

Utrecht University Repository

Title	Illustrating the financial consequences of outcome-based payment models from a payers perspective- the case of autologous gene therapy atidarsagene autotemcel (Libmeldy®)
Authors	Callenbach, Marcelien H E; Schoenmakers, Daphne; Vreman, Rick A; Vijgen, Sylvia; Timmers, Lonneke; Hollak, Carla E M; Mantel-Teeuwisse, Aukje K; Goettsch, Wim G
Published in	Value in Health
Publication Date	2024-08
Link	https://dspace.library.uu.nl/handle/1874/471573
Citation	Callenbach, M H E, Schoenmakers, D, Vreman, R A, Vijgen, S, Timmers, L, Hollak, C E M, Mantel-Teeuwisse, A K & Goettsch, W G 2024, 'Illustrating the financial consequences of outcome-based payment models from a payers perspective- the case of autologous gene therapy atidarsagene autotemcel (Libmeldy®)', Value in Health, vol. 27, no. 8, pp. 1046-1057. https://doi.org/10.1016/j.jval.2024.05.010
Versions / License	Publisher version
Rights	https://www.uu.nl/en/university-library/license-and-reuse-conditions

Health Policy Analysis

Illustrating the Financial Consequences of Outcome-Based Payment Models From a Payers Perspective: The Case of Autologous Gene Therapy Atidarsagene Autotemcel (Libmeldy®)

Marcelien H.E. Callenbach, MSc, Daphne Schoenmakers, MSc, Rick A. Vreman, PhD, Sylvia Vijgen, MSc, Lonneke Timmers, PhD, Carla E.M. Hollak, PhD, Aukje K. Mantel-Teeuwisse, PhD, Wim G. Goettsch, PhD

ABSTRACT

Objectives: To illustrate the financial consequences of implementing different managed entry agreements (managed entry agreements for the Dutch healthcare system for autologous gene therapy atidarsagene autotemcel [Libmeldy]), while also providing a first systematic guidance on how to construct managed entry agreements to aid future reimbursement decision making and create patient access to high-cost, one-off potentially curative therapies.

Methods: Three payment models were compared: (1) an arbitrary 60% price discount, (2) an outcome-based spread payment with discounts, and (3) an outcome-based spread payment linked to a willingness to pay model with discounts. Financial consequences were estimated for full responders (A), patients responding according to the predicted clinical pathway presented in health technology assessment reports (B), and unstable responders (C). The associated costs for an average patient during the time frame of the payment agreement, the total budget impact, and associated benefits expressed in quality-adjusted life-years of the patient population were calculated.

Results: When patients responded according to the predicted clinical pathway presented in health technology assessment reports (scenario B), implementing outcome-based reimbursement models (models 2 and 3) had lower associated budget impacts while gaining similar benefits compared with the discount (scenario 1, €8.9 million to €6.6 million vs €9.2 million). In the case of unstable responders (scenario C), costs for payers are lower in the outcome-based scenarios (€4.1 million and €3.0 million, scenario 2C and 3C, respectively) compared with implementing the discount (€9.2 million, scenario 1C).

Conclusions: Outcome-based models can mitigate the financial risk of reimbursing atidarsagene autotemcel. This can be considerably beneficial over simple discounts when clinical performance was similar to or worse than predicted.

Keywords: delayed payment, gene therapies, health technology assessment, managed entry agreements, orphan designated product, outcome-based reimbursement, pay-for-performance, pharmaceutical reimbursement, uncertainty.

VALUE HEALTH. 2024; 27(8):1046–1057

Highlights

- High-priced one-off gene therapies, such as atidarsagene autotemcel (AA, Libmeldy), are innovative treatments that often fulfill an unmet medical need. However, they represent a reimbursement challenge to many healthcare systems because of substantial upfront costs, which are often incurred all at once, with the claim of durability of effects.
- More guidance is needed to inform decision makers and healthcare payers which type of reimbursement and payment model is suitable. Therefore, a framework and calculation tool were used to help decision makers weigh the different payment scenarios for AA and help them negotiate and implement an outcome-based spread payment model.
- The results from this calculation tool demonstrated that for AA, outcome-based models could considerably mitigate the financial risks for the payer in cases when clinical performance was similar or worse than predicted. The exact outcomes of the calculations should be treated with caution as the discount rates used are arbitrary and should be updated with values from decision makers.

Introduction

Increasing numbers of advanced and regenerative medicines, such as cell and gene therapies, are obtaining regulatory approval in Europe and the United States. Many of these target small patient populations with high unmet medical needs and promise long-term, possibly curative, benefits after a one-off administration.^{1,2} These therapies represent a reimbursement challenge to many healthcare systems because of substantial upfront costs, which are often incurred all at once. Simultaneously, the claim of the durability of effects for years or even a lifetime is often not substantiated by equally long-term evidence.³ This makes the value in clinical practice of these medicines often uncertain at the time a reimbursement decision is made. Consequently, healthcare

payers face the risk of paying high upfront payments, whereas the actual effectiveness of a drug may be lower than predicted.⁴ At the same time, patients may be in need of these medicines, and the marketing authorization holder (MAH) wants to be rewarded for its investments.⁵ Extremely small patient populations complicate the generation of sufficient evidence even more. Delaying access to these innovative therapies until this is achieved seems undesirable.

Managed entry agreements (MEAs) are seen as a promising solution to addressing these high upfront costs and reducing

uncertainties.⁶⁻¹⁷ Such agreements can consist of several elements relating to the price-setting approach (eg, value-based pricing), conditions set to the reimbursement to mitigate the financial impact or remaining uncertainties (financial-based or outcome-based reimbursement models), the timing of the payments (eg, upfront or delayed payment models), and the level at which these payments can be made (eg, on a population, subpopulation, or individual level) (Table 1).^{7,13,18-20} The several elements of MEAs are not mutually exclusive. For example, most outcome-based agreements are accompanied by a modified payment model.⁸ Recently, attention has been paid to more innovative reimbursement and payment model combinations in which the therapy is not paid upfront but with rebates when a result is not achieved—or with a delayed or spread-out payment—possibly only after specific (prespecified) results have been achieved.^{6,7,13} This creates alternative approaches that allow price adjustment with increasing information on value over time.²¹

Although MEAs seem to be increasingly implemented, it is still debated how well the financial risk of reimbursing a novel therapy under significant uncertainties can be mitigated by implementing the more complex MEAs, such as outcome-based reimbursement models or delayed payment models, compared with the most commonly used arrangements, such as discounts or upfront payment models.^{7,9,22-24} Reasons for this ongoing debate are the limited knowledge about the effects of these MEAs in practice and whether they deliver on their promises. Moreover, little guidance is offered to inform pricing and reimbursement decision makers and healthcare payers on when to best use which type of reimbursement and payment model and implementation barriers remain.^{10,25-28} A few frameworks were developed to ease the negotiation process or provide insight into suitable agreements.^{4,29-31} Nevertheless, the provided frameworks and tools were often country-specific and did not quantify the financial and clinical advantages specific agreements can offer. As a result, there

Table 1. Elements of managed entry agreements, with nonexhaustive examples.

Value judgement and price setting	
<ul style="list-style-type: none"> •Reference pricing •Value-based pricing •Cost-based pricing •Two-part pricing 	
Conditions to reduce financial impact or uncertainties	
<ul style="list-style-type: none"> •Financial-based reimbursement models <ul style="list-style-type: none"> •Discount / Rebates: Simple price discounts, publicly or confidentially agreed upon between the payer and manufacturer. •Budget threshold: Maximum amount of reimbursement for an individual innovative treatment (budget threshold/cap) or therapeutic area (dedicated funds) to cap total expenditures. Translates into maximum number of patients treated per year (utilization capping) or sharing of costs with the manufacturer or patients after pre-defined budget threshold has been exceeded. •Price-volume agreement: Drug prices are progressively lowered as more patients receive the treatment. •Outcome-based reimbursement models <ul style="list-style-type: none"> •Pay-for outcome: The level of reimbursement is related to the future performance of the product in either a research or a real world (performance-based) environment. Therapy costs are fully or partially covered by the manufacturer if outcomes are not achieved. •Conditional treatment continuation: Continuation of coverage for individual patients is conditioned upon meeting short-term treatment goals. When agreed conditions are not met, coverage will end. •Coverage with evidence development: Provisional reimbursement of promising technologies with limited clinical evidence. Temporary reimbursement is granted with an obligation for the manufacturer to obtain and provide additional data. Can be organized either with patients only having access when included in the study (only in research) or with an obligation to generate data and unrestricted access (only with research). 	
Timing of payment	
<ul style="list-style-type: none"> •Upfront payment Agreement to pay treatment costs upfront to the manufacturer at time of treatment delivery. •Delayed payment models <ul style="list-style-type: none"> •Payments at outcome achieved: Paying treatment costs only after pre-defined results have been achieved. •Annuity/spread payments: Spreading payments over multiple years, with an agreement upon amount of treatment or outcomes delivered. •Health leasing/ subscription: Paying for unlimited use of a therapy during a predefined period. 	
Level of payment	
<ul style="list-style-type: none"> •(Sub)population level •Patient level 	

is currently a lack of guidance regarding the financial implications of different MEAs aiming to mitigate uncertainty about the clinical effectiveness. This poses challenges for reimbursement stakeholders who must navigate the complexities of determining the optimal conditions for reimbursing a novel, one-off, potentially curative therapy.

