CURRENT DEVELOPMENTS IN THE MARKET ACCESS CONDITIONS FOR GENE THERAPIES IN GERMANY

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OBJECTIVE

We aim to give an overview on the benefit assessment of those gene therapies (GT) currently or recently available on the German market (cutoff date 2022/10/15). In addition, we intend to give first insights regarding the new instrument of routine practice data collection and evaluation (anwendungsbegleitende Datenerhebung, AbD), which can be imposed by the Federal Joint Committee (G-BA) to evaluate innovative medicines.

METHODS

We searched the database of the G-BA for benefit assessment procedures on GT and assessed their outcome as well as whether AbD was requested. Additionally, we searched the database of the Institute for Quality and Efficiency in Health Care (IQWiG) for AbD concepts and evaluated these regarding study methodology.

BACKGROUND

GT directly modify genes on a cellular level and can potentially cure life-threatening diseases with just a single application. From a regulatory viewpoint GT are classified as advanced therapy medicinal products (ATMPs), along with somatic cell therapy medicines and bioengineered tissue products.

What are GT?

+ **GT contain or consist of a nucleic acid, the carrier of genetic information.**
+ **GT are used to regulate, repair, replace, add or remove a nucleic acid sequence.**
+ **GT have a therapeutic, prophylactic or diagnostic effect which is directly related to the recombinant nucleic acid sequence they contain or to the product formed on the basis of the genetic information.**

Like other innovative pharmaceuticals, GT have to undergo a benefit assessment in Germany according to the Act on the Reform of the Market for Medicinal Products (Arzneimittelmarkt-Neuordnungsgesetz, AMNOG). An overview on the benefit assessment in Germany is given in Figure 1.

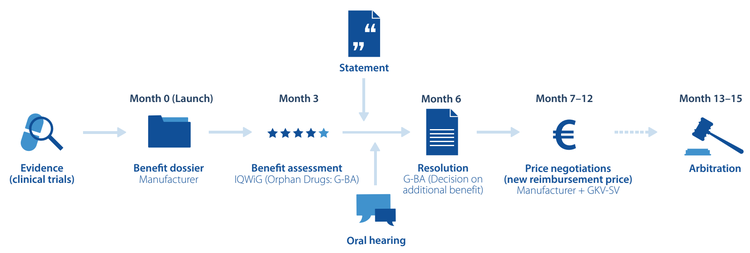

Figure 1: Early benefit assessment in Germany. IQWiG: Institute for Quality and Efficiency in Health Care. G-BA: Federal Joint Committee.

However, some particularities of GT present methodological challenges for the benefit assessment in Germany, compared to conventional drugs:

+ **Comparatively poor evidence base due to small study populations and non-comparative study designs, e.g. single arm studies**
+ **High costs for a potential curative one-time treatment**

Here, we present the results from our research into the market success of GT currently available on the German market and which future challenges these innovative products face.

RESULTS I

Overview: GT on the German market

In total, 17 GT have or had EMA approval status. (**Table 1**)

Currently, eleven GT are available in Germany. Two GT are EMA approved, but have not or not yet entered the German market. Four GT have lost EMA approval status. (**Figure 2**)

In total, eleven GT have undergone benefit assessment by the G-BA so far. For three GT, the benefit assessment procedure is ongoing. Two EMA approved GT have not (yet) entered the German market and have therefore not been subjected to the assessment procedure. One GT was withdrawn from the European market before market entry in Germany, and no benefit assessment was started. (**Figure 3**)

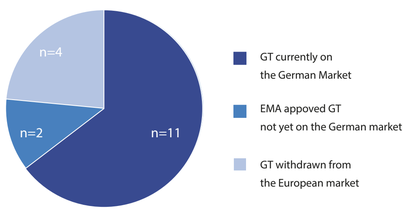

Figure 2: Availability of GT on the German market.

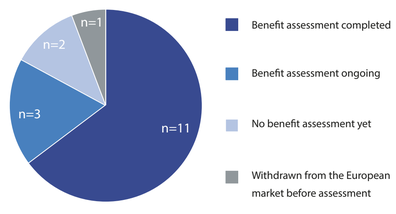

Figure 3: Benefit assessment of GT in Germany.

