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ACCESS TO GENE AND CELL THERAPIES AS INNOVATIVE HEALTH TECHNOLOGIES IN BULGARIA

ABSTRACT

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The thesis comprises 133 standard typewritten pages and is illustrated with 16 figures and 18 tables. The bibliography includes 204 references, 28 of which are in Cyrillic. Three scientific articles have been published in connection with the thesis.

The thesis has been discussed and approved by an extended scientific panel of the ‘Classification Systems, Standards and Innovations’ Directorate at the National Centre for Public Health and Analyses and has been proposed for defence before a scientific jury.

Contents

Abbreviations used

SG – State Gazette
EU – European Union
MPM – Medicinal Products in Human Medicine Act
EAM – Executive Agency for Medicines
MoH – Ministry of Health
NHIF – National Health Insurance Fund
NCPMP – National Council on Prices and Reimbursement of Medicinal Products
HTA – Health Technology Assessment
PLS – Positive Drug List
CHEERS – Consolidated Health Economic Evaluation Reporting Standards
EUnetHTA – European Network for Health Technology Assessment
HSCT – haematopoietic stem cell transplantation
ICU – Intensive Care Units
JCA – joint clinical assessment
MEA – managed entry agreements
MA – marketing authorisation
OECD – Organisation for Economic Co-operation and Development
OOP – out-of-pocket payments
PRIME – PRIME scheme for priority medicines (PRIority MEdicines)
RWD – real-world data
SUSAR – suspected unexpected serious adverse reaction

INTRODUCTION

In the European regulatory context, gene and cell therapies are primarily considered within the framework of advanced therapy medicinal products (ATMPs), which include: gene therapies, somatic cell therapies and tissue-engineered products. These definitions are key not only for marketing authorisation but also for subsequent processes relating to health technology assessment (HTA), reimbursement and funding.

Gene therapy, in a broad sense, refers to a therapeutic intervention in which genetic material is introduced or modified for the purpose of treatment, prevention or diagnosis. In a regulatory sense (EU), the concept is specified through a gene therapy medicinal product (GTMP). According to the definition in Annex I, Part IV of Directive 2001/83/EC (as amended/detailed), a GTMP is a biological medicinal product which contains or consists of recombinant nucleic acid and is administered to a human being with a view to regulating, restoring, replacing, addition or deletion of a genetic sequence, where the therapeutic/prophylactic/diagnostic effect is directly linked to the nucleic acid sequence or to the product of its gene expression. It is expressly stated that vaccines against infectious diseases are not included in this definition.

Cell therapy, as a general term, covers therapeutic approaches in which the active substance is a living cell or cell population. Within the EU, the regulatory term is somatic cell therapy medicinal product (sCTMP). According to the definition, an sCTMP is a biological medicinal product that contains or consists of cells or tissues that have undergone substantial manipulation (such that the biological characteristics, physiological functions or structural properties have been altered) or are intended to perform a different ‘essential function’ in the recipient compared to the donor. The product is presented as having therapeutic, prophylactic or diagnostic properties through the pharmacological, immunological or metabolic action of the cells/tissues or their products.

Tissue-engineered products (TEPs) are a specific subgroup of ATMPs, as defined in Regulation (EC) No 1394/2007. A tissue-engineered product is one that contains or consists of ‘engineered’ cells or tissues and is presented as having properties for, or is used/applied for the purpose of, regenerating, repairing or replacing human tissue. ‘Engineered’ cells/tissues are understood to mean those that have been substantially manipulated or are not intended to perform the same essential function in the recipient as they did in the donor.

In practice, the boundaries between GTMP, sCTMP and TEP are not always intuitive, which is why the EMA emphasises the role of scientific classification and demarcation rules for products that could fall into more than one category (e.g. genetically modified cells). This regulatory precision is essential for subsequent planning of access and funding, as it determines the quality/safety requirements, the logistics model, the need for registries and the method of measuring outcomes.

Bulgarian legislation adopts the definition ‘advanced therapy medicinal products’. Although there is no precise definition of them in the Law on Medicinal Products for Human Use, leading authors in our country characterise them as *“a group of modern medicines developed through gene therapy, cell therapy and tissue engineering, aimed at altering physiological functions through modifications to them. Due to the more complex chemical nature and frequency of adverse reactions of these products compared to conventional chemically derived medicines, they are subject to additional regulatory requirements, but compliance with these involves greater resources, which hinders their accessibility.”*

In recent years, gene and cell therapies have moved from experimental approaches to clinically established interventions with the potential for long-lasting effects and functionally cures in some patients. Key technological drivers for this transition include the refinement of vector platforms, the development of genetically modified cell products, and the advent of precision genome editing, which broadens the spectrum of therapeutic targets and enhances safety.

Against this backdrop, advanced therapy medicinal products (ATMPs) are positioned as ‘transformative’ technologies that shift the traditional therapeutic paradigm from chronic management to potentially single-dose or short-term treatment with delayed benefits. This transformation has not

only clinical but also systemic significance – it requires new criteria for value assessment, different payment models, and stricter requirements for long-term monitoring of outcomes and safety.

In parallel with clinical progress, there has been a steady increase in regulatory and market activity regarding ATMPs, including new marketing authorisations and extensions of indications. The Committee for Advanced Therapies (CAT) at the European Medicines Agency (EMA) publishes periodic reports on ATMP approvals and activities, reflecting the dynamics of the portfolio in the EU and serving as an indicator of the ongoing expansion of therapeutic areas.

Despite the centralised marketing authorisation regime, decisions on reimbursement and access remain primarily a matter of 'national competence'. This is precisely where the challenge for healthcare systems arises – ATMPs are often targeted at small populations, have a high unit price and rely on evidence from limited clinical programmes, which increases uncertainty in the assessment of clinical and economic value.

In Bulgaria, public funding for medicinal products is concentrated primarily within the budget of the National Health Insurance Fund (NHIF), subject to strict requirements for predictability and cost control. The NHIF maintains and publishes public reports on payments for medicines and annual financial statements, which allow for monitoring of expenditure trends and the burden on the medicines budget. Despite the formal existence of regulatory and HTA instruments, the specific characteristics of ATMPs (one-off use, high cost, complex logistics, need for registries and tracking) may lead to delays in actual access or to a limited number of patients being treated in the country.

The criticality of this issue for Bulgaria is determined by a combination of: (1) a growing number of ATMPs that will emerge as therapeutic options in key areas (oncohaematology, rare diseases, inherited degenerative conditions), (2) limited public resources and the system's sensitivity to high-value therapies, and (3) the risk of the system falling behind countries with functioning models for managed access.

From a health policy perspective, restricting access to ATMPs may lead to measurable health loss and exacerbate inequalities: patients with greater financial means or access to international channels may receive therapy, whilst others may not.

The scientific significance of this thesis stems from the need to integrate three lines of analysis: (1) the regulatory framework for ATMPs, (2) methodological features of Health Technology Assessment (HTA) under high uncertainty and one-off costs, and (3) the design of financial mechanisms to minimise budgetary risk and safeguard patient access. The practical significance is directly linked to the management of public resources and the reduction of inequalities in access.

The relevance of the thesis topic on advanced therapy medicinal products (ATMPs) is determined by the fact that it directly and meaningfully contributes to the understanding of the processes of: the development, evaluation, regulation and clinical application of these therapies. The thesis assesses in practice how the Bulgarian healthcare system manages to address unmet medical needs and the economic burden of disease.

AIM AND OBJECTIVES

The aim of the thesis is to conduct a comprehensive analysis of access to gene and cell therapies as innovative health technologies in Bulgaria, assessing the regulatory, organisational and financial pathway from obtaining marketing authorisation to actual application in patients. A secondary objective is to develop a practical model(s) for sustainable financing, adapted to the Bulgarian context and compatible with European regulatory and HTA frameworks.

To achieve and fulfil this objective, the following main tasks have been set:

1. To systematise the theoretical and regulatory framework for ATMPs at EU level and to identify the specific requirements that influence national access to these therapies.

2. To analyse European experience regarding HTA models and the reimbursement of ATMPs and to identify concepts and elements that are ‘transferable’ to Bulgaria.
3. To describe and map the institutional pathway in Bulgaria for innovative therapies and the critical points that determine the time to access and the conditions for funding.
4. To identify the available/actually used channels for access to ATMPs in Bulgaria (reimbursement; hospital budgets; individual mechanisms under Article 82; clinical trials) and to assess their sustainability, predictability and equity.
5. To conduct a comparative analysis between Bulgaria and selected EU/Central and Eastern European countries (e.g. Germany, France, Italy, Poland/Czech Republic/Romania) based on indicators and metrics for the access process, risk management tools, and the budget for ATMPs.
6. To develop a conceptual model for Bulgaria concerning the introduction/expansion of access to ATMPs, including budgetary impact, as well as an organisational ‘service model’.
7. To analyse the capabilities of the Ministry of Health and the National Health Insurance Fund to optimise and rationalise funding and manage uncertainty (registers, MEA/outcome-based contracts, budget corridor for innovation), in accordance with European requirements for clinical assessment and the national regulatory framework.

MATERIALS AND METHODS

Study design

This study has a non-interventional, analytical-descriptive and comparative design, based entirely on secondary (publicly available) data and documents, without direct patient involvement. The focus is on the pathway to access gene and cell therapies in Bulgaria – from regulatory status and health technology assessment to inclusion in the National Health Insurance Fund's reimbursement list, contracting and actual application, as well as on the financial mechanisms through which uncertainty and budgetary risk are managed in the case of high-value, often one-off therapies.

The design combines three interrelated analytical strands:

- Political, regulatory and institutional analysis – description and critical assessment of the regulatory framework, institutional roles and procedural steps (registration/assessment/National Reimbursement List/negotiation/payment).
- Country-by-country comparative analysis – benchmarking Bulgaria against selected EU and European countries (e.g. Germany, France, Italy, Poland, the Czech Republic, Romania) using standard indicators (processing times, types of contracts/MEA, regulatory infrastructure, early/conditional mechanisms).
- Economic scenario analysis (at a conceptual level) – development of simplified budget impact models and/or an organisational 'service model' for the introduction of ATMPs, based on published parameters and sensitivity analysis of assumptions, in accordance with best practices for budget analyses.

Data sources

The study uses secondary, publicly available data extracted from official registers, legislative acts, annual reports, methodologies and analytical reports.

Bulgarian institutional sources

- Conducting a health technology assessment of medicinal products, pursuant to Article 259(1)(6) of the Law on Medicinal Products for Human Use (State Gazette No. 102 of 2018, in force from 1 January 2019) and Article 1(8) and Chapter Six of the Ordinance on the conditions, rules and procedure for the regulation and registration of medicinal product prices (State Gazette No. 26 of 2019, in force from 1 April 2019).
- Regulation No 2 of 27 March 2019 on medical and other services under Article 82 of the Health Act – mechanism for approval/payment outside the scope of compulsory health insurance (including treatment in the country/abroad under certain conditions).
- Regulation No 10 of 17 November 2011 – conditions for treatment with unauthorised/unavailable medicinal products, including special orders and compassionate use.
- Annual reports and financial statements (including 'Medicinal Products' sections, income/expenditure statements, explanatory notes, cash flow statements).
- Documents relating to the 'mechanism ensuring predictability and sustainability' (including draft methodology/decisions for the relevant year), used as a source for the rules limiting budgetary risk for high-value technologies.
- Public information on treatment in Bulgaria and abroad as a channel of access, used to identify cases/practices involving highly specialised therapies (including cell therapies).

- Official information on clinical trials (including links to Regulation (EU) No 536/2014 and reporting of SUSARs to EudraVigilance).
- Public registers of authorised clinical trials by year, used for a descriptive assessment of opportunities for early access through clinical trials.
- Public registers and the PLS (portal/register with annexes).
- Described procedures for including a medicinal product in the PLS, used as a methodological basis for reconstructing the administrative pathway.

European/international sources

The following have been used from the European Medicines Agency and the European Commission:

- Official EMA overview of ATMPs (centralised authorisation, safety/efficacy monitoring).
- Documents from the Committee for Advanced Therapies (CAT) – CAT quarterly highlights with information on approved ATMPs and indications extensions.
- EC webpages on the implementation of Regulation (EU) 2021/2282 and on the JCA.
- Official text of Regulation (EU) 2021/2282 on EUR-Lex.
- Public lists/information on launched/ongoing JCAs, used to track the actual start of joint assessments.

The following have been used for internationally comparable indicators of expenditure and funding structure:

- Eurostat Statistics Explained – healthcare expenditure by function/provider/funding scheme, as well as methodological metadata under SHA 2011.

For contextual indicators (pharmaceutical sector, public coverage, out-of-pocket (OOP) expenditure and systemic constraints), the following were used:

- Country Health Profile 2025: Bulgaria (OECD/European Observatory) and the accompanying publications/pages of the Observatory, together with previous annual profiles for a historical comparison of trends.

The following were used for a systematic description of financing, accessibility and financial protection:

- Bulgaria: health system summary 2024 (European Observatory/WHO Europe).

The following were used to frame comparative clinical effectiveness and the methodology of European HTA practices:

- Publications and resources reflecting EUnetHTA relative effectiveness assessments (REA) and methodological aspects (e.g. indirect comparisons), used as a methodological guide when interpreting clinical uncertainty in ATMPs.

Literature search

The literature search was conducted in the following bibliographic databases: PubMed/MEDLINE; Scopus; Web of Science. The search period covers 01/01/2015–31/12/2025 (with the possibility of including older key publications if they are methodologically fundamental or frequently cited). Publications in English and Bulgarian were searched for.

The search combines terms relating to technology (ATMP), intervention (gene/cell therapy, CAR-T), economic evaluation and contractual models. A search is also conducted by

the names of specific therapies/platforms (e.g. CAR-T products; gene therapies for SMA, inherited retinal dystrophies) where necessary to extract economic analyses and HTA reports.

The synthesis of evidence is carried out at three levels:

- Narrative (qualitative) synthesis: structuring of results by ATMP type and therapeutic area; mapping of key sources of uncertainty; description of typical MEAs and organisational prerequisites (registers, centres, logistics).
- Quantitative descriptive synthesis: ICER ranges/medians (where methodologically comparable), BIA ranges for 1–N patients; frequency of contractual models used by country/indication; sensitivity of results to price, target population and duration of effect.
- Comparative synthesis for applicability to Bulgaria: assessment of the transferability of economic outcomes (perspective, clinical practice, organisational differences); derivation of parameters for a model with different scenarios and for recommendations.

Methods of analysis

The methods of analysis have been selected to correspond to the study design and to allow for:

(1) mapping of access processes;
(2) quantitative description of key indicators (where data are available);
(3) comparative interpretation against European practices;
(4) an assessment of policies and the regulatory framework.

Descriptive analysis

Data preparation and standardisation

- Creation of structured tables for: institutional processes, regulatory acts, PLS status, contractual mechanisms, publicly available financial parameters.
- Standardisation of units of analysis (e.g. year; therapy/indication; access channel; institution).

Empirical indicators and statistics

- Absolute values: number of ATMPs by type/indication; number of available access channels; number of documents/decisions by institution.
- Relative indicators: shares (%), frequencies, structures.
- Central tendencies and dispersion: mean/median, minimum-maximum, interquartile range.
- Process complexity index (e.g. number of mandatory steps from MA to payment);
- Readiness index for results-based financing (existence of a register, defined endpoints, interoperability, tracking rules).

Comparative analysis (Bulgaria versus selected countries)

The comparison includes:

- 'Reference' countries with developed OMT/contracting and high capacity (e.g. Germany, France);
- Countries with proven experience in registry-supported MEAs (e.g. Italy);
- Central and Eastern European countries with similar resource constraints and pragmatic models (e.g. Poland/Czech Republic/Romania).

Comparative indicators

- Process-related: time taken per stage, where measurable through public dates; availability of early/interim mechanisms; availability of centralised registries.
- Financial: MEA type (financial/outcome-based/deferred), existence of an 'innovation corridor'/special fund; level of public coverage and out-of-pocket pressure (structural contextual indicators).
- Organisational: hub models, logistics, tracking requirements.

Comparison method

- Quantitative comparison (where possible): normalisation of data (per capita; as % of total health expenditure/GDP; PPP adjustment for international comparisons).
- Qualitative comparison: structured matrix, supplemented with brief profiles and 'transferable elements' for Bulgaria.
- Analytical synthesis: identification of typical models and assessment of their applicability in the context of Bulgarian constraints.