To illustrate the potential consequences, the health benefit that can be within the time frame of the agreement and the financial implications of outcome-based reimbursement models with delayed payments, this study used the case study of atidarsagene autotemcel (AA, Libmeldy) in the treatment of metachromatic leukodystrophy (MLD) in which no curative treatment is currently available, focusing on the Dutch setting. In 2021, Orchard Therapeutics BV submitted a reimbursement dossier for AA to the Benelux Initiative, a collaboration between Belgium, The Netherlands, Luxembourg, Austria, and Ireland to deliver sustainable access to innovative medications.^{32,33} The joint health technology assessment (HTA) concluded that, although AA provides promising short-term results, the durability of long-term treatment effects remained uncertain.^{32,33} AA was only beneficial in the early stages of the disease, ie, before extensive irreversible damage to the nervous system has occurred. The precise tipping point after which AA is no longer beneficial is unclear, creating additional uncertainty.^{32,33} Moreover, AA came with a list price of €2 875 000 per patient, introducing a financial challenge because of large upfront payments. These reimbursement and payment challenges factors, among others, provided the opportunity for AA to be used as case study in which many of the common challenges and uncertainties of one-off potentially curative therapies exist.

To mitigate these remaining uncertainties and share the financial risk of reimbursing AA, an outcome-based reimbursement model with delayed payments was advised to the Dutch Minister of Health.²⁹ Unfortunately, the joint Benelux negotiations with the MAH did not lead to a final agreement in 2023, and AA did not gain reimbursement in these countries.^{30,31,34,35} This article aims to contribute to the ongoing discussion about the suitability of MEA by offering a quantitative overview by illustrating the potential consequences of implementing different MEAs by drawing on the case study of AA in the Dutch setting. It provides initial systematic guidance on constructing MEAs, supporting future reimbursement decision making, and facilitating patient access to high-cost, one-off potentially curative therapies addressing high unmet medical needs.

Methods

Case Study Selection

The case study of AA was chosen because when AA came to the market, the question arose whether an outcome-based reimbursement would be suitable because of the large upfront payment and the clinical uncertainties. Together with the Dutch National Healthcare Institute (Zorginstituut Nederland), stakeholders from the MLD initiative registry, and clinicians, the feasibility and desirability of such an outcome-based managed entry agreement were researched, creating a real-world practical opportunity. Other one-off potentially curative therapies with a high unmet medical need for which outcome-based reimbursement models were recommended (eg, Zolgensma, Yescarta, and Luxturna) could have also served as suitable case studies.³⁶ Nonetheless, because the practical opportunity to use AA as a case study presented itself, and given that AA can be seen as representing the typical reimbursement challenges of a one-off treatment, it was deemed to be a good case study to illustrate

the broader issue. Additionally, through the above-mentioned collaborations, there was the possibility to collaborate with stakeholders in the field, who could provide valuable insights into what feasible and clinically relevant input parameters could be, enhancing the value of the example.

MLD, AA (Libmeldy), and the Included Patient Population

MLD is an inherited neurometabolic disorder characterized by damage to the nervous system and other organs, causing progressive symptoms, such as walking difficulties, gradual cognitive deterioration, and eventual early death.³⁷ The clinical course of MLD can be broadly divided into a presymptomatic (PS) stage, a subsequent stage characterized by onset of first symptoms (early symptomatic [ES]), and a symptomatic stage with severe neurological deterioration.³⁷⁻³⁹ Based on the age at onset, 4 types can be distinguished, late-infantile (LI, <30 months), early-juvenile (EJ, 30 months-6 years), late-juvenile (LJ, 6-16 years), and adult (>16 years). There is currently no curative treatment for MLD. Recently, a lentiviral vector-based gene therapy (ie, AA) has been developed.³⁷

The therapeutic indication of AA for which Orchard Therapeutics BV, the MAH, has submitted a reimbursement dossier within the Benelux Initiative, is the “treatment of MLD characterized by biallelic mutations in the arylsulfatase A gene leading to a reduction of the arylsulfatase A enzymatic activity” in presymptomatic forms in children and specific cases in the ES-EJ form.^{29,40} Within the Benelux Initiative, the RIZIV-INAMI (Belgian HTA agency) authored the pharmacotherapeutic part and National Center for Pharmacoeconomics (HTA agency for Ireland) the pharmaco-economic part and budget impact for the 3 participating countries.³² The Dutch National Health Care Institute (Zorginstituut Nederland [ZIN]) reviewed the written reports, and all 3 agencies supported the reports. Based on these reports, ZIN, concluded that Libmeldy, within the Dutch setting, only complies with the statutory criterion “established medical science and medical practice” in children with LI (PS-LI) or EJ (PS-EJ) forms without clinical manifestations of the disease^{29,41} Therefore, this study will only focus on these 2 groups.

Study Design and Input Parameters

A developed framework and practical calculation tool were used to quantify and compare the costs and benefits of different payment scenarios. The used framework consists of several parts in which, first, reimbursement and payment models were matched to the disease and treatment characteristics by defining their main relevant uncertainties, followed by questions to specify the details of the included reimbursement and payment models. Hereafter, the input parameters needed for the operationalization of the calculation, multiple steps, and decisions were determined (more details can be found in [Appendix Materials B and C](#) in [Supplemental Materials](#) found at <https://doi.org/10.1016/j.jval.2024.05.010>). To make the calculation tool applicable to the case of AA for MLD, input was collected from experts in payment and reimbursement decision making, clinical experts, and relevant literature.^{3,7,8,10,13,17,24,42-47} Depending on the type of input parameter for the calculation tool, information was found in recent scientific literature, white papers, and publicly available HTA assessment reports from ZIN (as part of the Benelux Initiative), National Institute for Health and Care Excellence, and incremental cost-effectiveness ratio.^{29,34,48} Additionally, clinical experts in MLD from MLD initiative registry⁴⁹ were involved regarding the selection of relevant outcome measures, in which consensus was sought to define clinically and patient relevant outcome measures that were easily measured in clinical practice.

Table 2. The payment scenarios explored for AA.

Scenario	Assumption	Payment model
Scenario 1.A	All patients are full responders	Discount
Scenario 1.B	All patients respond according to the predicted clinical pathway presented in HTA reports	Discount
Scenario 1.C	All patients are unstable responders	Discount
Scenario 2.A	All patients are full responders	Outcome-based spread payment with a discount
Scenario 2. B	All patients respond according to the predicted clinical pathway presented in HTA reports	Outcome-based spread payment with a discount
Scenario 2.C	All patients are unstable responders	Outcome-based spread payment with a discount
Scenario 3.A	All patients are full responders	Outcome-based spread payment linked to the WTP*
Scenario 3.B	All patients respond according to the predicted clinical pathway presented in HTA reports	Outcome-based spread payment linked to the WTP
Scenario 3.C	All patients are unstable responders	Outcome-based spread payment linked to the WTP

Details of the payment models		
<p>1. Discounts:</p> <ul style="list-style-type: none"> 60%† discount paid upfront after treatment initiation (T=0) 	<p>2. Outcome-based spread payment with a discount:</p> <ul style="list-style-type: none"> Payments made at: 12-, 24-, 36-, 48- and 60-months Yearly payment proportions increase each year: T1=5%, T2=10%, T3=15%, T4=25%, T5=45% Height of payment depends on measured GMFC-MLD score and associated discount rates † 	<p>3. Outcome-based spread payment linked to the WTP:</p> <ul style="list-style-type: none"> Payments made at: 12-, 24-, 36-, 48- and 60-months Height payment at 12-, 24-, 36-, 48- months depends on measured QALY's and the Dutch WTP threshold. Payment at 60 months depends on measured GMFC-MLD score and associated discount rates†

AA indicates atidarsagene autotemcel; GMFC-MLD, Gross Motor Function Classification in metachromatic leukodystrophy; HTA, health technology assessment; QALY, quality-adjusted life-year; WTP, willingness to pay.

*For this disease, the Dutch willingness to pay is €80 000 per QALY gained.⁵¹

†Given that the authors of this article are not aware of the discounts and other agreements that may be achievable, the discount rates are chosen arbitrarily. The calculation tool enables easy modification of these scenarios to match the decision makers' preferences.

