in limbs, paraesthesia and presyncopy were reported in the post-treatment period. All of these reactions were transient, lasting in general one or a few days with no serious adverse reactions reported. Four cases of transient fever were noted across all studies, one of these events was classified as serious (subject 15 in CT-AMT-011-01, cohort 3). In CT-AMT-011-01 study, 22 infection events (in 12 subjects) were recorded during the main study phase, when subjects were immunosuppressed. Nasopharyngitis was recorded in 59% of infections; most of these colds were reported to have occurred during the fall or winter months. Three of the 12 subjects had an oral herpes simplex infection that occurred 5 and 9.5 weeks after AMT-011 administration. All other infections were single cases, mostly respiratory, and none were severe.

1 subject within cohort 1 (3×10^{11} gc/kg) in CT-AMT-011-01 study developed a lipoma in the right hypochondrium (categorised as neoplasm) described as mild in severity and deemed unrelated to LPLD and also unrelated to AMT-011 and the administration process.

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Serious adverse events and deaths

No deaths or serious adverse events were reported during the 12 weeks post dosing in CT-AMT-010-01 and SAEs reported during LTFU were due to acute pancreatitis events. In CT-AMT-011-01: 2 subjects experienced an SAE during the active treatment phase (acute pancreatitis considered severe in severity). This event was considered unrelated to AMT-011 itself and also unrelated to the administration procedure. Another subject had a transient fever, maximal approximately 10 hours post AMT-011 administration. This event was classified as probably related to AMT-011 and possibly related to the administration procedure. During the LTFU phase, 2 other subjects experienced an SAE; one patient experienced an acute pyelonephritis considered mild in severity and unrelated to AMT-011 and another experienced an acute pancreatitis (mild in severity) considered unrelated to AMT-011.

In the ongoing CT-AMT-011-02 study: 1 SAE was recorded in a subject who first presented with pain in the calves, and then complained of thoracic pain. A V/Q scan was performed and the diagnosis of 'high probability of pulmonary embolism' was established. The event was considered possibly related to AMT-011, possibly related to numerous haematomas and micro-emboli accumulating at the site of injections.

Another SAE occurred in a 49-year patient who required a 22 day hospitalisation due to severe polyarticular pain, myositis (CPK>750IU), myoglobinuria, raised CRP and ESR, polyarticular effusions in sacroiliac and knee joints, bilateral pleural effusions and pain in temporomandibular joints. The history of the subject contains numerous allergies/hypersensitivities with a history of some symptoms consistent with a pre-existing Raynaud phenomenon. Positivity for anti-RNP antibodies were found which the applicant maintained supported the presence of a pre-existing auto-immune disease or risk for such a disease. However the relationship with Glybera and/or immunosuppression cannot be excluded at this stage.

There was one death during Preparation-01: a cardiac arrest in a 47-year old male patient. This event was considered to be related to the disease.

There was 1 death of a male 71 old patient (metastatic lung cancer) reported in the course of the interventional (long term follow up) studies. All SAEs for this patient (9) were reported by the study investigator as unrelated to AMT-010 administration.

An additional death was reported in a 52-year old female who died suddenly approximately 2 years after the treatment with AMT-011. The patient had a history of chronic renal failure and haemodialysis. The causality of the death is difficult to interpret as no autopsy has been carried out. According to the principal investigator, the death is most likely of cardiac origin. The patient was TG responder and had no evidence of cellular or humoral immunogenicity against LPL, but did have an anti-AAV1 response.

Laboratory findings

Muscle biopsies

Histological assessments were performed to monitor local reactions to the study drug using open muscle biopsies in patients who consented to participate in the biopsy. Histopathological review showed variable cellular infiltrates consisting of T-cells, B-cells, and macrophages, with perivascular to endomysial infiltration present in some of the injected muscle biopsies. Some scattered inflammatory infiltrates with polymorphs and macrophages were seen. The degree of inflammatory and degenerative changes in non-injected muscles was minimal. Additional analysis of the muscle by MRI did not show any abnormalities, nor was muscle function affected, although muscle function was not formally tested.

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Formal evaluation of injected muscle strength and overall function would be required to assure that the histological changes in the injected muscles did not lead to clinically relevant effects.

Immunogenicity

The administration of immunosuppression has been gradually escalated from AMT-010 studies to the last study which also included pre-treatment bolus of IV steroid. The humoral immunogenicity was primarily attributed to anti-AAV1 antibodies which belonged to all IgG sub-classes as well as to IgM. The majority of patients had background anti-AAV1 antibodies which were clearly 'boosted' by Glybera. It is not possible to exclude that anti-AAV1 antibodies may be of relevance to a gradual antibody-dependent cytotoxicity in the injected muscle tissue. Anti-LPL antibodies were identified only in a few patients. Cellular responses with CD4, CD8 and other cell types were also identified. However ELISPOT assays were hampered by low cell viability specifically in patients which showed trends for an aberrant distribution of T lymphocytes. A delayed onset anti-AAV1 antibodies and cellular immunogenicity beyond 19 weeks of treatment was found in all patients treated with Glybera regardless of the immunosuppression used. In conclusion, the use of immunosuppression for 12 weeks did not result in a reduction of unwanted humoral and cellular immunogenicity in treated patients. Referring to SAG discussion that such delayed cellular and humoral responses are of no clinical relevance in the absence of muscle symptoms/weakness, the CAT considered that need for the utility of and the safety of immunosuppression remains unclear at this point.

Viral shedding

The shedding data illustrate that Glybera is gradually eliminated from various body fluids with only low DNA concentrations detected in the serum beyond 12 weeks.

Haematology & Biochemistry

No clinically significant changes in blood specimens were observed in any subject during the 12-week or 3-year study period. Some assessments were above the ULN, but these were considered to be related to the lipaemia of the samples interfering with the assays in most cases. The only case of elevated CPK to 750 IU in a remote from treatment period was recorded in the SUSAR (SAE for subject 3 in CT-AMT-011-02).

Safety in special populations

No clinical data from women exposed to Glybera during pregnancy or lactation are available. There was 1 patient with moderate renal impairment and 1 patient with heart failure. No adverse relationship between organ impairment and Glybera was reported in these patients.

Immunological events

An SAE from one patient from CT-AMT-011-02 study was reported which may potentially constitute a reaction to Glybera.

Discontinuation due to AES

No withdrawals due to adverse events occurred.

2.6.1. Discussion and conclusions on clinical safety

Overall, Glybera was well tolerated by all patients during initial 12 week observational period and during long-term phase of observation (up to 3 years with AMT-010 and up to 1.5 years with AMT-

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011). All reactions were self-limiting and mild in nature. There were no obvious serious adverse events seemingly related to Glybera. However in CT-AMT-011-02 study a subject was reported to have PE in immediate post-treatment period. Multiple intramuscular injections in lower limbs can be accompanied with swelling, bruising and potential formation of emboli, which can be dislodged into systemic circulation. Considering the SAE of polyarthralgia, bilateral temporomandibular pains, myositis and "possible acute inflammatory process", the role for Glybera and/or immunosuppression cannot be excluded particularly in view of the very small safety data set.

A degree of inflammatory, degenerative and sclerotic changes were identified in injected muscles up to 25-27 weeks following treatment. Delayed humoral (mainly anti-AAV1 antibodies) and cellular immunogenicity were identified across all studies. The use of immunosuppression for 12 weeks does not lead to a reduction of unwanted humoral and cellular immunogenicity in treated patients. Since the argument has been made and supported by SAG that such delayed cellular and humoral responses are of no clinical relevance in the absence of muscle symptoms/weakness, the need for the utility of and the safety of immunosuppression is unclear at this point.

In conclusion, the safety of Glybera in relation to immunogenicity remains unresolved and is considered insufficiently established and based on too limited data.

2.7. *Pharmacovigilance*

Detailed description of the Pharmacovigilance system

The CAT considered that the Pharmacovigilance system as described by the applicant fulfils the legislative requirements and provides adequate evidence that the applicant has the services of a qualified person responsible for pharmacovigilance and has the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country.

Risk Management Plan

The applicant submitted a risk management plan, which included an efficacy follow-up and risk minimisation plan.

2.8. *Significance Non-Conformity of paediatric studies*

Not applicable

2.9. *User consultation*

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

2.10. *GMO / Environmental risk assessment*

Under Regulation EC/726/2004, any medicinal product containing or consisting of live GMOs must be assessed in accordance with Directive 2001/18/EC (on the deliberate release into the environment of

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GMOs). As Glybera contains a Genetically Modified Organism, assessment of the risks to the environment has been conducted according to the requirements of Directive 2001/18/EC and the competent authorities of all member states have been consulted. The environmental risk assessment (Module 1.6.2) is therefore not included in the non-clinical assessment report but has been provided to the Competent Authorities as a separate document. A summary of the findings of the ERA is provided here.

The Applicant has provided a summary of general information on the medicinal product, the vector, the production system and key points regarding risk to the environment.

The product is for the treatment of lipoprotein lipase deficiency. The product consists of an AAV-1 capsid with AAV-2 backbone expressing human lipoprotein lipase. The Applicant was asked to consider the effects of over-expression of LPL in an otherwise healthy human. The response highlights that accidental inoculation even with a full syringe would not be the equivalent of a full dose, that inoculation would most likely result in a percutaneous injury rather than injection into the muscle and that therefore the level of transduction would be low. The applicant also highlights that no adverse reactions have been observed in clinical trials despite systemic exposure to the product and that vector could only be detected in muscle in non-clinical trials.

The ERA has been updated to include information on the pharmacodynamics of the product from animal studies of the effects of LPL over-expression (See ERA p25). Section 4.3 of Module 1.6.2 has been revised to include an estimate of the exposure that an accidental self-inoculation would result in (1% of the lowest dose tested in humans). This information combined with non-clinical and clinical data provide assurance that any risk from over-expression of LPL through accidental inoculation is very low.

The vector is replication defective and lacks the rep gene required for site-specific integration. Wild-type AAV is not considered by the applicant to cause human disease and can only replicate in the presence of a helper virus. The applicant was requested to consider publications regarding possible association of AAV with miscarriage and problems in pregnancy, and with male infertility, and to discuss these finding with respect to the AAV vector present in Glybera. The applicant has provided literature references which appear to indicate that although wt AAV might be involved in miscarriage and trophoblastic disease and other problems associated with pregnancy, it is not possible to rule out contributions from helper viruses in this problem, some of which also associate with such pregnancy problems. The applicant concludes that there is no conclusive evidence that the pathological conditions result directly from *in utero* infection with AAV.

The applicant have also addressed the question of whether the presence of AAV may contribute to male infertility and conclude that although both AAV and helper viruses have been found in the ejaculates of fertile and infertile males; there is no direct correlation between AAV and infertility. The applicant had proposed to recommend the use of physical barrier contraceptives during treatment and for 6 months after and this information has been added to the SmPC.

AAV require helper viruses for replication or remain latent in the nucleus of infected cells. Approximately 1% of wt AAV genomes integrate site-specifically, the remainder persist extrachromasomally. AAV-2 is considered by the applicant to be apathogenic and reports that most humans are seropositive for AAV.

The vector contains the expression cassette with AAV-2 ITRs and small intervening DNA sequences encased in AAV-1 capsid proteins. As *cap* and *rep* genes are not present in the vector, the vector is not capable of replication even in the presence of a helper virus such as adenovirus or HSV. As only the

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ITRs have homology with AAV-2, the possibility of homologous recombination is limited and in the event that it did occur, the expression cassette would be lost, resulting in wt AAV-2. Nevertheless, the applicant was asked to consider the possibility of non-site-specific integration of AAV. The applicant refers to literature which indicates that a non-human primate study with an AAV vector was unable to find integration but did find concatemeric arrangement of the AAV vector using LAM-PCR. The response also refers to other studies in which a PCR method detecting B1 sequences in mice failed to detect integration events. This technique has been used by AMT and failed to detect integration in Hepa1, 6 cell line with a GFP encoding rAAV vector. The applicant is investigating LAM-PCR for the detection of integration in injected muscle and liver.

The ERA has been updated to better reflect the risk of integration and potential insertional mutagenesis.

The applicant has described the origins of each of the vector genome sequences, the lipoprotein lipase S447X gene, the CMV immediate early promoter, the bovine growth hormone polyadenosine transcription termination signal and the woodchuck hepatitis virus posttranscriptional regulatory element (WPRE). Whilst the CMV IE promoter and the transcription termination signal from bovine growth hormone are commonly used in molecular biology and are have not been associated with any harmful effects to date, there have been suggestions in the literature that the Woodchuck Hepatitis Virus WPRE expressing X protein may be associated with oncogenesis. The applicant was asked to confirm whether the WPRE sequence used in Glybera contains the second enhancer, We2/En2, and to provide data to confirm whether or not WPRE X protein is expressed by Glybera transduced cells either alone or as a fusion protein with lipoprotein lipase.

The response indicates that the applicant has thoroughly considered the findings of Embury *et al* (Gene Ther Mol Biol. Vol 12, 69-76, 2008) and their relevance and relationship to the WPRE sequence present in Glybera. The applicant's response clarifies that the WPRE X protein open reading frame is truncated at the C-terminus and thus that WPRE X protein is highly unlikely to be expressed and that the tumourigenicity associated with HBV WPRE element is thought to be due at least in part to activation of N-myc2 oncogene by insertion of We2 and that only WHV We1 is present in Glybera.

The applicant has reviewed the possibility of WHX being expressed as a fusion protein with LPL and highlighted that the stop codon present in the WPRE element present in Glybera was not present in the construct used in the lentivirus associated with tumourigenicity by Embury *et al* (Gene Ther Mol Biol. Vol 12, 69-76, 2008).

The applicant concludes that the oncogenicity of the product is not increased by the presence of WPRE and refers to non-clinical studies in mice of 15 and 26 weeks which did not find an incidence of tumours above background.

The presence of WPRE in the vector sequence was also of concern for EU member states as it was not clear that WHV is endemic to marmot species found in the EU and therefore the WPRE might be a novel sequence for this environment. However, clinical trials with both AMT-010 and AMT-011 have already been conducted in EU member states. The applicant was nevertheless requested to assess the potential effect on the environment of release of this novel sequence, particularly regarding other hepatitis viruses or provide information to confirm the presence of WHV and WPRE in the EU environment.

The applicant describes literature data which indicate that European alpine marmots (Marmota *marmota*) are refractory to WHV infection and that it has not been reported in ground squirrels or any other rodent species. The authors conclude that sequence similarity of HBV and WHV WPRE elements

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mean that the WHV WPRE sequence can not be considered to be truly novel to Europe. Table 3.2.3.1 of version 2.0 of the ERA has been revised to include the sequence homology with the HBV PRE sequence demonstrating that WPRE is not a novel sequence in the EU.

The vector genome contains small intervening DNA sequences which have been acquired through assembly of the genetic elements. The applicant was asked to provide details of these small intervening DNA sequences. In addition, vector particles may contain fragments of baculovirus DNA which could encode for ORFs expressed late in baculovirus replication. The applicant states that in human cells, expression of these late genes is blocked, that expression of these ORFs is not expected and that pathogenicity of baculoviruses in humans is low. Further information on the role and potential effect of the presence of these baculovirus DNA fragments contained within the vector particle was requested.

Although the applicant has sequenced the baculovirus vectors, confirmation of the ITR sequences has not been possible with the method used. The applicant has considered the recombination events that might occur between baculovirus vectors during manufacture of Glybera and their potential to result in the formation of replication-competent AAV. The applicant notes that both the rep and cap vectors include PolH promoter but that any recombination events would result in exchange of identical material. The applicant also considered the possibility of recombination between a region of homology between LPL and AAV1 cap and notes the possible sequences that could be generated and that generation of a wt-like AAV is extremely remote.

The recombination possibilities and frequencies of baculovirus and glybera sequences to produce a replication competent AAV have been adequately discussed by the applicant and are considered to be negligible for humans other than the patient and the environment.

The applicant has also considered the frequency of homologous recombination with sequences in the environment to be negligible due to the low numbers of Glybera released and the very low frequency of horizontal gene transfer in the environment. The applicant also considers that if such an event did occur, residual baculovirus sequences would not present a risk to the environment.

The applicant has investigated the persistence of baculovirus sequences by determining the LPL genome and the residual baculovirus DNA levels before and after transduction of murine muscles after i.m. injection by QPCR which appears to indicate that baculovirus DNA is less stable in transfected cells than DNA containing the CMV promoter sequence.

The data provided indicate that baculovirus sequences associated with Glybera are not expressed in muscle and liver cells or lymph nodes.

The data provided indicate that baculovirus sequences present in Glybera are not transcribed and translated on transfection of muscle, liver or lymph nodes and thus present a negligible risk to those accidentally exposed to Glybera or to the environment.

The applicant states that recombination with another parvovirus is improbable as it would require illegitimate recombination between sequences of little or no homology. The applicant considers the possibility of recombination involving baculovirus sequences to be unlikely as data elsewhere indicate that these sequences are not expressed and such an event would negatively impact the infectivity of the virus. In the event that replication inactive genomes were packaged in the Glybera capsid with a low possibility of being shed, they would not replicate even if they were able to transduce a cell. The possibility of shed DNA being incorporated by an animal or plant species is also considered to be remote and even if LPL were expressed it could not be further transmitted. The applicant considers that all sequences in Glybera are already present in EU and do not confer any biological advantage.

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The response indicates that the applicant recognizes the possibility of gene transfer in the environment but highlights that most DNA release will be rapidly degraded. In the event that DNBA is protected by colloids in soil, these also inhibit transformation and DNA availability.

Manufacture

The GMO is manufactured using a system of 3 recombinant baculoviruses in an insect cell line. After incubation, cells are lysed; the lysate is treated to remove nucleic acid and is filtered. The filtrate is treated to inactivate enveloped viruses, is purified and formulated before sterile filtration and storage.

Full details of the three recombinant baculovirus sequences have been submitted by the applicant with an assessment of the likelihood of non-homologous recombination leading to the presence of replication competent AAV.

Insect cell DNA and protein levels in the product are considered by the applicant to be consistently low and are controlled through batch release testing. No baculovirus has been found in any of the 15 tested batches and the production process is reported to be capable of removing 10 logs of baculovirus. Animal studies used much higher doses and no toxicity was found. The applicant also reports that studies have been conducted which show that baculovirus genes are not expressed in transduced cell lines.

The Product

The GMO-containing product, Glybera, is proposed to correct lipoprotein lipase deficiency and prevent complications such as pancreatitis, by providing a working copy of the human lipoprotein lipase gene. It is not clear from the information provided how intramuscular injection of Glybera will result in lipoprotein lipase in the luminal side of the blood vessel; however this information is not critical for the environmental risk assessment.

The product will be provided in 1ml volumes contained in a glass vial with stopper and cap.

Glybera use will be limited to centres dealing with lipoprotein lipase deficiency. Each patient will receive 1 x 10^{12} gc per kg and a low number of patients across EU are expected to be treated.

The product will only be shipped to expert centres and will be administered by healthcare providers.

Transport

Product is transported in a protective case with absorbent wadding, thus minimizing the potential for breakage and accidental release prior to administration. The applicant indicates that packaging will be labelled as containing a genetically modified organism. This is confirmed by the proposed outer packaging and in Section 5 of the proposed PIL and is acceptable. Vials will be tracked to ensure that those sent by AMT are received by the treatment centre.

Administration

Administration of Glybera is through a single administration of multiple intramuscular injections. An immunosuppressant regimen is used to minimize any reduction in potential efficacy through immune responses to the AAV-1 capsid.

Immunosuppression with ciclosporin is used in patients to prevent immune responses to the AAV-1 capsid reducing transduction levels. In non-immunosuppressed humans, the possibility of transduction of cells through any accidental exposure is considered to be small. Warnings regarding pre-existing infections have been implemented in the SPC and PIL due to the use of immunosuppression and provide some assurance that a patient with active Adenovirus or herpes virus infections which could

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act as helper virus for any replication-competent AAV present, will be not be treated whilst infections are clinically symptomatic.

The applicant suggests that training records for healthcare providers handling Glybera should be established and maintained. Whilst this is endorsed the applicant is requested to clarify in Module 1.6.2 that these are standard training and records for healthcare workers as considered according to local rules.

The educational and training materials that the applicant intend to provide to treatment centres were outstanding at the time of opinion.

Accidental exposure is estimated to result in exposure to 0.01% of the number of particles injected into a patient ($8x10^{11}$ gc), and would not result in significant LPL expression. The applicant has now described the assumptions made in calculating accidental exposure.

Whilst it is apparent that the product could be used and hence released at any site in Europe, the incidence of the disease and the nature of the centres imply that in practice Glybera is likely to be used at a limited number of sites.

The applicant states that it is the responsibility of the hospital / clinic pharmacy to keep track of the medications. This is agreed.

The applicant has clarified that as the correct number of vials to treat an individual patient will be provided, return of unused vials is not anticipated.

The applicant considers the potential contact with the environment arising during administration to be limited. This assessment is endorsed.

Shedding

Data is available from shedding studies and shows that vector may be shed from patients through urine (3-4 weeks), faeces (to 8 weeks), saliva and seminal fluid (4-6 weeks) and thus may be released in waste water or result in exposure of contacts. The applicant presents a table showing shedding in urine as a % of dose. The applicant has clarified that the maximum shed infectious virus is 2×10^5 infectious particles per day. Information from Annex IV of M1.6.2 v 2 indicates that shedding can be detected for up to 4 weeks post inoculation. Thus, 5.6×10^6 infectious particles might be shed following treatment of each patient with an additional 8.4×10^7 genome copies of vector. This information has been included in the revised Module 1.6.2.

The applicant states that one patient with renal impairment was included in clinical trial. Data provided on shedding do not indicate prolonged shedding.

The applicant indicates, based on a single literature reference, that vector shed from patients is not infectious. The potential adverse effects to animal and plants and to the environment are discussed in the revised M1.6.2 and can be found tabulated in 4.1.2 and 4.1.3.

Non-Clinical and Clinical Data

Biodistribution studies found vector in muscle, local lymph nodes, liver and blood at high levels, and in brain, lung heart, gonads and reproductive organs and non-injected muscle groups at low levels. Vector copy numbers reduced on average by 1 log over 90 days. Immunosuppressive treatment did not alter biodistribution patterns.

The presence of vector sequences in gonads and reproductive organs raises the possibility of horizontal transfer of GMO sequences to offspring and is of concern. However, guideline EMEA/273974/2005

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indicates that the presence of vector in gonads does not in itself demonstrate that germ line cells have been altered. Although vector sequences were found in reproductive tissue, animal mating studies indicate that foetuses did not contain vector sequence. In rabbits, vector sequences were associated with seminal fluid rather than sperm and studies in humans indicate association with seminal fluid rather than sperm. All data to date suggest that germ line transmission is unlikely, however as indicated earlier, the use of barrier contraception is recommended. The opinion of the Pre-Clinical assessor has been sought and confirmed that the vector is present in semen but not sperm and was not detected in foetuses in a reproductive study. Toxicity testing in animals indicated an inflammatory reaction in injected muscle groups. However, the nature of material used in pre-clinical studies is questionable.

