Overview and Outlook for RNA-Based Therapies

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Executive Summary

Ribonucleic acid (RNA)-based therapies are an emerging area of therapeutic development that offer the potential to produce novel treatments for a range of conditions, including several rare diseases. These products, which leverage genetically targeted technology (GTT), encompass any product comprised of non-replicating nucleic acids used to modify disease pathways. RNA-based therapies include products that leverage RNA interference (RNAi) and many antisense oligonucleotide (ASO) therapies—which reduce the production of unwanted proteins—as well as messenger RNA (mRNA) therapies, which introduce novel therapeutic proteins.

In the US, there are at least 21 U.S. Food and Drug Administration (FDA) approved, on-market, RNA-based therapies, as well as a strong pipeline of products in clinical development. As of January 31, 2024, at least 131 RNA-based therapies are being studied in clinical trials, with many more in pre-clinical development. Products leveraging RNAi and mRNAs represent the largest portion of the RNA-based therapy pipeline at 40% and 37% respectively, but the broader pipeline includes oligonucleotide, double-stranded RNA (dsRNA), and micro-RNA (miRNA) products as well. Collectively, these therapies span 15 different therapeutic areas and have the potential to introduce new treatment options for rare diseases and other conditions with limited treatment alternatives. Some of these therapies have the potential to be dosed once or twice a year, offering differentiated options for patients. Although the vast majority (80%) of pipeline products are in early-stage development (i.e., Phase I or Phase II), the presence of 29 therapies in late-stage development indicates the potential for new RNA-based therapy approvals in the coming years.

RNA-based therapies can occasionally be considered gene therapies, which is a broader classification of innovative therapeutics that leverage RNA or deoxyribonucleic acid (DNA). Not all products in the broader gene therapy classification are regulated the same way by the FDA. For instance, some RNA-based therapies, such as products using RNAi, are regulated as small molecule drugs under a New Drug Application (NDA), while others, such as gene therapies leveraging viral vector delivery systems and mRNA vaccines, are regulated as biological drugs under a Biologics License Application (BLA). While complexities associated with product development and resource investment may often be comparable among these types of therapies, differences in FDA regulatory classifications can create important distinctions during review for approval and during time on market due to exclusivities and pathways for competition.

In addition, small molecule drug and biological drug products are impacted differently by policies such as the Inflation Reduction Act's (IRA) Medicare Drug Price Negotiation program, which considers biological drugs eligible to be selected for negotiation after 11 years on the market, compared to 7 years on the market for small molecule drugs. The differential treatment of RNA-based therapies that are reviewed under NDAs compared to certain gene therapy or mRNA products reviewed under BLAs may introduce new incentives to the market, which over time could influence investment decisions and pipeline strategies. In light of these shifting incentives, and as RNA-based therapies continue to be developed and approved, stakeholders should

assess how regulatory classifications for RNA-based therapies may affect product development and patient access in disease areas with limited treatment alternatives.

Overview of RNA-Based Therapies

RNA-based therapies are an emerging class of therapies. While discoveries in RNA biology go back to the late 1950s, more extensive research leading to developments in the field of RNA therapies has taken off since the early 1990s. In recent years, the broad clinical application for RNA-based therapies has garnered excitement and been recognized through Nobel Prize awards, including the 2006 Nobel Prize for the discovery of RNA interference and the 2023 Nobel Prize for discoveries that enabled the development of mRNA vaccines.

This class of treatments modifies disease pathways using RNA, which is a type of cellular building block that is in the same family as DNA. **The term "RNA-based therapy" describes the use of molecules built with RNA that modify disease pathways in the body by re-interpreting DNA's instructions in a way that provides therapeutic effect. Different types of RNA play different roles throughout the process of protein production. Due to these unique roles and properties, RNA is increasingly being researched as a mechanism to affect diseases that are caused by imbalances in protein levels.** Due to this mechanism, RNA-based therapies have the potential to treat conditions that historically do not respond to conventional treatments. In contrast to currently available protein-targeted and DNA-based medications, RNA-based therapies have unique properties and directly target other RNA sequences.[1] Consequently, RNA-based therapies can potentially target any gene of interest as long as the exact sequence on the target RNA has been identified and there is an established method for delivering the RNA to the right place in the body.

