Nucleic acid-based therapeutics for CVDs:

safety insights from EMA Scientific Advice and EU marketing authorisations

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ESC
European Society of Cardiology

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The presenters do not have any conflict of interests.

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Presentation Overview

- ✓ Regulatory framework - guidelines
- ✓ Oligonucleotides & Gene therapies
  - *Regulatory status*
  - *Drug development challenges*
- ✓ Scientific Advice / Safety aspects
  - *Oligonucleotides (ASO and siRNA)*
  - *Gene therapies (AAV, CRISPR-Cas)*

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Oligonucleotides (ASO and siRNA)

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✓ Synthetic oligonucleotides are at the interface of small molecules and biologicals

- EMA Concept paper addresses the need to establish a Guideline on the Development and Manufacture of Synthetic Oligonucleotides (EMA/CHMP/QWP/735423/2022) / end of consultation Dec 2022

- In general, ICH M3(R2) and especially ICH S6(R1) guidelines should be followed for non-clinical development of oligonucleotides.

Assessment of the genotoxic potential of antisense oligodeoxynucleotides - Scientific guideline (EMEA/CHMP/SWP/199726/2004)

ICH topic proposal: *Guideline on non-clinical safety studies for oligonucleotides-based therapeutics*.

- No specific EU clinical guideline

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Advanced therapy medicinal products (ATMPs)

Gene therapy medicinal products

Somatic cell therapy medicinal products

Tissue engineered products

21 May 2015
EMA/CAT/600280/2010 rev.1
Committee for Advanced Therapies (CAT)

Reflection paper on classification of advanced therapy medicinal products

https://www.ema.europa.eu/system/files/documents/scientific-guideline/wc500187744_en.pdf

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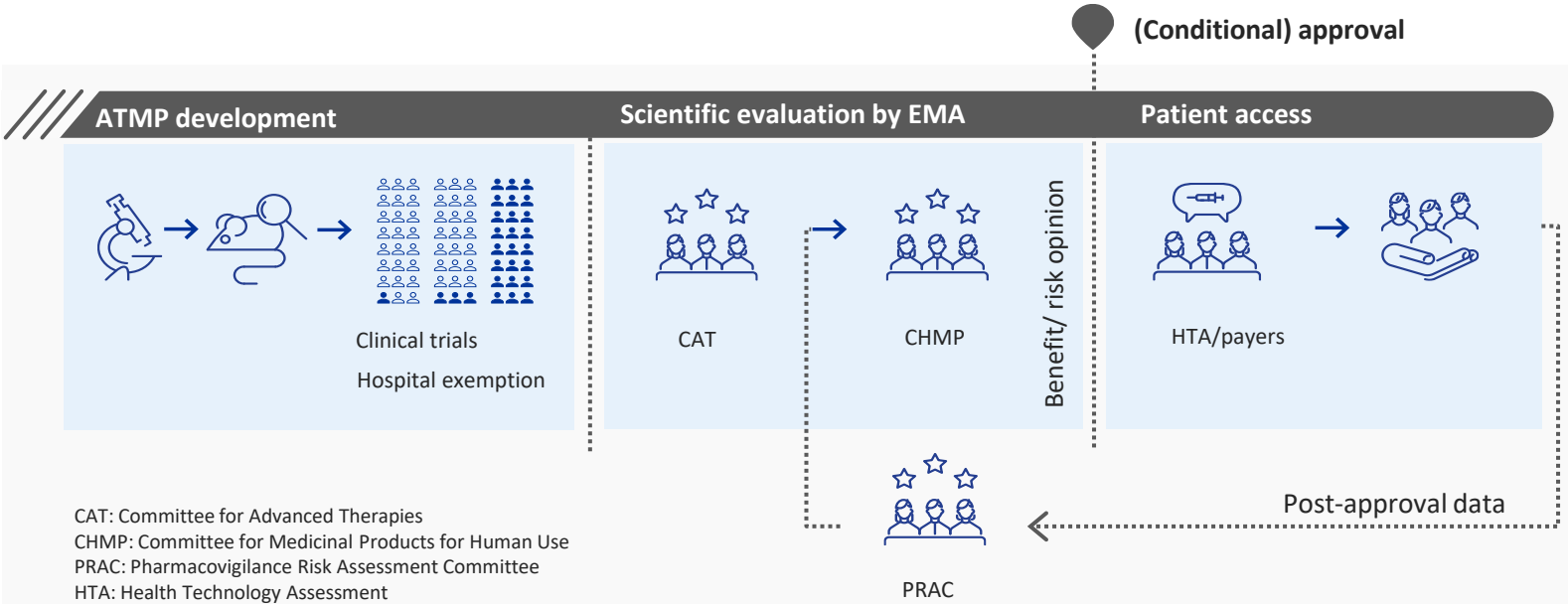
Advanced therapy medicinal products (ATMPs)

