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Annuity and Conditional Payment Schemes for the Reimbursement of One-Shot Advanced Therapies

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Annuity and Conditional Payment Schemes for the Reimbursement of One-Shot Advanced Therapies[1]

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Abstract

Advanced therapies represent a paradigm shift. They offer potentially curative solutions to life-threatening diseases through a single administration. However, this paradigm shift poses unprecedented challenges to the current model of drug access and reimbursement developed for the management of conventional therapies, where reimbursement typically occurs at the time of therapy administration. In this paper, we identify the key determinants of the paradigm shift and propose a new reimbursement model for advanced therapies. The proposed model relies on managed entry agreements to address payer uncertainty and is based on conditional and deferred payments. The potential impact of such deferred payments on spending is estimated through horizon scanning. Finally, we propose the establishment of a dedicated fund to enable timely access to advanced therapies while ensuring the sustainability of the impact on pharmaceutical expenditure.

[1] This contribution is partly based on Nutarelli, Riccaboni, Van Dick (2024), Advanced Therapy Medicinal Products: Pricing and Reimbursement Challenges and Potential Solutions, mimeo. The study was conducted with the unconditional support of #VITA.

Introduction

Reimbursement for advanced therapies poses unprecedented challenges for regulatory authorities, mainly due to the unique characteristics of these therapies (Overbeeke et al. 2021; Michelsen et al. 2020). Although numerous advanced therapy medicinal products (ATMPs) have been positively assessed by the European Medicines Agency (Iglesias-Lopez, Agustı, et al. 2021; Garcıa-González et al. 2021), only a limited number of ATMPs have been successfully reimbursed by the major European regulatory authorities (Hatzikou et al., 2020; ATMP Forum, 2023).

First, advanced therapies are generally aimed at treating severe diseases with a largely unmet therapeutic need that requires urgent therapeutic intervention (Angelis, Naci and Hackshaw 2020; Coyle et al. 2020; Pochopien et al. 2021). Consequently, evidence for the efficacy and safety of advanced therapies at the time of market authorization is often based on small-scale clinical trials with single-arm designs, leading to limitations such as small sample sizes, short follow-up periods and potentially heterogeneous treatment effects.

Second, advanced therapies are characterized by unique administration methods that often require a single or one-shot administration (Jørgensen and Kefalas 2021) and achieve curative or potentially curative long-term outcomes. However, this one-shot administration has a significant immediate financial impact, while the benefits only materialize over time. The price of these one-shot therapies, which typically ranges from around €300,000 to almost €2 million, appears very high compared to other therapies whose total cost is spread gradually over time due to the upfront expenditure (Ronco et al. 2021). The high costs incurred immediately and the uncertainty of whether the therapeutic effect will persist over time hinder the uptake of one-shot therapies and thus patient access to these transformative therapeutic products (Jørgensen and Kefalas 2021). This leads to undesirable distortions in access to treatment, simply due to differences in administration methods and the resulting differences in the timing of financial flows.
Other barriers preventing timely market access for ATMPs are infrastructure requirements and uncertainties in administration protocols (Overdose and Kefalas 2021).

Given the large number of advanced therapies currently in development and the expected introduction of many one-shot (or potentially one-shot) treatments, it is crucial to find appropriate reimbursement models to ensure their financial sustainability and timely patient access to advanced therapies.

In the recent past, increasing innovation pressure on pharmaceutical expenditure and the emergence of innovative, high-cost treatments have led regulatory authorities and pharmaceutical companies to increasingly rely on Managed Entry Agreement (MEA) models (Pani and Becker 2021; Ronco et al. 2021).
In particular, the emergence of advanced therapy medicinal products (ATMPs) has recently sparked a debate on how to combine pay-for-performance agreements and installment (annuity) payment systems in innovative MEAs to balance the one-shot administration of many ATMPs with their potential long-term benefits (Dabbous et al. 2020). In this context, Hanna et al. (2018) point out that outcome-based agreements between manufacturers and payers,

possibly including outcome-based installment payments, are necessary to address the significant additional uncertainty associated with advanced therapies compared to conventional therapies. In this area, it is therefore crucial to develop a theoretical framework for the identification and use of outcome-based MEAs and the methods for determining conditional payments.

Considering that advanced therapies benefit patients for life and can sometimes replace long-term treatments for chronic diseases, leading to potential savings for national health systems, it would be appropriate to spread the budgetary impact of ATMP-related expenditure over a timeframe comparable to that of more traditional therapies administered over time. This would avoid distortions due to the different timing of cash flows. However, financial reporting standards and most public accounting rules classify pharmaceuticals as current expenses and treat them as consumable goods that cannot be amortized over several years (Dabbous et al. 2021). More recently, outcome-based payment models have been introduced to address the high uncertainty about the long-term benefits of advanced therapies. Deferred payments are particularly suitable for the reimbursement of potentially curative one-shot therapies. In many cases, however, the solutions chosen do not take into account all the risks outlined by Grutters et al. (2015) and often lead to the setting of confidential discounts.

It is certainly not always necessary to resort to complex MEAs. In particular, the relationship between prevalence and incidence within the therapeutic area of advanced therapies is an important factor in determining the most appropriate reimbursement models.
In the following analysis, we will focus on a subset of advanced therapies that are characterized by the simultaneous presence of three factors:

- One-shot administration leading to immediate manifestation of therapy costs and potential long-term benefits;
- Curative or transformative outcomes for patients' clinical history and high uncertainty at the time of access to reimbursement;
- High prevalence to incidence ratio.

The rationale for this choice stems from the need to introduce conditional and deferred payment models in these cases, which combine the characteristics of reimbursement schemes such as success fee, payment at result, or annuity payment.

This paper proposes a model for the introduction of outcome-based annuity payment schemes for the reimbursement of one-shot or potentially one-shot advanced therapies that are curative or transformative for patients' clinical histories.
The model provides the theoretical framework for determining the contractual characteristics for reimbursement of Advanced Therapy Medicinal Products (ATMPs), including in particular:

- A methodology for determining deferred payments beyond the fiscal year;
- Conditions and criteria for determining conditional payments based on expected benefit;
- Methods for assessing the expected and realized savings for the National Health System.

The final section of the document also proposes the establishment of a dedicated fund for ATMPs, the potential allocation of which will be determined through a horizon scanning study.

Strategies for dealing with the uncertainty associated with one-shot ATMPs for high prevalence diseases

Having outlined the specific uncertainty profile of one-shot ATMPs in the previous section, it is necessary to identify the most appropriate tools to deal with this uncertainty. In particular, given the need to use MEAs as the primary tool for managing uncertainty in health technology assessment (HTA), the question arises as to which reimbursement model is most appropriate for advanced therapies. The choice of the most suitable MEA is based on the risk analysis applied to ATMPs.

The issue of selecting the most appropriate MEA for one-shot therapies is addressed with reference to the risk analysis model developed by Grimm et al. (2017) on behalf of the National Institute for Health and Care Excellence (NICE). This section presents a simplified model inspired by Grimm et al. (2017). The aim is to show why deferred payments and outcome-based payment systems are appropriate solutions to address the specific uncertainty profile of one-shot ATMPs. The conceptual framework outlined by Grimm et al. (2017) is based on three measures of uncertainty, known in the literature as:

- Payer Uncertainty Burden (PUB);
- Payer Strategy Burden (PSB);
- Payer Strategy and Uncertainty Burden (P-SUB).

These measures can be derived from the traditional cost-effectiveness analysis used in the evaluation of health technologies by regulatory bodies. The PUB represents the decision risk associated with the probability of an incorrect decision based on the current evidence and the costs that such an incorrect decision entails. The PSB is strategy-specific and captures the risk associated with abandoning currently used therapeutic options in favor of a non-optimal strategy. The P-SUB is the sum of the two sources of uncertainty (PUB and PSB).

Mathematically, the PUB corresponds to the expected value obtained under conditions of perfect information (Expected Value of Perfect Information, EVPI) and is defined as follows

$$PUB = EVPI = \left[E_\theta\{max_d\ NB(d,\theta)\} - max_d\ E_\theta\{NB(d,\theta)\}\right] \geq 0$$

where NB(d,θ) is the net benefit function, d indexes the strategies (technologies) in a set D and θ is a vector of uncertain parameters of the model (provided by a probabilistic sensitivity analysis).

The PSB is defined as

$$PSB(d') = \left[max_d\ E_\theta\{NB(d,\theta)\} - E_\theta\{NB(d',\theta)\}\right] > 0$$

where *d′* stands for a strategy that, according to current knowledge, is probably suboptimal in terms of costs. For the cost-effective strategy d^* the $PSB(d^*)$ is zero.

The result of the probabilistic sensitivity analysis that accompanies cost-utility or cost-effectiveness models shows the potential variation in the cost-effectiveness levels of the treatment in response to changes in the parameters of the assumed model (θ).
Figure 1 shows the plot of the incremental cost-effectiveness ratio of a hypothetical one-shot therapy. In the graph, the vertical distance of a point in the cost-effectiveness plane from the line representing the willingness-to-pay threshold indicates the contribution of that observation to the P-SUB. The total P-SUB results from the sum of the vertical distances of all points.

For simplicity, let us consider the case of a single treatment with a linear Probabilistic Sensitivity Analysis (PSA) trajectory, as shown in Figure 1. This is of course a simplified representation, but it allows a clearer observation of the different effects associated with the one-shot nature of many advanced therapies.

