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Regulation of RNA Oligonucleotides: Alnylam's Experience in the US and Other Territories

RNA Oligonucleotides: Emerging Clinical Applications

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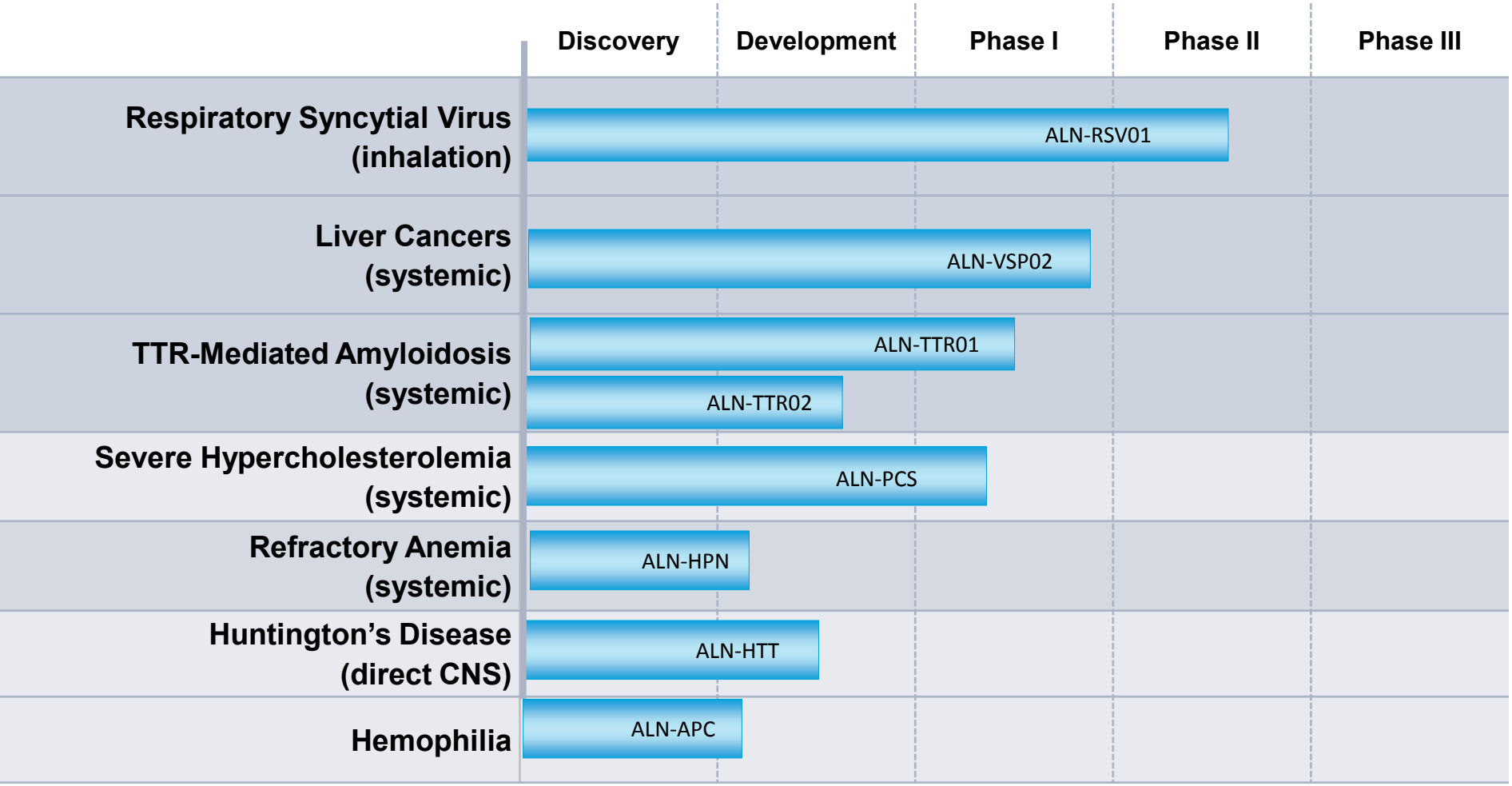
Agenda

- ☐ Background and Introduction
- ☐ Regulatory Resources for Oligonucleotides
- ☐ Examples of Issues Discussed with Agencies
- ☐ The Future

