Getting Ready:
Act now for access to ATMPs in Europe

INTRODUCTION

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12 December 2019

Alliance *for* Regenerative Medicine

About ARM

- **International advocacy organization**
  - Dedicated to realizing the promise of safe and effective regenerative medicines for patients around the world
  - Cell and gene therapy, tissue engineering
- **350+ members**
  - Small and large companies, non-profit research institutions, patient organizations, and other sector stakeholders
  - Across 25 countries
- **Priorities:**
  - Clear, predictable, and harmonized **regulatory** pathways
  - Enabling market access and value-based **reimbursement** policies
  - Addressing industrialization and **manufacturing** hurdles
  - Conducting key stakeholder outreach, **communication**, and education
  - Facilitating sustainable access to **capital**

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What Are Advanced Therapeutic Medicinal Products (ATMPs)?

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ATMPs include gene therapies, cell therapies, and tissue-engineered products intended to augment, repair, replace, or regenerate organs, tissues, cells, genes, and metabolic processes in the body. These therapies aim to alter the current practice of medicine by treating the root causes of disease and disorders.

ATMPs are now delivering benefits for patients, with further regulatory approvals for life changing and curative treatments expected soon

ATMP Technologies

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Gene Therapy

Gene Therapy seeks to modify or introduce genes into a patient's body with the goal of durably treating, preventing, or potentially even curing disease, including several types of cancer, viral diseases, and inherited disorders.

Genome Editing

Genome Editing is a technique by which DNA is inserted, replaced, removed, or modified at particular locations in the human genome for therapeutic benefit in order to treat cancer, rare inherited disorders, HIV, or other diseases.

Cell Therapy

Cell Therapy is the administration of viable, often purified cells into a patient's body to grow, replace, or repair damaged tissue for the treatment of a disease. A variety of different types of cells can be used in cell therapy.

Tissue Engineering

Tissue Engineering seeks to restore, maintain, improve, or replace damaged tissues and organs through the combination of scaffolds, cells, and/or biologically active molecules.

By ARM's standards, the following therapies are not considered ATMPs: Molecular medicines, including mRNA, RNAi, siRNA, and diagnostics-based products

