Final Version 2023-01-27

Skyddsnivå:

Sätt ett kryss (X) framför rätt skyddsnivå!

X (K0) Ingen/låg
(K1) Grundläggande
(K2) Utökad
(K3) Hög

RNA-based medicines: Opportunities and challenges in non-clinical development

The regulator's perspective

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The opinions expressed during this presentation are those of the speaker, and not necessarily those of the Swedish Medical Products Agency or the European Medicines Agency.

What's the purpose of the non-clinical evaluation

- **Provide support for the rational**
- **Identify target organs for toxicity**
  - severity and reversibility of toxicity and margins of exposure to therapeutic levels
- **Identify parameters for safety monitoring in humans**
- **Support dose selection in FIH/phase I studies**
- **Provide data for safety information on the label**

What non-clinical guidance is currently available for RNA-based products?

ICH guideline S6 (R1) – preclinical safety evaluation of biotechnology-derived pharmaceuticals
Step 5

June 2011 EMA/CHMP/ICH/731268/1998

ICH guideline M3(R2) on non-clinical safety studies for the conduct of human clinical trials and marketing authorisation for pharmaceuticals
Step 5

December 2009 EMA/CPMP/ICH/286/1995

CHMP SWP REFLECTION PAPER ON THE ASSESSMENT OF THE GENOTOXIC POTENTIAL OF ANTISENSE OLIGODEOXYNUCLEOTIDES

January 2005 EMEA/CHMP/SWP/19972/2004

RNA based medicines distinct from - and similar to - both small molecules and biologicals!
New ICH topic proposed on oligonucleotide-based therapeutics.

The principle of 3Rs needs to be considered

- Directive 2010/63/EU on the protection of animals for scientific purposes

Replace
animal studies with non-animal methods

If not possible >

Reduce
animal studies to minimum required and necessary

In addition >

Refine
Practices to minimise stress of study animals

- EMA support the implementation of 3Rs through (e.g.)
  - Guidelines development
  - Scientific/qualification advice on 3R approaches
  - Joint 3Rs Working Party

Opportunities & challenges

Opportunities

Safety largely dependent on platform + target

Possibility to leverage existing knowledge to optimise the non-clinical program in line with 3Rs without compromising risk assessment

> Could simplify development and assessment of RNA-based medicines

> Benefit to patients with rare diseases

Challenges

Defining platforms

Defining requirements for individualised products

New vehicles/ligands for delivery – understanding long term safety

Availability of a pharmacologically relevant species

Key points to address in non-clinical safety evaluation of RNA based medicines

On-target toxicity?

Off-target (hybridization-dependent) toxicity?

For full-length sequence and ’metabolites’.

In silico -> in vitro - >in vivo studies.

Chemistry-dependent class effects:

well-known or new chemistries.

Selection of test species:

Pharmacologically relevant

Responsive to class-effects

Key points… continued

PK

Distribution

Long half-life in target tissue -> durable effects

Reactogenicity/Immunogenicity:

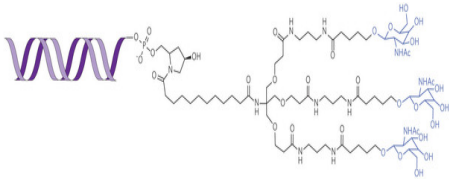
May be affected by chemical modifications and formulation differences between species

Safety of the formulation/conjugation

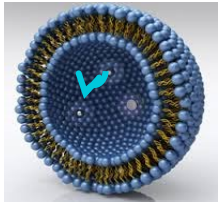
known or new?

distribution & potential for accumulation

-> long-term safety?



oligonucleotide with liver targeting ligand (GalNac)



Nanocarriers (e.g. liposomes)

Adaptations possible - when scientifically motivated

Early interaction with competent authorities is adviced!