ATMPs are regulated as medicinal products & authorised in the EU via the centralised procedure



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Advanced therapy medicinal products (ATMPs)

Guidelines relevant for advanced therapy medicinal products

Gene therapy

- ICH guideline S12 on nonclinical biodistribution considerations for gene therapy products - Step 2b (EMA/CHMP/ICH/318372/2021)
- Questions and answers on comparability considerations for advanced therapy medicinal products (ATMP) (EMA/CAT/499821/2019)
- The **overarching guideline** for human gene therapy medicinal products is the Guideline on the quality, non-clinical and clinical aspects of gene therapy medicinal products (EMA/CAT/80183/2014)
- **Questions and answers** on gene therapy (EMA/CAT/80183/2014)
- Guideline on scientific requirements for the **environmental risk assessment** of gene therapy medicinal products (CHMP/GTWP/125491/06)
- Reflection paper on **design modifications** of gene therapy medicinal products **during development** (EMA/CAT/GTWP/44236/2009)
- Reflection paper on quality, non-clinical and clinical issues relating specifically to recombinant adeno-associated viral **vectors** (CHMP/GTWP/587488/07)
- ICH Considerations - **Oncolytic Viruses** (EMEA/CHMP/ICH/607698/2008)
- Guideline on quality, non-clinical and clinical aspects of medicinal products containing **genetically modified cells** (CAT/CHMP/GTWP/671639/2008)
- Guideline on the non-clinical studies required **before first clinical use** of gene therapy medicinal products (EMEA/CHMP/GTWP/125459/2006)
- Guideline on non-clinical testing for **inadvertent germline transmission** of the gene transfer vectors (EMEA/273974/2005)
- Reflection paper on management of clinical risks deriving from **insertional mutagenesis** (CAT/190186/2012)
- Guideline on **follow-up of patients** administered with gene therapy medicinal products (EMEA/CHMP/GTWP/60436/2007)
- Guideline on **safety and efficacy follow-up and risk management** of advanced therapy medicinal products (EMEA/149995/2008)

https://www.ema.europa.eu/en/human-regulatory-overview/advanced-therapy-medicinal-products-overview/guidelines-relevant-advanced-therapy-medicinal-products

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Tavridou A, Rogers D, Bonelli M, Schiel A, Hidalgo-Simon A.

Towards a better use of scientific advice for developers of advanced therapies.

Br J Clin Pharmacol. 2021;87:2459–2464.
https://doi.org/10.1111/bcp.14672

Oligonucleotides for CVD in the EU

Product	Type / Target	Indication	Regulatory status
Mipomersen (Kynamro)	**ASO** **target: apolipoprotein B**	familial hypercholesterolaemia Initially including severe heterozygous' and 'homozygous'	**Dec 2012-refusal of MA** **Mar 2013- rexamination confirmation of MA refusal**
Inclisiran (Leqvio)	**siRNA** **GalNAc-ligand** **Target: PCSK9**	Homozygous familial hypercholesterolemia, primary hypercholesterolaemia (heterozygous familial and non-familial)	**Oct 2020 – approval of Full MA**
Volanesorsen (Waylivra)	**ASO** **target: ApoCIII**	familial chylomicronemia syndrome (FCS)	**Feb 2019 – approval of Conditional MA**

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Oligonucleotides for CVD in the EU

Product	Type / Target	Indication	Regulatory status
Patisiran (Onpattro)	**siRNA** **LNP formulation** **Target: variant and wtTTR mRNA**	transthyretin-mediated amyloidosis (ATTR amyloidosis) stage 1 or Stage 2 polyneuropathy **[benefit demonstrated in cardiomyopathy]**	**Orphan designation** **Accelerated assessment** **Jul 2018 – Full MA**
Vutrisiran (Amvuttra)	**siRNA** **GalNAc-ligand** **Target: variant and wtTTR mRNA**	transthyretin-mediated amyloidosis (ATTR amyloidosis) stage 1 or Stage 2 polyneuropathy **[benefit demonstrated in cardiomyopathy]**	**Orphan designation** **Jul 2021 – Full MA**
Inotersen (Tegsedi)	**ASO** **Target: variant and wtTTR mRNA**	transthyretin-mediated amyloidosis (ATTR amyloidosis) stage 1 or Stage 2 polyneuropathy [no benefit demonstrated in cardiomyopathy]	**Orphan designation** **Accelerated assessment** **May 2018 – Full MA**