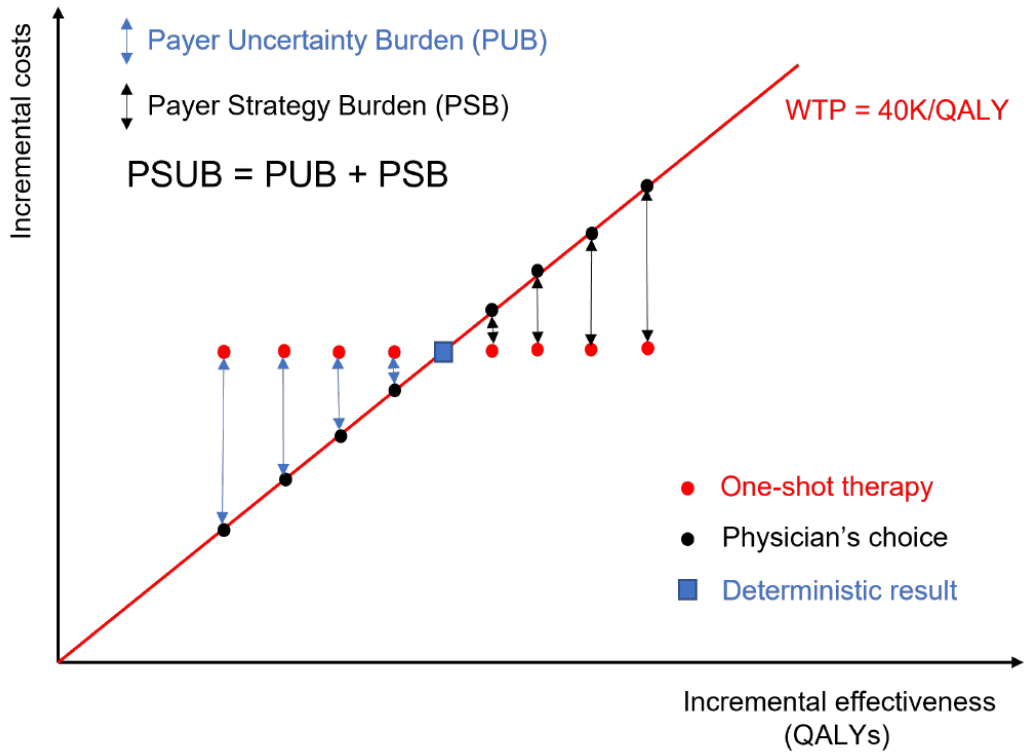


Figure 1: Hypothetical case of a PSA comparison between standard therapy and an analogous one-shot advanced therapy. In the case of one-shot therapy, a rotation of PSA is observed, corresponding to a higher level of Payer Strategy & Uncertainty Burden (P-SUB).

In this hypothetical case, the incremental costs of the different PSA instances increase linearly with the incremental effectiveness at the chosen threshold.
For example, consider a simplified version of the treatment in Figure 1, which could be a therapy that is administered to patients regularly for as long as they benefit (e.g., until progression). Now consider the hypothetical scenario in which the same therapy becomes available in a one-shot version with the same average cost-effectiveness. The only difference between the two treatments in this hypothetical case is that the advanced therapy is administered in a single dose (one-shot). If you vary only the administration method among

the parameters of the model vector θ, you get a higher degree of P-SUB. This is because one-shot therapies entail a higher degree of independence between the incremental cost of the therapy, which is largely the same for patients at the time of administration, and the incremental effectiveness, which may vary depending on the duration of the expected benefit.

Given the higher P-SUB resulting from the one-shot nature of therapies, it is appropriate to consider the use of Managed Entry Agreements (MEAs) to better manage the specific and additional risk profile of one-shot therapies. In Figure 2, we show the impact of a simple payment scheme that provides for conditional payments in the form of success fee based on patients achieving a certain threshold of incremental effectiveness. As an example, consider a scenario in which a simple measure of patient survival captures the incremental effectiveness of the advanced therapy and conditional payments are only made if patients are still alive in the years following treatment. Assuming that the MEA is neutral with respect to the cost per quality-adjusted life year (QALY), Figure 2 shows how the introduction of a payment-at-result MEA with deferred and outcome-based payments reduces the P-SUB of the one-shot therapy.

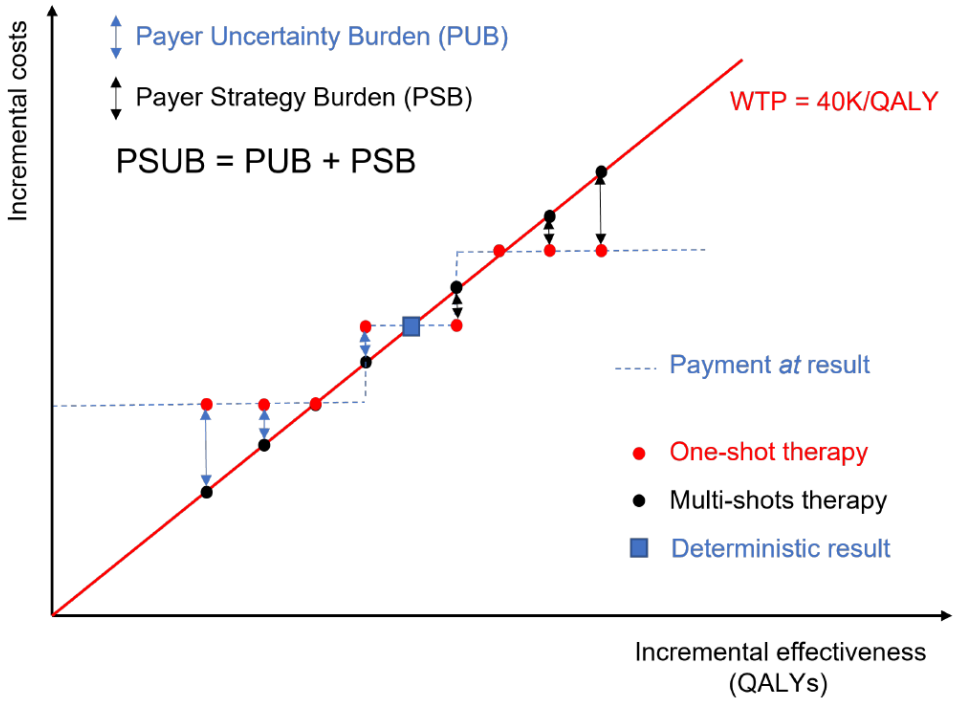


Figure 2: Impact of introducing a payment-at-result scheme to mitigate the P-SUB of a one-shot advanced therapy.

Although the example intentionally refers to a stylized and simplified version of the cost-effectiveness analysis of an advanced therapy, it nevertheless demonstrates the usefulness of the risk analysis framework originally developed by Grimm et al. (2017) to highlight the benefits of using appropriate MEAs to manage the uncertainty associated with one-shot ATMPs. Furthermore, this analysis provides the theoretical framework for the widespread use of MEAs with deferred payments by European regulatory authorities to ensure reimbursement of advanced therapies.
In the following analysis, we show how the method proposed by Grimm et al. (2017) can be used during cost-effectiveness HTA analysis to determine the extent of conditional payments

associated with one-shot advanced therapies. We then analyze the parameters responsible for decision uncertainty by performing the expected value of perfect information (EVPI) analysis as described in Strong, Oakley, and Brennan (2014). The second part of the analysis is to simulate the effects of the proposed MEAs. For this purpose, it is possible to re-estimate the cost-effectiveness models with and without MEAs.

Before explaining the application of the proposed methodology to determine MEAs, it is necessary to distinguish between the different types of ATMPs based on the incidence to prevalence ratio of diseases and other characteristics that may be useful for the implementation of specific conditional payment models. We then move to the methodological section and describe the payment systems in detail using a case study. In the case study, we illustrate the application of the Grimm et al. (2017) model for risk analysis in the context of health technology assessment. This approach makes it possible to determine the risk burden associated with the payer's decision problem. The decision problem in our framework is to determine which payment system should be considered optimal for dealing with the specific uncertainty associated with advanced therapies.

The role of prevalence and incidence in the choice of reimbursement model for one-shot advanced therapies

The prevalence and incidence of the target population for advanced therapies influence the choice of reimbursement models. The importance of the characteristics of the target population for advanced therapies arises primarily from the need to tailor reimbursement models specifically to ATMPs. This need arises from the different financial impact that different ATMPs will have on drug expenditure over time, as well as the different ways in which previous analyses, such as Kaplan-Meier curves, can be used.

For the healthcare system, the total number of patients requiring curative therapy over the course of a generation is composed of an initial prevalent population and an annual variation based on incidence, which increases by a factor of g over time due to new diagnoses. The main difference between ATMPs with a high prevalence/incidence ratio (prevalence dominant - PD) and ATMPs with a high incidence (incidence dominant - ID) lies in the different relationship between the backlog of already diagnosed patients (prevalence) and the flow of new diagnoses over time (incidence). Prevalence and incidence influence the timing of the impact on the budget and the associated financial flows (Noordzij et al. 2010). Table 1 provides an overview of the incidence and prevalence of some ATMPs.

Advanced Therapy	Indication	Prevalence	Incidence	Duration of Effect
Strimvelis	ADA-SCID	1-9/1000000	1-5/1000000	7 years of intervention-free survival (8-12)
Kymriah	B-cell ALL	1-5/100000	1-3/100.000	24 months of overall survival
Kymriah	DLBCL	4-13/100000	3-6/100.000	18 months of overall survival
Yescarta	DLBCL	4-13/100000	3-6/100.000	18 months of overall survival
Yescarta	PMBCL	0,1-2/100000	0,4/1000000	18 months of overall survival
Luxturna	RP	0,4-2/100000	0,01-0,4/1000000	4 years of improvement in MLMT score
Luxturna	LCA	1-5/1000000	NR	4 years of improvement in MLMT score
Zynteglo	TDT	1-2/100000	1/100000	4.3 years of transfusion independence
Zolgensma	SMA	10-20/1000000	1-2/10000	4.3 years of event-free survival

Table 1: Estimated incidence and prevalence for some advanced therapies

Legend: ADA-SCID, Severe combined immunodeficiency due to adenosine deaminase deficiency; ALL, acute lymphoblastic leukemia; DLBCL, diffuse large B-cell lymphoma; PMBCL, primary mediastinal large B-cell lymphoma; RP, retinitis pigmentosa; LCA, Leber's congenital amaurosis; TDT, transfusion-dependent β-thalassemia; SMA, spinal muscular atrophy; NR, not reported; MLMT, multi-luminance mobility test.

