INNOVATIVE CONTRACTING FOR ATMPS IN EUROPE:

Recent learnings from the manufacturer experience

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CONTENTS

1. EXECUTIVE SUMMARY

The distinct characteristics of Advanced Therapy Medicinal Products (ATMPs) – often single-administration treatments with great therapeutic potential, high upfront costs, and incomplete evidence at the time of launch – create unique challenges for health technology assessment (HTA) and pricing and reimbursement (P&R).

Stakeholders are overall in agreement that innovative contracting – agreements between ATMP manufacturers and payers involving outcomes-based or financial agreements such as split payments – can be a potential solution for improving patient access to ATMPs. There is, however, considerable room for improvement regarding the implementation and uptake of these agreements in practice across Europe.

This paper explores what needs to happen in practical terms to optimise patient access to ATMPs in Europe using innovative contracting. It reflects the experience of members of the Alliance for Regenerative Medicine (ARM) in negotiating and implementing these schemes with national payers and provides learnings for the future.

Interviews and workshops were conducted with industry representatives, including seven of the 10 manufacturers who have obtained marketing authorisation for one or more ATMPs in Europe since 2018. The feedback suggested that the use of innovative contracts for ATMPs in Europe has grown over the past five years relative to previous periods. Innovative contracts were discussed in nearly all negotiations. For five of eight ATMPs, successful agreements were reached in over half of the countries in which they were considered. For the remaining products, two had limited to no success in agreeing to innovative contracts and one product was withdrawn.

The increased use of innovative contracts has reflected a generally positive trend in attitudes towards them from European payers and policymakers, following a recognition of the potentially high value of ATMPs. Policy changes or proposals have been seen in several countries, including Spain, Italy, France, the UK, the Netherlands and Sweden, which increase the potential for innovative contracting. While most countries have become more open to the idea (e.g., France), others remain hesitant (e.g., Germany).

Despite initial concerns around the technical difficulty of implementing split payments, especially related to European accounting rules, in practice this has not been a major impediment. Outcomes-based agreements have also been widely used for ATMPs in Europe over the past five years, with manufacturers reporting good alignment between real-world data and predictions of clinical effects that had underpinned agreements. Real-world data collection challenges, while still a major consideration when designing outcomes-based agreements, are being addressed in many countries, and precedents have been established for collaborative data collection that has made the administration burden more manageable. This has been aided by the evolution of electronic health record technology, with improvements in infrastructure, platforms, and connections between medical centres.

Nevertheless, despite important progress in the past five years, ATMP manufacturers see the need for further effort and investment across all stakeholders to reach a point where innovative contracting can represent a 'bridge to access' for ATMPs, where necessary.

This effort starts with a commitment to engage in innovative contracting across all countries, particularly those currently least willing to consider them. Given the interconnectedness of European payer systems, the difficulties in negotiating an innovative contract in Germany, for example, can constrain access to ATMPs more widely across Europe.

Where there is the willingness to consider such agreements, more clarity and guidance are necessary – taking place earlier in the development process – on payer thinking regarding the structure and endpoints of a potential contract. The current lack of consistency in the approach to agreements between countries increases the complexity for manufacturers and further delays patient access. Pre-approval engagement between manufacturers and national payers could accelerate access by scoping out the nature of the uncertainty around an ATMP and the type of innovative contract that might alleviate it. Improved clarity should not come at the expense of flexibility – a consistent factor from successful schemes implemented to date was the tailoring of the agreement to the specific characteristics of the ATMP in question.

While data collection has improved, further effort is needed. It is recognised that questions of data ownership are complex, with competing interests between manufacturers, payers, patients, and physicians. Moving forward, the optimal approach is likely to be a collaborative approach that draws on the respective expertise and capability of each stakeholder, while providing common incentives, tailored to each stakeholder, for the quality and consistency of the data collected. Auditing of outcomes is a particularly sensitive area. There is an increasing consensus on the validity of manufacturer audits of data held by national organisations, but confidentiality issues mean in practice this is seldom possible. Third-party auditing is a possible solution.

A more fundamental challenge, which underpins every other facet of innovative contracts, is the need for mutual trust between payers and manufacturers. Advances in the design and governance of innovative contracts help to reduce the reliance on good faith, and successful experiences with innovative contracting are critical. However, concerns about manufacturer intentions (on the payer side) and fears that payers don't recognise ATMP exceptionalism (on the manufacturer side) mean that innovative contracts are less common and slower to finalise than they need to be. No quick solution exists, but it was felt that providing clarity on the nature and innovation model of ATMPs was important.

Despite the measured optimism among manufacturers for the role of innovative contracts in accelerating patient access to ATMPs, they were clear that innovative contracts are neither the exclusive route to access for ATMPs nor a sufficient remedy for the absence of P&R pathways appropriately adapted to the specificities of ATMPs. Innovative contracting should not be presumed to be the default: in many instances, timely and complete patient access should be achievable for ATMPs using more conventional P&R approaches. The presumption should always be towards the simplest and most efficient solution available.

Equally, innovative contracts are not a substitute for a willingness to pay that reflects the full value of new medicine. The economic viability of many ATMPs is challenging, given the small patient numbers and complexity. With the cost of goods high, and the ability to scale up manufacturing low, there is limited opportunity for price flexibility. There are serious questions within the industry about the medium-term economic viability of these technologies, and whether the cost and effort to implement innovative contracts can be justified by the economic return. The spectre of bluebird bio's departure from Europe continues to hang over this debate, and the extent to which innovative contracting is ultimately successful will influence the likelihood of this situation recurring.

It is therefore very important that the learnings from manufacturers' experience over the past five years are considered carefully. The opportunity represented by ATMPs for Europe is transformational: for individual patients, for public health, and for the scientific and industrial leadership of the continent. Innovative contracting alone will not deliver the full benefits of that opportunity, but it can create a bridge to patient access that is a meaningful step in the right direction.

2. PREFACE: INDUSTRY LEARNINGS FROM ENGAGING IN INNOVATIVE CONTRACTS FOR ATMPS ARE IMPORTANT

2.1 Context

Traditional discount-based contracting is straightforward to implement and is routinely used in P&R negotiations for chronic disease treatments in Europe. However, the introduction of ATMPs – primarily indicated for rare diseases with significant unmet need – has led to renewed interest in more innovative contracting options, which in the report will refer to contractual agreements between payers and manufacturers that are intended to address financial and clinical uncertainties or concerns within P&R negotiations (Facey, et al., 2021; Wenzl & Chapman, 2019; Goodman, et al., 2022) (See section 3.2 for more a more detailed definition).

The relevance of innovative contracting relates to the distinct characteristics of many ATMPs: often single-administration treatments with great therapeutic potential, high upfront costs, and immature evidence at the time of launch. Innovative contracting offers new ways of addressing the clinical and financial uncertainty associated with these therapies.

Given the potential to improve the speed and breadth of patient access to ATMPs, while addressing budgeting and evidential concerns, there has been increasing willingness amongst payers in Europe to engage in innovative contracting with ATMP manufacturers in the past five years.

Nevertheless, it should be recognised that innovative contracting is neither the only route to access for ATMPs nor a sufficient remedy for the absence of P&R pathways appropriately adapted to the specificities of ATMPs. Innovative contracting should not be presumed to be the default: in many instances, timely and complete patient access should be achievable for ATMPs using more conventional approaches. The presumption should always be towards the simplest and most efficient solution available.

When innovative contracts are appropriate and necessary, it is helpful to have a clear understanding of what is required for such agreements to be acceptable, workable, and effective in practice. This paper seeks to draw on recent industry experience of implementing innovative contracts for ATMPs in Europe to inform the future development of such agreements.

2.2 Objective and scope

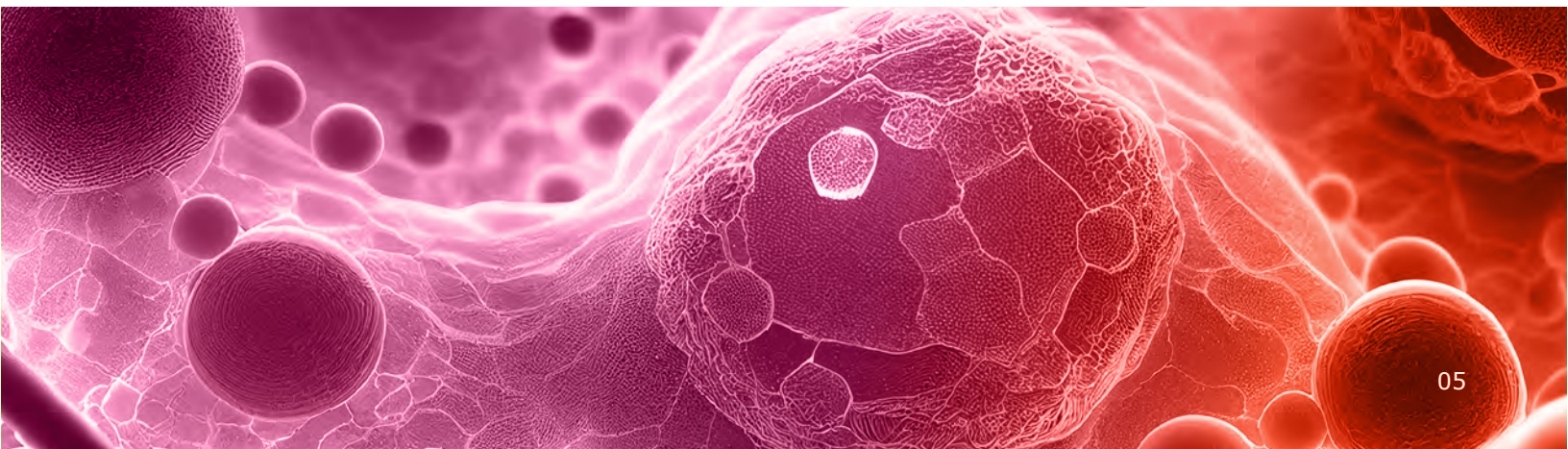
This paper explores what needs to happen in practical terms to optimise patient access to ATMPs using innovative contracting. It reflects on industry experience from negotiating and implementing these schemes and provides learnings for the future.

The perspective of this report is that of members of ARM, including all companies that have launched ATMPs in Europe. Manufacturers are not the only stakeholder with an interest in how innovative contracting should be used to effect access to ATMPs. Patients should be at the centre of all decisions around care and payers have as much interest as manufacturers in ensuring that innovative contracts are successful. While this report does not include perspectives from these stakeholders, constraints faced by payers and other stakeholders are recognised as much as possible. Integration of patient, payer, and clinician perspectives would be a natural progression for future multi-stakeholder dialogues on this topic. The hope is that this document could be a useful input into such an exercise.

This paper is based on experiences negotiating innovative contracts for ATMPs in Europe. Manufacturers' insights reflect experiences in larger European countries, where the majority of contracts have been agreed upon. But there are also many experiences of agreeing to innovative contacts in smaller countries, where the challenges are sometimes different, including reduced access to appropriate diagnostic and clinical infrastructure, and reduced government personnel to manage innovative contracts.

All ATMPs so far approved in Europe have been indicated in small patient populations. This paper, therefore, reflects experiences of innovative contracting for ATMPs in rare diseases.

Other papers have been written on the topic of innovative contracting for ATMPs in Europe. Some have focused on the conceptual arguments for using innovative contracts, others proposing algorithms for determining how they should be implemented (Whittal, et al., 2022; Wenzl & Chapman, 2019; EFPIA, 2022; Vreman, et al., 2020). This document does not seek to define under what exact circumstances innovative contracting should be considered, or which type of innovative contract is most appropriate for a given product. Instead, it identifies success factors, challenges, and recommendations for the implementation and adoption of innovative contracting for ATMPs in Europe, based on the real-life experience of manufacturers over the past five years (2017-2022).



2.3 Approach and structure

2.3.1 Approach

This work was informed through semi-structured 1:1 interviews with pharmaceutical manufacturers that are members of ARM and have obtained marketing authorisation for one or more ATMPs in Europe in the last five years. Following the interviews, a core group from the ARM secretariat and a subgroup of ATMP experts from ARM member companies participated in a sequence of roundtable meetings during which they contributed their perspectives on the topics discussed in this paper.

2.3.2 Paper structure

The rest of this paper is structured into five chapters.

In Section 3, the most prominent characteristics of ATMPs and key definitions of innovative contracting are described in order to establish a baseline understanding of key concepts. It should be noted that this paper does not aim to reiterate details provided in several recent, high-quality European summary reports such as those published by EFPIA, RARE IMPACT, and ARM (EFPIA, 2022; RARE IMPACT, 2020; ARM, 2019), and thus these key concepts are described only in outline form, with references to the aforementioned sources for further descriptive insights.

