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Market Access Series

Managed Entry Agreements

Aug 2021

Glossary

AIFA	Italian Medicines Agency (Agenzia Italiana del Farmaco)
ASMR	Improvement in Medical Benefit (Amélioration du Service Médical Rendu)
ATMP	Advanced Therapy Medicinal Products
CDF	Cancer Drugs Fund (UK)
CED	Coverage with Evidence Development
CMS	Centers for Medicare & Medicaid Services
CR	Continued Response
CT	Clinical Trial
CTC	Conditional Treatment Continuation
DoR	Duration of Response
FBA	Finance-Based Agreement
G-BA	Joint Federal Committee of German Public Health Agencies (Gemeinsamer Bundesausschuss)
HAS	French National Health Authority (Haute Autorité de Santé)
HCV	Hepatitis C Virus
MEA	Managed Entry Agreement
NICE	National Institute for Health and Care Excellence
ORR	Overall Response Rate
OS	Overall Survival
PBA	Performance-Based Agreement
PbR	Payment by Results
PFS	Progression-Free Survival
RD	Rare Disease
RWE	Real-World Evidence
SoC	Standard of Care

Managed Entry Agreements (MEAs) have a storied history, and performance-based agreements are being (re-)considered in the context of emerging trends

A Managed Entry Agreement (MEA) is an arrangement between a manufacturer and payer/provider that enables access to a health technology subject to specified conditions."[1,2]

Prior to 2000s

Mostly financial-based agreements (FBAs)

2000+

Experimentation with performance-based agreements (PBAs), but with mixed success

Now

Emerging trends:

- ATMPs launching with promise of transformative efficacy but limited long-term data
- Improving ability to capture and analyze RWD, and greater health system stakeholder acceptance of RWE
- Payers moving towards health technology management and periodic re-evaluations

Focus of this presentation:

- What products / countries are suitable for performance-based MEAs?
- What makes for a successful MEA for pharma, payers and healthcare providers?
- What is the role of MEAs in the future?

SOURCE: **1**. Klemp, M and Frønsdal, KB. What principles should govern the use of managed entry agreements? International Journal of Technology Assessment in Health Care, 27:1 (2011), 77–83. **2**. Carlson JJ, Sullivan SD, Garrison LP, Neumann PJ, Veenstraa DL. Linking payment to health outcomes: A taxonomy and examination of performance-based reimbursement schemes between healthcare payers and manufacturers. Health Policy. 2010;96:179-190.

MEAs can be grouped into financial-based (FBAs) and performance-based agreements (PBAs), each with benefits and challenges

	Financial-based agreements (FBAs)			Performance-based agreements (PBAs)		
	Discounts / rebates	**Price-volume agreements**	**Caps (patient, usage, total)**	**Population-level CED**	**Payment in installments**	**Patient-level PBA (outcomes guarantee, risk sharing)**
Frequency of utilization	✓✓✓✓✓	✓✓✓	✓✓✓	✓✓	✓	✓
Benefits	▲ Least burdensome ▲ Direct budget benefit to payers	▲ Predictable budget impact ▲ Reduce ”over-use” if based on accurate epi	▲ Reduces uncertainty in treatment duration ▲ Caps patient OOP	▲ Addresses uncertainty in clinical data	▲ Addresses uncertainty in long-term outcomes	▲ Directly links cost to treatment value
Challenges	▼ Impacted by affordability instead of product value	▼ Lack of accurate epi data in many indications ▼ Impacted by affordability instead of product value	▼ Need to track prescribing per patient ▼ Some uncertainty with overall budget remain	▼ Long study timelines ▼ Risk of poor data quality ▼ Risk of over-paying upfront ▼ Increase workload for HTA agencies	▼ Patient-level outcomes tracking (admin & infrastructure)	▼ Expensive to set up ▼ Burdensome ▼ Often based on surrogates ▼ Risk of poor data quality and inability to recover costs

Increasing complexity to administer

Patient support programs are also often considered MEAs, but these overlap with FBAs and PBAs outlined above and are not specifically considered in this paper