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Gene therapies authorised in the EU

AAVs

NAME	Condition	Orphan	PRIME	Comment
Glybera	Lipoprotein lipase deficiency	Yes	No	MA not renewed (MA ended Oct. 2017)
Imlygic	Melanoma	No	No	
Strimvelis	ADA-SCID	Yes	No	
Yescarta	B-cell cancers	Yes	Yes	
Kymriah	B-cell cancers	Yes	Yes	
→ Luxturna	Retinitis pigmentosa Leber's congenital amaurosis	Yes	No	
Zynteglo	beta-thalassaemia	Yes	Yes	MA withdrawn March 2022
→ Zolgensma	Spinal muscular atrophy	Yes	Yes	
Libmeldy	Metachromatic leukodystrophy	Yes	No	
Tecartus	B-cell cancers	Yes	Yes	
Skysona	Adrenoleukodystrophy	Yes	Yes	MA withdrawn Nov. 2021
Abecma	Multiple myeloma	Yes	Yes	
Breyanzi	Blood cancers	No	Yes	
Carvykti	Multiple myeloma	Yes	Yes	
Upstaza	Aromatic L-amino acid decarboxylase deficiency	Yes	No	
→ Roctavian	Haemophilia A	Yes	Yes	
→ Hemgenix	Haemophilia B	Yes	Yes	

CRISPR/Cas	Condition
Casgevy	beta-thalassemia & severe sickle cell disease

EMA positive opinion (December 2023)

EC decision pending

Drug development challenges

- **The regulatory perspective:**

- ✓ **Limited clinical pharmacology program**
- ✓ **Limited clinical data**
- ✓ **Limited follow-up**
- ✓ **Limited relevance of animal models**
- ✓ **Poor background**

KEY PRINCIPLEs in medicine's assessment
Positive B/R
Adequate risk mitigation strategies

❖ **RISK-BASED APPROACH for ATPMs:** - a strategy to determine the extent of quality, non-clinical and clinical data to be included in the Marketing Authorisation Application dossier

- early risk identification and consequent control strategies

[EMA/CAT/CPWP/686637/2011]

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Scientific Advice / Safety aspects

- ✓ Scientific advice and protocol assistance requests: 23 products reviewed by the SAWP
- ✓ Technology: 8 ASO, 9 siRNA, 5 AAV, 1 CRISPR-Cas
- ✓ **Scope of clinical questions related to safety**
  - Clinical Pharmacology [ADME, TQT; DDI, Special populations]
  - Dose selection
  - Safety monitoring & follow up

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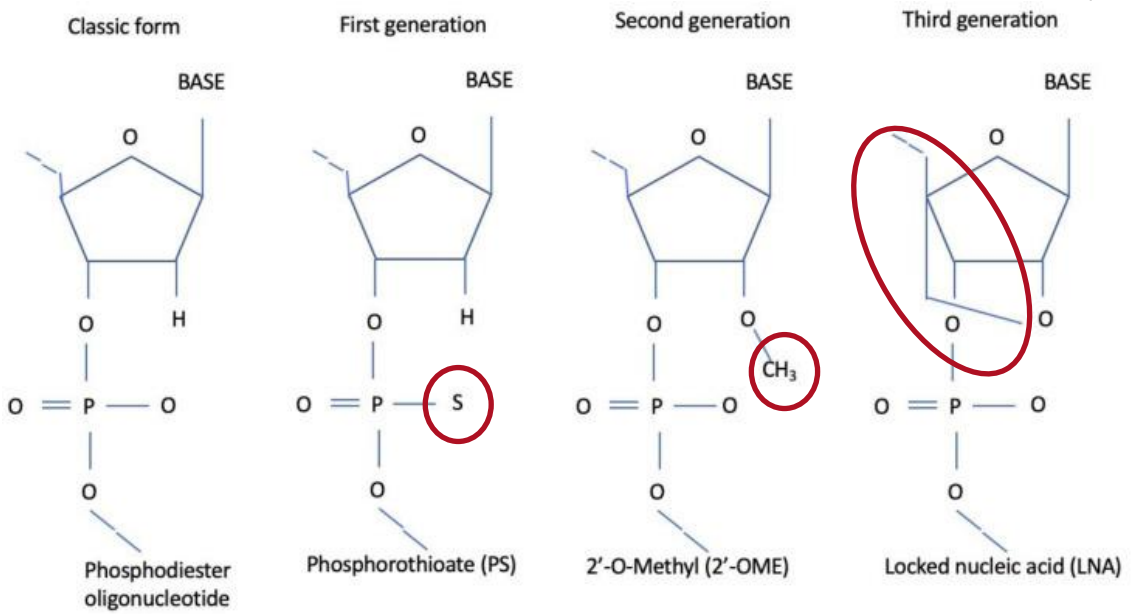
Scientific Advice / Safety aspects