The need to introduce different payment schemes for treatments with a high prevalence/incidence ratio stems from several key factors. First, and most importantly, the budget implications are very different for the two types of advanced therapies. In prevalence-dominant (PD) scenarios, the use of deferred payment solutions allows for a more even distribution of payment streams over time, within the given budget constraints. For advanced therapies for high incidence dominant (ID) indications, where the number of patients to be treated at launch is not high, the use of deferred payment does not significantly change the expenditure streams over time and is therefore not necessary to comply with the budget constraint. The different budgetary impact of PD and ID drugs can be easily understood with a simple example. Consider two diseases with the same total number of patients requiring treatment: The first PD-type disease has 1000 prevalent patients and a constant incidence of 100 patients per year, while the second ID-type disease has no prevalent patients but double the number of incident patients per year (200 instead of 100). Let us assume that the treatment

costs are the same and the budget constraint is set at the cost of treating 300 patients per year.

PD Case

Year (Y)		1	2	3	4	5	6	7	8	9	10	11	12	13	14
Patients	1000	100	100	100	100	100	100	100	100	100	100				
Annuities Prevalent patients (p.)		200	200	200	200	200									
Annuities Incident p., Y 1		20	20	20	20	20									
Annuities Incident p., Y 2			20	20	20	20	20								
Annuities Incident p., Y 3				20	20	20	20	20							
Annuities Incident p., Y 4					20	20	20	20	20						
Annuities Incident p., Y 5						20	20	20	20	20					
Annuities Incident p., Y 6							20	20	20	20	20				
Annuities Incident p., Y 7								20	20	20	20	20			
Annuities Incident p., Y 8									20	20	20	20	20		
Annuities Incident p., Y 9										20	20	20	20	20	
Annuities Incident p., Y10											20	20	20	20	20
Total Annuities	0	220	240	260	280	300	100	100	100	100	100	80	60	40	20

ID Case

Year (Y)		1	2	3	4	5	6	7	8	9	10	11	12	13	14
Patients	0	200	200	200	200	200	200	200	200	200	200				
Annuities, Prevalent Patients (p.)		0	0	0	0	0									
Annuities Incident p., Y 1		40	40	40	40	40									
Annuities Incident p., Y 2			40	40	40	40	40								
Annuities Incident p., Y 3				40	40	40	40	40							
Annuities Incident p., Y 4					40	40	40	40	40						
Annuities Incident p., Y 5						40	40	40	40	40					
Annuities Incident p., Y 6							40	40	40	40	40				
Annuities Incident p., Y 7								40	40	40	40	40			
Annuities Incident p., Y 8									40	40	40	40	40		
Annuities Incident p., Y 9										40	40	40	40	40	
Annuities Incident p., Y10											40	40	40	40	40
Total Annuities	0	40	80	120	160	200	200	200	200	200	200	160	120	80	40

Table 2: The results of a simulation to illustrate the budget impact of an advanced therapy with high prevalence/low incidence (PD) and a drug with low prevalence/high incidence (ID). The table shows the effectiveness of a deferred payment (annuity) scheme in mitigating the impact of a PD drug on the budget, while the introduction of the same scheme in the second case does not appear to be necessary to meet the assumed budget constraint of 300.

In our example, we assume for the sake of simplicity that the incidence remains constant over time and that — according to our framework— - it is a one-shot type. In this simple case, the impact of the payments (Annuity - A) on the fund (Budget Impact - BI) depends on the incidence and prevalence over the years (t) of the initial payment deferral ($t \leq n$) and is represented by the sum of the deferred payments for the prevalent patients in the first year and the incident patients. In the PD case, it can be seen that by deferring payments for the prevalent population, spending can be spread over time, avoiding the spike in outflows that would occur if implemented without annuity payments. Without an appropriate deferral, the initial expenditure (1000) would be well above the budget set at 300.
In this case, it is always possible to ensure compliance with the budget constraint (allocation of a potential dedicated fund for the reimbursement of ATMPs, the "ATMP fund") by adjusting the deferral appropriately. In contrast, in the case of ID, the use of payment deferrals is not immediately necessary, as the lack of a significant prevalent population and the associated high incidence only leads to a deferral of expenditure over time, which would always remain well below the budget constraint (300).

In both cases, the impact on the ATMP fund is greatest during the period of expenditure deferral (in our case, the first 5 years) and decreases thereafter. This effect depends on the decision to grant deferrals over a period that is not too long, but is nevertheless useful for gathering evidence that helps to reduce uncertainty about the outcomes of the treatments provided.
Of course, this simple principle — namely the need and opportunity to use payment deferrals for one-shot advanced therapies to treat diseases with a high prevalence/incidence rate — also applies in more complex situations where the number of patients fluctuates over time and an appropriate discount rate is applied to the deferred payments.

A second reason for the need for different reimbursement schemes for PD and ID advanced therapies is related to the different nature of the decision risk. ID therapies generally address life-threatening diseases with shorter Kaplan-Meier curves and more measurable treatment outcomes (e.g. death or progression). In contrast, therapies for PD-type diseases generally have longer Kaplan-Meier curves and require more complex assessments of treatment outcomes. The greater uncertainty associated with PD therapies therefore suggests the use of appropriate Managed Entry Agreements (MEAs). Probabilistic sensitivity analyzes highlight the importance of a lifetime time horizon for one-shot advanced therapies for PD-type diseases, as variations in patient survival have a direct impact on cost-effectiveness evaluations (e.g. in terms of ICER per QALY).

Finally, the risk profiles of PD and ID drugs differ considerably. In particular, the introduction of ATMPs in a market where effective therapies already exist poses a strategic challenge, as the existing therapies form the standard of care against which ATMPs are measured. For ID therapies, the expectation of an increase in the patient population in the future is often compounded by the existence of already effective treatments. This scenario introduces an additional layer of risk for ID therapies, characterized by the immediate need to address the Potential Savings Bias (PSB). The payment scheme for ID drugs should, therefore, focus more on mitigating the PSB. In the PD scenario, on the other hand, the unmet need is generally higher. This reduces the risk associated with PD drugs, as the lack of effective treatments means a potentially less competitive landscape for introducing new therapies.

Overall, it is therefore considered that access to the ATMP fund should be defined according to the prevalence profile of diseases and the potentially curative one-off nature of novel therapies, as outlined in the previous sections. In the next two sections, we will look at the details of the analysis of the relevant factors for determining deferred and conditional payments and provide a concrete example of how the mechanism is implemented.

A Theoretical Framework for Defining Reimbursement Models for ATMPs

In this section, we explain the methods for selecting the most appropriate reimbursement schemes for one-shot advanced therapies.
A first decision concerns the optimal duration of conditional payment schemes. While in theory it would be desirable to implement a payment system that covers all future developments in advanced therapies, several practical reasons argue against such an approach. For example, the monitoring of patients over long periods of time is dependent on the proper updating of patient registries, which is often associated with a significant administrative burden and potential measurement errors. In addition, the financial benefits of implementing long-term conditional payment systems over the lifetime would be significantly less than the implementation costs of managed entry agreements (MEAs).

A second important aspect concerns the possible use of annuity payments. In the previous section, we explained that the need to defer spending on one-shot advanced therapies is particularly evident in the case of PD conditions, as the one-shot cost per patient leads to a spike in overall spending at launch, when uncertainty about the actual efficacy of the therapy is usually still high. In the case of PD-type advanced therapies, it is advisable to make payments contingent on outcomes, whereas for ID-type therapies, more conventional outcome-based payments can be used to manage uncertainty over shorter time periods, typically within a year.

Specifically, for PD-type advanced therapies, we plan to quantify the "optimal duration" of the payment system by first estimating the price of the one-shot advanced therapy and determining the average annual cost of therapies currently used in the same therapeutic areas. This approach allows us to determine the average reimbursement period by assuming uniform payments. Using Evaluate Pharma's data, we estimate that the expected average cost of a one-shot advanced therapy is approximately $1.34 million. This estimate is consistent with Coquerelle et al. (2019) and Cook et al. (2020). The average annual cost of therapies currently used in the same areas is estimated to be between $240,000 and $250,000 (in line with Makurvet, 2021). Thus, if we assume an even distribution of the cost of advanced therapy over time, the conditional payments could be structured over a period of 4 to 5 years.

The design of the MEA also depends on the factors that contribute to the reduction of uncertainty. The most important factors, apart from the mere passage of time, are due to the generation of real-world data (RWD). The latter inevitably leads to a reduction in uncertainty. For example, if the product has already been on the market for a year, more information about

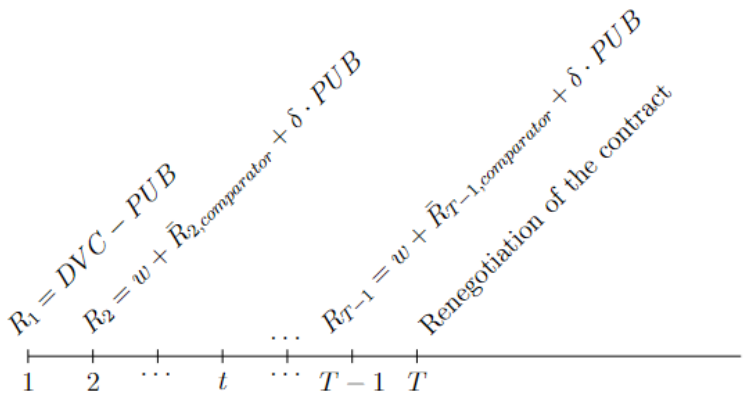
its effectiveness in the target population will inevitably be available, regardless of the generation of RWD-based measures. Taking into account this additional information resulting from the passage of time, the regulatory body has the option to take action (e.g. renegotiate the contract) if there are significant deviations between the expected and observed efficacy or other relevant changes in the reference context. If no further action is taken, the Agency implicitly accepts that the evidence collected is in line with the expectations that led to a particular assessment of the drug at launch (e.g. that overall survival evolves according to the Kaplan-Meier curve predicted in the initial HTA analysis phase).