SOURCE: 1. Dabbous, M., Chachoua, L. Caban, A., Toumi, M. Managed Entry Agreements: Policy Analysis from the European Perspective. Value in Health 23(4) 415-433 (2020) 2. Blue Matter in-house knowledge

With promise of great clinical value but often limited data, ATMPs* have been part of the impetus for major markets to (re)consider PBAs

Over the next 5 years, 20-30 advanced therapy medicinal products* (ATMP) EMA filings are expected annually[1,2]

ATMPs pose interesting case studies for managed entry agreements, given their high degrees of uncertainty in:

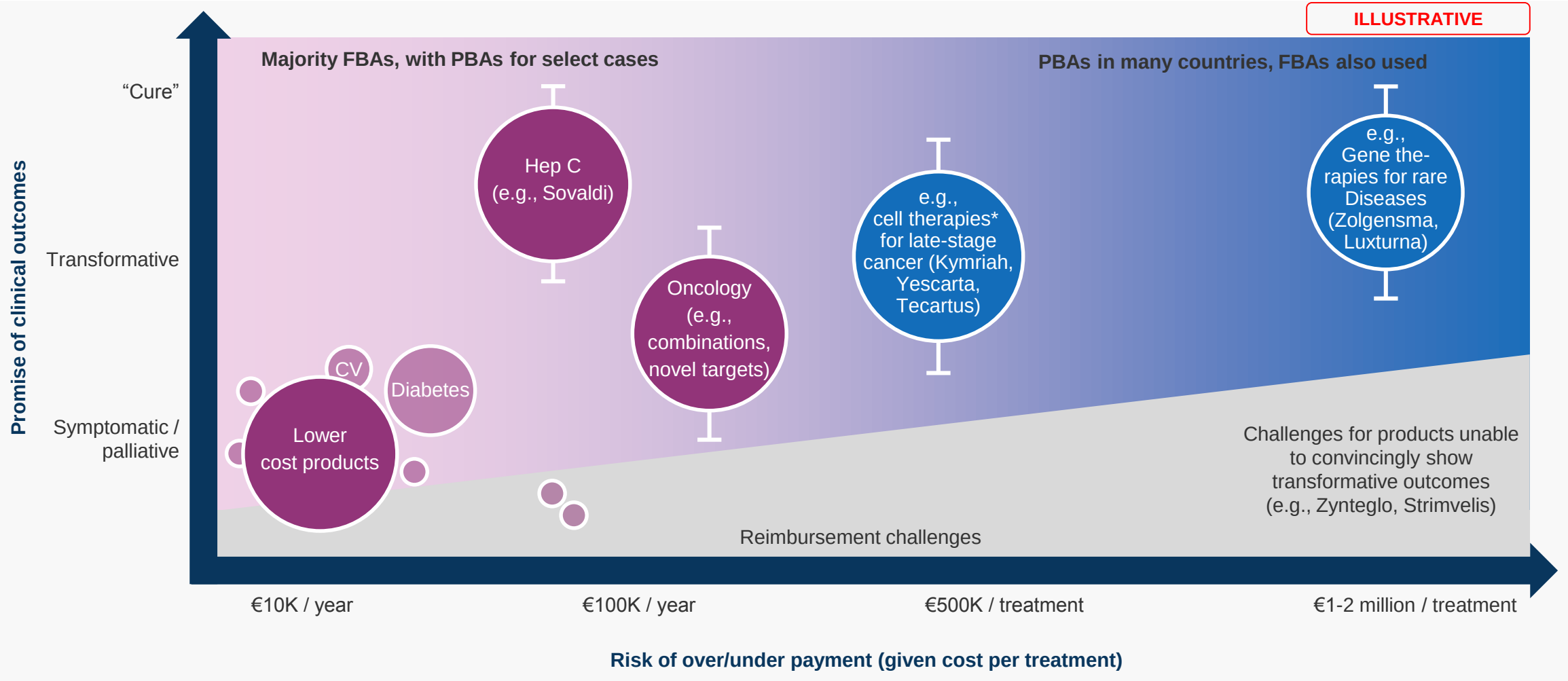
- Long-term clinical benefit
- Value for money / cost-effectiveness

While several ATMPs have recently launched with data packages that fell short of traditional payer requirements (e.g., single-arm studies, limited duration of follow-up), payers have nevertheless agreed to reimbursement at high (list) prices, using MEAs (including PBAs) to manage the outstanding clinical and financial uncertainties.

