Is EU Legislation favourable for innovation?

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CRT Meeting Amsterdam November 22nd, 2023

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Is EU Legislation favourable for innovation?

1. **What is innovation?**
2. Innovation in CVM
3. The Euroepan Medical Agency – current and new regualtion
4. European Medical Devices Regulation
5. Conclusion

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Is EU Legislation favourable for **innovation**?

What is innovation?

Wikipedia?


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2023
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CARDIOLOGICHE
TORINESI
35e GIORNATE

Is EU Legislation favourable for **innovation**?

Innovation refers to the process of introducing new ideas, methods, products, or services that bring about significant positive change or improvement. It involves the application of creativity, problem-solving, and inventive thinking to address existing challenges or meet new needs. Innovation can occur in various fields, including technology, business, science, healthcare, education, and more.

- Key aspects of innovation include:

1. **Creativity:** Innovation often starts with creative thinking, the ability to generate new and original ideas.
2. **Problem-Solving:** Innovations typically address specific problems or challenges, offering solutions that are more effective, efficient, or novel than existing approaches.
3. **Implementation:** Innovation involves turning ideas into practical and tangible outcomes, such as new products, services, processes, or business models.
4. **Risk-Taking:** Innovation often requires taking risks, as it involves venturing into uncharted territory. Not all innovative endeavors are successful, but the potential benefits can be substantial.
5. **Continuous Improvement:** Innovation is an ongoing process. It's not limited to groundbreaking inventions but also includes incremental improvements to existing systems, products, or services.
6. **Adaptability:** Innovators must be open to change and adaptable to evolving circumstances. Flexibility and a willingness to adjust strategies are crucial for successful innovation.
7. **Market Relevance:** Successful innovations often meet the needs and demands of the market, providing value to users or customers.

Innovation can take various forms, such as technological advancements, process improvements, business model changes, and more. It plays a crucial role in driving economic growth, improving quality of life, and addressing societal challenges. Companies and individuals that embrace innovation are often better positioned to stay competitive and thrive in dynamic environments.

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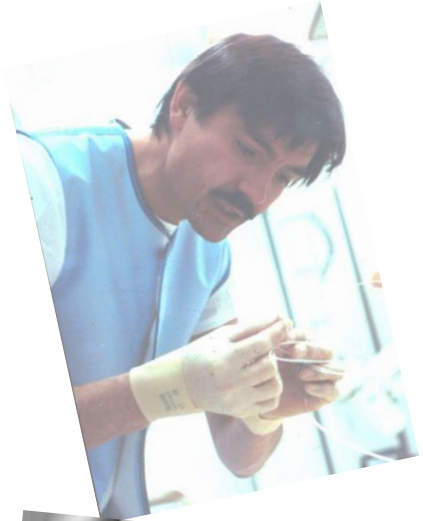
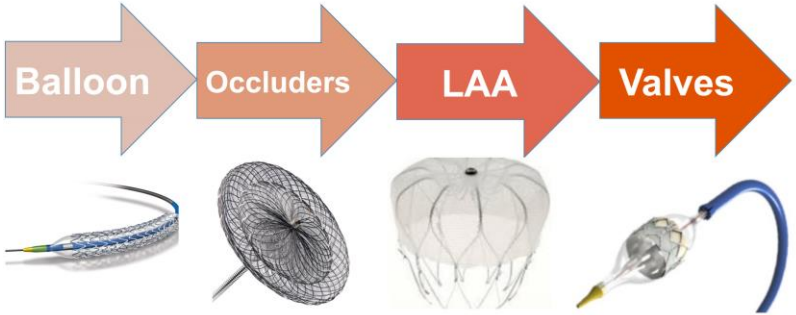
Innovation in Cardiovascular Medicine



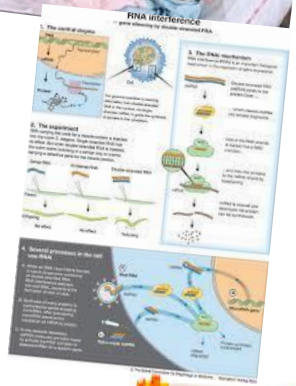


Coronary Artery Disease
Renal Artery Stentig
Carotid Stenting

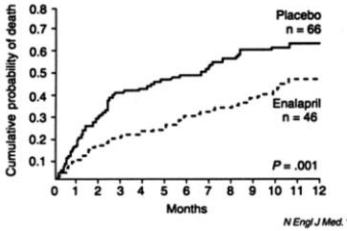
Patent Foramen
Ovale
Atrial Septal Defect
Ductus Botalli

