ARTICLE

Re-examination of regulatory opinions in Europe: possible contribution for the approval of the first gene therapy product Glybera

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The first commercially approved human gene therapy in the Western world is Glybera (alipogene tiparvovec), which is an adenoassociated viral vector encoding the lipoprotein lipase gene. Glybera was recommended for marketing authorization by the European Medicines Agency in 2012. The European Medicines Agency had only ever reviewed three marketing authorization applications for gene therapy medicinal products. Unlike in the case of Glybera, the applications of the first two products, Cerepro and Contusugene Ladenovec Gendux/Advexin, both of which were for cancer diseases, were withdrawn. In this report, we studied the European public assessment reports of the three gene therapy products. During the assessment process, Glybera was re-examined and reviewed for a fourth time. We therefore researched the re-examination procedure of the European Union regulatory process. Approximately 25% of the new medicinal products initially given negative opinions from the Committee for Medicinal Products for Human Use were ultimately approved after re-examination from 2009 to 2013. The indications of most medicines were changed during the re-examination procedure, and the products were later approved with a mode of approval. These results suggested that the re-examination system in the European Union contributed to the approval of both several new drugs and the first gene therapy product.

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INTRODUCTION

The first commercially approved gene therapy product in the Western world is Glybera (alipogene tiparvovec), which is based on an adenoassociated viral (AAV) vector for the treatment of the inherited metabolic disorder lipoprotein lipase (LPL) deficiency (LPLD).1,2 The marketing authorization for Glybera, which was valid throughout the European Union (EU), was issued on 25 October 2012. This approval made a great impact on the world, and it opened the door for a gene therapy market in the near future.

In the EU, advanced-therapy medicinal products (ATMPs) are medicines for human use that are based on gene therapy, somatic-cell therapy or tissue engineering. The regulatory framework for ATMPs was established in 2007,3 and the Committee for Advanced Therapies (CAT) was in place in the European Medicines Agency (EMA) in 2009. The CAT is a multidisciplinary committee of the best experts in Europe tasked to assess the quality, safety, and efficacy of ATMPs and to prepare a draft opinion on each ATMP application before the Committee for Medicinal Products for Human Use (CHMP) adopts their opinion. Several researchers have noted that this EU regulatory framework for advanced therapies contributed to their approval of the first gene therapy product.4 In addition, some groups have shown that many factors such as animal models and other regulatory aspects also encouraged the marketing approval of Glybera.5–10 From the viewpoint of the recapitulation of the features of human LPLD by animal models, the spontaneously generated LPL catalytically inactive mutant cats was critical for the approval of Glybera.5,7,10 though only 27 human patients were involved in the clinical trials.6,8 Glybera was designated as an orphan medicinal product in the EU.11 In their review article, Melchiorri et al. stated that all of the orphan drugs for ultra-rare diseases, which they defined as a prevalence of less than 1 in 100,000, ever assessed by CHMP were for disease conditions that follow either a continuously progressive course of deterioration or a very active disease course if left untreated.9 In contrast, LPLD results in pancreatitis, which exhibits a much more unpredictable and fluctuating disease course. Therefore, Melchiorri et al. explained that either a large clinical study or a long follow-up would be required as the clinical trial for Glybera. Because there were limitations incurred by its ultra-rare designation, Glybera was approved under exceptional circumstances after a re-examination of the CHMP’s opinion.5,63 “Under exceptional circumstances”12 and “conditional marketing authorization”13 are types of approval of a drug for early market access in the EU.14

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Before Glybera, the marketing authorization applications (MAAs) for other gene therapies, Cerepro\(^{15,16}\) and Contusugene Ladenovec Gendux (CLG)\(^{17}\) (formerly named Advexin),\(^{18}\) were submitted to the EMA but were withdrawn at the end of the process. Cerepro was intended for the treatment of high-grade glioma. CLG and Advexin were the same products but had different indications. CLG was for recurrent or refractory squamous cell carcinoma of the head and neck (SCCHN), and Advexin was for Li-Fraumeni cancer.

In this article, we studied the assessment processes of Glybera, Cerepro, and CLG/Advexin to discuss issues for gene therapy products as these three are the only gene therapy products to be evaluated by the EMA so far. Furthermore, we summarized the recent results of the re-examination of the new medicinal products and ATMPs in the EU because, in our opinion, we thought that the re-examination procedure was one of the key events in the approval of Glybera; there is no such re-examination system in the United States or Japan. In addition, we investigated the modes of approval for the re-examined new medicinal products.