The contextual overview in Section 3 is followed in Section 4 by an overview of the current state of play in innovative contracting for ATMPs. This includes aggregated views from seven ATMP manufacturer representatives on the degree of innovative contracting that has recently been achieved, and how this has related to patient access.

Sections 5, 6, and 7 provide an analysis of the success factors that underpinned the recent progress achieved by payers and manufacturers in agreeing on innovative contracts for ATMPS, based on ARM members' experience. Recommendations to improve contracting to maximise the success of these agreements while reducing cost and risk to payers and manufacturers are also included, and a number of persistent challenges related to innovative contracting for ATMPs are identified.

Finally, Section 8 provides practical next steps suggestions and an overview of how to continue leveraging innovative contracting to establish patient access to ATMPs in Europe.

Opinions from manufacturer representatives were offered on agreement of anonymity, and the views expressed are those of individuals. The statements made in this report are thus not necessarily representative of individual ATMP manufacturers or industry as a whole.

3. INTRODUCTION: INNOVATIVE CONTRACTING REPRESENTS A REAL OPPORTUNITY TO MITIGATE INHERENT CHALLENGES TO ATMP ACCESS

3.1 Why ATMPs represent a special case

3.1.1 The nature of ATMP innovation

According to the European Medicines Agency (EMA), ATMPs are "medicines for human use that are based on genes, tissues or cells. They offer ground-breaking new opportunities for the treatment of disease and injury" (EMA, 2023a). ATMPs have certain characteristics that differentiate them from more conventional medicines, and which are relevant to how they are assessed during HTA and P&R processes.

Indicated in diseases with great unmet need. Conditions presently targeted by ATMPs are typically characterised by high morbidity and mortality, few or no existing treatment options and poor outcomes. Comparator therapies are frequently non-existent or are represented by supportive care (Coyle, et al., 2020).

High potential for therapeutic and societal value. ATMPs have demonstrated the potential for transformative health outcomes, slowing or halting disease progression and changing the trajectory of a patient's prognosis (Melenhorst, et al., 2022). For example, NICE has recently published real-world findings from the Cancer Drugs Find indicating that people receiving Yescarta (axicabtagene ciloleucel) for diffuse large B-cell lymphoma (DLBCL) in third or later line demonstrated an overall survival of 28.5 months (at 36 months of follow-up), compared to 6.4 months for standard of care. Furthermore, 45% of people treated with Yescarta were alive after three years (NICE, 2023). The duration of therapeutic benefit is one of the key factors that make ATMPs different. Beyond the clinical benefit to the patients, ATMPs in some cases can reduce or remove the costs of long-term care associated with chronic conditions, and alleviate the burden on carers, healthcare systems, and wider economies (ABPI, 2021).

Single administration. An inherent premise of many ATMPs is the single-administration nature of the intervention, reflecting the fact that they target the underlying cause of the disease. Where transformational outcomes are achieved with single administration treatments, patients benefit from the reduced burden of alternative chronic therapies, and health systems benefit from the cost offsets generated by some ATMPs as they replace expensive treatments and prevent adverse clinical effects associated with long-term treatment(Simoens, et al., 2022; Gonçalves, 2022). Furthermore, a benefit of single-administration treatments may potentially include a reduction in non-adherence to therapy, the cost of which remains high in some diseases (ABPI, 2021).

Rare diseases. All ATMPs that have been approved in Europe to date have been indicated for rare diseases, and this trend is likely to continue in the near term given the pipeline of most companies developing ATMPs (noting that several longer-term pipeline ATMPs will target non-rare diseases) (Ronco, et al., 2021).

3.1.2 The characteristics of ATMPs create particular issues for pricing and reimbursement

The attributes of ATMPs as specified above can translate into challenges within HTA and P&R systems primarily designed to appraise conventional medicines used continuously for chronic conditions, coupled with continuous payments over (treatment) time.

The high unmet need in the conditions for which many ATMPs are approved means that they are often eligible for accelerated regulatory approval pathways, such as Conditional Market Authorisation and PRIority MEdicine (PRIME) designation (see Appendix Table 2)(EMA, 2023c). While regulators have been willing to expedite ATMPs based on interim or Phase II trial data, the same evidence is often considered immature by HTA bodies (RARE IMPACT, 2020).

The longer duration of therapeutic effect with ATMPs, especially with certain cell and gene therapies where benefits are expected over extended time horizons, means it is generally not possible to generate evidence of the complete benefit in a clinical trial setting. Thus, there is often uncertainty around the full value of the ATMP – in magnitude and duration of effect – at the point of HTA and even many years beyond that.

The single administration of most ATMPs means that the total cost of treatment is incurred at one point in time, in contrast to conventional medicine for a chronic disease which may be spread out over many years. Accordingly, the one-time price for ATMPs is significantly higher than for continuously dosed medicines. Although ATMPs have the potential to be cost-effective even at high price points, due to potentially considerable health gains and cost offsets (Coyle, et al., 2020; Simoens, et al., 2022), high upfront costs can present budget management challenges to healthcare systems in Europe.

For many ATMPS, these HTA and P&R challenges are compounded by the problems of developing drugs in rare and ultra-rare indications, irrespective of treatment modality. These include small trials, heterogeneous patient populations, lack of disease knowledge, absence of natural history data, no established endpoints, and poorly characterised or non-existent comparators (Nestler-Parr, et al., 2018; CCSO, 2017; Whittal, et al., 2022).

3.1.3 For ATMP innovation to be viable, price must reflect value

Cumulatively, the HTA and P&R challenges described above represent a significant challenge to the economic viability of ATMP innovation in Europe (RARE IMPACT, 2021).

The economics of ATMP innovation are difficult. ATMPs in rare diseases face the same economic challenges as other orphan medicines (Neez, et al., 2021), with small populations constraining the potential return on investment, while the costs and risks of research and development (R&D) are still very high. For ATMPs, this is further complicated by the need for substantial capital investment in new manufacturing, distribution infrastructure, maintaining distribution processes, and a much higher cost of production (RARE IMPACT, 2021). In addition, ATMPs that are personalised benefit minimally from manufacturing economics of scale typically seen with traditional off-the-shelf chronic therapies.

In addition, for some ATMPs, especially gene therapies in high unmet need diseases, there is often a cohort of prevalent patients awaiting approval of the product. The limited availability of funded early access programmes in Europe (see section 7.2) means there is significant pressure to provide the treatment for free to patients who may represent a significant proportion of the potential market.

Given this context, for ATMP innovation to be economically viable, prices at approval need to reflect the value of those medicines. Where value is not fully established at the point of P&R negotiations – which is common with ATMPs – the question is on what value should the therapy be priced: that reflecting only the available evidence at that time, or that representing the potential once the data is fully mature?

Prices in Europe almost never increase after launch, instead usually falling steadily over the lifecycle of the medicine. Therefore, establishing a price for single-administration therapies based only on the evidence available at launch is generally not a viable solution for the industry. For small and mid-sized companies in particular this can pose a major business threat. The RARE IMPACT report highlighted that at the time of publication, five out of the 13 ATMPs that had been granted market authorization were subsequently withdrawn from the market due to various reasons, including the absence of a sustainable business model (RARE IMPACT, 2020). This number is now reported at seven withdrawals of the 21 ATMPs that have been granted market authorisation since 2019.

Innovative contracting can help to address this challenge by linking P&R status to clinical benefit over time, as evidential certainty evolves.

3.2 Defining ‘innovative contracting’

Contractual agreements have been used by payers and manufacturers to facilitate reimbursement of new medicines for over 20 years (Brennan & Wilson, 2014; Montazerhodjat, et al., 2016; Walker & Mathews, 2019). Historically, the primary purpose of these agreements has been financial: to reduce net prices (e.g., through discounts) and contain total budget impact (e.g., caps or price-volume agreements).

The term 'innovative contracting' refers to contractual agreements between payers and manufacturers that are intended to address two types of payer uncertainties or concerns within P&R negotiations (Wenzl & Chapman, 2019; Facey, et al., 2021; Goodman, et al., 2022):

Financial concerns:

This relates to the size and timing of the budget impact (is it considered affordable within the budgetary period) and whether the uncertainty around that expenditure is acceptable;

Clinical concerns:

This relates to uncertainty around the magnitude and duration of clinical benefit of a treatment, and thus whether the treatment is value for money given the price.

As discussed previously, ATMPs have particular characteristics that mean that payer financial and clinical uncertainties can be higher than for conventional medicines. To address these uncertainties, over the last five years in Europe, agreements for ATMPs have in practice represented one or either of the following contractual agreements:

01 **Outcomes-based agreements**

02 **Split payments**

For the purpose of this paper, innovative contracts are therefore defined as agreements that involve either of these aspects, discussed in more detail below.

Outcomes-based agreements

Outcomes-based schemes explicitly address clinical uncertainty by linking reimbursement to evidence of therapeutic benefit. There is considerable variation in the structure of outcomes-based agreements, with differences in the type of evidence of benefit considered, the payment terms, and the logistical requirements (Facey, et al., 2021; Tempero, 2017; Kent & Spink, 2017).

There are broadly three types of evidence used within outcomes-based schemes:

Individual patient outcomes: real-world clinical results from individual patients covered under the agreement;

Population outcomes: real-world clinical results for cohorts of patients covered under the agreement;

Trial outcomes: additional data cuts from later time points of pivotal trials that show the long-term benefit of treatment.

Reimbursement and payment terms can also be structured in different ways:

Coverage with evidence development (CED): reimbursement is granted at a given price, subject to revision if therapeutic goals are hit or missed (may or may not include a rebate component);

Upfront with rebates: the manufacturer is paid in full at the time of administration with rebates if therapeutic goals are not achieved;

Split payments based on outcomes: payments paid in instalments as therapeutic goals are achieved.

Split payments

01 Split payments are those in which the total cost of the treatment is spread over time in instalments, rather than being paid at the time of treatment administration, as is the case with conventional medicines;

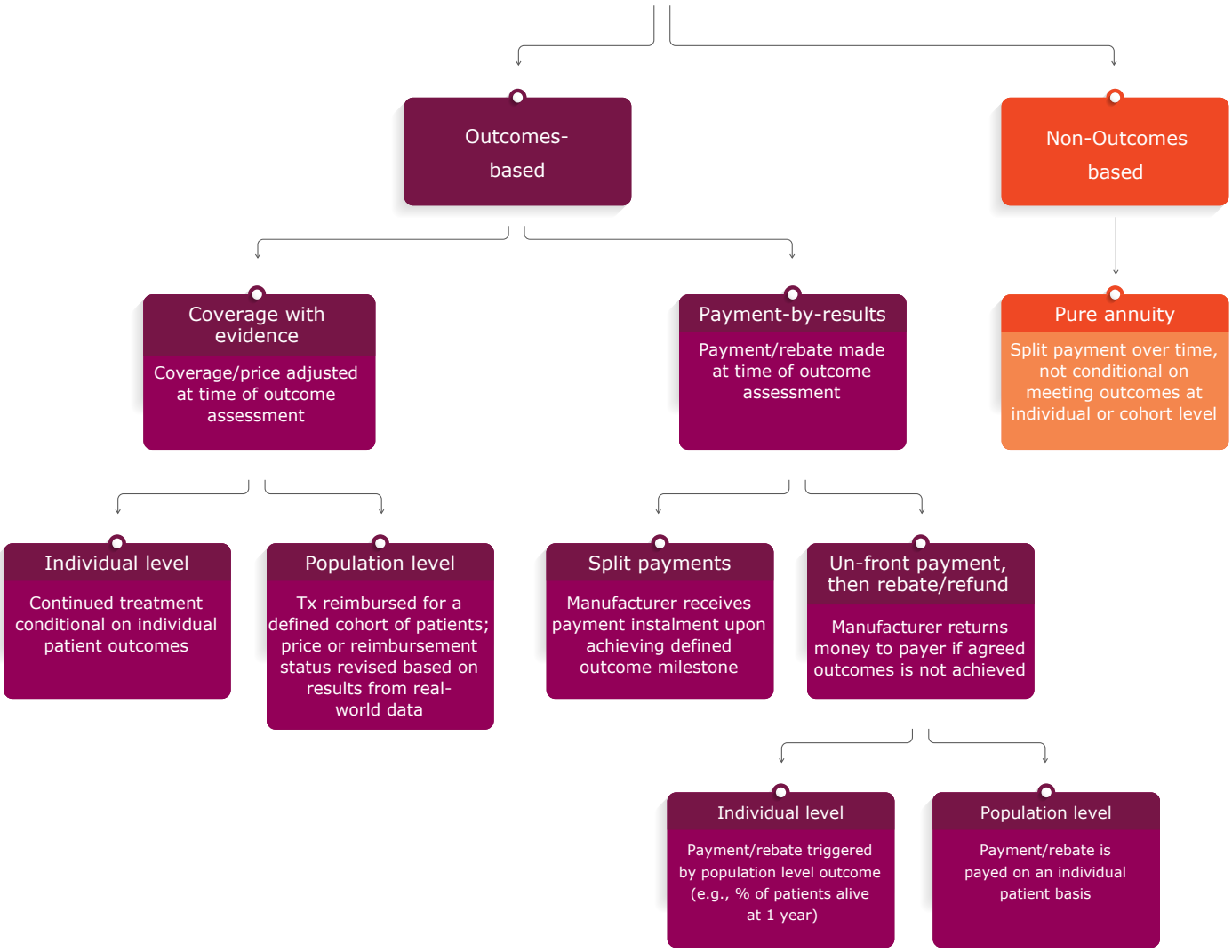
02 Pure split payment contracts (commonly referred to as 'annuity' payments) can be structured so that the schedule of payments over time is pre-determined, and the payments are not triggered or adjusted by any other factor. The main reason to undertake a pure annuity contract is to spread the total cost of treatment over a longer period (in order to help payers manage their budgets). As payments are not conditional on any event, they do not address the issue of clinical uncertainty, as payments are made irrespective of the outcome;

03 In practice, pure split payment contracts have seldom been used in Europe over the last five years. Instead, split payments are more commonly linked to clinical outcomes, either at the patient or population level (e.g., Zolgensma, Kymriah, Yescarta in Italy, see Table 1).