General Considerations
siRNA Therapeutics

- siRNAs are synthetic molecules
- siRNAs exhibit ‘drug-like’ properties
  - Reproducibility, high potency, specificity, known mechanism of action, rapid onset, durability of effects, reversibility
- Suitable for local or systemic delivery to target tissues
  - siRNAs in buffer for local delivery (e.g. eye, lungs, brain)
  - Other formulations (e.g. lipid nanoparticles, conjugates, polymers) for systemic delivery (e.g. liver, spleen)
- siRNAs are regulated as drugs
  - Under FDA’s Center for Drug Evaluation and Research [CDER]
  - Alnylam’s experience includes submissions to US, Canada, Australia, and several countries in the EU
  - Not considered as “Advanced Therapy” in the EU (not classified as gene therapy)

Alnylam Development Pipeline



Regulatory Interactions

- Pre-IND meetings with FDA
  - Division of Antiviral Products (also additional meetings post-IND)
  - Division of Oncology Drug Products
  - Division of Cardio-Renal Products
  - Division of Neurology Products
- Scientific Advice meetings
  - MHRA (UK)
  - Infarmed (Portugal)
  - MPA (Sweden)
  - CCMO (The Netherlands)
- All meetings above attended by multi-functional review teams including pharm/tox, chemistry, manufacturing and controls (CMC), and clinical/medical

Alnylam has also had teleconferences to discuss/resolve issues with FDA, MHRA, MPA

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Regulatory Guidelines for Oligonucleotides
US, Canada and Europe

- Currently, no formal guidelines available for oligonucleotide products from any regulatory authority
- Similarly, no guidance documents specifically addressing complex oligonucleotide formulations (FDA has a draft liposomal guidance)
- Oligonucleotide-based technologies in development include
  - Antisense oligonucleotides
  - DNA duplexes
  - Aptamers
  - Spiegelmers
  - Immunostimulatory oligonucleotides
  - siRNAs
  - miRNAs
- In view of diversity of oligonucleotide products currently in development as well as the different routes of delivery, generic guideline for oligonucleotide products appears unlikely

Useful Regulatory Resources
Pertaining Specifically to Oligonucleotides

Informal Guidance Documents from the US FDA

1. Regulatory Concerns for the Chemistry, Manufacturing and Controls of Oligonucleotide Therapeutics for use in Clinical Studies

   Rao V.B. Kambhampati, *et al*. *Antisense Res. and Dev't*, Vol. 3, p. 405-410, 1993

2. Points to Consider for the Submission of Chemistry, Manufacturing and Controls (CMC) Information in Oligonucleotide-Based Therapeutic Applications Rao V.B. Kambhampati, Ph.D., DIA Industry and Health Authority Conference, Bethesda, MD, April 20, 2007

   http://www.fda.gov/cder/Offices/ONDQA/presentations/DIAOligoConferenceSlides2007.pdf

Informal Guidance from BfArM

European Regulatory Perspectives on Oligonucleotides and Peptides

René Thürmer, Deputy Head, Unit Pharmaceutical Biotechnology, BfArM

- ☐ *DIA Industry and Health Authority Conference*, Bethesda, MD, April 20, 2007
- ☐ *EuroTides 2009*, Amsterdam, The Netherlands, December 2009

“White Papers”
Oligonucleotide Safety Working Group (OSWG)

- Formed in 2007 following the 1st DIA (Drug Information Association) Oligonucleotide-based Therapeutics Conference
- Includes representatives from regulatory agencies (FDA, Health Canada, BfArM) and > 70 pharmaceutical companies
- Focus on developmental aspects of short synthetic oligonucleotides
  - Includes antisense, siRNAs, aptamers, immunostimulatory oligonucleotides
- Open, inclusive membership with no restrictions
- Monthly sub-committee meetings to discuss safety issues and draft “white papers” on issues such as
  - Exaggerated pharmacology
  - Off-target effects
  - Genetic toxicology
  - Immune modulation
  - Impurities in drug substance and drug product
- The “white papers” reflect state of the art considerations and could serve as guideposts for the development of oligonucleotide therapeutics
  - White paper on off-target effects submitted to Nature Medicine (under review)

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Overview of Alnylam's Regulatory Submissions