The calculation tool was constructed using Microsoft Excel (Microsoft, Redmond, WA).⁵⁰ Detailed information about the included input parameters can be found in [Appendix Material C](#) in [Supplemental Materials](#) found at <https://doi.org/10.1016/j.jval.2024.05.010>.

Defining Scenarios to Calculate the Consequences of Implementing Different Payment Models

Different payment scenarios were defined to compare the consequences of implementing an outcome-based spread payment model with a simple discount model ([Table 2](#)⁵¹).

The scenarios and discount rates used are fictional but were loosely derived from information on the previously advised discount rates to the Ministry of Health for Dutch pricing negotiations and were not based on specific input from the involved stakeholders.⁵² A 5-year time frame for the payment agreement was chosen based on recommendations made in literature and input from clinicians as this time frame is long enough to allow for a reliable clinical assessment and adequate data collection but, at the same time, not so long that they become difficult to execute.^{10,13,47,53,54}

Three payment models were included: (1) a discount (60%, arbitrary choice), (2) an outcome-based spread payment model

Table 3. Framework to define relevant input parameters and justify the made decisions for the calculation tool.

Steps	Input
Step 1-Define relevant characteristics of the disease	
Subpopulations	PS-LI ^{38,56} PS-EJ ^{38,56} ES-EJ (not eligible for reimbursement, therefore excluded) ^{38,56}
Incidence	1 or 2 patients per year (8 patients over the 5-year time frame of the payment agreement) ²⁹
Prevalence	None ²⁹
Step 2-Define relevant characteristics of the treatment	
Outcome measure(s) that are both relevant clinically and to patients which are frequently measured	GMFC-MLD ^{*56}
Administration	One-off treatment
Step 3-Match reimbursement models with the disease and treatment characteristics	
What are the main clinical challenges/uncertainties that should be addressed	No long-term data available to support the sustainability of treatment effects (desired follow-up period needs to be 10-15 y) ²⁹ Limited patient number included in the clinical study (n = 29) ⁵⁵ (patients were treated and followed up at Ospedale San Raffaele, Milan, Italy) According to ZIN, clinical effectiveness in symptomatic EJ patients is unclear (not eligible for reimbursement, therefore excluded) ²⁹
Step 4-Matching a payment model with the disease and treatment characteristics	
What are the main financial challenges/uncertainties that should be addressed	High upfront payments
Step 5-Define the outcome-based spread payment specifications for the case of AA	
What is the main outcome measure to which the payment will be linked?	The GMFC-MLD score classifies motor function on 7 levels. Motor deterioration is a key feature characteristic of late-infantile and early-juvenile MLD patients. ⁵⁶ (Detailed information is provided in Appendix Materials C in Supplemental Materials found at https://doi.org/10.1016/j.jval.2024.05.010 .)
How do we define success?	Full responder GMFC-MLD 0 GMFC-MLD 1 Partial responder (defined as a maximum decline of one point) [†] GMFC-MLD 2 GMFC-MLD 3 Nonresponder GMFC-MLD 4 GMFC-MLD 5 GMFC-MLD 6 Death -
Will the payment be made at a patient or a population level?	A patient level
At which moment should this main outcome measure be measured?	At T = 0, 12-, 24-, 36-, 48, and 60 months after administration of the medicine
Is there a registry in place?	Yes, the MLDi registry ⁴⁹ (Detailed information is provided in Appendix Materials C in Supplemental Materials found at https://doi.org/10.1016/j.jval.2024.05.010 .)
Does it register the main outcome measure?	Yes, the GMFC-MLD score is routinely determined and registered
What is the chosen time frame to spread out the payments?	Five years
Step 7-Define input parameters (gained benefits and costs)	
Proportions subpopulations	PS-LI = 20,3% and PS-EJ = 35,4% (26). ES-EJ = 0,0% (not eligible for reimbursement, therefore excluded) ²⁹

continued on next page

Table 3. Continued

Steps	Input																				
Uptake assumptions for incident patients in ZIN	Year 1 = 2 patients Year 2 = 1 patient Year 3 = 2 patients Year 4 = 1 patient Year 5 = 2 patients																				
Health states relevant to measure the performance	The cost-effectiveness model was based on 8 health states: 7 motor function health states as defined by the GMFC-MLD score, and a death state ^{29,34,48}																				
Utilities per health state	Utilities (per year) for each subpopulation were used for BSC and AA ^{29,34,48}																				
Transition probabilities	Each subpopulation's transition probabilities (per month) were used for BSC and AA, calculated using information from the assessment reports of ZIN, NICE, and ICER ^{29,34,48}																				
Response classification	The transition between GMFC-MLD health states depends on a specific response classification of what proportion of each subpopulation will stabilize at which GMFC-MLD scores ^{29,34,48}																				
List price	€2 875 000																				
Payment scenario 1-Discount rates‡	60%																				
Payment scenario 2-Discount rates‡	<table border="1"> <tbody> <tr> <td rowspan="2">Full responder</td> <td>GMFC-MLD 0</td> <td>40%</td> </tr> <tr> <td>GMFC-MLD 1</td> <td>60%</td> </tr> <tr> <td rowspan="2">Partial responder</td> <td>GMFC-MLD 2</td> <td>80%</td> </tr> <tr> <td>GMFC-MLD 3</td> <td>85%</td> </tr> <tr> <td rowspan="3">Non responder</td> <td>GMFC-MLD 4</td> <td>Stop payments</td> </tr> <tr> <td>GMFC-MLD 5</td> <td>Stop payments</td> </tr> <tr> <td>GMFC-MLD 6</td> <td>Stop payments</td> </tr> <tr> <td>Death</td> <td>-</td> <td>Stop payments</td> </tr> </tbody> </table>	Full responder	GMFC-MLD 0	40%	GMFC-MLD 1	60%	Partial responder	GMFC-MLD 2	80%	GMFC-MLD 3	85%	Non responder	GMFC-MLD 4	Stop payments	GMFC-MLD 5	Stop payments	GMFC-MLD 6	Stop payments	Death	-	Stop payments
Full responder	GMFC-MLD 0		40%																		
	GMFC-MLD 1	60%																			
Partial responder	GMFC-MLD 2	80%																			
	GMFC-MLD 3	85%																			
Non responder	GMFC-MLD 4	Stop payments																			
	GMFC-MLD 5	Stop payments																			
	GMFC-MLD 6	Stop payments																			
Death	-	Stop payments																			
Payment scenario 2-yearly payment proportions	T1 = 5%, T = 2 = 10%, T3 = 15%, T4 = 25%, T5 = 45% (see Appendix Materials D in Supplemental Materials found at https://doi.org/10.1016/j.jval.2024.05.010)																				
Payment scenario 3-discount rates‡	60%																				
Payment scenario 3-yearly payment proportions	T1 = Linked to QALYs, T2 = Linked to QALYs, T3 = Linked to QALYs, T4 = Linked to QALYs, T5 = Projected QALYs																				

AA indicates atidarsagene autotemcel; BSC, best supportive care; EJ, early-juvenile; ES-EJ, Early-symptomatic early-juvenile; GMFC-MLD, Gross Motor Function Classification in metachromatic leukodystrophy; HTA, health technology assessment; ICER, incremental cost-effectiveness ratio; MLD, metachromatic leukodystrophy; MLDi, metachromatic leukodystrophy initiative; NICE, National Institute for Health and Care Excellence; NL, National Healthcare Institute (Zorginstituut Nederland); PS-EJ, presymptomatic early-juvenile; PS-LI, Presymptomatic late-infantile; QALY, quality-adjusted life-year; ZIN, Zorginstituut Nederland.

*GMFC-MLD is an assessment tool designed and evaluated to measure changes in gross motor function over time or with intervention in children with MLD.³⁹

[†]In line with the assumptions presented in HTA reports of ZIN, NICE, and ICER.^{29,34,48}

[‡]Given that the authors of this article are not aware of previously agreed upon confidential discounts or agreements, the discount rates were set arbitrarily. The calculation tool enables easy modification of these scenarios to match decision makers' preferences.

with a discount (depending on what outcome is measured), and (3) an outcome-based spread payment model linked to the Dutch willingness to pay (WTP, €80 000 per QALY gained⁵¹) for this disease with a discount (depending on what outcome is measured). For each type of payment model, 3 different outcome scenarios were proposed to illustrate the extremes and thus showcase the “gray” area (everything in between) of what the potential impact could be under the clinical uncertainty on the costs for AA. The included scenarios in which (1) patients are full responders, (2) a scenario that follows the transition probabilities to all health states according to the predicted clinical pathway presented in HTA reports,^{29,34,48} and (3) a scenario in which patients are assumed to be unstable responders and will not stabilize at any Gross Motor Function Classification (GMFC)-MLD score after being treated with AA but instead keep transitioning to worse health states. In [Appendix Materials B and C in Supplemental Materials](https://doi.org/10.1016/j.jval.2024.05.010) found at <https://doi.org/10.1016/j.jval.2024.05.010>, further elaboration on the different payment scenarios and their calculations can be found.