RNA-based therapies may be broadly categorized with other novel emerging therapeutics like gene therapies.[1] However, RNA-based therapies possess some unique characteristics. RNA-based therapies provide long-lasting modifications to disease pathways, while DNA-based therapies, which also leverage GTT, induce permanent changes to a person's non-heritable genetic makeup. Additionally, RNA-based therapies influence protein production, while DNA-based therapies treat or prevent diseases by introducing new genes, or by silencing or editing existing genes.[2] Furthermore, DNA-based therapies approved to date have been classified by FDA as biological drugs and regulated as BLAs at the FDA. To date, approved RNA-based therapies have used synthetic delivery mechanisms, and FDA has regulated such products as drugs requiring an NDA.[3]

Classification of RNA-Based Therapies

RNA-based therapies can be classified into a subset of categories, based on their modes of action, which include:

1. Agents of RNA interference (RNAi);
2. Inhibitors of mRNA translation (antisense therapy);
3. Catalysts of protein synthesis (mRNA); and
4. RNAs that bind proteins and other molecular ligands (aptamers).

RNA-based therapies differ by whether their mechanism of action is to silence protein production or generate protein production. Both RNAi and antisense modes of action reduce or eliminate the production of an unwanted protein, while mRNA products are intended to trigger the synthesis of a novel therapeutic protein. Additionally, within RNAi, small interfering RNAs (siRNAs) act in a very targeted manner, but miRNAs can have a broader set of targets. As described in Table 1, these features influence how certain types of therapeutic RNA are better suited for particular diseases.

In contrast to RNA-based therapies, DNA-based therapies are used to treat or prevent conditions in which mutated gene(s) cause a missing protein or the production of a faulty protein. Due to their mechanism of action, DNA-based therapies can permanently restore the normal function of that protein.[2]

Table 1: Objectives, Functions, and Targets of RNA-Based Therapies

	MOA	Details	Example Targets
RNA-Based	**RNAi**		
	Targets complementary mRNA for destruction, leading to blocked production of a protein.[4,5]	***siRNA*** • Double-stranded or hairpin RNA is cut up by an enzyme into siRNAs.[6] • siRNA is a part of the complex that targets specific mRNAs to form a double strand, which will be destroyed.[7]	***siRNA*** Can treat cancers, neurodegenerative disorders, and other conditions associated with uncontrolled protein production.[8,9]
		miRNA • Short double-stranded RNA that is loaded onto a specific enzyme within a cell to help destabilize mRNA.[10] • miRNAs can target many mRNAs to destabilize them.[11]	***miRNA*** Due to broad silencing mechanism, can treat conditions such as cancer, wound healing, drug resistance.[12]

	Antisense Therapy		
	Attaches to mRNA and stops a particular gene from producing a specific protein or reduces its production levels.[13,14]	• Non-coding single stranded RNAs that are complementary to a coding sequence of mRNA.[15] • ASOs target specific mRNAs to form a double strand that will be destroyed. ASOs may also inhibit the production of certain proteins.[16]	Can treat cancer, diabetes, and diseases with inflammation.[17]
	mRNA		
	Carries information from a DNA template, leading to the production of functional proteins.[18,19]	Once mRNA reaches the internal environment of cells and is converted into the targeted antigens, it will be recognized by the immune system and destroyed.[20,21]	Due to ability to create functional protein, can be used in cancer vaccines, immunotherapy, and infectious disease prevention.[22]
DNA-Based	Uses genetic material to treat, cure, or ultimately prevent disease by changing the expression of a person's genes.[23]	The DNA that encodes a functional, therapeutic gene is packaged within a vehicle ("vector") which carries a molecule inside a cell and replaces or silences a mutated gene or augments a faulty gene.[24]	Disorders caused by mutations in single or multiples genes and conditions caused by chromosomal abnormalities.[25]

ASO: Antisense Oligonucleotide; DNA: Deoxyribonucleic Acid; miRNA: Micro Ribonucleic Acid: MOA: Mechanism of Action; mRNA: Messenger Ribonucleic Acid; RNA: Ribonucleic Acid; siRNA: Small Interfering Ribonucleic Acid

The range of RNA molecule types and their genetically targeted nature create the potential for broad therapeutic applications. As of April 2024, at least 21 RNA-based therapies have been approved by the FDA, including ten ASOs, six siRNAs, and five mRNA-based vaccines. On-market ASOs and siRNAs are currently approved in the metabolic, cardiovascular, and neurology therapeutic areas, while on-market mRNA products consist exclusively of mRNA-based vaccines for the prevention of COVID-19.