The applicant states that there are no product characteristics that would affect mutagenesis or clastogenesis and thus that genotoxicity studies were not justified. The applicant recognizes the ability of wild-type AAV to insert into the chromosome in a site-specific manner and states that the insertion sequences are not present in the vector but that non-specific integration is possible and could result in proto-oncogene activation as has been seen in a study of an AAV vector administered IV to newborn mice. Studies by nrLAM-PCR have been conducted and the data have been provided. The data provided indicate that whlst at least 97% of the vector is maintained episomally a small proportion of the vector may integrate into the chromosome. However these integration events are not associated with CpG islands, are close to random and do not appear to result in clonal dominance.

In humans, T cell responses to AAV-1 peptides were found in 4 patients but were not associated with clinical symptoms and no T-cell responses to LPL were found in studies with Glybera. In clinical studies with AMT-011, one subject died from non-small cell lung cancer during the clinical study but because of the time course of the disease, this was not considered to be related to Glybera. Other neoplasms reported during the clinical studies were either non-malignant (one lipoma) or related to malignancies identified prior to Glybera administration.

Post-Marketing Surveillance

Monitoring is restricted to post-marketing risk plan activities. No monitoring of environmental exposure or survival of the GMO (for example in waste water) is proposed although primers for PCR analysis are available. Whilst the stability of the vector means that survival in waste water is likely for some time even in treated water, the dilution of any shed vector is likely to render any interaction with humans or animals unlikely and thus unlikely to result in transduction of humans or animals. In addition, the vector is replication incompetent even in the presence of helper viruses and non-homologous recombination in the environment is unlikely and would result in the removal of the transgene and WPRE sequences. Whilst it is possible that vector sequences could be taken up by microbes, the likelihood of expression or replication of such sequences can be considered to be low.

The applicant has provided sufficient justification for not conducting a post-marketing monitoring plan. This justification includes, the low number of patients to be treated, shedding data, absence of infectivity of AAV shed in urine, low risk to the environment, replication incompetent nature of the vector, the low probability of recombination with wtAAV and the negligible effects of such an event, the species specificity of AAV and low frequency of recombination with parvoviruses or any sequences in Glybera or associated with Glybera.

The risk management plan indicates that long term monitoring would be conducted on the health of patients and any healthcare workers accidentally exposed to the product in case of marketing. The monitoring plan indicates that needle-stick injuries are unlikely to result in high levels of expression of the LPL transgene.

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The applicant has provided a table comparing the characteristics of the GMO with wild-type AAV. The vector is replication defective and therefore will not compete with wild-type AAV. The possibility of chromosomal integration has been reduced by deleting the rep gene although the possibility of integration through non-homologous sequences can not be completed excluded. The expressed gene, lipoprotein lipase, is naturally present in humans.

The applicant recognizes that WPRE has been associated with oncogenicity in studies with lentiviral vectors. The possibility of WHX being expressed as a fusion protein with LPL has been reviewed providing some reassurance that the risk to humans and the environment from WPRE induced oncogenicity is very low.

According to literature data EU marmot species are refractory to WHV infection. Sequence similarity of HBV and WHV WPRE elements mean that the WHV WPRE sequence can not be considered to be truly novel to Europe.

The possibility of uptake of vector DNA by microorganisms is recognized and the applicant states that the vector does not contain any promoters to allow expression of any sequences acquired from the vector. Batch release tests preclude (within the limit of detection) the presence of replication competent vector. The applicant states that baculovirus DNA present in the vector would not be expressed in humans but has not considered the possibility of these sequences being expressed in other organisms.

The applicant has provided an assessment of the interaction of the GMO with the environment and with humans and animals. The applicant recognizes that vector DNA might be taken up by microbes through exposure to vector shed from patients in waste water. The applicant argues that whilst non-homologous recombination into microbe genomes is possible, it would be a very infrequent event and that the vector does not encode microbial promoter that would result in expression or that would alter persistence or survival.

Data from mice, cats, rabbits and humans indicate that the possibility of germ-line transmission is negligible and warnings to use barrier contraception had been proposed to be included in the SPC and PIL to address this point.

Assessment of the effect of genome integration is included and the applicant concludes that there is no tumorigenic effect, based on information on the frequency and sites of vector insertion

The applicant states that Glybera will not alter dissemination of infectious disease or create new reservoirs or vectors and Glybera does not contain sequences which would interfere with prophylaxis or treatment of pathogens in humans, animals or plants.

The greatest risks identified by the applicant are germ-line transmission in the event of self-inoculation and genome integration in the event of self-inoculation. All risks to the environment are considered to be negligible. Given the replication-incompetent nature of the GMO, the overall assessment of the risk to the environment is considered acceptable.

In conclusion, the CAT and Competent Authorities for Deliberate Release of GMOs into the Environment agrees with the applicant's conclusions regarding the negligible risk to human health (other than patients) and the environment presented by marketing of Glybera.

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3. Benefit-Risk Balance

Benefits

Beneficial effects

Familial lipoprotein lipase deficiency (LPLD) is a rare autosomal recessive disorder (1-2 persons per 1.000.000 in EU) characterized by absence of lipoprotein lipase activity and a massive accumulation of chylomicrons in plasma and a corresponding increase of plasma triglyceride concentration. The disease remains sometimes under diagnosed until adulthood and includes repeated episodes of abdominal pain, recurrent attacks of pancreatitis, eruptive cutaneous xanthomatosis, and hepatosplenomegaly. The severity of symptoms is proportional to the degree of chylomicronemia, which, in turn, is dependent on dietary fat intake. The duration of life may be impaired due to diabetes mellitus secondary to pancreatic insufficiency and to diabetes related complications. While compliance with the diet (maximum of 20 g/day) can be effective, in practice, it is quite challenging and dietary failures are very common.

Therefore gene therapy represents an attractive therapeutic tool aimed to correct monogenetic disorder such as loss-of-function defects in the lipoprotein lipase gene. Glybera consists of a non-integrating adeno-associated virus (AAV) vector construct, which confers the episomal expression of the overfunctional LPLS447X gene. The rationale of treatment is based on the theory that by adding an extra copy of the over-functional LPL gene into muscle cells lacking catalytically active lipoprotein lipase, Glybera could restore metabolic functions, by normalising the elimination of triglycerides from large circulating chylomicron particles.

The ultimate goals of LPLD treatment are to reduce the burden of the disease associated with pancreatitis, to reduce the incidence and size of eruptive cutaneous xanthomatosis, lipaemia retinalis and hepatosplenomegaly, to reduce the stringency of the life-long requirement to remain compliant with the diet and to improve the quality of life.

The effect on lipid profiles, such as a reduction in fasting triglycerides to <10 mmol/l, a >40% reduction in fasting triglycerides are surrogate markers of lipoprotein lipase activity related clinical benefit. A reduction in post-prandial chylomicronemia has been proposed as an alternative surrogate marker and subject to clinical validation a reduction in post-prandial CM could be accepted as a surrogate marker for efficacy.

The conducted clinical development programme consisted of three open label uncontrolled observational studies. The lipid reductions were variable between the three studies. Overall, less than 40% of subjects achieved a reduction in fasting triglycerides at 12 weeks but even this was not sustained in the majority of responders by 1 year. Long term data (at week 52) on post-prandial chylomicronemia are available for only 3 patients and the methological limitation of this approach in the absence of controls has been highlighted.

A reduction in pancreatitis events and severity of attacks were reported in some patients treated with Glybera, but a clinically significant reduction attributable to Glybera is not available. The retrospective analysis carried out showed that the frequency of this most important complication was of very variable frequency in the pre-treatment period. Several patients had long pancreatitis free intervals, running into a few years. The post-treatment follow-up was relatively short. Therefore, it is not possible to conclude that a beneficial effect in reducing this complication has been demonstrated, even in the absence of frequent pancreatitis post-treatment. Furthermore, an increased incidence of pancreatitis after treatment was observed in some patients.

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Glybera was reasonably well tolerated in terms of local reactions in the first few days after multiple intramuscular injections administered under spinal or regional anaesthesia.

Uncertainty in the knowledge about the beneficial effects

The size of the available dataset encompasses only 27 patients of 40-70 years of age and diagnosed with LPLD condition relatively late in life.

Glybera is unable to provide a complete cure to the LPLD since the episomal expression will cease to exist over time as the effect on lipids appears to decrease over time suggesting a loss of expression of the transgene over time.

None of conducted studies were designed to capture the effect of the gene-therapy treatment on rates of diseases complications.

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.

The retrospective review of the occurrence and nature of historical events of pancreatitis in the LPLD patients, aiming at comparing pre- and post-treatment intervals in LPLD patients to establish the effect of treatment with Glybera is not without weaknesses. It is in general accepted that a retrospective analysis comparing pre and post-treatment data is not in itself sufficient to provide conclusive evidence of efficacy, as it is difficult to attribute causality with certainty in the absence of concurrent control arm. Although such an approach in general can provide supportive information where the results are considered in the context of positive results from other surrogate makers of efficacy, the lack of supportive evidence for surrogate marker responses following Glybera treatment remains problematic. This means that the post-hoc review of pancreatitis events is not supported with robust surrogate marker results supportive of an effect from treatment. The limited number of events before and after treatment, when only similar periods pre- and post- treatment are evaluated, does not support efficacy in reduction of pancreatitis. Furthermore data analysis is limited to 17 treated cases with no information provided on the 5 untreated patients, out of the 22 patients included in the retrospective analysis. Overall efficacy in terms of reduction of episodes of pancreatitis has not been convincingly demonstrated.

A further uncertainty is the lack of any correlation between pharmacodynamic effects such as lipoprotein lipase activity, fasting triglycerides reduction, post prandial chylomicronemia effect, and pancreatitis rates and quality of life.

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Risks

Unfavourable effects

Multiple injections (up to 60 injection sites) were administered during a single procedure under regional or spinal anaesthesia. Most of adverse reactions are local and self-limiting within few days after the treatment.

However the following safety issues have been identified and are described below. Among them, the administration of Glybera confers risks of unwanted humoral and cellular immunogenicity. The cellular infiltration of the injected muscle tissue remains largely unresolved due to lack of relevant clinical data.

The main risks identified with Glybera are described below.

- Multiple injections may cause significant tissue swelling and pose thrombogenicity risks, particularly after multiple injections into calf muscles.
- Risks associated with 3-month course of immunosuppression;

The use of immunosuppression did not have an appreciable effect on maintaining the efficacy responses (fasting TGs) and did not prevent the unwanted immunogenicity during post-treatment period. Therefore, the proposed immunosuppression is not sufficiently justified and poses safety risks to patients with LPLD.

- Risk of rebound of unwanted immunogenicity;
- Reduction in SF36 Quality of Life scores has been observed at week 14 after the treatment in 3/5 patients in the last CT-AMT-011-02 study.

Uncertainty in the knowledge about the unfavourable effects

- The safety database remains very limited and consists of 27 patients only; making it difficult to conclude this product is safe with certainty. It is acknowledged that this is a rare disease.
- Biopsy data illustrated a significant degree of tissue damage due to inflammatory and degenerative changes in the injected muscle in a majority of biopsied patients. Whether such histological changes can have a clinical effect cannot be excluded as no relevant clinical data is available.
- Immunologically relevant risks with Glybera and / or immunosuppression remain plausible. A report of polyarthralgia, pleurisy, and myositis with raised CPK was temporally associated with the discontinuation of immunosuppression raised concern concluding that a link with Glybera therapy cannot be excluded.
- Additional potential risks are attributed to the adverse effects of the immunosuppression (cyclosporine A and mycophenolate mofetil), and are difficult to quantify.
- Further uncertainty relates to the clinical effects of anti-LPL antibodies and whether such antibodies could cross-react with endogenous LPL in subjects who have some residual functional lipoprotein lipase activity.

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Balance

Importance of favourable and unfavourable effects

Despite the fact that LPLD is an extremely rare orphan condition, the efficacy of this gene-therapy product must be clearly established even by using individual patient data, in order to conclude that efficacy has been demonstrated.

Available clinical findings thus far illustrate that the fasting triglycerides lowering effect of Glybera is not consistent between studies at week 12, not sustained beyond week 12 and does not persist beyond 1 year in the majority of patients.

There is insufficient evidence to demonstrate that Glybera has a positive effect in reduction of pancreatitis. In conclusion, this analysis did not provide clear evidence of a clinical benefit in terms of reduction in the rate of pancreatitis when comparing time periods of 1 or 2 years post-treatment with 1 and 2 years (plus prep/run in) periods prior to treatment.

In addition, if supportive data were available showing rate of pancreatitis after treatment were correlated with PK/PD/surrogate markers, this would have strengthened the data. However in the absence of such a correlation the available data on pancreatitis is not considered sufficient.

The administration of Glybera confers risks of unwanted humoral and cellular immunogenicity and cellular infiltration of the injected muscle tissue. The 12-week course of immunosuppression is associated with severe potential risks.

From a patient perspective it is not possible to identify any benefits which Glybera could add in terms of dietary restrictions. This is further illustrated by data on Quality of Life which showed a reduction in SF36 scores in 3/5 patients.

Benefit-risk balance

Discussion on the benefit-risk assessment

The effects of Glybera therapy relate to a reduction in fasting TGs in less than 40% of patients at week 12 and a reduction in postprandial chylomicronemia at week 52 in 3/5 patients. These data are not consistent between studies at week 12, not sustained beyond week 12 and does not persist beyond 1 year in the majority of patients and the proposed surrogate marker of post-prandial CM levels are far too limited. Furthermore, reduction of chylomicrons as surrogate marker is not validated at present.

Only data on 17 treated patients was used for the statistical analysis of pancreatitis event rates out of the 22 enrolled. No data was provided on the other 5 patients who were not treated with Glybera.

The data provided on pancreatitis provided do not support efficacy. The effect on a clinically relevant endpoint (rate of pancreatitis) is not considered to have been demonstrated in view of the infrequent events that occurred when equal periods pre- and post- therapy were analysed in the retrospective analysis.

The data on pancreatitis rates is not supportive particularly when combined with the lack of correlation between the surrogate markers and incidence of pancreatitis in individual cases.

The important unfavourable effects were histological evidence of muscle damage, risk of thromboembolism related to the procedure and the risks associated with 12 weeks of immunosuppression and a reduction in quality of life in 60% of patients (3/5).

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The administration of Glybera confers risks of unwanted humoral and cellular immunogenicity and cellular infiltration of the injected muscle tissue which remains largely unresolved. High rates of immune response in terms of antibody development were seen in all cases thereby precluding re-treatment. The favourable effects of Glybera are uncertain and not considered to be clinically relevant. The unfavourable effects outweight the possibly favourable effects.

The applicant has requested a marketing authorisation under exceptional circumstances consistent with the rarity of the condition. Even considering the exceptional circumstances for this application, a positive clinical benefit would be needed but has not been demonstrated. Even with a limited database, it should be possible to provide evidence for efficacy. This has not been provided.

In the light of the above findings and major deficiencies identified in the clinical data, the CAT concluded that the overall Benefit Risk for Glybera is negative.

4. Initial Recommendations June 2011

Outcome

Based on the CAT opinion and the CHMP review of data on quality, safety and efficacy for Glybera in the treatment of LPL deficiency, the CHMP considers by majority decision that

> the efficacy and safety of the above mentioned medicinal product is not properly or sufficiently demonstrated

and, therefore recommends the refusal of the granting of the Marketing Authorisation under exceptional circumstances for the above mentioned medicinal product.

The CHMP considers that:

In accordance with the draft opinion prepared by the CAT and following the oral explanation held in front of CHMP, CHMP accepted the grounds for refusal from the CAT and concluded the following were the most important issues of those that had been identified by the CAT:

Whilst this approach was promising, CHMP concluded that there was currently insufficient evidence of safety and efficacy to recommend approval at this stage.

Specifically

- The transient reduction in fasting TGs, the lack of correlation between TG responses and post-prandial chylomicronemia improvement and the limitation of the post-prandial CM data in longer term, e.g. at 52 weeks, based on currently only 3 subjects, do not provide consistent or convincing evidence of a long-lasting effect following Glybera administration.
- Insufficient evidence of a reduction in the rate of pancreatitis, based upon the retrospective review of pancreatitis events. CHMP noted the rarity of the disease and difficulty in providing robust data on pancreatitis, however in view of the lack of sufficiently robust data on TG's/ post-prandial CM's, the lack of sufficiently robust data on pancreatitis remained a concern.
- In view of the uncertainties over efficacy, CHMP remained concerned over the risks associated with the procedure needed to treat patients with Glybera, together with the associated requirements for immunosuppression.

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5. Re-examination of the CHMP opinion

The applicant submitted written notice to the EMA on 6 July 2011 to request the re-examination of the CHMP opinion dated 23 June 2011 and submitted the detailed grounds for the re-examination on 26 August 2011. In addition, in its letter the Applicant requested that the CAT/CHMP convene an ad hoc expert group meeting on Glybera during the re-examination procedure. The ad hoc experts group meeting on Glybera was held on 10 October 2011. During this meeting the experts were asked to address specific questions and also to express their views on the protocol CT-AMT-010-04 submitted by the applicant as a commitment.

Discussion of the detailed grounds for re-examination submitted by the applicant/CAT position/CHMP position

The CAT assessed all the detailed grounds for re-examination and argumentations presented by the applicant at the oral explanation at the CAT plenary meeting and considered the views of the ad hoc experts group held on 10 October 2011.

The CHMP, based on the CAT evaluation, assessed all the detailed grounds for re-examination and argumentations presented by the applicant at the oral explanation at the CHMP plenary meeting and considered the views of the ad hoc experts group held on 10 October 2011.

- ✓ *Ground for refusal 1:*

The transient reduction in fasting TGs, the lack of correlation between TG responses and post-prandial chylomicronemia improvement and the limitation of the post-prandial CM data in long term, e.g. at 52 weeks, based on currently only 3 subjects, do not provide consistent or convincing evidence of a long-lasting effect following Glybera administration.

Applicant's Position

Fasting plasma triglycerides (TG) was chosen as the primary efficacy marker, largely based on the empirical finding that pancreatitis risk is increased when plasma TG levels exceed 10-20 mmol/L (Brunzell & Deeb, 2001). However, while being a good diagnostic tool, fasting plasma TG was shown to be less appropriate as a marker to demonstrate clinical efficacy of Glybera. The threshold of 10 mmol/L for fasting plasma TG in the clinical setting was used as a target level to monitor the effect of dietary restriction (moderation of fat intake). Dietary restriction is aimed at reducing the production of chylomicrons (CM), thus limiting the influx of new CM into the total CM pool. When maintained, strict dietary restriction would be expected to result in the reduction of fasting plasma TG, although the studies indicate that the threshold of 10 mmol/L is almost never achieved in lipoprotein lipase deficient (LPLD) subjects. It is clear that diet is not sufficient to control CM metabolism and that slight variations in dietary fat intake contributed to a considerable variation in fasting plasma TGs. This variation might be in part due to a lack of LPL activity, which makes LPLD subjects extremely sensitive to fluctuations in fat intake. Therefore it has been difficult to show a consistent plasma TG reduction.

All three studies CT-AMT-010, CT-AMT-011-01 and CT-AMT-011-02, showed moderate but variable effects on fasting plasma TGs following Glybera administration. Glybera is designed to increase lipid metabolism and to break down CMs. It also has to be considered that CMs are only one fraction of the whole pool of TGs in the blood circulation. The TG-rich lipoprotein pool in LPLD plasma comprises a variety of TG-rich lipoprotein subclasses: large- and smaller-sized CMs as well as large and smaller-sized VLDLs. LPL is however, preferentially attacking large-sized CMs based on higher affinity towards

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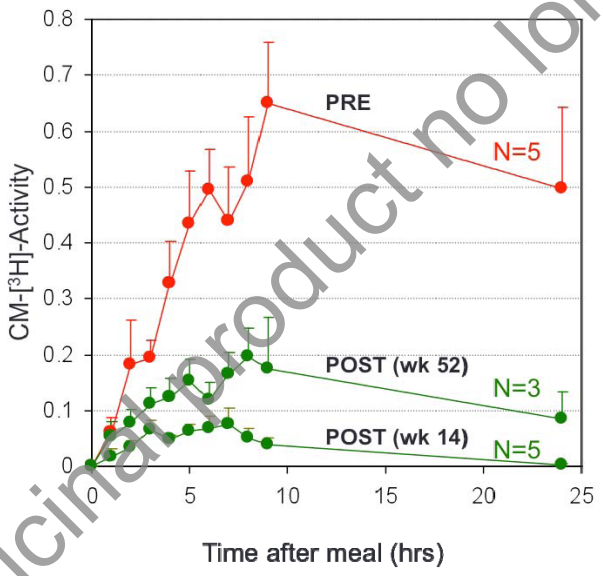
those particles. This characteristic of the LPL enzyme affected the sensitivity of using total fasting TG as the endpoint to monitor the efficacy of Glybera.

Based on those observations and considerations, large-sized CM was then selected as a new additional endpoint to monitor the efficacy of Glybera and was implemented for the first time in CT-AMT-011-02. To measure newly formed large-sized CMs, a postprandial study protocol was designed to monitor the kinetics of CM metabolism following a meal. The studies showed that, following Glybera administration the postprandial metabolism of newly formed, large CM was greatly improved (see Figure 1). Results of these studies also confirmed that the total TG pool was affected to a lesser degree.

The postprandial data set confirmed the proposed mode of action; that LPL is preferentially acting on large-sized CMs. The magnitude of effect was large and as a result, differences pre- versus post Glybera administration were statistically significant, even though a rather low number of LPLD subjects were tested.

To increase the database and confirm mode of action for postprandial CM metabolism, AMT has committed to perform a study (Protocol CT-AMT-011-04) to examine postprandial CM metabolism in more LPLD subjects after approval of the medicinal product. The study will include postprandial CM assessments for 3 cohorts: (1) LPLD subjects previously administered Glybera (n=8) in addition to the patients previously entered in the clinical study AMT-011-02; (2) LPLD subjects who did not receive Glybera (n=3); (3) healthy control subjects who did not receive Glybera (n=8).

Figure 1: Postprandial Metabolism of Newly-formed Chylomicrons



CAT position

The effect on lipid profiles, such as a reduction in fasting triglycerides to <10 mmol/l or a >40% reduction in fasting triglycerides was originally proposed by the Applicant as surrogate markers of lipoprotein lipase activity related to clinical benefit. Overall, less than 40% of subjects achieved a reduction in fasting triglycerides at 12 weeks but this was not sustained in the majority of responders by 1 year. However, during the procedure, the validity of such endpoints to assess the clinical benefit of Glybera was questioned. In fact, results from the two preparation studies clearly indicated that diet by itself was not able to consistently decrease fasting triglycerides plasma levels and showed large

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fluctuations of this parameter. It was noted that fasting triglycerides values ranged between 13.4 and 69.8 mmol/l in all studies submitted by the Applicant.

The Applicant clarified that this endpoint was chosen, mainly based on advice by experts at the beginning of the clinical development programme. Evolution of knowledge around disease endpoints is not unusual, especially in rare diseases. Regarding correlation between the PK/PD surrogate endpoints and the clinically relevant endpoint (pancreatitis), this was not considered feasible in the limited patient population for this very rare condition (1.5/1,000,000).