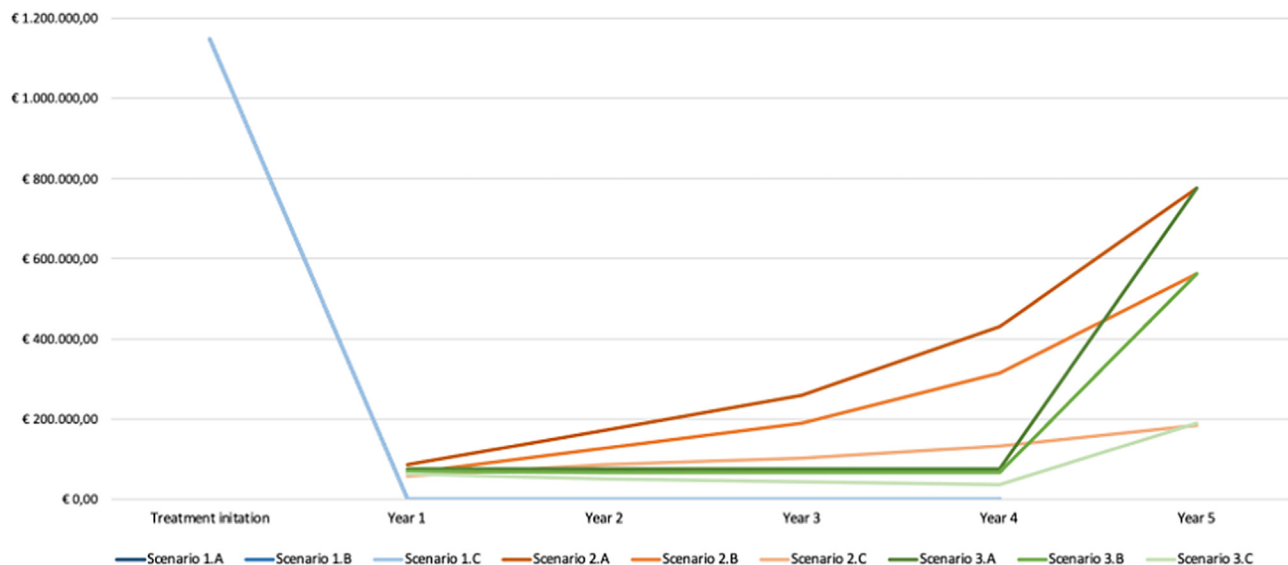
Data Analysis

[Table 3](https://doi.org/10.1016/j.jval.2024.05.010)^{29,34,38,39,48,49,55,56} summarizes the different input parameters and payment scenarios. For each of the 9 different payment scenarios, the calculation tool calculated the following:

- The health benefit gain for AA within the time frame of the payment agreement (expressed in undiscounted QALYs gained).
- The therapy costs associated with the MEA for an average patient.
- The total budget impacts.

Based on the calculations, first, the associated costs with reimbursing AA for an average patient by implementing the different MEAs are presented, followed by the results from the annual budget impact of the different payment scenarios. Hereafter, the results weigh the benefits and costs associated with implementing the various payment models under different scenarios.

Figure 1. Treatment costs per year for an average single patient (using the proportion of the 2 subpopulations, see Table 1) associated with the different payment scenarios*. *Scenario 1A = full responder + discount (60%); scenario 1B = all patients respond according to the predicted clinical pathway presented in HTA reports + discount (60%); scenario 1C = unstable responder + discount (60%). Scenario 2A = full responder + outcome-based spread payment with a discount; scenario 2B = all patients respond according to the predicted clinical pathway presented in HTA reports + outcome-based spread payment with a discount; scenario 2C = unstable responder + outcome-based spread payment with a discount. Scenario 3A = full responder + outcome-based spread payment linked to WTP with a discount; scenario 3B = All patients respond according to the predicted clinical pathway presented in HTA reports + outcome-based spread payment linked to WTP with a discount; scenario 3C = unstable responder + outcome-based spread payment linked to WTP with a discount.



HTA indicates health technology assessment; WTP, willingness to pay.

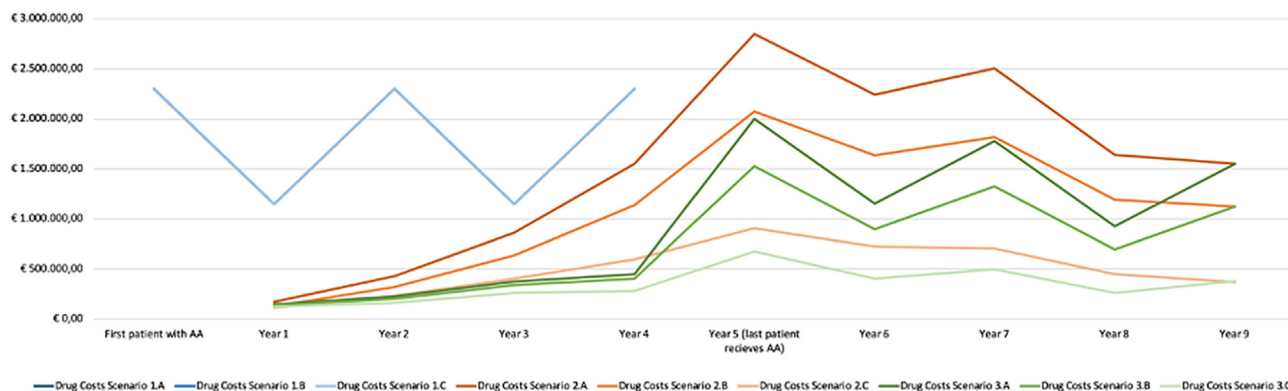
Results

The Costs Associated With Reimbursing AA For an Average Patient By Implementing the Different MEAs

Implementation of a discount leads to equal treatment costs of €1.15 million in all scenarios (1A, 1B, and 1C) (Fig. 1) for a single

average patient treated with AA. The therapy costs are paid upfront in the first year, whereafter no further payments are made within the time frame of the payment agreement. Implementing an outcome-based spread payment model with a discount for 5 years increases associated costs yearly (2A, 2B, and 2C). In the first year, these outcome-based discounted payments are relatively small (2A = €86 000; 2B = €64 000; 2C = €57 000). However, they

Figure 2. The budget impact of the different payment scenarios for all projected patients will be included in the agreement, ie, 8 patients spread over 5 years (see Table 1). Patients starting in year 4 (the last year of patient inclusion in the agreement) will be followed until year 9.*Scenario 1A = full responder + discount (60%); scenario 1B = all patients respond according to the predicted clinical pathway presented in HTA reports + discount (60%); scenario 1C = unstable responder + discount (60%). Scenario 2A = full responder + outcome-based spread payment with a discount; scenario 2B = all patients respond according to the predicted clinical pathway presented in HTA reports + outcome-based spread payment with a discount; scenario 2C = unstable responder + outcome-based spread payment with a discount. Scenario 3A = full responder + outcome-based spread payment linked to WTP with a discount; scenario 3B = all patients respond according to the predicted clinical pathway presented in HTA reports + outcome-based spread payment linked to WTP with a discount; scenario 3C = unstable responder + outcome-based spread payment linked to WTP with a discount.



HTA indicates health technology assessment; WTP, willingness to pay.

will increase over the years, specifically in the last years, the payment amounts diverge based on what will happen clinically (2A = €776 000; 2B = €562 000; 2C = €185 000). In payment scenarios 3A, 3B, and 3C, in which an outcome-based spread payment linked to the WTP with a discount is implemented, the first 4 payments, including the set discount rate, lie below the Dutch WTP threshold (<€80 000 per QALY gained⁵¹) in correspondence with measured GMFC-MLD score and their corresponding utilities (3A = €75 000; 3B = €70 000; 3C = €63 000). In the final fifth year, the payment amount increases substantially because of the remaining therapy costs that are to be paid (based on GMFC-MLD measurement in year 5 and including a discount) (3A = €776 000; 3B = €562 000; 3C = €189 000).

Comparing the annual budget impact of the different payment scenarios

Figure 2 presents the budget impacts of the different payment scenarios over the time frame of the different payment agreements. All payment scenarios 1 have the same budget impact because of the same discount rates applied and the fact that the payments are unrelated to patient outcomes and only the number of patients treated (€2.3 million or €1.15 million). The results for the outcome-based delayed payment models illustrate the extended time frame due to the delayed payment model compared with implementing a discount. In scenarios 2A, 2B, and 2C show that the financial burden is more evenly spread over the years compared with payment scenario 1A, 1B, and 1C. The budget impact estimates of payment scenarios 3A, 3B, and 3C illustrate that implementing an outcome-based spread payment linked to the WTP with a discount has the lowest annual budget impact, especially in the first 4 years.

