094

AMERICAN COLLEGE OF CLINICAL PHARMACOLOGY (ACCP)

Analyzing First-in-Human Trial Designs of Antisense Oligonucleotides: A Preliminary Review Across Subcutaneous, Intravenous & Intrathecal Routes of Administration

OBJECTIVE

This review aims to summarize insights from previously conducted first-in-human (FIH) trials of antisense oligonucleotides (ASOs) from various routes of administration, including subcutaneous (SC), intravenous (IV) & intrathecal (IT) to guide future design of ASOs FIH trials.

CONCLUSIONS

- ❑ **The current analysis highlights the diverse approaches & characteristics of FIH trials of ASOs administered by SC, IV & IT routes.**
- ❑ **The involved disease area highly impacted the trial design, target population, dose selection & escalation schemes.**
- ❑ **Understanding the nuances in trial design, dose strategies & therapeutic targets across different routes of administration & therapeutic areas is crucial for optimizing the design of future FIH trials & advancing the clinical development of ASO therapies.**

Mai Abdelmageed[1,2], Natalie Schmitz[1], Yan Xu[1]

[1]Clinical Pharmacology and Pharmacometrics, Biogen, MA, USA [2] Center for Pharmacometrics and Systems Pharmacology, Department of Pharmaceutics, University of Florida, Orlando, FL, USA

BACKGROUND

- Antisense oligonucleotides (ASOs) are emerging as significant players in modern therapeutic modalities.
- Despite numerous products in development, only 12 ASOs secured regulatory approval by 2023. First-in-human (FIH) trial design of ASOs represents a unique challenge in ASOs development programs.
- Among the difficult decisions in FIH design is the proper selection of the starting dose, the studied dose range, the dose escalation scheme, the total number of dose cohorts, the study size & power, the selection of the study population as well as safety issues considering preclinical safety/toxicity information & others[1,2].
- Previously conducted FIH trials with ASOs represent a valuable source of information that can help guide the design of future ASOs FIH trials.

METHODS

- A review of FIH ASO trials from 2010 – 2023 was conducted using four main data sources: PubMed, clinicaltrial.gov, CITELINE TrialTrove & an internal database.
- Retrieved trials were subdivided based on the route of administration (SC, IV & IT).
- The parameters of interest were summarized by descriptive statistics.

DATA & RESULTS

❑ A total of **71 FIH trials** were analyzed involving 24, 22 & 25 ASOs to be administered by SC, IV & IT routes, respectively.

SC ASO

Non-oncology

Indication

- SC ASOs primarily targeted cardiovascular diseases & metabolic/endocrinology (Figure 1).

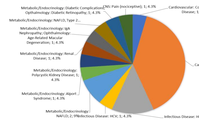

Figure 1. Indications of ASO-SC non-oncology trials. Data is presented as count (percent), n=23.

Study Population

- All non-oncology SC ASOs trials were conducted in adults (Figure 2).

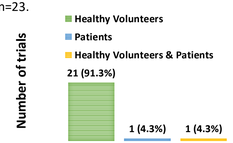

Figure 2. Study population of SC non-oncology ASOs FIH trials, n=23.

Trial Design

- All non-oncology SC ASOs trials were randomized, placebo-controlled trials (RCT) with 52.2% having 3:1 active-to-placebo randomization ratio (Figure 3).

Figure 3. Trial design of non-oncology SC ASOs FIH trials, n=23. SAD: Single ascending dose; MAD: Multiple ascending dose.

Oncology

- Only 1 oncology trial was found in SC ASOs category.
- The trial included only adult patients with advanced unresectable solid tumors for which no standard therapy was available.
- The trial followed an open-label (OL) design with a direct-to-multiple ascending dose (MAD) approach.

IV ASO

Non-oncology

- IV non-oncology ASOs primarily targeted muscular dystrophy (Figure 4).
- 75% of the trials were conducted in patients (Figure 5).
- The randomization ratio was highly variable with a 2:1 active-to-placebo randomization ratio being the most common (Figure 6).

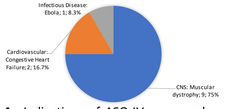

Figure 4. Indications of ASO-IV non-oncology trials. Data is presented as count (percent), n=12.

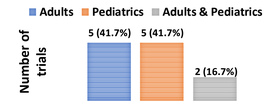

Figure 5. Study population of IV non-oncology ASOs FIH trials, n=12.

Figure 6. Trial design of non-oncology IV ASOs FIH trials, n=12. A) RCT versus OL trials. B) SAD versus MAD. RCT: Randomized controlled trial; OL: Open-label; SAD: Single ascending dose; MAD: Multiple ascending dose.