Drugs in Clinic

Program	Dose and Route	Indication	Status	Countries	Issues* Discussed with Regulators
ALN-RSV01 (formulation in PBS; inhalation delivery)	Up to 2.0 mg/kg; Dose of 0.6 mg/kg qd for 5 days in Phase 2	RSV infection	**Phase 2b** ongoing; 245 healthy subjects/RSV-infected adult patients dosed	**US** **Canada** **Germany** **Austria** **France** **Netherlands** **Australia**	Discussions with FDA on: • Observed flu-like AEs in Phase 1 • Clinical development path • Microbiology • Interim analysis Responses to HealthCanada, BfArM mostly on CMC related issues
ALN-VSP02 (formulation in lipid nanoparticles; IV infusion)	Up to 1.5 mg/kg; Doses of 1.0 mg/kg once every 2 weeks in extension phase	Advanced solid tumors to the liver	**Phase 1** completed; 41 patients dosed (up to 35 doses in 1 patient)	**US** **Spain**	Discussions with FDA on: • CMC • Protocol inclusion/exclusion criteria
ALN-TTR01 (formulation in lipid nanoparticles; IV infusion)	Up to 1.0 mg/kg (SD); IV infusion	TTR amyloidosis	**Phase 1** nearing completion; 24 ATTR patients dosed	**Portugal** **Sweden** **France** **UK**	Discussions with Infarmed, MPA on: • PK/PD • Starting dose • CMC • Protocol inclusion/exclusion criteria
ALN-PCS02 (formulation in lipid nanoparticles; IV infusion)	Up to 250 µg/kg (SD); IV infusion	Hyper-cholesterol emia	**Phase 1** ongoing; 12 healthy volunteers dosed	**UK**	Discussions with MHRA on: • Protocol inclusion/exclusion criteria and stopping rules • CMC

** Issues were resolved and enabled proceeding to the clinic*

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Issues Discussed with Agencies
Pharmacokinetics/Pharmacodynamics

- Clarification of exposure based on dose
  - » Sophisticated, sensitive and specific assays are key
  - » Is more complex when formulations are involved
  - » PK of novel excipients in formulations
- Discussion on starting dose based on potential PD effect based on extrapolation from animal model
  - » Scaling from animal model to human
  - » As more data become available, better handle on translatability from animal to humans

Issues Discussed with Agencies
Chemistry, Manufacturing and Controls

- Details on raw materials, including limits for impurities, potential for carry-over of impurities from raw material to drug substance; similar details for functional excipients
- Inclusion of validation data for key analytical methods used
- Justification of analytical methods used and/or specifications proposed
  - Aspects relating to single versus double strand
  - Assay of duplex in drug product
  - Formulation components in drug product
- Provide impurity profiles, and (in some cases) limits for impurities; justification of coverage based on toxicology
- Discussion of requirement for bioassay for activity as a characterization/release assay
- Details and specifications on solvents, heavy metals, etc.
- For future
  - Suggested improving purity levels of single strands
  - Identification of DS impurities

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Issues Discussed with Agencies
Nonclinical Toxicology