Table 1: Gene therapies in Germany: availability and benefit assessment.

Drug product	EMA approval date	Market availability in Germany	Benefit assessment in Germany
Glybera® Alipogene tiparvovec	25/10/2012	No (EMA approval status withdrawn)	Yes
Provenge® Sipuleucel-T	06/09/2013	No (EMA approval status withdrawn)	Yes
Imlygic® Talimogene laherparepvec	16/12/2015	Yes	Yes
Strimvelis® An autologous CD34+ enriched cell fraction that contains CD34+ cells transduced with retroviral vector that encodes for the human adenosine deaminase (ADA) cDNA sequence from human haematopoietic stem/progenitor (CD34+) cells	26/05/2016	No	No
Kymriah® Tisagenlecleucel	23/08/2018	Yes	Yes
Yescarta® Axicabtagene ciloleucel	23/08/2018	Yes	Yes
Luxturna® Voretigene neparvovec	22/11/2018	Yes	Yes
Zynteglo® Betibeglogene autotemcel	29/05/2019	No (Withdrawal after price negotiations and arbitration)	Yes
Zolgensma® Onasemnogene abeparvovec	18/05/2020	Yes	Yes
Tecartus® Brexucabtagene autoleucel	14/12/2020	Yes	Yes
Libmeldy® Atidarsagene autotemcel	17/12/2020	Yes	Yes
Skysona® Elivaldogene autotemcel	16/07/2021	No (EMA approval status withdrawn)	No
Abecma® Idecabtagene vicleucel	18/08/2021	Yes	Yes
Breyanzi® Lisocabtagene maraleucel	04/04/2022	Yes	Ongoing
Carvykti® Ciltacabtagene autoleucel	25/05/2022	No	No
Upstaza® Eladocagene exuparvovec	18/07/2022	Yes	Ongoing
Roctavian® Valoctocogene roxaparvovec	24/08/2022	Yes	Ongoing

RESULTS II

Correlation of data base, benefit rating and reimbursement

For our analysis of the benefit assessment of GT, we excluded those two GT with withdrawn EMA approval status for more than five years (Glybera and Provenge). We included all other GT with a completed benefit assessment. In addition to the benefit assessment analysis, we searched the literature for information on the reimbursement of the assessed GT. (**Table 2**) The result of the latest rating is displayed.

Table 2: Gene therapies in Germany: data base, benefit rating and reimbursement.

Drug product	Pharmaceutical company	Label	Benefit assessment in Germany	Data base	Reimbursement
Imlygic®	Amgen	Melanoma	Open-label RCT	3 x No added benefit	Price determined by the arbitration board
Kymriah® (Orphan drug)	Novartis	ALL DLBCL	2 Single arm studies + matched-adjusted indirect comparison Single arm study + indirect comparisons	1 x Non-quantifiable 1 x Non-quantifiable	Innovative Pay-for-performance model
Yescarta® (Orphan drug)	Gilead	DLBCL PMBCL	Single arm study + historical comparisons	1 x Non-quantifiable 1 x Non-quantifiable	Innovative Pay-for-performance model
Luxturna® (Orphan drug)	Novartis	Retinal dystrophy	Open-label RCT + non-randomized observational study	1 x considerable	Innovative Pay-for-performance model
Zynteglo® (Orphan drug)	bluebird bio	β-Thalassemia	Non-controlled studies	1 x Non-quantifiable	Product was withdrawn from the German market after arbitration
Tecartus® (Orphan drug)	Kite	MCL	Single arm study + 2 indirect comparisons	1 x Non-quantifiable	Reimbursement price agreed upon
Zolgensma® (Orphan drug*)	Novartis	SMA	Single arm studies and a double blind RCT on the comparator	4 x No added benefit	Agreement on reimbursement price expected
Libmeldy® (Orphan drug)	Orchard Therapeutics	MLD	Integrated data set of 4 studies and a historical comparison, sibling analysis	1 x Major 1 x Non-quantifiable	Reimbursement price agreed upon
Abecma® (Orphan drug)	Bristol-Myers Squibb	MM	Single arm studies + historical comparison	1 x Non-quantifiable	Agreement on reimbursement price expected