Trend analysis

Where annual series are available, trends are analysed in:

- public expenditure on medicines/hospital medicines (aggregated);
- the dynamics of budgetary mechanisms and reporting parameters;
- the number/proportion of innovative therapies in specific channels;
- access indicators (e.g. cases of treatment abroad in specific categories as a proxy for lack of domestic capacity).
- Year-on-year growth rate (%).

Policy and regulatory framework analysis

Systematic collection and coding of regulatory acts, methodologies, reports and public procedures according to predefined categories: 'institution', 'stage', 'access condition', 'payment condition', 'data/monitoring', 'budgetary control'.

A framework is used that combines:

- Policy triangle (context-stakeholder-content-process) for structuring health policy decisions;
- assessment based on criteria: effectiveness, efficiency, equity, feasibility, sustainability;
- stakeholder mapping (identification of key stakeholders: Ministry of Health, National Health Insurance Fund, National Centre for Public Health and Analyses, Bulgarian Drug Agency, healthcare facilities, professional organisations, patient groups) and analysis of interests/influence.

The policy analysis includes:

- A process map of access (registration → HTA → PLS → negotiation → authorisation → implementation → monitoring).
- Identification of critical points and difficulties
- Formulation of policy options for the funding of ATMPs, with the prerequisites, risks and resource costs assessed for each option.

Pharmacoeconomic approaches

The pharmacoeconomic component plays a supplementary role to the main systemic analysis and is aimed at assessing the sustainability of the payer's budget and modelling the

effect of various ATMP funding mechanisms in the Bulgarian context. Due to a lack of proprietary primary clinical data, the models are based on published parameters (prices/ranges, clinical outcomes, incidence of adverse reactions, resource consumption) and on official public documents regarding the national budgetary framework and reimbursement rules. The reporting of pharmacoeconomic results is based on ISPOR best practices for budget impact analysis and on CHEERS 2022 for the documentation and transparency of economic analyses.

Budget impact analysis (BIA)

Objective and perspective

Budget impact analysis (BIA) assesses the financial change for the public payer upon the introduction of a new therapy, in contrast to cost-effectiveness, which assesses the value of the added health benefit. In this thesis, BIA is defined from the perspective of:

- the public payer (the National Health Insurance Fund and/or the state budget) and
- the hospital sector (where funding is channelled through inpatient care facilities),

with a clear distinction made by channel (outpatient care) and by organisational model (inpatient care, treatment abroad).

Time horizon and population

- Time horizon: 3–5 years (BIA standard), with an additional 'Year 1' scenario to assess the initial financial burden for 'one-off' therapies.
- Population: target population defined by (a) epidemiology/registers (where available), (b) published estimates, (c) expert-defined assumptions, documented and subject to sensitivity analysis.

BIA is implemented as a 'cost-accounting' model at payer level, including:

- Therapy costs: price/net price (where known; if not – range), single course (one-off or as per regimen), potential discounts/agreements.
- Administration and care costs: pre-treatment preparation, hospitalisation, monitoring, concomitant medications; specific costs for ATMPs (apheresis, cryopreservation, laboratory tests, ICU in case of complications).
- Adverse event (AE) costs: frequency and cost of managing key serious events (e.g. CRS/ICANS), based on publications and/or HTA reports.
- Cost offsets: avoided future costs from alternative therapy/maintenance treatment, where there is sufficient justification (and with clearly defined limitations).

Costs are grouped by year and by scenario.

BIA output results

- Incremental (net) budgetary impact calculated using the formula:

$$\Delta Costs = Costs\ with\ ATMP - Costs\ without\ ATMP$$

- Cost/patient/year and total cost/year for N patients.
- Threshold affordability assessment: number of patients treated within a fixed budget corridor or subject to a cost growth limit (depending on applicable national rules/mechanisms).

Scenario analysis (baseline versus alternative financing options)

The scenario analysis models how different financing mechanisms alter the annual budgetary exposure and risk for the payer. The baseline and alternative scenarios are defined in such a way as to be comparable and transparent.

Base-case scenario ('status quo')

- Upfront (one-off) payment upon initiation of therapy;
- funding via the existing channel (NHIF/hospital budget/individual mechanism);
- no formalised outcome-based condition (or with minimal monitoring requirements).

Alternative funding scenarios

At least three realistic alternatives are modelled, drawn from international practice and adapted to Bulgarian instruments:

(S1) Financial MEA with a cap and/or price-volume

- a maximum annual exposure for the payer is set;
- above the cap, the producer bears the cost/provides an additional discount.

(S2) Pay-over-time/annuity

- the total price is divided into 3–5 annual instalments;
- optional: 'payment suspension' in the event of proven failure/lack of effect (conditional continuation).

(S3) Outcome-based agreement (payment upon outcome)

- Endpoints and time intervals are defined (e.g. 12 and 24 months);
- payment is partial/in stages or includes a refund in the event of failure;
- requires a registry/tracking data.

(S4) Special 'innovation corridor'/fund

- a separate budget line is established for ATMPs (centralised), which may combine S1-S3;
- the aim is to reduce the risk of crowding out other expenditure and improve predictability.

For each scenario, the following are assessed: annual exposure, administrative requirements (data, contracts, monitoring), risk of delay, and expected effect on the number of patients with timely access.

Sensitivity analysis (one-way/probabilistic analysis)

One-way analysis

Key parameters are varied individually within predefined ranges:

- number of patients per year (±50% or 1-N for rare diseases);
- net cost of treatment (±20–30%);
- incidence of severe complications and need for ICU;
- percentage of 'dropouts'/non-response under outcome-based conditions;
- deferral rate and discount factor in annuity models.

Probabilistic analysis

Adverse and favourable assumptions are combined to assess the worst-case and best-case scenarios:

- high price + large number of applications + higher incidence of complications;
- lower net price (after discount) + controlled inclusion + higher percentage of lasting effect.

Ethical considerations

This study is based entirely on secondary sources and does not involve primary collection of clinical data, direct contact with patients or interventions. Consequently, ethical and legal considerations focus primarily on the proper use of public data and documents, the protection of personal data in the event of identifiable information being present, transparency, and the avoidance of conflicts of interest.

ANALYSIS OF RESULTS

European trends in ATMPs

Number and types of therapies approved by the EMA (by year/category)

For the purposes of this analysis, 'approved ATMPs' are ATMPs that have been granted a marketing authorisation (MA) in the EU following a scientific assessment by the EMA's Committee for Advanced Therapies and a subsequent decision by the European Commission. The source for the number, type and date of authorisation is the official 'List of authorised ATMPs' in the CAT quarterly highlights (report June–November 2025).

As of November 2025, 30 ATMPs with an MA issued between 2009 and 2025 have been identified. By regulatory category, gene therapies dominate - 21/30 (70.0%), followed by somatic cell therapies - 5/30 (16.7%), and tissue-engineered products - 3/30 (10.0%), with MACI classified as a TEP/combined ATMP.

Table 1. ATMP approvals in the EU by year and type (2009–2025)*

Year	GTMP	CTMP	TEP	TEP/combined	Total new MA
2009	0	0	1	0	1
2012	1	0	0	0	1
2013	0	1	0	1	2
2015	1	0	1	0	2
2016	1	1	0	0	2
2017	0	0	1	0	1
2018	3	1	0	0	4
2019	1	0	0	0	1
2020	3	0	0	0	3
2021	2	0	0	0	2
2022	4	1	0	0	5
2023	1	0	0	0	1
2024	2	0	0	0	2
2025**	2	1	0	0	3

**According to the 'List of authorised ATMPs' (CAT quarterly highlights, June–November 2025). Categories: GTMP – gene therapies; CTMP – cell therapies; TEP – tissue-engineered products; TEP/combined – combined ATMP (MACI).*

***For 2025, products with a marketing authorisation (MA) issued by 25 August 2025 are included (Vyjuvek, Aucatzyl, Zemcelpro). The list also includes a product with an 'Opinion Nov. 2025' (Waskyra), which does not count as an issued MA.*

There has been a marked increase since 2018 – 9 ATMPs were approved between 2009 and 2017, whilst 21 ATMPs were approved between 2018 and 2025.

A significant proportion of the products with early approval have had their MA suspended/withdrawn/not renewed (e.g. Chondrocelect, Glybera, MACI, Provenge, Zalmoxis, Alofisel, Zynteglo, Skysona, Beqvez) – 9 out of 30 according to the status/comment in the list, which highlights that regulatory approval is not equivalent to sustainable market and reimbursement access.

Early approvals (2009–2017) included relatively more tissue-engineered and cell-based products, whilst after 2018 growth has been driven primarily by gene therapies, including genetically modified cell products (e.g. CAR-T, classified as GTMP in the list) (Figure).

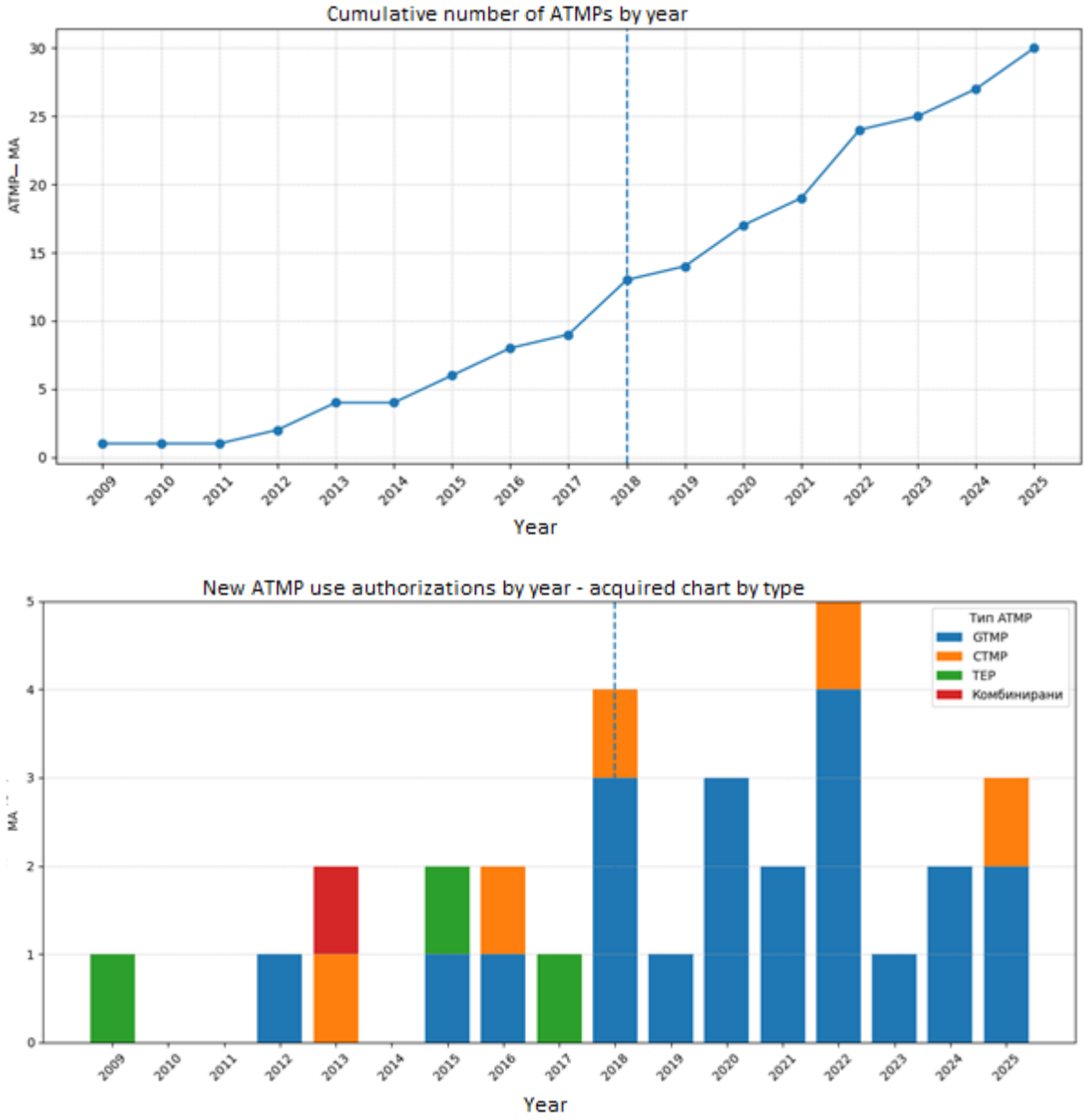

Figure 1. A. Line graph of the cumulative number of ATMPs with MA by year; B. Stacked bar chart of new MAs by year, broken down by type (GTMP/CTMP/TEP/combined).

Main indications and therapeutic areas

In terms of structure, the portfolio is characterised by a clear focus on diseases with high unmet medical needs, which is also reflected in the high proportion of therapies with 'orphan medicinal product' status (orphan medicinal product) – 23/30 (76.7%), as well as therapies that have undergone accelerated procedures such as PRIME – 17/30 (56.7%). Table 2 presents the distribution of ATMPs by therapeutic area.

Table 2. Distribution of ATMPs by therapeutic area (EU; n = 30; classification by primary indication)

Therapeutic area	n	Share (%)	Product names
Oncohaematology and transplantation	12	40.0	Yescarta, Kymriah, Tecartus, Abecma, Carvykti, Breyanzi, Ebvallo, Aucatzyl, Zemcelpro, Zalmoxis, Imlygic, Provenge

Inherited haematological/coagulation disorders	5	16.7	Zynteglo, Casgevy, Roctavian, Hemgenix, Beqvez
Neurology (rare genetic disorders)	4	13.3	Zolgensma, Libmeldy, Skysona, Upstaza
Orthopaedics/cartilage regeneration	3	10.0	Chondrocelect, MACI, Spherox
Ophthalmology	2	6.7	Luxturna, Holoclar
Dermatology/wounds	1	3.3	Vyjuvek
Gastroenterology	1	3.3	Alofisel
Metabolic disorders	1	3.3	Glybera
Immunodeficiencies	1	3.3	Strimvelis

Note: The distribution is based on the EMA/CAT list of authorised ATMPs (including therapies with withdrawn/suspended authorisation, as indicated in the list).

Oncohaematology and transplantation

The largest group of indications in the EU is in oncohaematology, where personalised cell therapies are the key driver, primarily CAR-T therapies for B-cell malignancies and multiple myeloma. Typical examples are:

- Yescarta – for diffuse large B-cell lymphoma (DLBCL) and other high-risk B-cell lymphomas.
- Kymriah – for B-cell acute lymphoblastic leukaemia (ALL) and DLBCL/follicular lymphoma in adults.
- Aucatzyl – a CAR-T product for relapsed/refractory B-cell precursor ALL in adults.

Alongside CAR-T, this cluster also includes ATMPs related to transplant/post-transplant oncohaematology:

- Ebvallo – for EBV-positive post-transplant lymphoproliferative disorder (EBV+ PTLD).
- Zemcelpro – cell therapy for adults with haematological malignancies requiring allogeneic haematopoietic stem cell transplantation (allo-HSCT) in the absence of a suitable donor.
- Zalmoxis (with subsequent withdrawal of the authorisation, noted in the list) – as adjuvant therapy in haploidentical HSCT for high-risk haematological malignancies.

The oncology section of the group also includes indications for solid tumours:

- Imlygic – for unresectable melanoma.

Oncohaematology accounts for the largest share of the ATMP portfolio, most likely for several reasons:

(1) the clinical effect is often measurable in the short term (remission/relapse);

(2) there is scope for relatively clear endpoints and follow-up;

(3) there is existing infrastructure in major centres for transplantation and highly specialised oncohaematology, which can be adapted to meet the needs of ATMPs.

Inherited haematological and coagulation disorders

The second most significant group of indications comprises inherited (non-oncological) haematological and coagulation disorders, where ATMPs are aimed at achieving a functional cure or a long-term reduction in the need for chronic replacement therapy/transfusions:

- Casgevy – the first gene editing treatment for transfusion-dependent β-thalassaemia (TDT) and sickle cell disease (SCD).
- Zynteglo – for TDrT in certain genotypes.
- Roctavian – gene therapy for severe haemophilia A.
- Hemgenix and Beqvez – gene therapies for haemophilia B.

In this group, health technology assessment (HTA) and budget planning are heavily dependent on assumptions regarding the duration of the effect and the choice of an appropriate comparator (e.g. modern prophylactic regimens, including non-factor therapies for haemophilia), which directly influences the preferred payment model (lump sum versus deferred/outcome-based).