Another option is to create RWD measures, for example using patient registries. RWD offers a potential reduction in uncertainty that complements the inevitable passage of time. In practice, however, real-world data are often collected in non-randomized and uncontrolled settings. It is not clear in principle whether data collected during the clinical phase are more reliable than real-world data. Even though the study population in the real world is larger and more diverse, it is not subject to the necessary controls that are performed in clinical trials to ensure correct statistical inference. For example (and this is critical), the real-world population is not balanced, and data from patient registries is often incomplete. In other words, even if real-world results are obtained, it may in principle be necessary to take into account the additional uncertainty factors associated with the use of RWD. However, we believe that the use of RWD in this context can be seen as complementary to the other sources of uncertainty reduction mentioned in the literature. It is important to recognize that the uncertainty associated with RWD is significantly lower in the context of incidence-dominant (ID) advanced therapies, where outcomes are more easily quantifiable. As mentioned above, ID drugs primarily affect patients with incurable diseases, and the effectiveness of these drugs is often assessed by their ability to prolong the patient's life.

The proposed payment scheme for PD-type advanced therapies involves the use of conditional and deferred payments (payment at result). At the patient level, payments will be discontinued in the event of patient death or registry-detectable treatment failure (e.g., if a transplant becomes necessary). If the regulatory body receives other negative signals indicating an incomplete recovery of the patient, it may decide to wait for further future signals. In particular, the Agency could decide to suspend the payment installment at the time t when the negative signal occurred and carry out further checks according to the terms originally agreed in the contract. If the checks confirm a treatment failure, the regulatory body may consider a permanent suspension of the payment. Otherwise, payment will continue and the installment will be refunded. The exact implementation details of the payment plan must be determined ex-ante at the time the contract is drawn up.
When an ATMP drug is administered in the last phase of a patient's life, the arrival of newly diagnosed patients becomes a primary driver of spending, and the focus shifts from patient prevalence to the incidence of new patients. Therefore, from a spending policy perspective, payment systems based on annuity payments are not appropriate for ID-type ATMPs. In this context, the use of the previously described payment system becomes redundant and often counterproductive. This assertion is supported by the analysis developed in the previous session, which makes it clear that deferred payments do not allow adequate management of the impact on the budget. Furthermore, the use of shorter Kaplan-Meier curves supported by clearer outcomes (e.g. patient survival) renders the payment system developed for PD therapies redundant for ID therapies.

Framework for Determining Conditional Deferred Payments for One-Shot PD Therapies

In this subsection, we propose a model for determining deferred payments (success fee) for PD-type advanced therapies. As explained in the previous section, the payment scheme is designed to manage the uncertainty associated with one-shot advanced therapies. The proposed methodology is based on the Payer Uncertainty Burden (PUB) estimation introduced by Grimm et al. (2016, 2017) to quantify the uncertainty associated with the HTA analysis. The payment scheme is described as follows



In particular, we consider a situation in which the one-shot PD advanced therapy is administered at time t = 1 and the total payment is spread over T periods (up to a maximum of 5 years, as described in the previous section).
The first installment, paid at time t = 1 (i.e. R1 in the figure), is determined based on the present value of the comparator (Discounted Value of the Comparator, DVC), adjusted for the uncertainty (PUB) arising from the one-shot nature of the advanced therapy compared to its comparator. From t = 2, the uncertainty is partially resolved due to the passage of time and the generation of RWD. Thus, on the one hand, the subsequent rates, R_t for t = 3, . . . T - 1, carry the partial reduction of uncertainty through time by restoring a constant fraction δ of the PUB. On the other hand, they also take into account the resolution of uncertainty due to RWD by the term w, defined as

$$w = \left[\overline{(EO_t - RWO_t)} + \overline{(AV_{Tot.QALY})}\right],$$

where EO_t is the expected outcome at time t, RWO_t is the real outcome at time t, and $AV_{\text{Tot.QALY}}$ is the added therapeutic value of the unique drug (compared to the comparator) in terms of total QALYs. The rate at time t is given by

$$R_t = w + \bar{R}_{t,comparator} + \delta \cdot PUB$$

and consists of three parts. The first part, w, represents the conditional component of the payment, which varies according to the difference between the expected and observed patient outcomes. The second element (annuity) serves to balance the temporal evolution of

expenditures for one-shot advanced therapies with those for corresponding therapies that are continuously administered over time. Finally, the third element is related to the resolution of uncertainty over time according to a factor δ that is assumed to be constant and equal to $1/T$.

Continuous modulation by factor w is feasible, especially because PD therapies usually require ongoing monitoring of RWD by registries. These data can be rigorously compared with expected outcomes derived from the HTA model and extrapolation of Kaplan-Meier curves to examine the gain in overall survival (OS) for patients treated with PD advanced therapies. Longer Kaplan-Meier curves require a longer adjustment period, but provide increasingly robust evidence in the medium to long term. The expected QALY gains of patients treated with PD therapies need to be compared with actual outcomes, which can be monitored using patient registries. These findings are crucial for the determination of installment payments and the subsequent contract renegotiation phase. It should be noted that the last installment, R_T, reflects the presence of residual uncertainty (ε). In an ideal scenario where the number of patients remains constant over time, the financial difference between the long-term observed values and the rate structure would be negligible. However, the need to limit the overall duration of conditional payment programs may result in residual uncertainty. The contract renegotiation process could significantly reduce ε and address the Payer Strategy Burden (PSB) in a contextualized manner. During this process, the payer could request a repricing that takes into account the residual uncertainty of the original contract.

Finally, it is important to emphasize that in the case of PD therapies, PSB is not initially covered, but will be addressed later in the renegotiation phase. Consequently, the pharmaceutical company agrees to provide the customer with a substantial discount in the initial phase and in return provide a delayed discount on the PSB in the renegotiation phase. This approach compensates for the fact that, unlike ID drugs where the P-SUB is "paid back" through subsequent discounts, the company provides a discount on the PUB in the initial period. This discount is offset by the assurance of the P-SUB to the company, which represents the cost to the customer of choosing that therapy over potentially better ATMP comparators that might emerge after the renegotiation period. Essentially, for PD therapies, companies respond to the need for an immediate discount by deducting the PUB from the DVC at the original rate.

An example of the application of conditional and deferred payment schemes for One-Shot PD Advanced Therapies

This section presents the results of the proposed payment system for reimbursement of a PD therapy as a case study. In our setting, a PD product represents an ideal case study, as many PD-type ATMPs are among the most expensive in the world (Saha et al. 2021). As a result, numerous challenges have arisen in defining reimbursement models (Picecchi et al. 2020), making it necessary to find an innovative reimbursement model.

Product X is an intravenous one-shot gene therapy. At the time of the market launch of product X, other comparator products were available. In our analysis, we are guided by the Italian

Medicines Agency (AIFA) and have taken the direct comparator of product X identified by AIFA. In addition, like AIFA, we consider an ICER/QALY of €51,690. AIFA has applied a discount reserved for Product X as part of the negotiation terms. The data available to us come from a dedicated study to evaluate the safety and efficacy of X. In particular, they provide information on tolerability, pharmacokinetics, pharmacodynamic costs and monetary benefits of the drug. In addition, the cost-effectiveness analysis of X was carried out over the entire lifetime of the patient based on the type of disease to be treated. The study contains detailed data on X and its comparator drugs in specific sections. This includes the monthly costs (hospitalization, medical care, travel costs and more) and the net monetary benefit of the treatments considered.

The rates for reimbursement of therapy X follow the proposed scheme for PD therapies. Specifically, the first installment is calculated as the difference between the net present value (NPV) of the direct comparator and that of the PUB. The PUB is calculated based on the information available in the literature on the NB of X and its comparator. In practice, we have calculated the components of the PUB separately. To obtain $E_\theta\{\max_d NB(d,\theta)\}$, we first calculated the maximum NB between X and its comparator product for each month. We then averaged this result to obtain $E_\theta\{\max_d NB(d,\theta)\}$.
Next, we derived $\max_d E_\theta\{NB(d,\theta)\}$ by first averaging the *NB*s of X and its comparator and then taking the maximum between the two averages, i.e., the average *NB* of X and the average *NB* of its comparator. For the sake of completeness, we also calculated the PSB of the two treatments and obtained a PUB of € 67,470 and a PSB of € 436,178.
To calculate the net present value (NPV) of the comparator treatment of X, we used both the available data on the monthly costs of the comparator treatment and the overall survival (OS) associated with the drug. The NPV was calculated by weighting the monthly installments by the estimated OS of the comparator drug of X in month *s* at an interest rate $i = 4\%$

$$NPV_{comparator} = \frac{CF_s}{(1+i)^s},$$

where CF_s is the net cash flow in the month *s*. The $NPV_{comparator}$ was calculated at € 658,723. Finally, the first installment was set at $NPV_{comparator}$ - PUB, i.e. € 598,723.
We then calculate the following installments, R_t, up to a point in time of $T = 5$ years.
R_t is the sum of the average annual costs of the comparator and the term *w*, as described above. In addition, the term *δ* PUB is added to each installment. As mentioned before, the idea is that the term *δ* PUB takes into account the resolution of uncertainty (measured by PUB) due to the passage of time, while the term *w* deals with the resolution of uncertainty due to the presence of RWD. In this particular case, the calculation results in the following deferred payments.

R_1	R_2	R_3	R_4	R_5
598723€	237112€	130126€	68054€	71794€

Of course, the actual value of the payments may differ from the expected value if the observed results differ from the predicted ones.
Finally, we come to the last installment R_t. In principle, R_t should correspond to the difference between the total price of product X and the installments paid up to T - 1. The amount of the last installment reflects the remaining uncertainty to be resolved.
An alternative solution is for the two parties to agree to a longer contract term to eliminate most of the remaining uncertainty or to determine a lump sum for the remaining uncertainty and spread it over the installments. The lump sum should in principle be proportional to the deviation of the observed Kaplan-Meier (KM) curve for the OS of product X compared to the expected curve.
In summary, it is possible to define a deferred payment model depending on the observed outcomes that adjusts the actual reimbursed price for the one-shot advanced therapy to the observed outcomes, thus ensuring a budget impact equivalent to that of conventional therapies.