Left Atrial Appendix
Occluder in Cardiac
Thromboembolism

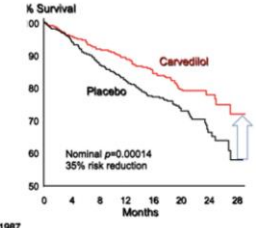
TAVI for Aortic Stenosis
Mitralclip for Mitral
Regurgitation
Percutaneous Mitral
Valve Replacement



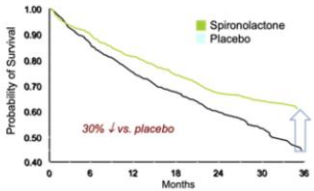
CONSENSUS TRIAL
(ENALAPRIL vs. Placebo)
NYHA IV



COPERNICUS TRIAL
(Carvedilol vs. Placebo)
LVEF <35%

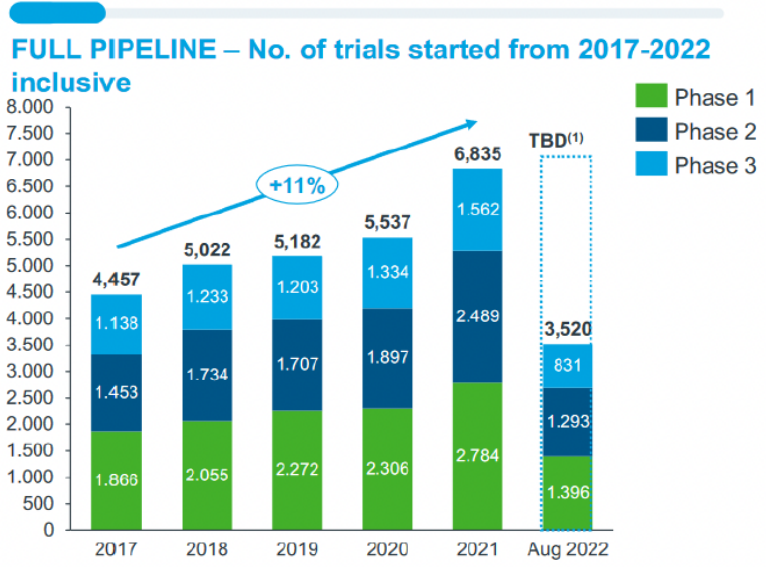


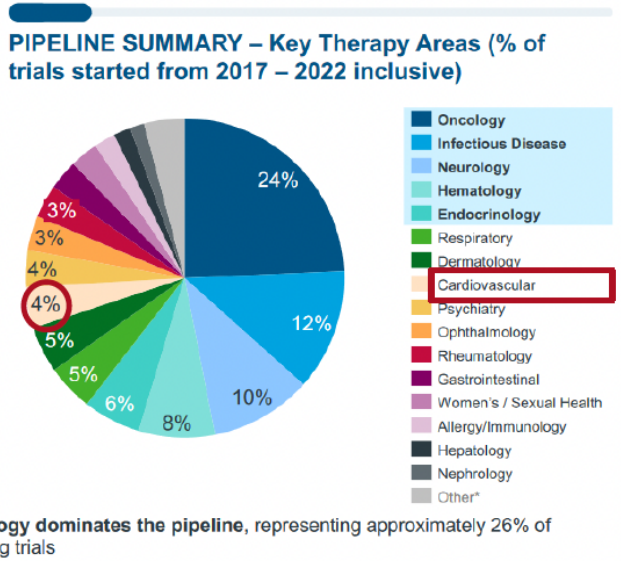
RALES TRIAL
(Spironolactone vs. Placebo)
LVEF < 35%



N Engl J Med. 1987

…but now a shrinking pipeline!