Weighing the Benefits and Costs Associated With Implementing the Different Payment Models Under the Various Scenarios

Without implementing any form of reimbursement or payment agreement to mitigate the high upfront costs or remaining

uncertainties, the total assumed treatment costs (for the theoretical 8 patients) when reimbursing AA for 5 years will be €23 million.

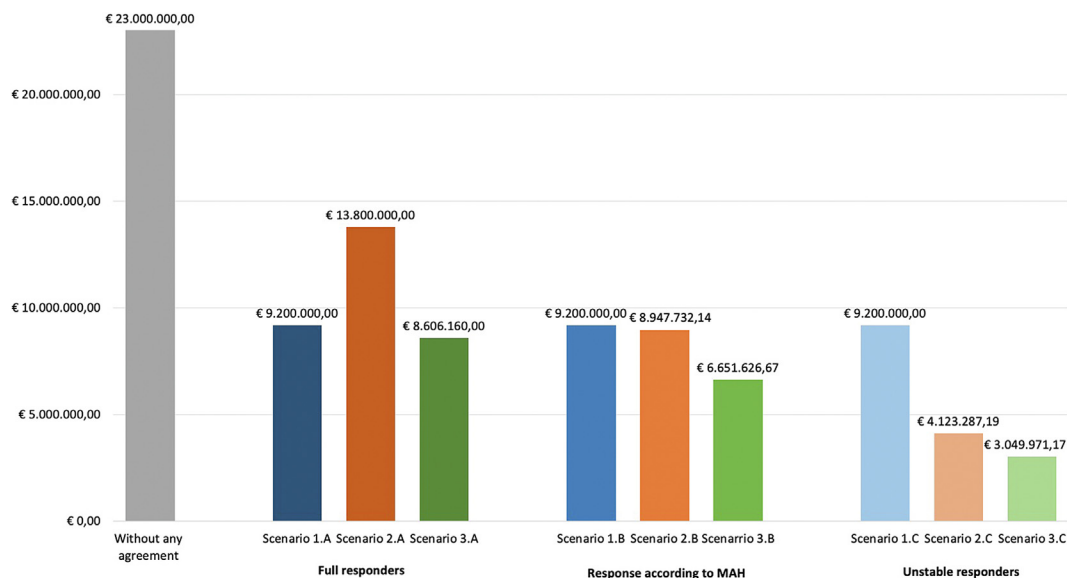
In total, 11.40 QALYs (n = 8) can be gained during the 5-year time frame of the payment agreement (scenario B). When assuming that all 8 patients will be full responders (scenario A), a total of 13.60 QALYs can be gained during this time frame. Under scenario C (unstable responder), a total of 6.00 QALYs can be gained.

Figure 3 presents the total assumed treatment costs (n = 8) of the different payment scenarios with a 5-year payment agreement under the assumptions used in the present study. If patients will be full responders, implementing an outcome-based spread payment model (2A) with a discount is financially the least favorite option from a healthcare payer perspective, whereas implementing a discount (1A) or an outcome-based spread payment linked to the WTP with a discount (3A) will lead to considerably lower associated costs. When patients responded according to the predicted clinical pathway presented in HTA reports, implementing a discount (1B) or an outcome-based spread payment with a discount model, the associated costs of AA (2B) will not differ substantially. However, when an outcome-based spread payment model linked to the WTP is implemented (3B), a considerable saving can be seen compared with the other 2 payment scenarios. Finally, if patients turn out to be unstable responders (ie, perform worse than the assumptions according to the predicted clinical pathway presented in HTA reports), implementing an outcome-based spread payment with a discount (2C) or an outcome-based spread payment linked to the WTP with a discount (3C) will lead to substantially lower costs compared with implementing a discount (1C).

Discussion

Our study aimed to illustrate the financial consequences of implementing different payment models for AA to accommodate the uncertain long-term benefits and associated financial risk.

Figure 3. Total calculated costs of AA according to the different payment scenarios* over 5 years. *Payment model 1 = discount (60%); payment model 2 = outcome-based spread payment with a discount; payment model 3 = outcome-based spread payment linked to WTP with a discount.



AA indicates atidarsagene autotemcel; WTP, willingness to pay.

Stakeholders are provided with an analysis of implementing an outcome-based spread payment model compared with a simple discount. The results showed that the associated costs for an average patient differed substantially per payment model under different scenarios of patient response to therapy. A simple discount is obvious in the case of sufficient evidence that all patients are full responders, which is not the case for AA. If patients respond according to the predicted clinical pathway presented in HTA reports, an outcome-based spread payment linked to the WTP model with a discount will lead to significantly lower associated costs for equal health benefits. The financial consequence of using this model becomes even greater when patients do not respond according to the predicted clinical pathway presented in HTA reports but are unstable responders. However, the reality might be that some patients will fully stabilize, whereas others may show some deterioration, resulting in average patient outcomes falling in the gray area between the presented extreme scenarios.⁵⁵ Given the unavoidable assumptions regarding the long-term effectiveness of AA in MLD, our results show that although an outcome-based spread payment model might incur higher associated costs should all patients achieve optimal responses, the critical distinction lies in their adeptness at handling the risk of potentially lesser treatment effects. For risk-averse decision makers, the prospect of allocating €9.2 million for a treatment that fails to yield desired outcomes could pose a graver concern than investing €13.8 million in a treatment that proves less effective. Thus, although acknowledging the complexity inherent to more innovative payment models, implementing outcome-based delayed payment models could offer a pragmatic solution to navigating the uncertainties of treatment effectiveness, ultimately ensuring both careful resource allocation and improved patient access.

In previous studies, the potential of outcome-based reimbursement and delayed payment models, when correctly implemented, has frequently been described, and stakeholders' preferences to implement them more regularly have been highlighted.^{11,24,43,57-60} Specifically for high-priced innovative therapies, some frameworks and tools were developed to ease the negotiation process or provide insight into what suitable agreements could be but not consider the economic and clinical advantages specific agreements can offer.^{4,61-63} Hence, multiple aspects need to be considered to determine whether the agreement is fit to fly. Literature has outed that this should not (solely) be measured by their impact on costs and health-related benefits but also by what the further impact on the healthcare system will be.^{4,44,64} An important consideration in this is the implementation costs, in which it could be argued that the implementation costs of an outcome-based spread payment should not exceed the budget impact of implementing a simple discount payment model. The current study illustrated the difference between the budget impact of implementing a simple discount payment model under the worst-case scenario and the budget impact of a simple discount. Using these results, stakeholders are given a first estimation of how the maximum implementation-related costs could be estimated, which is not more than the difference between the costs associated with the best and worst-case scenario.

One-off gene therapies, such as AA, often come with the promise of delivering long-term, possibly curative, benefits.^{1,2} Given that this long-term effectiveness data are often unavailable, assumptions and extrapolations must be made at some point in all scenarios. In the case of AA, multiple European countries faced a similar reimbursement challenge arising from these assumptions, and substantial price reductions were argued. For example, the National Institute for Health and Care Excellence agreed on a significant price reduction in their reimbursement

decision making.⁶⁵ In other countries, similar questions were raised about whether the high upfront payments are justified and should be linked to achieved outcomes.⁶⁵⁻⁶⁸ With upfront payment and a simple discount, these assumptions are made at the start of treatment. Whereas, with the outcome-based spread payment models, assumptions about long-term effects are delayed, gradually phased in with the partial payments made each year over for example 5 years. With the outcome-based spread payment model linked to WTP, payments are directly related to health benefits (in QALYs) gained in the first 4 years. Only after 5 years, when more information is available about the stabilization of the patient, the bulk payment for the rest of the patient's lifetime is paid. In summary, the outcome-based models delay the financial impact and allow for anticipation of changing assumptions about effectiveness. Moreover, after the agreement, the additional information gathered about the treated patients may lead to a better estimate of what a fair discounted price might be, possibly leading to a more simplified payment model in the future.^{19,20,69,70}