The plasma levels of triglycerides (TGs) are a poor predictor of efficacy. As a result, both the threshold of <10 mmol/L and the 40% reduction of fasting TGs represent inadequate markers of successful LPLD therapy from a clinical standpoint. The change of endpoint during the clinical programme was due to the evolving scientific knowledge and scientific progress in this very rare condition Therefore, the use of plasma levels of post prandial chylomicrons (pp-CMs) as a surrogate efficacy marker is considered acceptable. The data on pp-CMs at 14 weeks show a significant biological effect on 5 patients. Even though more limited in number (n=3 patients), data at 52 weeks on each patient showed a clear improvement of pp-CM metabolism vs. baseline, suggesting the presence of a metabolically relevant amount of LPL activity and transgene expression. The clinical importance of these findings has been agreed by the Ad hoc Expert Group. On this basis, although the results are limited in terms of patient numbers, pp-CM data obtained following Glybera treatment seem to be clinically meaningful and relevant in terms of showing increased enzyme activity. In addition, the Applicant has committed to further enrich the database by collection of pp-CM data in 12 additional LPLD patients in study CT-AMT-011-004.

The proposed study CT-AMT-011-04, designed to assess postprandial chylomicron metabolism in patients previously treated with Glybera will allow to further substantiate the efficacy of Glybera by providing additional data on 12 new patients and monitored in the risk management plan.

CHMP position

The CHMP agreed that TG plasma levels are not the appropriate biomarker for efficacy. The CHMP considered that the change of endpoint during the clinical programme due to evolving scientific knowledge and scientific progress in this very rare condition and the use of pp-CMs as a surrogate efficacy marker was acceptable. However, even accepting pp-CMs as an alternative biomarker, there is currently insufficient data on pp-CMs to demonstrate the efficacy of Glybera based on only 3 patients at 52 weeks (of the 27 patients enrolled in the clinical trial programme), even taking into account the extreme rarity of the disease. Further data on pp-CMs are required to support the currently available data (e.g. from study CT-AMT-011-04 and/or additional data from patients who have already been treated with Glybera). These data will further substantiate the current hypothesis on efficacy of Glybera on the pp-CM levels as a biomarker.

When looking at individual patient data, there is currently insufficient evidence of persistence of LPL activity post treatment with Glybera.

- ✓ *Ground for refusal 2:*

Insufficient evidence of a reduction in the rate of pancreatitis, based upon the retrospective review of pancreatitis events. CHMP noted the rarity of the disease and difficulty in providing robust data on pancreatitis, however in view of the lack of sufficient robust data on TG's/ post-prandial CM's, the lack of sufficiently robust data on pancreatitis remained a concern.

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Applicant's position

Pancreatitis events are very variable in LPLD patients, and the identification of confirmed, definite pancreatitis events is compromised because of co-morbidities and confounding factors in the patients. The present studies were the first data collection on pancreatitis and abdominal pain events in the LPLD patient population, and therefore the scientific knowledge grew throughout the clinical trial programme.

The rarity of the disease made it virtually impossible to complete a comprehensive clinical package with a controlled study on pancreatitis reduction. An estimate for a controlled trial sample size to allow 80% power to detect a reduction in pancreatitis rate of 50% at 2 years post treatment is 342 patients. The use of each patient as their own historical control can therefore be considered as a valid approach.

In the design of the case note review study CT-AMT-011-03 AMT historical data was used in a retrospective manner. Collection of data in the case note review was not limited by the age of the records. Nevertheless it is inevitable that in such a study, the amount and the quality of clinical records will change going back further in time. Therefore, and to investigate the importance of the cut-off point for the historic control period, a sensitivity analysis was undertaken as part of the statistical analysis plan.

The methodology to address the impact of Glybera treatment on the risk of pancreatitis was developed by an independent multidisciplinary consensus group of six experts in the field adjudicating the data in a blinded fashion. Based on their recommendations, a pre-specified protocol for adjudication of possible pancreatitis events including a prospective statistical analysis plan was designed.

Study CT-AMT-011-03

The study CT-AMT-011-03 was designed to assess and confirm data previously recorded about the incidence and severity of acute abdominal pancreatitis episodes in LPLD subjects previously enrolled on clinical studies PREPARATION-02, CT-AMT-011-01 and CT-AMT-011-02.

From the available total population of 27 patients, 22 subjects that agreed to participate in CT-AMT-011-03. Five subjects from PREPERATION-02 (untreated), five subjects from CT-AMT-011-02 and 12 subjects from CT-AMT-011-01 (treated) consented and took part in this study.

Therefore, the available data of all acute abdominal pain events leading to hospital presentation/admission was retrieved and adjudicated by three independent experts who were blinded to whether the subjects had been treated and whether the events occurred before or after treatment.

The experts used the Revised Atlanta Diagnostic Criteria for assessment of acute pancreatitis:

Two of the following three features should be present:

- Abdominal pain strongly suggestive of acute pancreatitis,
- Serum amylase/lipase activity at least 3 times greater than the upper limit of normal,
- Characteristic findings of acute pancreatitis on ultrasonography or on CECT

Due to the retrospective nature of the review and consequently missing data, the application of the stringent Atlanta Criteria is a conservative approach and may underestimate the true incidence of LPLD pancreatitis. Therefore, an adjudication system of abdominal pain events was proposed, based on a stratification of the probability of having pancreatitis and using the following categories: "definite pancreatitis", probable pancreatitis" and "abdominal pain". Pain events that could not be classified accordingly were classified as "other".

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A Cox Regression analysis, time-between-event data (event-free time) was used to estimate the risk and allows comparison of periods of different lengths (e.g. historic control with post treatment). Event risk rather than the raw number of events was compared. A hazard ratio was calculated comparing risks for pre- and post- treatment period. A hazard ratio (HR) below 1.0 indicated a lower risk for post-treatment events. A HR of 0.5 is equivalent to a 50 % reduction of risk.

Results of the case note review

In total, 512 pain events were classified as definite pancreatitis, probable pancreatitis, abdominal pain, or other. In the group of patients treated with Glybera (17 patients) there were a total of 354 events recorded where 77 were adjudicated as "Definite Pancreatitis" events conformed to the Revised Atlanta Diagnostic Criteria for pancreatitis. Four of these events occurred following treatment.

A further 33 acute abdominal pain events that may have been pancreatitis but failed to fully meet the Atlanta Criteria were adjudicated as "Probable Pancreatitis" events. Only one such event occurred following treatment.

In 17 treated patients 156 abdominal pain events occurred, with only 3 after treatment. 88 events were declared as "Others".

In the group of untreated patients (5) a total of 158 events were recorded; composed as 65 "Definite Pancreatitis" events, 21 "Probable Pancreatitis" events, 47 "Abdominal Pain" events and 25 "Other" events. The median post treatment follow up period was 1093 days. Table 1 provides an overview of the adjudicated events.

Table 1: Adjudicated acute abdominal pain events

	Glybera treated patients	Non-treated Subjects	Total Subjects
Number of subjects	17	5	22
Number of "Definite Pancreatitis" events	77	65	142
Number of "Probable Pancreatitis" events	33	21	54
Number of "Abdominal Pain" events	156	47	203
Number of "Other" events	88	25	113
Total number of adjudicated events	354	158	512

Figure 2 illustrates the individual events collected in all treated patients that participated in CT-AMT-011-03.

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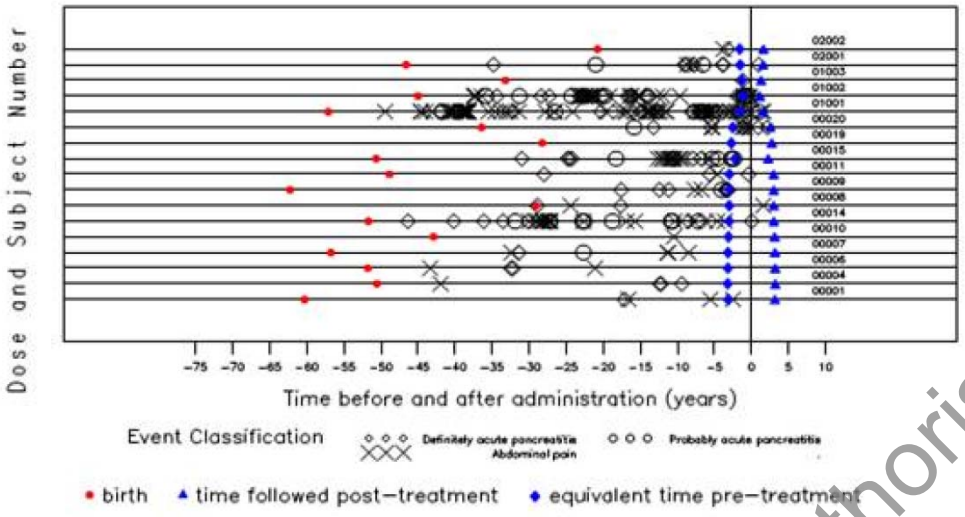
Figure 2: Overview of adjudicated definite and probable pancreatitis and abdominal pain events over time



The review of the recorded data concerning the duration of hospitalizations (Table 2 below) and ICU (intensive care unit) stay (Table 3 below) showed the duration of hospitalization reported as medians for the different groups (pre/post treatment and untreated patients) which had different length of observations. Nevertheless, the results for untreated patients are comparable with pre-treatment data. A trend in reduction in days of hospitalisation was observed, but there were too few events to draw definite conclusions.

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

About half of the subjects required an ICU stay due to a pancreatitis attack. Table 3 shows that most ICU stays were triggered by a definite pancreatitis event. After treatment, no ICU stay was recorded.

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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

Results of the Cox Regression Analysis

To assess the importance of the length of historic control period, a sensitivity analysis was performed using 14 different periods, each ending on the day before treatment (see Table 4).

Results were found to be consistent for historic periods ranging between a minimum of 3 years up to 10 years before treatment. Both, the estimates for the magnitude of risk reduction (HR) and the corresponding confidence intervals were comparable, independent of the length of historic control within this range.

For very short (prep / run-in period plus 1 year) and very long (from birth), historic control periods the Cox regression model did not consistently find a relation with the treatment, which is most likely due to the high variability of event incidence in these periods.

A statistically significant reduction in definitive pancreatitis events was found in half of the historic control periods and consistently positive results were found in the other half, indicating the stability of the outcome of the model. The reduction of events ranges 51% to 59% (hazard ratios (HR) of 0.49-0.41) with p-values ranging from 0.032 to 0.087. Analysis using historic control periods of 2 years and shorter did not select treatment as a variable in the Cox Regression model.

Significant outcomes in reduction of risk after treatment were obtained for the data sets combining definite and probable pancreatitis events with HRs of 0.31 to 0.38 (p-values between 0.007 and 0.043). A highly significant reduction of event risk post-treatment was found for the dataset combining definite and probable pancreatitis and abdominal pain events. The HRs ranged from 0.33 to 0.44 (p-values between <.0001 and 0.0193).

The sensitivity analysis shows that the outcome of the Cox regression analysis was consistent when a period between 3 and 10 years prior to treatment was used as a historic control. According to the applicant, this confirmed the robustness of the Cox regression analysis for the data set of this study showing that the frequency of acute abdominal pain events and pancreatitis in LPLD patients significantly decreased following treatment with Glybera.

A consistent effect post treatment with a risk reduction between 51% to 59% (HR of 0.49-0.41) was observed. Similar results, with higher significance were obtained, when the other categories of events (probable pancreatitis, abdominal pain) were included in the analysis. Post treatment, there was a trend for shorter hospital stays in case of a hospitalization and no ICU stay was recorded in this period.

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To further increase the growing scientific knowledge of the disease and treatment with Glybera, AMT has committed to an annual safety update that will contain pancreatitis event data, and the patients in the LPLD registry (both treated and untreated) will be followed for 15 years.

Table 4: Comparison of pre and- post treatment rates of pancreatitis and abdominal pain events in LPLD subjects treated with Glybera

Time interval for pre-treatment period	Pancreatitis and abdominal pain events		Definite and probable pancreatitis		Definite pancreatitis	
	Hazard ratio[a] (95% CI)	p value	Hazard ratio[a] (95% CI)	p value	Hazard ratio[a] (95% CI)	p value
prep/run-in	0.21(0.023 to 1.936)	0.1680	NA	NA	NA	NA
prep/run-in + 1 year prior to start	0.41 (0.197to 0.866)[c]	0.0193	NA	NA	NA	NA
prep/run-in + 2 years prior to start	0.38 (0.188 to 0.768)	0.007	0.31 (0.101 to 0.966)[c]	0.0433	NA	NA
prep/run-in + 3 years prior to start	0.44 (0.276 to 0.698)	0.0005	0.38 (0.180 to 0.795)	0.0103	0.42 (0.159 to 1.133)	0.0872
prep/run-in + 4 years prior to start	0.41(0.239 to 0.705)	0.0013	0.36 (0.162 to 0.784)[c]	0.0103	0.42 (0.182 to 0.927)	0.0435
prep/run-in + 5 years prior to start	0.39 (0.234 to 0.640)	0.0002	0.35 (0.160 to 0.758)[c]	0.0079	0.41 (0.181 to 0.927)	0.0321
prep/run-in + 6 years prior to start	0.38 (0.223 to 0.636)	0.0003	0.38 (0.164 to 0.888)	0.0254	0.49 (0.224 to 1.080)	0.0769
prep/run-in + 7 years prior to start	0.33 (0.200 to 0.541)	< 0.0001	0.36 (0.168 to 0.757)	0.0073	0.46 (0.208 to 1.037)	0.0614
prep/run-in + 8 years prior to start	0.33 (0.202 to 0.539)	< 0.0001	0.37 (0.165 to 0.836)	0.0168	0.44 (0.201 to 0.964)	0.0402
prep/run-in + 9 years prior to start	0.33 (0.187 to 0.587)	0.0002	0.38 (0.165 to 0.877)	0.0233	0.41 (0.176 to 0.969)	0.0422
prep/run-in + 10 years prior to start	0.33(0.185 to 0.599)	< 0.0001	0.37 (0.155 to 0.889)	0.0262	0.45 (0.191 to 1.067)	0.0701
pre-treatment interval equivalent to time followed post treatment	0.44 (0.226 to 0.846)[c]	0.0140	0.95 (0.924 to 0.983)	0.0022	NA	NA
history from birth to start of treatment	0.37 (0.215 to 0.638)	0.0003	0.50 (0.209 to 1.216)[c]	0.1276	NA	NA
history from first reported event to start of treatment.	0.29 (0.159 to 0.516)	< 0.0001	0.37 (0.164 to 0.835)[c]	0.0167	0.37 (0.142 to 0.971)	0.0434

[a] Hazard ratio – Pre/post treatment; CI = confidence interval; NA = not available; Prep/run-in = period during screening prior to receiving treatment..
Source: Statistical analysis preliminary report (11 Apr 2011); Table 4.1; Table 4.2; Table 4.3

Additional information provided by the applicant as part of the re-examination procedure

Study CT-AMT-011-02 is the only study yielding data allowing the possibility to make a link between surrogate and clinical endpoints (pp-CM metabolism, fasting TG, serum LPL activity, pancreatitis).

LPL Activity

In CT-AMT-011-02, evidence of persistence of Glybera-derived vector DNA sequence (encoding LPLS447X) in the injected muscle was found in 5/5 subjects enrolled in the study. This is concluded from Q-PCR analysis carried out on muscle biopsy samples, taken between 14 and 52 weeks post Glybera administration. The amount of vector DNA sequence found was variable, which is a likely consequence of variability in the biopsy procedure, combined with a limited spread of vector within muscle tissue following injection. In these same samples, LPL protein and LPL activity was found, in 4/5 and 3/5 subjects respectively. LPL protein was measured using an ELISA, LPL activity was measured using an LPL activity assay; there was good correlation between the ELISA results and LPL activity measurements. LPL protein was also detected by staining muscle tissue cross-sections generated from these same biopsy samples, showing positivity in 4/5 subjects. Staining of these same cross-sections with Oil Red O indicated lipid accumulation in the same area, indicative of local LPL.

Detection of LPL activity in plasma after the administration of Glybera used the standard LPL activity assay that is often used as a diagnostic tool to verify (type I) LPL deficiency. For this assay, blood is collected after injection of heparin, which helps to release LPL present within the blood compartment but tethered to the vascular endothelium. However, the assay failed to show increased LPL activity above background following Glybera administration. Extensive assay development revealed that the sensitivity of the assay is limited to a LOQ of >10% of normal.

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In pre-clinical experiments in LPL deficient mice, similar results were seen as in the clinical studies, with the clinical dose of 1x1012 gc/kg. In mice expression of LPL protein and activity in muscle was seen, yet post-heparin LPL activity was close to background levels. Nevertheless, in mice with this dose a reduction in chylomicronemia was observed. These results suggested that high LPL activities in post-heparin plasma at this dose of Glybera should not be expected. The results further indicated that plasma LPL activity is <10%, but sufficient for meaningful reductions in chylomicronemia (Ross, 2004).

AMT has also committed to further investigate alternative, more sensitive methods for the detection of Glybera-derived LPL in plasma as part of the post-approval follow-up programme.

Lipid Metabolism

In CT-AMT-011-02, a range of different assessments were carried out to address effects on TG and CM metabolism before and after Glybera administration.

Postprandial metabolism of newly-formed, large CM was monitored by supplementing the test meal with a trace amount of [3H]-palmitate. Improved postprandial metabolism of these newly formed CMs was observed over a 24-hour period post meal, in all subjects tested; the effect was persistent and observed both at week 14 and week 52 after Glybera administration.

Postprandial total plasma TG and CM-TG/Total TG ratio were also monitored over the 24-hour time frame. Plasma TG was reduced in 4/5 subjects at Week 14 post, and the mean CM-TG/Total TG ratio was greatly reduced indicating a shift towards a smaller-sized population of TG-rich lipoproteins. These effects were more variable and less robust at week 52. The week 52 results suggested lower efficacy at this time point, although the number of subjects analysed was too small to make final conclusions.

Link LPL Activity and Effects on Lipid Metabolism

Glybera-derived LPL expression was found in biopsy samples taken between 14-52 weeks after Glybera administration, in 4 out of 5 subjects. In parallel, there was clear evidence for improvement of lipid metabolism, as assessed by monitoring metabolism of newly-formed CMs. This improved CM metabolism was found in 5/5 subjects at week 14 and 3/3 at week 52.

Whereas direct evidence for plasma LPL activity, assessed by classical LPL activity assay, cannot be provided at this time, the improved CM metabolism was a clear indication of elevated levels of active LPL protein in plasma. This was further supported by the fact that primarily the larger CM pool was affected which is in line with the higher affinity of LPL for large CM particles.

Link with Pancreatitis

Within the capillaries of the pancreas, aggregation of large CM particles can lead to obstruction and damage of the underlying tissue. Damage of the acinar cells can then result in leakage of pancreatic lipase, which can act on the TG within CM or CM aggregates, resulting in release of free fatty acids (FFA). FFA in high concentration are toxic to the underlying tissue, thus creating a vicious circle of damage release of pancreatic lipase followed by inappropriate TG hydrolysis and release of FFA-further damage.

Further data will be gathered in the proposed study CT-AMT-011-04 that will help to substantiate whether improved CM metabolism post Glybera administration is maintained over time.

CAT position

The applicant calculated that a sufficient power to detect a statistically significant reduction in pancreatitis events following treatment would require enrolling 342 patients. Considering the

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prevalence of the disease and that about half of the patients will not meet inclusion criteria, such a study would require identification and enrolment of all LPL-deficient patients living in Europe, which is considered unfeasible. Since LPLD is an autosomal recessive disorder with most likely different levels of genetic penetration and considering that the proposed gene therapy approach also bears a certain level of inherent variability, e.g. in gene expression, the combination of these two aspects will generate, inherently, a very limited and non-homogeneous database, where an expectation of a high consistency cannot reasonably be anticipated. Hence, the results of such a specific therapy for such a rare disease cannot be evaluated by the application of traditional statistics. Furthermore, occurrence of pancreatitis is a fluctuating clinical event, confounded also by other factors, which makes the comparison in a small dataset of patients inherently difficult.

Nevertheless, it was considered that the applicant provided statistical evaluation for a reduction of pancreatitis risk in the treated patient population.

The statistical analysis used by the applicant to evaluate pancreatitis risk is considered adequate; however, it was not able to eliminate the bias due to the high variability of the observed events and the long pre-treatment period as compared to limited post-treatment period. If a higher number of subjects were included in the analysis, it would have been possible to reduce or even eliminate the variability induced bias. Longer follow-up would be required for further observation of pancreatitis events. This is considered unfeasible in a clinical study setting and can only be solved with systematic post-authorisation clinical follow-up data.

Therefore, a descriptive analysis of efficacy data on each single patient appears to be justified as it is the most objective way to discuss and interpret the available data.

Interestingly, two subjects suffered both from multiple recurrent pancreatitis and abdominal pain events before treatment. During the follow-up period after Glybera administration, one patient suffered from only one pancreatitis event and the other patient experienced no new event. Both patients exhibited LPL mass expression, as well as a sustained improvement of pp-CM (both at 14 and 52 weeks). The findings from these two individual subjects, although highly limited by the paucity of the number of observations, do suggest a correlation between biochemical and clinical data. A sustained improvement in pp-CM was observed also in the third subject followed up to 52 weeks with pp-CM. This subject had only one pancreatitis event before treatment, and no event during post-treatment follow-up.

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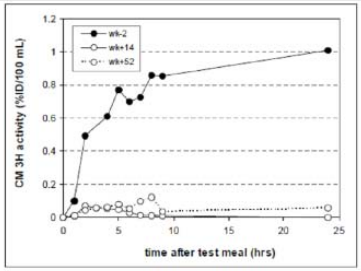
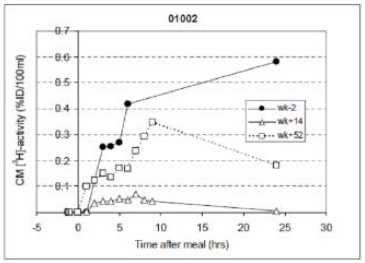
Subject	Pancreatitis prior to Glybera administration	Date of administration of Glybera/ Pancreatitis after Glybera	24-hour time course for [3H]-tracer within the postprandial chylomicron (CM) fraction, 2 weeks before and 14 and 52 weeks after Glybera administration.	LPL expression and activity
	14 (10 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(2) / 0.2 / 0.0 / - / - / 1[illegible] I / Wk52 / 188.3 / 54.1 / 1+ / 3+ / 1000000 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 -

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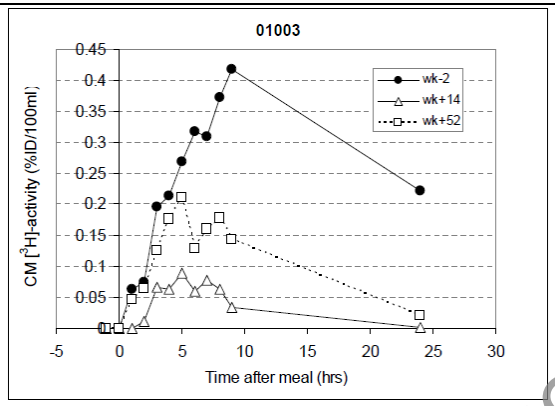
Subject	Pancreatitis prior to Glybera administration	Date of administration of Glybera/ Pancreatitis after Glybera	24-hour time course for [3H]-tracer within the postprandial chylomicron (CM) fraction, 2 weeks before and 14 and 52 weeks after Glybera administration.	LPL expression and activity
	1 definite	Glybera adm.:29 Sep 2009 **0** pancreatitis		14 weeks post Glybera administration

QPCR (gc/mg g DNA)		LPL mass (ng/mg)		LPL Activity (nmol FFA/min/mg)		LPL IHC		Oil Red O	
I	C	I	C	I	C	I	C	I	C
730000	2400	45.00	1.90	13.00	0.00	+	-	+	-

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This analysis indicates that Glybera treatment can result in a benefit for patients in terms of reduced pancreatitis risk, as compared to those not treated with Glybera.