Oncology dominates the pipeline, representing approximately 26% of ongoing trials

Since 2017, the volume of pipeline activity has increased steadily year-on-year

Nevertheless, only 4% of the trials started between 2017 and 2022 were in the CVD area

EFPIA Pipeline Innovation Review, 2022

A decreasing number of newly authorised medicines…

Out of 89 medicines authorized by the EMA in 2022,
0 new medicines in the cardiovascular disease area

Oncology	**23**
Neurology	14
Endocrinology	12
Hematology	6
Metabolism	5
Immunology/Rheumatology	4
Other	25
Cardiovascular Disease	**0**

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Pharma Products

One Institution

Streamlined regulatory procedures: Proposals are in place to streamline the EU's regulatory procedures, reducing review and approval timeline >50 days (from 277 to 226 days) for centrally authorized products and reducing to 2 Committes, i.e. Committee for Medicinal Products for Human Use (CHMP) and Pharmacovigilance Risk Assessment Committee (PRAC).

should be granted marketing authorization.

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Table 1 **Obtaining an EU marketing authorization**

What?	When?	Why?
Submission of eligibility request	7–18 months before submission	To find out whether a product can be evaluated under the centralized procedure
Notification of intention to submit an application	7 months before submission	To notify EMA of the intended submission date
Appointment of rapporteurs by the EMA Committee for Medicinal Products for Human Use (CHMP) and the Pharmacovigilance Risk Assessment Committee (PRAC)		
Pre-submission meetings	6–7 months before submission	To obtain regulatory advice from EMA
Reconfirmation of communicated submission date by the applicant	2–3 months before submission	To inform EMA of any delays or cancellations
submission of the application and its technical validation by EMA		To make sure all essential regulatory elements required for scientific assessment are included
Scientific evaluation	Up to 210 active days	
CHPM scientific opinion		Opinion on whether or not the medicine may be authorized
European Commission decision on marketing authorization	Within 67 days of receipt of CHMP opinion	The European Commission is the authorizing body for all centrally authorized products and takes a legally binding decision based on EMA's recommendations

), 1–3

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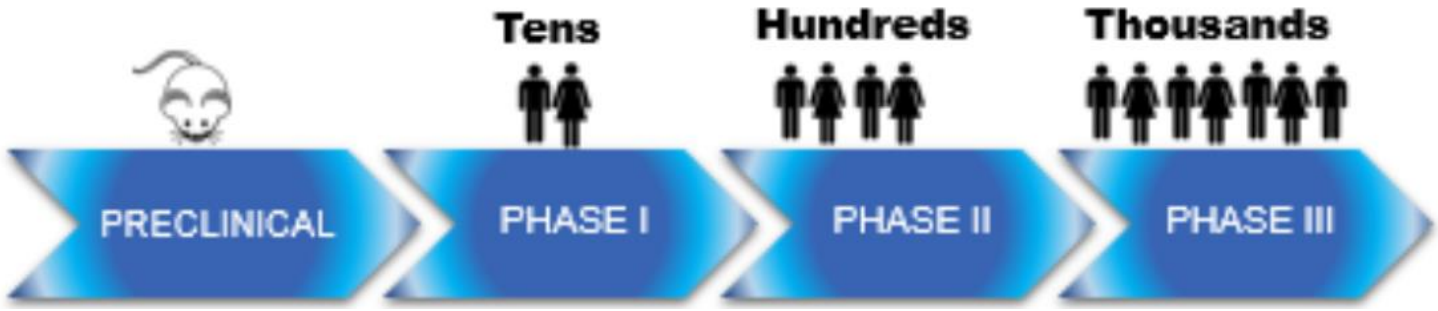

Novelty?

Breakthrough?

Incremental?

Rehash?

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Is **EU Legislation** favourable for innovation?

Innovative Product?

- Unique
- Very safe
- Improves quality of life (PRO)
- Reduces MACE
- Addresses unmet medical need
- Cost-Effective, Affordable

Breakthrough
Incremental

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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Unmet Medical Needs (UMN)

Products can receive +6 months of regulatory data protection, if the product addresses UMN, that is:

- if they are an **orphan medicinal product** (1:2'000 or less).
- if at least one of its indications relates to a **life threatening** or severely debilitating disease.
- there is **no product authorised in the EU** for such disease.
- despite products being authorised for such disease, the disease is associated with a remaining **high morbidity or mortality**
- AND the use of the medicinal product results in a **meaningful reduction in disease morbidity or mortality** for the relevant patient population.

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Unmet Medical Needs (UMN)

What would it mean for Cardiovascular conditions?