Patient Impact of Recently Approved Products

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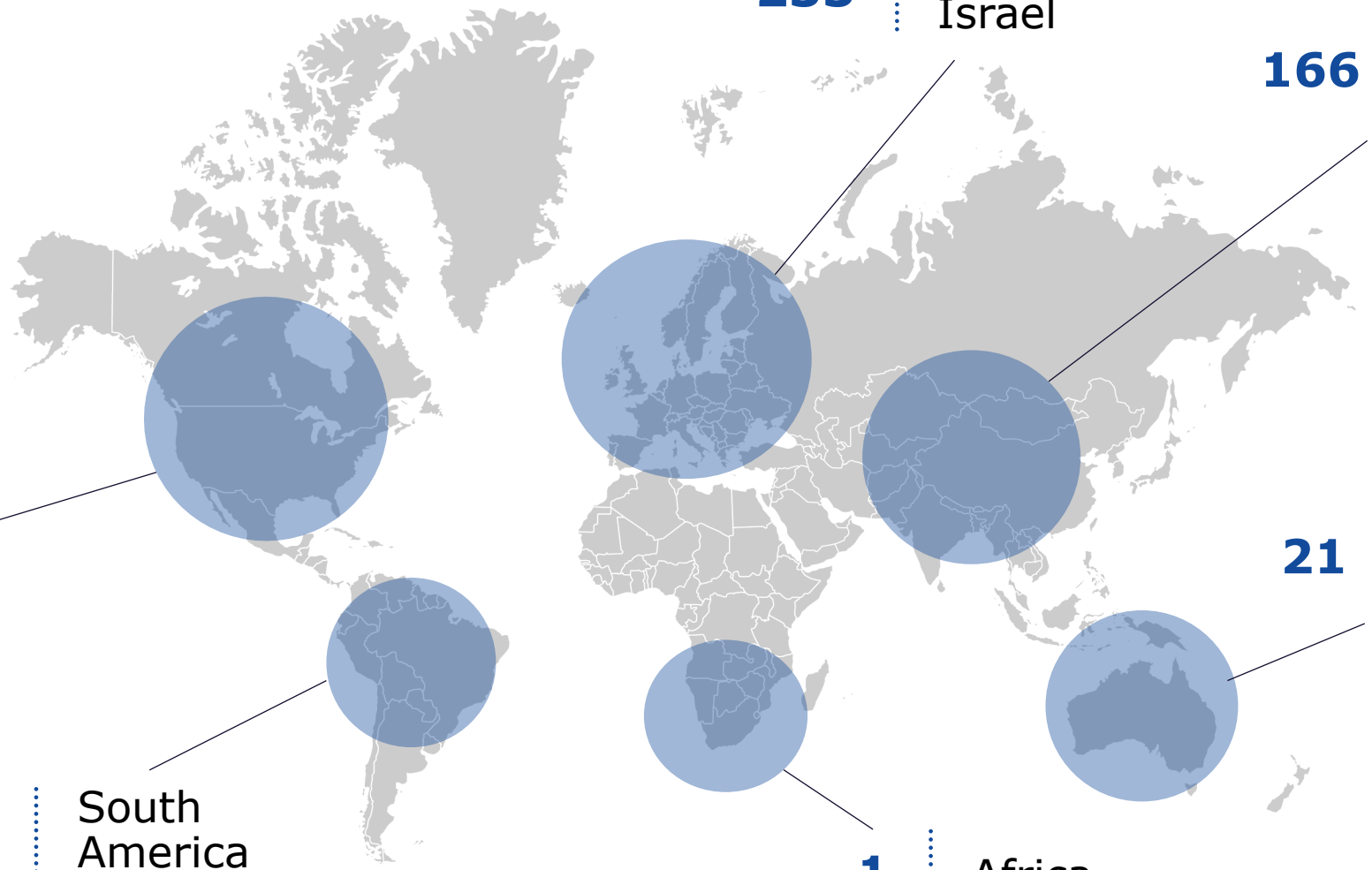
Therapy	Patient Impact	Developer	Response
Kymriah *Reimbursed in several European countries, including Germany, UK, and France*	**8,700+** Potential patient population in Europe	Novartis	• **40%** of patients with R/R DLBCL treated experienced a complete response • **82%** of patients with R/R B-Cell ALL treated experienced complete remission or complete remission with incomplete hematologic recovery
Yescarta *Reimbursed in several European countries, including Germany, UK, and France*	**7,700+** Potential patient population in Europe	Kite / Gilead	• **58%** of patients with R/R DLBCL treated experienced a complete response
LUXTURNA *Reimbursed in Germany*	**1,000-2,000** Potential patient population in Europe	Spark Tx	• **55%** of patients treated showed an improvement of 2+ light levels darker after treatment
Zynteglo *Initial launch countries include UK, Italy, Germany, France*	**2,750+** Potential patient population in initial launch countries	bluebird bio	• **75%** of patients with TDT without β0/β0 genotype treated achieved transfusion independence

Current Global Sector Landscape

959+
Regenerative Medicine Companies Worldwide, including Gene and Cell Therapies, and Tissue Engineering Therapeutic Developers



