THE BENEFIT ASSESSMENT OF GENE THERAPY MEDICINES IN GERMANY

Meyer-Acs M, Phung YT, Domke T, Esser M

co.value, Berlin, Germany

POSC268

BACKGROUND

Gene therapy medicines directly modify genes on a cellular level and can potentially cure life-threatening diseases with just a single application. From a regulatory viewpoint, gene therapies (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 (Arzneimittel-markt-Neuordnungsgesetz, AMNOG). An overview on the benefit assessment in Germy is given in **Figure 1**.

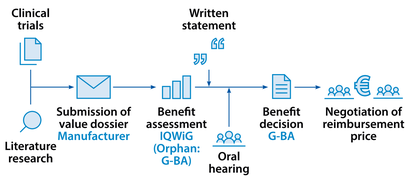

Figure 1: Early benefit assessment in Germany. IQWiG: Institute for Quality and Efficiency in Health Care. G-BA: Federal Joint Committee.

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.

OBJECTIVE

We analyzed benefit assessment of GT in Germany to identify challenges and strategies for future benefit assessment and reimbursement of these products (cutoff date 31/10/2021).

RESULTS I

Overview: GT on the German market

Currently, seven GT are available in Germany (**Table 1**). Three GT are EMA approved, but have not or not yet entered the German market. Two GT have lost EMA approval status and are therefore no longer available in Germany. One GT has been withdrawn from the German market after negotiation of the reimbursement price. (**Figure 2**)

In total, eight GT have undergone benefit assessment by the G-BA so far. For two GT, the benefit assessment procedure is ongoing. Three EMA approved GT have not (yet) entered the German market and have therefore not been subjected to the assessment procedure. (**Figure 3**)

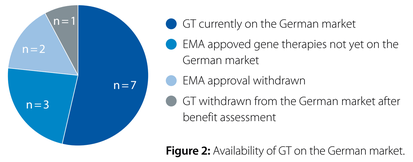

Figure 2: Availability of GT on the German market.

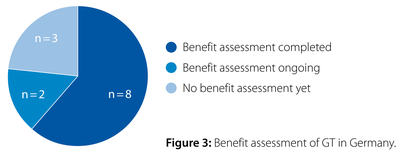

Figure 3: Benefit assessment of GT in Germany.

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

GT	EMA approval date	Market availability in Germany	Benefit assessment in Germany
Glybera®	25/10/2012	No EMA approval status withdrawn	Yes
Provenge®	06/09/2013	No EMA approval status withdrawn	Yes
Imlygic®	16/12/2015	Yes	Yes
Strimvelis®	26/05/2016	No	No
Kymriah®	23/08/2018	Yes	Yes
Yescarta®	23/08/2018	Yes	Yes
Luxturna®	22/11/2018	Yes	Yes
Zynteglo®	29/05/2019	No Withdrawal after price negotiations	Yes
Zolgensma®	18/05/2020	Yes	Ongoing
Tecartus®	14/12/2020	Yes	Yes
Libmeldy®	17/12/2020	Yes	Ongoing
Skysona®	16/07/2021	No	No
Abecma®	18/08/2021	No	No

RESULTS II

Correlation of data base, benefit rating and reimbursement

For our analysis of the benefit assessment of GT, we excluded those with withdrawn EMA approval status (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**)

Table 2: Gene therapies in Germany: data base, benefit rating and reimbursement.
Abbreviations: ALL: Acute Lymphoblastic Leukemia, DLBCL: Diffuse Large B-Cell Lymphoma, MCL: Mantle Cell Lymphoma, PMBCL: Primary Mediastinal Large B-Cell Lymphoma.

GT	Pharmaceutical company	Label	Data base	Benefit rating	Reimbursement
Imlygic®	Amgen	Melanoma	Open-label RCT	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 studies + indirect comparisons	Non-quantifiable	Innovative pay-for-performance model
Yescarta® (Orphan drug)	Gilead	DLBCL PMBCL	Single arm study + historical comparison	Non-quantifiable	Innovative pay-for-performance model
Luxturna® (Orphan drug)	Novartis	Retinal dystrophy	Open-label RCT	Considerable	Innovative pay-for-performance model
Zynteglo® (Orphan drug)	bluebird bio	β-Thalassemia	Non-controlled studies	Non-quantifiable	Product was withdrawn from the German market after price negotiations
Tecartus® (Orphan drug)	Kite	MCL	Single arm study + 2 indirect comparisons	Non-quantifiable	Price negotiation ongoing

Of the six 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 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. 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.

Despite a non-quantifiable benefit rating, Zynteglo was withdrawn from the German market after unsuccessful price negotiations. 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 do not necessarily improve the benefit rating, but are clearly supportive for successful price negotiations.

RESULTS III

Outlook: Future opportunities and challenges for GT

The market entry of GT is challenging (**Table 3**). 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. A recent development is that the G-BA can demand register studies based on § 35 a subparagraph 3b SGB V (Anwendungs-begleitende Datenerhebung). Such register studies take several years to complete and the results will be assessed based on new benefit assessment dossiers.

Table 3: Outlook on GT in Germany.

GT	Procedure status
Imlygic®	Benefit assessment procedure completed
Kymriah®	Resolutions expire: 01/09/2023 Register study is expected to be demanded by the G-BA
Yescarta®	Resolutions expire: 15/05/2022 Register study is expected to be demanded by the G-BA
Luxturna®	Resolution expires: 01/04/2022
Zynteglo®	Withdrawn from the German market
Zolgensma®	50 Mio € turnover limit for Orphan drugs is exceeded Register study demanded by the G-BA German benefit assessment result expected
Tecartus®	Register study demanded by the G-BA
Libmeldy®	German benefit assessment result expected
Skysona®	European market entry cancelled
Abecma®	German market entry expected

METHODS

Information on all benefit assessment procedures of GT were retrieved from the Joint Federal Committee (Gemeinsamer Bundesausschuss, G-BA) database and analyzed regarding:

+ **Therapeutic indication**
+ **Evidence**
+ **Outcome**

Additionally, a literature search was performed to gather supplemental information on the benefit assessment and reimbursement of GT in Germany.

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 price negotiations with health insurance providers even though they do not necessarily have an impact on the benefit rating.**
+ **Due to the poor data situation, the G-BA passes resolutions with a time limitation for GT and demands data from register studies.**
+ **Several GT have been successfully introduced to the German market, achieving reimbursement by innovative pay-for-performance models.**

Contact:
Dr. Mira Meyer-Ács
co.value, Rosenstraße 2
10178 Berlin, Germany
meyeracs@covalue.de
www.covalue.de