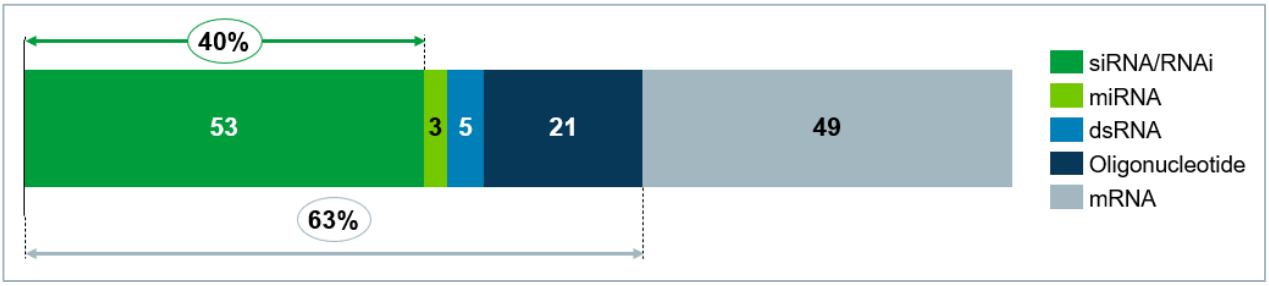
RNA aptamers are not discussed in Table 1 but may one day become another type of commercialized RNA-based therapy. Aptamers are short, single-stranded RNA molecules that bind very closely to a variety of targets. Although aptamers are a promising biomolecule in pharmaceutical research, their review is outside of the scope of the current paper due to their mostly pre-clinical phases of development and limitations from being successful in vivo.[26,27]

RNA-Based Therapy Pipeline

As RNA-based therapies take footing in the market, the pipeline of future products continues to grow, both in number and in therapeutic applications. To assess the pipeline, the term “RNA-based therapy" was defined as any product physically comprised of non-replicating nucleic acids, including RNA. This definition includes products classified as siRNA/RNAi, mRNAs, miRNAs, dsRNAs, and other oligonucleotides not classified in those categories. For the purposes of this review, the definition excludes DNA-based therapies.

As of January 31, 2024, there are an estimated 131 unique RNA-based therapies in clinical development across therapeutic areas. As displayed in Figure 1, products classified as siRNA/RNAi represent 40% of the total pipeline, which is the largest single category within the RNA-based therapy analysis. This percentage may be an underestimation, as other product types that leverage RNAi mechanisms were classified separately, such as miRNAs, dsRNAs, and certain oligonucleotides. Figure 1 demonstrates that as much as 63% of the total pipeline could be considered a product leveraging RNAi if these product categories are included.

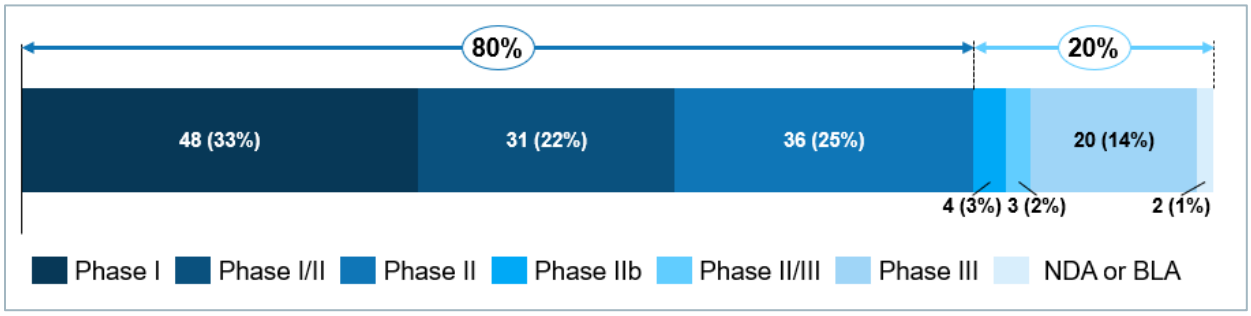
Figure 1: Number of RNA-Based Therapies in Development, by Product Classification



Pipeline assessment conducted January 31, 2024.
dsRNA: Double Stranded Ribonucleic Acid; miRNA: Micro Ribonucleic Acid; mRNA: Messenger Ribonucleic Acid; RNAi: Ribonucleic Acid Interference