Oncology

- 10 oncology trials in IV ASOs category (Table 1).
- 90% of the trials included adult patients with various types advanced tumors.
- 90% of the trials were designed as OL with a direct-to-MAD approach.
- Only 1 trial was still under-planning & had unknown design & patient population.

IT ASO

Non-oncology

- IT ASOs primarily targeted neuromuscular diseases (Figure 7).
- 96% of the trials were conducted in patients (Figure 8).
- 56% of RCT trials followed a 3:1 active-to-placebo randomization ratio (Figure 9).

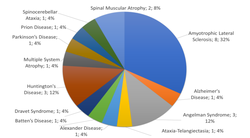

Figure 7. Indications of IT ASOs FIH trials. Data is presented as count (percent), n=25.

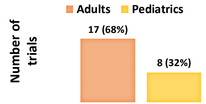

Figure 8. Study population of IT ASOs FIH trials, n=25.

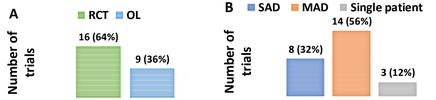

Figure 9. Trial design of IT ASOs FIH trials, n=25. A) RCT versus OL trials. B) SAD versus MAD & single patient trials. RCT: Randomized controlled trial; OL: Open-label; SAD: Single ascending dose; MAD: Multiple ascending dose.

Table 1. Summary of dose levels, dose range & the dose escalation ratio across FIH trials conducted with ASOs administered via the SC, IV & IT routes.

	SC (n=24)		IV (n=22)		IT (n=25)
Indication	Non-oncology (n=23)	Oncology (n=1)	Non-oncology (n=12)	Oncology (n=10)	Non-oncology (n=25)
Number of dose cohorts[a]	5 [2-11], (19)	5 [NA], (1)	4 [3-7], (10)	4 [3-5], (3)	4 [3-6], (17)
Dose range[b]	12 [2-5333.3], (15)	8 [NA], (1)	23.6 [3-150], (10)	3 [2.3-7.7], (3)	10 [3.75-24], (17)
Dose escalation ratio[c]					
Cohort 2/Cohort 1	2 [2-4], (13)	2 [NA], (1)	3.1 [2-6.2], (9)	1.5 [NA], (1)	3 [2-4], (17)
Cohort 3/Cohort 2	2 [2-3.3], (10)	2 [NA], (1)	2 [2-4], (9)	1.5 [NA], (1)	2 [1.3-3], (17)
Cohort 4/Cohort 3	2 [1.5-3], (9)	1.5 [NA], (1)	1.9 [1.5-3.3], (8)	NA	1.8 [1.5-2], (14)
Cohort 5/Cohort 4	1.5 [1.3-2.5], (5)	1.3 [NA], (1)	2 [2-2], (3)	NA	1.5 [1.3-2], (6)

[a]Median number of dose cohorts (median, [range]), number of trials included in the calculation of this value (n), [b]Median dose range (median, [range]), number of trials included in the calculation of this value (n), [c]Median dose escalation ratio (median, [range]), number of trials included in the calculation of this value (n), IT: Intrathecal; IV: Intravenous; SC: Subcutaneous; NA: Not applicable.

Dose Selection

- Generally, ASO FIH dose selection followed a balance between a NOAEL-based approach & pharmacologically active dose (PAD) approach.
- Only 3 non-oncology SC ASO FIH trials included criteria for dose selection. Starting doses had minimal pharmacological activity & top dose selection depended on the absence of adverse events in 13-wk NHP studies. Safety margins for the starting dose & top dose ranged 9.6-1500x & 5.6-22x, respectively. 1 study used hepatic concentration for safety margin calculation due to the agent hepatic accumulation in pre-clinical animal testing .
- For the 22 IV ASO FIH trials, rationale of dose selection was not provided in the public domain.
- 21 IT ASO FIH trials included dose selection criteria. 12 studies followed a NOAEL based approach with safety margins ranging 10-70x & 0.63-7.7x for starting & top doses, respectively. 9 studies followed a PAD approach with pharmacological activity ranging 7.5-50% & 50-90% for the starting & top doses, respectively. All calculations were based on data from NHP studies.

REFERENCES

1. Shen J, et al. Clin Transl Sci. 2019 Jan;12(1):6-19.
2. Clinical Pharmacology Considerations for the Development of Oligonucleotide Therapeutics Guidance for Industry. FDA, 2024 Jun. https://www.fda.gov/media/159414/download.

DISCLOSURES

No funding was received for this work. The views expressed are those of the authors & not necessarily those of Biogen.

Let's meet for coffee ☺

Biogen

UF UNIVERSITY of FLORIDA