### RESULTS

**Overview of gene therapy products in the EU**

The information for Glybera, Cerepro, and CLG/Advexin is summarized in Table 1. The regulatory events for the products are illustrated in the timeline in Figure 1. Glybera, Cerepro, and Advexin were granted orphan designations in 2004, 2002, and 2006, respectively. CLG is the same product as Advexin but is not an orphan drug because its indication SCCHN is not a rare disease in the EU. The MAA of Advexin was submitted before the framework for ATMPs because its indication SCCHN is not a rare disease in the EU. The MAA of Advexin was submitted before the framework for ATMPs had been established. CLG is classified as an ATMP. The second application of Cerepro was assessed by the CAT as an ATMP and was withdrawn after an adoption of a negative opinion but before the re-examination was finished.

**Table 1 Approved or withdrawn gene therapy product applications for marketing in the EU**

| Trade name (INN) | Applicant | Vector | Transgene | Approval/withdrawal date | Indication |
|-----------------|-----------|--------|-----------|--------------------------|------------|
| Glybera (alipogene tiparvovec) | Amsterdam Molecular Therapeutics B.V./uniQure biopharma B.V.* | Adenoassociated virus | Human lipoprotein lipase (LPL) gene variant LPL\(^{1447X}\) | Approved, 25 October 2012 | For adult patients diagnosed with familial LPL deficiency and suffering from severe or multiple pancreatitis attacks despite dietary fat restrictions |
| Cerepro (sitimagene ceradenovec) | Ark Therapeutics Ltd.* | Adenovirus | Herpes simplex virus-thymidine kinase gene | Withdrawn, 8 March 2010 | In combination with ganciclovir sodium for the treatment of operable high grade glioma |
| (Adenovirus-mediated herpes simplex virus-thymidine kinase gene) | | | | Withdrawn, 13 July 2007 | |
| Contusugene Ladenovec Gendux (contusugene ladenovec) | Gendux Molecular Ltd. (Introgen Therapeutics Inc.)* | Adenovirus | Human p53 tumor suppressor gene | Withdrawn, 12 June 2009 | In adults for the treatment of patients with recurrent or refractory squamous cell carcinoma of the head and neck as monotherapy |
| Advexin (contusugene ladenovec) | | | | Withdrawn, 17 December 2008 | For the treatment of Li-Fraumeni cancer patients |

EU, European Union; INN, International nonproprietary name.

*Applicant for the marketing authorization for Glybera was changed from Amsterdam Molecular Therapeutics to uniQure biopharma B.V. on 12 July 2012. Ark Therapeutics Group plc sold its operating subsidiaries, including Ark Therapeutics Ltd., to WKD Holding Oy on 15 March 2013. Introgen Therapeutics, Inc. was a parent company of Gendux Molecular Ltd.

Glybera is indicated for LPLD. Cerepro and CLG/Advexin were indicated for cancer. The clinical trials of Glybera, Cerepro, and CLG/Advexin are summarized in Table 2. The clinical trials for Glybera used only historical controls. The clinical trials for Cerepro or CLG/Advexin were controlled to compare the efficacy with the standard therapy. There were no treatment approaches for LPLD, which is Glybera’s target, available for comparison, except for dietary restrictions that are difficult to maintain and do not always have a sufficient effect.\(^{11}\) The most severe complication associated with LPLD is pancreatitis, and the frequency of the attacks of pancreatitis varied across the patients. The frequency of pancreatitis is a patient-oriented outcome, i.e., its clinical relevance is high. This value is the possibly best measure of efficacy and can be used with a historical control to compare before and after administration of Glybera per each patient. Gene therapies must be established in regard to their efficacy, as for all other medicines. Glybera was shown to reduce the frequency of pancreatitis and was ultimately approved.

### Re-examination procedure of Glybera

Glybera encountered negative opinions from the CHMP three times during its assessment process (Figure 1). The CAT and the CHMP noted these concerns in their negative opinions in June 2011: insufficient evidence of a persistent effect in lowering blood fats, insufficient evidence at this stage of a reduction in the pancreatitis rate, concern over the risk associated with the administration of Glybera into patients’ muscles, and the use of immunosuppressive medicines.\(^{11}\) During its first re-examination in October 2011, the CAT thought that the efficacy and safety of Glybera was sufficiently demonstrated in selected patients with LPLD suffering from at least one pancreatitis episode and concluded that the concerns could be addressed with additional postmarketing studies. However, the CHMP maintained their negative opinion, and the
Figure 1  Regulatory timeline of gene therapy products; Glybera, Cerepro, and Contusugene Ladenovec Gendux (CLG)/Advexin. Glybera was approved after the third negative opinion. Each marketing authorization application of Cerepro or CLG/Advexin was submitted twice and withdrawn. The adenovirus-mediated herpes simplex virus-thymidine kinase (Cerepro, first time) was submitted before the advanced-therapy medicinal products (ATMPs) framework started. CLG was not designated as an orphan medicine, whereas Advexin (the same product as CLG) was granted an orphan designation. AMT, Amsterdam Molecular Therapeutics Holding N.V.; CHMP, Committee for Medicinal Products for Human Use; CLG, Contusugene Ladenovec Gendux; EC, European Commission; HSV-tk, herpes simplex virus-thymidine kinase; MAA, Marketing Authorization Application; uniQure, uniQure N.V.; WKD, WKD Holding Oy.