233 Europe & Israel

166 Asia

525 North America

21 Oceania
Australia, New Zealand, Marshall Islands

13 South America

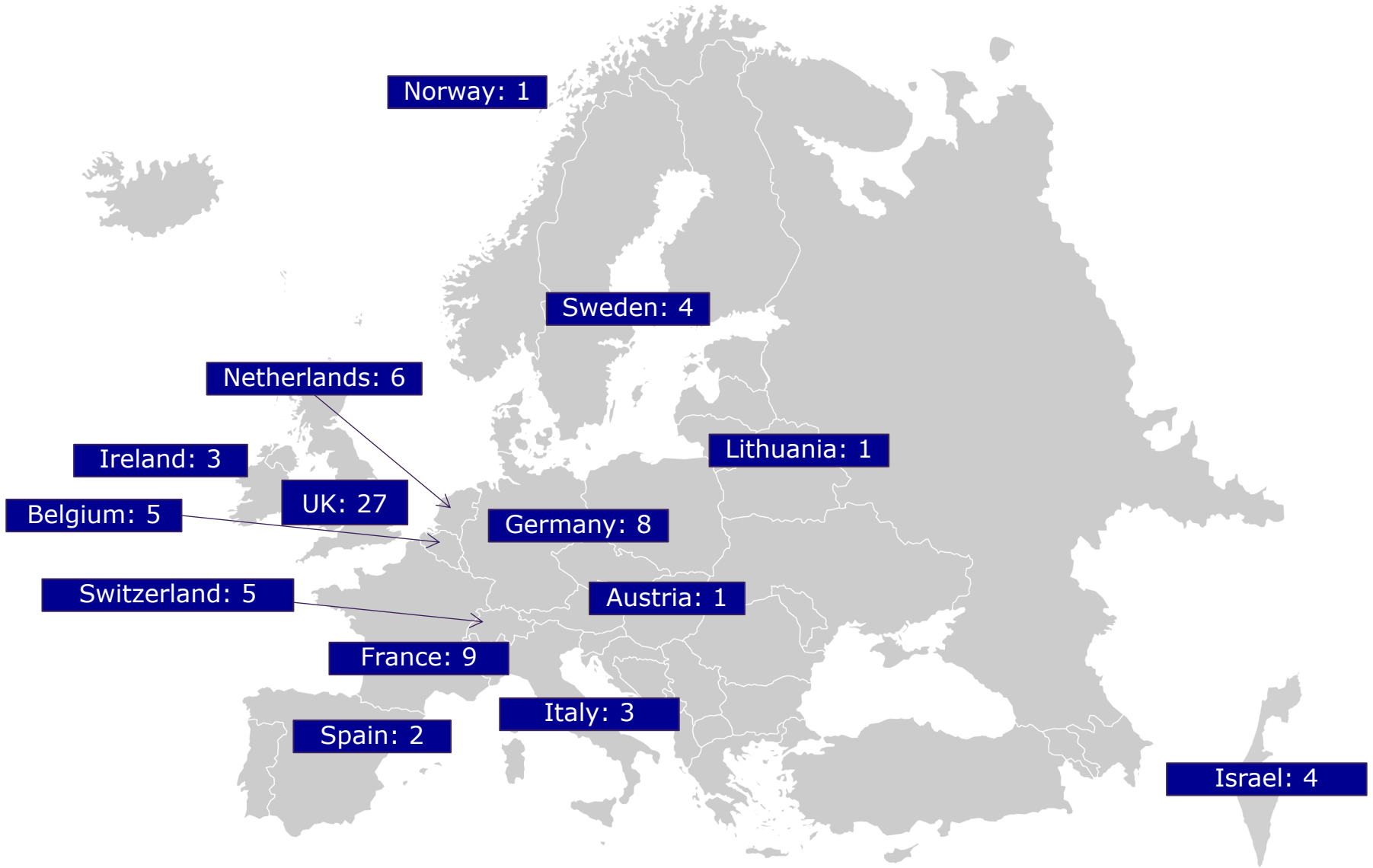
1 Africa

Source data provided by: informa

ARM's European Membership

81 Members

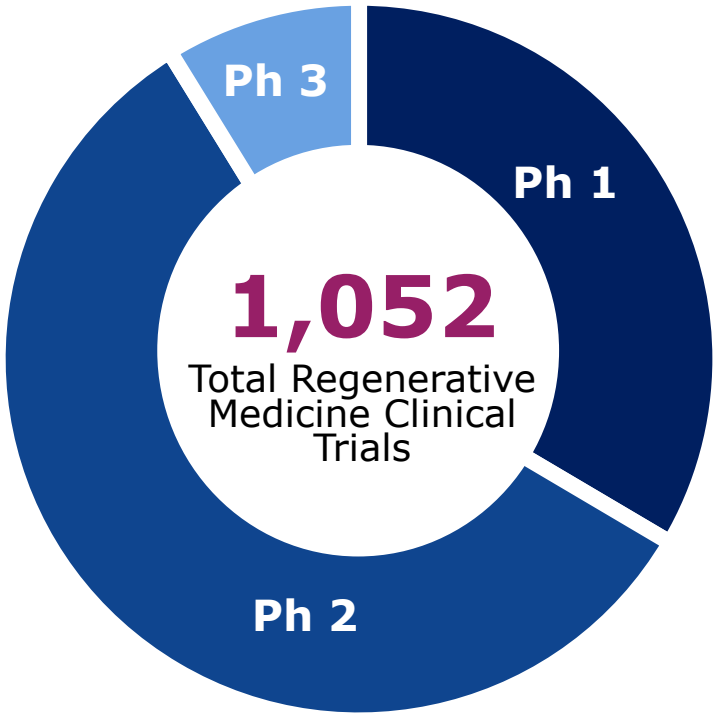
Representing 23% of ARM's total membership