Data on hospitalization and ICU stay support this conclusion, even though without reaching statistical significance due to the low number of events considered. Of particular note, about half of 17 patients required an ICU stay due to pancreatitis before treatment, while no ICU stay was recorded in the same patients after treatment, as compared to non treated patients.

The lack of correlation between fasting TG and the clinically relevant endpoint (i.e. pancreatitis) is not surprising, since hypertriglyceridemia in the absence of pancreatitis can partly be due to increased TG-rich VLDL rather than CM, as a result of improved CM metabolism after Glybera administration (of note VLDL-associated hypertriglyceridemia does not result in pancreatitis). Moreover, the plasma assay for LPL activity is not sensitive enough to detect the relatively low levels of activity expected after Glybera administration. Indeed, in normal individuals LPL activity is expressed both in muscular and in adipose tissue, thus yielding a large enzymatic mass. Since Glybera is injected locally in a limited muscular site, expressed LPL activity will only be a small fraction of normal activity. Levels of LPL activity <10% of normal, as is likely the case after Glybera, will not be detected in human post-heparin plasma, but can exert a significant effect on CM metabolism.

In summary, the evidence generated by the reduction of pancreatitis events and severity of attacks, although hampered by statistical limitations and by fluctuations in the occurrence of pancreatitis, suggested that Glybera leads to a clinically relevant reduction of pancreatitis risk at least in some patients. This is also supported by the reduction in hospital admissions and ICU stay. Of particular note is the fact that while about half of 17 patients required an ICU stay due to pancreatitis before treatment, no ICU stay was recorded in the same patients after treatment, as compared to non-treated patients.

As a result, the CAT proposed to restrict the indication in a subset of patients as follows:

"Glybera is indicated for adult patients diagnosed with familial lipoprotein lipase deficiency (LPLD) and suffering from at least one pancreatitis episode 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."

CHMP position:

The absence of robust data on pp-CM could have been addressed by clinical data. CHMP recognised the difficulty in collecting clinical data in rare diseases. However, the retrospective analysis of pancreatitis data, failed to provide convincing evidence of efficacy in support of a clinically meaningful reduction in the incidence of pancreatitis. The follow-up data on pancreatitis are not sufficient in view of the relatively short duration of post-treatment follow-up and year to year variability in historical pancreatitis rates. Further, there were long pancreatitis-free intervals in several patients in the pre-treatment period. The rate of pancreatitis during the run in period was comparable to that seen after administration of Glybera. It cannot be excluded that the decrease of pancreatitis risk seen in patients treated with Glybera is due to factors other than Glybera (i.e. changes in lifestyle/diet). Therefore, it can not currently be concluded that any changes seen in pancreatitis events were definitely attributable to Glybera. The reduction in hospital admissions and ICU stay are important to consider, although hampered by the lack of evidence of their relation with pancreatitis events.

Therefore, based on the uncertainties and limitations of the efficacy data, it is not possible at present to define an appropriate subset of patients in which Glybera could be administered.

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In the event that more data become available concerning pp-CMs and the effect on this surrogate marker is clearly demonstrated, data on pancreatitis and other clinical important parameters, like quality of life could be followed post-marketing.

- ✓ *Ground for refusal 3:*

In view of the uncertainties over efficacy, CHMP remained concerned over the risks associated with the procedure needed to treat patients with Glybera, together with the associated requirements for immunosuppression.

Applicant position

The regimen of immunosuppressants used in the Glybera clinical studies was tailored to mitigate any anticipated T cell immune response against AAV during the period of presence of the capsid. Activation of T cells directed against the AAV capsid antigen has been documented in several clinical studies and in some of them this was associated with loss of therapeutic efficacy. Such cellular immune responses against the viral capsid protein may occur without immunosuppressants and the amplitude of this response and especially its clinical relevance for the long-term expression of LPL is still not completely understood. Indeed, a T cell mediated immune response is expected to be triggered only in the presence of the epitopes from the viral capsid proteins in the muscle tissue, which is a transient process after administration of an AAV vector. The data collected during the clinical studies so far suggest that by using a short and moderate regimen of immunosuppressants, a mild or delayed cellular immune response to the AAV capsid proteins occurs that does not eradicate the expression of the LPL protein, since the protein is still expressed in the injected muscle up to one year after administration, and therefore does not seem to influence efficacy.

The immunosuppressant regimen used during the clinical studies is given for three months corresponding to the maximal period of time where the viral capsid proteins are assumed to be present in the injected muscle. A three month duration is generally considered by clinicians as short and is not expected to lead to any detrimental effect.

Although none of these have been seen during the clinical studies, the long-term (years) use of immunosuppressants increases the risk of malignancies and long-term use of mycophenolate mofetil increases the risk of gastrointestinal bleeding and perforation. The use of mycophenolate mofetil during pregnancy is associated with increased risk of pregnancy loss and congenital malformations and women of childbearing potential must use contraception. Ciclosporin is known for its possible nephrotoxic and hepatotoxic effects next to an increased vulnerability to opportunistic fungal and viral infections.

Among the reported adverse events during the clinical development and follow-up after Glybera administration, none has been definitely related to the concurrent use of immunosuppressant drugs. However, one subject presented with a serious adverse event termed 'polyarthralgia of imprecise origin' at week 14, i.e. 2 weeks after cessation of the immunosuppressant regimen. Relatedness of this event to Glybera is considered unlikely. The event however may possibly be related to the concomitant use of immunosuppressants.

The proposed SmPC for Glybera contains appropriate warnings related to the use of immunosuppressants such as contraception recommendations and the advice to avoid sun exposure of the skin. Patients presenting with symptoms of infections at the scheduled time of treatment should not start the immunosuppressant regimen. In addition, patients with risks of acute inflammatory events should be monitored closely prior to, during and after the use of immunosuppressants.

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Muscle damage. Within the 3-5 year time period of follow up, documented histological alterations for 20 patients were mild, never resulting in necrosis and/or scarring. No biochemical signs of muscle damage were detected, in particular serum CPK was not altered by the procedure. No sign of muscle dysfunction was reported.

Long term immunogenicity was addressed by testing anti-LPL antibodies. Anti-LPL antibodies were not detected in any of the patients.

It is the CAT opinion that any longer term clinical impact of unwanted immunogenicity can be addressed with the post-authorisation measures and are sufficiently addressed in the RMP.

In the study CT-AMT-010-01 eight patients have been followed up for 5 yrs, while in study CT-AMT-011-01 twelve patients have been followed up for more than 3 years. Therefore a total of 20 patients have been followed up for 3 to 5 yrs.

Additional comments: Clinical Safety Summary Update provided by the MAH

The company has submitted new data with their grounds for re-examination that have not been considered in the re-examination assessment (see below). In addition, a draft protocol of study AMT-011-04 and further safety information have been provided.

Applicant's position

The safety database across the three clinical studies encompasses more than 5 years follow-up of treated patients. After administration of alipogene tiparvovec or it predecessor AMT-010, the most frequent adverse reactions consisted of intramuscular injection-associated local reactions that developed immediately after and/or directly related to the administration procedure such as myalgia, pain in the legs and oedema. Bruising was commonly seen a few days after administration. These reactions were mild to moderate. In the main phase and the long term follow-up headache and nausea were also reported. These may be related either to the administration procedure, when appearing close to the injection, or be related to the LPLD disease, when appearing at later time-points.

All of these reactions were transient, lasting in general one or a few days. The following adverse reactions were considered certainly, probably or possibly related to AMT-010 or alipogene tiparvovec: burning/smarting feeling in thighs, stiffness or formication, pain or tiredness in the legs, moderate hypertension, fatigue and dizziness. Transient fever was noted across all studies, one of these events was classified as serious.

One subject presented a SAE termed "polyarthralgia of imprecise origin". This case is still under investigation and follow-up. Relatedness of this event to Glybera is currently considered unlikely but the case will continue to be followed. The risk of "late onset acute inflammatory process" has been included as a potential risk that may be related to the concomitant use of immunosuppressants.

The only other serious adverse event related to the administration of Glybera was a case of abnormal perfusion on V/Q scanning in a non-critically ill subject with thoracic pain, diagnosed as high probability of pulmonary embolism. Although possibly related to Glybera and classified as such this event is likely to be related to the disease since embolisms are a typical risk of the LPLD condition.

No pattern of significant change in any laboratory parameter was noted other than in the lipid parameters. No new risks were identified during the updates of the safety database.

The Annual Safety Report provided summarises the suspected serious adverse reactions reported globally in the four clinical studies (three interventional, one non-interventional) and one case (highly

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probable pulmonary embolism) was reported as a Suspected Serious Adverse Reaction as (highly) probably related to the use of Glybera.

Additionally, all fourteen unrelated SAE case reports received for these clinical studies are of special interest due to the ATMP nature of the product and therefore, the Annual Safety Report also discusses non-related SAEs occurring during the reporting period 25 June 2010 to 24 June 2011.

The clinical safety summary update issued on June 24, 2011, encompasses more than 5 years follow-up of treated patients and no new risks were identified during the updates of the safety database.

In the present gene therapy approach, the rationale for immunosuppression is three-fold:

- To reduce immune response to AAV vector, that could impair efficacy;

- To reduce the risk of transgene product being recognised by an activated immune system;

- To alleviate inflammation and its symptoms related to Glybera injection.

Since the immunosuppression treatment was limited to three months, associated risks are considered minimal.

An increased risk of infection must be carefully evaluated and monitored and even more in those patients with pre-existing liver or kidney disease. However, the risk of infection is modest in an otherwise healthy individual, and can be usually managed with antibiotic or antiviral treatment.

CAT position

1) Additional safety data provided

The CAT briefly discussed the above justifications on the additional safety data.

However it has to be emphasized that the re-examination procedure may be based only on the scientific data available when the Committee adopted the initial opinion. Even if the updated safety data were to be considered, outstanding issues would remain that would need to be addressed in relation to safety.

The CAT taking into account the recommendations from the ad hoc expert group, considered the proposal from the AMT 011.04 study overall acceptable, provided that the protocol is reviewed before the start of the study by the Scientific Advice Working Party/CAT/CHMP.

2) Grounds for refusal 3

It should be noted that the results presented by AMT in CT-AMT-011-03 are mostly (15/17 treated patients) obtained in patients with immunosuppression. It is noted that the reported case of polyarthralgia above discussed was not related to immunosuppression by the investigator.

Long term immunogenicity was addressed by testing anti-LPL antibodies. Anti-LPL antibodies were not detected in any of the patients.

The CAT considered that failure to apply the immunosuppresion treatment would represent a major change in the therapeutic protocol, possibly affecting patient outcome. With regards to concerns regarding the 12 weeks of immunosuppression, the CAT considered these concerns to be clinically manageable given the short term immunosuppression regimen proposed in addition to Glybera. The procedure of local intramuscular (IM) administration is also considered acceptable as 1) no major histological alterations were evident within the 3-5 years of follow-up and 2) no biochemical signs of

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muscle damage were detected. The safety profile of Glybera is considered acceptable, although the safety data base is limited.

In conclusion the CAT considered that the grounds related to immunogenicity have been addressed satisfactorily by the MAH and considered that the risk associated with the immunosuppression regimen are well addressed in the agreed Risk Management Plan and risk minimisation measures and the revised SmPC.

The agreed controlled distribution system, the measures defined in the risk management plan and the Specific obligations are considered adequate by the CAT to ensure appropriate control and use of Glybera under safe conditions.

CHMP position

The 12 weeks of immunosuppression is considered relatively short and therefore the associated risks are now considered minor. The concerns initially expressed would be considered solved if efficacy had been satisfactorily demonstrated.

At its plenary meeting, the CHMP also discussed the additional information provided by the Company on 19 and 20 October 2011

- ✓ The proposal of the company to provide interim data of AMT-011-004 study at the end of March 2012 for the 3 patients groups (6 patients in Glybera treated group, 6 LPLD non treated patients and 3 healthy volunteers).
- ✓ The commitment that no patients will be treated with Glybera before delivery/review and acceptance of the interim clinical study report, and prior information is given to the Agency.
- ✓ The proposal to define every single patient dose/pack as its own batch, which would need batch release approval by the EMA/Rapporteur.

The CHMP acknowledged the proposal of receiving interim data of AMT 011-04 study in March 2012. However the CHMP maintained its view that such additional data are considered critical and essential to be generated and assessed prior to possible approval of the drug.

The batch release as proposed by the applicant would require Official Medicine Control Laboratory (OMCL) batch release which is legally not foreseen for gene therapy products.

CHMP conclusion on benefit/risk

Taking into account the CAT recommendations and draft opinion, the arguments of the applicant presented at the oral explanation at CHMP and all the supporting data on quality, safety and efficacy, the CHMP is unable to establish a positive benefit/risk balance for Glybera in the claimed indication as defined by the CAT in its draft opinion.

Recommendation following re-examination

CAT Recommendation

Based on the arguments of the applicant and all the supporting data on safety and efficacy, the CAT re-examined its initial opinion and in its final opinion concluded by majority that the efficacy and safety

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of Glybera is sufficiently demonstrated in selected patients as defined by the restricted indication in patients diagnosed with LPL deficiency and suffering from at least one pancreatitis episode despite dietary fat restrictions. The indication is restricted to patients with detectable levels of LPL protein (see section 4.4).

Therefore, the CAT has recommended the approval of the granting of the marketing authorisation under exceptional circumstances for Glybera.

CHMP Recommendation

The CHMP, taking into account the CAT's recommendations, the arguments of the applicant presented at the oral explanation at CHMP and all the supporting data on quality, safety and efficacy, re-examined its initial opinion and in its final opinion concluded by majority decision that the safety and efficacy of Glybera is not sufficiently demonstrated, and therefore has recommended the refusal of the granting of the Marketing Authorisation under exceptional circumstances for Glybera.

The CHMP considered that:

> Whilst this approach is promising, CHMP concluded that there is currently insufficient evidence of efficacy from either clinical outcome data or an appropriate surrogate marker.
>
> Specifically,

- The data on pancreatitis is not considered robust, even recognizing the rarity of the disease. The retrospective analysis of pancreatitis data failed to provide sufficiently convincing evidence of efficacy in support of a clinically meaningful reduction in the incidence of pancreatitis. Pancreatitis rates during the run-in part of the trial were comparable to those seen after Glybera administration. The follow-up data on pancreatitis are limited and not sufficient in view of the relatively short duration of post-treatment follow-up and year to year variability in historical pancreatitis rates. It cannot be excluded that the apparent decrease of pancreatitis risk seen in patients treated with Glybera is due to factors other than Glybera (i.e. changes in lifestyle/diet). Therefore, it cannot currently be concluded that any changes seen in pancreatitis events were definitely attributable to Glybera.
- In the absence of robust clinical outcome information, data from an appropriate surrogate marker could have provided sufficient evidence of efficacy. However, there is currently insufficient evidence of persistence of LPL activity post treatment with Glybera. Furthermore, even accepting the pp-CMs as an alternative biomarker instead of the reduction in fasting TG, there is currently insufficient data on pp-CMs to demonstrate the efficacy of Glybera based on only 3 patients at 52 weeks (of the 27 patients enrolled in the clinical trial programme). Further data on pp-CMs are required to support the currently available data, (e.g. from study AM011-04 and/or additional data from patients who have already been treated with Glybera). Such additional data are considered critical and essential to be generated and assessed prior to possible approval of the drug. These data will further substantiate the current hypothesis on efficacy of Glybera based on the pp-CM levels as a biomarker.
- The immunosuppression regimen is considered relatively short and therefore the associated risks are now considered minor. The concerns initially expressed would be considered solved if efficacy had been satisfactorily demonstrated.

Furthermore, the CHMP, in light of the negative recommendation, is of the opinion that it is not appropriate to conclude on the new active substance status at this time.

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Divergent positions to the majority recommendation are appended to this report.

6. CAT assessment following the EC Request to CHMP dated 30 January 2012

6.1. *Background information*

Following the European Commission Standing Committee meeting held on 23 January 2012, with regard to the CHMP re-examination opinion of 20 October 2011 for Glybera, the European Commission sent a letter to the CHMP Chair dated 30 January 2012 asking the CHMP to assess the benefit risk of Glybera in patients with severe or multiple pancreatitis attacks.

Consequently, the CHMP adopted a List of Questions (LoQ) on 16 February 2012 to be addressed by the applicant as follows:

Question 1) The applicant is requested to confirm whether he supports the use of Glybera in a restricted indication in patients with severe or multiple pancreatitis attacks.

Question 2) Taking into account the data that have been submitted in the application (initial /re-examination), the applicant is requested to provide an overview by summarising and discussing the relevant data in support of such restricted indication. In his response, the applicant should take into account the expert panel adjudication of pancreatitis events (definite, probable, abdominal pain and other).

In particular it was pointed out by the Standing Committee that eight out of the seventeen patients from study CT-AMT011/03 had multiple (>8) pancreatitis attacks, some of them requiring ICU admission before Glybera treatment. Half of these patients were aged between 36 and 44 years. These patients have a long life expectancy and are potentially at high risk for developing further pancreatitis attacks.

6.2. *Assessment of the answer provided by the applicant*

Question 1

The applicant is requested to confirm whether he supports the use of Glybera in a restricted indication in patients with severe or multiple pancreatitis attacks.

The applicant confirmed that he supports the use of Glybera in a restricted indication in patients with severe or multiple pancreatitis attacks. The applicant's proposed indication for Glybera is:

"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)."

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Question 2

Taking into account the data that have been submitted in the application (initial /re-examination), the applicant is requested to provide an overview by summarising and discussing the relevant data in support of such restricted indication. In his response, the applicant should take into account the expert panel adjudication of pancreatitis events (definite, probable, abdominal pain and other).In particular it was pointed out by the Standing Committee that eight out of the seventeen patients from study CT-AMT011/03 had multiple (>8) pancreatitis attacks, some of them requiring ICU admission before Glybera treatment. Half of these patients were aged between 36 and 44 years. These patients have a long life expectancy and are potentially at high risk for developing further pancreatitis attacks.

Pancreatitis data

In response to the CHMP question, the applicant has presented a summary of data on 12 out of the 17 patients who received Glybera and were included in CT-AMT-011-03 based on the presence of multiple attacks and/or at least one episode of severe pancreatitis in the pre-treatment period as identified below:

- 5 patients suffered from 8 or more pancreatitis attacks and at least one severe attack;
- 3 patients suffered from 8 or more pancreatitis attacks;
- 4 patients suffered from at least one severe pancreatitis attack.

The assessment of the cases and classification of the pancreatitis attacks as presented above by the applicant is discussed in detail below in the pancreatitis results section.

The applicant has also provided a more detailed description of each of the 12 patients presented now based on the data acquired.

The response, based on a descriptive analysis of a subset of treated patients can be accepted as it covers the population referred to in the CHMP question. The population is somewhat heterogeneous, as the clinical aspects of those with multiple attacks as opposed to those with one severe attack can be different, making any generalisation challenging. No new data was to be submitted as part of this procedure following EC letter from 30 January 2012. The database of 12 patients, which forms a subgroup of the 27 patients that received Glybera, is relatively small, making definitive conclusions challenging. However, considering the rarity of the disease, the CAT considered by majority that the data are nevertheless relevant.

In order to adjudicate the abdominal pain events the following scheme was used in which definite pancreatitis attacks were diagnosed according to the Revised Atlanta Diagnostic Criteria:

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	Typical pain	Amylase/lipase >3xULN	Positive imaging	Amylase/lipase >1xULN but <3xULN	History of definite pancreatitis	Clinical judgement
Definite pancreatitis	X	X				
Definite pancreatitis	X		X			
Definite pancreatitis		X	X			
Definite pancreatitis	X	X	X			
Probable pancreatitis	X			X	X	X
Abdominal pain	X					X
Other						X

The diagnostic criteria as outlined above were previously agreed as it is consistent with the Atlanta criteria to diagnose definite pancreatitis. This is a conservative approach. It is possible that some episodes of pancreatitis were underestimated because of practical issues such as amylase estimation issues in the presence of TG, lack of availability of tests or a clinical diagnosis made without further testing considered necessary.

As for the blinding of experts, in the absence of a concurrent blinded control arm which would be ideal, the applicant's approach is acceptable as the only possibility. A concurrent control would have given more definitive information on the background incidence in untreated patients against which to compare the treated group.

The only possible control available is from the pancreatitis data from 5 untreated patients. Two of these patients had several attacks of pancreatitis during the period 2007-2010. As the numbers are small it is difficult to draw any definite conclusion about the background incidence. Further these patients did not have a long pancreatitis free interval before, also making comparison of the untreated group to the treated group difficult.

A detailed narrative for each of the 12 patients was submitted and this was considered sufficient to understand the background to each patient and to make an informed assessment of the data. The data on the incidence of pancreatitis in tabular and graphical form complement each other. The decision to leave certain events adjudicated as "other" is accepted as it would be difficult to interpret the clinical significance of these events. Therefore, the CAT considered that these events classified as "other" are not considered further in the discussion of the efficacy data.

It should be highlighted that results from lipid measurements (TG, PP-CM) are not included by the applicant in this response as this forms an important part of clinical assessment of these patients. Thus, the individual patient data is considered incomplete. The changes in lipids was the initial primary end-point of clinical confirmatory studies and would have been valuable as part of the individual patient data to make a proper assessment. However, the overall data were previously provided and assessed in the context of the previous opinions by the CAT and CHMP. Therefore, this approach is accepted.

Individual patient's benefit in the restricted patient population

The following information was extracted from the patient narratives and presented per patient by the applicant :

- Time-corrected incidence of total pancreatitis attacks ("definite pancreatitis" + "probable pancreatitis" + "abdominal pain" + "other") in pre-treatment period versus post-treatment period.

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- Time-corrected incidence of "definite pancreatitis" attacks in pre-treatment period versus post-treatment period;

- Time-corrected incidence of "probable pancreatitis" attacks in pre-treatment period versus post-treatment period;

- Time-corrected incidence of "abdominal pain" attacks in pre-treatment period versus post-treatment period;

- Number of pancreatitis attacks requiring ICU-admission and range of duration of ICU-stay in pre-treatment period versus post-treatment period;

- Number of pancreatitis episodes requiring hospitalization, time-corrected incidence of hospitalization, and range of duration of hospitalization in pre treatment period versus post-treatment period.

The time-corrected incidences for the pre-treatment period entails the time from the first reported episode per patient to Glybera treatment. For the post-treatment period the time from Glybera treatment to end of follow up is considered.

- ***CAT discussion***

As described previously, all 12 patients had one or more episodes of pancreatitis in the pre-treatment period.

It is considered that the classification provided by the applicant presented before is not fully adequate. Therefore the CAT considered the following classification:

- 6 patients suffered from 8 or more pancreatitis attacks;
- 6 patients suffered from 2 to 7 pancreatitis attacks.