Many other considerations can also vary across agreements, including timings, endpoints, data ownership, adjudication process, and much more. The practical implications of different approaches – which can be major determinants of their ultimate success – will be discussed later in this paper.

Figure 1 presents a taxonomy of outcomes-based agreements with different combinations of evidence types and financial terms. It is beyond the scope of this paper to attempt to define which sort of innovative contract is most appropriate for which ATMP. Other authors have attempted such analysis (Maes, et al., 2019; Wenzl & Chapman, 2019) or proposed frameworks to that end (Whittal, et al., 2022). Disease factors such as prevalence, age of onset, prognosis and outcomes, as well as the duration of treatment effect and nature of current therapies, can all have implications for how an innovative contract might be structured. However, based on their experience of implementing innovative contacts over the last five years, ARM members highlight the importance of developing agreements that are context-, product-, and country-specific, and most efficient in addressing the P&R challenges that are of greatest relevance to a particular therapy.

Figure 1: Taxonomy of recent innovative contracting models for ATMPs (Dolon 2023, unpublished)



4. CURRENT LANDSCAPE: OVER THE LAST FIVE YEARS INNOVATIVE CONTRACTING HAS PLAYED AN INCREASING ROLE IN FACILITATING ATMP REIMBURSEMENT

4.1 ATMPs in Europe

Figure 2 depicts all the ATMPs that have been approved in Europe by the EMA since the introduction of the ATMP legislation in 2007 (EMA, 2023b). Table 1 provides more specific details on each product, including manufacturer, type of ATMP, disease, regulatory status and any innovative agreements in place in Italy and the UK. These two countries were selected on the basis that they comprehensively publish the reimbursement terms negotiated with manufacturers, usually including reference to any innovative contracts that may have been agreed upon.

As of January 2023, the EMA has granted marketing authorisation to 24 (excluding one pending) ATMPs, including ATMPs that received conditional approval or have authorisation under exceptional circumstances. Within the period of focus of this paper (Jan 2018 – Jan 2023), 15 ATMPs have obtained marketing authorisation in the European Union (see Figure 2).

Seven of the 24 approved ATMPs (29%) have subsequently been withdrawn from Europe, including two since 2018 (Zynteglo and Skysona). Further details on these withdrawals can be found in the Appendix, Table 2 and Table 3).

4.2 Sample included in this paper

Ten manufacturers were responsible for the 15 ATMPs approved in Europe since 2018 (see Table 1). All companies are members of ARM, but not all participated in the process culminating in this report. Manufacturer interviews were conducted with seven of the 10 ATMP manufacturers representing nine of the 15 approved ATMPs (Table 1).

4.3 Status of innovative contracting for ATMPs in Europe based on ARM member feedback

Due to the confidential nature of pricing agreements, feedback from manufacturer interviews was a mixture of semi-quantitative information (for example, the approximate number of negotiations undertaken across Europe, the proportion where innovative contracts were considered, etc.) and qualitative feedback. This data is presented in the paper in an aggregated and generalised form to maintain confidentiality.

In general, the feedback suggested that the use of innovative contracts for recent ATMPs in Europe has been quite high. Innovative contracts were discussed in nearly all the negotiations that the manufacturers undertook across European countries for the ATMPs in question. Across this sample of ATMPs, the number of countries with which an individual manufacturer discussed innovative contracting agreements ranged from six to 20. In more than half of these negotiations, an innovative agreement was proposed up-front by the manufacturer or the payer, and in the rest, it was proposed later in the process.

Of the eight ATMPs for which the manufacturer shared specific feedback on the proportion of innovative contracts agreed, five had successfully agreed to innovative contractual agreements with over 50% of the countries in which negotiations had taken place. For example, one manufacturer discussed innovative contracts in 20 negotiations and successfully agreed in 10.

Of the remaining three ATMPs, two had demonstrated limited to no success in agreeing to innovative contracts (at the current point in time) and one product was withdrawn before agreeing to any contracts.

The types of innovative contracts that were most frequently mentioned by manufacturers are listed below (note these are not mutually exclusive).

Payment-over-time (i.e., split payments/instalments):

Subject to outcomes being achieved/sustained

Involving refunds if a patient has to receive another therapy

Not dependent on outcomes (pure annuity)

Outcomes-based agreements:

Rebates linked to individual-patient data based on e.g., survival/response

Rebate if patients required retreatment

National schemes, subnational schemes (e.g., in Germany with sick funds), and supra-national schemes (e.g., with BeNeLuxA)

Coverage with evidence development:

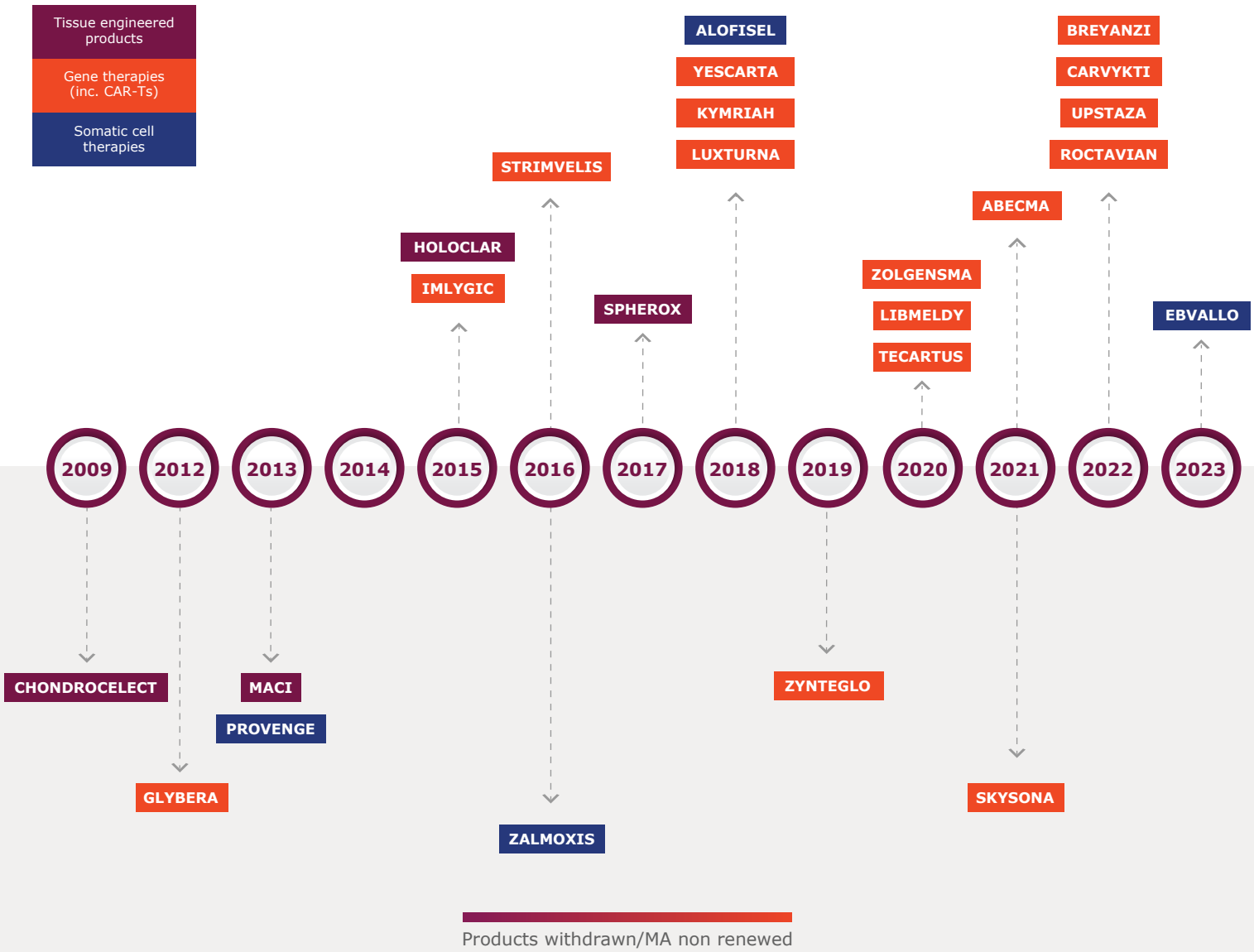
Conditional price based on achieving five-year target with trial data or with collection of real-world evidence (RWE), otherwise price reassessment (in practice, price reduction)

Annual health technology reassessments based on additional cohort data, which may include:

- data from routine use in national registry
- data from long-term follow-up from pivotal trials
- data from de-novo registries

Seven out of the eight ATMPs that have launched and were included in the interviews for this report achieved some degree of reimbursement across Europe – the exception was bluebird bio's Zynteglo. In countries where innovative contracts were not implemented, manufacturers commonly entered into more conventional agreements. One manufacturer reported that in 11 countries (including two non-European), access was gained solely via simple discounts without innovative contracting.

Figure 2: EMA-published decisions on ATMPs, 2009-January 2023



Adapted from EMA, CAT quarterly highlights and approved ATMPs, Oct 2022 (EMA, 2023c). Further detail on EMA-approved ATMPs is available in the Appendix (Table 2 and Table 3)

Table 1: ATMPs receiving EMA approval, pending approval, or withdrawn since 2018. Includes innovative contracting information from the two EU countries that provide full details of reimbursement terms