Neurology

Neurological indications are concentrated in rare, highly fatal or disabling diseases where time to treatment is critical:

- Zolgensma – for spinal muscular atrophy (SMA).
- Libmeldy – for metachromatic leukodystrophy (MLD).
- Skysona – for early-onset cerebral adrenoleukodystrophy (CALD).
- Upstaza – for aromatic L-amino acid decarboxylase (AADC) deficiency.

For these indications, the requirements for early diagnosis (screening/genetic verification), referral to a specialist centre and logistics are often decisive for actual access; in other words, regulatory approval does not automatically translate into clinical availability.

Regenerative medicine and tissue engineering

Earlier ATMPs in the EU are related to regenerative medicine:

- Spherox – for symptomatic defects of the knee cartilage.
- Holoclar – for limbal stem cell deficiency following ocular burns.

The EMA/CAT list shows that some of the earlier tissue-engineered products (e.g. Chondrocelect, MACI) have had their authorisation withdrawn or not renewed, which indirectly highlights that the sustainability of these models requires clinical efficacy, manufacturing stability and economic viability.

Other areas

Although they account for a small relative share, these indications are of high health policy significance, as they often involve small patient populations, high disease burden and limited alternatives:

- Vyjuvek – local gene therapy for wounds in dystrophic epidermolysis bullosa (DEB).
- Alofisel – cell therapy for complex perianal fistulas in Crohn's disease (with subsequent withdrawal from the EU market, noted by the EMA).
- Strimvelis – for severe combined immunodeficiency due to ADA deficiency (ADA-SCID).

AtFigure shows the share of ATMPs by therapeutic area.

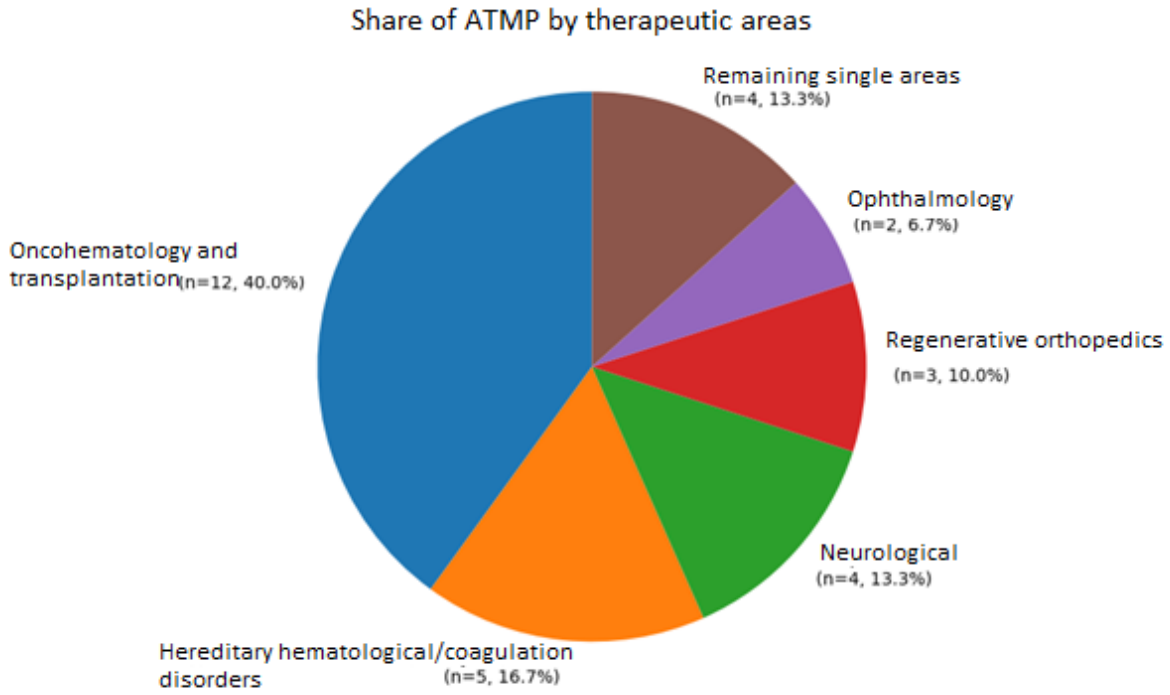

Figure 2. Pie chart showing the share of ATMPs by therapeutic area

Funding models in the EU – mapping

MEA/risk-sharing/outcomes-based – frequency and typology

Mapping of payment models for innovative therapies in Europe shows a dominance of managed access agreements (MAAs), with financial schemes being significantly more widespread than outcomes-based/performance-based schemes. This is explained by a combination of:

- the need for rapid access where medical needs are unmet;
- high costs and budgetary pressures;
- limited practical capacity for routine measurement and validation of final clinical outcomes in the short term.

According to data from an OECD review of MEA in OECD and EU member states (summarising public sources, an expert survey and interviews), as of 2019, MEA were used (or had been used in the past) in at least 28 of the 41 countries that are members of the OECD and/or the EU. The same analysis highlights that:

- financial MEAs (without a formal link between payment and clinical outcome) are/have been in place in at least two-thirds of the countries examined;
- performance-based MEAs are less common and, in most countries, have a limited scope (fewer than 10 product/indication pairs), with exceptions such as England and Italy, where their share is significantly higher.

Among a group of 14 countries for which comparable data is available, the OECD reports that payment based on response/outcome at patient level is the most common design, whilst reimbursement upon generation of additional evidence is the second most common design.

Bulgaria is listed among the countries where MEAs are used; the OECD table notes that MEAs are required for all new medicines covered since 2015.

In practice, the term ‘risk-sharing’ is used ambiguously: in some countries it refers to financial rebates/ceilings, whilst in others it refers to the return of funds in the absence of a response (i.e. outcomes-based). Therefore, this analysis applies a functional classification derived from the OECD and recent reviews of European experience (table 3).

Table 3. Taxonomy of MEAs and associated payment mechanisms for ATMPs

Group	**Subtype (example)**	**Payment logic**	**Main objective**	**Data type/condition**
Financial MEA	confidential discounts; price-volume; budget ceilings; cost-sharing	reduction of net price/budget cap	access + budget control	administrative/volume data
Outcome-based MEA	Pay-for-performance (refund/money-back in case of failure); conditional treatment continuation	payment only if criteria are met/refund if not met	control of clinical and financial uncertainty	clinical criteria, follow-up
CED	temporary coverage against RWE generation and reassessment	provisional funding + future reassessment	reduction of evidential uncertainty	registers/observational data
Deferred contributions under ‘ ’ upon achievement of results	Deferred contributions, capitalised upon achieving an ' ' interim/final results	payment ‘in tranches’ upon sustainable effect	management of a one-off high cost	long-term follow-up

An empirical snapshot of the frequency of the main outcomes-based designs (based on expert interviews in the OECD review) shows: patient-level PbR is available in 8 countries; population-based CED – in 6 countries; other designs (CTC and others) – less frequently.

CAR-T therapies are emerging as a model group of ATMPs, with European payers experimenting with outcomes-based solutions. A review of schemes in the EU5 (France, Germany, Italy, Spain, the United Kingdom) for two early-stage CAR-T therapies (reference period – the last quarter of 2019) shows the following distribution of approaches:

- France and the United Kingdom – CED/collection of additional data and subsequent reassessments;
- Germany – outcomes-based rebates (discounts/rebates linked to individual outcomes);
- Italy and Spain – outcomes-based staged payments (deferred payments linked to outcomes).

In support of the infrastructure capacity for outcome-based MEAs, Italy stands out with an institutionalised system of national registries managed by AIFA: an analysis covering a 15-

year period describes 283 registries, including those with financial schemes and outcome-based payment arrangements, with the architecture funded by manufacturers but managed by the agency.

The role of registries and RWD in outcomes-based payment

Outcomes-based/performance-based payment for ATMPs requires an operational infrastructure for RWD that enables:

(1) the definition of a measurable outcome;

(2) validated tracking over time;

(3) auditability and transparency of payment/reimbursement rules.

The OECD review of outcomes-based MEAs emphasises that these contracts are aimed at managing budgetary risk and/or uncertainty through payment only upon response or through CED, but their practical implementation depends on the availability of functioning registries and processes.

Registers in the context of outcome-based payment have four main functions:

- Appropriateness registry – verifies that the patient meets the inclusion criteria (diagnosis, treatment line, biomarkers), i.e. prevents inappropriate use;
- Outcomes registry – collects and validates endpoints (e.g. remission, event-free survival, functional status) at predefined time points, which act as triggers for payment/reimbursement;
- Safety registry – systematically records serious adverse reactions and complications.
- Financial and Administrative Module – links the clinical outcome to the contractual clause (e.g. partial/instalment payments, repayment in the event of a lack of response, suspension of instalments in the case of deferred payment).

In European practice, RWD for outcome-based MEAs is derived from a combination of:

- Hospital information systems (EHR) – strong on clinical details, but require standardisation and interoperability;
- Administrative/payment data (claims) – strong for tracking resources and costs, but often with limited clinical endpoints.
- National/indicator registries – most suitable because they are designed around specific criteria and endpoints, but require sustainable management and resources.

From a regulatory perspective, the EMA maintains a framework for the use of RWE, including through DARWIN EU, which aims to generate evidence from real-world practice more rapidly at European level. This supports the use of medicines (lifecycle evidence), but does not replace the national mechanisms required for value-based payment.

In Bulgaria, there is an institutional framework for monitoring the effect of therapy, administered by the National Centre for Public Health and Analyses (NCPHA), under which healthcare facilities collect information and provide it via automated transfer from hospital information systems. This is a key outcome in the context of ATMPs, as it essentially lays the groundwork for a shift from purely financial rebates to contracts with measurable outcomes, provided that appropriate endpoints are defined and data quality/auditability is ensured.

Bulgaria – regulatory and organisational mechanisms

Process map for inclusion and funding

As a result of this analysis, a process map has been reconstructed of the 'standard' pathway for access to innovative therapies (including ATMPs) in Bulgaria, as well as of the alternative/bridge channels in the absence of a sustainable reimbursement route. The map brings together the regulatory framework, public registers and published procedures of key institutions.

'Standard' pathway: marketing authorisation → OZT/price → PLS → negotiation → actual payment and application

Stage 1. Marketing authorisation and national regulatory oversight

The starting point is a centralised marketing authorisation at EU level, followed by national functions for supervision/import/distribution and pharmacovigilance via the BDA.

Stage 2. Health technology assessment and value assessment

For medicinal products with a new INN (and certain extensions), an HTA is prepared in accordance with the current framework, with the National Centre for Medicines and Medical Devices (NCMMD) playing the key institutional role in the Bulgarian model.

Stage 3. Price regulation/registration and inclusion in the Public List

This is followed by a decision on price/reimbursement status and inclusion in the PLS (public register), with inclusion in the PLS acting as a critical 'junction' determining the funding channel (e.g. payment by the NHIF, from hospital budgets or under specific schemes).

Stage 4. Negotiation and budgetary conditions (where payment is via the NHIF)

Actual payment often requires centralised negotiation of discounts/terms, as well as the implementation of a mechanism for budget predictability and sustainability (including methodologies for specific years). For ATMPs, this is a key stage as it manages budget risk, but may add time to access.

Stage 5. Actual implementation in clinical practice and reporting

The final stage includes: organisational readiness (centre/team), logistics (delivery/storage), clinical criteria, and reporting to the payer in accordance with the applicable payment rules.

Stage 6. Outcome tracking and post-marketing surveillance

For some therapies, an outcome tracking framework is activated, which is a prerequisite for managed access and outcome-based agreements, provided there is sufficient data quality and standardisation.

Branches by funding channel in the PLS

Branch A: PLS + NHIF (reimbursement)

Typically for products positioned for NHIF reimbursement (depending on the application/conditions). Requires compliance with Regulation No. 10/2009 and contractual terms/discounts where applicable.

Branch B: Hospital budgets (payment via healthcare facilities)

For hospital-based positioning in the National Health Insurance Fund and/or where the therapy is centre-dependent and requires hospitalisation/resources. Actual access is sensitive to internal limits and organisational capacity.

Branch C: Outside the scope of compulsory health insurance (individual mechanisms)

Where provision via standard routes is not possible, individual mechanisms under Article 82 of the Health Act apply, as detailed in Regulation No 2/2019 (including treatment in the country/abroad subject to conditions).

'Bridge' and additional channels

(1) Special order/treatment with unauthorised or unavailable products – Regulation No 10/2011 regulates the procedure for treating a specific patient with medicinal products not authorised for use in Bulgaria, via a special order for a hospital and associated regimens.

(2) Compassionate use – under certain conditions, compassionate use programmes are utilised, structured and coordinated in accordance with the procedure published by the BDA.

(3) Clinical trials – clinical trials remain an important channel for early access and the accumulation of experience, traceable through the BDA's public registers and the European framework (CTIS/Regulation).

Table 4 presents a possible flowchart.

Table 4. Flowchart

Stage	**Lead institution**	**Main outcome**	**Typical critical points for ATMPs**
1. Authorisation/supervision	EMA/EC; national – BDA	MA + national supervision	Post-marketing conditions; safety profile
2. HTA	NSCRLP (HTA framework)	report/summary + decision	high uncertainty; small population; comparator
3. Price + PLS	NSCRLP	inclusion in the PLS + application	channel selection (App. 1/2/3); deadlines
4. Negotiation	NHIF (where applicable)	discounts/terms + budget mechanism	lengthy negotiations; confidentiality; limits
5. Actual implementation	Hospitals/centres + payer	treatment + reporting	logistics; centre capacity; pathways/procedures
6. Monitoring	NSCRLP/IAL/NHIF	Outcome monitoring + adjustments	lack/incompleteness of RWD; auditability

Available tools for negotiating/controlling costs

The study shows that in Bulgaria, control of public expenditure on medicinal products is achieved through a combination of price regulations, negotiation of discounts and annual mechanisms for the recovery of excess funds, supplemented by tools for monitoring use/effect and regulatory conditions for payment.

Pricing instruments: price regulation and reference values

- External reference pricing (ERP) and rules for the regulation/registration of prices of medicinal products included in the Reimbursement List and paid for with public funds – regulated by the Ordinance on the Prices of Medicinal Products (Council of Ministers Decree No 97/2013 and subsequent amendments).
- Internal reference values and public parameters in the National Reimbursement List (including reference value/DDD and grouping by ATC/INN), which form the basis for controlling reimbursement levels and comparability within therapeutic groups.

Negotiation of rebates with marketing authorisation holders

Regulation No 10/2009 introduces the negotiation of rebates between the NHIF and marketing authorisation holders/authorised representatives as a central tool for reducing the net price and managing costs.

Mechanism for budget predictability and sustainability (payback/clawback in the event of overspending)

A key tool for cost control is the Mechanism ensuring the predictability and sustainability of the NHIF budget, applicable for the relevant year, which is supported by an annual Implementation Methodology. For 2025, the Methodology published at sets out the principle that holders of marketing authorisations for medicinal products, reimbursed in full or in part by the NHIF, shall reimburse the funds exceeding the specified target values in the NHIF budget (i.e. a 'payback' mechanism). The practical role of this instrument in high-value therapies is that it allows for:

- the prior definition of target funds/limits (at a systemic level);
- subsequent financial adjustment in the event of overspending through reimbursement from the PRU according to an algorithm described in the methodology for the relevant year.

'Terms and Conditions' and individual payment contracts

The NHIF publishes and applies the "Terms and Conditions" for the conclusion of individual contracts for the payment of medicinal products pursuant to Article 262(6)(1) of the Law on Medicinal Products for Human Use, including amendments published in the State Gazette (State Gazette No. 109/2024) and subsequent amendments/additions. These documents serve as a control mechanism through:

- standardised contractual clauses (parties, reporting, deadlines);
- formalised requirements for payment and document flow (which reduces variability and unforeseen costs).

Tracking the effect of therapy as a tool for managing uncertainty

A complementary tool with potential applicability in outcome-based risk-sharing agreements is the framework for monitoring treatment outcomes, administered by the NCPD. The published procedure explicitly states that healthcare facilities collect information on the specific medicinal product and provide it daily via automatic transfer from the hospital information system. This represents an existing RWD infrastructure that can support contractual decisions and subsequent reassessments. Table 5 summarises the available cost-control tools.