Discussion

This work proposes a payment scheme for one-shot advanced therapies. In particular, we have examined the main challenges related to the reimbursement of one-shot ATMP drugs and the current reimbursement methodologies in the European Union. By applying the risk analysis proposed by Grimm et al. (2016, 2017), we identified outcome-based payments as the most appropriate MEA to ensure the reimbursability of ATMPs. The need to introduce ad hoc reimbursement schemes stems from the inability of currently used MEAs to capture a significant portion of the risk associated with the one-shot nature of advanced therapies. This refers to the risk of decision uncertainty, i.e. the risk of making the wrong decision based on the available evidence (reimbursement of non-cost-effective therapies or non-reimbursement of cost-effective therapies).
Following Grimm et al. (2016, 2017), we synthesized the decision maker's risk with a measure called P-SUB, which can be derived from HTA analysis. We then identified and addressed the two main sources of uncertainty resolution arising from the passage of time and the collection of RWD. As a further contribution — recognizing the diversity of the scope and administration methods of ATMP drugs — we made a distinction between prevalence-driven (PD) and incidence-driven (ID) drugs and proposed the activation of a dedicated fund to cover deferred payments for PD-type advanced therapies. In cases where regulatory bodies consider the use of MEAs based on multi-year conditional payment deferrals to be the most appropriate tool to address uncertainty and ensure immediate access to advanced therapies, coverage of deferred payments will be ensured through a dedicated fund.

Finally, we have applied the proposed payment models to a real case. The payment model for PD product X uses the PUB to incrementally increase the ICER per QALY reimbursed to the company, which acts as a precautionary reward to compensate for the one-shot nature of the ATMP. The theoretical framework of the payment scheme applied to PD product X establishes an ex- ante decision on the installment amounts with conditional weighting based on observed real-world outcomes. Again, our approach assumes that outcomes are observed through the use of patient registries.
Although we have considered the key determinants of risk-based payment models for one-shot drugs, such as the removal of uncertainty and the resulting sharing of risk between the

parties involved in the contract, there is scope to modify and adapt the proposed methods. An initial assessment relates to the use of registries as tools for collecting RWD.
However, this approach may not be sufficient, as the registers are incomplete for various reasons (see e.g. Wah, 2020). Consequently, uncertainty can only be partially reduced by observing real-world outcomes. To quantify this partial reduction of uncertainty, we used the PUB. Theoretically, the PUB is calculated using outcome measures such as PFS and OS (cf. Grimm et al., 2017). In practice, payer registries only collect some of these measures, usually OS or other indicators of patient health status. Therefore, one could assume that, from the payer's perspective, the only decisive variable that determines uncertainty is that which is present in the registries. The remaining uncertainty for the payer therefore results from the difference between the actual PUB and that measured by the registries. This correction is not implemented in this work, and the rates are calculated using only the actual PUB. In future applications of the method, this correction could be included in the calculation of deferred payments.

The ATMP Fund

In the near future, more advanced payment models can be developed by relaxing some of our assumptions. However, to ensure timely access to advanced therapies, a dedicated fund must be established to enable the implementation of the reimbursement models described above and facilitate the development of payment models over multiple years. This would also ensure the proper accounting of the annuity payment by results model. Under the principle of extended financial competence and consistent with an annuity payment-at-result model, the expenditure obligation for purchases can be assumed at the time the legal obligation is formalized but allocated to the fiscal years in which the related payments are expected to be made, as contractually agreed. The ATMP fund would provide cover guarantees for future payments while ensuring adequate monitoring of therapeutic outcomes and spending trends.

The ATMP fund should be adequately resourced to ensure coverage of deferred payments. This fund would also allow an assessment of the distribution of benefits and potential savings over a multi-year time horizon. A two-stage process is required to determine an appropriate financial allocation for the fund:

1. First phase: estimate the average amount of conditional and deferred payments for each new eligible indication of the upcoming ATMPs over a multi-year reference horizon (2025-2030).
2. Second phase: Evaluate the number of new indications that could potentially access the ATMP fund during the reference period, estimated by horizon scanning.

To estimate the average level of conditional payment deferrals, an additional analysis of the impact on spending per indication (Anatomical Therapeutic Chemical Classification, ATC level 3) for the arrival of ATMPs was conducted. The analysis, developed using Evaluate Pharma

data, utilized a causal machine learning model through the application of matrix completion techniques (Athey et al., 2021).

For the estimation, the development of expenditure per indication in the period 2010-2024 was taken into account, whereby a distinction was made between "treated" indications —i.e. those for which an ATMP has been introduced — and "control" indications" for which no ATMP has yet been introduced. The approach adopted allows the estimation of a counterfactual trend in expenditure without ATMPs to determine the average treatment effect, i.e. the increase in expenditure per indication attributable to the introduction of advanced therapies (for more details on the methodology, see Nutarelli and Riccaboni, 2024).

The analysis shows that in the model with additional covariates that take into account the number of products on the market (differentiated by type), potentially emerging generic treatments or biosimilars, pipelines and development costs, a significant increase in expenditure can be observed in the first two years, which should be deferred by conditional and deferred payments (Figure 4). Specifically, a potential additional expenditure of 3.7 million on average per new reimbursed indication is estimated. It should be noted that this is a conservative overestimate of the additional expenditure that could be incurred on average if the savings from not paying some outcome-based annuities do not materialize. The actual impact of the additional expenditure will therefore be lower if some contingent payments are not made. Alternatively, the incremental expenditure can be calibrated based on the data available to AIFA on the actual value of deferred payments for reimbursed ATMPs.

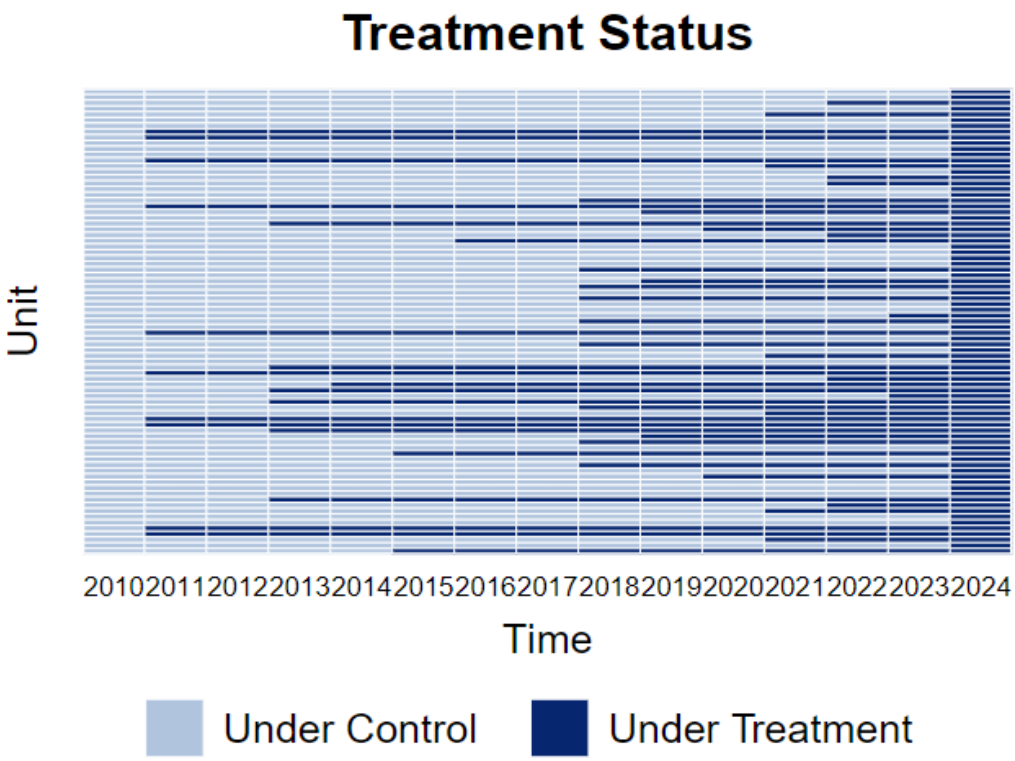


Figure 3: Schematic representation of the method used to estimate the average impact of new ATMPs on average expenditure per therapeutic indication

The Figure 3 illustrates the methodological approach taken to estimate the incremental impact of ATMPs on spending per therapeutic indication. The process includes the following key steps:

1. Data collection: historical spend data (2010-2024) is collected for each therapeutic indication (ATC level 3), distinguishing between "treated" indications (those with ATMP adoption) and "control" indications (those without ATMP adoption).
2. Causal machine learning model: A matrix completion technique is used to estimate the counterfactual spending trend for treated indications without ATMP.
3. Calculation of the average treatment effect (ATE): The difference between the observed expenditure in treated indications and the counterfactual expenditure results in the ATE, which represents the additional effect of ATMPs.
4. Covariate adjustment: The model takes into account covariates such as the number of products on the market, upcoming generics, developments in the pipeline and development costs to refine the estimates.
5. Estimation of additional expenditure: The analysis shows that spending increases significantly in the first two years after ATMP launch, which can be deferred through contingent and deferred payments.

The figure visually depicts these steps and illustrates the comparative analysis between treated and control groups and the estimation of the counterfactual scenario to quantify the ATE. This approach provides a solid framework to understand the financial impact of ATMPs and support the design of reimbursement models.