Table 2  Main clinical trials of approved or withdrawn gene therapy products

| Trade name     | Clinical trial phase | Patients number | Investigational medicine | Types of study                                                                 |
|----------------|----------------------|-----------------|--------------------------|--------------------------------------------------------------------------------|
| Glybera        | 1/2                  | 8               | 8                        | Subjected Control | Single-center (the Netherlands), two doses, open-label                           |
|                | 2/3                  | 14              | 14                       | Subjected Control | Single-center (Canada), dose-escalation, open-label                              |
|                | 2/3                  | 5               | 5                         | Control          | Dual-center (Canada), single dose, open-label                                   |
| (total 27)     |                      |                 |                          |                    |                                                                                  |
| Cerepro        | 1                    | 12              | 0                        | 12a               | Single-center (Finland), dose defining                                           |
|                | 1                    | 14              | 7                        | 7a, 7b            | Single-center (Finland), single dose, nonrandomized, open-label                 |
|                | 2                    | 36              | 17                       | 19                 | Single-center (Finland), single dose, randomized, open-label                    |
|                | 3                    | 251            | 124                      | 126               | Multicenter (Europe and Israel), single dose, randomized, open-label            |
| (total 313)    |                      |                 |                          |                    |                                                                                  |
| CLG/Advexin    | 1                    | 34              | 34                       | 0                  | Single-center (USA), nonrandomized, open-label                                  |
|                | 2                    | 61              | 61                       | 0                  | Multicenter (USA), open-label                                                  |
|                | 2                    | 112             | 107                      | 5                  | Multicenter (USA), dose controlled (two doses), randomized, open-label          |
|                | 3                    | 123             | 63                       | 60                 | Multicenter (USA), dosing study, randomized, open-label                         |
| (total 330)    |                      |                 |                          |                    |                                                                                  |

CLG, Contusugene Ladenovec Gendux.

aRetroviral herpes simplex virus-thymidine kinase gene treated. bHistorical control from the asterisked(*) clinical trial. cThe data from this phase III clinical trial was used only for the second marketing authorization application submission. dOne patient withdrew consent.
Figure 2  Summary of re-examination from 2009 to 2013. The numbers and results of the re-examination of the new medicinal products and ATMPs from January 2009 to December 2013 are shown as a flow chart. ATMP, advanced-therapy medicinal products; CHMP, Committee for Medicinal Products for Human Use.

Table 3  Re-examined and approved new medicinal products in the EU from 2009 to 2013

| Trade name (INN) | Therapeutic indication before re-examination | Approved indication | Orphan designation (prevalence in the EU) | Patient numbers in main clinical trials | Mode of approval |
|------------------|---------------------------------------------|---------------------|------------------------------------------|----------------------------------------|-----------------|
| Deltyba (delamanid) | Multidrug-resistant tuberculosis | Use as part of an appropriate combination regimen for pulmonary multidrug resistant tuberculosis in adult patients when an effective treatment regimen cannot otherwise be composed for reasons of resistance or tolerability | Yes (2/10,000) | 481 CMA |
| Defitelio (defibrotide) | Treatment and prevention of hepatic veno-occlusive disease in blood stem cell transplantation therapy | Severe hepatic veno-occlusive disease in hematopoietic stem-cell transplantation therapy | Yes (0.4/10,000) | 356 (prevention), 102 (treating) | UEC |
| Glybera (alipogene tiparvovec) | 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 | Familial lipoprotein lipase deficiency and suffering from severe or multiple pancreatitis attacks despite dietary fat restrictions | Yes (0.02/10,000) | 27 UEC |
| Bronchitol (mannitol) | Cystic fibrosis used either as add-on therapy to rhDNase (another treatment for cystic fibrosis) or on its own in patients who do not benefit from or cannot use rhDNase | Cystic fibrosis in adult patients as an add-on therapy to best standard of care | Yes (1.3/10,000) | 642 N/A |
| Fampyra (fampridine) | Multiple sclerosis to improve their walking | To improve walking ability of adult patients suffering from multiple sclerosis with walking disability | No (8/10,000) | 540 CMA |
| Cayston (aztreonam) | Treatment of chronic airway infections due to *Pseudomonas aeruginosa* in patients with cystic fibrosis aged 18 years and older to improve pulmonary function and respiratory symptoms | Suppressive therapy of chronic pulmonary infection due to *Pseudomonas aeruginosa* in patients with cystic fibrosis aged 18 years and older | Yes (1.3/10,000) | 375 CMA |
| Vedrop (tocofersolan) | Vitamin E deficiency due to digestive malabsorption in pediatric patients suffering from cystic fibrosis, congenital chronic cholestasis or hereditary chronic cholestasis | Vitamin E deficiency due to digestive malabsorption in pediatric patients suffering from congenital chronic cholestasis or hereditary chronic cholestasis, from birth to 16 years of age | No (intended for rare diseases without orphan designation, prevalence is unknown) | 92 UEC |