Table 5. Available cost control tools

Tool	**Type of control**	**Primary medium**	**Data type**	**Relevance to ATMP**
Price regulation/registration; ERP	Input price	NCPP (prices)	price references	high (but limited for orphan therapies)
PLS and reference values	payment levels/grouping	NSCRLP (PLS)	PLS/DDD/ATC	medium-high

Negotiation of rebates	net price	NHIF	Contractual/financial	High (the most widely used financial lever)
Mechanism + Methodology (payback in the event of overspend)	overall budgetary risk	NHIF	expense reports	high (systemic safeguard)
Individual contracts ('Terms and Conditions')	Procedural control/accountability	NHIF	contractual/administrative	medium (critical for implementation)
Outcome monitoring (RWD)	Uncertainty/real-world use	NSCRLP + LZ	clinical + administrative	potentially high (for outcomes-based)

Organisational capacity

The organisational capacity for implementing innovative therapies in Bulgaria is determined by three interrelated components:

(1) a hub model and concentration of expertise;

(2) infrastructure for monitoring outcomes in real-world settings;

(3) standardised reporting and data exchange.

The analysis shows that regulatory and organisational elements exist but are fragmented, whilst some highly specialised services suffer from capital and staffing shortages, which directly affect access to ATMPs.

Hub model: designated centres of expertise and concentration of expertise

In Bulgaria, there is an institutionalised mechanism for designating centres of expertise on rare diseases, reflected in a public register containing data on the healthcare facility, the head of the centre and the date of designation for specific groups of rare diseases. The register demonstrates a real concentration of expertise in university and highly specialised facilities (e.g. Alexandrovska University Hospital, Prof. Ivan Mitev Specialised Hospital for Paediatric Diseases, St. Naum National Hospital for Paediatric Diseases, UMHAT 'St. Marina' – Varna), which is fundamentally consistent with the requirements for the centralised administration of ATMPs.

The role of the Ministry of Health's Commission on Rare Diseases includes:

- issuing opinions on the inclusion of diseases in the list of rare diseases;
- proposals for the designation of centres of expertise;
- assessment of the activities of the National Register of Patients with Rare Diseases and of the centres of expertise/reference networks. This is an important organisational pillar, as ATMPs in Europe are concentrated precisely in rare and high-need indications, where the centre-based model is a prerequisite for safety, quality and control.

As a result, the existing centre mechanism is more advanced in the field of rare diseases, but does not in itself constitute specific ATMP accreditation. For ATMPs (particularly *ex vivo* cell therapies), additional functional criteria are required (equipment, 24-hour readiness, multidisciplinary teams, intensive care unit, supply chain), which are not standardised in Bulgarian public registers as a single centre passport.

The Bulgarian system has a legally defined tool for monitoring the effect of therapy as a source of real-world data, which is key to managed access and potential outcome-based contracts for highly uncertain and high-value therapies. Several organisationally significant requirements follow from the current regulations:

- Monitoring is carried out by inpatient care facilities and other healthcare facilities under the Healthcare Facilities Act, which have departments specialising in the relevant disease;
- Healthcare facilities ensure the integration of the hospital information system with that of the National Centre for Health Information (NCHI) within the specified timeframes and submit structured data on a daily basis for the monitoring of outcomes, which the NCHI collects, stores and analyses.

In applications/procedures relating to inclusion/change and when ordering outcome monitoring, the NHIF/MoH must specify in their opinion the healthcare facilities where the outcome will be monitored, as well as the conditions/criteria and the projected number of patients.

As a result, the monitoring of the effect represents an existing organisational mechanism for RWD, which can support negotiation, reassessment and the management of uncertainty. At the same time, the requirements for compatibility and daily data transfer make the system dependent on the digital maturity of hospital information systems and on the standardisation of endpoint definitions.

The National Health Information System (NHIS) is defined as a unified environment for the exchange of medical data, which sets a uniform format and codification of terminology in common nomenclatures. This is fundamentally relevant to ATMPs, as the monitoring of outcomes and contract reporting require interoperability and standardised data. Thus, the digital infrastructure exists as a foundation, but its application to ATMPs requires the targeted design of minimum datasets, auditability, and a link between clinical outcomes and payment events.

Public information from the National Health Insurance Fund (NHIF) regarding treatment options abroad explicitly states that payment may be justified where a multidisciplinary approach is required and where specialised centres are available, which are lacking in Bulgaria in certain areas (e.g. specialised centres for paediatric liver/kidney transplantation and stem cell transplantation in children). In the same context, an example is given of therapies/methods such as CAR-T cell therapy as part of the spectrum of highly specialised interventions that may necessitate treatment abroad. Thus, for some indications (particularly paediatric ones and/or those requiring exceptionally high technological and organisational readiness), centre capacity remains a constraint, transforming the problem of ‘ATMP funding’ into a problem of ‘funding + logistics + access to a centre’. Table 6 presents a matrix of readiness for ATMPs at the organisational level.

Table 6. ATMP readiness matrix at the organisational level

Domain	**Minimum elements at the centre**	**Available public support in Bulgaria**
Centre model	designated centre/structure by profile; multidisciplinary approach	register of centres of expertise on rare diseases; committee on rare diseases
Tracking (RWD)	defined criteria; IS compatibility; daily transfer	regulatory framework for monitoring the effect; requirement for interoperability and daily transfer

Reporting/interoperability	standardised formats; terminological nomenclatures; registries	NHSIS as a unified environment for exchange and standardisation; strategic framework for registries and EHR
Capacity deficits	lack of specialist centres in certain areas	NHIF criteria that explicitly indicate the absence of certain specialist centres

Trends in pharmaceutical expenditure and the role of innovation

Public expenditure on medicinal products (in the broad sense of the NHIF budget line for 'medicinal products, medical devices and dietary foods for special medical purposes') is among the most rapidly growing items in health insurance payments and represents a structural factor for the sustainability of the system. For the period 2019–2024, total expenditure and transfers as reported by the NHIF are set to rise from BGN 4,433.6 million to BGN 8,340.2 million (+88.1%), whilst expenditure on medicines and related products will rise from BGN 1,132.0 million to BGN 2,074.1 million (+83.2%) (Table).

Table 7. Trends in NHIF expenditure and the 'medicines, medical devices and dietary foods' category (2019–2024; reported data)

Year	Expenditure and transfers – total (million BGN)	'Medicinal products…' (million BGN)	Share of total expenditure (%)	Annual growth of the item (%)
2019	4,433.6	1,132.0	25.5	-
2020	4,738.2	1,246.2	26.3	10.1
2021	5,857.3	1,390.6	23.7	11.6
2022	6,373.9	1,524.8	23.9	9.7
2023	7,046.4	1,766.4	25.1	15.8
2024	8,340.2	2,074.1	24.9	17.4

Source: reported data and calculations based on published NHIF series.

The share of the medicines budget in total expenditure remains relatively stable (around 24–26%), but the absolute growth is significant. Following the acceleration in 2023 (15.8% compared to 2022), the growth rate is maintained in 2024, when the item increases by approximately 17.4% compared to 2023. In terms of the structure of health insurance payments, it is hospital care and medicinal products that make the largest contributions to the annual increase in absolute terms, which is an indicator of the concentration of cost pressures in technology-intensive and high-value segments (Figure).

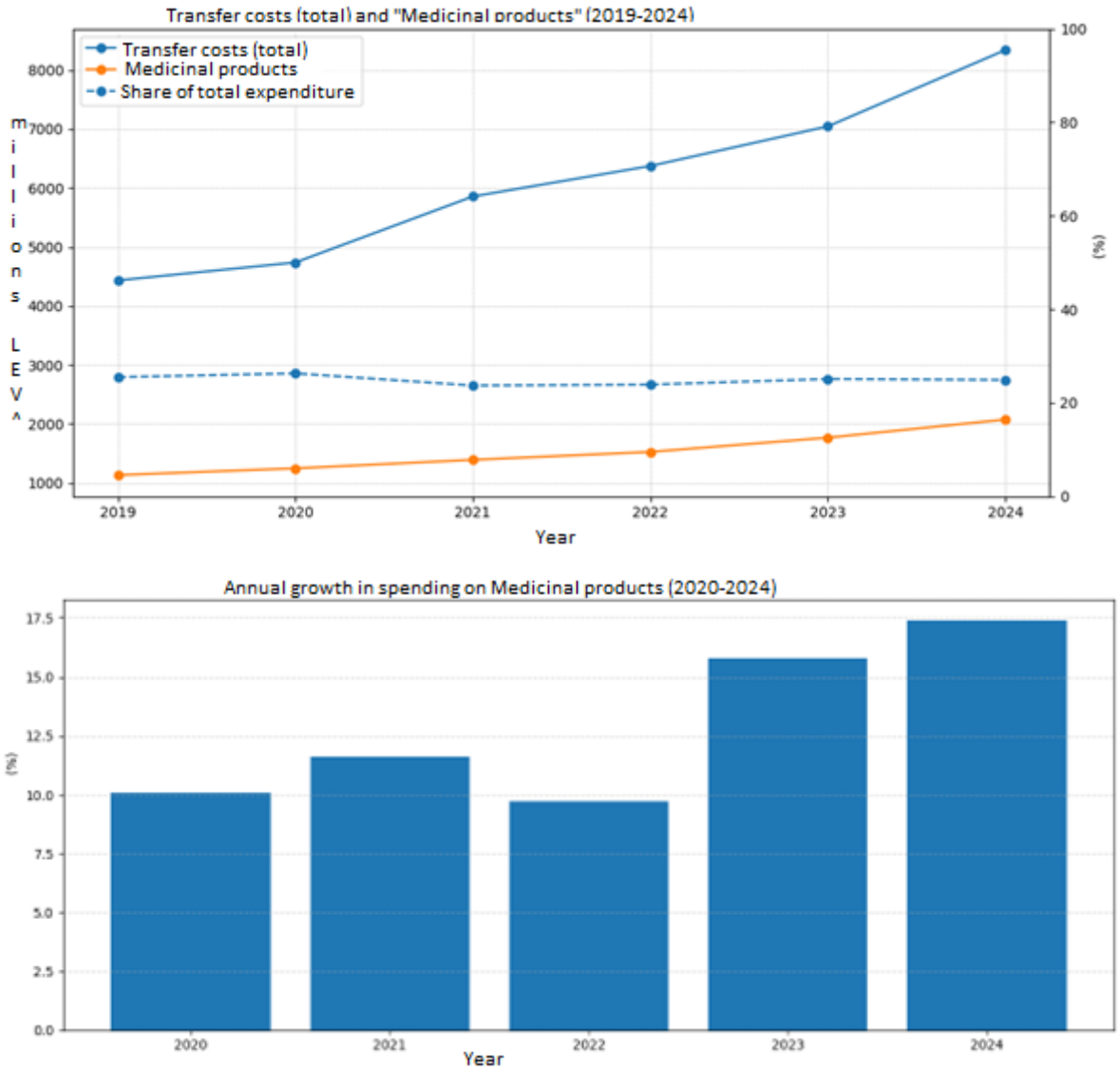

Figure 3. Chart for the period 2019–2024 for A: 'Expenditure and transfers – total'; B: 'Medicinal products…'.

In 2024, the net reported expenditure under line 1.1.3.5 reaches approximately BGN 2,074.1 million, which corresponds to around 24.9% of the NHIF's total expenditure and transfers for the year. Three cost-driving sub-components stand out in the implementation, which functionally represent the main part of innovative medicine consumption:

- Home treatment prescribed under a protocol (Medicines main group 'A') – reported expenditure of BGN 690.9 million (99.6% of the plan), an increase of +13.4% compared to 2023.
- Home treatment without a protocol (Medicines main group 'B') – reported expenditure of BGN 376.7 million (100% of the plan), an increase of +14.0% compared to 2023
- Medicinal products in hospital care, paid for separately from the cost of medical services (MPs in hospital care; main group 'C') – reported expenditure of BGN 899.3 million (99.8% of the plan), an increase of +18.5% compared to 2023.

The NHIF applies a 'Mechanism ensuring predictability and sustainability', under which net expenditure is calculated after deducting agreed discounts and reimbursements and is compared with provisional quarterly budgets by group; any overspend constitutes grounds for reimbursement by marketing authorisation holders. In the actual implementation for 2024,

overspends by group are documented on a quarterly basis (e.g. for Q3), which empirically confirms that cost pressures materialise during the year and require active financial management.

In terms of access to innovative health technologies, the highest growth rates in 2024 are reported precisely in the segments that typically include therapies with a high unit price and a high degree of innovation (oncology and haematology, rare diseases, biological products, etc.) – protocol-prescribed medicines and hospital-administered medicines outside the cost of the medical service.

For gene and cell therapies, this has direct implications: due to the method of administration and the need for specialised centres, monitoring and often hospital-based administration, a significant portion of potential future expenditure on ATMPs would be added to the already growing drug components in the BMP and/or the protocol segment, which increases the risk of a 'budget shock' in the event of one-off or short-term concentrated payments. The existence of a mechanism for predictability and reimbursement of cost overruns is an important tool for short-term management, but does not negate the need for specific funding models for ATMPs.

Options for financing high-value therapies

An analysis of public documents and registers reveals several channels actually used to fund high-cost therapies in Bulgaria, as well as a set of budgetary control instruments that determine the conditions and predictability of access:

(1) NHIF – home treatment under a protocol (highly specialised/innovative segment)

In the implementation of the NHIF budget for 2024, 'Medicinal products for home treatment prescribed under a protocol' (main group 'A') amounted to BGN 690.9 million, representing an increase compared to 2023, which empirically positions the protocol-based segment as the primary provider of high-value pharmacotherapy in outpatient care.

(2) NHIF – home treatment without protocol (mass market segment with partial innovative contribution)

'Medicinal products for home treatment without protocol' (main group 'B') amounted to BGN 376.7 million for 2024, also showing annual growth.

(3) NHIF – medicinal products in hospital care outside the cost of the medical service (key hospital innovation segment)

"Medicinal products in hospital care, paid for outside the cost of medical services" (main group 'B') are estimated at BGN 899.3 million for 2024, with this component being particularly relevant for therapies administered in hospital, with a high unit price and the need to organise specialist centres.

Contractual and budgetary control mechanisms

(1) Negotiating rebates as a standard financial instrument

The NHIF's public calls/procedures for negotiating rebates on medicinal products indicate that rebates are a systemic tool for reducing the net price and managing access when innovations enter the market.

(2) Mechanism for predictability and sustainability – payback/clawback

In its 2024 implementation, the NHIF accounts for expenditure by medicinal product group using a 'net' planning/control approach that takes into account discounts and clawbacks,

whilst the annual Methodology (for 2025) formalises the mechanism for recovering funds exceeding target values.

(3) Monitoring the effect of therapy as a prerequisite for managed access

The publicly described framework of the National Health Insurance Fund for monitoring the effect of therapy represents an existing infrastructural prerequisite for contractual models in which conditions can be linked to outcomes.

'Bridge' and individual channels in the absence of a standard reimbursement route

(1) Individual funding under Article 82 (Regulation No 2/2019)

Where treatment cannot be provided through standard mechanisms, an individual procedure for medical and other services under Article 82 of the Health Act (including treatment in the country or abroad subject to conditions) is used, which functions as a compensatory channel for highly specialised and/or interventions unavailable in the country.

(2) Special order/access to unauthorised or unavailable products (Regulation No 10/2011) and compassionate use

These mechanisms are used as interim solutions in specific clinical situations and are relevant for technologies with limited availability/logistics and delayed inclusion in standard channels.

(3) Clinical trials

Clinical trials represent an important early channel for access to and accumulation of experience with innovative therapies, particularly in university and highly specialised settings.

Table 8 presents the channels for funding and cost control for high-value therapies in Bulgaria.

Table 8. Channels for funding and cost control for high-value therapies in Bulgaria

Channel/mechanism	**Subject of funding**	**Main control instrument**	**Public document/report**
NHIF – protocol medicines (Group 'A')	High-cost therapies in outpatient care	protocols + discounts + budgetary mechanism	Budget implementation 2024
NHIF – hospital medicines not covered by the service (Group 'B')	hospital use, often innovative therapies	negotiation + sustainability mechanism	budget implementation 2024
NHIF – discounts	reduction in net price	contractual discounts	calls/procedures; regulatory framework
Sustainability mechanism (payback)	systematic control of overspending	recoveries in the event of overrun	Methodology 2025; reporting descriptions
Art. 82 / Regulation No. 2/2019	Individual cases/treatment abroad	individual approval and reporting	Regulation No 2/2019

Outcome monitoring (NSCRLP)	RWD for outcomes/use	criteria + data from healthcare providers	Procedure/guidance

Identified 'bottlenecks' in the budget/process

Based on an analysis of the NHIF's public reporting data, regulatory procedures (PLS/OZT) and regulatory documents for contracting and monitoring impact, several systemic critical points have been identified that limit predictability and timely access to high-value therapies.