ALL: acute lymphoblastic leukaemia, DLBCL: diffuse larwge B-cell lymphoma, MCL: mantle cell lymphoma, MLD: metachromatic leukodystrophy, MM: multiple myeloma, SMA: spinal muscular atrophy, PMBCL: Primary mediastinal large B-cell lymphoma.
* Although having an orphan drug status, Zolgensma was subjected to a regular benefit assessment because the € 50 million turnover limit was exceeded.

Of the nine GT currently on the German market with a completed benefit assessment, only one product has no orphan drug status, Imlygic. Amgen provided a complete benefit dossier for Imlygic with data from an open-label RCT, however, the appropriate comparator, defined by the G-BA, was not implemented. Imlygic received no additional benefit. Although the reimbursement price was settled by the arbitrary board, the ongoing availability of Imlygic in Germany is evidence for a successful market entry.

GT with an orphan designation received the obligatory non-quantifiable benefit rating with the exception of Luxturna (Novartis) and Libmeldy (Orchard Therapeutics). Novartis presented an open-label RCT for Luxturna and received a considerable added benefit. In the price negotiations with the German health insurance providers, Novartis achieved an innovative pay-for-performance model. Orchard Therapeutics presented an integrated data set of four pivotal studies and a historical comparison including a sibling analysis. They achieved a major benefit rating for one predefined patient population and successfully negotiated a reimbursement price.

Innovative pay-for-performance models were also achieved by Kymriah and Yescarta. Novartis and Gilead presented single arm studies supported by additional data, such as indirect comparisons (Kymriah) or a historical comparison (Yescarta) which appears to have been a good base for the price negotiations.

Since the turnover limit of € 50 million was exceeded by Zolgensma, it was subjected to a regular benefit assessment with Spinraza, an antisense oligonucleotide, as the appropriate comparator. Zolgensma achieved no added benefit. An agreement on the reimbursement price is expected, yet outstanding.

Despite a non-quantifiable benefit rating, Zynteglo was withdrawn from the German market after unsuccessful price negotiations and arbitration in 2021. Bluebird bio had based the assessment on non-controlled studies without any comparative data.

The analysis of the correlation of data base, benefit assessment rating and reimbursement of the available GT with a completed benefit assessment in Germany shows that comparative data such as indirect or historical comparisons can improve the benefit rating and are clearly supportive for successful reimbursement price negotiations.

RESULTS III

A new instrument to evaluate GT

In 2020, the new instrument of routine practice data collection and evaluations (anwendungsbegleitende Datenerhebung, AbD) was introduced by the G-BA based on § 35 a subparagraph 3b SGB V in order to evaluate innovative medicines with a poor evidence base from clinical studies. So far, AbD was imposed on four GT. Two of them, Zolgensma and Tecartus, have already undergone benefit assessment, while the benefit assessment of one GT, Roctavian, is ongoing. For one GT, EtranaDez, an AbD was demanded even before the GT has achieved EMA approval status. All of the AbD concepts published so far are based on register studies. (**Table 3**)

Zolgensma was the first product an AbD was demanded for by the G-BA, and it is the only one for which data collection was started already. The procedure was marked by a considerable delay: E. g., instead of six months, it took almost ten months to finalize the study protocol and statistical analysis plan. From the first resolution of the G-BA for an AbD to the start of data collection, it took approximately 1.5 years. (**Figure 4**)

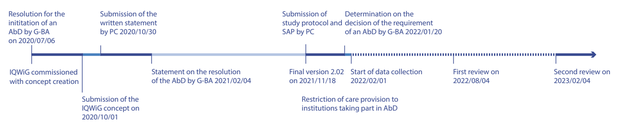

Figure 4: Timeline of the AbD procedure of Zolgensma. It took almost 10 months to finalize the study protocol and SAP.

Table 3: AbDs imposed on GT.