Recommendations to Reimbursement Decision Makers

Several recommendations to reimbursement decision makers can be made. First, it is recommended to only accept a simple discount as the preferred reimbursement model if the discount is so high that it mitigates the clinical uncertainties (ie, for the Dutch situation: the discounted incremental cost-effectiveness ratio should be well below the Dutch €80 000 per QALY threshold by using a "minimally effectiveness" outcome scenario). If, indeed, a negotiated discount is high enough that even when patients perform very poorly in clinical practice the treatment would still be cost-effective, there is no benefit of an outcome-based agreement. However, without adequate projections of effectiveness, the exact percentage of what constitutes an acceptable discount cannot be calculated. Additionally, it is recommended only to implement an outcome-based spread payment model if the mitigation of clinical (and associated financial) uncertainties is deemed more important than the simplicity of the agreement. There is a large uncertainty "gray" area between these 2 (best-case and worst-case) payment scenarios: it is in these cases that outcome-based agreements can be beneficial. Finally, the implementation feasibility should be thoroughly considered. Implementing outcome-based spread payment models will be more resource intensive (eg, higher transaction and administrative costs), and stakeholders need to be willing to collaborate more closely to determine each aspect of the payment structure in detail where mutual trust is needed and invest their time and resources to answer challenging questions regarding contracts, data collection, and privacy.^{10,44,62,64,71}

Strengths and Limitations

The used framework and calculation tool can be easily added to stakeholders preferences and applied in negotiating MEAs for one-off high-priced gene therapies in which extremely small patient populations complicate generating sufficient evidence, and a high unmet medical need exists. AA yields several advantages to be used as a test case to try these novel outcome-based agreements, especially because the clinical uncertainties are substantial. Still, the budget impact of AA is relatively limited; therefore, (partial) failure of the agreement due to, eg, implementation difficulties, would likely not lead to critical financial problems. Additionally, many of the secondary conditions to a successful implementation of an outcome-based agreement are present for AA, such as a

frequently measured, patient-relevant outcome and the registry already in place.

This study's calculations underlying the results were based on multiple decisions and assumptions. First, the presented QALY results are undiscounted and calculated combining information from several publicly available HTA reports. Hence QALY's might slightly differ from the results in the HTA reports based on the submitted cost-effectiveness model of the MAH. Because the main objective of this study was to illustrate and provide end-users with an overview of different possible scenarios and their consequences, we feel that these simplified assumptions are still valid. Moreover, from an implementation feasibility perspective, it was chosen to select a 5-year time frame for the proposed outcome-based delayed payment models and to focus on 1 main outcome measure, the GMFC-MLD score, which would be easily measured in daily practice and for which consensus existed to be clinically relevant. However, it should be noted that a longer or shorter time frame could have also been possible, and several other relevant outcome measures were described in HTA reports and scientific literature and could also be included in the MEA if preferred.^{29,34,39,48,56} Additionally, the discount rate in the presented scenarios was arbitrarily set at 60%. Therefore, the calculated payment scenarios might only partially reflect the actual situation for AA or any other similar therapy. No published data are available that provide a clear insight into which discounts are negotiated between the payers (in The Netherlands, this is the Ministry of Health, Public Welfare, and Sports for these products) and the industry. However, the Dutch National Health Care Institute recently recommended discount rates for other gene therapies such as Zynteglo (35%) and Zolgensma (50%).^{72,73} This means that the calculated results of implementing a simple discount might be overestimated, making an outcome-based spread payment model even more suitable. Furthermore, it should be noted that the presented results do not reflect the actual costs associated with implementing the agreement in practice (eg, costs related to the data collection and registration, additional administrative burden, or setting up new contracts) because it was considered outside the scope of this research. Therefore, conclusions on which MEA is financially most feasible from a broader perspective should be made with caution. Nonetheless, given the limited expected patient numbers (1 or 2 per year), we expect these costs to be relatively low.

Finally, the study was conducted in a Dutch, single-payer setting. Therefore, the results may not be directly generalizable to other settings. However, many of the mentioned considerations will also apply to other countries, eg, it is very likely that patients will respond comparably in different settings and that the MAH will provide similar information to HTA organizations that can serve as input parameters. Consequently, the main conclusions on the financial consequences of an outcome-based spread payment model for AA could be transferable to other settings. Moreover, the study specifically focused on AA, limiting the generalizability to other cases. Nonetheless, the framework and calculation tool offer flexibility to adjust parameters to include, for example, other health states or define different definitions of the best- and worst-case scenarios, eg, death, if deemed relevant.

Further Research

Future research could focus on what possible unintended positive and negative effects could occur after the implementation of outcome-based payments. For example, pharmaceutical companies could ask for higher initial prices, especially if they believe patient populations will be more restricted once effectiveness data become available.⁷⁴ In contrast, healthcare payers might be more willing to

accept uncertainties or include more diverse subpopulations because of sharing the financial risk when the therapy does not show the expected results, which is specifically relevant for ES-EJ MLD patients. For further exploration of models, all stakeholders need to be involved because only a win-win situation will, in the end, provide access to innovations at fair prices. More insight into the exact implementation costs associated with outcome-based delayed payment models and who will be responsible for this would be beneficial to support this discussion (additional human resources needed, data registry costs, etc). Finally, it could be explored what the feasibility of successfully implementing an outcome-based spread payment would be when lengthening the time frame of the payment agreement within the existing reimbursement system structure to, eg, 10 years or more to mitigate the remaining uncertainties even more. For further development of the calculation tool, threshold analysis could be considered to provide end-users with more insight into the exact discounts needed to equate the different calculated payment scenarios in terms of total costs or what costs per QALY thresholds would be needed to equate one scenario to another in terms of gained value.

Conclusion

This study adds to the discussion on the possible benefits and applications of outcome-based reimbursement and delayed payment models. The scenarios used in this report demonstrated that for AA (Libmeldy), implementing an outcome-based payment model can be more beneficial than when solely a simple discount would be implemented, specifically when clinical performance was similar or worse than predicted. The additional costs related to the implementation, eg, administrative burden, should be further studied to assess the feasibility of successfully implementing an outcome-based spread payment model. The studied model could aid in reimbursement decision making and mitigating challenges that hamper timely access to innovative therapies in rare diseases.

Author Disclosures

Author disclosure forms can be accessed below in the [Supplemental Material](#) section.

The views expressed in this article are the personal views of the authors. They may not be understood or quoted as being made on behalf of or reflecting the position of the agencies or organizations with which the authors are affiliated.

Supplemental Material

Supplementary data associated with this article can be found in the online version at <https://doi.org/10.1016/j.jval.2024.05.010>.

Article and Author Information

Accepted for Publication: May 4, 2024

Published Online: July 12, 2024

doi: <https://doi.org/10.1016/j.jval.2024.05.010>

Author Affiliations: Division of Pharmacoepidemiology and Clinical Pharmacology, Utrecht Institute for Pharmaceutical Sciences (UIPS), Utrecht University, Utrecht, The Netherlands (Callenbach, Vreman, Mantel-Teeuwisse, Goettsch); Department of Child Neurology, Expertise Center Amsterdam Leukodystrophy Center, including lead of MLDi

registry, Emma's Children's Hospital, Amsterdam UMC, Amsterdam, The Netherlands (Schoenmakers); Medicine for Society, Platform at Amsterdam UMC location University of Amsterdam, Amsterdam, The Netherlands (Schoenmakers, Hollak); National Health Care Institute (ZIN), Diemen, The Netherlands (Vreman, Vijgen, Timmers, Goettsch); Department of Endocrinology and Metabolism, Expertise Center for Inborn Errors of Metabolism, Amsterdam UMC location University of Amsterdam, Amsterdam, The Netherlands.

Correspondence: Wim G. Goettsch, PhD, Division of Pharmacoepidemiology and Clinical Pharmacology, Utrecht Institute for Pharmaceutical Sciences (UIPS), Utrecht University, Utrecht, The Netherlands. National Health Care Institute (ZIN), Diemen, The Netherlands. Email: w.g.goettsch@uu.nl

Author Contributions: *Concept and design:* Callenbach, Schoenmakers, Vreman, Vijgen, Timmers, Hollak, Mantel-Teeuwisse, Goettsch
Acquisition of data: Callenbach

Analysis and interpretation of data: Callenbach, Schoenmakers, Vreman, Vijgen, Timmers, Hollak, Mantel-Teeuwisse

Drafting of the manuscript: Callenbach

Critical revision of the paper for important intellectual content: Callenbach, Schoenmakers, Vreman, Vijgen, Timmers, Hollak, Mantel-Teeuwisse, Goettsch

Statistical analysis: Callenbach

Provision of study materials: Callenbach

Obtaining funding: Mantel-Teeuwisse, Goettsch

Supervision: Hollak, Mantel-Teeuwisse, Goettsch

Funding/Support: The Dutch National Health Care Institute (Zorginstituut Nederland) commissioned and funded this project as part of the Research Network for Health Technology Assessment.

Role of Funder/Sponsor: The results were not contingent on the sponsor's approval. The funder as an institute had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication. However, there has been cooperation between the research team and several Dutch National Health Care Institute employees when drafting the manuscript.

Acknowledgment: The authors express their gratitude toward N.I. Wolf (Amsterdam UMC location Vrije Universiteit Amsterdam) for providing critical feedback on the clinical and epidemiological characteristics of the disease MLD and R. Effe (Zorginstituut Nederland) for providing critical feedback on the HTA content.