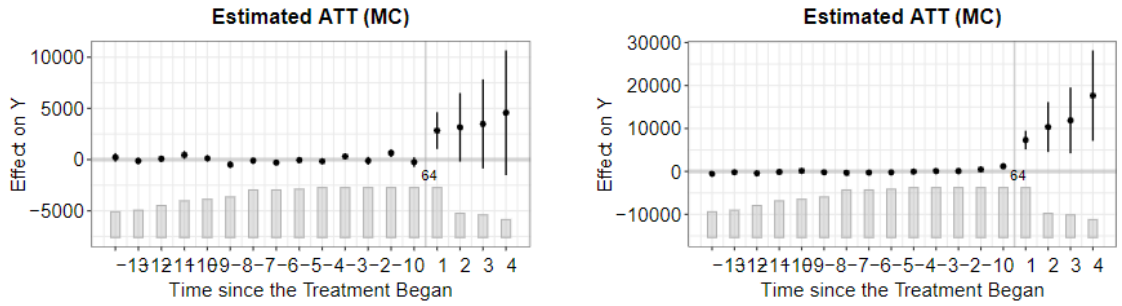


Figure 4. Impact of ATMP arrival on expenditure per indication, model with (right) and without controls (left)

Figure 4 compares the impact of the introduction of ATMPs on expenditure per therapeutic indication using two models: one without controls (left) and one with controls (right). The model with controls includes covariates such as the number of products on the market, generics, pipeline developments and development costs to refine the estimates. The analysis shows that the inclusion of controls significantly improves the accuracy of the estimate of the impact on expenditure, particularly in the first two years following the introduction of the ATMP, where a significant increase in expenditure is observed.

To determine the total amount of the fund, it is also necessary to estimate the number of potential new ATMP indications that will be reimbursed by 2030. This is a very complex undertaking that is subject to considerable uncertainty.

Based on an analysis of the research pipelines, considering only ATMPs with an estimated launch date by 2030 and a probability of success above 50%, 54 potential indications are estimated to be approved by the EMA (see Table 3 in the Appendix). This number would decrease to 51 potential indications if we consider approximately two years from the start of the European assessment process until publication in the Official Journal (ATP Forum, 2023). In this case, only indications that will be reimbursed by 2028 would be considered. Assuming that all products approved by the EMA are reimbursed in Italy, the potential allocation for the ATMP fund is estimated at €200 million.

This estimate remains conservative for the following reasons:

1. The actual impact of the additional expenditure could be lower: The actual additional expenditure could be lower due to unpaid contingent payments. Confidential rebates and MEAs are expected to significantly reduce the estimated incremental expenditure.
2. Fewer reimbursed therapies: The actual number of therapies reimbursed could be lower than planned as some therapies may not be eligible for reimbursement.
3. Limited access to the fund: Access to the fund could be limited to new indications for widely used ATMPs. AIFA is expected to assess the level of uncertainty for each product and determine the most appropriate MEA to manage it. Access to the fund will only be activated if AIFA deems it necessary to use deferred payment schemes (annuity payments) to guarantee future payments.

However, it is important to allocate an appropriate amount to the fund, which may be adjusted over time based on additional information as it becomes available.

Conclusions

Advanced therapies represent a paradigm shift in 21st-century medicine. However, their effectiveness is still very uncertain at the time of market launch. In addition, they are usually associated with high initial costs due to their one-shot administration. These unique characteristics pose unprecedented challenges for access to reimbursement. The reimbursement system proposed in this study represents a potential solution to ensure timely and sustainable access to advanced therapies. Our approach is based on conditional payment schemes to align the costs of therapies with observed outcomes while respecting budget constraints.

Another contribution of this work is the formalization of the distinction between ATMP drugs into two categories: prevalence-driven (PD) and incidence-driven (ID) drugs. We have shown the importance of this distinction for the budgetary impact of the two types of ATMPs and emphasize the need for different payment schemes for PD and ID ATMPs. Other factors may influence the choice of the most appropriate MEAs (e.g., the availability of easily measurable clinical outcomes that can be linked to outcome-based schemes), which is the responsibility of regulators.

For PD therapies, our analysis emphasizes the need for conditional payments that adjust over time, taking into account the removal of uncertainty and the collection of RWD. In the case of these therapies, the multi-year collection of evidence to address uncertainty requires access to a dedicated fund to manage multi-year conditional payments. This approach not only

mitigates the financial impact on healthcare budgets, but also aligns payment structures with the long-term benefits and risks of ATMPs. The Product X case study illustrates how the proposed payment system can be applied to ensure that financial strategies are appropriate to balance the significant initial costs with the potential long-term benefits.
In particular, the first installment is determined by subtracting the Payer Uncertainty Burden (PUB) from the Discounted Value of the Comparator (DVC), reflecting the need to mitigate the initial financial impact while considering the therapeutic value compared to existing treatments. Subsequent payments are then determined by a combination of the average annual spend on the comparator, a constant proportion of the PUB to account for the reduction in uncertainty over time, and adjustments based on real-world outcomes compared to expected outcomes, allowing for dynamic financial planning. Towards the end of the payment period, the possibility of renegotiating the contract based on the evidence gathered and adjusting the final amount to reflect the actual value of the therapy is considered.

Our research has significant implications for the definition of innovative and evidence-based reimbursement schemes for ATMPs. This thesis is also supported by several studies in the literature (Pizevska et al., 2022; Ronco et al., 2021; Gozzo et al., 2021; Panteli et al., 2015). For PD-type therapies, policy should allow for installment payments that can be adjusted over time to reflect the evolving therapeutic landscape and financial implications.
In addition, our study promotes the integration of real-world evidence into reimbursement decision-making, enabling the implementation of dynamic, outcome-focused financial agreements. By aligning reimbursement structures with therapeutic outcomes, health systems can improve access to innovative therapies while ensuring financial sustainability (Noone, Coffin, and Pierce, 2021). In summary, our research contributes to the ongoing dialog on optimizing pricing and reimbursement strategies for ATMPs (e.g., Eichler et al., 2022; Noone, Coffin, and Pierce, 2021; Fischer et al., 2023). By addressing the specific challenges of ATMPs, the proposed methods provide a way to balance the spending sustainability requirements of healthcare systems with the transformative potential of advanced therapies, as supported in the literature (Bloom et al., 2019; Kamusheva et al., 2021; Noone, Coffin, and Pierce, 2021).

The establishment of a dedicated fund will also ensure the coverage of deferred payments in full compliance with the accounting standards for the outcome-based reimbursement of ATMPs. The establishment of an ATMP fund will eliminate the need to set aside funds as guarantees for future payment obligations of payers. In addition, it will be possible to demonstrate the savings resulting from the introduction of outcome-based reimbursement models for therapies.

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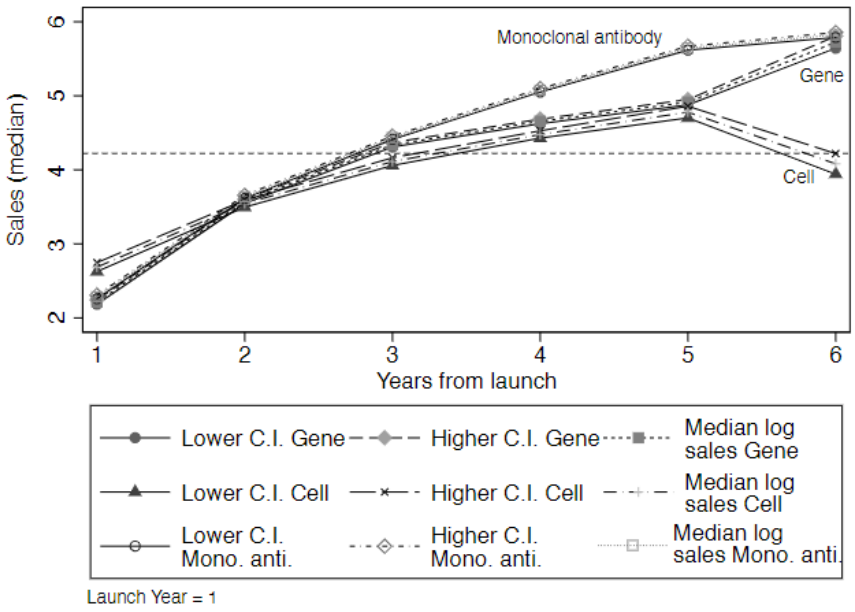
Appendix

Table A.1. Number of ATMPs in Development

Phase	Gene Therapy	Cell Therapy	Gene-Modified Cell Therapy	Total
Marketed	6	15	7	28
Approved	7	6	10	23
Filed	5	0	1	6
Phase III	16	6	1	23
Phase II	38	8	25	71
Phase I	5	2	19	26
Preclinical	16	1	8	25
Withdrawn	0	2	0	2
Total	93	40	71	204

Source: Our elaborations based on Evaluate Pharma data.

Figure A.1. Temporal Trend of Expenditure for Gene and Cell Therapies Compared to Expenditure for Monoclonal Antibodies



Source: Our elaborations based on Evaluate Pharma data.