SOURCE: 1. Official Journal of the European Union. Regulation (EC) No 1394/2007 of the European Parliament and of the Council of 13 November 2007 on advanced therapy medicinal products and amending Directive 2001/83/ EC and Regulation (EC) No 726/2004. https://ec.europa.eu/health//sites/health/files/files/eudralex/vol-1/reg_2007_1394/reg_2007_1394_en.pdf; 2. Horgan, Denis, et al, Propelling Healthcare with Advanced Therapy Medicinal Products: A Policy Discussion, Biomedicine Hub, 2020, https://www.karger.com/Article/Pdf/511678

*Advanced therapy medicinal products (ATMPs) as defined by the EU comprise gene therapies, somatic-cell therapies, tissue-engineered therapies, and combined ATMPs (containing one or more medical devices)1

Payer are more willing to engage in PBAs for products with promise of transformative outcomes and high financial risks

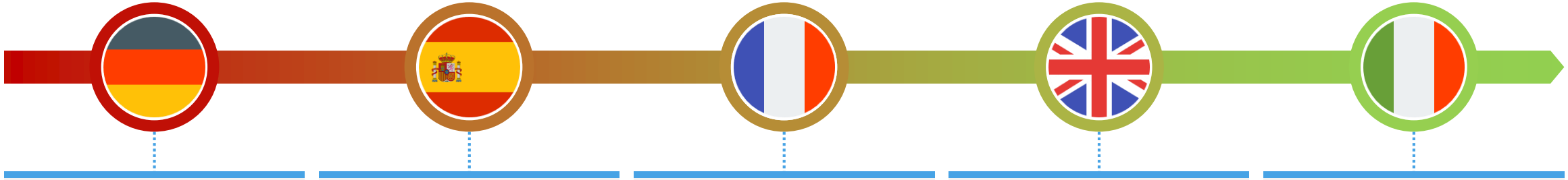


*Cost of administering cell therapy and managing side effects is also considerable, and need to be considered in addition to cost of the product itself

Major markets have different levels of experience and interest for engaging in performance-based agreements

ILLUSTRATIVE

Experience with PbAs:



- Limited use of MEAs beyond simple discounts historically
- In the last few years Germany has begun to **experiment with PBAs**[1]
- Sick Funds have entered into **time-limited** patient-level PBAs, especially for the free pricing period[2]

- Spain has recently invested in the **Valtermed** registry for RWD collection and is leveraging the registry for PBAs for selected therapies[3]

- The ATU and RTU system contain elements of PBA, as ATU data can support reimbursement submission[4]
- Historically preferred discounts, rebates and price-volume agreements for formal reimbursement

- Established infrastructure (Cancer Drugs Fund) and experience with **population-level CEDs**[1]
- Interest in extending CDF to Innovative Medicines Fund could see greater use of CEDs beyond oncology

- Established infrastructure (**AIFA registries**) and most PBA experience[2]
- However, success of these PBAs has been questioned, there has been a move to simpler discount/rebates for more "traditional" products[1]

Overall, there is greater openness to CEDs for transformative therapies; investments in RWD/RWE infrastructure also enhance countries' ability to better evaluate outcomes of different products in the real-world setting