REFERENCES

- EUR Lex - 32007R1394. EUR-Lex. https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=uriserv%3AOJ.L_.2007.324.01.0121.01.ENG&toc=OJ%3AL%3A2007%3A324%3AFULL. Accessed November 29, 2021.
- Jørgensen J, Kefalas P. The use of innovative payment mechanisms for gene therapies in Europe and the USA. *Regen Med*. 2021;16(4):405–421.
- Eichler H, Trusheim M, Schwarzer-Daum B, et al. Precision reimbursement for precision medicine: using real-world evidence to evolve from trial-and-project to track-and-pay to learn-and-predict. *Clin Pharmacol Ther*. 2022;111(1):52–62.
- Holleman MS, Uyl-de Groot CA, Goodall S, van der Linden N. Determining the comparative value of pharmaceutical risk-sharing policies in non-small cell lung cancer using real-world data. *Value Health*. 2019;22(3):322–331.
- Nicod E, Annemans L, Bucsics A, Lee A, Upadhyaya S, Facey K. HTA programme response to the challenges of dealing with orphan medicinal products: process evaluation in selected European countries. *Health Policy*. 2019;123(2):140–151.
- Carlson JJ, Sullivan SD, Garrison LP, Neumann PJ, Veenstra DL. Linking payment to health outcomes : a taxonomy and examination of performance-based reimbursement schemes between healthcare payers and manufacturers. *Health Policy (New York)*. 2010;96(3):179–190.
- Wenzl M, Chapman S. *Performance-Based Managed Entry Agreements for New Medicines in OECD Countries and EU Member States: How They Work and Possible Improvements Going Forward*. OECD health working papers, No. 115. Paris: OECD Publishing; 2019. <https://doi.org/10.1787/6e5e4c0f-en>.
- Vreman A, Broekhoff TF, Leufkens HG, Mantel-Teeuwisse AK, Goettsch WG. Application of managed entry agreements for innovative therapies in different settings and combinations: a feasibility analysis. *Int J Environ Res Public Health*. 2020;17(22):8309.
- Facey KM, Espin J, Kent E, et al. Implementing outcomes-based managed entry agreements for rare disease treatments: nusinersen and tisagenlecleucel. *Pharmacoeconomics*. 2021;39:1021–1044.
- Michelsen S, Nachi S, Van Dyck W, Simoens S, Huys I. Barriers and opportunities for implementation of outcome-based spread payments for high-cost, one-shot curative therapies. *Front Pharmacol*. 2020;11:1.
- Dunlop WCN, Stauffer A, Levy P, Edwards GJ. Innovative pharmaceutical pricing agreements in five European markets: a survey of stakeholder attitudes and experience. *Health Policy (New York)*. 2018;122(5):528–532.
- Antonanzas F, Juárez-Castelló C, Lorente R, Rodríguez-Ibeas R. The use of risk-sharing contracts in healthcare: theoretical and empirical assessments. *Pharmacoeconomics*. 2019;37(12):1469–1483.
- Hanna E, Toumi M, Dussart C, et al. Funding breakthrough therapies : a systematic review and recommendation. *Health Policy (New York)*. 2018;122(3):217–229.
- Makady A, van Veelen A, de Boer A, Hillege H, Klungel OH, Goettsch W. Implementing managed entry agreements in practice: the Dutch reality check. *Health Policy (New York)*. 2019;123(3):267–274.
- Ferrario A, Kanavos P. Dealing with uncertainty and high prices of new medicines: a comparative analysis of the use of managed entry agreements in Belgium, England, the Netherlands and Sweden. *Soc Sci Med*. 2015;124:39–47.
- Vogler S, Paris V, Ferrario A, et al. *How can pricing and reimbursement policies improve affordable access to medicines? lessons learned from European countries Article (Accepted version) (Refereed) Original citation*. Published online. 2017.
- Koleva-Kolarova R, Buchanan J, Vellekoop H, et al. Financing and reimbursement models for personalised medicine: a systematic review to identify current models and future options. *Appl Health Econ Health Policy*. 2022;20(4):501–524.
- Vreman RA, Leufkens HGM, Kesselheim AS. Getting the right evidence after drug approval. *Front Pharmacol*. 2020;11:569535.
- Ádám I, Callenbach M, Németh B, et al. Outcome-based reimbursement in Central-Eastern Europe and Middle-East. *Front Med (Lausanne)*. 2022;9:940886.
- Ádám I, Callenbach M, Németh B, et al. Delayed payment schemes in Central-Eastern Europe and Middle-East. *Front Med (Lausanne)*. 2022;9:940371.
- Improving Patient Access to Gene and Cell Therapies for Rare Diseases in Europe A Review of the Challenges Proposals for Improving Patient Access to Advanced Therapeutic Medicinal Products in the Netherlands*. Published Online 2020.
- Makady A, van Acker S, Nijmeijer H, et al. Conditional financing of drugs in the Netherlands: past, present, and future—results from stakeholder interviews. *Value Health*. 2019;22(4):399–407.
- Neumann PJ, Chambers JD, Simon F, Meckley LM. Risk-sharing arrangements that link payment for drugs to health outcomes are proving hard to implement. *Health Aff (Millwood)*. 2011;30(12):2329–2337.
- Callenbach MHE, Vreman RA, Goettsch WG, Mantel-Teeuwisse AK. Payment and reimbursement models.: Payment and Reimbursement Models for Innovative Hi.
- Gamba S, Pertile P, Vogler S. The impact of managed entry agreements on pharmaceutical prices. *Health Econ*. 2020;29(suppl 1):47–62.
- Efthymiadou O, Kanavos P. Impact of Managed Entry Agreements on availability of and timely access to medicines: an ex-post evaluation of agreements implemented for oncology therapies in four countries. *BMC Health Serv Res*. 2022;22(1):1066.
- Zaric GS. How risky is that risk sharing agreement? Mean-variance tradeoffs and unintended consequences of six common risk sharing agreements. *MDM Policy Pract*. 2021;6(1):1–15.
- Antonanzas F, Juárez-Castello C, Rodríguez-Ibeas R. Should health authorities offer risk-sharing contracts to pharmaceutical firms? A theoretical approach. *Health Econ Policy Law*. 2011;6(3):391–403.
- Pakketadvies sluisgeneesmiddel atidarsagene autotemcel (Libmeldy®) voor de behandeling van metachromatische leukodystrofie (MLD) | Advies. Zorginstituut Nederland. <https://www.zorginstituutnederland.nl/publicaties/adviezen/2022/09/27/pakketadvies-sluisgeneesmiddel-atidarsagene-autotemcel-libmeldy>. Accessed August 25, 2023.
- Outcome of joint negotiations for Libmeldy | BeNeLuxA. <https://beneluxa.org/Libmeldy>. Accessed August 25, 2023.
- Geneesmiddel Libmeldy niet in verzekerd pakket | Nieuwsbericht. Rijksoverheid.nl. <https://www.rijksoverheid.nl/actueel/nieuws/2023/04/12/geneesmiddel-libmeldy-niet-in-verzekerd-pakket>. Accessed August 25, 2023.
- Joint HTA assessment on autologous gene therapy Libmeldy ongoing | BeNeLuxA. <https://beneluxa.org/news3>. Accessed June 24, 2022.
- Beneluxa initiative | BeNeLuxA. <https://beneluxa.org/collaboration>. Accessed December 10, 2020.
- Final Evaluation Determination-Atidarsagene Autotemcel for Treating Metachromatic Leukodystrophy Final Evaluation Determination Atidarsagene Autotemcel for Treating Metachromatic Leukodystrophy 1 Recommendations*. Published Online 2022.
- Orchard therapeutics announces agreement enabling. *GlobeNewswire*. <https://www.globenewswire.com/news-release/2023/02/27/2615939/0/en/Orchard-Therapeutics-Announces-Agreement-Enabling-Reimbursed-Access>