ATMP	Cell/Gene/ Tissue	Disease	Manufacturer	EMA status (MA issue date)	Product-expert interviewed	Publicly available innovative contracting information	
						Italy (AIFA)	UK (NICE)
Ebvallo (Tabelecleucel)	Allogeneic T-cell therapy	R/r Epstein-Barr virus-positive post-transplant lymphoproliferative disease	Atara Biotherapeutics Ireland/Pierre Fabre	Exceptional circumstances (Jan-23)	No	N/A	N/A
Upstaza (Eladocagene exuparvovec)	Gene therapy	AADC deficiency	PTC	Exceptional circumstances (Jul-22)	Yes	N/A	N/A
Roctavian (Valoctocogene roxaparvovec)	Gene therapy	Severe haemophilia A	BioMarin	Conditional approval (Aug-22)	No	N/A	N/A
Carvykti (Ciltacabtagene autoleucel)	CAR T	R/r Multiple myeloma	Janssen-Cilag	Conditional approval (May-22)	No	Evaluation in progress	N/A
Breyanzi (Lisocabtagene maraleucel)	CAR T	R/r diffuse large B-cell lymphoma	BMS	Approved (Apr-22)	Yes	Evaluation in progress	Suspended
Abecma (Idecabtagene vicleucel)	CAR T	R/r Multiple myeloma	BMS	Conditional approval (Aug-21)	Yes	Evaluation in progress	In progress
Skysona (Elivaldogene autotemcel)	Gene therapy	Cerebral adrenoleukodystr-ophy	Bluebird	Withdrawn 2021 (Jul-21)	Yes	Withdrawn	Withdrawn
Libmeldy (Autologous CD34+ cells encoding ARSA gene)	Gene therapy	Metachromatic leukodystrophy	Orchard Therapeutics	Approved (Dec-20)	Yes	Mandatory discount	Simple discount
Tecartus (Brexucabtagene autoleucel)	CAR T	R/r mantle cell lymphoma (r/r acute lymphocytic leukaemia in 2022)	Gilead	Conditional approval (Dec-20)	Yes	Withdrawn	CED (included in the CDF)
Zolgensma (Onasemnogene abeparvovec)	Gene therapy	Spinal muscular atrophy	Novartis	Conditional approval (May-20)	Yes	Confidential discount; pay per result (at delivery, 12, 23, 36, 48 months)	CED (included in the CDF)
Zynteglo (Betibeglogene autotemcel)	Gene therapy	Beta-thalassemia	Bluebird bio	Withdrawn 2022 (May-19)	Yes	Withdrawn	Withdrawn
Luxturna (Voretigene neparvovec)	Gene therapy	Retinal dystrophy	Spark/Novartis	Approved (Nov-18)	No	Confidential discount; budget cap	Simple discount
Yescarta (Axicabtagene ciloleucel)	CAR T	R/r B-cell lymphoma (r/r follicular lymphoma in Jul 2022)	Kite Pharma (acquired by Gilead in 2017)	Approved (Aug-18)	Yes	Payment at results (at 180, 270, and 365 days from infusion)	CED (included in the CDF)
Kymriah (Tisagenlecleucel)	CAR T	R/r paediatric B-cell acute lymphocytic leukaemia and r/r diffuse large B cell lymphoma (r/r Follicular lymphoma in 2022)	Novartis	Approved (Aug-18)	No	Confidential discount (for diffuse large B-cell lymphoma); payment at result (6 and 12 months from infusion, both indications)	CED (included in the CDF)
Alofisel (Darvadstrocel)	Stem/somatic cell therapy	Perianal fistulas in Crohn's disease	TiGenix (acquired by Takeda in 2018)	Approved Mar-18)	Yes	Not reimbursed	Not reimbursed

Abbreviations: AADC: Aromatic L-Amino Acid Decarboxylase; AIFA: Italian medicines agency; ARSA: Arylsulfatase A; CAR T: Chimeric Antigenic Receptor T; CDF: Cancer drug fund; CED: Coverage with evidence development; EMA: European medicines agency; MA: Marketing approval; NICE: National institute for health and care excellence; R/r: Relapsed/refractory.

5. REASONS FOR OPTIMISM: PROGRESS HAS BEEN ACHIEVED BY PAYERS AND MANUFACTURERS IN AGREEING TO INNOVATIVE CONTRACTS

5.1 Uptake, willingness and impact: on balance, innovative contracting has helped in advancing patient access to ATMPs in Europe over the last five years

As discussed in the previous section, the experience of ARM members suggests a higher use of innovative contracting for ATMPs in Europe over the last five years, compared with preceding periods and with non-ATMPs. It was not the case that every manufacturer was able to secure an innovative agreement in every country in which they felt it could have facilitated access, and the degree of success varied by manufacturer and by country. Nevertheless, it was felt that on balance, innovative contracts have had a material impact on the ability to reach agreements during P&R negotiations for ATMPs over the last five years, and ultimately improved patient access to these recent innovations. However, the situation is still imperfect in many ways, as discussed in the next chapter, nor is future success guaranteed.

The increased number of agreements being implemented over the last five years reflects a greater willingness among payers to consider innovative contracts. Part of this is an increased recognition from payers of the utility of such agreements for ATMPs.

Manufacturers suggested that it also reflects positive sentiment towards ATMPs and innovative contracting from non-payer policymakers. For example, in Sweden politicians created a public mandate for the Swedish Dental Health and Medicines Agency (TLV) to implement innovative contracting, though ultimately the TLV were still reluctant to engage in these agreements (Dabbous, et al., 2020). In Spain, the Valtermed registry system - designed to collect real-world clinical data through a web-based tool to reduce the uncertainty associated with new therapies - was mandated by the Spanish Ministry of Health (MSCBS, 2019).

In France, the 2023 Social Security Finance Bill (PLFSS) proposes measures that are aimed at promoting access to innovation by facilitating the financing of ATMPs. The proposals involve negotiation and financial risk sharing between manufacturers and the healthcare system, via the implementation of outcomes-based agreements (based on real-world results) and staggered payments (French government, 2022). The process will still be based on negotiations between the manufacturer and the health committee responsible for pricing.

"France was open to a lot of things. They preferred a rebate structure and were upfront with us about not wanting to do payment over time. Interestingly, they took long-term cost-effectiveness into account more than they would normally do and we were actually making progress." (ARM member, 2022)

In October 2022, Germany passed the new "German statutory health insurance (GVK) financial stabilisation" bill which will be implemented in 2023 (APMHE, 2022). Following the introduction of the new bill, the G-BA and German payers are looking for approaches to keep ATMPs on the market after the initial product assessment, given that this stage of the process can require the negotiation of large discounts which may not be viable for the manufacturer. Alongside adjusting HTA criteria (e.g., recognising new surrogate endpoints), innovative contracts are expected to play a bigger role in pricing negotiations (Sukharchuk, 2022a; Sukharchuk, 2022b).

While there has been a largely positive trend towards more willingness and acceptance of innovative contracting, manufacturers still highlighted that a lack of full trust between payers and manufacturers was constraining the adoption of agreements. This is discussed further in section 6.4.3. It is also not certain that progress will continue in the same direction. While most countries have become more open to the idea of innovative contracting (e.g., France) others remain hesitant (e.g., Germany). Therefore, it is necessary to continue engaging on the value of these types of agreements while trying to minimise the challenges that create scepticism.

5.2 Split payments and outcomes-based agreements: working in practice

Split payments have long been recognised as potential components of solutions for ATMP P&R challenges. Previous reports have highlighted payer concerns about the practicalities of implementing split payments (RARE IMPACT, 2020). However, in practice, the manufacturer's perspective is that there is now considerable experience in negotiating and implementing agreements with a split payment component.

Despite an initial concern around the technical difficulty of implementing split payments, manufacturers say that in practice this has not been a major issue and in fact, some manufacturers have found split payments easier to administrate than rebates. If a payer agrees to reimburse the manufacturer via split payments and an outcome is not met, then it is procedurally simpler for the payer to stop payments, rather than the manufacturer having to issue a rebate. Similarly, some payers have shown a preference for this kind of contracting mechanism.

"In countries where cash flow was a problem, payers requested split payments instead of up-front payment." (ARM member, 2022)

Another practical concern about split payments commonly expressed was compliance with European System of Accounts (ESA) rules (also called EUROSTAT rules) (Maes,et al., 2019). In theory, the rules label spread payments as debt that must be aggregated in a single amount that is incurred at the time of therapy administration from an accounting perspective (Eurostat, 2013). In practice,however, there is no indication from the manufacturers involved in this report that these rules have represented the main obstacle to the agreement of an innovative contract.

For some manufacturers what has prevented them from doing split payments were national accounting rules. The UK's treasury rules were highlighted by several respondents as representing a hurdle in this regard. Notwithstanding this, for most manufacturers, accounting hurdles were related more to how the split payments were reported, rather than restrictions limiting their use completely. Tax considerations were also a major factor. In totality, the view from manufacturers was that accounting concerns were related mostly to choices around how things were implemented, as opposed to being about contravention of explicit rules. France has been put forth as an example of how payers can find a way to implement innovative contracting despite national accounting concerns (see section 5.1).

As noted in the RARE IMPACT Report (European level) "As these agreements have been successfully established in many countries, it would suggest that the potential barriers to their development, such as ESA requirements, can be overcome at the country level." (RARE IMPACT, 2020)

Outcomes-based agreements have been used widely for ATMPs in Europe over the last five years; a recent publication has explored the publicly available details of these deals (Jørgensen & Kefalas, 2021).

Manufacturers suggested that for contracts that had concluded, outcomes had been well-aligned with predictions of clinical effects that had underpinned the financial projections. A caveat to this finding is that many agreements are still in the early stages of implementation, and it is therefore potentially too soon to make a holistic judgement on this point. In one case, however, the manufacturer asserted that the real-world outcomes demonstrated by their ATMP were in fact better than expected, which in Italy resulted in a change in the financial terms associated with the contract. When outcomes are better than expected, payers do not always account for the fact that the net level of discount they receive in association with outcomes not achieved will be lower than planned.

"In some markets, we are getting better outcomes and getting paid more than we thought we would be. In many countries that consideration then became part of the contracts." (ARM member, 2022)

Manufacturers also reported some success with CED agreements. These are population-level agreements where the therapy is reimbursed for a limited duration, after which the price (or level of access) is re-negotiated (Wenzl & Chapman, 2019). At least one manufacturer stated that they found themselves in a better position to negotiate

at this later timepoint than they were at launch, as they were able to address the uncertainty in their data, both with their real-world data and five-year data.

Examples of CED include the UK's NHS Cancer Drugs Fund (CDF) and the Innovative Medicines Fund (IMF); each has an allocated £340 million per year budget (NICE, 2023). While manufacturers consider the particular approach taken by the CDF/IMF to be tough and not without flaws, it is considered by most as a good precedent for facilitating ATMP access. A particular benefit of CED from the manufacturer's perspective is that it can accommodate different deals for different indications, allowing for strategic launch sequencing and supporting the longer-term interests of the company.

It should be noted that not all manufacturers felt that split payments and outcomes-based agreements represented an appropriate innovative contracting mechanism for their product(s), with some considering these deals as being associated with inordinate data provision demands. In the case of a patient-level agreement, for example, clinicians might be required to submit patient data to the manufacturer. This process can be complicated by privacy laws (see section 6.3.4) and difficulties in obtaining patient information from decentralised healthcare systems. Moreover, this process demands high-quality data and clearly measurable outcomes (Michelsen, et al., 2020).

5.3 'A bridge to access': agreement timelines reflecting disease characteristics

The timeframe under which an innovative scheme operates is of major importance for ATMPs, and several implemented deals reflect this finding (ARM interviews, October/November 2022). In roundtable workshops, manufacturers agreed that it is vital to note that the duration of an innovative contract should not be equated with the duration of treatment effect. Instead, the contract represents a bridge over the uncertain period (see section 3.1), reducing risk over the short term. The general point is that innovative contracts must incorporate relevant, measurable outcomes that can be reliably captured in a time frame over which it is feasible to have an agreement.

As an example, a one-year contract could be most appropriate for products whose one-year performance is indicative of their longer-term performance (Maes, et al., 2019). CAR Ts can generally demonstrate outcomes over two or three years and thus commonly involve contracts to manage uncertainty over a shorter timeframe (e.g., one to two years). This is not to imply that the product efficacy can be fully demonstrated in one year. With CAR Ts there is the expectation that many indications will be launched within a short time period, which is another reason manufacturers may prefer a shorter assessment period.

With ATMPs, outcomes-based schemes are intended to represent an access solution that buys more time to generate the required evidence. This additional time may also allow patients to capitalise on additional medical innovation (e.g., patients could cross-over to other treatments). Manufacturers' consensus is that rather than an exceedingly long contract, it is preferable to identify a good durability metric/tracker that can demonstrate that patients with a good

outcome over the medium term will likely maintain that over the longer term. This sentiment has been echoed by payers, e.g. Sweden's TLV:

> "We need to find a relevant outcome measure that we can follow up. It may not be the outcome measure that we are most interested in, for example, what the treatment effect looks like after 40 years. Instead, we may need to have a surrogate measure that somehow gives an indication of how the treatment is working."
> Johanna Ringkvist, project manager at the TLV (Ericsson, 2022)

For some ATMPs a timeframe of five years or more has been negotiated. Biomarin, for example, has reported publicly that outcomes-based agreements for Roctavian (a gene therapy for haemophilia A) will guard against the risk of a non-response to treatment for at least five to eight years. Not all payers are supportive of longer schemes: one gene therapy manufacturer noted that in Germany the sick funds were not amenable to longer-term agreements (e.g., five to ten years in duration).

Manufacturers and payers generally agree that contracts are not 'forever'. Manufacturers felt that the most productive innovative contracting arrangements would be those that allow a transition over time from an outcomes-based scheme to a more traditional flat discount. Countries with several years of data and more certainty in their results may feel that indication-based deals become overly complex when several concurrent indications are marketed. Even countries such as Italy that are classically considered well placed to administrate outcomes-based agreements, faced at least one occasion in which outcomes were better than expected and payers preferred to move to a flat discount to avoid continuing to pay more than initially planned. Other countries such as Spain tend to want to maintain existing outcomes-based agreements, at least with some ATMPs.