(1) Concentration of cost pressures in segments relevant to innovation

The largest annual increases are observed in the protocol and hospital drug segments ('drugs in hospital treatment plans outside the cost of medical services'), which are the main drivers of high-value therapies. This narrows the budgetary scope for introducing new, one-off or highly concentrated costs, such as many ATMPs.

(2) Annual budget framework and risk of one-off high expenditure

The one-off high expenditure associated with ATMPs is structurally incompatible with traditional annual budgeting. Even with a small number of patients, payment may lead to in-year overspending and the need for compensation through the sustainability mechanism.

(3) Predictability and sustainability mechanism

The payback/clawback mechanism stabilises the budget at a systemic level, but where unit costs are high, it may shift the focus towards short-term financial controls (limits/ceilings) rather than towards an optimal model of deferred payment and/or payment based on outcomes. This increases the likelihood of administrative delays in the introduction of new therapies.

Several difficulties are also observed at the process level:

(1) A multi-stage decision-making process

The path to actual funding is sequential and dependent on numerous decisions and deadlines (evaluation, inclusion in the Reimbursement List, subsequent negotiation/payment terms). For therapies with high uncertainty and complex contractual parameters, this increases the time to access.

(2) Dominance of confidential financial rebates as the primary tool

Public discount procedures show that financial negotiation is central. With ATMPs, however, the financial discount alone often does not address the key risk (duration of effect), which creates a difficulty in the need for outcome-based risk-sharing agreements and the actual administrative readiness to implement such an agreement.

Barriers to data and monitoring (RWD/registers) include:

(1) Outcome monitoring

Regulations provide for the monitoring of treatment effects and the daily transfer of data from hospital information systems to the National Centre for Public Health and Analyses (NCPHA), as well as a requirement for compatibility within a short timeframe. In practice, this creates a risk of uneven readiness among healthcare facilities and potential gaps in data quality/completeness.

(2) Lack of 'standardised minimum data sets' by indication

For ATMPs, clearly defined endpoints and time windows (e.g. 6/12/24 months) are required, which are comparable across centres. When such standards are not unified, outcome-based payment becomes difficult to audit and administratively risky.

Critical organisational and logistical issues are:

(1) Limited capacity for certain highly specialised activities

It has been publicly noted that there is a lack of sufficiently specialised centres in the country for certain complex interventions and multidisciplinary care, which increases reliance on cross-border treatment and individual arrangements – a channel that is less predictable and more difficult to budget for.

(2) Supply chain and centre readiness

For *ex vivo* therapies (e.g. CAR-T), the organisational requirements (apheresis, cryopreservation, timely delivery, management of complications) necessitate a highly reliable infrastructure. In the absence of clearly defined ATMP accreditation for centres and a standardised service model, the process remains dependent on individual facilities and *ad hoc* solutions.

Time to access

For the purposes of the comparative analysis, the indicator 'time from central approval to availability' , defined as the number of days between the date of the EMA's marketing authorisation and the date on which the product becomes available to patients (in most countries, the moment of inclusion in the public reimbursement list). The data covers the period 2020–2023 (Table 9). It is important to emphasise that this indicator primarily measures the transition from EMA approval to national availability/reimbursement, but does not fully capture the final step of 'actual use'. This limitation is explicitly noted in the supplementary access analyses, which distinguish formal P&R processes from actual accessibility in practice.

Table 9. Average time (days) from EMA approval to national availability (2020–2023)

Country	**Average time to availability (days)**	**Difference from the EU average (578 days)**
Germany	128	−450
Italy	439	−139
Czech Republic	581	+3
France	597	+19
Poland	723	+145
Bulgaria	**768**	**+190**
Romania	828	+250

Bulgaria ranks among the countries with a high average lead time (768 days), which is 190 days above the EU average and significantly slower than early-access markets (e.g. Germany – 128 days).

To interpret 'time to market' more accurately, the delay needs to be broken down into two components:

- Time to price and reimbursement (P&R) filing by the marketing authorisation holder (MAH).
- Time from submission to reimbursement decision.

Aggregated data from the European Access Hurdles Portal show that, on average, 69% of the total time between EMA approval and reimbursement is attributable to the post-filing period (time to decision), and 31% to the pre-filing period by the manufacturer. In absolute

terms, this amounts to approximately 503 days in total, of which ~163 days are prior to submission and ~340 days are for the decision. The same analysis also reveals regional specificities relevant to Bulgaria – in Central and Eastern Europe, both the proportion and the absolute duration of delays are greater – for both the 'pre-submission' and 'decision' phases.

The observed longer time to availability (768 days) is consistent with a combined effect of:

- later/less frequent submission of dossiers in smaller markets;
- longer national evaluation and negotiation procedures.

In the case of ATMPs (gene/cell therapies), the gap between reimbursement status and actual availability/use is more pronounced due to manufacturing complexity, the supply chain, centralised organisation and traceability requirements. A European analysis of ATMP availability shows significant variability between Member States and highlights that central authorisation does not guarantee actual access, with the influence of MAH decisions and commercialisation capacity being key factors beyond P&R processes.

Availability of outcome-based contracts and registries

The comparative analysis shows that outcome-based contracts in the EU are applied selectively and to varying degrees, with the availability of registries and real-world data being the key limiting factor for scaling up. The OECD review highlights that this type of MEA is used less frequently than financial MEAs, with the most common design being payment for results at patient level, and CED being the second most common approach.

Italy is in a class of its own due to its institutionalised registry platform. AIFA registries enable the systematic implementation of contractual schemes over a long period (hundreds of registries), which addresses the key weakness of outcome-based approaches: implementation, auditing and comparability between centres.

The EU5 experience with CAR-T demonstrates the practical typology. In an EU5 analysis of schemes for two CAR-T therapies, different solutions are observed: CED in France/UK, reimbursement of funds in the absence of results in Germany, and payment of instalments in Italy/Spain. This empirically supports the view that pay-for-performance is not a single model, but a spectrum of contracts dependent on data capacity and early access policies.

The Bulgarian framework for monitoring the effect of therapy (NSCRLP) is structurally relevant to pay-for-results, but at present the publicly reported cost-control mechanisms are dominated by discounts and mechanisms for sustainability/recovery of excesses. This implies readiness (RWD), but also a need to further develop standardised definitions of outcomes by indication, rules for payment/reimbursement and audit, and data transparency.

Indicators of relative burden on the budget

Gene and cell therapies, as part of innovative therapies, pose a specific sustainability challenge for public payers due to the combination of very high costs per patient and limited predictability of the actual clinical effect over the long term. In cross-country comparisons, the direct comparison of net prices and actual amounts paid is methodologically problematic, as discounts and reimbursement schemes are often confidential. Therefore, this analysis employs an approach using ranges and proxy indicators, which allow for a comparable assessment of relative burden without claiming to provide exact net values.

Indicators (proxies) of budgetary sustainability

The following indicators, calculable from public international sources and national budget documents, are used:

- Share of expenditure on retail pharmaceuticals in total health expenditure (%): an indicator of structural displacement of other functions (outpatient care, prevention) in the event of a high pharmaceutical burden.
- Expenditure on medicines per capita (EUR PPP): approximates fiscal capacity and the level of consumption/prices at comparable price levels.
- Public coverage of pharmaceutical expenditure (%): an indicator of the extent to which risk is socialised (public payer) or transferred to households through co-payments/exclusions from the package.
- 'Single therapy' index (I_1): ratio of indicative ATMP price to per capita expenditure on medicines, i.e. how many person-years of average expenditure on medicines are equivalent to one therapy. For ATMPs, prices are considered as ranges typical for Europe:
    - CAR-T: approximately €0.28–0.42 million per dose (launch list price);
    - One-off gene therapies: around €1.9–3.0 million for individual products/indications.
- Illustrative share of the public pharmaceutical budget (%): (price × number of patients)/annual budget for medicines and related costs, where there is a publicly documented budget line. For Bulgaria, the framework of the NHIF budget can be used, where for 2025 the total budget is around EUR 4.7 billion, and 'medicines and medical devices' account for around EUR 1.2 billion (26.7%).

Country profile: medicines as a share and as expenditure per capita

Bulgaria stands out for its combination of an exceptionally high share of expenditure on medicines in outpatient settings (31% compared to the EU average of 13%), high per capita expenditure, close to the EU average, and low public coverage of medicine costs (below 25% in the profile), which signals systemic tension between demand, the benefits package and public resources (Table 10).

Table 10. Indicators of medication burden and coverage (2023)

Country	**Expenditure on medicines in outpatient settings (EUR PPP/capita)**	**Share of total health expenditure (%)**	**Note on coverage/co-payment**
Bulgaria	**644**	**31%** (highest in the EU)	Coverage from compulsory insurance **<25%**; OOP 36% of all healthcare expenditure
France	560	~13%	Very high public coverage ~**83%**
Poland	352	~16%	Limited coverage for outpatient medicines; ~**1/3** coverage of the cost of medicines in outpatient settings
Czech Republic	449	~15%	OOP ~39% (i.e. ~61% coverage)
Italy	539	~17%	High OOP share (around 42%)

Romania	~10% below the EU average (≈450–470)	**26**	Public coverage ~**50%**; high OTC share

Sources: official sites of paying institutions

'Single Therapy Index' and illustrative budget burden

- Index I_1 (indicative): for Bulgaria, at 644 EUR PPP/capita, a single CAR-T therapy costing 0.28–0.42 million EUR is equivalent to approximately 435–652 person-years of expenditure on medicines in the pharmacy network, whilst gene therapy costing EUR 1.9–3.0 million is equivalent to 2,950–4,660 person-years. This indicator does not represent the actual cost, but illustrates the massive disparity between expenditure per patient and the average drug expenditure within the system.
- Illustrative share of the NHIF's drug budget (Bulgaria, 2025), with 'drugs and medical devices' amounting to around EUR 1.2 billion per year:
    - 1 CAR-T patient/year (0.28–0.42 million) → 0.02–0.04%
    - 10 CAR-T patients/year → 0.23–0.35%
    - 1 gene therapy/year (1.9–3.0 million) → 0.16–0.25%
    - 10 gene therapy patients/year → 1.6–2.5%

Even with a small number of patients, the ranges indicate that ATMPs could account for a significant portion of annual growth or the innovation reserve, particularly in a system with an already high proportion of drug expenditure and limited public resources.

Summary of Bulgaria's comparative position

The comparison using proxy indicators supports the argument that Bulgaria is in a less favourable starting position compared to high-income EU countries due to a higher structural share of medicines in healthcare expenditure, lower public coverage and tighter budgetary scope for absorbing one-off high-value payments (Figure).

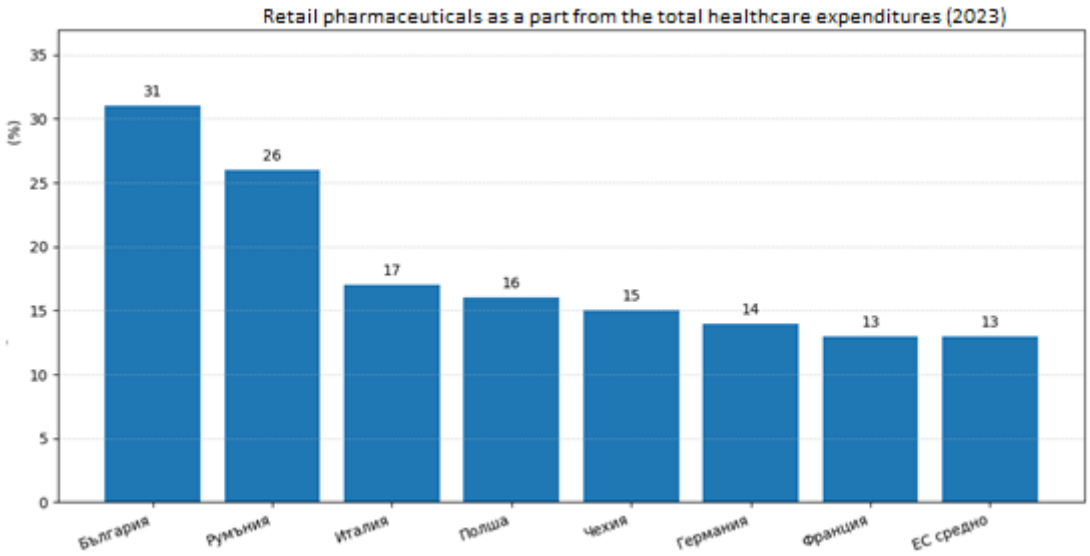

Figure 4. Share of retail pharmaceuticals in total healthcare expenditure in 2023 across different countries.

Scenario/model analysis for Bulgaria

Selection of example therapy/population and assumptions

For the purposes of the modelling analysis, CAR-T cell therapy is selected for adult patients with DLBCL following ≥2 lines of systemic therapy. The selection is justified by:

- the high unit cost of the therapy and its relevance to 'one-off'/concentrated payments;
- clinical significance – proven potential for long-term remissions in a proportion of patients (five-year follow-up in ZUMA-1);
- strong dependence on organisational capacity, which is a key limitation in the Bulgarian context.

Definition of the population and algorithm for estimating the number of patients (range)

The target population (base-case) consists of adults (≥18 years) with r/r DLBCL following ≥2 lines of therapy, suitable for CAR-T (medical criteria, functional status, organ function).

As public Bulgarian data on indications are limited, the number of patients is estimated using a stepwise algorithm with ranges:

- Baseline incidence of DLBCL: approximate crude incidence in Europe ~3.8/100,000/year (used as a proxy for Bulgaria).
- Population of Bulgaria: ~6.44 million (2024–2025).
- Expected new cases of DLBCL per year: 3.8/100,000 × 6.44 million = ~245 (rounded; proxy estimate).
- Relapse/refractoriness after first-line treatment: up to ~50% (upper limit).
- Proportion reaching and suitable for ≥3rd-line treatment and CAR-T: a range of 5–12% of newly diagnosed DLBCL cases is set as a working framework (reflecting limitations due to age, comorbidity, rapid progression, access to a centre, and patient dropout).

As a result, approximately 12–30 patients/year meet these criteria, with 15 patients/year assumed for the base case (a conservative-realistic value for the initial phase).

Selected therapy and clinical assumptions (efficacy and uncertainty)

The base-case scenario models CAR-T therapy with published long-term data, using key parameters from the clinical programme:

- objective response rate (ORR) 83% and complete response (CR) 58% at long-term follow-up;
- 5-year overall survival (OS) 42.6%.

In the model, the effect is introduced not as a precise forecast but as ranges for scenarios (optimistic/base/pessimistic), due to: differences between clinical trials and real-world practice, varying centre expertise and the inevitable heterogeneity of patients.

Prices and cost components – assumptions for budget modelling

The perspective of the analysis is that of a public payer (NHIF/public budgets), including direct medical costs. Due to confidential discounts, publicly available list/representative values and a 'discount' parameter are used in the sensitivity analysis.

<u>Cost of the medicinal product (CAR-T)</u>

- Publicly documented list prices/ranges in the EU are around EUR 307,200–350,000 for the first CAR-T products;
- in the German context (G-BA), a published value for axi-cel of ~€272,000 (as 'annual treatment costs per patient');

- Further analyses of pricing in Germany indicate that, upon market entry, prices range from ~€282,000 to €420,000 (per product).

Additional medical costs (non-drug)

- These are included as separate components: apheresis, 'bridging', lymphodepletion, hospitalisation, CRS/ICANS management, follow-up. Published estimates are used for calibration, according to which 'non-drug' costs associated with CAR-T therapy can add tens of thousands of EUR per patient (depending on the system/centre).

Fixed costs for launching the activity (centre capacity)

The 'introduction in Bulgaria' scenario includes a one-off component for organisational implementation (training, processes, IT integration, logistics), using published estimates of the cost of implementing CAR-T activity at the organisational level as a benchmark.

Scenarios

- Base case (current practice): treatment with standard regimens (rescue chemotherapy ± ASCT) and/or individual arrangements/referrals abroad in the absence of capacity, without systematic payment for results.
- Alternative scenarios:
    - Scenario A: introduction of CAR-T in Bulgaria with a standard upfront payment + financial discounts.
    - Scenario B: introduction with pay-over-time and contractual 'stop clauses' in the event of failure.
    - Scenario C: Outcomes-based payment with a predefined endpoint (e.g. CR/no progression at 12 months) and mandatory RWD follow-up.