- **Orphan Disease:** Genetic CMP, TTS, SCAD.
- **Life threatening disease**: Cardiogenic shock, acute heart failure, aortic dissection, sudden death (e.g. CMP, Channelopathies) among others.
- N**o product authorised in the EU**: Novelty.
- **High morbidity or mortality:** Most CVD, but commonly associated in the **l**ong-term CVD.
- **Meaningful reduction in morbidity or mortality, QoL:** 5, 10, 20% in 1, 3 or 5years??

Current definition of UMN – regulatory pathways

Conditional marketing authorisation:

- → for products where the benefit-risk balance is such that the immediate availability outweighs the limitations of less comprehensive data than normally required, i.e. medicines with an established potential to address an unmet medical need.

- Article 4 paragraph 2 of Commission Regulation (EC) No. 507/2006 specifies that unmet medical needs mean a condition for which ***there exists no satisfactory method of diagnosis, prevention or treatment in the Union*** *or, even* ***if such a method exists****, in relation to which the medicinal product concerned will be of* ***major therapeutic advantage*** *to those affected.*

The question is what does ".. *no satisfactory method*…" mean?

- Small effect size?
- Considerable safety risk?
- Incremental benefirt vs. breakthrough?
- Cure vs. treatment?

- unmet medical need definition concept "borrowed" from CMA and applied in context of fostering accelerated assessment

https://www.ema.europa.eu/en/documents/presentation/presentation-unmet-medical-need-j-llinares-ema_en.pdf

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Cancer Drugs

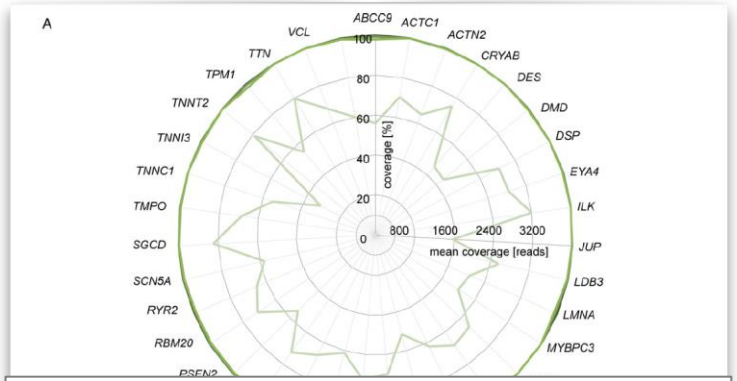
- Short duration
- Small numbers (Phase II
- Surrogate endpoints
- Conditional approval

Cardiovascular Drugs

- Phase I to III
- Huge numbers
- Hard endpoints
- Huge investment

Unmet medical need in CVD

Unmet medical need: Cure vs. Treatment



What surrogates could we consider?

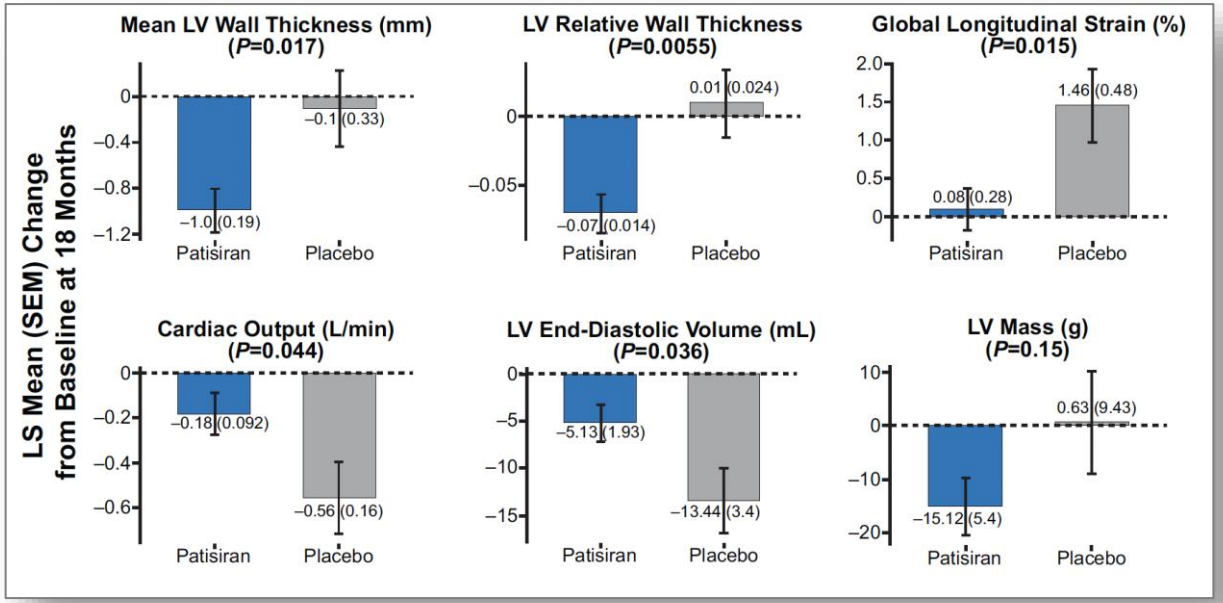
- Patient-reported Outcomes
- QoL 8KCCQ, 6 minute walk test)
- Biomarkers (NT-proBNP, others)
- LVOT pressure gradients
- ICD activities