Underlines in the “Therapeutic indication before re-examination” column highlight withdrawn part of the indication. Underlines in the “Approved indication” column highlight additional eligibility for the indication.

CMA, conditional marketing authorization; EU, European Union; INN, International Nonproprietary Name; N/A, not applicable; rhDNase, recombinant human deoxyribonuclease; UEC, under exceptional circumstances.

*Extended of therapeutic indications to 6 years and older (June 2012). *Switched to full approval (September 2011).
allowed the regulatory boards to refine the studies to hone in on a specific indication. Orphan drugs are often developed for diseases without effective therapies, so appropriate indications may be difficult to determine before the clinical trial is complete. This may be why the re-examined and approved medicines were almost always orphan drugs that were approved with a mode of approval.

**DISCUSSION**

In this study, we reviewed the regulatory timeline of the first approved gene therapy products in the Western world, Glybera, and the two withdrawn gene therapy products, Cerepro and CLG/Advexin (Figure 1). Moreover, we focused on the re-examination procedure of the EMA because this system played an important role in the assessment of Glybera.

Glybera, Cerepro, and Advexin were designated as orphan medicines (Figure 1). The target diseases for gene therapy in this opening era are more likely to be rare diseases. As orphan diseases often have no approved therapies, researchers must try to cure the diseases with novel technologies such as gene therapy. It should be noted that ~80% of rare diseases are of genetic origin.26 However, these states have a small number of patients with severe symptoms, which might make clinical trials for gene therapy more difficult to conduct and the benefits of the medicines more difficult to show. Melchiorri et al. demonstrated that the Glybera's case were unique as LPLD results in unpredictable and fluctuating pancreatitis,9 and the product was approved under exceptional circumstances with the implementation of a specific measures and conditions that would, after approval, allow for systematic enlargement of the database of safety and efficacy.

Regulation (EC) No 726/2004 outlined the maintenance of a centralized procedure for the authorization of medicines and is the legal basis for re-examination. This regulation emerged to consider the probable development of science and technology and the future enlargement of the EU. Thus, the EMA must retain a scientific assessment to ensure the consent of the members with different cultures. At the same time, this regulation guarantees the applicants’ rights to re-examination, as stated in the Whereas clause, the Recital 25 of the Regulation (EC) No 726/2004. The re-examination system was enacted to give opportunities for a new independent assessment system by different rapporteurs and to give the researchers an opportunity to change or refine the indication if the regulatory agency issues a negative opinion. Thus far, most of the products that were approved after re-examination were orphan medicinal products. For some orphan drugs like Glybera, to a priori build the application around a sound indication(s) with an appropriate dataset might have been difficult because of the extremely small number of patients, and the disease symptom. This might be the reason why the applicants started developing drugs for several or broader indications, and the appropriate indication(s) were determined during the re-examination procedure. As science and technology develop, medicines will be more personalized or for rare or severe diseases and will be difficult to evaluate initially. Both regulators and companies should engage to find an appropriate patient population where benefit/risk is positive already in the initial assessment procedure, thus avoiding a time- and resource consuming re-examination. The re-examination system and the modes of approval, however, contributed for the approvals of the medicinal products shown in this study at least as of the moment.

**MATERIALS AND METHODS**

Information of approved/withdrawn gene therapy products

In this article, we refer to both gene therapy products and gene therapy product candidates (i.e., investigational medicines) as “gene therapy products.”
Information of re-examined medicinal products

The information about the re-examined new medicinal products were obtained from the following documents: the CHMP monthly reports, and the CAT monthly reports, and the European public assessment reports or the questions and answers for each product; Deltyba (INN: delamanid), Defitelio (INN: defibrotide), Bronchitol (INN: mannitol), Fampyra (INN: fampridine), Cayston (INN: aztreonam), and Vedrop (INN: tocopherolan).

CONFLICT OF INTEREST

K.Y. is an employee of Asahi Kasei Medical Co., Ltd and Asahi Kasei Pharma Co., Ltd. and the holding company, Asahi Kasei Co., Ltd. (JAPAN). T.O. and M.Y. are shareholders of CellSeed Inc. (JAPAN). The other authors declare no conflict of interest.

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