> "Length of agreements is a consideration - what is the exit strategy, and how long do you need them for. There is the idea that this is the only type of contract and we'll be doing them for a long time. But it's based on the type of problem you're trying to solve. These schemes are not for life." (ARM member, 2022)
>
> "Companies are looking for a time horizon allowing them to plan for the future. And companies talk about value, whereas for payers - it's affordability. Payers want to fit the schemes into one year. It is hard for industry to commit to something in the short term if that will not bring dividends in the longer term. Longer-term interests for the company may involve future indications. Whereas payers look at immediate cost savings in a year." (ARM member, 2022)

5.4 Data collection: increasing efficiency through stakeholder collaboration

5.4.1 Precedents have been set for collaborative data collection that reduces the payers' administration burden and increase confidence in associated contracting schemes

Precedent has been established around collaborative data collection approaches, for instance, whereby a national clinical group is involved in the evidence gathering which increases the payers' confidence in the innovative contracting scheme. As an example, in France, the French National Authority for Health (HAS) requested the collection of RWE for CAR Ts through the DESCAR-T registry. The costs are covered by the manufacturers, while the Lymphoma Academic Research Organization (LYSARC) oversees the centralised data collection for both academic and health authorities' purposes (Broussais, et al., 2021).

As another example, the Dutch Healthcare Advisory Institute (ZIN) advised the Ministry of Health, Welfare and Sport (VWS) to reimburse Libmeldy under specific conditions, given the uncertainty around the long-term effects of the drug. The VWS agreed on a pay-for-performance scheme, which will be supported by Utrecht University (ZIN, 2022). Such a scheme is particularly beneficial for payers who may not want to engage in setting up de-novo data monitoring systems, for example, if there are notably small numbers of patients.

Manufacturers felt that while collaborative data collection involving third parties could represent a replicable solution for ATMPs used in one centre in a small country with few patients, clinical groups might be less willing to collaborate and share data in other settings or across several centres. Manufacturers reported that in large countries the systems to collect data and the information sharing between centres can be difficult to coordinate. Notwithstanding this point, there has also been a significant amount of progress in the past few years.

On a related note, in smaller countries in which there is not a sufficient number of patients to contribute data that would allow a reasonable adjudication of results within a reasonable timeframe (e.g. five years), there may be a particular benefit to implementing cross-national data collection/registries. The metachromatic leukodystrophy (MLD) international registry was cited by one manufacturer interviewed as a successful case in this regard, stating that local registries have contributed data to this registry in a highly collaborative manner. The manufacturer did however note that this experience could represent an outlier given the limited number of MLD products currently available.

5.4.2 The technology behind electronic data collection has evolved and can be leveraged to capture ATMP-relevant outcomes and improve the compatibility of data systems for use with innovative contracting

Manufacturers noted that the operationalisation of technology in the electronic health records (EHR) space has evolved, with improvements in infrastructure, platforms, and connections between medical centres. With EHR a lot of data will be collected even when patients change

their physicians. Tracking is still a challenge when the patient moves to another country, or if the records are not well-coordinated at European level - but with a general shift towards going digital, countries may be moving towards improvements in this space.

Given a move towards the digitisation of data, EHR should be leveraged as a supportive tool for innovative contracting. As more and more ATMPs are developed electronic health records will become the means for patients to access ATMPs. As an example, in future, the creation of the European Health Data & Evidence Network may facilitate the collection and analysis of standardised real-world data for ATMPs (EHDEN, 2022).

6. AREAS FOR FURTHER EFFORT: OPPORTUNITIES TO IMPROVE INNOVATIVE CONTRACTING

6.1 Payer openness to innovative contracting: the need for greater European consistency

As noted in the previous section, ARM members recognised an increased willingness amongst European payers to consider innovative contracting for ATMPs over the last five years. However, this is not a uniform trend across all European countries and the lack of consistency in payer willingness to engage in innovative contracting in some markets can have an outsized effect on total European access. This reflects the interconnectedness of European payer processes, in particular, the use of international reference pricing (IRP) to link price levels between countries. Within this framework, some countries have a disproportionate impact.

For example, while Germany has historically been the most successful country in Europe in providing quick and funded access to innovative medicines, it has been relatively slow to embrace innovative contracting. Only one ARM member reported an innovative agreement negotiated for an ATMP at the national (GKV) level. Negotiations with individual sick funds were reported, with mixed success. One manufacturer of an ATMP for a disease with very few patients stated that they negotiated with approximately 60% of the sick funds, via conglomerates representing multiple sick funds, and managed to achieve innovative agreements that collectively covered the majority of the German population. Another manufacturer also attempted to negotiate sick fund by sick fund (or via conglomerates), before receiving feedback from the GKV that unless all sick funds agreed to the contract, then none would be allowed to engage in the innovative agreement. It subsequently failed to be implemented, despite a high degree of interest from many sick funds.

It is possible that payers in Germany do not perceive that there is a need for innovative contracts due to the broad and quick access that medicines have historically achieved in Germany, including for orphan drugs. However, for ATMPs, a confluence of characteristics of the Germany P&R system means the absence of innovative contracting can make it a major barrier to access, both in Germany and beyond:

Public net prices:
Germany is the only country in Europe in which post-discount prices are publicly visible;

Strict interpretation of evidence:
e.g., limited opportunity for extrapolation of data; strong resistance to surrogate endpoints;

Rigid benchmarking vs comparators:
Including against generic and off-label products;

Inflexible arbitration process:
Decisions from arbitration committee are final.

The combined effect of these factors leads to prices that may not reflect the potential long-term value of an ATMP, beyond the (often surrogate) data available at the time of the AMNOG assessment. These prices then become visible net prices, impacting the price in many other countries in Europe and beyond through IRP.

Under this scenario, companies are faced with difficult decisions about withdrawing from Germany (and in the case of Zynteglo, Europe).

The strictures of IRP mean that confidentiality of net prices is of critical importance to the economic viability of innovation globally, and the combined lack of willingness to engage in innovative contracting and lack of net price confidentiality is a barrier to products launching in Germany, and sometimes in Europe.

> "If we can get an agreement with Sick Funds that doesn't lead to a visible price, then we can be flexible and can look at margins and decide on a financially feasible price. We have seen this Germany issue lead to decisions for launching / not launching." (ARM member, 2022)

6.2 Predictability and harmonisation of payer expectations around innovative contracts

6.2.1 There is a need for a framework providing guidance on the design and implementation of innovative contracts

Access delays to therapies with significant clinical potential can often be attributed to the differing perspectives of manufacturers and payers around the value of the product, clinical and

financial uncertainties, and questions around sustainability. Innovative contracts or 'managed entry agreements' (MEAs) can help to mitigate such concerns, however, they can be difficult to decide upon and implement and there is currently no structured process to come to agreements on MEAs (Whittal, et al., 2022).

Where policies and rules are in place, members report that application can be irregular in practice; this is supported by a systematic review of the literature (Michelsen, et al., 2020). Currently, manufacturers can only infer what might be acceptable by looking at previous agreements (which are often not public) or conducting indirect 'payer research' with experts in those markets. Manufacturers assert that it would be very helpful for payers to provide more explicit guidance to manufacturers about the types of innovative contracts that are acceptable in their country and how they should be structured.

This sentiment has been echoed in the recent literature:

> "There is a need for a legislative framework and a roadmap that provides guidance to manufacturers, payers and health care providers on how to design and implement outcomes-based managed entry agreements for advanced therapies in terms of data collection, quality and analysis; outcome selection and payment correction; funding and data ownership." (Simoens, et al., 2022)

In the same way that there was an evolution over time around the documentation of individual HTA system requirements, it would be highly beneficial to manufacturers to have consistent advance knowledge of the circumstances around innovative contracting for ATMPs, by country. This point has also been recognised in the literature. For example, Facey et al. suggested that the 'constructs' of outcomes-based agreements should be published in an international public repository in order to support learnings across jurisdictions, in a similar manner to the HTA database published by the International Network of Agencies for Health Technology Assessment (INAHTA) (Facey, et al., 2021).

The innovative contracts that manufacturers agree on often represent barriers to efficient negotiations in a manner that is potentially deal-limiting include (list is not exhaustive):

01 Patient data privacy concerns (see sections 6.3.4 and 6.3.5)

02 Requirements around transparent contracting (see section 6.4.1)

03 Specifics around national accounting rules and how they relate to considerations around split payments (see section 5.25.2)

04 Core data needs and questions around what to measure, and how (see section 7.1)

Notwithstanding the above, it is important to recognise that with transformative therapies there is still a need to apply a degree of flexibility in contracting to account for disease- or product-specific considerations that warrant a different approach (see section 6.3.1).

6.2.2 Early dialogue between manufacturers and national payers

Several manufacturers believe there is a need to include opportunities for manufacturers to engage in simultaneous regulatory and payer dialogues (preferably even joint discussions). This is particularly true in the context of life-threatening diseases for which no effective treatments currently exist and rapid patient access is paramount.

Early guidance is needed from payers on their expectations of innovative contracts for the following reasons [see previous ARM report for a more detailed discussion of these and other considerations (ARM, 2019)]:

01 To facilitate recognition of the need for an innovative contract, e.g., in cases of economic necessity. Manufacturers believe that payers do not always understand the cost structure of various kinds of ATMPs, in particular, single-administration therapies or gene therapies and that this needs to be better explained.

02 To get alignment with payers on the main source of the uncertainty that needs to be addressed in the innovative contract. The need to classify uncertainties and make their impact more explicit and transparent have been discussed in detail elsewhere (Whittal, et al., 2022).

03 To allow sufficient development time to create effective innovative contracting schemes. For example, the infrastructure needs to be in place, and therefore the earlier this is planned, the better.

04 To avoid unnecessary delay. Waiting until negotiations stall before initiating thinking around innovative contracts means extending time to patient access and funding. For some manufacturers, this delay reduces the viability of their business case, given cash flow and other business concerns. More than one respondent noted that small companies cannot afford the cost of engaging in protracted negotiation.

Manufacturers agreed that early dialogues are vital as these allow companies to be more transparent, in addition to establishing consensus on evidence requirements. To this end,

a methodology for exploring uncertainty early and constructing innovative contracting proposals accordingly has been published in the form of a value-based negotiation framework (Whittal, et al., 2022). The optimal timeframe to begin discussions would be approximately 18 months prior to regulatory approval, in parallel with scientific advice discussions with the regulator. An investment in resources should be made for those payers who lack the sufficient resource to do this routinely [as per ARM recommendations for additional EU and national funding for early dialogue activities (ARM, 2019)]. Similarly, a recent publication from the European Alliance for Transformative Therapies (TRANSFORM[1]) notes that to unlock safe and timely patient access to ATMPs, there is a need to "extend existing early dialogues such as those between the EMA and developers (e.g. PRIME) to be more iterative and inclusive of HTA bodies, payers, patients/caregivers and ATMP developers" (TRANSFORM, 2022).

6.2.3 Alignment between regulators and national payers

Some ATMP manufacturers (though not all) have found that establishing milestones that are acceptable to payers is extremely difficult and that these were usually different to the milestones acceptable to regulators. One manufacturer stated that "with the label [the marketing authorisation], the payer redoes the work of the regulator". While it was acknowledged that in the rare diseases that are targeted by most ATMPs, outcome measures are not always well established, the general belief was that payers are more demanding than regulators, without presenting good scientific rationale to support requests for different outcomes/assumptions than what was accepted at registration in the context of the clinical trial.

While the EMA has evolved and has established the Committee for Advanced Therapies (CAT), HTA bodies and payers do not have a group with dedicated expertise in ATMPs. In general, payers continue to take the same approach for ATMPs as they take for other chronic off-the-shelf drugs. For example, one manufacturer noted that in Spain the conversation is often the same for ATMPs as it is for therapies treating chronic illnesses.

Another comment was that when payers have set up specialised systems to assess ATMPs, these systems are often inadequate for their products. With reference to the UK, one manufacturer noted that while the Highly Specialised Technologies assessment process generally works and is a move in the right direction, no CAR T fits there given that these are haematology products and thus have to be considered via the usual NICE process.

As stated in the 2019 ARM report "There is a paradox between regulators' approaches in providing early access for ATMPs for patients' benefit and HTA/payers' reluctance to provide access until the long-term profile has been fully characterised." (ARM, 2019). Joint advice has

[1] TRANSFORM is a multi-stakeholder Alliance that connects Members of the European Parliament (MEPs) and policymakers with patient groups, medical experts and associations, scientists, researchers, industry actors, networks and other relevant stakeholders.

been put forth as a mechanism to improve coordination between regulatory and HTA bodies, and conceptually manufacturers see this as a potential means to unify outcomes tracking and avoid concerns around data ownership and stakeholder conflicts of interest. Nevertheless, at least one manufacturer felt this process was unproductive. While it can be a way forward in theory, in practice it can be unproductive, and industry finds itself having to find other methods of accounting for payer insights at the earliest opportunity.