SOURCE: 1. Ronco, V., Dilecce, M., Lanati, E. et al. Price and reimbursement of advanced therapeutic medicinal products in Europe: are assessment and appraisal diverging from expert recommendations?. J of Pharm Policy and Pract 14, 30 (2021). https://doi.org/10.1186/s40545-021-00311-0; 2. Wenzl, M. and S. Chapman (2019), "Performance-based managed entry agreements for new medicines in OECD countries and EU member states: How they work and possible improvements going forward", OECD Health Working Papers, No. 115, OECD Publishing, Paris, https://doi.org/10.1787/6e5e4c0f-en; 3. Jesper Jørgensen, Eve Hanna & Panos Kefalas (2020) Outcomes-based reimbursement for gene therapies in practice: the experience of recently launched CAR-T cell therapies in major European countries, Journal of Market Access & Health Policy, 8:1, DOI: 10.1080/20016689.2020.1715536; 4. https://solidarites-sante.gouv.fr/soins-et-maladies/medicaments/professionnels-de-sante/autorisation-de-mise-sur-le-marche/article/autorisations-temporaires-d-utilisation-atu;

Despite the different levels of interest, EU4 + UK have been largely consistent in the use of MEAs for cell and gene therapies

	Germany	Spain	France	UK	Italy
Kymriah	CED (G-BA), PBR (sick funds, time limited)	PBR with staged payments	ATU, CED (annual re-assessment)	CED (after 5 years)	PBR with staged payments
Yescarta	CED (G-BA), PBR (sick funds, time limited)	PBR with staged payments	ATU, CED (annual re-assessment)	CED (after 5 years)	PBR with staged payments
Luxturna	CED	CED	ATU, CED (annual re-assessment)	Discount[3] (long-term data collection per EMA requirements)	CED
Zolgensma	CED (G-BA), PBR (sick funds, time limited)	No decision to date	ATU, CED (re-assessment within three years)	CED (reviewed biannually)	CED
Zynteglo	CED, PBR but price negotiation failed, and product withdrawn	No decision to date	ATU, CED	Negative decision in draft guidance	No decision to date

SOURCE: 1. Jørgensen, J., & Kefalas, P. The use of innovative payment mechanisms for gene therapies in Europe and the USA (2021), Regen. Med. 16(4), 405–422, DOI: 10.2217/rme-2020-0169;
2. https://mapbiopharma.com/home/2020/04/landmark-pay-for-performance-contract-agreed-in-germany/ 3. https://www.g-ba.de/downloads/40-268-6053/2019-10-17_AM-RL-XII_Voretigen-Neparvovec_D-436_TrG_akt.pdf 4.

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3. CED not used as data collection beyond maximal available follow up (7.5 years) would place a significant administrative burden on the NHS. In addition, the EMA require company follow up of 15 years to assess efficacy and safety.

- CED & PbR (time limited)
- Payment by results (PbR)
- Coverage with evidence development (CED)
- No reimbursement decision yet
- Negative reimbursement outcome
- Discount

While Spain, UK and Italy have infrastructure in place for data collection, Germany and France have required de novo registries

In addition to clinical trial long-term follow up and EMA mandated safety studies, different countries require use of different registries for data collection:

	Germany	Spain	France	UK	Italy
Kymriah	German Registry for Stem Cell Transplantation / European Bone Marrow Transplantation Registry (DRST/EBMTR)	Valtermed	CAR-T registry (Lymphoma Academic Research Organisation (LYSARC) data platform)	SACT dataset	AIFA registry
Yescarta	German Registry for Stem Cell Transplantation / European Bone Marrow Transplantation Registry (DRST/EBMTR)	Valtermed	LYSARC platform	SACT dataset	AIFA registry
Luxturna	SPKRPE-PASS dataset	Valtermed	EMA registry	Manufacturer registry	AIFA registry
Zolgensma	RESTORE registry	No reimbursement decision yet	SMA France national register	SMA Reach registry	AIFA registry
Zynteglo	Manufacturer registry	No reimbursement decision yet	De novo registry for all treated French patients	Negative reimbursement decision	No reimbursement decision yet

SOURCE: Jørgensen, J., & Kefalas, P. The use of innovative payment mechanisms for gene therapies in Europe and the USA (2021), Regen. Med. 16(4), 405–422, DOI: 10.2217/rme-2020-0169;