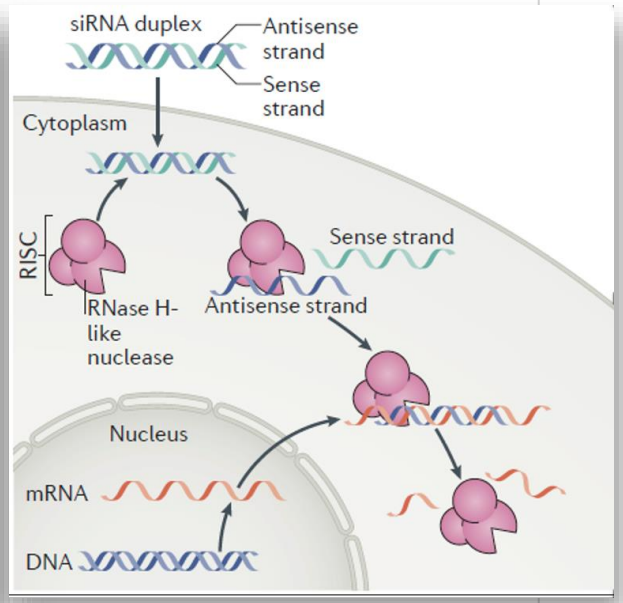
Precision Medicine in Cardiomyopathies

- Genetic characterization of CMP
- Heterogenous populations
- Potential targets for gene therapy
- Relatively small patient population (not suitable for large trials)
- Precision medicine requires new trials with defined surrogate EPs
- The next generation CVD needs a different approval scheme than traditional CVD

Effects of Patisiran, an RNA Interference Therapeutic, on Cardiac Parameters in Patients With Hereditary Transthyretin-Mediated Amyloidosis

Analysis of the APOLLO Study





Circulation. 2019;139:431–443.