- **Oligonucleotides (ASO and siRNA)**

- The role of chemistry:

Chemical modifications can improve ASO-RNA hybridization affinity, enhance nuclease resistance, decrease toxicity like immunostimulation and modulate pharmacokinetics.



Karaki S. et al., DOI: 10.5772/intechopen.82105;
Fig.: Gareri C et al., J Clin Med. 2022; 11: 3884

Scientific Advice / Safety aspects

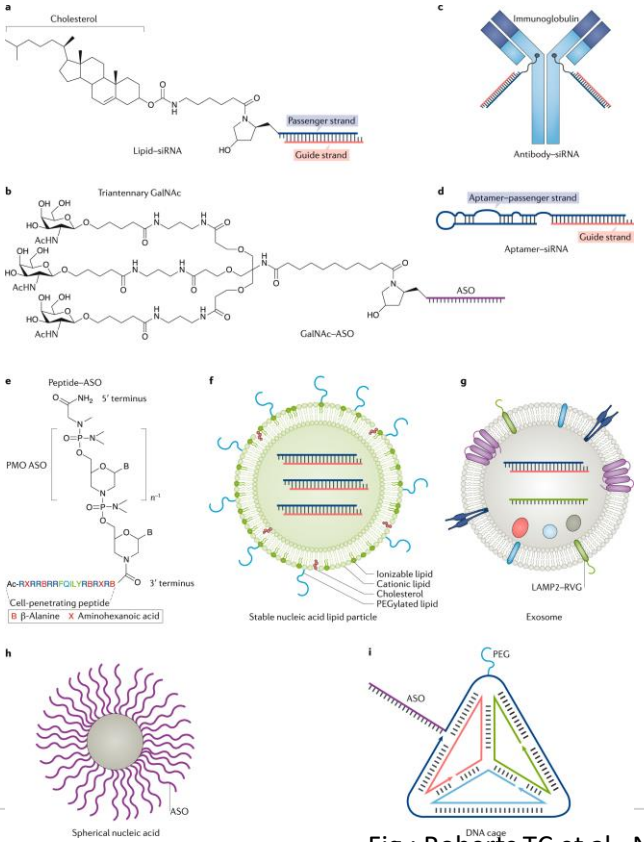
- The role of chemistry: delivery strategies

Lipid–siRNA conjugate

GalNAc conjugated to ASO

Peptide–ASO conjugate

Spherical nucleic acid nanoparticle



Antibody–siRNA conjugate

Aptamer–siRNA conjugate

Nucleic acid lipid particle encapsulating siRNAs

Engineered exosome with brain-targeting rabies virus glycoprotein (RVG) peptide displayed on the outer surface

Self-assembled DNA cage tetrahedron nanostructure

Fig.: Roberts TC et al., Nature Reviews Drug Discovery 2020; 19: 673–694

Scientific Advice / Safety aspects

- **Gene therapies (AAV and CRISPR/Cas)**

- **Quality considerations:**

In vivo and ex vivo approaches
Gene editing techniques
Delivery systems
Extent of genomic modifications

- **Safety implications:**

- Toxicity caused by transgene overexpression as well as immune responses towards transgene or vector could all influence the durability of effect (**on-target effects**)
- **Off-target** potential to be addressed (genomic integrity, including chromosomal rearrangements, large insertions or deletions, integration of exogenous DNA, and potential oncogenicity or insertional mutagenesis)
- Toxicity associated to **delivery modality**