The table below describes the pancreatitis attacks observed for each individual patient :

Table 1

Patient	Total pancreatitis pre Glybera	Diagnosis	Severity	Total pancreatitis post Glybera
	3	3 definite	all mild	0
	2	2 definite	all severe	0
	2	1 definite	severe	0
		1 probable	mild	
	2	2 definite	1 severe 1 mild	0
	8	7 definite	all mild	0
		1 probable	mild	
	3	3 definite	2 mild and 1 severe	0
	16	8 definite	6 severe + 2 mild	1*
		8 probable	1 severe + 7 mild	
	13	6 definite	2 severe + 4 mild	0
		7 probable	all mild	
	7	6 definite	1 severe + 5 mild	2 definite (both mild)
		1 probable	mild	
	14	10 definite	all mild	1 probable (mild)
		4 probable	all mild	
	24	16 definite	1 severe + 15 mild	0
		8 probable	all mild	
	8	6 definite	all mild	1 definite (mild)**
		2 probable	all mild	

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** Since this patient experienced one pancreatitis episode one week after Glybera administration, when no transgene expression is observed, this episode can be considered as occurring "pre Glybera Treatment".*

*** Associated with cholelithiasis leading to cholecystectomy*

Considering the prevalence of the disease ($1:1x10^6$), a sufficient power to detect a statistically significant reduction in pancreatitis events following treatment would require enrolment of 342 patients. This is clearly unfeasible. The statistical analysis used by the Applicant during the re-examination procedure (on 27 patients) is considered adequate from a statistical point of view, however it was not able to eliminate the potential bias due to high variability of the observed event. The variability-induced bias could only be eliminated if a higher number of subjects were included in the analysis which is not feasible in view of the restricted numbers of pancreatitis cases.

To facilitate the analysis of data, all episodes of definite and probable pancreatitis occurred in each patients were plotted in the two figures below (Fig.1 and Fig. 2).

As shown in Figure 1, 6 out of 12 patients with multiple pancreatitis attacks experienced ≥ 8 definite or probable pancreatitis episodes before Glybera treatment. Out of these six patients, four patients had 16-13-14-24 episodes, respectively.

Out of 12 patients experiencing multiple pancreatitis attacks during the pre-treatment period, 4 patients had definite or probable pancreatitis attacks after Glybera.

For one patient, the post-treatment pancreatitis attack was associated with imaging evidence of cholelithiasis, and cholecystectomy was performed seven weeks later. For one patient with a single episode of definite pancreatitis post- Glybera, the presence of cholelithiasis and resulting cholecystectomy makes interpretation difficult. The single episode of pancreatitis could have been caused by chylomicronaemia, in which case, Glybera was not effective. On the other hand, it could have been caused by gall stones, in which case, the absence of further attacks in the long run might support a role for Glybera in prevention of pancreatitis.

For one patient, the 2 definite post-treatment pancreatitis attacks were reported to be triggered by severe diet violation and alcohol consumption.

Another patient declared a very low (50%) compliance with the restricted diet and experienced alcoholic hepatitis.

The last patient experienced one pancreatitis attack one week after Glybera treatment. The CAT discussed the interpretation of the result regarding this patient. It was considered that since the pancreatitis episode occurred at a time when no transgene expression is observed, this episode could be considered as occurring "pre-treatment."

Thus, the CAT concurred with the applicant that this does not reflect any failure of Glybera as onset of efficacy takes 3-4 weeks and highlighted that there is also no biologically plausible reason to believe that Glybera could have caused it. This patient had several episodes of pancreatitis in the past and this is more likely to be part of the natural history of the disease. Therefore, this patient can be excluded from the final analysis and conclusions.

When <u>equal pre- and post-treatment periods</u> of observation are considered (Fig. 2), from a clinical perspective, 6 patients could be considered to have experienced pancreatitis episodes in the pre-treatment phase whereas 3 patients had pancreatitis attacks after Glybera. The description of each patient is provided below:

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One patient experienced 4 episodes (probable pancreatitis) before treatment and no episode after Glybera treatment;

One patient had 1 definite pancreatitis episode in the pre-treatment period and 1 probable pancreatitis episode following Glybera;

One patient had 4 definite pancreatitis episodes in the pre-treatment period vs 2 definite pancreatitis events post-Glybera treatment; both post-treatment episodes were triggered by severe diet violation including alcohol consumption;

One patient had 2 probable pancreatitis episodes and no episode after Glybera;

One patient had 1 episode of definite pancreatitis one week after Glybera administration, at a time point when no transgene expression is observed;

One patient had 1 episode of definite pancreatitis pre-treatment and no episode post-treatment.

Figure 1 - Definite and probable pancreatitis events per patient

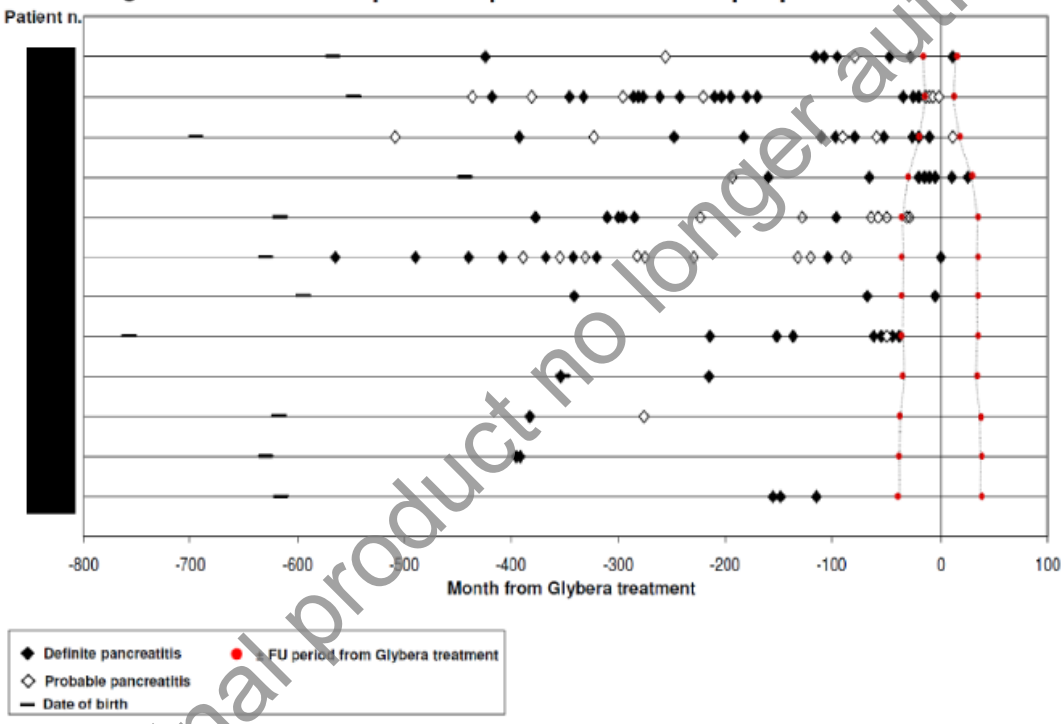

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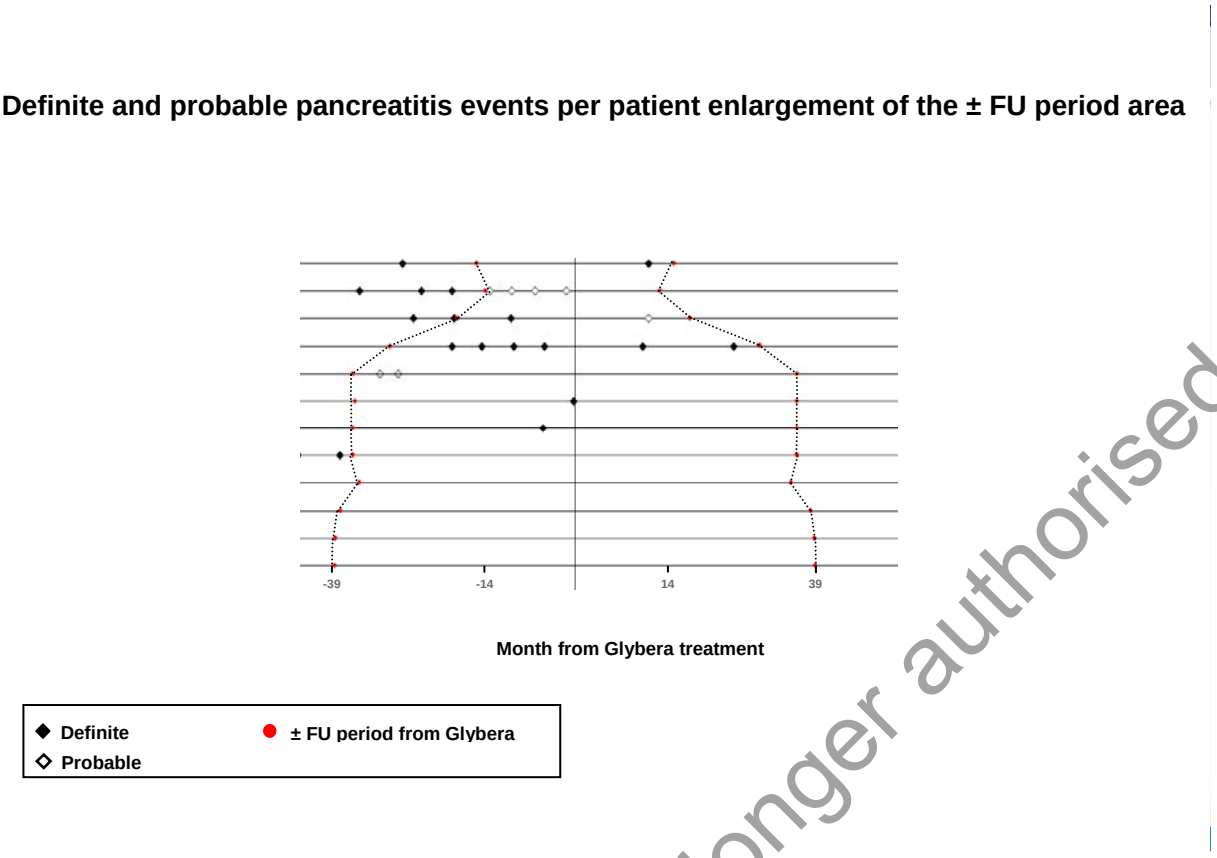
Figure 2 : Definite and probable pancreatitis considering equal pre and post treatment periods



Pancreatitis data followed for a period ranging from 1.19 to 3.26 years are presented from the analysis of individual patient data in the 12 Glybera treated patients who experienced multiple or severe pancreatitis attacks.

When comparing the mean yearly incidence of pancreatitis in the full life period pre-Glybera with that post-Glybera, there is a trend in the reduction of definite pancreatitis risk to zero attacks in 9 out of 12 patients.

This comparison however does not take into account pre and post treatment period which are not equivalent over time as the post treatment period is shorter than the pre-treatment period. However, the CAT considered that there is no alternative, since the pre-treatment period is considerably long, and thus a requirement for an equally long post-treatment follow-up is impossible. The CAT considered that three year data, which have now been achieved for the majority of patients, is considered a favourably long time period for a pre-approval setting.

When considering the patients with no pancreatitis episode post Glybera, all patients except 1 had a follow-up for about 3 years and one for 62 weeks.

Of these patients who did not have any post-treatment attacks of pancreatitis, 4 might be considered as possible responders on an equal period comparison basis. Of these, the two who are stated to have gained weight make efficacy of Glybera probable.

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Intensive Care Unit (ICU) rates and hospitalisation

ICU admissions

As shown in the table below, in total 7 patients with multiple pancreatitis attacks had ICU admission for pancreatitis before Glybera treatment, while no ICU admission was recorded post-Glybera. Two patients experienced 1 pre-treatment ICU admission during the temporal window consisting of equal pre- and post-treatment periods and no ICU admission after Glybera. Four patients were admitted to ICU for abdominal pain prior to Glybera treatment, whereas no ICU admission for abdominal pain was recorded post-Glybera.

ICU admission for definite/probable pancreatitis and abdominal pain

Table 2 – ICU admission for definite/probable pancreatitis and abdominal pain

Patients		Definite Pancreatitis (duration range)	Probable Pancreatitis (duration range)	Abdominal Pain (duration range)	Other (duration range)	Total ICU admissions
	Pre Glybera	2 (8 days)	0	1 (29 days)	0	**3**
	Post Glybera	0	0	0	0	0
	Pre Glybera	1 (13 days)	0	0	0	**1**
	Post Glybera	0	0	0	0	0
	Pre Glybera	2 (2-NA)	0	0	0	**2**
	Post Glybera	0	0	0	0	0
	Pre Glybera	5 (3-14 days)	1 (3 days)	2 (2-3 days)	1 (3 days)	**9**
	Post Glybera	0	0	0	0	0
	Pre Glybera	1 (NA)	0	0	0	**1**
	Post Glybera	0	0	0	0	0
	Pre Glybera	1 (10 days)	0	0	0	**1**
	Post Glybera	0	0	0	0	0
	Pre Glybera	0	0	1 (2 days)	2 (4-NA)	**3**
	Post Glybera	0	0	0	0	0
	Pre Glybera	2 (2-3)	2 (NA)	1 (NA)	0	**5**
	Post Glybera	0	0	0	0	0

Hospitalisations

Ten out of 12 patients had acute abdominal pain episodes requiring hospital admission pre Glybera treatment.

Four of these patients had a total of 1 pre-treatment episode of abdominal pain requiring hospital admission, whereas 6 patients experienced from 2 to 56 episodes of hospital admission for pre-treatment abdominal pain.

All pancreatitis events have required hospitalisation. The figure below reports the total number of hospitalisation both for pancreatitis and for abdominal pain episodes.

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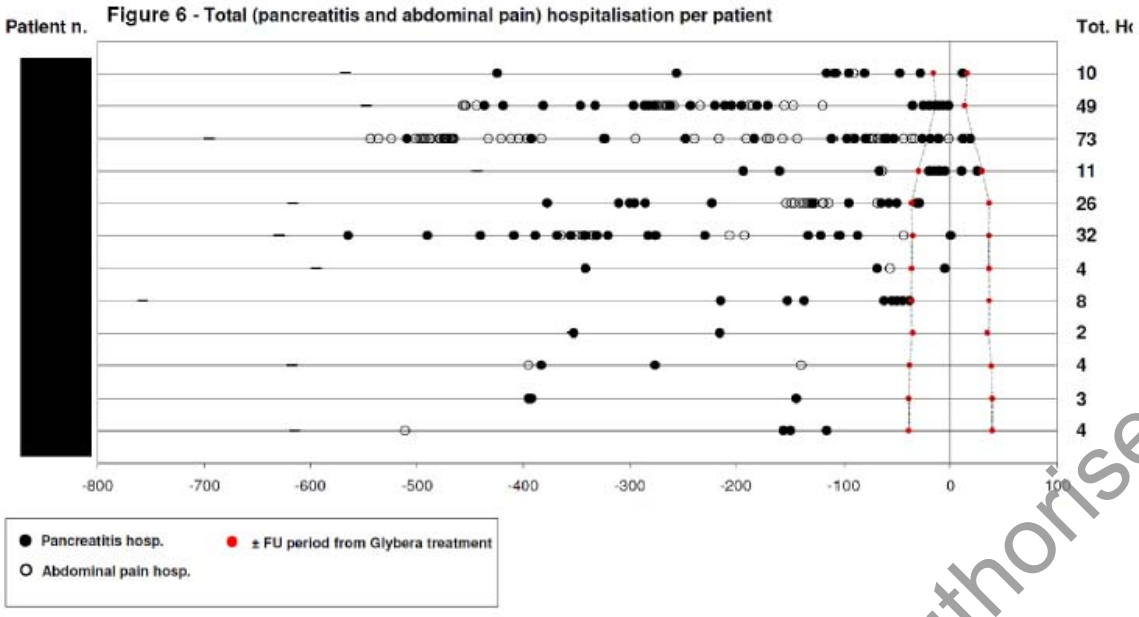

Following Glybera treatment, only 1 patient had 2 post-treatment episodes of abdominal pain leading to hospital admission. The same patient had 56 pre-treatment hospital admissions, declared a very low (50%) compliance with the restricted diet and experienced alcoholic hepatitis.

CAT discussion

Apart from two patients, where the ICU admission was in the recent pre-treatment period, the admissions to ICU for other patients appeared to be in the distant past, several years before Glybera administration. In addition, the clinical management practice has continually evolved towards a reduction in hospitalisation, reduction in length of stay and other new ways of managing such as "High-dependency medical ward" as opposed to ICU. Therefore, the limitations of these data are acknowledged. However, these data parallel the pancreatitis episodes as described above and complement the pancreatitis data by providing additional evidence to support efficacy.

LPLD associated features

The applicant has presented data on diet, body weight, presence/ absence of diabetes mellitus and other pathologies.

Diabetes

Pancreatic insufficiency in LPLD patients may impact on the clinical outcomes through development of diabetes mellitus and diabetes related complications. In the limited data set of patients with multiple pancreatitis attacks enrolled in study CT-AMT-011-03, as many as 5 out of 12 patients developed diabetes mellitus. These data support the need for a specific therapy in this disease which could reduce the incidence and severity of pancreatitis.

While the limitations of these data are acknowledged, these however need to be taken into consideration in the overall efficacy data generated in the restricted patient population.

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Weight gain

6 of the 12 patients are reported to have gained weight, but two of these were marginal weight gain. Of the 4 patients with weight gain of 2 Kg to 7 Kg, 3 had no attacks of pancreatitis and 1 had a further attack of pancreatitis, in association with cholelithiasis. The applicant argues that evidence of weight gain is a favourable sign as it indicates that patients could increase dietary fat intake. Although it is acknowledged that the increase in weight gain could be indicative of an increase quality of life, no direct evidence, e.g. in form of dietary record, has been provided.

The CAT considered in its majority that the data on weight gain provide data that supports efficacy, although it is acknowledged that the data is based on small numbers. Nevertheless, the weight gain observed in 3/6 patients is considerable, given that patients are usually hampered by low weight.

Diet compliance

While compliance with diet can be effective in controlling the clinical manifestations of the disease in some cases, in practice, it is quite challenging and dietary failures are very common thus leading to acute attacks of abdominal pains or pancreatitis even in patients undergoing a less severe clinical course of the disease. Difficulties in complying with the diet was particularly evident in some of the patients enrolled in study CT-AMT-011-03. Glybera treatment is intended to be administered together with a low-fat diet. A dietary record would have provided useful information. However, it is acknowledged that the information related to diet is very limited in this application, thus contributing to the difficulty in the assessment of the efficacy data. This information was discussed at CAT and considered difficult to obtain in such a rare disease with potential bias in the interpretation of the data. The CAT considered that for optimal planning of a post-authorisation follow-up further discussion as regards recording of diet in a feasible way is necessary.

LPL activity in the injected muscles

The applicant also carried out 8 muscle biopsies in the 7/12 patients, in those who consented for the procedure, 14-52 weeks after Glybera administration. The majority (6/8) were carried out at 25-26 weeks, except for one patient where it was done twice, first at 18 weeks and another at 52 weeks. The biopsies were tested for expression of vector DNA, LPL activity and LPL protein mass.

The results presented show that all the injected muscle biopsies showed evidence of vector DNA expression.

LPL mass was detectable in 6/7 patients including at 52 weeks for the patient who had a second biopsy performed, LPL activity was observed in 5/7 patients and 7/7 patients shown enzyme function (Oil Red O staining). (refer to page 44 of the report for the overall population data)

Presence of vector DNA and LPL activity protein/ mass can be described as a local PK/PD measure of persistence of vector and continued gene expression. The results indicate such persistence at 26 weeks and beyond in most samples obtained in these patients. LPL activity was measured at Dr Brunzell's laboratory in the USA. All 12 patients were reported to have 0% LPL activity in the plasma at inclusion.

With the limited dataset available, there is strong suggestion that vector and gene expression persist for at least 6 months. Longer term data would be informative from a scientific point of view, but obtaining repeated muscle biopsies is impractical and invasive and not considered an option in the clinical setting. During the Oral Explanation, the Applicant presented data on Oil Red O staining in one muscle biopsy, indicating lipid uptake in injected muscles only. This can only be explained by a functioning enzyme following expression of the gene delivered by Glybera.

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In summary, the CAT was of the view that sufficient evidence of enzyme activity was obtained in muscle biopsies.

Overall discussions regarding efficacy data

The decrease in the number of pancreatitis attacks is considered to be a clinically meaningful endpoint as it directly correlates with disease severity resulting in serious consequences for patients with LPLD. Reduced risk of pancreatitis represents a true benefit for patients as it translates into a lower risk of being hospitalised and a lower risk to get into Intensive Care Unit (ICU).

Overall data on hospitalization clearly indicate the extremely poor quality of life experienced by these patients aged between 32-65 years with 4 patients experiencing 70, 49, 32 and 26 pre-treatment hospitalizations during their life prior to Glybera treatment, and 8 patients experiencing from 2 to 7 pre-treatment hospitalization during their life prior to Glybera treatment. Further, pancreatic insufficiency in LPLD patients may impact on the clinical outcomes through development of diabetes mellitus and diabetes related complications. In the limited data set of patients with multiple pancreatitis attacks enrolled in study CT-AMT-011-03, as many as 5 out of 12 patients developed diabetes mellitus. These data support the need for a specific therapy in this disease which could reduce the incidence and severity of pancreatitis.

A consistent trend in the reduction of pancreatitis risk emerges from the analysis of individual patient data in 9 out of 12 Glybera treated patients who experienced multiple or severe pancreatitis attacks, followed for a period ranging from 1.19 to 3.26 years. Considering the rarity of the disease, the highly variable pattern of onset and presentation of pancreatitis in LPLD patients, and the limited number of patients meeting the restricted criteria for treatment requested by CHMP, a patient-based description of all pre- and post-treatment pancreatitis events is considered acceptable. In order to interpret these data, it is worth noting that the Applicant had previously sought an expert group opinion on what could be considered a clinically relevant effect of Glybera treatment.

The evidence generated by overall efficacy data, although hampered by the paucity of the observations and by the disproportionate duration of the pre- and post-treatment periods, suggests that Glybera leads to a clinically relevant reduction of pancreatitis risk in these patients. When <u>equal pre- and post-treatment periods</u> of observation are considered:

- 6 patients experienced a total of 14 pancreatitis episodes in the pre-treatment phase. These 6 patients include the patient who had an episode of pancreatitis attack one week after Glybera when no transgene expression is observed. This episode of pancreatitis attack is thus considered as occurring pre-Glybera treatment. Only 3 out of these patients had pancreatitis attacks after Glybera, including one in association with cholelithiasis leading to cholecystectomy:

- 2 Patients experienced 1 pre-treatment ICU admission and no ICU admission after;

- When looking at hospitalisation rates, these data generally mirror the pancreatitis data to a large extent, as would be expected.

Glybera treatment is intended to be administered together with a low-fat diet. Interestingly, 3 patients who experienced weight gain after Glybera treatment had no pancreatitis attacks or acute abdominal pain.

Based on post-prandial chylomicronemia as accepted surrogate marker, Glybera showed efficacy in 5 out 5 patients enrolled in study CT-AMT-011-02 tested at 14 weeks, and in 3 out of 3 patients tested at 52 weeks. A consistent correlation in Glybera effect on pancreatitis, post-prandial chylomicronemia and LPL mass expression is shown in 3 patients with multiple pancreatitis attacks and 1 patient with

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one pancreatitis attack pre-Glybera treatment. For three of these patients post-prandial chylomicronemia data are available both at 14 and 52 weeks, showing a persistent effect of Glybera.