Unmet medical need: Cure vs. Treatment

In vivo CRISPR base editing of *PCSK9* durably lowers cholesterol in primates

https://doi.or
Received: 6 D
Accepted: 11
Published or
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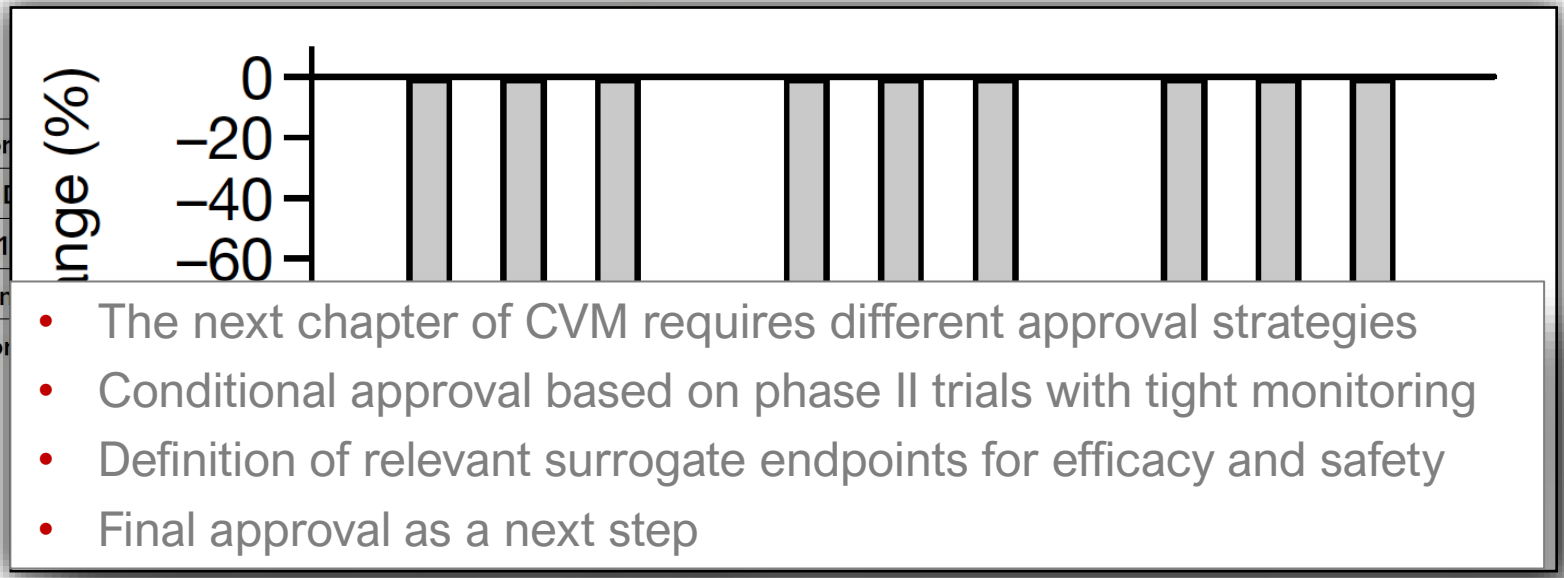


- The next chapter of CVM requires different approval strategies
- Conditional approval based on phase II trials with tight monitoring
- Definition of relevant surrogate endpoints for efficacy and safety
- Final approval as a next step

Unmet medical need: Cure vs. Treatment

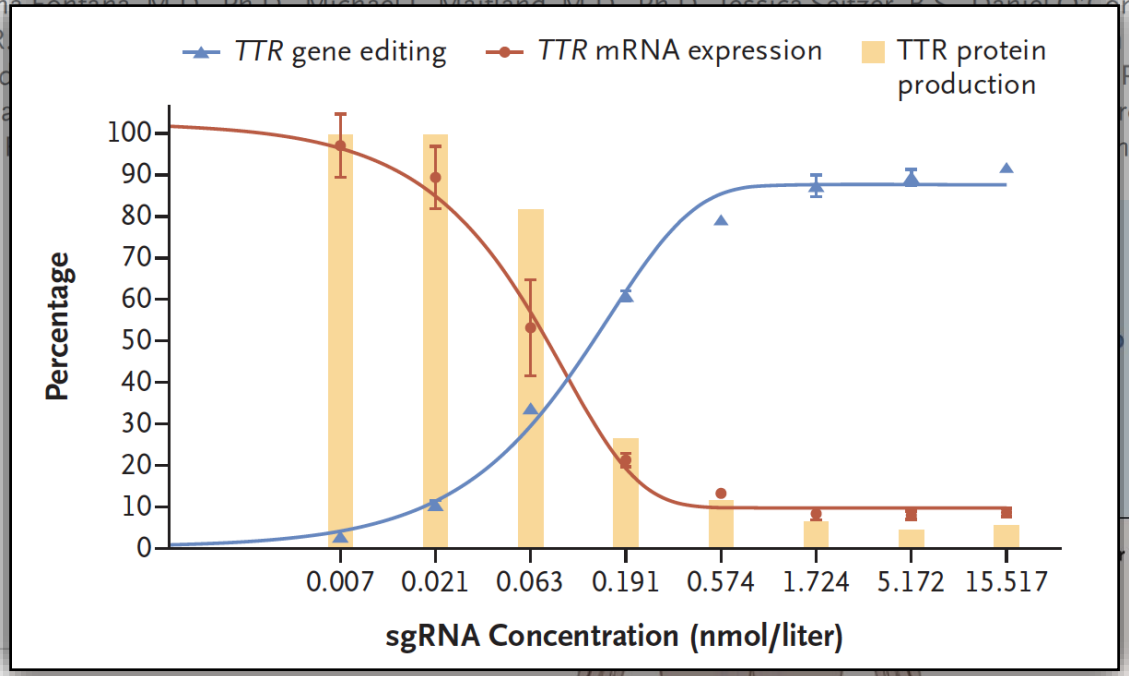
Verve Therapeutics Announces Clearance of Investigational New Drug Application by the U.S. FDA for VERVE-101 in Patients with Heterozygous Familial Hypercholesterolemia