Table A.2. Horizon Scanning of ATMP Products

Prodotto| Indicazione	Meccanismo di azione	Data Approvazione FDA	Exp. Prob.	Imprese coinvolte	Lancio in Europa
MACI | Bone repair & regeneration	Chondrocyte regulator	13/12/2016		Sanofi, Vericel	31/12/1998
Vavelta | Facial wrinkles/Nasolabial folds	Fibroblast cell therapy			Regenerative Medicine Assets, Ember Therapeutics	30/06/2008
Provenge | Prostate cancer	Anti-prostatic acid phosphatase (PAP) T-cell stimulant	29/04/2010		Bausch Health Companies, Nanjing Xinjiekou Department Store, Sanpower	06/09/2013
Strimvelis | Severe combined immunodeficiency disease (SCID)	Adenosine deaminase gene therapy			GSK, AGC Biologics, Orchard Therapeutics	31/10/2016
Alofisel | Gastro-intestinal fistula	Mesenchymal stem cell therapy			Takeda	31/03/2018
Yescarta | Non-Hodgkin lymphoma (NHL)	B-lymphocyte antigen CD19 CAR-T cell therapy	18/10/2017		Gilead Sciences, Daiichi Sankyo, Fosun International, Fosun Pharma Kite Biotechnology	31/08/2018
Kymriah | Non-Hodgkin lymphoma (NHL)	B-lymphocyte antigen CD19 CAR-T cell therapy	01/05/2018		The University of Pennsylvania, Novartis	22/10/2018
Kymriah | Leukaemia, acute lymphocytic (ALL)	B-lymphocyte antigen CD19 CAR-T cell therapy	30/08/2017		Verismo Therapeutics, The University of Pennsylvania, Novartis	30/11/2018
Zynteglo | Thalassaemia	βA-T87Q-globin gene transference	17/08/2022		bluebird bio	30/01/2020
Luxturna | Retinitis pigmentosa	Retinoid isomerohydrolase gene therapy	19/12/2017		The Children's Hospital of Philadelphia, Roche, Novartis	28/02/2020
Chondroseal | Osteoarthritis	Cartilage stimulant	29/06/2020		Theracell, Orgenesis	29/06/2020
Cartil-S | Osteoarthritis	Chondrocyte regulator	30/06/2020		Theracell, Orgenesis	30/06/2020
Zolgensma | Spinal muscular atrophy	Survival of motor neuron 1 (SMN1) gene transference	24/05/2019		Novartis, Bayer, Suzuken Group	01/07/2020
Tecartus | Non-Hodgkin lymphoma (NHL)	B-lymphocyte antigen CD19 CAR-T cell therapy	24/07/2020		Gilead Sciences	31/12/2020
Lenmeldy | Metachromatic leukodystrophy	Arylsulfatase A (ARSA) gene therapy	18/03/2024		Kyowa Kirin, AGC Biologics	31/12/2020
Skysona | Other metabolic indications	Adrenoleukodystrophy (ALD) transduced CD34 cell therapy	16/09/2022		bluebird bio	21/07/2021
Abecma | Multiple myeloma	Anti-B-cell maturation antigen (BCMA) CAR-T cell therapy	26/03/2021		bluebird bio, Bristol Myers Squibb, 2Seventy Bio	18/08/2021
Luxturna | Leber's congenital amaurosis	Retinoid isomerohydrolase gene therapy	19/12/2017		The Children's Hospital of Philadelphia, Roche, Novartis	31/12/2021
Breyanzi | Non-Hodgkin lymphoma (NHL)	B-lymphocyte antigen CD19 CAR-T cell therapy	05/02/2021		Seattle Children’s, Bristol Myers Squibb, Fred Hutchinson Cancer Research Center	04/07/2022

Upstaza | Other metabolic indications	Aromatic-L-amino-acid decarboxylase (AADC) gene transference	13/11/2024	93%	National Taiwan University, PTC Therapeutics	18/10/2022
Ebvallo | Epstein-Barr virus (EBV) infections	Anti-Epstein-barr virus (EBV) antigen cytotoxic T-lymphocyte (CTL) cell therapy	20/03/2025	93%	Memorial Sloan-Kettering Cancer Center, Atara Biotherapeutics, Pierre Fabre	31/03/2023
Hemgenix | Haemophilia B	Coagulation factor IX gene therapy	22/11/2022		University of Padua, CSL, uniQure	30/06/2023
Roctavian | Haemophilia A	Coagulation factor VIII gene therapy	29/06/2023		St. Jude Children's Research Hospital, BioMarin Pharmaceutical	30/08/2023
Carvykti | Multiple myeloma	Anti-B-cell maturation antigen (BCMA) CAR-T cell therapy	28/02/2022		Johnson & Johnson, Legend Biotech	31/03/2024
Tecartus | Leukaemia, acute lymphocytic (ALL)	B-lymphocyte antigen CD19 CAR-T cell therapy	01/10/2021		Gilead Sciences	31/08/2024
Beqvez | Haemophilia B	Coagulation factor IX gene therapy	25/04/2024		The Children's Hospital of Philadelphia, Roche, Pfizer	31/12/2024
Vyjuvek | Epidermolysis bullosa (EB)	Collagen type VII alpha 1 chain (COL7A1) gene transference	19/05/2023		Krystal Biotech	31/12/2024
SRP-9003 | Limb-girdle muscular dystrophy	Sarcoglycan beta (SGCB) gene transference	31/12/2025	51%	Nationwide Children's Hospital, Sarepta Therapeutics	31/12/2024
Upstaza | Other neurological indications	Aromatic-L-amino-acid decarboxylase (AADC) gene transference	31/12/2025	93%	National Taiwan University, PTC Therapeutics	31/12/2024
RP-L102 | Anaemia, other	Fanconi anaemia complementation group A (FANCA) gene transference	31/12/2026	97%	Rocket Pharmaceuticals	31/12/2024
Amtagvi | Melanoma	Programmed cell death protein 1 (PD1) inhibitor; Tumour infiltrating lymphocytes (TIL) cell therapy	16/02/2024		Iovance Biotherapeutics	30/06/2025
Elevidys | Duchenne muscular dystrophy	Dystrophin synthesis gene therapy	22/06/2023		Sarepta Therapeutics, Roche, Chugai Pharmaceutical	31/12/2025
Pz-cel | Epidermolysis bullosa (EB)	Collagen type VII alpha 1 chain (COL7A1) gene transference	31/12/2024	81%	Stanford University, Abeona Therapeutics	31/12/2025
Revascor | Chronic heart failure (CHF)	Mesenchymal stem cell therapy	31/12/2025	15%	Mesoblast	31/12/2025
Lumevoq | Leber's hereditary optic neuropathy	NADH-ubiquinone oxidoreductase chain 4 gene therapy	28/05/2025	5%	GenSight Biologics	31/12/2025
DTX301 | Urea cycle disorders	Ornithine transcarbamylase (OTC) gene transference	31/12/2026	57%	Ultragenyx Pharmaceutical	31/12/2025
DTX401 | Other metabolic indications	Glucose-6-phosphatase gene transference	31/12/2025	91%	Ultragenyx Pharmaceutical	31/12/2025
SB-525 | Haemophilia A	Coagulation factor VIII gene therapy	01/07/2025	78%	Sangamo Therapeutics, Pfizer	31/12/2025
AAV-GAD | Parkinson's disease	Glutamic acid decarboxylase (GAD) gene transference	31/12/2026	7%	MeiraGTx	31/12/2025
ECT-001 | Multiple myeloma	Stem cell stimulant		93%	ExCellThera	31/12/2025

Kresladi | Other immune indications	Leukocyte adhesion deficiency (LAD) I gene therapy	31/01/2025	81%	Rocket Pharmaceuticals	31/12/2026
Afami-cel | Soft tissue sarcoma	Melanoma antigen A4 (MAGE-A4) protein cell therapy	02/08/2024	97%	Adaptimmune	31/12/2026
Obe-cel | Leukaemia, acute lymphocytic (ALL)	B-lymphocyte antigen CD19 CAR-T cell therapy	16/11/2024	97%	University College London, Autolus Therapeutics	31/12/2026
Deramiocel | Duchenne muscular dystrophy	Cardiac stem cell therapy	30/07/2025	60%	The Johns Hopkins University, Lonza, Nippon Shinyaku, Capricor Therapeutics	31/12/2026
UX701 | Wilson's disease	Copper-transporting ATPase beta (ATP7B) gene transference	31/12/2026	52%	The University of Pennsylvania, Ultragenyx Pharmaceutical	31/12/2026
OTL-203 | Hurler's syndrome (Mucopolysaccharidosis I or MPS I)	Alpha-L-Iduronidase gene transference	31/12/2026	56%	Kyowa Kirin	31/12/2026
OCU400 | Retinitis pigmentosa	Nuclear receptor subfamily 2 group E member 3 (NR2E3) gene transference	31/12/2026	74%	Ocugen	31/12/2026
IMC-F106C | Melanoma	Anti-preferentially expressed antigen in melanoma (PRAME) T-cell stimulant; T-Cell stimulant	31/12/2026	71%	Immunocore	31/12/2026
SPK-8011 | Haemophilia A	Coagulation factor VIII gene therapy	31/12/2026	20%	Roche	31/12/2026
jCell | Retinitis pigmentosa	Human retinal progenitor cell therapy	07/08/2029	5%	jCyte, Santen Pharmaceutical	31/12/2026
LN-145 | Cervical cancer	Tumour infiltrating lymphocytes (TIL) cell therapy	31/12/2026	3%	Iovance Biotherapeutics	31/12/2026
AAV-RPE65 | Leber's congenital amaurosis	Retinoid isomerohydrolase gene therapy	31/12/2026	0%	University College London, MeiraGTx	31/12/2026
AMT-130 | Huntington's disease	Huntingtin (HTT) RNAi therapeutic; microRNA gene transference	31/12/2026	31%	uniQure	31/12/2026
TSHA-118 | Batten disease	Ceroid-lipofuscinosis, neuronal 1 (CLN1) gene transference	31/12/2026	57%	The University of North Carolina, Taysha Gene Therapies, Abeona Therapeutics	31/12/2026
MB-104 | Multiple myeloma	Universal Chimeric Antigen Receptor T (U-CART) cell therapy		1%	Fortress Biotech, Mustang Bio	31/12/2026
TSC-101 | Leukaemia, acute lymphocytic (ALL)	T-cell receptor (TCR) cell therapy	31/12/2026	10%	TScan Therapeutics	31/12/2026
RGX-314 | Wet age-related macular degeneration (AMD)	Vascular endothelial growth factor receptor (VEGFR) A antagonist	31/12/2025	80%	REGENXBIO, AbbVie	31/12/2027
OpRegen | Dry age-related macular degeneration (AMD)	Retinal pigmented epithelial (RPE) cell therapy	31/12/2026	2%	Roche, Lineage Cell Therapeutics	31/12/2027
AVR-RD-02 | Gaucher's disease	Glucocerebrosidase (GCase) gene transference	31/12/2026	19%	Lund University, Tectonic Therapeutic	31/12/2027