Near-Term Anticipated ATMP Approvals in the EU

Product	Developer	Indication	Timeline
Valoctocogene roxaparvovec	BioMarin	Hemophilia A	Expects to receive approval in 2020
OTL-200	Orchard Tx	Metachromatic leukodystrophy	Expects to receive approval in 2020
Zolgensma	AveXis / Novartis	Spinal muscular atrophy	Expects to receive approval in 2020
KTE-X19	Kite / Gilead	Mantle cell lymphoma	Expects to receive approval in 2020
GS010	GenSight Biologics	Leber hereditary optic neuropathy	Expects to submit MAA in Q3 2020
AT132	Audentes Tx	X-linked myotubular myopathy	Expects to submit MAA by EOY 2020
OTL-103	Orchard Tx	Wiskott-Aldrich syndrome	Expects to submit MAA in 2021
Lenti-D product	bluebird bio	Cerebral adrenoleukodystrophy	Potential approval in 2021

Global ATMP Clinical Trials by Phase and Technology Type



Phase 1: 363
across all tech types and indications

Gene Therapy: 115
Gene-Modified Cell Therapy: 201
Cell Therapy: 41
Tissue Engineering: 6

Phase 2: 594
across all tech types and indications

Gene Therapy: 223
Gene-Modified Cell Therapy: 201
Cell Therapy: 147
Tissue Engineering: 23

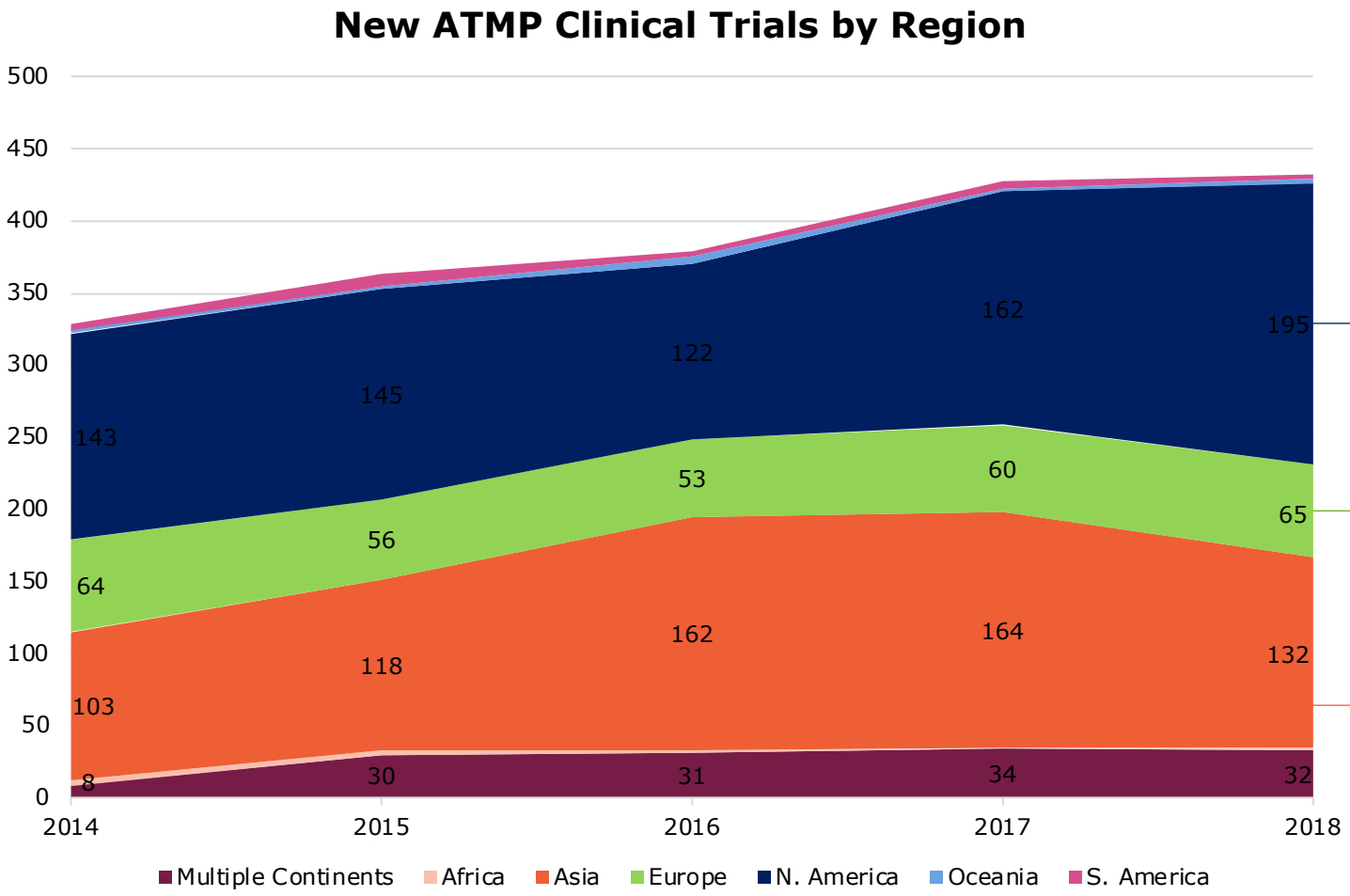
Phase 3: 95
across all tech types and indications