The FDA announced on October 23, 2023 the lifting of the clinical hold and clearance of its Investigational New Drug (IND) application by the U.S. Food and Drug Administration (FDA) to conduct a clinical trial in the United States evaluating VERVE-101 for the treatment of heterozygous familial hypercholesterolemia (HeFH). VERVE-101 is an investigational, in vivo base editing medicine designed to be a single-course treatment that inactivates the PCSK9 gene in the liver to durably lower blood low-density lipoprotein cholesterol (LDL-C).

Unmet medical need: Cure vs. Treatment

CRISPR-Cas9 In Vivo Gene Editing for Transthyretin Amyloidosis

Julian D. Gillmore, M.D., Ph.D., Ed Gane, M.B., Ch.B., Jorg Taubel, M.D., Justin Kao, M.B., Ch.B.,



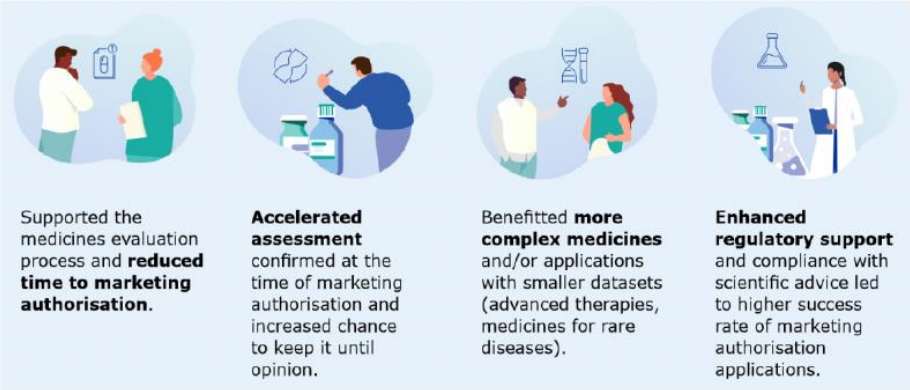
PRIME scheme: overview

- PRIME is a scheme run by EMA to enhance support for the development of medicines that target an UMN.
- The scheme is based on enhanced interaction and **early dialogue** with developers of promising medicines to optimise development plans and **speed up evaluation** so these medicines can reach patients earlier.
- Early and proactive support to medicine developers to optimise the generation of robust data on a medicine's benefits and risks and enable accelerated assessment of medicines applications.

PRIME:

Analysis of the first 5 years' experience

Findings, learnings and recommendations



Supported the medicines evaluation process and **reduced time to marketing authorisation**.

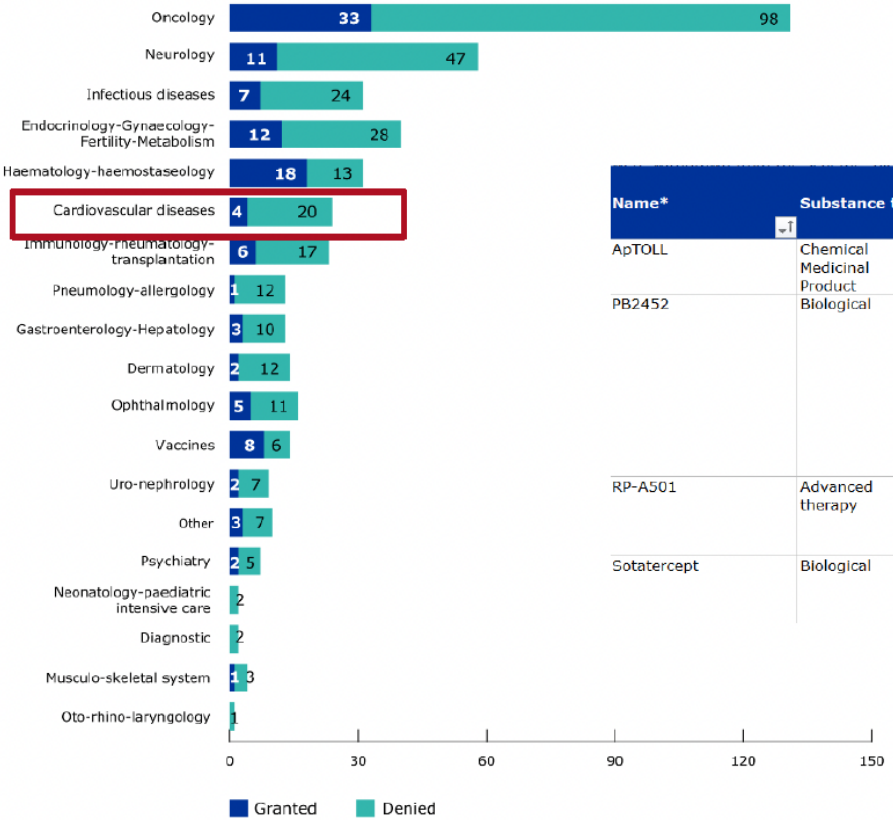
Accelerated assessment confirmed at the time of marketing authorisation and increased chance to keep it until opinion.