Data on enzyme expression and function (including Oil Red O staining as presented during the oral explanation) in one histology/biopsy data injected and non-injected muscles, in conjunction with other relevant clinical and paraclinical data support functional expression. In a totality of evidence approach, the majority of CAT considered efficacy to be sufficiently established to allow for a positive benefit-risk estimation in an exceptional circumstances approval setting. The CAT by consensus was of the opinion that further data need to be generated, and the majority of CAT considered that this should be done post-authorisation.

Persistence of the therapeutic effect

Glybera consists of a non-integrating adeno-associated virus (AAV) vector construct, which confers the episomal expression of the overfunctional LPLS447X gene. The treatment rationale is based on the theory that, by adding an extra copy of the over-functional LPL gene into muscle cells lacking catalytically active lipoprotein lipase, Glybera could restore metabolic functions, by normalising the elimination of triglycerides from large circulating chylomicron particles. According to the Applicant Glybera is intended as a single treatment of a life-long disease. This raises the issue of the long-term maintenance of the effect. AAV vectors hold great promise for gene therapy and have become the vector of choice for in vivo gene transfer (Grieger JC and Samulski RJ. 2012; High KA and Aubourg P, 2011). Although a site of insertion of human chromosome 19 was originally identified, this turned out to be exceedingly rare, thus in practice AAV are considered non integrating vectors. While this eliminates any problem of insertional mutagenesis, AAV vectors, that cannot replicate, tend to be diluted at each cell division, and thus are rapidly lost by actively dividing cells. In contrast, they may persist for years in non dividing or slowly renewing tissues such as muscle and liver (see Jiang et al. 2006; Buchlis et al. 2012).

As expected with AAV vector therapies, the host immune response, both humoral and cellular is directed against the vector proteins and, as in all cases of null mutations, against the therapeutic gene that is a novel antigen for the host. Moreover neutralizing antibodies, consequence of previous infections, are already present in a large fraction of the human population (Rogers GL et al. 2011; Mingozzi F and High KA. 2011) and in such case, vector administration may be ineffective. Even when a pre-existing response is not present, the host will mount an immune response to the vector so that in any case a second administration would be impossible. However, there are many different serotypes of AAV, some less common in the human population, so that the vector type may be chosen on the basis of the immune situation of the patient and a second administration may be possible using a vector derived from a different serotype (Gao G, et al., 2011). Interestingly, it was reported that a transient immune suppression, at the time of vector administration, greatly reduces the immune response to the vector (Wang Z, and Kuhr CS, 2007). However, this is not expected for Glybera since only one series of multiple IM local injection is planned.

The literature reports numerous examples of long-term persistence (years) of AAV vectors and expression of their therapeutic gene product in different animal species including primates. On the other hand, there are also numerous examples of progressive reduction of the transgene expression up to return to pre-transduction levels, and this is usually ascribed to the development of an immune response. However, most of rapidly accumulating evidence from clinical trials (Buchlis et al. 2012; Zhang P, and Sun B, 2012 [Epub ahead of print]; Nathwani AC et al. 2011 ; Flotte et al., 2011; Mendell JR et al. 2010; Maguire AM et al., 2009; Brantly ML and Chulay JD. 2009; Jiang et al. 2006) supports the evidence of long term expression, despite the presence of a variable immune response.

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In the specific case of Glybera, the long-term persistence of postprandial chylomicron level reduction, though not at the initial level and available only in few patients, suggests that a major immune response has not occurred and, in the absence of SAE, the protocol is considered to be safe and efficacious, with no obvious reasons to hypothesize rapid loss of activity of the transgene.

In addition, the applicant proposes, as a post-authorization commitment, to further assess postprandial CM metabolism as surrogate marker of successful LPLD treatment with Glybera and will be done in the post approval setting as defined in the Specific Obligations.

Conclusion on maintenance of the therapeutic effect

On the basis of the above considerations, the CAT by majority considered that although the data for post-prandial chylomicronemia is limited, overall evidence seems to indicate persistance of activity of the transgene for a reasonably long time period. However, additional data for the demonstration of long-term efficacy of Glybera, is considered necessary, but it is acknowledged that, given the extreme rarity of the disease and the flunctuation in the temporal presentation of pancreatitis attacks, it can be showed only by post-marketing data. The CAT by majority considered that a follow-up of three years, as obtained now in the majority of patients (8/12), is a sufficiently long post-therapy observation period in a pre-authorisation setting. A detailed program of post-marketing studies has been agreed by the Applicant and is illustrated in section 8 of this assessment report. These data will further substantiate long term efficacy of Glybera, which will be further assessed through regular reports (PSURs and Annual reassessments)

Clinical safety data in the restricted patient population

One patient was reported to develop a related SAE, pulmonary embolism (PE), as demonstrated by radiography and a V/Q scan and was treated for it. The occurrence of pulmonary embolism is likely to be related to the administration of multiple IM injections of Glybera. This is a potentially life-threatening complication. While this cannot be completely prevented, steps should be taken in such a situation to minimise the risk with measures such as mobilisation and, if necessary, consideration of anticoagulation administration in line with usual standard of care. Appropriate information has been included in the SmPC in this regard.

Most patients had pre-existing antibodies to AAV, which is not unexpected, but developed a substantial increase in antibody levels, in spite of the 12 week immunosuppressive therapy. The potential impact of this finding in clinical practice is considered to be appropriately covered in the proposed SmPC.

In the muscle biopsy data presented, the presence of inflammatory reaction appears specific to injected muscles and can be interpreted as specific against Glybera. However, this did not result in abolishing vector DNA expression or LPL activity, both of which are present in the majority of samples.

In relation to findings observed in the non clinical data related to muscle toxicity, information is provided in the SmPC and a contraindication in this regard has been included in the SmPC section 4.3. The data regarding tumorigenicity do not substantiate a concern. The available evidence taking all available data and literature into account suggests that the risk is either absent or likely to be very low and of little clinical relevance in humans.

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Even though no non clinical data were presented in the restricted indication, the CAT considered that the non clinical data in particular findings identified during the initial application are adequately reflected by the information provided in the SmPC sections 4.6, 5.3 and 4.8 for related clinical data.

Risks associated with 3-month course of immunosuppression

In the present gene therapy approach, the rationale for immunosuppression is three-fold:

- To reduce immune response to AAV vector, that could impair efficacy;

- To reduce the risk of transgene product being recognised by an activated immune system;

- To alleviate inflammation and its symptoms related to Glybera injection.

Moreover, in order to prevent immune response against the transgene protein, treatment is restricted to patients with detectable levels of LPL protein.

Since the immunosuppression treatment was limited to three months, associated risks are considered minimal. An increased risk of infection must be carefully evaluated and monitored and even more in those patients with pre-existing liver or kidney disease. However, the risk of infection is modest in an otherwise healthy individual, and can be usually managed with antibiotic or antiviral treatment. Appropriate information has been included in the product information in this regard.

The rationale and need for the 3 month course of immunosuppressive regimen after administration of Glybera is accepted as it corresponds to the time where the immune system would prevent the gene therapy approach to work properly.

Long term immunogenicity was addressed by testing anti-LPL antibodies. Anti-LPL antibodies were not detected in any of the patients.

A formal proof of the immunoregimen effectiveness would require a head-to-head comparison of patients with and without such treatment. This is considered challenging for this very rare disease.

However the applicant will extend the safety information regarding potential immune response in patients treated with Glybera as requested in the post authorisation setting through the registry.

This will also include re-assessment of potential anti-LPL response, follow up on antibody and T-cell responses will further substantiate the available data.

The safety database is small, which cannot exclude adverse events other than those that will occur commonly. Only 13 patients received the intended commercial dose. Of these, many were followed up for up to 3 years.

In conclusion, on the basis of available information, there are no major safety issues that will preclude approval.

7. Overall CAT and CHMP discussion on the restricted patient population

CAT discussion (overall approach and ground for refusal related to pancreatitis data adopted in October 2011 by CHMP)

The CAT had an extensive discussion on the overall evidence provided in support of the quality, safety and efficacy data assessed for Glybera with a "totality of evidence approach" concept in mind.

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The Glybera application also needs to be considered in the context of an extremely orphan indication with very limited patients together with a new emerging era of gene therapy medicinal products in clinical practice together with a limited but evolving scientific knowledge. Taking all this into account, and compared to other "new concepts" in the past, (for example monoclonal antibodies), it may be unrealistic to expect a similar level of evidence for the demonstration of quality, safety and efficacy and the overall benefit/risk as for "classical" medicinal products.

As published in the literature, potential risks associated with the use of AAV vector systems can be considered as minimal.

Most of the rapidly accumulating evidence from clinical trials (Buchlis et al. 2012; Zhang P, and Sun B, 2012 [Epub ahead of print]; Nathwani AC et al. 2011 ; Flotte et al., 2011; Mendell JR et al. 2010; Maguire AM et al., 2009; Brantly ML and Chulay JD. 2009; Jiang et al. 2006) supports the evidence of long term expression, despite the presence of a variable immune response.

Even though publications are generated in a different indication, the general scientific knowledge of AAV vectors has increased in particular with regard to long term expression of protein and knowledge related to long term safety of AAV vector therapies. These data should also be taken into consideration for Glybera using a broader approach.

However, it was emphasized that these considerations should not set a precedent for standards for future AAV- based gene therapy products and that each individual application should be looked at in the light of the existing knowledge in the field at a given point in time.

The CAT also highlighted that the methodological issues and inconsistencies observed in the Glybera application now considered solved, should not undermine the need for highly designed development plans and well performed clinical studies for other AAV based gene therapy medicinal products in the future.

With reference to the restricted patient population studied, the majority of CAT considered that all clinical data are favorable (with the exception of Quality of Life parameters; however, the scale chosen was previously already considered to be unsuitable for this clinical condition and it is considered that other data such as weight gain could be considered as an indirect marker of a better quality of life). Previous regulatory decisions were taken for orphan medicinal products without requiring formal statistics for feasibility reasons (although it was recognized that it might have been more straightforward to conclude on efficacy in those cases).

Nevertheless, the limited efficacy and safety data is acknowledged, as pancreatitis data are available for 12 patients only of which 9 are considered pancreatitis free post Glybera treatment. However, considering the limitations of the retrospective analysis, the pancreatitis data are considered sufficiently robust, in particular taking into account the rarity of the disease in the restricted patient population suffering from severe or multiple pancreatitis attacks, thus the majority of CAT considered the reduction in the incidence of pancreatitis, ICU hospitalisation data clinically meaningful. The follow-up data on pancreatitis up to 3 years is also sufficient even considering year to year variability in historical pancreatitis rates. Furthermore, convincing supportive data on weight gain and ICU hospitalization have been provided.

Therefore the CHMP grounds adopted in October 2011 related to the pancreatitis data are considered solved in view of the data analysed for the restricted patient population.

CHMP discussion (overall approach and ground for refusal related to efficacy (pancreatitis and surrogate marker) adopted by CHMP in October 2011)

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The CHMP took into account the CAT scientific discussion and recommendation related to the pancreatitis data and other supportive efficacy data in the restricted patient population. Acknowledging the limited dataset in the sub group of 12 patients with severe or multiple pancreatitis attacks, the CHMP discussed the pancreatitis results on the basis of individual patient data.

Final robust conclusion on pancreatitis efficacy data is considered difficult in particular in view of historical comparisons and limitations of the data. This was discussed within the Committee with divergent views expressed.

The CHMP overall agreed that, when considering the equal pre- and post-Glybera treatment observation periods, a total of 13 pancreatitis episodes in 7/12 patients (including one pancreatitis attack occurred one week after Glybera administration when no trans- gene expression is expected and can be considered pre-treatment from a clinical stand-point) in the pre-treatment phase versus 4 episodes in the post treatment phase were observed, 3 out of the seven patients being pancreatitis free, and one additional patient experiencing no pancreatitis episodes after the single pancreatitic attack occurred one week after Glybera administration. These data are supported also by the weight gain recorded in 3 patients, suggestive of diet violation which was not followed by subsequent pancreatitis episodes or acute abdominal pain.

Further evidence of efficacy is derived by the observed reduction in hospital admissions and ICU stay suggested in patients treated with Glybera. In total, 7 patients with multiple pancreatitis attacks had ICU admission for pancreatitis before Glybera treatment, two of which experienced ICU admission in the equal follow-up period pre- and post-Glybera treatment, while no ICU admission was recorded after Glybera.

Furthermore, the CHMP considered the argumentation provided by the applicant in the oral explanation and the CAT detailed scientific review which provides further evidence of efficacy, in particular the LPL mass observed in 6/7 patients, LPL activity in 5/7 patients and 7/7 patients in whom enzyme function was observed as demonstrated by lipid uptake and who also showed vector DNA expression.

The CHMP agreed that these data are relevant, thus contributing to reinforce the robustness of the efficacy in the restricted patient population.

The CHMP, in reaching its conclusion, took into consideration the extreme rarity of the condition and the high degree of unmet medical need, particularly in patients with severe or recurrent pancreatitis events.

In reviewing the evidence to support authorisation under exceptional circumstances, the CHMP considered the totality of the evidence, as proposed by the CAT, given that each component of the data supporting efficacy was subject to intrinsic limitations, and agreed that each element of the data supporting efficacy should not be considered in isolation.

Looking at the totality of the available evidence for efficacy, the CHMP considered

- the persistence of LPL activity in patients who had had biopsies (8 biopsies performed in 7 patients; one patient had two biopsies, the first at 18 weeks and the second at 52 weeks),

- the evidence of an effect on lipids, in particular the post prandial CM, (in 5/5 patients at 14 weeks and 3/3 patients at 52 weeks),

- the evidence presented on the reduction in the rate of pancreatitis.

and concluded by majority, that there was sufficient evidence to confirm a positive effect on Glybera in this sub group of severe patients with a high degree of unmet medical need.

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In conclusion, the 2 negative grounds related to efficacy, previously adopted for the broad indication are considered resolved by the CHMP in its majority, when considering the restricted indication and the unmet medical need.

CAT discussion (surrogate marker ground for refusal adopted in October 2011 by CHMP)

The clinical data are further supported by biological marker data showing a convincing reduction in post prandial chylomicronaemia in 5/5 patients at 14 weeks and 3/3 patients at 52 weeks.

The CAT considered the data on post prandial chylomicrons sufficient, and highlighted that the use of ppCM as a surrogate endpoint was considered acceptable by the Ad hoc Expert Group even though not fully validated. Furthermore, taking into consideration the argumentation provided by the applicant during the Oral Explanation, the chylomicrons test methodology and assay used performed by the applicant is considered adequate. As highlighted by the applicant during the Oral Explanation, measurement of post prandial CM at baseline is required, thus no control data in untreated patients would be requested post approval. The negative grounds related to the biomarker data adopted by the CHMP in October 2011 are thus considered solved.

On the basis of the above considerations, it is considered that, although the follow-up period for post-prandial chylomicronemia is short, overall evidence from the literature seems to indicate persistance of activity of the transgene for a resonably long time period (Buchlis G. et al. 2012, Jiang H. et al. 2006). However, the demonstration of long-term efficacy of Glybera, is considered necessary. It is acknowledged that, given the extreme rarity of the disease and the fluctuation in the temporal presentation of pancreatitis attacks, this can be showed only by the provision of post-marketing data. A detailed program for the collection of post-marketing data has been agreed by the Applicant to further support the currently available data and will be obtained in the clinical trial (at baseline and every 12 months) from patients followed in the post surveillance programme.

These post- marketing pp-CM data will further support the currently available efficacy data of Glybera together with pancreatitis and hospitalisation data collected as part of the long term surveillance programme. A collection of these data over 15 years has been requested in order to obtain sufficient information over time, taking into consideration variability of data and natural evolution of the disease. The very limited number of patients to be treated and restricted access programme in place by the company with adequate traceability and individualised pack provided to the patients will ensure standardisation of information and minimisation of risks. The restriction of the indication is justified and strengthens the control for such a complex product.

CHMP discussion (overall approach, surrogate marker, changes introduced related to CM)

The CHMP took into account the CAT scientific argumentation and argumentation provided by the applicant in the Oral Explanation. Looking at the totality of evidence, and considering the restricted indication of more severely affected patients, the grounds previously addressed related to surrogate marker are considered solved (see previous CHMP discussion).

In addition, the CHMP discussed the need for monitoring of CM at baseline and after 12 months as proposed in the draft SmPC proposed by the CAT. The procedure associated with the CM measurement, including the need for a low fat standardised meal, was discussed and considered not necessary at an individual patient level as it would not influence further treatment as Glybera is to be given only once.

Furthermore, the additional CM data to be collected through a controlled study will be robust enough and are considered sufficient to further substantiate the efficacy in the post authorisation setting. In

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addition, a minimum of enrolment rate of 4 patients per year is introduced for the CM study, together with a study start date of July 2013 to ensure regular collection of data and reporting in a limited timeframe, enabling re-assessment of the benefit/risk on a yearly basis, according to the regulatory framework established for products authorised under exceptional circumstances.

CAT discussion (safety negative grounds adopted by CHMP in October 2011)

With regards to safety, the immunosuppression regimen is considered relatively short and therefore the associated risks considered solved and manageable in the clinical practice.

In the specific case of Glybera, in view of the long-term persistence of postprandial chylomicron level reduction, although not at the initial level and admittedly available only in few patients, it suggests that a major immune response has not occurred and, further to the absence of SAEs, the protocols considered to be safe and efficacious, with no obvious reasons to hypothesize rapid loss of activity of the transgene.

Furthermore, the concerns related to immunosuppression regimen are sufficiently addressed in the SmPC such as recommending 12 months barrier contraception after Glybera treatment. The existing safety database in 27 patients is considered sufficient with minor risks associated with Glybera administration. Consequently the CHMP grounds adopted in October 2011 related to safety/efficacy are considered sufficiently addressed.

CHMP discussion (safety negative grounds adopted by CHMP in October 2011, changes introduced by CHMP related to safety)

In view of the efficacy being demonstrated in the restricted indication of more severe patients suffering from severe or multiple attacks, the safety is now considered acceptable and concurs with CAT that the CHMP grounds adopted in October 2011 related to safety/efficacy are considered sufficiently addressed.

The CHMP, introduced measurement of immune response at regular time points (baseline, 6 months and 12 months) in the proposed CM study, instead of collecting these data through the registry as proposed in the CAT opinion. This will ensure regular collection of safety data related to immune response in a controlled manner and in a limited timeframe.

Re-assessment of the immune response of all patients previously treated in study CT-AMT-011-01 using a newly validated assay agreed with CAT/CHMP will also be done providing further safety data in relation to immunogenicity.

In addition, the MAH following the Oral Explanation proposed to introduce immune response measurements as standard practice in the SmPC in section 4.2 at regular time points (baseline, 6 months and 12 months). This was considered acceptable by the CHMP.

CAT discussion (overall discussion)

The CAT emphasized that the efficacy database could only be completed in the post-authorisation setting for such a rare disease and considering the even more rare restricted indication. Thus approval under exceptional circumstances is justified and the limited efficacy and safety data available considered sufficiently robust. Furthermore the post marketing surveillance programme will enable prospective regular collection of safety information which will be further assessed regularly during 6 monthly PSURs and annually through the annual reassessment of the Marketing Authorisation considering a positive approval under exceptional circumstances.

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Residual baseline level of LPL is also important due to potential immunogenicity/tolerance and there should be further follow-up in this respect since it has been published that antibodies can in some instances neutralize LPL. Additional data will be collected in post marketing setting in this respect.

The Applicant in its updated risk management plan provided further information regarding two Juvenile non clinical studies mentioned below. These studies are now completed and the applicant is requested to provide the results for further assessment post authorisation. It is acknowledged that there was no possibility for the applicant to provide additional data as part of the re-examination procedure.

Non clinical studies

Juvenile pharmacokinetics: To assess the biodistribution and potential for germline transmission in immature mice at 7 and 180 days after IM administration of Glybera

Juvenile toxicology. To assess the toxicity in immature mice (3-4 weeks up to 180 days after administration of Glybera

Finally, the quality data remain unchanged and previous recommendations adopted in October 2011 by the CAT remain valid for the restricted patient population.

The CAT by majority considered that the available data, in a totality of evidence approach, are sufficient to allow for a positive benefit-risk of Glybera and maintained its view by majority that the benefit/risk for Glybera is positive in the indication below:

"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)."

CHMP discussion (overall discussion)

The CHMP by majority agreed with the above discussion (refer to the above CHMP discussions parts).

8. Pharmacovigilance

Detailed description of the Pharmacovigilance system

The CAT and CHMP considered that the Pharmacovigilance system as described by the applicant fulfils the legislative requirements.

Risk Management Plan

The applicant submitted an updated risk management plan related to the restricted indication, which included a risk minimisation plan and an efficacy follow up plan.

The CHMP agreed in principle with the CAT proposal related to the risk management plan. However subsequently to the changes introduced in the CHMP specific obligations and final agreed PI adopted by the CHMP, modifications to the RMP were introduced as discussed above. These changes related to:

- introduction of measurement of immune response (at baseline, 6 months and 12 months) in the CM study proposed in the specific obligation.

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-the re-assessment of immune response in all patients enrolled in study AMT-CT 011-01.

- the removal of the monitoring of CM in standard practice at baseline and 12 months after treatment.