RNA-based therapies are present across all stages of clinical development and especially concentrated in earlier stages. As displayed in Figure 2, 80% of products are in early-stage development (i.e., Phase I or Phase II), with one-third of products (33%) in Phase I alone. **While late-stage development (i.e., Phase IIb or greater) represents a smaller share of the pipeline at 20%, the number of products in late-stage development (29) is greater than the total number of RNA-based therapy products currently on the market (21), indicating that significant growth for RNA-based therapies is likely in the near future.**

Figure 2: Pipeline RNA-Based Therapies, by Phase of Clinical Development

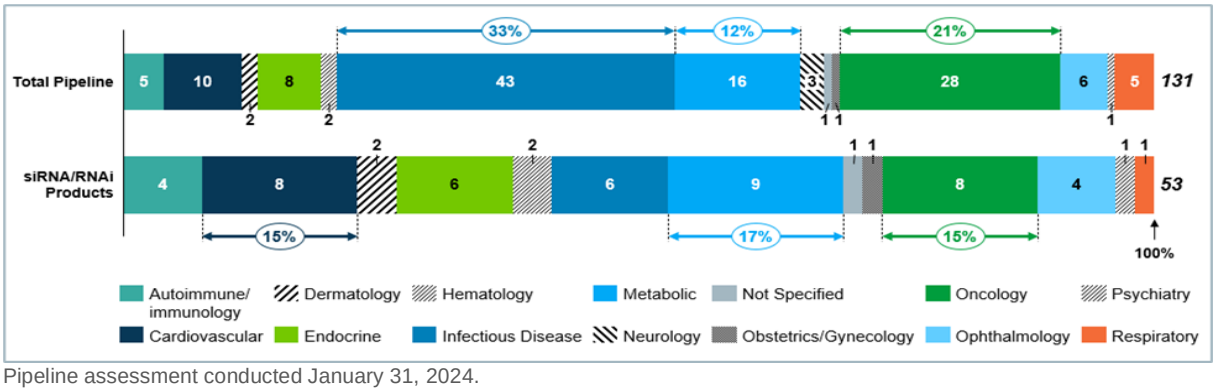


Pipeline assessment conducted January 31, 2024.
Note: "NDA or BLA" includes products that have submitted an NDA or BLA to the FDA but have not been granted approval. BLA: Biologics License Application; NDA: New Drug Application

Furthermore, RNA-based therapies are being developed across many therapeutic areas, with a host of potential indicated uses. As displayed in Figure 3, 15 unique therapeutic areas were identified. Across all pipeline therapies, development is concentrated within the infectious disease (33%), oncology (21%), and metabolic (12%) therapeutic areas. However, this therapeutic area distribution varies by molecule type, with certain molecule types more commonly targeting a subset of therapeutic areas (e.g., mRNA therapy indications in infectious disease). For instance, when specifically examining siRNA/RNAi therapies, the top therapeutic areas are metabolic (17%), cardiovascular (15%), and oncology (15%). In addition, Figure 3 shows how the pipeline in some therapeutic areas is composed entirely of siRNA/RNAi products, which is seen in dermatology, hematology, obstetrics/gynecology, and psychiatry.

This therapeutic area distribution also varies by product phase. While products in late-stage development are more concentrated across the infectious disease, oncology, and metabolic therapeutic areas, products in earlier development span a wider array of therapeutic areas.

Figure 3: Distribution of Pipeline RNA-Based Therapies by Therapeutic Area, Total Compared to siRNA/RNAi



Pipeline assessment conducted January 31, 2024.
RNAi: Ribonucleic Acid Interference; siRNA: Short Interfering Ribonucleic Acid

Additionally, within these therapeutic areas, a significant number of RNA-based therapies are being studied for the treatment of rare diseases or for indications with limited on-market treatment alternatives. Overall, more than one-third of pipeline RNA-based therapies (37%) are being investigated for rare disease indications. In addition, 21% of pipeline-RNA based therapies are being developed for indications with less than two approved disease modifying therapies (DMTs) and approximately 50% of pipeline RNA-based therapies are being developed for indications with five or fewer approved DMTs. This indicates that in addition to addressing a wide range of therapeutic areas, **RNA-based therapies have the potential to provide new treatment options for diseases that currently lack sufficient therapeutic alternatives.**

This broad pipeline has been driven in part by the entrance of new stakeholders to the RNA-based therapy landscape. Almost half (43%) of pipeline RNA-based therapies are being developed by emerging biopharmaceutical companies (i.e., less than $500M in annual revenue) and 61% are being developed by a manufacturer that does not currently have an FDA-approved RNA-based therapy.