Gene Therapy: 32
Gene-Modified Cell Therapy: 16
Cell Therapy: 30
Tissue Engineering: 17

Source data provided by: informa

New ATMP Clinical Trials by Region, 1 Jan 2014 – 30 June 2019

Clinical trial growth in Europe is significantly lower than in other regions



Growth, 2014 to 2018
↑32% Globally

N. America: ↑36%

Europe: ↑2%

Asia: ↑28%

Total new trials started during the 2014-2018 period = 2,097
(All new trials started in more than 1 continent are under Multiple Continents category)

Market Access Landscape

As of December 2019

France	Germany	UK	Italy	Spain
		Imlygic ★	Imlygic ★ ✓	
		Holoclar ★	Holoclar ★ ✓	
	Strimvelis ★	Strimvelis ★	Strimvelis ★ ✓	
Alofisel ★	Alofisel ★ ✓			Alofisel ★
Kymriah ★ ✓	Kymriah ★ ✓	Kymriah ★	Kymriah ★ ✓	Kymriah ★
Yescarta ★ ✓	Yescarta ★ ✓	Yescarta ★	Yescarta ★ ✓	Yescarta ★
Luxturna ★	Luxturna ★ ✓	Luxturna ★		

✓ Product has received a positive pricing decision

★ Product has received a positive reimbursement decision

- Europe has been a leader in scientific innovation and regulatory advancement for ATMPs in Europe
- Europe is at the forefront of ATMP regulation and commercialization
- The region has seen commercial failures (Glybera, Chondrocelect, Provenge and Zalmoxis), as well as several recent approvals
- Not all of these products are available across Europe due to country-specific reimbursement challenges

As an increasing number of ATMPs receive approval in Europe, it is vital that the barriers that have delayed or precluded access to early ATMPs are addressed

Getting Ready

Recommendations for Timely Access to Advanced Therapy Medical Products (ATMPs) in Europe

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Getting Ready for ATMPs in Europe

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Report overview

- Overview of the characteristics and benefits of ATMPs
- Assessment of current regulatory and market access frameworks in six European countries: France, Germany, Italy, Spain, Sweden and the United Kingdom
- Identifies hurdles to adoption and makes EU-wide policy recommendations to address those challenges
- The report brings together the views of a number of European policy makers and experts