The final Summary of the RMP agreed with the CHMP is presented below

Summary of the Risk Management Plan:

Safety concern	**Proposed pharmacovigilance activities(routine and additional)**	**Proposed risk minimisation activities (routine and additional)**
1) Muscle pain or damage	Routine pharmacovigilance LPLD Registry	SmPC section 4.2: "Glybera therapy must be prescribed by and administered under the supervision of a physician with expertise in treating LPLD patients and in gene therapy administration." and "To ensure intramuscular injection, ultrasound or electrophysiological guidance of injections is advised." Educational programme for healthcare professionals and patients Restricted access programme Pre- and post administration events diary
2) Fever following administration	Routine pharmacovigilance LPLD Registry	SmPC section 4.4: "Immediately prior to Glybera administration the absence of an active infectious disease of any nature has to be confirmed. In case of such an infection administration of Glybera must be postponed until after the patient has recovered." Educational programme for healthcare professionals and patients Restricted access programme Pre- and post administration events diary
3) Immune response to capsid proteins or the transgene	Routine pharmacovigilance Assessment of immune response at baseline, 6 months and 12 months in a clinical study Re-evaluation of antibody responses in CT-AMT-011-01 LPLD Registry	SmPC section 4.2: The treatment should be monitored by measuring neutralising antibodies and T-cell response against AAV1 and LPL^{s447x} and T-cell response at baseline as well at 6 and 12 months after treatment. SmPC section 4.4: "From three days prior to and for 12 weeks following Glybera administration an immunosuppressive regimen should be administered: ciclosporin (3 mg/kg/day) and mycophenolate mofetil (2 x 1 g/day) is recommended. In addition, half an hour prior to Glybera injection an intravenous bolus of 1 mg/kg of methylprednisolone should be administered." Educational programme for healthcare professionals and

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		patients Restricted access programme Pre- and post administration events diary Improve the sensitivity of impurity assays in view of the potential of immune reaction against cellular DNA, SF+ protein or a combined SF+/Baculovirus protein, residual Rep and Cap genes and replication competent AAV. The validation of release assays for cellular DNA, SF+ protein or a combined SF+/Baculovirus protein, residual Rep and Cap genes and replication competent AAV should be completed, and the drug product specification revised accordingly.
4) Risks associated with spinal administration of an anaesthetic	Routine pharmacovigilance LPLD Registry	Spinal or regional anaesthesia should always only be administered by a qualified anaesthetist. Educational programme for healthcare professionals and patients Restricted access programme Pre- and post administration events diary
5) Haematoma, haemorrhage or bleeding	Routine pharmacovigilance LPLD Registry	Administration by experienced physician under electrophysiological guidance as per SmPC section 4.2 "To ensure intramuscular injection, ultrasound or electrophysiological guidance of injections is advised." Administration by experienced physician as per SmPC. SmPC section 4.3: "Anti-platelet or other anti-coagulant medicinal product must not be used concomitantly with Glybera at the time of injection and for at least one week before the leg injections or one day after the injection." SmPC section 4.5: "Anti-platelet or other anti-coagulant medicinal product must not be used concomitantly with Glybera at the time of injection. Correction of bleeding parameters must be instituted prior to Glybera administration. Anti-platelet or other anti-coagulant medicinal product should not be taken for at least one week before the leg injections or one day after the injection." Educational programme for healthcare professionals and patients

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		Restricted access programme Pre- and post administration events diary
6) Systemic exposure	Routine pharmacovigilance LPLD Registry	Administration by experienced physician. SmPC. Precautions in SmPC section 4.2 also state: "Glybera should under no circumstances be administered intravascularly." and "To ensure intramuscular injection, ultrasound or electro-physiological guidance of injections is advised." Educational programme for healthcare professionals Restricted access programme Pre- and post administration events diary
7) Concurrent administration of immunosuppressant drugs and late onset of inflammation	Routine pharmacovigilance LPLD Registry	Precautions for use in SmPC section 4.4 "From three days prior to and for 12 weeks following Glybera administration an immunosuppressive regimen should be administered: ciclosporin (3 mg/kg/day) and mycophenolate mofetil (2 x 1 g/day) is recommended. In addition, half an hour prior to Glybera injection an intravenous bolus of 1 mg/kg of methylprednisolone should be administered. Immediately prior to initiation of the immunosuppressant regimen and prior to Glybera injection the patient must be checked for symptoms of active infectious disease of any nature, and in case of such infection the start of treatment must be postponed until after the patient has recovered. Educational programme for healthcare professionals and patients Restricted access programme Pre- and post administration events diary
8) Risks associated with stopping anticoagulants and thromboembolic events	Routine pharmacovigilance LPLD Registry	SmPC section 4.4: "LPLD involves a state of hyperviscosity/hypercoagulability. Spinal anaesthesia and multiple intramuscular injections may further increase the risk of (thrombo) embolic events at and shortly after administration of Glybera. Assessment of each individual subject's risk profile prior to Glybera administration is advised. Follow applicable local or international guidelines for prophylaxis". Educational programme for healthcare professionals and patients

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		Restricted access programme Pre- and post administration events diary
9) Reduced efficacy	Routine pharmacovigilance Clinical study to provide CM data in 12 new patients and healthy volunteers Long term follow-up of CT-AMT-011-01	SmPC section 4.4: "Diet: Patients are advised to continue to follow their standard low-fat diet and keep refraining from drinking alcohol." Educational programme for healthcare professionals and patients Restricted access programme
10) Risk of germline transmission	Routine pharmacovigilance LPLD Registry	SmPC section 4.6: Contraception in males and females "Women of childbearing potential must be advised to use reliable barrier contraception methods in accordance with the guidelines for immunosuppressants for a minimum of 12 months from the start of therapy (9 months following cessation of immunosuppressants). Therefore, use of barrier contraception methods for at least 12 months following Glybera administration is recommended. Oral contraceptive use is contraindicated in LPLD patients (see section 4.3) as this may exacerbate the underlying disease. Male patients, including vasectomised males, are advised to practise barrier contraception methods for at least 12 months following Glybera administration. Educational programme for healthcare professionals and patients Restricted access programme
11) Tumorigenicity	Routine pharmacovigilance LPLD Registry	Information is given SmPC in section 5.3 "Carcinogenicity studies have not been conducted. However in toxicity studies, no increase in tumour was identified. Although there is no fully adequate animal model to address the tumourigenic potential, the available toxicological data do not suggest any concern for tumourigenicity.". No risk minimisation is needed at this point in time.
12) Exposure of healthcare professionals and	Routine pharmacovigilance	Precautions in SmPC section 4.2 "Glybera therapy must be prescribed by and administered under the supervision of a physician with expertise in treating LPLD patients and in gene

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close associates / transmission to third parties		therapy administration." Section 4.4 "This medicinal product contains genetically-modified organisms. Local biosafety guidelines applicable for such products should be followed." Section 6.6 "Refer to local biosafety guidelines applicable for handling and disposal of medicinal products containing genetically-modified organisms. Work surfaces and material which have potentially been in contact with Glybera must be decontaminated with appropriate virucidal disinfectants with activity for non-enveloped viruses (such as hypochlorite and chlorine releasers) for at least 10 minutes." "Glybera is delivered in a patient-specific pack and will therefore contain the precise amount of vials per patient, calculated according to the patient's weight." Educational programme for healthcare professionals Restricted access programme
13) Risk of off-label use	Routine pharmacovigilance LPLD Registry	As per SmPC section 4.1 "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." Educational programme for healthcare professionals Restricted access programme
14) Risks associated with (unintended) re-administration	Routine pharmacovigilance LPLD Registry	Glybera is intended for a single administration per patient as per SmPC section 4.2 "Glybera is authorised for single treatment only. No data on re-administration of Glybera are available, therefore Glybera should not be re-administered." Educational programme for healthcare professionals Restricted access programme
15) Long term effects of novel gene therapy platform	Routine pharmacovigilance LPLD Registry Long term follow-up of study CT-AMT-011-01	Adequate information in SmPC section 4.2 "Glybera therapy must be prescribed by and administered under the supervision of a physician with expertise in treating LPLD patients and in gene therapy administration." Section 4.4 "This medicinal product contains genetically-modified organisms. Local biosafety guidelines applicable for

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		such products should be followed." Educational programme for healthcare professionals and patients. Restricted access programme
15) Use in pregnancy	Routine pharmacovigilance LPLD Registry	SmPC section 4.6: Pregnancy: Very limited data on pregnancies exposed to Glybera is available. Animal studies do not indicate any harmful effects on pregnancy or embryonal/foetal development from Glybera (see section 5.3). Glybera should not be administered to pregnant women unless the possible benefit to the mother outweighs the possible risk to the foetus. Breast-feeding: It is not known whether Glybera is excreted in human milk. Glybera should not be administered to women who are breast-feeding as long as breastfeeding is ongoing. Educational programme for healthcare professionals and patients Restricted access programme
17) Use in the paediatric population	Routine pharmacovigilance LPLD Registry	Glybera is intended for administration to adult patient as per SmPC section 4.1 "Glybera is indicated for adult patients." Section 4.2 "The safety and efficacy of Glybera in children and adolescents below 18 years has not been established. No data are available." Educational programme for healthcare professionals Restricted access programme

The CHMP taking into account the CAT opinion and following the oral explanation discussion updated the pharmacovigilance activities in line with the final agreed specific obligations adopted in the CHMP opinion.

The final agreed pharmacovigilance activities are described below.
In addition to the use of routine pharmacovigilance the following pharmacovigilance activity(ies) are needed to further investigate some of the safety concerns:

Pharmacovigilance activity	Due date
The MAH shall set up a disease registry to collect information on the epidemiology of the disease and the demographics, safety and effectiveness outcomes of patients with familial LPLD treated with Glybera.	Before launch Reports will be submitted within

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	PSURs
Clinical study for assessment of postprandial chylomicron metabolism in at least 12 patients, before and 12 months after treatment with Glybera, to be chosen in addition to the patients included in study AMT.011.02; and eight healthy subjects in the second cohort. In addition assessment of immune response at baseline, 6 months and 12 months in at least 12 newly treated patients.	Protocol to be submitted immediately after the EC decision Start of the study by July 2013 Progress reports to be submitted within PSURs and annual reassessment Final report by December 2017
Long term follow-up of patients, who have been treated with Glybera in a clinical trial. Patients shall be enrolled in the registry at the end of the trial.	Reports will be submitted within PSURs

The following additional risk minimisation activities were required

- The MAH shall implement a restricted access programme prior to launch to ensure that Glybera will only be supplied if healthcare professionals have received the educational programme and if the prescriber and the patient agree to participate in registry.
- The MAH shall implement an educational programme to ensure that prior to launch all health care professionals involved in the treatment of patients with Glybera are provided with an educational pack.
- The MAH shall also provide a patient alert card in each medication pack, the text of which is included in Annex III.
- Details are included below under "conditions or restrictions with regard to the safe effective use of the medicinal product".

8.1. *User consultation*

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

8.2. *GMO / Environmental risk assessment*

Reference is made to Section 2.10 of this report.

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9. CAT BENEFIT-RISK BALANCE

Benefits

Beneficial effects

Familial lipoprotein lipase deficiency (LPLD) is a very rare autosomal recessive disorder (1.5 persons per 1.000.000 in EU) characterized by absence of lipoprotein lipase activity and a massive accumulation of chylomicrons in plasma and a corresponding increase of plasma triglyceride concentration. The disease remains sometimes under diagnosed until adulthood and includes repeated episodes of abdominal pain, recurrent attacks of pancreatitis, eruptive cutaneous xanthomatosis, and hepatosplenomegaly. The severity of symptoms is proportional to the degree of chylomicronemia, which, in turn, is dependent on dietary fat intake. The duration of life may, part from severe and potentially fatal pancreatic episodes, also be impaired due to diabetes mellitus secondary to pancreatic insufficiency and to diabetes related complications. While compliance with the diet (maximum of 20 g/day) can be effective, in practice, it is quite challenging and dietary failures are very common.

Therefore gene therapy represents a potential therapeutic tool aimed to correct monogenetic disorder such as loss-of-function defects in the lipoprotein lipase gene. Glybera consists of a non-integrating adeno-associated virus (AAV) vector construct, which confers the episomal expression of the over functional LPLS447X gene. The rationale of treatment is based on the principle that by adding an extra copy of the over-functional LPL gene into muscle cells lacking catalytically active lipoprotein lipase, Glybera could restore metabolic functions, by normalising the elimination of triglycerides from large circulating chylomicron particles.

The ultimate goals of LPLD treatment are to reduce the burden of the disease associated with pancreatitis, to reduce the incidence and size of eruptive cutaneous xanthomatosis, lipaemia retinalis and hepatosplenomegaly, to reduce the stringency of the life-long requirement to remain compliant with the diet and to improve the quality of life.

The reduction in fasting TGs was initially considered an appropriate endpoint to assess the efficacy of Glybera based on expert advice when the clinical studies were planned. Meanwhile, as science evolved, a reduction in post-prandial chylomicronemia has been proposed as an alternative surrogate marker for efficacy and was considered the best metabolic parameter at present and therefore acceptable.

A clear indication of a consistent and significant biological effect of Glybera was demonstrated on post-prandial chylomicronemia data in a sub group at both week 14 (5/5 patients) and week 52 (3/3 patients).

A reduction in pancreatitis events and severity of attacks were reported in some patients treated with Glybera. The evidence generated by overall efficacy data, although hampered by statistical limitations, suggested that Glybera leads to a clinically relevant reduction of pancreatitis risk in patients with severe or multiple pancreatitis attacks. This is supported also by the reduction in hospital admissions and ICU stay.

A clinical benefit is considered shown in a subset of patients defined by the restricted indication proposed for Glybera in adult patients diagnosed with familial lipoprotein lipase deficiency (LPLD) and suffering from severe or multiple pancreatitis attacks despite dietary fat restrictions. The indication is restricted to patients with detectable levels of LPL protein.

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A link between LPL mass expression, sustained improvement of pp-CM (both at 14 and 52 weeks) and significant reduced risk of pancreatitis attacks was observed in 2 subjects who suffered from multiple recurrent pancreatitis and abdominal pain events before treatment. These findings, although highly limited by the paucity of the number of observations, do suggest a correlation between biochemical and clinical data in these two individual subjects with comprehensive clinical and biochemical evaluation. A sustained improvement in pp-CM was observed also in the third subject followed up to 52 weeks with pp-CM. Data on enzyme expression and function (LPL activity 5/7and Oil Red O staining 5/7) in injected and non-injected muscles, along with other relevant clinical and paraclinical data support functional expression.

Uncertainty in the knowledge about the beneficial effects

The presented dataset in relation to the restricted indication includes 12 out of 27 patients treated with Glybera, aged 40-70 years of age and diagnosed with LPLD condition relatively late in life.

The reduction in post-prandial chylomicronemia as an alternative surrogate marker for efficacy, although not at present validated, was considered biologically plausible and acceptable.

The retrospective analysis carried out on pancreatitis events showed that the occurrence of this most important complication was of very variable frequency in the pre-treatment period. Several patients had long pancreatitis free intervals, running into a few years. The post-treatment follow-up was relatively short when compared to the pre-treatment period. The data on pancreatitis remain very limited and in a very small number of patients (12 patients) with limitations acknowledged in the statistical analysis.

The data on hospitalisation and/or ICU admissions also suffer from the above weakness. In addition, it does not reflect the change in the clinical management practice that has continually evolved towards a reduction in hospitalisation, reduction in length of stay and other new ways of managing such as "High-dependency medical ward" as opposed to ICU.

Considering the combination of the rarity of the indication as well as the fact that this is an autosomal recessive disorder with different levels of genetic penetration, a high consistency in the results is challenging to achieve. A lack of full consistency is acknowledged as a limitation of the data, but this does not rule out a favourable effect of Glybera.

Risks

Unfavourable effects

Multiple injections (up to 60 injection sites) were administered during a single procedure under regional or spinal anaesthesia. Most of the adverse reactions are local and self-limiting within few days after the treatment, and the type of anaesthesia is a standard clinical procedure.

One patient was reported to have a confirmed episode of pulmonary embolism, requiring anti-coagulation.

Risk associated with the administration procedure: multiple injections into muscles

Within the 3-5 year time period of follow up, documented histological alterations for 20 patients were mild, never resulting in necrosis and/or scarring. No biochemical signs of muscle damage were detected, in particular serum CPK was not altered by the procedure. No sign of muscle dysfunction was reported.

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Risks associated with 3-month course of immunosuppression

In the present gene therapy approach, the rationale for immune suppression is three-fold:

- To reduce immune response to AAV vector, that could impair efficacy;
- To reduce the risk of transgene product being recognised by an activated immune system;
- To alleviate inflammation and its symptoms related to Glybera injection.

Since the immunosuppression treatment was limited to three months, associated risks are considered minimal.

An increased risk of infection must be carefully evaluated and monitored and even more in those patients with pre-existing liver or kidney disease. However, the risk of infection is modest in an otherwise healthy individual, and can be usually managed with antibiotic or antiviral treatment.

The rationale and need for the 3 month course of immunosuppressive regimen after administration of Glybera is accepted as it corresponds to the time where the immune system would prevent the gene therapy approach to work properly.

Long term immunogenicity was addressed by testing anti-LPL antibodies. Anti-LPL antibodies were not detected in any of the patients.

Uncertainty in the knowledge about the unfavourable effects

The safety database remains limited and consists of 27 patients only. However, it is acknowledged that this is a very rare disease.

The occurrence of pulmonary embolus is likely related to the administration of multiple IM injections in the legs rather than a direct effect of Glybera.

A formal proof of the immunoregimen effectiveness would require a head-to-head comparison of patients with and without such treatment. This is considered challenging for this very rare disease.

However the applicant will extend the safety information regarding potential immune response in patients treated with Glybera as requested in the post authorisation setting through the registry.

This will also include re-assessment of potential anti-LPL response, follow up on antibody and T-cell responses will further substantiate the available data.

The quality of life results in patients at 52 weeks are considered not reliable as the questionnaire used was not considered validated and not considered appropriate in LPL deficient patients. Furthermore it does not provide information on symptoms of the disease.

Balance

Importance of favourable and unfavourable effects

In view of the fact that LPLD is an extremely rare orphan condition, sufficient evidence of efficacy of the gene-therapy has to be assessed also by using individual patient data.

The effect of Glybera on post-prandial CM levels, although measured in a limited number of patients (5 patients at 14 weeks and 3 patients at 52 weeks), is biologically significant and consistent providing sufficient evidence suggesting improvement in the clinical outcome.

Both the statistical analysis on the reduction in the risk of pancreatitis following Glybera treatment as well as the single patient evaluation of the occurrence of pancreatitis pre- and post- Glybera treatment suggest the benefit of the drug in LPL deficient patients. However, the effect seems particularly evident in patients that underwent repeated attacks of pancreatitis in the pre-treatment period. Therefore, it is

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acceptable and justified to restrict the indication of Glybera to patients suffering from severe or multiple pancreatitis attacks despite dietary fat restrictions. Data on enzyme expression and function (Oil Red O staining) in injected and non-injected muscles, are considered important supportive data.

It is acknowledged that dietary restrictions are essential in LPLD patients and that a strict compliance to low fat diet is difficult to achieve. However Glybera treatment should still be associated with a low fat diet.

The immunosuppression regimen is considered acceptable with clinically manageable risk for the patients. The multiple injections into muscles are considered acceptable as 1) no major histological alterations were evident within the 3-5 years of follow up nor 2) biochemical signs of muscle damage were detected. Although the safety data base is limited, the safety profile of Glybera is considered acceptable.

Benefit-risk balance

Discussion on the benefit-risk assessment

It is acknowledged that the reduction in fasting TGs is not an appropriate endpoint to assess the efficacy of Glybera, as reinforced by the Ad Hoc Experts Group on Glybera. The experts agreed that the reduction in post-prandial chylomicrons is a biologically plausible and relevant alternative acceptable endpoint, albeit not fully validated.

The effect of Glybera on post-prandial CM is biologically significant even if tested in a limited number of patients. In addition, post-prandial CM data at 52 weeks (n=3 pts) suggest the presence of a metabolically relevant amount of LPL activity and transgene expression 9 months after the end of any immunosuppressive therapy and at a time where a potential cytotoxic T cell response against LPL would already exist. The clinical importance of these findings was also agreed by the Ad Hoc Experts Group. Post prandial chylomicronaemia levels will be monitored at baseline and every 12 months in Glybera treated patients and a pp CM test will be made available after approval.

The evidence generated by the reduction of pancreatitis events and severity of attacks, although hampered by statistical limitations, suggested that Glybera leads to a clinically relevant reduction of pancreatitis risk in some patients. This is also supported by the reduction in hospital admissions and ICU stay. The evidence generated by the overall efficacy data, acknowledging the limitations, is considered to be sufficiently robust. The majority of the Ad Hoc Experts Group concurred with this opinion. An acceptable and clinically manageable safety profile was observed in 27 Glybera treated patients. Furthermore, as the concomitant immunosuppression treatment was limited to three months, associated risks were considered minimal and clinically manageable in this population. A positive benefit risk is considered shown in a subset of patients as defined by the restricted indication proposed for Glybera in adult patients diagnosed with familial lipoprotein lipase deficiency (LPLD) and suffering from severe or multiple pancreatitis attacks despite dietary fat restrictions. The indication is restricted to patients with detectable levels of LPL protein.

In a totality of evidence approach, the majority of CAT considered efficacy to be sufficiently established to allow for positive benefit-risk estimation in an exceptional circumstances setting. The CAT by consensus was of the opinion that further data need to be generated, and the majority of CAT considered that this should be done post-authorisation with clear-cut post-authorisation specific obligations.

Based on the quality, efficacy and safety results, it is considered that the granting of a Marketing Authorization under exceptional circumstances can be recommended. A stringent control of patients treated with Glybera can be ensured in the post authorisation setting with a strict controlled distribution system. Patients will be prescribed and administered the drug only by appropriate trained physicians within specialised centres and under close monitoring. It is recommended that patients

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treated with Glybera are enrolled in a dedicated registry. In addition, the diagnosis of LPLD has to be confirmed by genetic testing. In order to prevent an immune response against the transgene protein, treatment is restricted to patients with detectable levels of LPL protein. In addition, the efficacy database will be enriched by collection of post-prandial CM data at baseline and every 12 months. Furthermore, additional efficacy data will be provided through the patients treated as part of the registry for up for 15 years, in particular pancreatitis and hospitalisation events/ICU events. Regarding safety, long term immunogenicity will be explored by testing anti-LPL antibodies and T cell response, allowing reassessment of the potential impact of immune response on Glybera treatment. These data will form the basis of the annual reassessment of the benefit/risk profile of the medicinal product considering the rarity of the disease, in the setting of a marketing authorisation under exceptional circumstances.

A minority of the CAT members were of divergent opinion with regard to the benefit-risk of Glybera and did not agree with the CAT's opinion recommending the granting of a Marketing Authorisation for this product. In the opinion of these CAT members, despite the very careful re-evaluation of the dossier in patients with severe or multiple pancreatitis attacks and the arguments of the Applicant in re-analyzing their data and presented in the Oral Explanation in June 2012, the grounds for refusal have not been satisfactorily answered and there are still uncertainties on the relevance of the clinical results submitted in the dossier. The Divergent positions are appended to this report.

10. CHMP BENEFIT-RISK BALANCE

The CHMP by majority agreed in principle with the Benefit risk proposed by the CAT in its draft opinion adopted in June 2012 and presented below.

However in line with the CHMP discussion and adopted CHMP opinion, some changes were introduced by CHMP, to highlight that the proposed restricted indication corresponded to more severely affected patients with high unmet medical need, thus justifying approval under exceptional circumstances on the basis of the available data on safety and efficacy and considering a totality of evidence approach. Furthermore, the changes associated with the CM study together with the changes associated to section 4.2 previously discussed in the CHMP discussions parts are introduced.

The final CHMP benefit risk balance is detailed below.

Benefits

Beneficial effects

Familial lipoprotein lipase deficiency (LPLD) is a very rare autosomal recessive disorder (1.5 persons per 1.000.000 in EU) characterized by absence of lipoprotein lipase activity and a massive accumulation of chylomicrons in plasma and a corresponding increase of plasma triglyceride concentration. The disease remains sometimes under diagnosed until adulthood and includes repeated episodes of abdominal pain, recurrent attacks of pancreatitis, eruptive cutaneous xanthomatosis, and hepatosplenomegaly. The severity of symptoms is proportional to the degree of chylomicronemia, which, in turn, is dependent on dietary fat intake. The duration of life may, apart from severe and potentially fatal pancreatic episodes, also be impaired due to diabetes mellitus secondary to pancreatic insufficiency and to diabetes related complications. While compliance with the diet (maximum of 20 g/day) can be effective, in practice, it is quite challenging and dietary failures are very common.

Therefore gene therapy represents a potential therapeutic tool aimed to correct monogenetic disorder such as loss-of-function defects in the lipoprotein lipase gene. Glybera consists of a non-integrating adeno-associated virus (AAV) vector construct, which confers the episomal expression of the

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overfunctional LPLS447X gene. The rationale of treatment is based on the principle that by adding an extra copy of the over-functional LPL gene into muscle cells lacking catalytically active lipoprotein lipase, Glybera could restore metabolic functions, by normalising the metabolism of triglycerides from large circulating chylomicron particles.

The ultimate goals of LPLD treatment are to reduce the burden of the disease associated with pancreatitis, to reduce the incidence and size of eruptive cutaneous xanthomatosis, lipaemia retinalis and hepatosplenomegaly, to reduce the stringency of the life-long requirement to remain compliant with the diet and to improve the quality of life.