FDA Regulatory Classifications for NDAs and BLAs

The FDA reviews and approves new drugs and biologics through either an NDA or a BLA. Principally, the data requirements for approval are similar between NDAs and BLAs, and for RNA and DNA-based therapies, product development can have similar complexities. However, the implications of a regulatory classification as an NDA or BLA materially differ in terms exclusivities associated with the marketing authorization, as well as the available pathways associated with generic or biosimilar competition, as seen in Table 2.

Table 2: Licensing Details for an NDA vs BLA

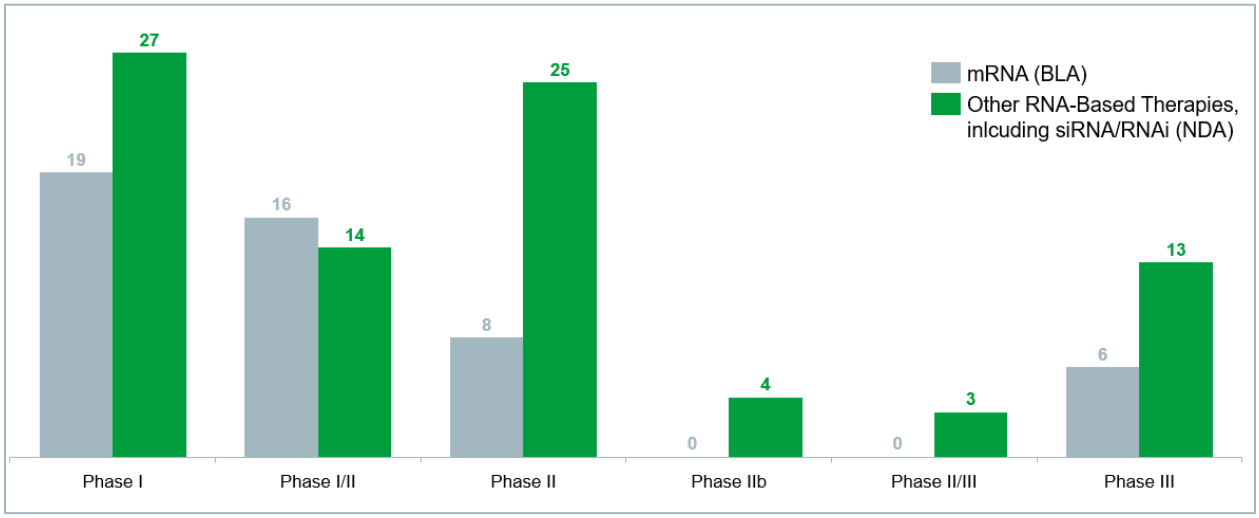
	NDA[28]	BLA[29]
Regulatory Exclusivities	• New Chemical Entity: **5 years** • New Clinical Investigation: + 3 years for indication	• New Molecular Entity: **12 years**
	• Orphan Drug: + 7 years • Pediatric: + 6 months for indication	
Follow-on Product Pathways	• Generics - 505(j) ANDA filing pathway with no clinical study requirement. No differences from originator product. Label is automatically the same as originator product*; no branding • 505(b)(2) NDA filing pathway, permits product differences from originator (e.g., dosage, strength, formulation)	• Biosimilar - 351(k) BLA filing pathway with potential for conduct of clinical studies. Label is not automatically the same as originator product; can be branded

ANDA: Abbreviated New Drug Application; BLA: Biologics License Application; NDA: New Drug Application
*This interpretation does not consider "skinny labeling", which can occur if an originator product indication retains patent protections that prohibit the generic from being approved for that indication.