Time horizon, scaling and key constraints

- Budget horizon (BIA): 3 years (standard for budget impact analysis), undiscounted.
- Capacity/'slots' (ramp-up): Year 1 – 10 patients; Year 2 – 15; Year 3 – 20 (indicative operational plan; sensitivity analysis required).
- Limitations:
    - lack of public Bulgarian indication registries with complete data;
    - confidential net prices;
    - variability in actual patient flow and centre readiness.

  Table 11 presents the assumptions for the base model.

Table 11. Assumptions for the base model

Parameter	Base case	Range (sensitivity analysis)
Population	6.44 million	6.3–6.5 million
DLBCL incidence	3.8/100,000	3.0–4.5/100,000
New DLBCL cases/year (proxy)	245	190–290
r/r after 1L	40	30–50%
Suitable for ≥3L CAR-T	15	12–30 patients/year
ORR / CR	83% / 58%	±10 p.p.
Cost of CAR-T product	€320,000	EUR 272,000–420,000
Additional costs (non-medicinal)	Parameter	20,000–80,000 EUR
Fixed start-up costs	Parameter	0.5–1.5 million EUR

Base case (status quo)

Under the status quo, patients are treated with existing standard approaches for r/r DLBCL: salvage systemic regimens and supportive/palliative care; in suitable patients, subsequent high-dose therapy with autologous stem cell transplantation (ASCT) where clinically feasible. In the literature, the outcome for r/r DLBCL following failure of second-line treatment is poor, which is a key motivation for ATMPs; however, in the baseline scenario, it is assumed that SoC remains the primary realistic option for a significant proportion of patients.

For a subgroup of patients, the status quo includes referral for treatment outside Bulgaria via the individual mechanisms under Article 82 (Regulation No 2/2019) – particularly where there is a case for a lack of the necessary specialist capacity or multidisciplinary approach within the country.

Clinical trials are an additional channel of access for some patients, but their scale is structurally limited by the availability of active centres and inclusive protocols during the specific period.

For the modelling part, a parameterised scheme is introduced that allows for analysis using ranges:

- Annual number of CAR-T candidates: N = 15; range 12–30).
- Distribution by channel in the status quo (assumptions for scenario analysis, subject to sensitivity analysis):
    - *p_BG* – proportion treated with SoC in Bulgaria: 60–90%
    - *p_ABR* – proportion treated abroad via individual arrangements: 10–40%;
    - *p_CT* – proportion included in clinical trials: 0–10%

where $p\_BG + p\_ABR + p\_CT = 100\%$.

These ranges reflect that the status of 'lack/insufficiency of specialist capacity' may redirect some of those in need to treatment abroad, but does not imply a mass export of cases due to procedural and organisational limitations of individual mechanisms.

The BIA model accounts only for direct medical costs from the perspective of the public payer. Under the status quo, these are grouped as follows:

(A) Costs of medicinal products and associated pharmacotherapy (C_DRUG_SoC) – including systemic therapies, maintenance medications, anti-infective prophylaxis, etc.

(B) Costs of hospital care and procedures (C_HOSP_SoC) – hospitalisations, diagnostic procedures, transfusions, management of complications, possibly ASCT (if administered to some patients), intensive care in the event of severe events.

(C) Follow-up and monitoring costs (C_FU_SoC) – outpatient and inpatient follow-up, imaging studies, laboratory monitoring.

(D) Costs of treatment abroad (C_ABROAD) – for p_ABR patients: sum of treatment costs under cross-border/individual mechanisms and logistical components, where relevant according to the specific protocol.

(E) Administrative/procedural costs (non-monetary effects) – in the BIA these are not directly monetised, but are described as a systemic burden: additional assessment/approval cycles, coordination with external centres, risk of delay.

Calculation formulas (annual and three-year values)

For year t (t = 1–3), total public expenditure under the status quo is defined as:

$$Cost\_SQ(t) = N(t) \times [p\_BG \times C\_BG\_SoC + p\_CT \times C\_CT + p\_ABR \times C\_ABROAD]$$

where:

$$C\_BG\_SoC = C\_DRUG\_SoC + C\_HOSP\_SoC + C\_FU\_SoC$$

C_CT (clinical trials) is generally low for the payer for the drug component, but is not zero for part of the diagnostics/services (depending on the contractual framework).
Cumulative over 3 years:

$$Total\_SQ(3y) = \Sigma\ Cost\_SQ(t)$$

As the status quo does not include a one-off ATMP payment, the cost profile is more spread out over time, but is susceptible to rising costs in the hospital drug segment and the protocol segment, which is already observed at an aggregate level in the reports. The parameters of the base case are presented in table 12 .

Table 12. Status quo parameters

Parameter	Base scenario	Range
N (applicants/year)	15	12–30
p_BG (SoC in Bulgaria)	0.75	0.60–0.90
p_ABR (treatment abroad)	0.20	0.10–0.40
p_CT (clinical trials)	0.05	0.00–0.10
C_BG_SoC	parameter	broad
C_ABROAD	parameter	broad

The baseline scenario is structurally linked to:

- lower predictability of access for the subgroup of patients dependent on individual mechanisms and cross-border treatment;
- pressure on the hospital pharmaceuticals segment, which is already showing accelerated growth at an aggregate level;
- suboptimal clinical outcomes for a proportion of the r/r DLBCL population following failure after second-line treatment, which is the main clinical argument for considering ATMPs as ‘innovative health technologies’ and for seeking specific funding models.

Alternative scenarios (deferred payment; pay-for-performance; special fund; combined model)

The alternative scenarios are designed as manageable financial and organisational models aimed at reducing the ‘upfront shock’/initial payment and limiting the risk to the public payer in the face of high clinical and economic uncertainty. They are comparable to the status quo and are based on European practices for MEA, outcome-based schemes and registry-based monitoring.

Scenario S1: Deferred payment (pay-over-time/annuity) with an optional ‘stop clause’
Objective: to transform the one-off expenditure on ATMPs into a multi-year cash flow that is more compatible with annual budgeting and reduces the risk of in-year overspending.
Contract design (example): the net price Pnet is divided into k equal (or indexed) instalments (k=3 or k=5); Optional: termination of payment in the event of proven failure (e.g. lack of response within 3 months or relapse within 12 months), which brings the model closer to the logic of payment for results.
Formalisation (for BIA, cash flow):

- interest-free: Pay(t)=Pnet/k;

- with interest/financing component r: Pay(t)=Pnet × a(r,k) (annuity factor), where r is tested in a sensitivity analysis (e.g. 0–3%).

Key requirements: minimum data for identifying the course, date of administration, survival/recurrence at interim points.
European practice: payment of instalments/deferral is described as an approach for CAR-T in some EU5 practices, including in Italy and Spain.

Scenario S2: Outcomes-based / performance-based MEA
Objective: to reduce the payer's risk by linking payment to predefined clinical endpoints in real-world practice.
Two operational subtypes:

- Payment-by-results (PbR) / money-back in the event of non-response – partial/full refund if the target outcome is not achieved at patient level.
- CED – provisional coverage subject to systematic generation of RWD and subsequent reassessment.

Example endpoints for CAR-T:

- interim: objective response/complete remission after 3 months;
- endpoint: progression-free survival (PFS) after 12 months / overall survival (OS) after 24 months.

Formalisation (step-up payment):
Payment is divided into tranches $\alpha 0$, $\alpha 1$, $\alpha 2$ (sum = 1), triggered upon meeting criteria:
$Paid = Pnet \times (\alpha 0 + \alpha 1 \cdot I12m + \alpha 2 \cdot I24m)$
where I12m, I24m are success indicators (1/0).
Data and control: Outcome-based MEAs are practically dependent on registries and auditable RWD.

Scenario S3: Special fund/budget corridor for innovation
Objective: to separate the financial risk of ATMPs into a centralised budgetary mechanism which:

- allows for the planning of 'slots' for patients (annual quotas);
- prevents crowding out of other expenditure in hospitals/the protocol segment;
- facilitates centralised contracting and coordination of centres.

Design:

- an annual 'corridor' B_{ATMP} (e.g. 0.3–1.0% of the medicines budget);
- centralised committee/expert panel for indications and criteria;
- centralised contracts (minimum financial MEA; optionally outcomes-based where data is available).

Link to existing instruments: the fund can operate in conjunction with the budget sustainability mechanism, but its aim is to reduce the frequency of in-year overspends and make expenditure predictable at system level (rather than compensating for it retrospectively).

Scenario S4: Combined model (fund + deferral + outcome-based payment)
Objective: to manage the three main risks associated with ATMP as effectively as possible:

- budgetary risk (initial lump-sum payment) → via a fund + payment in instalments;
- clinical uncertainty (duration/actual effect) → through outcome-based triggers;

- operational risk (centre readiness, monitoring, reporting) → through centralised rules and a registry.

Design:

- funding from Fund B $_{ATMP}$;
- annuity k=5 years;
- 'stop clause': cessation of future payments in the absence of a response within 3 months or recurrence within 12 months;
- mandatory registry/monitoring: minimum data set + audit.

European practice: in the EU5 context, combinations of instalment payments and outcome-based payments are described (e.g. Italy/Spain), and Italy is a reference example of institutionalised registries that enable the systematic implementation of contractual schemes.

Table 13 presents the parameters of the various scenarios.

Table 13. Scenarios – key characteristics

Scenario	What it addresses best	Main weakness	Minimum data
S1 Deferral	Budgetary predictability	does not fully address uncertainty	Baseline status/monitoring
S2 Outcome-based payment	clinical/economic uncertainty	need for a registry and audit	patient-level outcome
S3 Special fund	systemic predictability and 'corridor'	risk of underfunding/quotas	Aggregated + criteria
S4 Combined	simultaneous budget + result + organisation	most complex to implement	full RWD package

Expected budgetary impact and organisational requirements

The assessment is from the perspective of the public payer (NHIF/public budget) with a 3-year horizon. Due to the confidentiality of net prices, an approach using ranges and illustrative base values is employed, which are subject to sensitivity analysis.

Base-case assumptions:

- Number of patients treated with CAR-T in Bulgaria during the patient ramp-up: 10 (Year 1), 12 (Year 2), 15 (Year 3).
- Net product price Pnet: EUR 256,000 (visible public price EUR 320,000 with a 20% net reduction – parameter).
- Additional direct costs (apheresis, hospitalisation, complications, monitoring): EUR 50,000 per patient (parameter).
- One-off start-up organisational costs (training, processes, IT integration, logistics): EUR 1,000,000 (Year 1; parameter).
- Currency conversion for presentation: 1 EUR = 1.95583 BGN (fixed exchange rate).

Table 14 presents the expected budget payments under four alternatives compared to the status quo. In the outcome-based model and the combined model, payments are 'spread out' and conditional; therefore, the results are interpreted as expected values given specified probabilities of success.

Table 14. Expected budgetary impact by scenario (EUR million; in brackets – million BGN)

Scenario	Year 1	Year 2	Year 3	Total 3 years	Comment on 'hidden' liabilities after the third year

SQ (status quo)	parameter	parameter	parameter	parameter	Depends on the proportion of treatment provided in abroad/individual schemes and the cost of SoC; used as a baseline.
S0 Upfront (one-off payment)	4.06 (7.94)	3.672 (7.18)	4.59 (8.98)	12.322 (24.10)	No future liabilities, but there is a risk of a high initial payment and in-year overspends.
S1 Deferral (5-year payment with no payment for results)	2,012 (3.94)	1,726 (3.38)	2,644 (5.17)	6,383 (12.48)	Low 3-year costs, but accumulates future liabilities: ~€5.94 million (BGN 11.61 million) in unpaid contributions after year 3.
S2 Pay-for-performance	2.78 (5.44)	2.482 (4.86)	3.264 (6.38)	8.526 (16.68)	Reduces expected expenditure but requires records; a conditional payment of approximately EUR 1.00 million (BGN 1.96 million) remains after year 3 (mainly 24-monthly instalments).
S4 Combined (deferral + discontinuation of treatment if unsuccessful after 12 months)	2,012 (3.94)	1.445 (2.83)	2.025 (3.96)	5,482 (10.72)	Lowest 3-year costs under specified assumptions; future contingent payments after year 3 ~€2.67 million (BGN 5.23 million). Requires high auditability.

Notes on the calculations (transparency of assumptions):
S0 Upfront: (Pnet + Cother) × N(t) + Cstartup for year 1.
S1 Deferred payment: Pnet/5 is paid annually for each 'active' contract + Cother in the year of implementation + Cstartup in year 1.
S2 Outcomes-based: example design α0 = 50% upfront, α1 = 30% upon success at 12 months, α 2 = 20% upon success at 24 months; baseline p12 = 0.45, p24 = 0.35 (parameters).
S4 Combined: 5-year instalment plan, with payments after 12 months continuing only in the event of success – a combination of an annual payment and payment for achieved results.

With a pharmaceutical budget of around ~1–1.2 billion EUR per year for Bulgaria, the expected annual costs for the baseline programme (10–15 patients) are in the range of ~0.1–0.5% of the pharmaceutical budget (depending on the scenario and price), but are highly sensitive to the number of patients and the net price.

Link between budgetary impact and organisational model

With ATMPs, expenditure and organisation are inseparable: the chosen financial model determines what data is needed, what reporting is required and how quickly the programme can be scaled up.

Deferral (S1) optimises costs but creates multi-year liabilities, which requires budgeting beyond the one-year horizon and clear accounting treatment (analogous to a 'capital commitment').

The outcome-based model (S2) reduces expected expenditure and addresses uncertainty, but shifts the cost to administrative and tax capacity (registers, audit, definition of endpoints).

The special fund (S3) (as an organisational framework) does not alter the cost per se, but makes expenditure predictable and sets aside a corridor for innovation, which is particularly important in a growing hospital pharmaceutical segment.

The combined model (S4) is best suited for risk management, but places the greatest demands on the system.

Organisational requirements by scenario

(A) General minimum requirements (applicable to all scenarios)

Centre-based model (1–2 national centres in the initial phase):

- multidisciplinary team (haematology/oncology, transfusion haematology, intensive care, infectious diseases, clinical pharmacy);
- capacity for apheresis, lymphodepletion, 24/7 readiness to manage CRS/ICANS and access to intensive care;
- standardised protocols and patient pathway: referral → assessment → apheresis → bridging therapy → infusion → early monitoring → long-term follow-up.

Supply chain and identity control:

- transport/cryologistics contracts and procedures for product receipt/release;
- clear SOPs for incidents and deviations.

Pharmacovigilance and safety monitoring:

- reporting of serious adverse reactions and integration with national surveillance (IAL).

(B) Specific requirements for an outcome-based model and a combined model (S2/S4)

Registry infrastructure and RWD:

- defined endpoints and time windows;
- minimum data set and validation/audit rules.

Integration with existing national post-marketing surveillance mechanisms

Contractual and administrative capacity:

- mechanism for verifying final results and triggering payment/reimbursement;
- independent audit (internal/external) to minimise disputes regarding implementation.

(B) Specific requirements for a special fund (S3)

Centralised management of indicators and quotas (‘slots’):

- criteria for inclusion, prioritisation and transparent rules where resources are limited.

Centralised contracting and reporting:

- the fund can provide better predictability and reduce fragmentation between hospitals.

In conclusion, the lowest short-term budgetary pressure is achieved through deferral, but the cost is a hidden multi-year commitment. The best management of uncertainty is achieved with outcome-based/combined models, but only if there are functioning registries, RWD and audit (i.e. organisational capacity). A special fund/corridor is the most appropriate organisational approach for the first 3–5 years, as it allows for planning, centralisation and better compatibility with financial control, which is already highly active within the system.

Sensitivity analysis

The aim of sensitivity analysis is to assess the robustness of the conclusions when key parameters vary; in the context of ATMPs, these are typically uncertain: net price (after discounts), actual number of patients, additional medical costs, and probabilities of treatment

success. This is methodologically necessary, as contractual discounts for high-cost therapies are often confidential, and outcome-based MEAs are highly dependent on the availability of reliable RWD and registries.

Three complementary approaches were used:

- One-way analysis – changing a single parameter within a predefined range whilst keeping other assumptions fixed.
- Probabilistic (multi-way) analysis – 'optimistic' and 'pessimistic' sets of assumptions (combinations) to assess the potential variation in budgetary impact.
- Threshold assessment – determining the maximum number of patients/maximum net price within a given budget corridor (e.g. a special fund), with a view to practical applicability to the management of limits and quotas.