> "We went through the joint consultation process with the EMA, the European Network for Health Technology Assessment (EUnetHTA), and ourselves. The first mistake was that while it was a joint consultation the outcome was two separate reports. The second mistake was that in the EUnetHTA report, there was no forced consensus. So it was just a sequence of individual HTA reports. So there was disagreement between individual HTA agencies, leave alone with the EMA. In the meeting, there were in fact two chairs – one from the EMA and one from EUnetHTA – as a company you are still then left with a 'yes' from one chair and a 'no' from the other. So when the company were invited to engage in another consultation, we said no, as it was not productive." (ARM member, 2022)

6.2.4 Alignment across countries

It is generally understood that there are two main reasons for engaging in outcomes-based approaches: evidence uncertainty and budgetary limitations. Yet across European countries there is widespread heterogeneity in innovative contracting for ATMPs and a lack of agreement on what represents a good outcomes-based approach, as every country engages with industry from a different starting point, particularly in the context of discussions around data requirements (Facey, et al., 2020).

Several of the manufacturers interviewed noted that every country requires something different with regards to ATMP contracting, for example, different sub-cuts of the data, selection of varying subpopulations, or different endpoints for response-based contracting schemes. For CAR Ts, a manufacturer noted that different countries have quite substantially different perspectives on outcomes (and that anecdotally, health-care practitioners (HCPs) state that each hospital has a different way of measuring outcomes):

> "Complete Response (CR) based schemes were requested in a couple of countries. In both, we pushed back and said that is not the right endpoint because that starts introducing uncertainty – e.g., are you doing positron emission tomography (PET) / Computed tomography (CT), can you guarantee that the patient will be there for their

scan at the 1-year mark, what if the scan happens a month later and the patient has progressed? [Country A] agreed with us and fell back. In [Country B] the HTA group met with clinicians, and they said CR is the outcome, and wouldn't move from this." (ARM member, 2022)

Lack of alignment on innovative contracting across countries poses a substantial hurdle for manufacturers launching in multiple European nations, particularly for smaller manufacturers without an extensive presence in multiple markets. Starting from scratch with 27 different negotiations is highly unsustainable for industry, especially if each agreement can take a year to negotiate. A recurring theme amongst the manufacturers interviewed was that the effort expended in finding solutions to address evidence concerns in the context of reimbursement discussions was often not commensurate with the gain. This was particularly true given that the manufacturer would often need to account for a separate back-and-forth process for every upcoming indication.

Manufacturers and policymakers alike have commented on the need for a vision in contracting, for example, stating that "in Sweden, we develop the process while we are in the middle of it. Perhaps we need to have a long-term goal at the beginning instead." (Novartis Country Manager, Sweden) (Ericsson, 2022). Referring to the agreement with Novartis, a representative from the Danish payer organisation stated "It was the first outcomes-based model we actually accepted. And now we actually are trying to have a system and a process around it so that maybe we can have that for the future as well" (Meek, 2022).

6.3 Data, registries and contractual administration: further investment is needed

6.3.1 Innovative contracting schemes should always have some degree of flexibility

While manufacturers called for improved clarity in payer contracting expectations around ATMPs, it was emphasised that this clarity and structure should not come at the expense of flexibility. In general, innovative contracting schemes should have some level of flexibility. As an example, a guideline on rebate payment timelines designed in the context of an innovative contract for CAR Ts may not be appropriate for gene therapies or future transformative ATMPs.

Flexibility not only allows for a tailored approach to contracting, but also reduces the time stakeholders spend negotiating administrative details and instead allows for more opportunities to discuss ways to maximise the ATMP's benefit, and the implementation steps required to bring about access (see section 6.3.6 for a discussion of ATMP-specific health system challenges). Reimbursement alone does not equate to patient access, and for ATMPs in particular it is clear that while some degree of standardisation is welcome, there are

particularities for many products that require planning around therapy delivery infrastructure supported by commitments from multiple health system stakeholders. This relates to the recommendation on the benefits of early dialogue (see section 6.2.2); a preliminary stage will permit a fuller understanding of how the product will fit into the health system, which will facilitate faster and more efficient patient access.

6.3.2 Innovative contracting schemes, if needed, should be simple – particularly in small populations

Manufacturers are united in the belief that innovative contracts should be as simple as necessary to mitigate the core uncertainty or uncertainties associated with an ATMP. In particular, the smaller the population for which the ATMP is indicated, the simpler the scheme should be. In ultra-rare diseases (affecting less than 1 in 50,000 people (European Parliament, 2014)), there is less appetite for all stakeholders to engage in innovative contracting due to the effort required to establish and run an agreement, relative to the total amount of uncertainty. In particular, the total budget at risk is often low in very small populations, even when the price per patient is high (for example, Libmeldy in metachromatic leukodystrophy (MLD). In such circumstances, it can sometimes be more straightforward to achieve reimbursement via more established contracting methods without necessitating innovative contracting.

6.3.3 Registries: necessity, funding and control

A frequently mentioned concern from manufacturers was the extensive variation in the way that outcome data is collected across countries for the purpose of monitoring innovative agreements. There is substantial variability in how data is collected between countries, between ATMPs within countries, and even for the same ATMP across different treatment centres/hospitals.

One topic that repeatedly arose from the interviews with ARM members was the question of the need for a national registry to collect outcomes data. A centralised process could, in an ideal situation, reduce data discrepancies and facilitate interpretation and auditing processes as compared to multiple uncoordinated data collection initiatives. While some manufacturers acknowledged that small patient populations (e.g., those in ultra-rare diseases) make it difficult to warrant payer investment in full-scale data collection/monitoring systems, others believed that in some therapeutic areas, there are a relatively small number of treatment centres and this makes it relatively straightforward to capture data, as compared to diseases with larger patient populations.

Another subject of frequent discussion was the role of the manufacturer in collecting outcomes data for use in innovative contracts. Most manufacturers said that where they had established global or regional registries, payers (or clinical experts) were not willing to use them. Specifically, one manufacturer reported building a registry incorporating links between invoicing and outcomes, but found that payers were reluctant to use these systems and no countries opted in; instead the data was/is collected mainly through local registries managed by payers.

A proposed solution that was discussed amongst manufacturer representatives was that the company could consult with the payer on the registry design, but would be responsible for funding it, managing it, and data collection. A prevailing concern with this proposal was that physician associations are likely to refuse this arrangement as they prefer to have ownership of their datasets (e.g., for publication purposes), and are not sufficiently incentivised to want to share the data (see section 6.3.7). Ownership has also been a prevailing concern from the industry perspective. Manufacturers noted that smaller companies may not be able to set up registries in every country or maintain several different registries over the long term.

> "Regarding tracking of data/outcomes – there's a thought that you could use the pivotal trials instead of a new registry – there's a whole pile of stuff about registries tracking outcomes. But if you have many centres that do the registry a slightly different way, then it's a nightmare – so you need a good national registry. In a big country with different ways of data collection/centres – coordination gets very difficult." (ARM member, 2022)

> "There were a lot of follow-ups over who owns the data - for medical and pharmacy claims, how far in arrears - but the pharmacy owned the data. They were worried that someone would give a transfusion to a patient, and they wouldn't have captured it." (ARM member, 2022)

6.3.4 Data confidentiality can create a hurdle to surmount

Concerns around data confidentiality are often specific to particular countries and rely on how the laws are interpreted.

In Sweden, for example, payers have publicly stated that the reason they could not implement an innovative contract for Zolgensma was because of restrictive privacy legislation intended to protect patient confidentiality. The proposed payment-by-results scheme would have involved follow-up of data from the National Board of Health and Welfare's health data register to assess actual treatment outcomes. Party representatives called for a state inquiry to review the privacy legislation, highlighting a need to assess how well treatments work via data collection based on patient consent (Ericsson, 2022).

A similar example cited by a manufacturer described a situation where despite willingness on the part of all stakeholders, after four months an agreement was not reached due to the belief that patients could potentially have been identified via the shared data.

Manufacturers state that this is often quite a sensitive issue. Since supply agreements are often with hospitals, it is the hospital's responsibility to manage the data collected for innovative contracts.

6.3.5 Patient data auditing remains a challenge

When all parties are willing to engage in innovative contracting and the agreements are signed, auditing of outcomes data can still represent a stumbling block. In contracts

companies often include a clause reserving the right to audit data that comes from the payer, but in practice, as per the data confidentiality regulations discussed above, the payers cannot allow individual patient data to be transmitted to the company.

Even in circumstances where the manufacturer is permitted to audit outcomes, if the outcomes are complex and not easily tracked, there can be signficant uncertainty around whether a certain outcome should be accepted. For example for some ATMPs, outcome auditing would require extensive viewing of patient videos to determine whether an outcome had been adequately reached. Manufacturers stated that due to the sensitivity around these kinds of judgements, they usually prefer that a degree of trust is established between stakeholders. For particularly small patient populations, one manufacturer stated that it is vital to choose objectively assessed outcome measures because there is not a large enough sample size in the dataset to audit and accurately identify outliers.

Whilst trust is the preferred strategy, manufacturers stated that they would involve third-party firms for data auditing purposes if there were major deviations in the data as compared to trial results. In multiple instances, companies agreed that adjudication would be the right approach if they had to refund money to the payer.

6.3.6 Data collection infrastructure is imperfect

Limitations to health system infrastructure and suboptimal process standardisation continue to be barriers to the successful implementation of innovative contracts.

> "Even when there is willingness, the practical considerations around data collection are considerable. There is a lack of standardization, and a lack of resources to collect data – they don't have the staff, but don't trust the industry to do it." (ARM member, 2022)

Given the small patient numbers in most diseases targeted by ATMPs, there are often few specialists and limited knowledge and skill sets available in individual European countries. Manufacturers mentioned that there are a host of rare diseases where the infrastructure of care is highly fragmented and difficult to operationalise. There can also be a real lack of ability for the payer to cohesively pull systems and processes together to address the clinical need for therapy in the context of the economics of the country. For example, there can be a lack of clarity around who will measure outcomes, and who will pay for this (e.g., a PET scan to monitor the outcome).

Manufacturers expressed a view that there is still a need for payers to clarify the nature of these system-level complexities and target them with solutions. Joint procurement was cited as an example of European-level initiatives to address current health system challenges. While there was a lack of consensus on whether joint procurement itself is an appropriate initiative for ATMPs, there was agreement that the complexity of the market access environment should

be more explicitly addressed.

Notwithstanding this, there is an acknowledgement that healthcare registry systems are not prepared for necessary long-term follow-up, particularly in smaller countries. A representative from Latvia's State Agency of Medicines noted, for example, that she wanted more value-based agreements but that it is "tough" for Latvia due to the large investment in human resources that is required (Meek, 2022).

6.3.7 Healthcare practitioners play a vital role in data collection

Manufacturers acknowledged that usually, it is HCPs that enter data, and that can be the consideration that poses the biggest challenge in contracting. Physicians play a vital role, especially with more complex outcomes. If the physician is not committed to an outcomes-based scheme involving any degree of complexity, the scheme will not be successful. To support data collection, manufacturers acknowledged that outcomes should be simple, easy to measure, easily captured and consistently recorded by HCPs.

It was recognised that the HCP's commitment to entering data is linked to infrastructure and incentives:

> "Payers are not set up to monitor outcomes, but there are challenges on the physician side as well. A major part of any clinical trial expense is the cost of setting up monitoring systems with physicians – just to run the trial. When you flip that to RWE/post-approval clinical trial – to reconfirm the marketing authorisation – the cost element is more obscure and we haven't figured out the compensation for physicians to do that. Physicians don't have an infrastructure."
>
> "How do you incentivise doctors – the clinical community needs to be on board. In Italy and Belgium and other places, they have a system where physicians can't keep on ordering drugs or prescribing if they don't fill in the registry. The scientific community needs to commit to being part of the discussion – not just key opinion leaders. The physicians' view is crucial."
>
> "In Germany data needs to be submitted according to the Federal Joint Committee (Gemeinsamer Bundesausschuss, G-BA) guidelines – if not then you cannot get a contractual agreement. In addition, some contracts mandate that you must submit data, and if you don't, you cannot commence treatment."
>
> "In Belgium, the last payment is only provided after patient data is entered."
> (ARM member, 2022)

It is generally the responsibility of HCPs to recognise and identify the patients who will benefit from and need treatment. As an example, payers are concerned with regard to longer-term haemophilia treatments that there will no longer be a touchpoint with the HCP and that as a result, they will not be able to monitor these patients. Conversely, manufacturers noted that HCPs can often be more motivated to follow patients from small populations as there can be a more personal connection. Similarly, it was noted that the feasibility of outcomes-based agreements is greatly increased when data collection is centred on a small number of treatment centres.