The reduction in fasting TGs was initially considered an appropriate endpoint to assess the efficacy of Glybera based on expert advice when the clinical studies were planned. Meanwhile, as science evolved, a reduction in post-prandial chylomicronemia has been proposed as an alternative surrogate marker for efficacy and was considered the best metabolic parameter at present and therefore acceptable.

A clear indication of a consistent and significant biological effect of Glybera was demonstrated on post-prandial chylomicronemia data in a sub group at both week 14 (5/5 patients) and week 52 (3/3 patients).

A reduction in pancreatitis events and severity of attacks were reported in some patients treated with Glybera. Using a totality of evidence approach, the evidence generated by overall efficacy data, although hampered by statistical limitations, suggested that Glybera leads to a clinically relevant reduction of pancreatitis risk in patients with severe or multiple pancreatitis attacks. This is supported also by the reduction in hospital admissions and ICU stay.

A clinical benefit is considered shown in a subset of patients, with a substantially increased risk of pancreatitis, a particular unmet medical need, as reflected by the restricted indication proposed for Glybera in adult patients diagnosed with familial lipoprotein lipase deficiency (LPLD) and suffering from severe or multiple pancreatitis attacks despite dietary fat restrictions. The indication is restricted to patients with detectable levels of LPL protein.

A link between LPL mass expression, sustained improvement of pp-CM (both at 14 and 52 weeks) and significant reduced risk of pancreatitis attacks was observed in 2 subjects who suffered from multiple recurrent pancreatitis and abdominal pain events before treatment. These findings, although highly limited by the paucity of the number of observations, do suggest a correlation between biochemical and clinical data in these two individual subjects with comprehensive clinical and biochemical evaluation. A sustained improvement in pp-CM was observed also in the third subject followed up to 52 weeks with pp-CM. Data on enzyme expression and function (LPL activity 5/7and Oil Red O staining 7/7) in injected and non-injected muscles, along with other relevant clinical and paraclinical data support functional expression.

Uncertainty in the knowledge about the beneficial effects

The presented dataset in relation to the restricted indication includes 12 out of 27 patients treated with Glybera, aged 30-62 years of age and diagnosed with LPLD condition relatively late in life.

The reduction in post-prandial chylomicronemia as an alternative surrogate marker for efficacy, although not at present formally validated and is not part of standard clinical practice, was considered biologically plausible and acceptable.

The retrospective analysis carried out on pancreatitis events showed that the occurrence of this most important complication was of very variable frequency in the pre-treatment period. Several patients had long pancreatitis free intervals, running into a few years. The post-treatment follow-up was

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relatively short when compared to the pre-treatment period. The data on pancreatitis remain very limited and in a very small number of patients (12 patients) with limitations acknowledged in the statistical analysis.

The data on hospitalisation and/or ICU admissions also suffer from the above weakness. In addition, it does not reflect the change in the clinical management practice that has continually evolved towards a reduction in hospitalisation, reduction in length of stay and other new ways of managing such as "High-dependency medical ward" as opposed to ICU.

Considering the combination of the rarity of the indication as well as the fact that this is an autosomal recessive disorder with different levels of genetic penetration, a high consistency in the results is challenging to achieve. A lack of full consistency is acknowledged as a limitation of the data, but this does not rule out a favourable effect of Glybera.

Risks

Unfavourable effects

Multiple injections (up to 60 injection sites) were administered during a single procedure under regional or spinal anaesthesia. Most of the adverse reactions are local and self-limiting within few days after the treatment, and the type of anaesthesia is a standard clinical procedure.

One patient was reported to have a confirmed episode of pulmonary embolism, requiring anti-coagulation.

Risk associated with the administration procedure: multiple injections into muscles

Within the 3-5 year time period of follow up, documented histological alterations for 20 patients were mild, never resulting in necrosis and/or scarring. No biochemical signs of muscle damage were detected, in particular serum CPK was not altered by the procedure. No sign of muscle dysfunction was reported.

Risks associated with 3-month course of immunosuppression

In the present gene therapy approach, the rationale for immune suppression is three-fold:

To reduce immune response to AAV vector, that could impair efficacy;

To reduce the risk of transgene product being recognised by an activated immune system;

To alleviate inflammation and its symptoms related to Glybera injection.

Since the immunosuppression treatment was limited to three months, associated risks are considered minimal.

An increased risk of infection must be carefully evaluated and monitored and even more in those patients with pre-existing liver or kidney disease. However, the risk of infection is modest in an otherwise healthy individual, and can be usually managed with antibiotic or antiviral treatment.

The rationale and need for the 3 month course of immunosuppressive regimen after administration of Glybera is accepted as it corresponds to the time where the immune system would prevent the gene therapy approach to lead to successful gene expression.

Long term immunogenicity was addressed by testing anti-LPL antibodies, inaddition to antibodies and cell-mediated immunity against AAV. Anti-LPL antibodies were not detected in any of the patients.

Uncertainty in the knowledge about the unfavourable effects

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The safety database remains limited and consists of 27 patients only. However, it is acknowledged that this is a very rare disease.

The occurrence of pulmonary embolus is likely related to the administration of multiple IM injections in the legs rather than a direct effect of Glybera.

A formal proof of the immunoregimen effectiveness would require a head-to-head comparison of patients with and without such treatment. This is considered challenging for this very rare disease.

However the applicant will extend the safety information regarding potential immune response in patients treated with Glybera as requested in the post authorisation setting through a clinical dedicated study and the registry. In addition monitoring of immune response is introduced at regular time points in the SmPC as standard practice.

This will also include re-assessment of potential anti-LPL response, follow up on antibody and T-cell responses will further substantiate the available data.

The quality of life results in patients at 52 weeks are considered not reliable as the questionnaire used was not considered appropriate for LPL deficient patients. Furthermore it does not provide information on symptoms of the disease.

Balance

Importance of favourable and unfavourable effects

In view of the fact that LPLD is an extremely rare, orphan condition, sufficient evidence of efficacy of the gene-therapy has to be assessed also by using individual patient data.

The effect of Glybera on post-prandial CM levels, although measured in a limited number of patients (5 patients at 14 weeks and 3 patients at 52 weeks), is biologically significant and consistent, providing additional evidence in favour of positive clinical benefit.

Both the overall analysis on the reduction in the risk of pancreatitis following Glybera treatment as well as the single patient evaluation of the occurrence of pancreatitis pre- and post- Glybera treatment suggest the benefit of the drug in LPL deficient patients. However, the effect seems particularly evident in patients that underwent repeated attacks of pancreatitis in the pre-treatment period. Therefore, it is acceptable and justified to restrict the indication of Glybera to patients suffering from severe or multiple pancreatitis attacks despite dietary fat restrictions. Data on enzyme expression and function (Oil Red O staining) in injected and non-injected muscles, are considered important supportive data.

It is acknowledged that dietary restrictions are essential in LPLD patients and that a strict compliance to low fat diet is difficult to achieve. However Glybera treatment should still be associated with a low fat diet.

The immunosuppression regimen is considered acceptable with clinically manageable risk for the patients. The multiple injections into muscles are considered acceptable as 1) no major histological alterations were evident within the 3-5 years of follow up nor 2) biochemical signs of muscle damage were detected. Although the safety data base is limited, the safety profile of Glybera is considered acceptable.

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Benefit-risk balance

Discussion on the benefit-risk assessment

It is acknowledged that the reduction in fasting TGs is not an appropriate endpoint to assess the efficacy of Glybera, as reinforced by the Ad Hoc Experts Group on Glybera. The experts agreed that the reduction in post prandial chylomicrons is an biologically plausible a and relevant alternative acceptable endpoint, albeit not fully validated.

The effect of Glybera on post-prandial CM is biologically significant even if tested in a limited number of patients. In addition, post-prandial CM data at 52 weeks (n=3 pts) suggest the presence of a metabolically relevant amount of LPL activity and transgene expression 9 months after the end of any immunosuppressive therapy and at a time where a potential cytotoxic T cell response against Glybera would already exist. The clinical importance of these findings was also agreed by the Ad Hoc Experts Group. The evidence generated for the reduction of pancreatitis events and severity of attacks, although hampered by statistical limitations, suggested that Glybera leads to a clinically relevant reduction of pancreatitis risk. This is also supported by the reduction in hospital admissions and ICU stay. The evidence generated by the overall efficacy data, acknowledging the limitations, is considered to be sufficiently robust. The majority of the Ad Hoc Experts Group were of a similar opinion. An acceptable and clinically manageable safety profile was observed in 27 Glybera treated patients. Furthermore, as the concomitant immunosuppression treatment was limited to three months, associated risks were considered minimal and clinically manageable in this population. A positive benefit risk is considered shown in a subset of patients as reflected by the restricted indication proposed for Glybera in adult patients diagnosed with familial lipoprotein lipase deficiency (LPLD) and suffering from severe or multiple pancreatitis attacks despite dietary fat restrictions. The indication is restricted to patients with detectable levels of LPL protein.

In a totality of evidence approach, the majority of CHMP considered efficacy to be sufficiently established to allow for positive benefit-risk conclusion in an exceptional circumstances setting. The CHMP by consensus was of the opinion that further data need to be generated, and the majority of CHMP considered that this should be done post-authorisation with clear-cut post-authorisation specific obligations.

Based on the quality, the efficacy and safety results, it is considered that the granting of a Marketing authorization under exceptional circumstances can be recommended. A stringent control of to ensure the most appropriate prescription and administration of Glybera can be ensured in the post authorisation setting with a restricted access programme. Patients will be prescribed and administered the drug only by appropriate trained physicians within specialised centres and under close monitoring. It is recommended that patients treated with Glybera are enrolled in a dedicated registry. In addition, the diagnosis of LPLD has to be confirmed by genetic testing. In order to prevent an immune response against the transgene protein, treatment is restricted to patients with detectable levels of LPL protein. The efficacy database will be enriched by collection of post prandial chylomicrons data at baseline and every 12 months in at least 12 patients through the CM clinical study starting not later than July 2013. Furthermore, additional efficacy data will be provided through the patients treated as part of the registry for up for 15 years, in particular pancreatitis and hospitalisation events/ICU events. Regarding safety, long term immunogenicity will be explored by testing anti LPL antibodies and T cell response, allowing reassessment of the potential impact of immune response on Glybera treatment. Appropriate safety measures are introduced in the post marketing clinical setting in particular through monitoring of immune response at baseline, 6 months and 12 months as standard practice. These data will form

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the basis of the annual reassessment of the benefit/risk profile of the medicinal product considering the rarity of the disease, in the setting of a marketing authorisation under exceptional circumstances.

A minority of the CHMP members were of divergent opinion with regard to the benefit-risk of Glybera and did not agree with the CHMP's opinion recommending the granting of a Marketing Authorisation for this product. In the opinion of these CHMP members, despite the very careful re-evaluation of the dossier in patients with severe or multiple pancreatitis attacks and the arguments of the applicant in re-analyzing their data and presented in the Oral Explanation in July 2012, the grounds for refusal have not been satisfactorily answered and there are still uncertainties on the relevance of the clinical results submitted in the dossier. The Divergent positions are appended to this report.

11. CHMP Final Recommendation July 2012

Outcome

The CHMP, based on the draft opinion prepared by the CAT, having considered the detailed grounds for the re-examination, having considered the European Commission request and based on the arguments of the Applicant presented at the oral explanation at CHMP and the overall review of supporting data on quality, safety and efficacy, concluded by majority decision that the benefit-risk balance of Glybera is favourable in the treatment of "*adult patients diagnosed with familial lipoprotein lipase deficiency (LPLD) and suffering from severe or multiple pancreatitis episodes 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*)", and therefore recommends the granting of the marketing authorisation under exceptional circumstances subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription (See Annex I: Summary of Product Characteristics, section 4.2).

Conditions and requirements of the Marketing Authorisation

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

Pharmacovigilance system

The MAH must ensure that the system of pharmacovigilance, presented in Module 1.8.1. of the Marketing Authorisation Application, is in place and functioning before and whilst the medicinal product is on the market.

Risk Management Plan (RMP)

The MAH shall perform the pharmacovigilance activities detailed in the Pharmacovigilance Plan as agreed in the Risk Management Plan version 4.6 presented in Module 1.8.2. of the Marketing Authorisation Application and any subsequent updates of the RMP agreed by the Committee for Medicinal Products for Human Use (CHMP).

As per the CHMP Guideline on Risk Management Systems for medicinal products for human use, the updated RMP should be submitted at the same time as the next Periodic Safety Update Report (PSUR).

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In addition, an updated RMP should be submitted

- When new information is received that may impact on the current Safety Specification, Pharmacovigilance Plan or risk minimisation activities
- Within 60 days of an important (pharmacovigilance or risk minimisation) milestone being reached
- At the request of the European Medicines Agency.

PSURs

The PSUR cycle for the medicinal product should follow a half-yearly cycle until otherwise agreed by the CHMP.

- **CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE EFFECTIVE USE OF THE MEDICINAL PRODUCT**

The MAH shall set up a disease registry to collect information on the epidemiology of the disease and the demographics, safety and effectiveness outcomes of patients with familial LPLD treated with Glybera. Details of the operation of the registry shall be agreed with the National Competent Authorities in each Member State.

All patients treated with Glybera shall be enrolled in the registry. In addition, patients, who have been treated with Glybera in a clinical trial shall be enrolled in the registry at the end of the trial. Doctors shall be encouraged also to enrol patients with familial LPLD who are not treated with Glybera.

The MAH shall agree the details of a restricted access programme with the National Competent Authorities and must implement such programme nationally prior to launch. Glybera shall only be supplied if the healthcare professionals involved in the treatment of a patient have received the educational pack and if the prescriber confirms that the patient agrees to participate in the registry.

The educational pack for healthcare professionals must be agreed with the National Competent Authorities prior to distribution and consist of the following components:

- Product information (summary of product characteristics, patient information leaflet and patient alert card)

- Educational materials for health care professionals

- Educational materials for the patients

- Patient's events diary

1) Educational material for Pharmacists including the following key safety elements:

- Detailed guidelines for product receipt and storage, procedure for the preparation, handling and disposal of Glybera
- Guidance to ensure that patients receive the Patient Alert Card included in the pack.

2) Educational material for physicians and other healthcare professionals involved in the treatment of patients with Glybera including the following key safety elements:

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- Guidelines for the safe handling, administration and disposal of Glybera
- Guidance on the selection of suitable patients for treatment with Glybera including:
    - the need for genetic testing to be performed prior to the initiation of treatment in order to identify the patients who are eligible for treatment
    - that patients should not be taking anti-platelet or other anti-coagulation medicinal products at the time of injection
    - the need to exclude infection before starting immunosuppressant treatment
    - the need for all patients to be entered into a long term surveillance programme
- The need for regional or spinal anaesthesia
- Guidance on the need for immunosuppressive administration prior to and after treatment
- Guidance on the need to measure immune response at baseline and at 6 and 12 months after treatment
- Guidance on the prevention of risks associated with Glybera intramuscular injections, including the need for injections to be administered under ultrasound or electrophysiological guidance
- Detailed instructions on the dose, number and localization of the injections
- Guidance on the aftercare of the patient including monitoring for fever
- Information on the use of Glybera and avoidance of pregnancy
- The need to provide the educational material to patients and request their informed consent to be enrolled into the registry prior to treatment
- The need to advise patients on:
    - the need and duration of barrier contraception
    - not to donate organs nor blood nor cells
    - on the need to continue on a low-fat diet and avoid drinking alcohol
    - the necessity to carry the patient alert card, that is included in each pack, with them at all times
    - the use of the events diary
- Details of the disease registry:
    - that enrolment is mandatory for patients treated with Glybera
    - that patients treated with Glybera in a clinical trial should be enrolled in the registry at the end of the trial
    - that, where possible, patients with familial LPLD who are not treated with Glybera should be enrolled.
    - the need to obtain the patient's informed consent prior to treatment
    - how to enter patients in it – including those not treated with Glybera

3) Educational materials for patients treated with Glybera including the following key safety elements:

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- Information on the treatment procedure with Glybera
- Information about the signs and symptoms to be monitored after treatment including:
    - information on the signs and symptoms of a reduction/loss of efficacy
    - the use of the events diary and what should be recorded
- Information on the need for long term follow-up for Glybera, including the registry
- Information on the need to avoid pregnancy
- Advice on the need and duration of barrier contraception
- Not to donate organs nor blood nor cells
- Advice on the need to continue on a low-fat diet and avoid drinking alcohol
- The necessity to carry the patient alert card, that is included in each pack, with them at all times

The MAH shall also provide a patient alert card in each medication pack, the text of which is included in Annex III.

In addition, in view of the potential for immune reaction against cellular DNA, SF+ protein or a combined SF+/Baculovirus protein, residual Rep and Cap genes and rcAAV impurities in Glybera, the MAH should improve the sensitivity of these impurity assays. The validation of release assays for cellular DNA, SF+ protein or a combined SF+/Baculovirus protein, residual Rep and Cap genes and rcAAV should be completed, and the drug product specification revised accordingly by 31.12.2012.

- **SPECIFIC OBLIGATION TO COMPLETE POST-AUTHORISATION MEASURES FOR THE MARKETING AUTHORISATION UNDER EXCEPTIONAL CIRCUMSTANCES**

This being an approval under exceptional circumstances and pursuant to Article 14(8) of Regulation (EC) No 726/2004, the MAH shall conduct, within the stated timeframe, the following measures:

Description	Due date
The MAH shall set up a long term surveillance programme/ disease registry to collect information on the epidemiology of the disease and the demographics, safety, and the effectiveness outcomes of patients treated with Glybera. The registry should be performed according to an agreed protocol. The patients enrolled in clinical studies (CT-AMT-010 -10, CT-AMT 011-01, CT-AMT 011-02) should be followed up in the LPLD registry. All patients treated with Glybera should be enrolled in the registry and systematic data collection carried out to enrich the database: 1) on efficacy data such as biochemical markers as part of normal practice and frequency and severity of pancreatitis and 2) on safety including immunogenicity against Glybera and LPL.	Before launch of the product in each country Protocol should be submitted immediately after the EC decision PSUR/ annual reassessment

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3) Dietary diary and quality of life data should also be recorded. The diagnosis of LPLD has to be confirmed by genetic testing. 15 years follow-up is recommended for every patient treated.	
Assessment of postprandial chylomicron metabolism in at least 12 patients before and 12 months after treatment with Glybera to be chosen in addition to the patients included in study AMT.011.02; and eight healthy subjects in the second cohort. Assessment of immune response at baseline, 6 months and 12 months in at least 12 newly treated patients. The study should be performed according to an agreed protocol. The study should start by July 2013 and should enroll at least 4 patients per year. Results from the study to be reviewed annually. Re-evaluation of immune responses from all patients enrolled in study CT-AMT-011-01 by using a validated assay method should also be provided. The assay to be used in the study need to be agreed.	December 2017 Protocol should be submitted immediately after the EC decision July 2013 PSUR/ annual reassessment

- **OBLIGATION TO CONDUCT POST-AUTHORISATION MEASURES**

The MAH shall complete, within the stated timeframe, the following measures:

Description	Due date
To improve the virus safety profile of the product, an additional manufacturing process step should be developed and validated to ensure that the process is capable of inactivating or removing at least the maximal baculovirus load used in production. Ideally, the inactivation or removal capacity of this additional step should be higher than the maximal baculovirus load.	31.12.2013
To complete the validation of the residual infectious baculovirus assay (800 wells), the LOD should be experimentally confirmed. In addition, the presented risk assessment should be revised taking into account the experimentally determined LOD.	31.12.2012

- **CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT TO BE IMPLEMENTED BY THE MEMBER STATES**

Compared to the Annex 127a proposed by the CAT, the Annex 127a has been refined to only include the conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the members states:

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The Member States shall agree the details of a restricted access programme and a disease registry with the MAH. They shall ensure that Glybera is only supplied if the healthcare professionals involved in the treatment of a patient have received the educational pack and if the prescriber confirms that the patient agrees to participate in the registry.

Divergent position to the majority recommendation is appended to this report.

New Active Substance Status

Based on the CHMP review of data on the quality properties of the active substance, the CHMP considers that Glybera alipogene tiparvovec is qualified as a new active substance.

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Appendix I

Divergent Positions

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Appendix - Divergent Position(s)

The undersigned member of CHMP did not agree with the CHMP opinion recommending the granting of a Marketing Authorisation for Glybera in adult patients diagnosed with familial Lipoprotein lipase deficiency and suffering from severe or multiple pancreatitis attacks despite dietary fat restrictions.

The reasons for divergent opinion were as follows:

Despite the very careful re-evaluation of the dossier and the arguments of the company in re-analyzing their data, the grounds for refusal initially voted have not been satisfactorily resolved and there are still uncertainties on the robustness and the relevance of the clinical results submitted in the dossier. As such, the Benefit Risk ratio remains negative. The following points are noted.

- The efficacy has not been sufficiently demonstrated. In the majority of patients, a sustained reduction in fasting triglycerides (TG) was not demonstrated at 6-months and beyond. Furthermore, the post-prandial chylomicron (CM) level is based on a very limited number of patients (5/5 patients at 14 weeks and 3/3 patients at 52 weeks).
- Pancreatitis data, which were analysed retrospectively, have not sufficiently established a reduction attributable to Glybera even in the proposed restricted indication of LPLD patients with multiple or severe pancreatitis attacks. Pancreatitis rates during the run in part of the trial were comparable to those seen after Glybera administration. The interpretation of the data was difficult due to the fact that the follow-up period after Glybera treatment was considerably shorter than the pre-Glybera treatment period. The robustness of the data is hampered by the highly variable number of events in the historical data where several patients had long pancreatitis-free intervals followed by cluster of events. This proposed restricted indication included data on 12 patients, six of whom had not experienced pancreatitis events in the pre-treatment period comparable to the duration of follow up post therapy. Further, as noted in the SAG meeting, it cannot be excluded that potential decrease of pancreatitis events in patients treated with Glybera is due to other factors (i.e. changes in lifestyle/diet). It can therefore not currently be concluded that any changes seen in pancreatitis events were definitely attributable to Glybera.
- The natural course of disease is highly influenced by dietary and life style habits. There are insufficient pretreatment data concerning these factors to support a positive clinical effect of Glybera in terms of diet relaxation or quality of life in treated patients.
- There remain concerns related to a large number of i.m. injections under epidural anaesthesia, and immune suppression for 3 months.

The applicant requested consideration of its application for a Marketing Authorisation under exceptional circumstances. The rarity of the disease is well acknowledged, as well as the evolution of the knowledge in both the physiopathology of the disease and the variability of the population. It is acknowledged that the overall data show suggestion of efficacy and the difficulty in obtaining pancreatitis data in such a rare disease is understood and accepted. However, the efficacy data are not considered robust enough and need to be further demonstrated prior approval, by providing for example additional CM data in patients with LPLD. Even accepting a limited dataset, better evidence of a positive clinical benefit would be required for a positive opinion. As explained above, the efficacy and safety have, with the current data, not been sufficiently demonstrated. Based on the lack of evidence of efficacy and safety and a correlation between PK/PD/surrogate markers and pancreatitis events it is concluded that clinical benefit has not been sufficiently demonstrated.

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The post authorization CM study imposed in the conditions should have been completed before authorisation.

Bonn, 19 July 2012

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Concepcion Prieto Yerro

David Lyons

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