Coverage with evidence development (CED)
Payment by results (PbR)
CED & PbR
Country-specific registries
De novo registries
No reimbursement decision yet
Negative reimbursement outcome

While all manufacturers have a plan for MEA at launch, AveXis/ Novartis set a recent benchmark in proactive public engagement and awareness generation

AveXis receives EC approval and activates "Day One" access program for Zolgensma®, the only gene therapy for spinal muscular atrophy (SMA)

Zolgensma

European "Day One" access program[1]

- Retroactive rebates ensuring early access costs are aligned with negotiated prices
- Deferred payments and installment options during early access
- Outcomes-based rebates can be applied to early access patients
- Robust training for treating institutions on administration and follow-up care
- Access to RESTORE, a global registry of patients who have been diagnosed with SMA that draws upon existing country registries

AveXis / Novartis proactively made significant investments into Zolgensma launch:

- AveXis reportedly met with more than 100 European stakeholder organisations to ensure the "Day One" program meets individual payer's needs
- Global Managed Access Program (MAP) – 100 free doses in 2020 in countries without marketing authorization; Renewed for 2021

While launch was successful, efforts around MEAs also received criticism:

- Zolgensma achieved ATU in France and negotiated outcomes-based agreements quickly in Germany; reimbursement in the UK, Italy and Spain took 10 months, 10 months, and awaiting decision at 14 months, respectively
- However, the Krankenkassen, GBA and VUD criticized Novartis for its "unprecedented media campaign" which risks compromising the early benefit assessment process[2]
- Patient groups (e.g., SMA Europe, TreatSMA) and health ministers (e.g., members of BENELUXA-I) criticized the "lottery" system for MAP

With (one of) the first gene therapies to market, AveXis/Novartis was highly proactive in proposing MEAs to facilitate access. Future products may face pressure to propose similar options (while addressing shortcomings in the Zolgensma program)

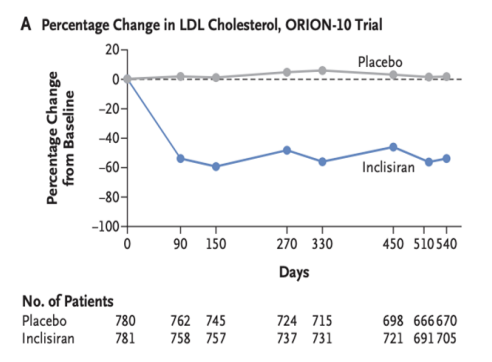
SOURCE: 1. https://www.novartis.com/news/media-releases/avexis-receives-ec-approval-and-activates-%22day-one%22-access-program-zolgensma-only-gene-therapy-spinal-muscular-atrophy-sma

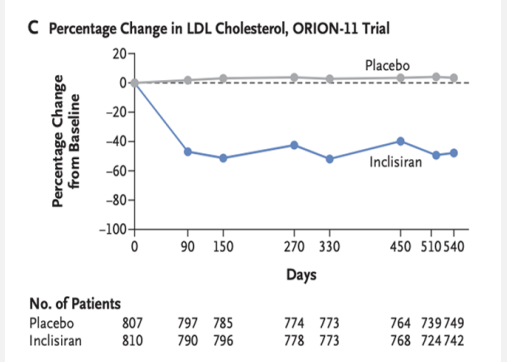
2. https://www.pharmazeutische-zeitung.de/novartis-soll-haertefallprogramm-bezahlen/ GBA: Gemeinsamer Bundesausschuss (Joint Federal Commission), VUC: Verband der Universitätsklinika Deutschlands (Association of University Hospitals of Germany)

Beyond the traditional paths of MEAs to support patient access, Leqvio provides an innovative example of clinical trial collaboration with the UK's NHS

Company	Novartis
Therapeutic type	siRNA targeting PCSK9
Indication	Primary hypercholesterolaemia / mixed dyslipidaemia
FDA/EMA approvals	NA / Dec 2020
Study	ORION-4 to be conducted within the NHS (double blind RCT)