	Zolgensma® Onasemnogen Abeparvovec	Tecartus® Brexucabtagene autoleucel	Roctavian® Valoctocogene Roxaparvovec	EtranaDez® Etranacogene Dezaparvovec
Indication	Spinal muscular atrophy	Mantle cell lymphoma, pretreated patients	Haemophilia A	Haemophilia B
Orphan drug status	Yes	Yes	Yes	Yes
Resolution for the initiation of AbD procedure	2020/07/06	2021/10/07	2022/03/02	2022/08/04
Reason for initiation of AbD procedure	Insufficient data basis regarding long-term outcomes, no valid comparison against therapy alternatives	Questionable representativeness of study population, insufficient causality of therapeutic effect	No comparison against therapy alternatives	No comparison against therapy alternatives
IQWIG concept published	Yes (register study)	Yes (register study)	Yes (register study)	No
AbD procedure status	Data collection ongoing since February 2022, first review on 2022/08/04	Resolution for the demand of an AbD by G-BA from 2022/07/21, PC commissioned with creation of study protocol and SAP until December 2022	IQWIG commissioned with concept creation until September 2022	IQWIG commissioned with concept creation until January 2023

RESULTS IV

Outlook: Future opportunities and challenges for GT

The market entry of GT remains challenging (Table 4). In 2021, one company, bluebird bio, has withdrawn its GT Zynteglo and Skysona completely from the European market, instead focusing on the US market.

In order to enable market entry of these innovative treatments in Germany, for which the evidence base is poor and drug costs are high, the G-BA passes resolutions with a time limitation. AbD is increasingly imposed and even developed further: In April 2022, the IQWiG published a novel concept for the market access of several medicinal products from one active substance class. As an example, the group of GTs for the treatment of diffuse large B-cell lymphoma (DLBCL), primary mediastinal large B-Cell lymphoma (PMBCL) and follicular lymphoma grade 3B (FL3B) was chosen, among them Kymriah, Yescarta and Breyanzi. As a conclusion, the IQWiG suggested the performance of AbDs as adaptive platform studies.

Table 4: Outlook on GT in Germany.

Drug product	Procedure status
Imlygic®	Benefit assessment procedure completed
Kymriah®	Resolutions expire: 01/09/2023AbD with a platform study design might be imposed by the G-BA
Yescarta®	Resolutions expired 15/05/2022, Benefit reassessment result expected for November 2022AbD with a platform study design might be imposed by the G-BA
Luxturna®	Benefit assessment procedure completed
Zynteglo®	Withdrawn from the German market
Zolgensma®	German benefit assessment completed AbD ongoing (register study)
Tecartus®	German benefit assessment completed AbD demanded by the G-BA (register study)
Libmeldy®	Resolution expires: 01/07/2024
Skysona®	European market entry cancelled
Abecma®	German benefit assessment completed
Breyanzi®	German benefit assessment result expected for February 2023 AbD with a platform study design might be imposed by the G-BA
Carvykti®	German market entry expected
Upstaza®	German benefit assessment result expected for February 2023
Roctavian®	German benefit assessment result expected for March 2023 AbD demanded by the G-BA (register study)
EtranaDez®	EMA approval expected AbD demanded by the G-BA (study design yet unclear)

CONCLUSIONS

+ **GT are highly innovative products with large curative potentials. However, the evidence data base is often poor and the costs are very high.**
+ **We found that comparative supporting data such as indirect or historical comparisons are beneficial for the reimbursement price negotiations with health insurance providers even though they do not necessarily have an impact on the benefit rating.**
+ **Several GT have been successfully introduced to the German market, achieving reimbursement by innovative pay-for-performance models.**
+ **Due to the poor data situation, the G-BA passes resolutions with a time limitation for GT. AbD is increasingly demanded and may become standard in Germany for GT evaluation.**
+ **Besides register studies, the concept of adaptive platform studies was suggested by IQWiG to further develop the AbD instrument. Therefore, platform studies might be demanded by G-BA to evaluate new classes of innovative medicinal products such as GT in the future.**

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