6.3.8 Loss-to-follow-up patients

Once patients are cured or no longer require treatment, there can be considerable complexity around how tracking of these patients continues. This can result in a problem of loss-to-follow-up and questions about who is responsible for managing these patients' long-term outcomes, as well as difficulties in administering innovative contracts.

This issue is possibly of the highest relevance to gene therapies, and it should be noted that while members have recognised this as a potential problem, there is as yet no extensive reporting on the practicalities given most applicable schemes have not been in place for very long.

"There is a burden to consider – e.g. are you contracting for every patient, vs. at the population level. Many countries are introducing registries and mandatory follow-up and want the manufacturer to pay for a registry – in Germany, we are seeing this. The problem is what do you do with loss-to-follow-up patients. For some countries, these patients are considered deceased, and they don't want to pay for them – that's not going to work for the manufacturer who believes the job of follow-up is for the payers. That's why the pay-up-front option is better. bluebird's deal covering 4 years gives a huge allowance for loss-to-follow up, which was a problem." (ARM member, 2022)

6.4 Mutual understanding of interests and constraints: the journey towards trust

It is recognised that payers are constrained by practical challenges including budget, infrastructure, administration resources, stakeholder interests and legal obligations, as described above. Manufacturers also noted a number of constraints on the industry side, namely those related to contracting transparency and corporate accounting.

6.4.1 Contracting transparency hampers deals

In contrast to the need for confidentiality around patient-level data, on a contracting level, some countries demand high levels of transparency. As the most prominent example, manufacturers stated that the German payers' commitment to transparent contracting has been challenging for industry. In the worst-case scenario, it is noted that the requirement for high contracting transparency has in fact led to the country having to forego access to products. This is due to industry

deciding not to attempt a launch to avoid the risk of payers publicly disclosing sensitive industry information such as the net price. Manufacturers unreservedly agreed that transparency laws should be addressed, particularly in Germany (see section 6.1).

6.4.2 Corporate accounting relating to innovative contracting can be a challenge

While hurdles around accounting rules at the EU / National level are often discussed, manufacturers state that company accountants also find outcomes-based agreements over time to be challenging. For example, key considerations for company accountants include deciding how much money to keep in reserve in case paid or not, and how much to book this year vs. next. The three types of money-back schemes (rebates, refunds, free stock) are very different from an industry perspective. Industry has to account for the cost of capital, cash flow, and standard accounting principles.

> "Corporate accounting is a major consideration for companies who are starting with a franchise. They have to decide – is this a good investment? If the investment happens now, but revenue is realised only some years down the line – this creates a hole." (ARM member, 2022)

Another point made by industry representatives is that while split payments are theoretically easier to administer, in practice the timeliness of up-front payments from payers is variable. Unlike schemes involving rebates or free stock, for which the onus is on the manufacturer to transfer the funds or goods, with split payments the payer is responsible for managing the transfer of funds. One manufacturer felt that this made the payer less incentivised to track outcomes adequately, given that the risk of not doing so lies largely with the manufacturer.

6.4.3 There is a continued need to engender mutual understanding and trust between payers and industry

Beyond technical issues, there was a widespread consensus in the membership that future progress on innovative contracting will require increased trust between manufacturers and payers. More than one industry representative reflected that payers are generally sceptical of industry intentions with innovative contracting, stating that some payers perceive manufacturers to be pushing complex payment models when simple discounts would suffice. While this is not specific to ATMPs, industry's consensus is that there is little recognition by payers that ATMPs do genuinely warrant innovative approaches due to their particular uncertainties.

> "There is a lot of scepticism and distrust on the payer side – but this is not specific to ATMPs. Affordability, war, and inflation also play a role. Payers just do not trust that this will be something good for them." (ARM member, 2022)

When the starting point is marked by scepticism or mistrust, there is a sense that this can lead directly to resistance on the part of payers to engage in any kind of innovative contracting. A point made by several

manufacturers was that even when potential solutions to payers' challenges around evidence were proposed, there was still a reluctance on the part of the payer to move forward.

> "Data collection was always a discussion. But even where there was an intention to solve it, the payer always preferred to say, "let's do something simpler". So we had a foot in the door then suddenly had to go backwards" (ARM member, 2022).
>
> "We found that when you get to a certain point then the payer pulls out" (ARM member, 2022).

The question of trust was considered to be a key factor impacting the design of contracts. For instance, 'lack of trust' was cited by one manufacturer as the reason for a misalignment in endpoint selection. The general view amongst manufacturers is that payers suspect that industry chooses endpoints that they already know they will be able to show good data for, as opposed to choosing the most relevant/valid/simple endpoint. While this is a general industry concern, it should be noted that this suspicion is aggravated when the product is a first therapy, which most ATMPs are, as there is limited established evidence available for comparison purposes.

Two other concerns that industry representatives attributed to a lack of trust include the often-mentioned payer reluctance to use company-owned data registries, and the restrictive payer-imposed clauses in agreements related to product delivery timelines.

Manufacturers would like to create a better understanding of the challenges faced by each stakeholder group, and settle misperceptions around the price, acknowledging that innovative contracting is only one potential solution to patient access.

Restrictive payer demands and protracted negotiations are generally being accommodated by industry, but manufacturers suggest that in future they will not always be inclined to accept restrictive conditions. Notwithstanding this, the general consensus from industry is that they do want to be flexible and that if governments show willingness to come to the table to discuss practical solutions to patient access, companies are less inclined to walk away.

7. WHILE INNOVATIVE CONTRACTING SHOWS REAL PROMISE, IT DOES NOT OBVIATE THE NEED FOR P&R SYSTEMS THAT WORK FOR ATMPS

This paper is focused on recent manufacturer experience of innovative contracting for ATMPs in Europe. While the feedback generally suggests that innovative contracting can indeed help to ensure access to ATMPs, manufacturers emphasised that they were not sufficient alone to ensure systematic and successful access to ATMPs therapies.

The preceding sections highlight a need to minimise friction in various aspects of the current reimbursement processes for ATMPs, however, if the underlying systems are not structurally adapted to the particular characteristics of ATMPs, then over time the situation will become increasingly untenable for all stakeholders. This mirrors a conclusion from the RARE IMPACT initiative:

> "While removing barriers to innovative contracting will aid in accelerating patient access, these models are created on an individual basis and reflect sub-optimal assessment processes for ATMPs. Moving towards HTA assessment pathways for ATMPs, alongside innovative contracting, could provide a more sustainable and future-proof system of evaluating ATMPs" (RARE IMPACT, 2020)

These topics have been discussed in detail elsewhere, such as in ARM and RARE IMPACT reports (ARM, 2019; RARE IMPACT, 2020), but here we summarise some of the elements that were repeatedly raised with industry representatives during discussions of innovative contracting.

7.1 Evidence assessment processes need to account for the specificities of ATMPs and small populations

Patients' access to therapies in Europe relies on products gaining both regulatory approvals from the EMA and reimbursement from payers within Member States. ATMP-specific regulatory pathways were introduced by European legislation in 2007 and created the CAT, a specialist subgroup within the EMA to assess ATMPs. This has proven successful, with 24 ATMPs approved since, however, market access has been less successful, with seven out of 24 either failing to launch or being withdrawn (bluebird bio's Zynteglo being a notable example.)[2] For many of these products, withdrawals reflected commercial challenges linked to restricted access and

funding (RARE IMPACT, 2020). Other ATMPs have had to navigate lengthy pricing and reimbursement procedures that have significantly delayed patient access (e.g., time to reimbursement post-marketing approval in the EU4 and UK varies from seven months in Germany to 20 months in France) (Mycka, et al., 2022). In effect, despite EMA taking positive actions to facilitate access to innovation (e.g., PRIME designation) and the granting of conditional approvals, this has not translated to a similar degree of improvement in patient access, since payers generally still represent the ultimate access hurdle.

One of the main reasons for the disparate outcomes between regulators and payers is the difference in interpretation of the clinical evidence. Manufacturers reported that payers frequently sought data on different endpoints than had been accepted by the regulators, sometimes without a clear scientific rationale. While this issue is not unique to ATMPs, the disconnect between regulatory and payer perceptions of endpoints seems amplified for ATMPs.

Associations between diseases, therapies and outcomes can be complex in severe diseases, making it particularly difficult to identify the 'right' endpoint to measure. For example, in cases where a patient cannot walk, this may not be directly attributable to the disease, but to the fact that the patient has been lying down for extended periods and this has diminished their muscle strength. With regards to overall survival (OS) endpoints for CAR Ts, therapies now exist that are given after CAR T therapy to extend survival, making it difficult to differentiate outcomes attributable to the CAR T from those attributable to the subsequent therapy.

It was also noted that the outcomes of relevance to patients/caregivers are often different from those considered priorities within HTA. For example, in neurological diseases a variety of treatment outcomes can be exhibited, ranging from head control to standing unassisted. One manufacturer stated that finding endpoints in claims data represents an inadequate way of describing the real benefits of therapies to patients.

Related to endpoints, the time horizon of benefit considered in HTA processes was a constant concern raised by manufacturers. For ATMPs, particularly those that are potentially curative, manufacturers felt the appropriate timeframe over which to value the benefits of the therapy is the lifetime. However, some payers have been reluctant to accept that the therapy provides life-long benefit on the basis of short-term data.

> "We did a lot of modelling and cost-effectiveness analyses, and [the product value] worked really well in terms of the Incremental Cost-Effectiveness Ration (ICER). But it required a lifetime consideration. But asking people to extrapolate short-term data – the negotiation becomes as much about [bargaining for] extra years than about costs. This is despite the phrase 'life-long benefit' being in the product label." (ARM member, 2022)

[2] As of January 2023, out of 24 ATMPs considered by the EMA, 17 ATMPs obtained EMA approval and 7 have been withdrawn.

Beyond endpoints, manufacturers highlighted other examples of elements in HTA processes that are problematic for ATMPs in rare diseases. For example, there can be large discrepancies in the prevalence/incidence estimates provided by the manufacturer and the academic literature, those cited in the label, and the payers' estimates that may come from other sources. This can have a major impact on the subsequent price negotiations, as well as the structuring of innovative contracts.

7.2 Pricing and funding processes need to be economically viable for manufacturers

Manufacturers further flagged the disconnect that can exist between HTA and pricing negotiations in some countries. The UK and Germany were highlighted as countries where the complex scientific assessments performed by NICE and the G-BA stood in contrast to the price and funding negotiations with NHS England and the GKV, in which clinical uncertainty was used to exert pressure on price.

> "In Germany - despite a scientific HTA, when you get to the GKV price negotiation it becomes a bare-knuckled negotiation and that makes no sense. Science should align with price more logically."

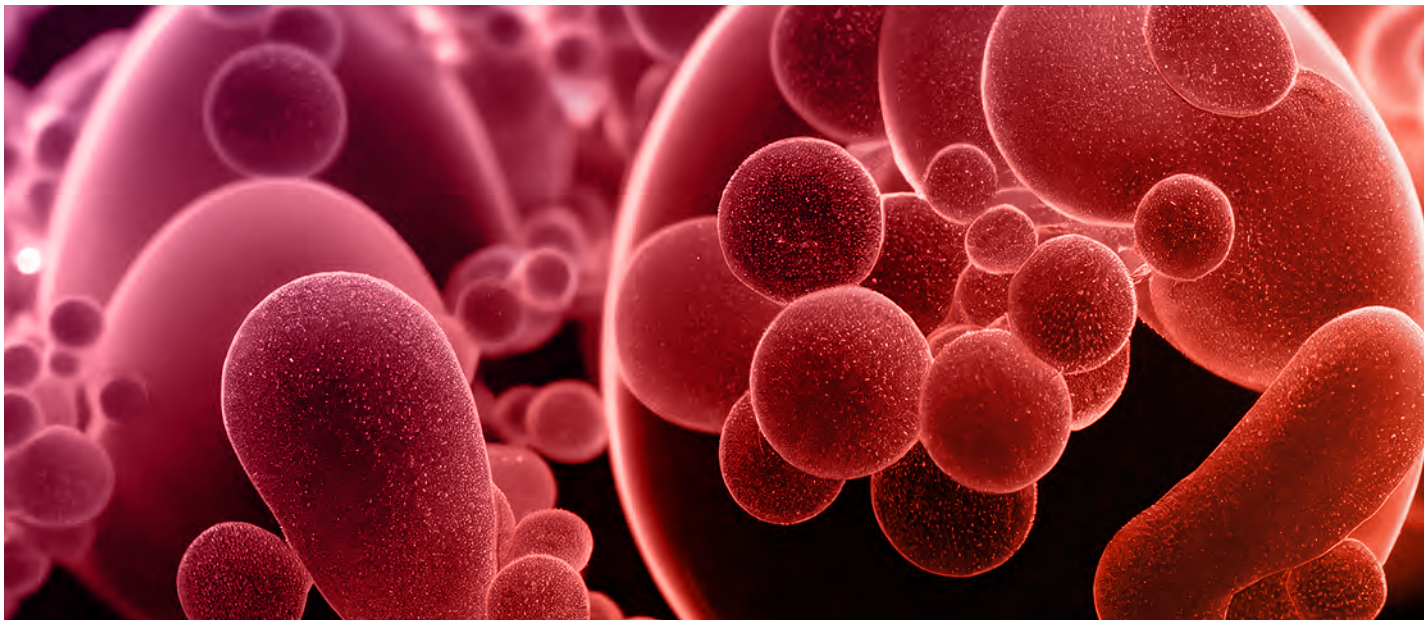
This touched on a broader theme from the manufacturers that pricing and funding mechanisms within European payer processes sometimes posed a challenge to the economics of the innovation model of ATMPs. The pioneering nature of ATMPs means that the costs of developing, manufacturing and developing these products are especially high, making products potentially economically unviable if prices do not reflect value (RARE IMPACT, 2021). One manufacturer noted that the price point agreed upon in some markets for their product meant that they made a loss on a treatment that they provided successfully to 40-50 patients. While the manufacturer accepted the loss in that situation, it was noted that this was not sustainable at an industry level, especially for smaller companies facing cash-flow constraints. Another participant in the interviews highlighted that in negotiations for its gene therapy in France the payer appeared not to differentiate between the profile of a gene therapy and a CAR T, and wanted to benchmark the former to the latter.