Efficacy[1]





ORION-4 to be conducted within the NHS - data not yet published

Previous phase 3 trials (external to UK NHS):

- **ORION-10** (n=1561)
  - 52.3% reduction in LDL-C at 17 months
- **ORION-11** (n=1617)
  - 49.9% reduction in LDL-C at 17 months

Countries

UK

Timing

Study start: Oct 2018

Expected publication of NICE review: July 2021

Terms of agreement

Leqvio phase 3 clinical trial (ORION-4) to be run within the NHS:

- UK partial funding via National Institute for Health Research (NIHR) (part of the Department of Health and Social Care)
- NHS medical records are being used to identify eligible patients
- Faster access through a NICE accelerated review

Payer agreement

15,000 patients enrolled in the UK NHS and in the US.

ORION-4 NHS trial

- First-in-class, large-scale clinical trial conducted within the health service
- Innovative methodology for national identification of eligible patients through their digital NHS records
- All potentially eligible patients will be invited to a screening at their local NHS trial center (40 across the UK)

Next steps

- NICE accelerated review
- Proposed discount and novel population-level commercial agreement

The UK is aiming to make the route to market faster, cheaper and more efficient for all parties, ensuring it remains a priority launch market for innovative medicines

Reimbursed in Germany. No ATU in France, to date no published MEAs in Italy and Spain

SOURCE: 1. Ray, et al. Two Phase 3 Trials of Inclisiran in Patients with Elevated LDL Cholesterol. N Engl J Med 2020; 382:1507-1519 (https://www.nejm.org/doi/full/10.1056/NEJMoa1912387)
2. https://www.gov.uk/government/news/new-heart-disease-drug-to-be-made-available-for-nhs-patients

Trends and implications for Biopharma

Trends in MEAs	Implications for biopharma
Across markets: Greater use of CED as payers move to Health Technology Management and develop infrastructure to capture RWD	Manufacturers should be prepared with MEA proposals at launch. These proposals should be tailored to evidence gaps / uncertainties of the product (please see next slide)
Across markets: PBR with staged payments will likely be reserved for a small number of very high-cost therapies	For high-cost products with promise of transformative outcomes, real world registries should be designed and implemented well in advance of launch
Across markets: For majority of products, FBAs will likely remain the “default” option, as payers are unwilling to invest significant additional effort to track patient outcomes	Payer engagement and co-creating solution are important but high degree of publicity is likely to attract payer pushback
For individual markets: Some markets are more open to experimentation than others (e.g., UK post-Brexit, Spain with Valtermed), and can be approached for innovative agreements	Depending on a manufacturer’s appetite for risk, there is opportunity to seek out innovative collaborations with individual health systems (e.g., study collaboration in the UK)

MEAs should be tailored to payer-specific objections to the product

NOT EXHAUSTIVE

Key considerations for MEAs

1. Have **clarity internally** on the **range of acceptable MEAs** (simpler is better)
2. Pull through to the **business case** and **clarify upside**
3. Be proactive in **payer engagement** with proposed solutions
4. Have a system in place to **track outcomes** and **derive insights**
5. Plan for **contingencies and risks** (e.g., disclosure, parallel trade) and leave options to renegotiate if possible

Challenges to demonstrating product value	Examples for MEA solutions
Insufficient competitive differentiation	Discounts/rebates, price-volume agreements
Different value in different indications	Discounts/rebates in specific indications or adjusted across indications
Unmanageable budget impact	Price-volume agreements
International price referencing	Discounts/rebates
Uncertainty with transformative or “curative” clinical benefit	CED, patient-level PBA
High risk of over/under-payment (high uncertainty with cost-effectiveness)	CED, patient-level PBA, discounts/rebates, patient caps

Given the administrative burden, CEDs and patient-level PBAs will likely be limited to transformative, very high-cost therapies. Feasibility for implementation also needs to be considered (e.g., measure outcomes in months not years)

FBA PBA

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