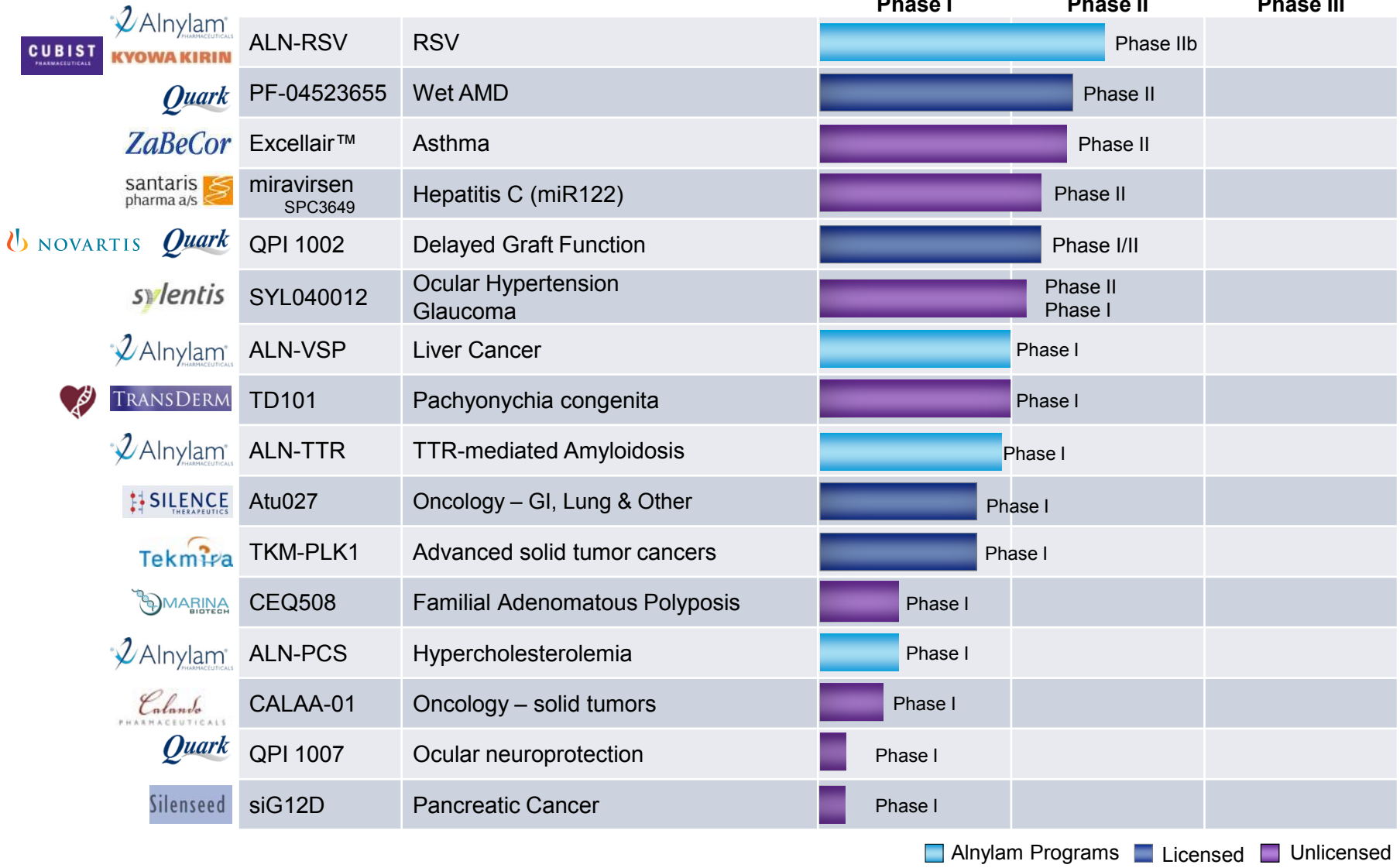
- Inclusion of rodent as toxicology species even if siRNA only cross-reacts with non-human primate (NHP) and human
- Use of rodent surrogate siRNA (at a single dose level) to evaluate on-target toxicity in rodent
- With lipid nanoparticle formulations, justification of control used in toxicology studies (empty lipid nanoparticle versus that with an irrelevant non-mammalian siRNA)
- Justification for starting dose based on toxicology data

Issues Discussed with Agencies
Clinical

- Regarding protocols
- Inclusion/exclusion criteria – e.g. levels of certain laboratory parameters
- Clear definition of stopping rules
- Safety data from one siRNA-LNP program have provided support for study of other siRNAs in same/similar formulations
- Several amendments have been approved to study higher dose levels/amend criteria
- Regarding safety
- Helpful discussions with Division on flu-like symptoms and cytokine changes observed with ALN-RSV01 in early Phase 1 inhalation study at high dose
  - » Obtained more data
  - » Changed from total dose to mg/kg dose
  - » Decided to start lower during MAD phase of study
  - » Restarted dosing that enabled arriving at a safe and well tolerated dose that was taken into Phase 2

RNAi Clinical Programs

Active Programs



Summary of Global Clinical Experience with siRNAs

- Approximately 1,000* humans exposed to siRNAs
- Includes delivery to lung, liver, eye, kidney, tumors
- Different routes of delivery including inhalation, intranasal, systemic and intravitreal
- No clinical holds due to safety
- No class-specific safety issues reported that preclude the development of this class of oligonucleotide therapeutics

* *Numbers are estimates based on public domain information on various programs, based on total subjects/patients expected to be enrolled and dosed with siRNA*

Conclusions

- Regulatory interactions have been supportive, productive and science-based
- Issues raised by regulatory agencies were satisfactorily resolved and have enabled successful study initiation
- Does not appear to be any specific concern about the use of siRNAs as potential therapeutic agents
- siRNAs, as with antisense oligonucleotides, are held to same standards and expectations as other small molecule drugs
- Have been no major safety issues in the clinic with unformulated siRNAs, nor with siRNAs in complex lipid nanoparticle formulations
- Translation from animals (specifically from NHP) to humans has been demonstrated with regard to PK as well as PD effects

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Future

- Data from longer-term dosing in animals and humans
  - Maximum known duration of dosing with siRNAs is 18 months (Alnylam's ALN-VSP02 program in liver cancer)
- Additional novel technologies are being developed that will enable
  - Alternate dosing paradigms
  - Targeting of other tissues
  - Better delivery
- Bioanalytical and analytical methods will continue to evolve to help better characterize drug product as well as PK/PD relationships
- With more programs in clinic, the safety database of siRNAs with various modes of delivery is growing
- RNAi therapeutics have potential to be an important class of new medicines to fulfill unmet medical needs