EUCOPE efpia EHC european haemophilia consortium EuropaBio EURORDIS RARE DISEASES EUROPE NICE

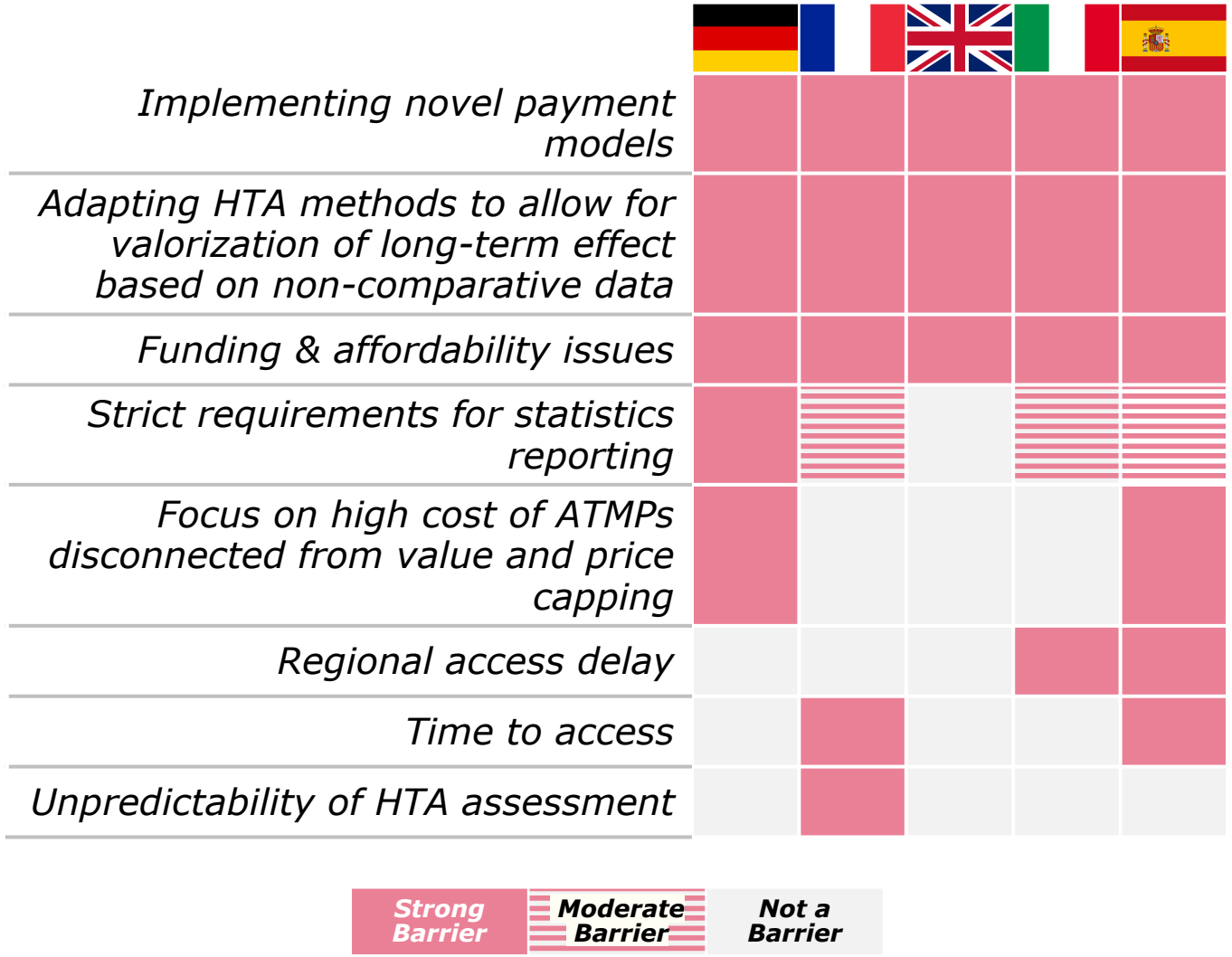
- The report was funded by the Alliance for Regenerative Medicine (ARM).