RP-L301 | Anaemia, haemolytic	Pyruvate kinase (PK) gene therapy; Pyruvate kinase (PK) gene transference	31/12/2027	32%	Rocket Pharmaceuticals	31/12/2027
RP-A501 | General cardiovascular indications	Lysosome-associated membrane glycoprotein 2 (LAMP2) gene transference	31/12/2026	30%	University of California, Rocket Pharmaceuticals	31/12/2027
SRP-9004 | Limb-girdle muscular dystrophy	Sarcoglycan alpha (SGCA) gene transference	31/12/2026	1%	Sarepta Therapeutics	31/12/2027
KB105 | Mucocutaneous dryness	Transglutaminase (TG) 1 gene transference	31/12/2026	21%	Krystal Biotech	31/12/2027
BBP-631 | Adrenal hyperplasia, congenital	Steroid 21-hydroxylase gene transference	31/12/2026	27%	BridgeBio Pharma	31/12/2027
Cemacabtagene Ansegedleucel | Non-Hodgkin lymphoma (NHL)	B-lymphocyte antigen CD19 CAR-T cell therapy	05/09/2027	53%	Allogene Therapeutics, Servier	31/12/2027
PBFT02 | Dementia, frontotemporal	Granulin precursor (GRN) gene transference	31/12/2027	33%	Passage Bio	31/12/2027
ADP-A2M4CD8 | Head & neck cancers	Melanoma antigen A4 (MAGE-A4) protein cell therapy; T-cell surface glycoprotein CD8 stimulant	31/12/2027	2%	Adaptimmune, Galapagos	31/12/2027
ADP-A2M4CD8 | Bladder cancer	Melanoma antigen A4 (MAGE-A4) protein cell therapy; T-cell surface glycoprotein CD8 stimulant	31/12/2027	4%	Adaptimmune	31/12/2027
ADP-A2M4CD8 | Ovarian cancer	Melanoma antigen A4 (MAGE-A4) protein cell therapy; T-cell surface glycoprotein CD8 stimulant	31/12/2026	15%	Adaptimmune	31/12/2027
AOC 1020 | Facioscapulohumeral muscular dystrophy (FSHD)	Double homeobox 4 (DUX4) regulator	31/12/2027	57%	Avidity Biosciences	31/12/2027
ALLO-715 | Multiple myeloma	Anti-B-cell maturation antigen (BCMA) CAR-T cell therapy	31/12/2027	15%	Allogene Therapeutics, Overland Pharmaceuticals, Allogene Overland Biopharm	31/12/2027
AUTO4 | Non-Hodgkin lymphoma (NHL)	T-cell receptor beta chain 1 (TRBC1) CAR-T cell therapy	12/12/2027	10%	Autolus Therapeutics	31/12/2027
KB301 | Other dermatoses	Collagen type III receptor stimulant	31/12/2027	3%	Krystal Biotech	31/12/2027
PRGN-3006 | Leukaemia, acute myeloid (AML)	Anti-CD33 CAR-T cell therapy	31/12/2026	21%	Precigen	31/12/2027
PRGN-3005 | Ovarian cancer	Anti-mucin-16 (MUC16) CAR-T cell therapy	31/12/2026	3%	Precigen	31/12/2027
AUTO1/22 | Leukaemia, acute lymphocytic (ALL)	B-lymphocyte antigen CD19 CAR-T cell therapy; B-lymphocyte antigen CD22 CAR-T cell therapy	31/12/2027	2%	University College London, BioNTech, Autolus Therapeutics	31/12/2027
AUTO8 | Multiple myeloma	Anti-B-cell maturation antigen (BCMA) CAR-T cell therapy	31/12/2027	2%	Autolus Therapeutics (Listed: $928m): Organic	31/12/2027
TSC-100 | General blood malignancies	T-cell receptor (TCR) cell therapy		16%	TScan Therapeutics	31/12/2027

Obe-cel | Leukaemia, chronic lymphocytic (CLL)	B-lymphocyte antigen CD19 CAR-T cell therapy	31/12/2027	4%	University College London, Autolus Therapeutics	31/12/2027
bota-vec | Retinitis pigmentosa	Retinitis pigmentosa GTPase regulator (RPGR) gene transference	31/12/2025	57%	Johnson & Johnson, MeiraGTx	31/12/2028
SPK-3006 | Pompe's disease	Alpha-glucosidase regulator	31/12/2027	4%	Généthon, Roche	31/12/2028
Trem-cel | Leukaemia, acute myeloid (AML)	Haematopoietic cell replacement	31/12/2027	73%	Vor Biopharma	31/12/2028
PR006 | Dementia, frontotemporal	Granulin precursor (GRN) gene transference	31/12/2028	8%	Eli Lilly	31/12/2028
PBGM01 | Other lysosomal storage disorders	Beta-galactosidase-1 (GLB1) gene transference	31/12/2026	30%	Passage Bio	31/12/2028
BNT211 | Ovarian cancer	Anti-claudin 6 (CLDN6) CAR-T cell therapy	31/12/2027	1%	BioNTech	31/12/2028
BEAM-201 | Leukaemia, acute lymphocytic (ALL)	Anti-CD7 CAR-T cell therapy	31/12/2028	12%	Beam Therapeutics	31/12/2028
FLT201 | Gaucher's disease	Glucocerebrosidase (GCase) gene therapy		1%	Syncona	31/12/2028
VCAR33 | Leukaemia, acute myeloid (AML)	Anti-CD33 CAR-T cell therapy	31/12/2027	31%	Vor Biopharma	31/12/2028
BNT211 | Solid tumour indications	Anti-claudin 6 (CLDN6) CAR-T cell therapy		3%	BioNTech	31/12/2028
BEAM-201 | Leukaemia, acute myeloid (AML)	Anti-CD7 CAR-T cell therapy	31/12/2028	1%	Beam Therapeutics	31/12/2028
SGT-003 | Duchenne muscular dystrophy	Dystrophin synthesis gene therapy	31/12/2028	39%	Solid Biosciences	31/12/2028
Rapcabtagene Autoleucel | Systemic lupus erythematosus (SLE)	B-lymphocyte antigen CD19 CAR-T cell therapy	31/12/2028	8%	Novartis	31/12/2028
UCART22 | Leukaemia, acute lymphocytic (ALL)	Anti-CD22 CAR-T cell therapy	31/12/2027	0%	Cellectis	31/12/2028
P-BCMA-ALLO1 | Multiple myeloma	Anti-B-cell maturation antigen (BCMA) CAR-T cell therapy	31/12/2028	4%	Poseida Therapeutics, Roche, Amgen	31/12/2028
DeTIL-0255 | Non-small cell lung cancer (NSCLC)	E3 ubiquitin ligase Cbl-b inhibitor; Tumour infiltrating lymphocytes (TIL) cell therapy	31/12/2028	15%	Nurix Therapeutics	31/12/2028
Sepofarsen | Leber's congenital amaurosis	Centrosomal protein 290 (CEP290) RNAi therapeutic	31/12/2029	40%	ProQR Therapeutics, Laboratoires Théa	31/12/2029
LN-145 | Non-small cell lung cancer (NSCLC)	Tumour infiltrating lymphocytes (TIL) cell therapy	17/02/2029	14%	Iovance Biotherapeutics	31/12/2029
KYV-101 | Systemic lupus erythematosus (SLE)	B-lymphocyte antigen CD19 CAR-T cell therapy	31/12/2028	26%	National Institutes of Health, Kyverna Therapeutics	31/12/2029
KYV-101 | Myasthenia gravis	B-lymphocyte antigen CD19 CAR-T cell therapy	31/12/2028	81%	National Institutes of Health, Kyverna Therapeutics	31/12/2029
KB407 | Cystic fibrosis (CF)	Cystic fibrosis transmembrane conductance regulator (CFTR) corrector;	31/12/2028	32%	Krystal Biotech	31/12/2029

	Cystic fibrosis transmembrane conductance regulator (CFTR) regulator				
CB-012 | Leukaemia, acute myeloid (AML)	Anti-C-type lectin domain family 12 member A (CLEC12A) T-cell stimulant	31/12/2027	2%	Caribou Biosciences	31/12/2029
RP-A601 | Hypertrophic cardiomyopathy	Unclassified	31/12/2028	23%	Rocket Pharmaceuticals	31/12/2029
Obe-cel | Non-Hodgkin lymphoma (NHL)	B-lymphocyte antigen CD19 CAR-T cell therapy	31/12/2029	5%	University College London, Autolus Therapeutics	31/12/2030
KYV-101 | Scleroderma	B-lymphocyte antigen CD19 CAR-T cell therapy	31/12/2029	12%	National Institutes of Health (NIH; USA), Kyverna Therapeutics	31/12/2030
CB-010 | Non-Hodgkin lymphoma (NHL)	B-lymphocyte antigen CD19 CAR-T cell therapy	19/09/2027	75%	Caribou Biosciences, Intellia Therapeutics	31/12/2030
CB-011 | Multiple myeloma	Anti-B-cell maturation antigen (BCMA) CAR-T cell therapy	31/12/2026	54%	Caribou Biosciences	31/12/2030
TSC-200 | Head & neck cancers	T-cell receptor (TCR) cell therapy	31/12/2026	1%	TScan Therapeutics	31/12/2030
TSC-200 | Melanoma	T-cell receptor (TCR) cell therapy	31/12/2029	5%	TScan Therapeutics	31/12/2030
TSC-200 | Cervical cancer	T-cell receptor (TCR) cell therapy	31/12/2029	9%	TScan Therapeutics	31/12/2030
DeTIL-0255 | Melanoma	E3 ubiquitin ligase Cbl-b inhibitor; Tumour infiltrating lymphocytes (TIL) cell therapy	31/12/2028	9%	Nurix Therapeutics	31/12/2030
KYV-101 | Multiple sclerosis (MS) unspecified	B-lymphocyte antigen CD19 CAR-T cell therapy		49%	Kyverna Therapeutics	31/12/2031
DeTIL-0255 | Head & neck cancers	E3 ubiquitin ligase Cbl-b inhibitor; Tumour infiltrating lymphocytes (TIL) cell therapy	30/11/2029	8%	Nurix Therapeutics	31/12/2031

Source: Our elaborations based on Evaluate Pharma data.

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