Table 15 shows key parameters and ranges

Table 15. Sensitivity parameters

Parameter	Base-case	Range	Justification for uncertainty
Net product price (Pnet)	EUR 256,000	EUR 200,000–420,000	Unknown net price (confidential discounts/schemes)
Additional costs (Cother) (apheresis, hospitalisations, complications)	EUR 50,000	€20,000–€80,000	Variability by centre/complications
Patients/year (ramp-up)	10/12/15	8/10/12 to 20/24/30	Uncertain flow + organisational capacity
Start-up costs (Cstartup)	EUR 1.0 million	EUR 0.5–1.5 million	Varying scale of preparation/IT integration
Probability of success at 12 months (p12) (for outcome-based/stop-clause)	0.45	0.30–0.60	Differences between RCT and real-world practice
Probability of success at 24 months (p24) (for outcome-based)	0.35	0.20–0.50	greater uncertainty in the long term
Duration of deferral (k)	5 years	3–5 years	trade-off between 'cash-out now' and future liabilities

One-way analysis

With a 3-year BIA horizon, two indicators dominate:

- Number of patients (N) and net price (Pnet) – the greatest impact across all scenarios, including the deferred payment and combined models.
- Additional medical costs (Cother) – a secondary but significant factor, particularly for hospital-oriented ATMPs.

In the outcome-based scenario, the 12-month probability of success (p12) has a significant impact on expected payments, whilst p24 has a smaller effect over the 3-year horizon (part of the payments are 'deferred' beyond year 3).

Under the various scenarios, the total expenditure over 3 years (EUR million) with the other parameters held constant is:

- Initial payment (S0):
  - at Pnet=200-420k: 10.25-18.39
  - with ramp-up 8/10/12 to 20/24/30: 10.18–23.64
- 5-year instalment plan (S1): 5.61–8.65 (for the Pnet range), whereby lower expenditure over 3 years results in higher future liabilities.
- Outcome-based model (S2): 7.28–12.16 (for the Pnet range); for p12 = 0.30–0.60, the total varies approximately between 8.27 and 8.78.
- Combined model (S4): 4.91–7.17 (for the Pnet range); it is also sensitive to k (3 years versus 5 years), because the shorter time horizon increases payments within the BIA horizon.

Probabilistic sensitivity analysis

To assess the actual extent of the budgetary impact, a set of assumptions is tested:

- Optimistic set: low net price, low incremental costs, low number of new patients, low start-up costs, lower p12/p24 (lower expected reimbursement rate under outcome-based payment).
- Pessimistic set: high net price, high additional costs, rapid uptake by new patients (higher volume), high start-up costs and a shorter deferral period (higher expenditure over 3 years).

The total 3-year cost may vary approximately:

- S0: ~7.1 to 38.5 million EUR
- S2: ~4.5 to 27.1 million EUR
- S4: ~€2.6 to €23.2 million

These wide ranges demonstrate that access management requires not only a model, but also an active pricing/contractual policy and volume governance.

Threshold estimate for a budget corridor (fund)

For a fund/corridor with a pre-fixed annual resource B, the threshold for the maximum number of patients in year 1 (when there are start-up costs) can be expressed as:

$$N_{max} = \left\lfloor \frac{B - C_{startup}}{P_{net} + C_{other}} \right\rfloor$$

For example, with B = BGN 10 million per year and a base-case scenario (Pnet + Cother), this gives an order of magnitude of ~13 patients in the first year (due to the inclusion of start-up costs), and more in subsequent years (once Cstartup is eliminated). This type of threshold logic is useful for designing quotas/slots and for managing the risk of intra-year overspends, which are particularly sensitive in the 'hospital medicines outside the cost of the medical service' segment, where the pressure for innovation is concentrated.

Organisational sensitivity

The most significant non-financial sensitivity is the quality and completeness of the data:

- if there is a lack of interoperability/daily data transfer/data validation, outcome-based and combined models become unauditable and are effectively reduced to purely financial rebates;

- if the number of centres is too small or the capacity for complex cases is limited, the number of new patients effectively decreases, which reduces short-term expenditure but increases the time to access and the need for treatment abroad through individual mechanisms.

In conclusion, the sensitivity analysis shows that control of volume (N) and net price (Pnet) are crucial for budgetary sustainability, whilst RWD/registry capacity is crucial for determining whether outcome-based/combined models are realistically applicable in Bulgaria.

DISCUSSION OF THE RESULTS

Interpretation of the results in the context of the international literature

The results of the analysis confirm the structural dilemma described in the international literature regarding gene and cell therapies — the high potential clinical value (including the possibility of a long-lasting effect) is accompanied by one-off/concentrated costs and uncertainty regarding the effect in real-world conditions, which makes classic pricing/reimbursement models difficult to apply without adaptation. It is precisely for this reason that managed access schemes (MEA) and, less frequently, performance- or outcomes-based MEA are being adopted in practice, with the OECD emphasising that the latter are more limited due to administrative burden and the need for reliable data.

The comparative result for time to availability (EMA → national availability) places Bulgaria among the countries with longer lead times relative to the EU average on the W.A.I.T. indicator, which is consistent with the thesis of 'lagging' small markets and longer national P&R processes. At the same time, Bulgaria's profile in the State of Health in the EU reveals a particularly unfavourable combination: the highest share of expenditure on medicines in the EU and the lowest public coverage for outpatient medicines, which naturally heightens budgetary sensitivity to ATMPs and increases the risk of unequal access.

Financial instruments (discounts/control mechanisms) dominate the studies, whilst outcome-based approaches are emerging as desirable but difficult to scale up. This is fully in line with the OECD review: outcome-based MEAs are used less frequently and most often in pay-for-performance or CED designs, as they require defined endpoints, monitoring and auditability. Separately, experience with one-off high-value therapies (including CAR-T) in major European markets shows that outcome-based approaches and instalment payments can work, but are highly dependent on institutional infrastructure and clear implementation rules.

International practice cites Italy as an example of the systematic application of outcome-based models and risk-sharing schemes through national registries (AIFA registries). In the Bulgarian context, there is a regulatory and organisational framework for monitoring the effect of therapy and for the automated transfer of data from hospital information systems to the National Centre for Public Health and Analyses (NCPHA), which is an important prerequisite for future outcome-based contracting. The difference is that in order to move from 'data collection' to outcome-based payment, the following are required:

- standardised endpoints by indication;
- validation/audit rules;
- a clear procedure for how the outcome triggers payment/reimbursement – components that the international literature identifies as key conditions for functioning OBR models.

The model outcomes (pay-over-time; results-based; special fund; combined model) are logically consistent with international findings:

- Deferral (pay-over-time/annuity) reduces short-term budgetary pressure but shifts the risk to multi-year liabilities, which requires specific budgeting and accounting treatment – an issue also discussed in the experience of countries that have experimented with payment of contributions for CAR-T/gene therapies.
- Outcome-based approaches reduce the risk of 'paying for failure', but are administratively burdensome and data-dependent.
- A special fund/corridor can be interpreted as a tool for systemic predictability and protection against the displacement of other costs. This type of organisational solution

is particularly relevant for Bulgaria given the high relative pharmaceutical burden and low public coverage, which limit the buffers for absorbing ATMPs.

- A combined model (fund + instalments + outcome indicators) corresponds to best practice in the literature for one-off therapies, but is only realistic where established registries and a clear division of responsibilities exist.

The introduction of the JCA under Regulation (EU) 2021/2282 has the potential to reduce duplication of clinical assessment and support national HTA processes. This may improve the consistency of the clinical part of the assessment for ATMPs, but does not in itself resolve the key issues for Bulgaria – budget sustainability, contractual mechanisms, and infrastructure for monitoring and outcome-based payment.

Specifics of the Bulgarian model

Bulgaria is characterised by an unfavourable starting point for integrating high-cost innovations: a high relative share of expenditure on medicines and low public coverage of outpatient medicine costs, which systematically increases the risk of crowding out other healthcare activities and of unequal access upon the introduction of ATMPs. This is reinforced by the observed cost dynamics in innovation-intensive segments (protocol medicines and medicines in hospital care excluding the cost of medical services), which have shown marked growth in recent years.

The Bulgarian model for access to innovative therapies is multi-stage and sequential (assessment/decision → inclusion in the National Reimbursement List → negotiation/terms → actual implementation), which increases the risk of cumulative delays. This is reflected in the comparative indicators for time to availability (EMA → national availability), where Bulgaria is among the lagging countries in the EU. Furthermore, international analyses show that part of the delay is also due to the period until the manufacturer submits a P&R dossier, which is typically more pronounced in smaller/lower-income markets – a structural problem that Bulgaria cannot resolve solely through internal procedural optimisations.

The system has powerful tools for short-term cost containment: centralised negotiation of discounts and a mechanism for budget predictability and sustainability (including annual methodologies and clawbacks in the event of overspending). The critical issue is that these tools primarily address price/volume risk, but do less to address the fundamental characteristic of ATMPs – uncertainty regarding the duration of the effect. This creates a structural tension: the system can control expenditure financially, but there is limited experience and public visibility regarding genuinely results-based implementation.

ATMPs pose a problem of inter-budgetary compatibility: a one-off expenditure or deferred payment creates a multi-year financial commitment that is difficult to fit within annual limits and quarterly control mechanisms. The practice of reporting on a quarterly basis and managing overspending is effective for conventional therapies, but with ATMPs it may induce restrictive behaviour (delays/quotas) rather than optimising payment models.

Hospital medicines, paid for separately from the cost of medical services, are both a critical channel for high-value therapies and an area of the greatest budgetary pressure. With ATMPs (particularly *ex vivo* therapies), the centre-based model and hospital administration imply that a significant proportion of future expenditure will be concentrated there, increasing sensitivity to in-year overspending and the need for centralised coordination.

Bulgaria has a regulatory and organisational framework for monitoring the effect of therapy and a mechanism for transferring data from hospital information systems to the

National Centre for Public Health and Analyses (NCPHA). This is a real prerequisite for CED and for outcomes-based contracts. The critical limitation is that these contracts require not merely data collection, but standardised endpoints, validation, auditability and comparability between centres. With uneven interoperability and data quality, the result is 'pseudo-outcome' contracting (in practice, financial), which the literature regards as a typical reason for the limited uptake of this type of MEA.

The existence of designated centres of expertise for rare diseases and functioning committees provides a strong foundation for a centre-based model. However, ATMPs (particularly CAR-T) require specific operational criteria (24/7 management of complications, ICU capacity, cryopreservation, tracking of the product from manufacture to administration) which are not standardised as a single 'ATMP accreditation'. For some highly specialised interventions, the public framework acknowledges a lack of sufficient capacity within the country and permits treatment abroad through individual mechanisms – which in practice makes access 'case-by-case' and hinders planning.

The combination of high drug costs, low public coverage and concentration in centres leads to an increased risk of unequal access (geographical and social), particularly if ATMPs are introduced via limited quotas or through individual mechanisms. This makes transparent inclusion criteria, publicly reported indicators (without disclosing confidential prices) and mechanisms for second opinions/appeals critically important.

Barriers and solutions

Legal and regulatory barriers

- A multi-stage and sequential regulatory pathway (assessment/decision → PLS → negotiation → actual implementation), which takes time and requires coordination between institutions. This is a prerequisite for the longer time-to-availability observed in Bulgaria compared to other European indicators.
- Lack of an ATMP-specific conditional framework at national level to define accelerated steps in cases of high unmet need (analogous to CED/early access in some countries), without compromising safety and control.
- Regulatory uncertainty regarding multi-year contracts (pay-over-time) – even when permissible as a contractual arrangement, they require clear budgetary/accounting treatment and rules on continuity in the event of a change in the status of the patient/payer.
- Limited public formalisation of outcome-based contracting – general tools are available (rebates, resilience mechanisms), but this type of MEA requires legal and procedural definition of: outcome, verification method, audit, deadlines, and procedures for reinstatement/termination.

Decisions

- Establishment of a national 'ATMP pathway' (procedural standard) describing the critical steps, deadlines and responsibilities between the NHIF, the Ministry of Health, the National Centre for Public Health and Preventive Medicine, the Bulgarian Drug Agency and the centres – with a clear distinction between regulatory availability and actual application.
- Introduction of a CED framework as a regulatory/procedural solution for therapies with high uncertainty: provisional coverage + mandatory registry + pre-planned reassessment (e.g. 18–24 months).

- Legal and methodological clarification regarding the payment of contributions: eligibility, minimum clauses, rules on migration/death/loss of follow-up, link to the sustainability mechanism.
- Alignment with the European HTA framework, so that national efforts focus on budget assessment, negotiation and organisation (rather than duplicating clinical assessment).

Financial and contractual barriers

- Upfront payment for one-off therapies and annual budgeting → risk of in-year overspending and restrictive management (quotas/delays).
- Dominance of discounts and rebates in the event of overspending as the main control tools – effective for price risk, but insufficient for the uncertainty regarding the durability of the effect with ATMPs.
- Limited buffers due to high relative drug burden and low public coverage of drug costs.
- Volume risk (unpredictable number of candidates with pent-up demand) and lack of a sustainable volume management model.

Solutions

- A combination of 4 financial elements (adaptation of international practices to Bulgaria):
    - basic financial MEA (discount/price-volume);
    - deferred payment (annuity/pay-over-time);
    - suspension of payment in the event of failure (performance-based hybrid);
    - budget corridor/innovation fund.
- Special fund/corridor for ATMPs with transparent eligibility rules and limits – separates the risk from general hospital budgets and allows for 'slot' planning.
- Volume reference thresholds and automatic triggers: upon reaching a certain number of patients or expenditure (e.g. 0.3% of the pharmaceutical budget), additional discounts/reimbursements or a temporary freeze on new cases pending review should be activated.
- Operational 'cost map' for ATMPs (product + hospital costs + complications) as a condition for negotiation, to avoid underestimating non-financial components (ICU, toxicities).
- Alignment with the sustainability mechanism – defining whether and how ATMP costs are treated within the mechanism (exclusion, separate group, separate limit) to avoid discouraging implementation through systemic fear of overspending.

Organisational and logistical barriers

- Insufficient critical mass of centres meeting the full range of ATMP requirements (24/7 toxicology, ICU, apheresis, cryopreservation, multidisciplinary approach).
- Lack of formalised ATMP accreditation and standardised SOPs for process management and handling complications.
- Reliance on treatment abroad for some highly specialised services due to a recognised lack of specialised capacity in the country – this reduces predictability and hinders planning.
- A complex supply chain and logistical risk that is atypical for conventional medicines.

Solutions

- Start with 1–2 national centres (pilot) with clear functional criteria and subsequent expansion following evaluation (learning phase).
- ATMP accreditation criteria (national standard): centre capacity, training, minimum number of cases, ICU arrangements, CRS/ICANS algorithms, logistics and pharmacovigilance.
- Logistics contracts and quality: certified operators, monitoring, contingency plans in the event of deviations.
- Scenarios for cross-border care: whilst capacity is being built, there should be formalised rules on when treatment abroad is used, to minimise inequalities and delays.

Data, registries and outcome tracking – barriers

- Insufficient standardisation of endpoints and datasets by indication, making outcome-based models difficult to implement
- Uneven digital maturity among healthcare facilities and the risk of incomplete or delayed data
- Limited auditability
- Legal and technical data protection requirements (GDPR, information security) – risk of delays in integration.

Solutions

- Operationalisation of outcome tracking as an ATMP registry
- The Bulgarian framework provides for the collection of information and its transfer from hospital information systems to the National Centre for Public Health and Analyses (NCPHA). This should be enhanced by:
    - defining a minimum data set by indication;
    - standardised definitions of response/relapse/PFS/OS;
    - automatic checks for quality and missing values.
- CED as an interim solution – temporary coverage + RWD + reassessment (e.g. 24 months).
- Audit model: independent verification of results for payment (committee/external auditor), audit trail and transparent rules for missing data.
- Interoperability: technical specifications and a testing period for hospital information systems; minimisation of manual forms and duplication.
- Public reporting indicators (excluding confidential prices): number of patients treated, follow-up, safety, key outcomes by score.

Optimal funding models

The proposal for Bulgaria is based on a phased approach: starting with feasible financial and administrative solutions (short term), moving to structured contractual schemes and centralised implementation (medium term), and achieving a sustainable architecture that combines predictability, results-based payment, and institutionalised generation of real-time data (long-term).

Minimum package (short-term measures, 6–12 months)

Objective: rapid establishment of a working risk management framework and preparation for pilot implementation, without waiting for full regulatory maturity.