Scientific Advice / Safety aspects

- **Oligonucleotides (ASO and siRNA)**

ADME

- Conventional radio-labelled ADME study limited by long drug half-life in tissues
- **Supported by non-clinical data** for distribution, absorption not a requirement for i.v. or s.c administration, metabolism and excretion to be profiled in humans

TQT

- **Totality of evidence** to establish QT prolongation risk (hERG, non-clinical data, exposure-response analysis covering highest therapeutic exposures); cardiovasuclar toxicity to be included in the **safety monitoring** program (ref. EMA/CHMP/ICH/415588/2020; CHMP/ICH/2/04)

Scientific Advice / Safety aspects

- **Oligonucleotides (ASO and siRNA)**

DDI

- **Low risk for DDIs** (CYP-enzymes, transporters) in the absence of novel chemical modifications, linkers, ligands, or formulations.

In depth evaluation whether **in vivo DDI studies may be warranted**

- novel chemical modifications, linkers, ligands, or formulations
- In vitro: interaction potential
- disease with impact on drug metabolizing enzymes, transporters or siRNA related protein activity
- mechanism based interactions, direct inhibition and induction of siRNA-related proteins (ASPGR and AGO2)

Scientific Advice / Safety aspects

- **Oligonucleotides (ASO and siRNA)**

Special Populations

- PK/PD profiling in renal and hepatic impairment is a **requirement**
- Experimental data (mild, moderate and severe impairment patients) are needed, also in the event of **Modelling&Simulation** exercise (i.e. to inform/validate the modelling)
- Dissociation between plasma PK and PD to be considered (i.e. population PD analysis are encouraged, population PK modelling less relevant)
- **Safety** in these subgroups to be explored
- Non-clinical distribution data predictive of drug effect on kidney and liver function (i.e.off-target effects)

Scientific Advice / Safety aspects

ESC

- **Oligonucleotides (ASO and siRNA)**

Dose selection and dosing interval

- Generally supported by PK/PD modelling due to difficulties for a long dose-response study:
  - dose-PD rather than exposure-PD relationships
  - informed by pre-clinical drug distribution studies
  - supportive clinical data from early phase trials are required

- Targeted protein reduction level to be substantited
  (thresholds for therapeutic effects are disease-specific)

- Withdrawal extension study eventually needed (based on clinical setting)

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Scientific Advice / Safety aspects

- **Oligonucleotides (ASO and siRNA)**

Safety monitoring and follow-up

- Based upon chemistry and delivery system, non-clinical and clinical experience, as well as known drug class effects
- The sample size and length of follow-up must be adequate to capture safety for an intended chronic use (extension studies and appropriate RMP are generally required)
- Stopping rules can be considered at patient level for toxicity management

Common Adverse Events of Interest : Injection site reactions
Hypersensitivity
Immunogenicity
Hepatic and renal disorders
Cardiovascular safety (EMA/CHMP/50549/2015)

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Scientific Advice / Safety aspects

- **Gene therapies (AAV and CRISPR/Cas)**

Safety monitoring

- Limited role of non-clinical data for AAV toxicity (mediated by immune response)
- Testing for neutralising antibodies to adenovirus prior to treatment
- Cytotoxic T lymphocytes (CTL) responses should also be evaluated, both in the primate model and in the safety trial, against capsid and against transgene.
- Plasma/serum type I interferon levels should be documented
- Concomitant administration with immunoregulators (i.e. steroids)

Scientific Advice / Safety aspects

- **Gene therapies (AAV and CRISPR/Cas)**

Safety follow-up

- Post-marketing follow-up must be carefully planned
- 15 years is the recommended follow-up period
- Deviation from this general rule could be justified on a case-by-case basis using the risk-based approach for ATMPs (Guideline on the risk-based approach, EMA/CAT/CPWP/686637/2011)
- Factors to be considered: dose level, delivery route (targeted or systemic), the vector design (type of enhancer-promoter), whether it encodes genome editing components, the proliferative activity of the (target) tissue, the need for concomitant (mutagenic) therapy during the viremia phase and the patient's age range, comorbidities and life expectancy

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Conclusions

- CV Experience mainly based on oligonucleotides profile

- At the time of drug development:

- Conventional clinical pharmacology program not feasible
- Need for early identification of risks and planning consequent control strategies
- Gene therapies require follow-up extended up to 15 years

- At the time of a MA application:

- risk-based approach
- assuming a clear demonstration of POSITIVE benefit/risk balance, adequate risk management plan to address safety uncertainties (obligatory or requested studies)

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Thank you for your attention

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