Getting Ready for ATMPs in Europe

	Conventional Therapy	ATMP
Degree of Personalization	+ Prepared and prescribed for a broad population	+++ Custom-made cell and gene therapies
Length of Administration	+ Majority are given as long-course or lifetime treatment	+++ Usually administered once
Cost Distribution	+ Cost spread over time of administration	+++ Upfront cost
Outcomes Durability	+ Outcomes observed after administration	+++ Outcomes observed on the long-term

- The potential for durable, life-changing solutions and upfront costs present challenges within current pricing & reimbursement assessment frameworks
- **Barriers exist which could prevent patients from receiving new therapies in a timely manner.**

Challenges Faced by ATMP Developers in EU5



Main Challenges for ATMP Market Access

Need for Innovative Payment Models
Need to implement outcomes-based payments, annuities, and other innovative financing models

Rigidity of HTA Requirements
HTA bodies require head-to-head RCTs and long-term data at time of launch

Affordability
There is a lack of funding for ATMPs

The Need for Harmonization of HTA Assessments

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The decentralized nature of HTA assessments creates additional barriers for developers looking to bring their product to market in Europe.

HTA Agency	HTA Method	HTA Perspective (economic analysis)	Value Judgement			Acceptability of extrapolation	Uncertainty Analysis
			Clinical Benefit	Cost-effectiveness Analysis	Budget Impact		
HAS (TC, CEESP) *France*	Mixed model	Payer (collective perspective)	++++	++++	++++	+	+
IQWiG, G-BA *Germany*	Clinical model	Payer (only drug budget impact)	++++	+	+	+	+
AIFA, regions *Italy*	Mixed model	Payer	++++	+	+++	+	+
AETS, regions *Spain*	Mixed model	Payer	++++	+	++++	+	+
TLV *Sweden*	Health economic model	Societal	+++	++++	++	++++	+++
NICE (*England*), SMC (*Scotland*)	Health economic model	National health insurance	+++	++++	++++ (NHS England)	++++	+++
ZIN *Netherlands*	Health economic model	Societal	+++	++++	++++	++	++
Danish Health Authority	Mixed model	Societal	++++	++++	+++	+	+

High: Critical driver in HTA decision	Moderate: Secondary / complementary driver in HTA decision	Low: Marginal impact in HTA decision

Getting Ready for ATMPs in Europe

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Recommendation 1: Better adapt Health Technology Assessment (HTA) frameworks to ATMPs.

- Enhancing acceptability of validated surrogate endpoints to estimate long-term outcomes
- Conducting further research to improve methodology of indirect comparisons
- Supporting development, validation and use of pan-European natural history datasets
- Leveraging scientific, clinical and HTA expertise from centres of excellence
- Adopting changes in economic modelling such as improving methods for extrapolation

Recommendation 2: Favor wider application of conditional reimbursement schemes

- Conditional reimbursement schemes have the potential to mitigate uncertainty on duration of effect based on data available at time of regulatory approval.

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Recommendation 3: Develop pan-European initiatives to create:

- Real-World-Evidence (RWE) infrastructure
- New early-dialogue opportunities
- Timely & effective access to cross-border healthcare for all EU patients

Recommendation 4: Favor wider application of innovative access and funding arrangements

- Without the adoption of new models such as pay-for-performance, annuity payments, and special funds, ATMPs may not reach patients and may be at risk of withdrawal from the market

Key Takeaways

- ATMPs have extraordinary potential to alleviate suffering and provide a long-lasting, curative effect for patients with debilitating or fatal disorders
- There is a robust pipeline with a wave of new therapies expected to come to market soon
- Europe has been at the forefront of scientific and regulatory innovation in the ATMP sector, but significant work is still needed to ensure timely patient access to these therapies post-approval
- ARM works with stakeholders across the sector to develop and promote sustainable solutions for ATMP patient access

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For More

This presentation will be available on our website and shared via Twitter at @alliancerm

Visit **www.alliancerm.org** to access additional resources, including:

- Quarterly sector data reports
- Upcoming near-term clinical trial milestones & data readouts
- Access to slides, graphics, and figures from ARM presentations
- Our weekly sector newsletter, a robust round-up of business, clinical, scientific, and policy news in the sector
- Commentary from experts in the field

Thank You!

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