As has been considered, RNA and DNA-based therapies have been regulated differently by FDA despite their similarities from a chemical structure, manufacturing, and therapeutic action standpoint. The FDA defines a biological drug as being a protein, virus, vaccine, blood component, or 'analogous product' to a virus, therapeutic serum, toxin, or antitoxin.[30] These products are reviewed under BLAs. This definition of a biological drug *does not* explicitly include information on RNA or DNA; however, the FDA currently considers gene therapies to be considered biologicals when meeting certain criteria,[31] which adds ambiguity to interpreting how products using GTT should be reviewed as BLAs or NDAs. Currently, all siRNA/ASO products approved by FDA have been reviewed under NDAs. In contrast, all currently FDA-approved gene therapy products have been reviewed under BLAs, using viruses to deliver genetic material.[32] Additionally, all currently FDA-approved mRNA-based products have been reviewed under BLAs, being classified as vaccines. Looking ahead, there could be questions surrounding how products made of either DNA or RNA will be regulated if they do not contain product components listed in the definition of a biological drug (e.g., viruses, vaccines).

As highlighted in Figure 4, the pipeline of RNA-based therapies in Phase II or greater consists primarily or exclusively of products that are likely to be regulated under NDAs. Given current regulatory interpretations, it is expected that a significant number of future RNA-based therapies will come to market via an NDA regulatory pathway.

Figure 4: Pipeline RNA-Based Therapies, Based on Current Regulation Under NDA/BLA



BLA: Biologics License Application; mRNA: Messenger Ribonucleic Acid; NDA: New Drug Application; RNA: Ribonucleic Acid; RNAi: Ribonucleic Acid Interference; siRNA: Short Interfering Ribonucleic Acid

Outlook

Most RNA-based therapies (e.g., siRNAs, oligonucleotides) are expected to be regulated as small molecules under an NDA. On the other hand, mRNA vaccines, as well as other gene therapies are regulated as biologicals under BLAs. Amid ambiguity on regulatory classifications for these products that leverage GTT, differential market treatment could create novel dynamics within this product class in the future, raising several important considerations related to long-term product development, commercialization, and access.

Development and Commercialization

These differences in FDA classifications create distinctions in how RNA-based therapies will continue to be developed and commercialized in the US. For example, the longer exclusivity period for biologics and the dynamics governing biosimilars may offer biological drug manufacturers greater long-term investment opportunity, relative to small molecule drugs. Additionally, as technology advances RNA and DNA-based therapy delivery mechanisms, the potential for NDA classifications could influence incentives for long-term investment for these products, which are often designed to treat complex diseases with limited treatment options.

Policy and Access Implications

In addition to product development and the competitive landscape, FDA regulatory pathways can have implications for pricing and access. In the coming years, the potential approval of new RNA-based therapies could offer new treatment options across a range of therapeutic areas and diseases with limited approved alternatives. As RNA-based therapies continue to be studied, approved, and commercialized, stakeholders can assess how the unique regulation of RNA-based therapies, compared to other novel products, will affect their investment levels, development, and commercialization in the long term and what that means for patient access to novel treatments.

Most notably, the IRA includes different criteria for biological drugs and small molecule drugs under the Medicare Drug Price Negotiation Program. Under the IRA, biologics do not become eligible for Medicare negotiation until 11 years after FDA approval, while small molecule drugs become eligible for negotiation 7 years post-approval. Since the Medicare Drug Price Negotiation Program defines negotiation eligibility based on the type of FDA license, this means that RNA-based therapies may have different lifecycle considerations solely based on how they are classified by FDA. **This differential treatment of RNA-based therapies that are regulated as small molecules, compared to other gene therapy or mRNA products regulated as biological drugs, introduces new incentives to the market. Over time, these incentives could influence investment decisions, pipeline strategies, and the number and types of treatment options that are available to patients**.

Appendix

Pipeline Methodology

Avalere performed a search of publicly available asset data with the keyword "RNA" using Citeline Commercial BioMed tracker, Copyright © 2024 Citeline, a Norstella Company. The search results returned any product in any stage of development that is either comprised of RNA, or targets RNA, and has not received FDA approval as of Jan 31, 2024. Avalere manually filtered this data to exclude products that do not definitively meet the RNA-based therapy definition. Avalere then further condensed product classifications to filter, clean, and de-duplicate the data set, using secondary research, clinical, and industry knowledge.

To determine the number of disease modifying therapies available for an indication, Avalere performed secondary research to identify the number of approved therapies that treat the cause of a disease or pathology; symptomatic, systemic, or procedural treatment options were excluded.

To determine sponsor market presence, Annual revenue cut-off point was identified using the IQVIA Institute Global Trends in R&D 2024 Report, which defines an emerging biopharmaceutical company as having less than $500M in revenue based on SEC form 10k filings.[33] Determination of products on market and RNA-based therapy products on market was corroborated using publicly available sources.

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