Some specific factors relating to the pricing and funding processes in European payer systems were identified by multiple manufacturers as areas for focus.

One issue that was emphasised by gene therapy manufacturers was the need for funded early access schemes for ATMPs, such as the Early Access Authorisation scheme (that replaced the ATU in July 2021) in France (HAS, 2022). These are especially important for treatments that offer lifesaving or potentially curative effects in populations that have no effective treatment options. Given the urgency in the patient community to access such treatments, it is deemed unethical to wait until long reimbursement processes are complete. While it is possible in some countries to provide free-of-charge access before reimbursement (or even approval), this is not economically viable in diseases with a very low incidence where the prevalent population constitutes a significant proportion of all treatable patients. Manufacturers proposed that early funded access could be provided at an economically viable price for the therapy, with ongoing data collection and a pay-back mechanism if the therapy does not deliver.

As mentioned in section 6.1, the confidentiality of net prices within P&R processes is of great importance to manufacturers, given the IRP systems used within and beyond Europe. As long as IRP is used, industry will require net price confidentiality to support the viability of their products (Drummond, et al., 2011; Whittal, et al., 2022). Many European countries recognise the importance of this confidentiality: for example since Spain has started to engage in innovative contracting, it has kept the negotiated price confidential (Oliva-Moreno, et al., 2020).

Finally, the choice of comparator within the HTA/P&R process is also particularly sensitive for ATMPs. In rare genetic diseases for which many ATMPs are approved, there is generally no licensed comparator already in existence, leading to the risk of price being benchmarked to off-patent or off-label best supportive care. Price negotiation from this basis devalues innovation and risks leading to market withdrawals.



8. CONCLUSIONS: BUILDING A BRIDGE TO ACCESS FOR ATMPS IN EUROPE

ATMPs represent a challenge to traditional European P&R systems, because of their often single-administration, personalised nature, long-term benefits, and one-time prices. Given the transformative potential of these interventions, and the rapid evolution of science, in the medium-term health system processes will need to evolve if the public health benefit from these innovations is to be realised in Europe. In the meantime, innovative contracting can serve as a bridge to patient access (see section 5.3).

The last five years have represented a proof-of-concept for the utility of innovative agreements in serving this purpose for ATMPs. The relatively high number of contracts agreed upon and the broadly positive experiences of ARM's members support the potential for innovative contracting to materially improve patient access to ATMPs in Europe. This contrasts with the experience of the previous wave of ATMPs, many of which were subsequently withdrawn from the European market. As such, progress should be recognised and the effort expended by all stakeholders to achieve it should be commended.

Many member states have stretched their P&R processes to incorporate solutions that support access via innovative contracting. The fact that even smaller European countries, such as Latvia (Meek, 2022), are beginning to engage in innovative contracting for the first time supports the view that perceived obstacles, such as national accounting rules, can indeed be overcome when there is a willingness to do so. Those countries that have yet to embrace innovative contracting for ATMPs can adopt learnings from those that have.

It is critical that Europe builds on the success to date and creates an infrastructure for innovative contracting that extends across all Member States, and that is capable of implementing split payment and outcomes-based agreements for a future in which breakthrough ATMP innovation is increasingly common. For that to happen, further effort is needed from all stakeholders across the key themes explored in this report, summarised below.

01

Recognition of the exceptionalism of ATMPs. The fundamental need for innovative contracting reflects the transformational difference of ATMPs from the chronic therapies for which HTA and payer systems have been designed. Innovative contracts are a response to restrictive payer systems and are intended to mitigate uncertainty and optimise treatment pathways (Facey, et al., 2021). The unique characteristics of ATMPs should be reflected both in the design of innovative agreements, but also in the broader P&R process of which these contracts are a component.

02

Building infrastructure and capabilities. The implementation of innovative contracts is still constrained by limitations in both the infrastructure and processes of healthcare systems. The uncertainty of the payer requirements from innovative contracts, and the variation in approaches across countries, increase the complexity for manufacturers and delay uptake and patient access. Further effort and investment are necessary both in countries' infrastructural capabilities, such as data collection and payment systems and in clarity of process and requirements, including through earlier engagement with manufacturers. Equally importantly, there is a need from all stakeholders for the commitment and pragmatism to make innovative contracts work in practice, which means creating sufficient flexibility in processes to reflect the distinctive characteristics of each ATMP, and challenging orthodoxy on what is possible.

03

Reciprocal willingness and trust. Even with greater clarity on the process and parameters around innovative contracts, the broad adoption of such agreements for ATMPs will continue to rely on willingness and trust between payers and manufacturers. For agreements to work in practice, both stakeholders require a sincere intention to manage and share the inherent clinical and economic uncertainty that is the central challenge for the pricing of many ATMPs. If innovative contracts are just a veil for aggressive net price discounts, then cynicism will undermine the very real potential that they represent to improve access to exciting new treatments.

04

Sustainability of ATMP innovation is a real, not theoretical risk. Innovative contracts are not a substitute for a willingness to pay that reflects the full value of a new medicine. The economic viability of many ATMPs is low, given the small patient numbers and complexity. With the cost of goods high, and the ability to scale up manufacturing low, there is limited opportunity for price flexibility. For some manufacturers to date, ATMP investments have been seen as a loss leader, forgoing profit today to build capabilities for future launches. But there are serious questions within industry about the medium-term economic viability of these technologies, and whether the cost and effort to implement innovative contracts justified the financial gain. The spectre of bluebird bio's departure from Europe continues to hang over this debate, and the extent to which innovative contracting is ultimately successful will influence the likelihood of this situation recurring.

It is therefore very important that the learnings from manufacturers' experience over the last five years are considered carefully. The opportunity represented by ATMPs for Europe is transformational: for individual patients, for public health, and for the scientific and industrial leadership of the continent. Innovative contracting alone will not deliver the full benefits of that opportunity, but it can create a bridge to patient access that is a meaningful step in the right direction.

9. APPENDIX

Table 2: List of authorised ATMPs (January 2023) (EMA, 2023c)

Product (Type of ATMP)	Authorisation date	Orphan	PRIME	Comment
Chondrocelect (TEP)	5/10/2009	✗	✗	Withdrawn Jul 2016
Glybera (GTMP)	25/10/2012	✓	✗	MA not renewed (ended Oct 2017)
MACI (TEP, combined ATMP)	27/06/2013	✗	✗	MA not renewed (ended Jun 2018)
Provenge (CTMP)	06/09/2013	✗	✗	Withdrawn May 2015
Holoclar (TEP)	17/02/2015	✓	✗	-
Imlygic (GTMP)	16/12/2015	✗	✗	-
Strimvelis (CTMP)	26/05/2016	✓	✗	-
Zalmoxis (CTMP)	18/08/2016	✓	✗	Withdrawn Oct 2019
Spherox (TEP)	10/07/2017	✗	✗	-
Alofisel (CTMP)	23/03/2018	✓	✗	-
Yescarta (GTMP)	23/08/2018	✓	✓	-
Kymriah (GTMP)	23/08/2018	✓	✓	-
Luxturna (GTMP)	22/11/2018	✓	✗	-
Zynteglo (GTMP)	29/05/2019	✓	✓	Withdrawn Mar 2022
Zolgensma (GTMP)	18/05/2020	✓	✓	-
Libmeldy (GTMP)	17/12/2020	✓	✗	-
Tecartus (GTMP)	14/12/2020	✓	✓	-
Skysona (GTMP)	16/07/2021	✓	✓	Withdrawn Nov 2021

Product (Type of ATMP)	Authorisation date	Orphan	PRIME	Comment
Abecma (GTMP)	18/08/2021	✓	✓	-
Breyanzi (GTMP)	4/04/2022	✗	✓	-
Carvykti (GTMP)	25/05/2022	✓	✓	-
Upstaza (GTMP)	18/07/2022	✓	✗	-
Roctavian (GTMP)	24/08/2022	✓	✗	-
Ebvallo (CTMP)	16/12/2022	✓	✓	-
Hemgenix (GTMP)	Opinion Dec 2022	✓	✓	EC decision pending

Adapted from "List of authorised ATMPs". (EMA, 2023c). Abbreviations: ATMP: advanced therapy medicinal product; GTMP: gene therapy medicinal product; CTMP: cell therapy medicinal product; EC: European Commission; TEP: tissue engineered product; MA: Marketing authorisation

Table 3: Committee for Advanced Therapies overview of product-related activities (January 2023) (EMA, 2023c)

	2009-2020	2021	2022	2023*	Total
Submitted MAA	32	3	1	0	36
Positive draft opinion	18[i]	2	6	0	26[#]
Negative draft opinions	4[i,ii,iii]	0	0	0	4
Withdrawals	8[ii,iv]	0	1[v]	0	9
Ongoing MAA					1

Adapted from "Overview of product-related activities" (EMA, 2023c). Abbreviation: MAA: Market authorisation application

*As of January 2023

[i]One negative draft opinion and two positive draft opinions for the Glybera

[ii]Negative draft opinion and withdrawal for the Cerepro

[iii]Two negative draft opinions for Heparesc

[iv]Luxceptar, Roctavian, Artobend

[v]Sitoiganap

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11. LIST OF ABBREVIATIONS

Abbreviation	Definition
AADC	Aromatic L-amino acid decarboxylase
AIFA	Italian medicines agency
ARSA	Arylsulfatase A
AMNOG	Pharmaceuticals market reorganisation act
ASMR	Improvement in clinical benefit
ATMP	Advanced therapy medicinal product
CAR T	Chimeric antigen receptor T-cell
CAT	Committee for advanced therapies
CDF	Cancer drugs fund
CED	Coverage with evidence development
CR	Complete response
DLBCL	Diffuse large B-cell lymphoma
DRG	Diagnostic-related group
EAP	Early access program
EMA	European medicines agency
ESA	European system of accounts
EUnetHTA	European network for health technology assessment
EUROSTAT	Statistical office of the European Union
FL	Follicular lymphoma
GKV	German statutory health insurance
HCP	Health-care practitioner
HER	Electronic health records
ICER	Incremental cost-effectiveness ratio
IMF	Innovative medicines fund

Abbreviation	Definition
INAHTA	International Network of Agencies for Health Technology Assessment
IRP	Iinternational reference pricing
LYSARC	Lymphoma Academic Research Organization
MA	Marketing approval
MEP	Member of the European Parliament
MLD	Metachromatic leukodystrophy
MSCBS	Spanish ministry of health, consumption and social welfare
NHS	National health system
NICE	National institute for health and care excellence
PET / CT	Positron Emission Tomography / Computed Tomography
PLFSS	Social Security Finance Bill
PMBCL	Primary mediastinal large B-cell lymphoma
PRIME	PRIority MEdicine
P&R	Pricing and reimbursement
r/r	Relapsed / refractory
RWE	Real-world evidence
TLV	Swedish Dental Health and Medicines Agency
VWS	Dutch ministry of health, welfare and sport
ZIN	Dutch Healthcare Advisory Institute