- s-to-Libmeldy-for-All-Eligible-MLD-Patients-in-Sweden.html. Accessed August 29, 2023.
36. Pakketadvies sluisgeneesmiddel onasemnogene abeparvovec (Zolgensma[®]) bij de behandeling van spinale musculaire atrofie (SMA) | Advies. Zorginstituut Nederland. <https://www.zorginstituutnederland.nl/publicaties/adviezen/2021/05/06/pakketadvies-sluisgeneesmiddel-onasemnogene-abeparvovec-zolgensma>. Accessed December 16, 2022.
 37. Libmeldy. European Medicines Agency. <https://www.ema.europa.eu/en/medicines/human/EPAR/libmeldy>. Accessed December 5, 2021.
 38. Zin. *Evaluatierapport Libmeldy Dag*. 90. 2022.
 39. Kehrer C, Blumenstock G, Raabe C, Krägeloh-Mann I. Development and reliability of a classification system for gross motor function in children with metachromatic leukodystrophy. *Dev Med Child Neurol*. 2011;53(2):156–160.
 40. Libmeldy (autologous CD34+ cell enriched population that contains haematopoietic stem and progenitor cells transduced ex vivo using a lentiviral vector encoding the human arylsulfatase A gene). European Medicines Agency. www.ema.europa.eu/contact/telephone+31. Accessed January 5, 2022.
 41. Verslag van de Vergadering van de Wetenschappelijke Adviesraad (WAR) Over latidarsagene Autotemcel (Libmeldy[®]) | Verslag | Zorginstituut Nederland. <https://www.zorginstituutnederland.nl/publicaties/verslag/2022/07/11/verslag-war-latidarsagene-autotemcel-libmeldy>. Accessed November 21, 2022.
 42. Efthymiadou O, Kanavos P. Determinants of Managed Entry Agreements in the context of Health Technology Assessment: a comparative analysis of oncology therapies in four countries. *Int J Technol Assess Health Care*. 2021;37(1):1–7.
 43. Nazareth T, Ko JJ, Sasane R, et al. Outcomes-based contracting experience: research findings from U.S. and European stakeholders. *J Manag Care Spec Pharm*. 2017;23(10):1018–1026.
 44. Garrison LP, Towse A, Briggs A, et al. Performance-based risk-sharing arrangements - Good practices for design, implementation, and evaluation: report of the ISPOR good practices for performance-based risk-sharing arrangements task force. *Value Health*. 2013;16(5):703–719.
 45. Yeung K, Suh K, Basu A, Garrison LP, Bansal A, Carlson JJ. Paying for cures: how can we afford it? Managed care pharmacy stakeholder perceptions of policy options to address affordability of prescription. *drugs*. 2017;23(10):1084–1090.
 46. Cole A, Cubi-Molla P, Pollard J, et al. Making outcome-based payment a reality in the NHS. <http://www.cancerresearchuk.org/>. Accessed March 17, 2022.
 47. Maes I, Boufraioua H, Dyck W Van, Schoonaert L. *Innovative Funding Solutions for Paradigm Changing Advanced Therapy Medicinal Products (ATMP) in Belgium Multi-stakeholder Consensus on Gene Therapy Funding Solutions Policy Report*. Published Online 2019.
 48. Metachromatic leukodystrophy. Incremental Cost-Effectiveness Ratio. <https://icer.org/assessment/metachromatic-leukodystrophy-2023/#related>. Accessed August 25, 2023.
 49. The MLD initiative - disease registry for metachromatic leukodystrophy. <https://www.mldinitiative.com/>. Accessed February 23, 2023.
 50. Excel-spreadsheetsoftware | Microsoft 365. <https://www.microsoft.com/nl-nl/microsoft-365/excel>. Accessed January 20, 2022.
 51. Richtlijn voor het uitvoeren van economische evaluaties in de gezondheidszorg | Over ons. Zorginstituut Nederland. <https://www.zorginstituutnederland.nl/over-ons/werkwijzen-en-procedures/adviseren-over-en-verduidelijken-van-het-basispakket-aan-zorg/beoordeling-van-ge2223neemsmiddelen/richtlijn-voor-economische-evaluatie>. Accessed April 11, 2024.
 52. Uitgaven aan dure geneesmiddelen stijgen naar 2,1 miljard | Nieuwsbericht. Nederlandse Zorgautoriteit. <https://www.nza.nl/actueel/nieuws/2019/01/30/uitgaven-aan-dure-geneesmiddelen-stijgen-naar-21-miljard>. Accessed November 29, 2020.
 53. Jørgensen J, Kefalas P. Reimbursement of licensed cell and gene therapies across the major European healthcare markets. *J Mark Access Health Policy*. 2015;3(1):29321.
 54. Jönsson B, Hampson G, Michaels J, Towse A, von der Schulenburg JMG, Wong O. Advanced therapy medicinal products and health technology assessment principles and practices for value-based and sustainable healthcare. *Eur J Health Econ*. 2019;20(3):427–438.
 55. Fumagalli F, Calbi V, Natali Sora MG, et al. Lentiviral haematopoietic stem-cell gene therapy for early-onset metachromatic leukodystrophy: long-term results from a non-randomised, open-label, phase 1/2 trial and expanded access. *Lancet*. 2022;399(10322):372–383.
 56. Schoenmakers DH, Beerepoot S, van den Berg S, et al. Modified Delphi procedure-based expert consensus on endpoints for an international disease registry for metachromatic leukodystrophy: the European metachromatic leukodystrophy initiative. *Orphanet J Rare Dis*. 2022;17(1):48.
 57. Maskineh C, Nasser SC. Managed Entry Agreements for Pharmaceutical Products in Middle East and North African countries: payer and Manufacturer Experience and Outlook. *Value Health Reg Issues*. 2018;16:33–38.
 58. Pauwels K, Huys I, Vogler S, Casteels M, Simoons S. Managed entry agreements for oncology drugs: lessons from the European experience to inform the future. *Front Pharmacol*. 2017;8:249392.
 59. Godman B, Hill A, Simoons S, et al. Potential approaches for the pricing of cancer medicines across Europe to enhance the sustainability of healthcare systems and the implications. *Expert Rev Pharmacoecon Outcomes Res*. 2021;21(4):527–540.
 60. Callenbach MHE, Vreman RA, Németh B, Kaló Z, Goettsch WG. Reimbursement and payment models in Central and Eastern European as well as Middle Eastern countries: a survey of their current use and future outlook. *Drug Discov Today*. 2023;28(1):103433.
 61. Toolkit home. NEWDIGS. <https://newdigs.tuftsmedicalcenter.org/toolkit/>. Accessed December 14, 2022.
 62. Whittall A, Jommi C, De Pouvourville G, et al. Facilitating more efficient negotiations for innovative therapies: a value-based negotiation framework. *Int J Technol Assess Health Care*. 2022;38(1):e23.
 63. Kolasa K, Kalo Z, Hornby E. Pricing and reimbursement frameworks in Central Eastern Europe: a decision tool to support choices. *Expert Rev Pharmacoeconomics Outcomes Res*. 2015;15(1):145–155.
 64. Bohm N, Bermingham S, Grimsey Jones F, et al. The challenges of outcomes-based contract implementation for medicines in Europe. *Pharmacoeconomics*. 2022;40:13–29.
 65. Overview. Atidarsagene autotemcel for treating metachromatic leukodystrophy | Guidance | NICE.
 66. Europe cross-country HTA of gene therapy Libmeldy calls for price cut. Pink Sheet. <https://pink.pharmaintelligence.informa.com/PS147150/Europe-Cross-Country-HTA-of-Gene-Therapy-Libmeldy-Calls-For-Price-Cut>. Accessed December 18, 2022.
 67. France renews early access scheme for Libmeldy | Navlin Daily. <https://www.navlindaily.com/article/14352/france-renews-early-access-scheme-for-libmeldy>. Accessed December 18, 2022.
 68. AIFA approves Orchard's gene therapy Libmeldy for MLD | Navlin Daily. <https://www.navlindaily.com/article/11378/aifa-approves-orchard-s-gene-therapy-libmeldy-for-ml>. Accessed December 18, 2022.
 69. Bouvy JC, Sapede C, Garner S. Managed entry agreements for pharmaceuticals in the context of adaptive pathways in Europe. *Front Pharmacol*. 2018;9:280.
 70. Andersson E, Svensson J, Persson U, Lindgren P. Risk sharing in managed entry agreements—a review of the Swedish experience. *Health Policy (New York)*. 2020;124(4):404–410.
 71. Herholz H, Ofierska-Sujkowska G, Adamski J, et al. Risk sharing arrangements for pharmaceuticals: potential considerations and recommendations for European payers. *BMC Health Serv Res*. 2010;10(1):1–6.
 72. Pakketadvies sluisgeneesmiddel betibeglogene autotemcel (Zynteglo[®]) voor de behandeling van een vorm van erfelijke bloedarmoede | Advies. Zorginstituut Nederland. <https://www.zorginstituutnederland.nl/publicaties/adviezen/2021/07/21/pakketadvies-sluisgeneesmiddel-betibeglogene-autotemcel-zynteglo>. Accessed December 13, 2022.
 73. ACP advies over onasemnogene abeparvovec (Zolgensma[®]) | Advies. Zorginstituut Nederland. <https://www.zorginstituutnederland.nl/publicaties/adviezen/2021/04/23/acp-advies-over-onasemnogene-abeparvovec-zolgensma>. Accessed December 13, 2022.
 74. Zampiroli Dias C, Godman B, Gargano LP, et al. Integrative review of managed entry agreements: chances and limitations. *Pharmacoeconomics*. 2020;38(11):1165–1185.