Benefitted **more complex medicines** and/or applications with smaller datasets (advanced therapies, medicines for rare diseases).

Enhanced regulatory support and compliance with scientific advice led to higher success rate of marketing authorisation applications.

https://www.ema.europa.eu/en/documents/report/prime-analysis-first-5-years-experience_en.pdf

PRIME scheme: where does CVD stand?



Name*	Substance type	Therapeutic area	Therapeutic indication	Type of data supporting request	Type of applicant	Date of granting PRIME eligibility
ApTOLL	Chemical Medicinal Product	Cardiovascular diseases	Acute Ischemic Stroke	Nonclinical + Clinical exploratory	SME	1/26/2023
PB2452	Biological	Cardiovascular Diseases	Reversal of antiplatelet effects of ticagrelor in patients with uncontrolled major or life-threatening bleeding or requiring urgent surgery or invasive procedure	Nonclinical + Clinical exploratory	Other	1/30/2020
RP-A501	Advanced therapy	Cardiovascular Diseases	Treatment of Danon disease	Nonclinical + Clinical exploratory	Other	5/25/2023
Sotatercept	Biological	Cardiovascular diseases	Treatment of pulmonary arterial hypertension (PAH)	Nonclinical + Clinical exploratory	SME	4/30/2020

Recommendations adopted by June 2023 – tot. granted: 118

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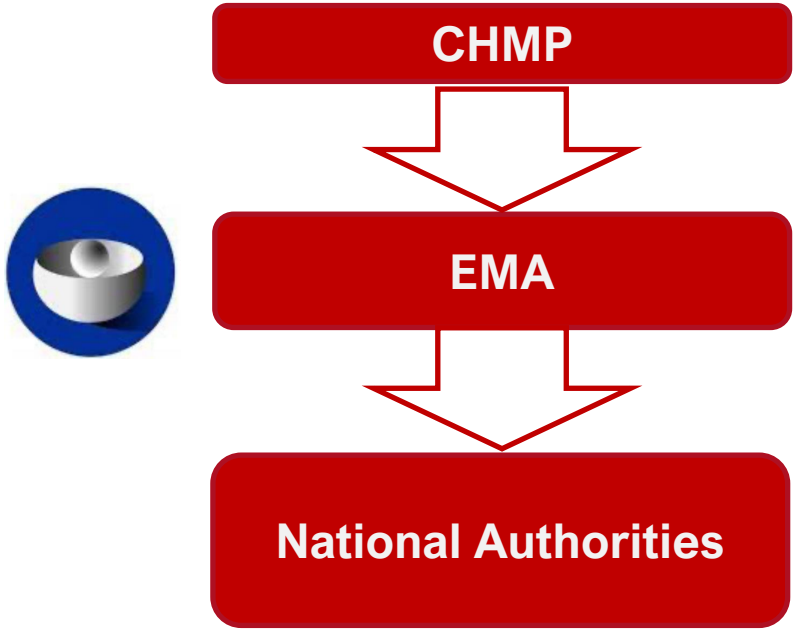

Recomm

Confirm

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Market A

European Heart Journal (2023) 00, 1–3

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EU-MDR

- No EU Institute
- Decentralized
- Heterogenous
- Complex

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