1. National ‘ATMP pathway’ (procedural standard)

- A concise and clear process map: selection criteria, centre competence, timetable for decision-making and negotiation;
- definition of the roles of the NHIF/MoH/NSCRLP/BDA and the centres.

2. Pilot centre model (1–2 centres) with minimum readiness criteria

- ICU access; 24-hour protocol for complications; multidisciplinary team;
- training programmes and initial audit ('learning phase').

3. Financial instruments that are easy to implement
    - financial MEA (discount + volume-based pricing);
    - volume control (quotas/slots);
    - clear treatment within the sustainability mechanism (separate sub-group/limit) to avoid blocking implementation due to fear of exceeding limits.
4. Minimum RWD package

- minimum data for identifying the course, date of administration, baseline characteristics, key short-term outcomes (e.g. 3 months) and safety;
- use of the existing framework to track the effect of the therapy.

Expected outcome (6–12 months): a functional pilot with volume control, partial predictability of expenditure and technical readiness for upgrading to outcome-based models.

Medium-term model (1–3 years)

Objective: transition from pilot to sustainable funding by combining a predictable budget corridor, instalments and an initial outcome-based mechanism (CED/stop-clause).

1. Establishment of a budget corridor/special fund for ATMP
    - annual allocation + rules on quotas by indication;
    - centralised contracting and publicly accountable indicators.
2. Pay-over-time as a basic cash-flow instrument
    - 3–5-year annuity;
    - contractual clauses in the event of loss to follow-up/death/migration;
    - accounting planning for future commitments.
3. CED as the standard in cases of high uncertainty (particularly for new indications)
    - temporary coverage + mandatory registry + reassessment (18–24 months);
4. Standardisation of endpoints and minimum data requirements by indication
    - definitions for response/relapse/PFS/OS;
    - validation algorithms and rules for missing data;
    - audit mechanism (internal/external) for result verification.
5. Expansion of the network of centres (if necessary) and capacity plan
    - criteria for opening a second/third centre (volume, quality, safety);
    - contractual requirements for reporting and training.

Expected outcome (1–3 years): predictable expenditure (fund/corridor), reduced short-term pressure (deferral) and control of uncertainty (CED + initial, outcome-based triggers).

Long-term architecture (3–5 years)

Objective: an institutionalised, mature model in which ATMP funding is sustainable and managed through data, audit and adaptive contracts.

1. Established, performance-based model (performance-based MEA) for selected ATMPs
    - staged payment (0-12-24 months) or reimbursement of funds spent in the absence of a response;

    - clear rules for verifying outcomes and a mechanism for reimbursement/termination;
    - independent audit and transparent dispute resolution procedures.
2. National ATMP Registry Platform (indicator registries)
    - integration with the National Centre for Public Health and Medical Information and the National Health Information System;
    - automated data quality, traceability and auditability;
    - public annual reports with aggregated results and completion rates.
3. Institutionalised reassessment
    - re-evaluation every 24–36 months based on RWD (efficacy, safety, budgetary impact);
    - adjustment of contracts and criteria; suspension/restriction in the event of unproven value.
4. Stabilisation of the cross-border component
    - clear criteria for when treatment remains abroad (rare paediatric/highly complex cases) and when it is localised;
    - reducing *ad hoc* decisions and increasing predictability.
5. Equity and legitimacy as a permanent component
    - centralised criteria; a mechanism for second opinions/appeals; monitoring of regional disparities;
    - public reporting on time to treatment and access.

Expected outcome (3–5 years): a sustainable model, aligned with European best practices, featuring effectively functioning results-based contracts, a registry platform and a predictable financial corridor, adapted to the Bulgarian budgetary framework and organisational capacity.

In conclusion, this research paper integrates a systematic literature review, an analysis of policies and the regulatory framework, a comparative analysis between countries, and a scenario-based/model-based examination of budgetary impact. This combination allows for the tracing of the logical link 'regulation → HTA/reimbursement → negotiation → actual implementation', which is critical for ATMPs. The analysis is based on internationally recognised institutional sources (OECD, European Commission/European Observatory, EFPIA W.A.I.T. indicator) and national public reporting documents (NHIF – budgets and reports; regulatory methodologies), which minimises the risk of unverifiable claims and ensures the reproducibility of the findings.

The study uses established comparative indicators of access (time to availability according to the W.A.I.T. methodology) and structural indicators of drug burden/coverage (State of Health in the EU profiles), which allows Bulgaria to be positioned without relying on incomparable national definitions. The proposed financial solutions are structured across time horizons (6–12 months; 1–3 years; 3–5 years) and distinguish between the minimum necessary prerequisites (centre readiness, RWD package) and more complex mechanisms (full outcome-based contracting). This is a strength, as the international literature highlights the administrative burden of this type of MEA and the need for data.

The model module does not claim to provide exact net prices, but uses ranges and parameters (price, volume, 12/24-month success rate, payment terms), which is methodologically appropriate given confidential discounts. The sensitivity analysis identifies the actual drivers of the budget (volume and net price) and examines organisational sensitivity (data/registers). The study identifies the national framework for tracking treatment outcomes

and data transfer to the National Centre for Health Research and Development (NCHRD) as a concrete foundation for future outcome-based/CEA/CED approaches, rather than proposing solutions incompatible with the actual infrastructure.

Limitations

This study is based entirely on secondary sources and does not include the collection of clinical data at national level. This limits the possibility of drawing causal conclusions and making precise assessments of efficacy/safety in Bulgarian practice.

A key methodological limitation in the analysis of ATMPs and high-value therapies is that actual net prices (after discounts), contract terms (MEAs, risk-sharing agreements) and reimbursement mechanisms are often not publicly available. Consequently, budget estimates are scenario-based and operate with ranges, whilst cross-country comparative analysis relies on proxy indicators and publicly available sources.

In Bulgaria, detailed data at product/indication level is lacking (or not systematically published) for: date of submission of the dossier, time to decision, time to actual start of treatment, and number of patients by indication. This does not allow for an accurate breakdown of the delay (EMA → submission → decision → actual use) and necessitates the use of European comparative indicators (W.A.I.T.) as an approximation. Indicators such as W.A.I.T. mainly measure the time from EMA approval to national availability/reimbursement, but do not fully capture the final step of actual implementation ( ). For ATMPs, this discrepancy is significant and may underestimate the actual barriers in practice.

Comparative international sources use different definitions (e.g. pharmacy products vs. medicines in general; public coverage of medicines; availability/reimbursement), which limits direct comparability and requires careful interpretation.

The model analysis uses a sample population and parameters from the international literature and public data for the purpose of methodological demonstration and to support policy conclusions. It does not replace official health technology assessments, nor can it be used directly for an individual decision on a specific product without local data on volume, clinical outcomes and contractual terms.

The analysis is from a public payer perspective and does not include a full societal perspective (lost productivity, burden on carers, social transfers), nor a quantitative measurement of value over the long term. This may underestimate the overall economic value of ATMPs for certain indications, but is a deliberate choice to align with budgetary planning practices.

The regulatory and financial environment for innovation is dynamic (e.g. development of the European HTA framework, changes in national methodologies and contractual mechanisms). Consequently, some of the procedural details and the applicability of the proposed models should be updated in line with future regulatory changes.

CONCLUSIONS

Gene and cell therapies, as innovative therapies, represent highly complex, resource-intensive health technologies for which regulatory approval (EMA) is a necessary but not sufficient condition for actual access. The path to the patient inevitably involves health technology assessment, negotiation and organisational readiness, which makes ATMPs systemically dependent on the quality of governance, rather than merely on product availability.

International practice shows a predominance of financial MEAs (discounts, volume-based pricing), whilst outcome-based contracts are applied less frequently and selectively due to administrative burdens, the need for standardised endpoints and reliable real-world data.

Comparative indicators for 'time to availability' (EMA → national availability) show that Bulgaria is among the countries with a longer time-to-availability, approximately 768 days for the 2020–2023 cohort, which is above the EU average and significantly slower than early-access systems such as Germany's. Consequently, the main barrier is not just price, but a combination of process duration, budget sensitivity and organisational constraints. In the Bulgarian context, the barriers are grouped into four critical blocks: budgetary and contractual; procedural; organisational and logistical; data/registers.

The scenario analysis shows that for small volumes (e.g. 10–15 patients/year), upfront payment creates the highest short-term risk to the budget, whilst deferred payment reduces the 3-year expenditure at the cost of accumulating multi-year liabilities. Outcome-based and combined models have the potential to limit the 'pay-for-failure' risk, but are only realistic with functioning registries, standardised endpoints and auditable data.

The most suitable model for Bulgaria is a phased architecture, starting with a minimum viable package (financial MEA + quotas + minimum RWD), moves on to a special fund/budget corridor and deferred payment, and culminates in a combined, outcome-based model once the registry and audit infrastructure have been strengthened.

RECOMMENDATIONS

Recommendations to the Council of Ministers and Members of Parliament

1. Continuous updating of legislation relating to access to innovative therapies, including gene and cell therapies, in line with European regulations and ethical standards.
2. Inclusion of gene and cell therapies as a priority in the National Health Strategy, with an emphasis on stimulating scientific research and clinical trials in Bulgaria.
3. A legislative framework to protect patients' rights**, including informed consent, access to information and participation in treatment decisions.

Recommendations to the Ministry of Health

1. Establishment of a centralised information platform on gene and cell therapies – indications, risks, access, registered products.
2. Establishment of a national register of patients treated with gene and cell therapies, to monitor efficacy and safety.
3. Establishment of a special fund for the treatment of rare diseases, through which critically important therapies can be provided, particularly to ensure timely treatment.
4. Launching educational campaigns for healthcare professionals and patients regarding the possibilities and limitations of gene and cell therapies.

Recommendations to the Executive Agency for Medicines

1. Accelerating approval procedures and access to gene and cell therapies through streamlined administrative mechanisms.
2. Intensify the work of the Commission on Medicinal Products for Advanced Therapies under Article 47(1)(7) of the Law on Medicinal Products for Human Use and strengthen its role in communicating with healthcare professionals and providing expert opinions and recommendations.
3. Increasing transparency regarding ATMPs through a dedicated public register of approved therapies and ongoing clinical trials.

Recommendations to the institution conducting HTA in Bulgaria (NCHTA)

1. Developing a mechanism for the funding and reimbursement of innovative therapies, including co-funding with international partners.
2. Include patients and their representatives from patient organisations in expert groups for the evaluation of gene and cell therapies.
3. Establish more specific criteria for inclusion in the National Health Insurance Fund (NHIF) and reimbursement of gene and cell therapies, based on data from real-world clinical practice.
4. Publicly reporting on the progress of health technology assessments of gene and cell therapies, with the aim of increasing transparency and the confidence of doctors and patients in them.

Recommendation to the National Health Insurance Fund

- Use of real-world clinical practice data to assess the therapeutic and cost-effectiveness of gene and cell therapies, with a view to their inclusion in the reimbursement scheme.

Recommendations to patient organisations

- 1. Active participation in health technology assessment (HTA) processes relating to gene and cell therapies.
- 2. Organising educational initiatives to raise patient awareness of the possibilities offered by gene and cell therapies.

Recommendation to medical universities

- Inclusion of topics on gene and cell therapies in curricula, as well as the creation of continuing education modules for doctors and pharmacists.

Recommendation to the media

- Responsible reporting on the topic of ‘gene and cell therapies’ through consultation with experts and the presentation of balanced information on innovative therapies, their benefits and risks.

CONTRIBUTIONS

Scientific and theoretical contributions

1. A framework has been formulated that defines access to gene and cell therapies as the result of the interaction of four subsystems: regulation and assessment (EMA/HTA), funding and contracting, organisational readiness of centres, and data/registries for monitoring.
2. The budgetary sustainability of ATMPs in Bulgaria is significantly influenced by the high relative weight of medicines, meaning that these medicines have a significant impact on the budget due to high costs and the need for effective treatment, as well as limited public coverage of medicine costs, which defines a narrower corridor for high-value innovations.
3. A comparative analytical model has been developed to position Bulgaria relative to selected EU countries, using: a time-to-availability indicator (EMA → national availability), based on W.A.I.T., and structural indicators for drug burden and public coverage. This allows for the reproducibility of the comparison given limited national data series at product/indication level.
4. A methodology has been developed for working under conditions of confidential discounts and net prices, using range assumptions and indices, and a threshold assessment of capacity within a budget corridor. This approach is appropriate for ATMPs, where public transparency of actual prices is limited.

Practical contributions

1. A practical ‘roadmap’ for ATMP funding has been developed, combining: short-term measures, a medium-term model and a long-term architecture.
2. A combined model has been proposed that simultaneously addresses the initial budgetary risk, clinical uncertainty, and the need for accountability and legitimacy.
3. A specific opportunity has been identified to transform the existing mechanism for monitoring outcomes and transferring data to the National Centre for Public Health and Analyses (NCPHA) based on outcome-based contracting through a minimal database, standardised endpoints and audit.
4. A practical management tool has been developed: a systematisation of risks and corresponding mitigation measures, which can be used in the planning of pilot programmes and in contract negotiations.
5. A threshold formula has been proposed for determining the maximum number of patients within a fixed budget corridor, which allows for manageable implementation and reduces the risk of in-year overspending in segments with high drug pressure.

Scientific publications related to the PhD thesis:

1. **Bankovski, S.**, E. Grigorov. Access to innovative health technologies with medicinal product status in Bulgaria. *Health and Science (ISSN 1314-3360)*, 2026 (16), No. 1.
2. Grigorov, E., **S. Bankovski**, P. Salchev. International experience in market access, health technology assessment and reimbursement models for modern therapy medicinal products. *Annual for Hospital Pharmacy (ISSN print: 2367-8763, ISSN online: 2603-3852),* 2026 (12), No. 1. (Indexed in ROAD, Crossref, Google Scholar, ICI and Bulgarian Medical Literature, Web of Science)
3. **Bankovski, S**., E. Grigorov. Gene and cell therapies – regulatory aspects and practical application in modern medicine. *Social Medicine (ISSN print: 1310-1757, ISSN online: 2603-3739)*, 2025 (33), No. 2

Participation in scientific events with posters:

- Stefanova, T., **S. Bankovski**, E. Grigorov. GENE THERAPY AS A POTENTIAL ALTERNATIVE FOR THE TREATMENT OF X-LINKED MYOTUBULAR MYOPATHY. 8th Congress on Pharmacy with International Participation, 27–30 April 2023, Hotel Rila, Borovets Resort. *E-book of abstracts from the congress (ISBN 978-954-8137-16-4), poster 147.*
- **Bankovski S.**, S. Tsenov. THE FUTURE OF THE TREATMENT OF SOCIALLY SIGNIFICANT DISEASES (GENE AND CELL THERAPIES). Eighth Pharmaceutical Business Forum with Scientific and Practical Conference "Pharmacists and doctors - united to support the patient" HYBRID on 28–29 October 2022, Medical University of Varna, Bulgaria, *Scripta Scientifica Pharmaceutica (ISSN print: 2367-6000, ISSN online: 2367-5500)*, 2022, Vol. 9, No. 1, Suppl. 1, p.14.
- Kar, D., **S. Bankovski**, E. Grigorov. THE EMERGING PHARMACIST ROLE IN PHARMACOVIGILANCE FOR GENE AND CELL THERAPIES. Eighth Pharmaceutical Business Forum with Scientific and Practical Conference "Pharmacists and doctors - united to support the patient" HYBRID on 28–29 October 2022, Medical University of Varna, Bulgaria, *Scripta Scientifica Pharmaceutica (ISSN print: 2367-6000, ISSN online: 2367-5500)*, 2022, Vol. 9, No. 1, Suppl. 1, p.49.
- Kar, D., **S. Bankovski**, E. Grigorov. THE GROWING INVOLVEMENT OF THE PHARMACIST IN EVALUATING THE SAFETY OF GENE AND CELL TREATMENTS. International Biomedical Congress Sofia 2022, 4–6 November, Sofia, Bulgaria, *Book of abstracts*, p. 30
- Boyanova, D., **S. Bankovski**, E. Grigorov. PROSTATE CARCINOMA - NEW PHARMACOTHERAPY OPPORTUNITIES. Sixth Pharmaceutical Business Forum with Scientific and Practical Conference "Pharmaceutical education – knowledge transfer to practice" 25–27 October 2019, Medical University of Varna, Hotel Cherno More, Bulgaria, *Scripta Scientifica Pharmaceutica (ISSN print: 2367-6000, ISSN online: 2367-5500),* 2019, Vol. 6, No. 1, Suppl. 1, p.25.