BofA SECURITIES

Ionis

Previewing ION582 (UBE3A) updates for Angelman Syndrome in mid/2H24E

Maintain Rating: BUY | PO: 62.00 USD | Price: 49.98 USD

ION582: previewing upcoming Angelman's data

This report provides a deep dive into pipeline therapeutics for Angelman Syndrome (AS) with a focus on Ionis' (IONS) Ph1/2 (for ION582) data update by mid/2H24E. AS is a genetic neurodevelopmental disease and an estimated >$5bn peak category sales (no approved drug). ION582 is a disease-modifying antisense drug (ASO) aimed at restoring the Ube3a protein missing in AS patients. We believe ION582 is not yet priced into the stock and good data (more below) could drive stock upside (+$2-5/share); validation for the ASO approach comes from: 1) class preclinical/clinical AS data have shown reduction in disease severity; 2) ION582 has shown a positive impact on a key disease biomarker (EEG) and clinical outcome measure (Bayley) in a preliminary update. We maintain Buy on favorable setup ahead of catalyst rich 2024-25. Deep dive starts on page 3.

IONS' proof-of-concept update has de-risking potential

IONS' mid-year Ph1/2 update is expected to feature a full analysis of 3-month MAD (multi-ascending dose) portion and a cut of the LTE (long-term extension). We expect the update to be more informative than a typical Ph1, as biomarkers, clinical outcomes (eg Bayley, CGI) and safety will be assessed in ~50 patients treated over 4-12+ months. While Ph1/2 is open-label (no placebo), longitudinal data on disease progression from natural history studies will provide a historical control for comparison vs drug effect.

Improvements on EEG and Bayley would be a positive

One of the key risks for AS pipeline drugs is the lack of a validated regulatory pathway. Based on our KOL checks, we believe there could be challenges framing a positive ION582 clinical outcome but improvements in EEG and Bayley (vs. natural history) are thought to offer the most directional support. EEG is an AS biomarker for target engagement -- improvement correlates with cognitive function, while Bayley has been widely used in natural history studies and is one of the more objective disease measures. Physician global assessment of the patient (known as CGI endpoint) assesses a wider range of disease domains than Bayley but has relatively limited natural history data.

Catalyst path for ION582 in Angelman Syndrome

ION582 Ph1/2 topline data is expected by mid-year, followed by detailed data at a medical meeting (2H24) and a Biogen partnership opt-in decision (IONS could get up to a mid-teens royalty). We look to competitor Ultragenyx's 1H24 Ph2 data (GTX-102) for read-across. To move the stock, we believe consistent improvement in '582 treated patients over natural history on Bayley, EEG and clarity on reg path (2H24) are needed.

Estimates (Dec) (US$)	2021A	2022A	2023E	2024E	2025E
EPS	(0.21)	(1.90)	(3.20)	(3.23)	(2.85)
EPS Change (YoY)	94.0%	-804.8%	-68.4%	-0.9%	11.8%
Consensus EPS (Bloomberg)			(3.17)	(3.53)	(2.74)
DPS	0	0	0	0	0
Valuation (Dec)					
EV / EBITDA*	696.1x	NM	NM	NM	NM
Free Cash Flow Yield*	0.3%	-1.1%	-4.1%	-4.5%	-4.0%

* For full definitions of *IQmethod℠* measures, see page 24.

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Refer to important disclosures on page 25 to 27. Analyst Certification on page 23. Price Objective Basis/Risk on page 23. **12657556**

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Stock Data

Price	49.98 USD
Price Objective	62.00 USD
Date Established	2-Jan-2024
Investment Opinion	B-1-9
52-Week Range	32.69 USD - 54.44 USD
Mrkt Val (mn) / Shares Out (mn)	7,171 USD / 143.5
Free Float	96.5%
Average Daily Value (mn)	58.24 USD
BofA Ticker / Exchange	IONS / NAS
Bloomberg / Reuters	IONS US / IONS.OQ
ROE (2023E)	-101.2%
Net Dbt to Eqty (Dec-2022A)	67.3%
ESGMeter™	High

ESGMeter is not indicative of a company's future stock price performance and is not an investment recommendation or rating. ESGMeter is independent of BofA Global Research's equity investment rating, volatility risk rating, income rating, and price objective for that company. For full details, refer to "BofA ESGMeter Methodology".

Acronyms:
CGI: clinical global impression
EEG: electroencephalogram
FAST: Foundation for Angelman Syndrome Therapeutics
KOL: expert
Ph: Phase
Reg: regulatory
TBD: to be determined
Ultragenyx (RARE): covered by Tazeen Ahmad

*iQ*profile℠ Ionis

iQmethod℠ **– Bus Performance***

(US$ Millions)	2021A	2022A	2023E	2024E	2025E
Return on Capital Employed	-0.5%	-10.3%	-19.8%	-22.9%	-21.0%
Return on Equity	-3.6%	-38.7%	-101.2%	-127.6%	-142.1%
Operating Margin	-3.7%	-70.1%	-66.7%	-79.1%	-61.8%
Free Cash Flow	19	(78)	(297)	(325)	(286)

iQmethod℠ **– Quality of Earnings***

(US$ Millions)	2021A	2022A	2023E	2024E	2025E
Cash Realization Ratio	NM	NM	NM	NM	NM
Asset Replacement Ratio	0.3x	0.3x	0.3x	0.3x	0.3x
Tax Rate	3.3%	NM	NM	15.0%	17.0%
Net Debt-to-Equity Ratio	41.7%	67.3%	266.3%	122.8%	NM
Interest Cover	-3.4x	-41.1x	-26.8x	NA	NA

Income Statement Data (Dec)

(US$ Millions)	2021A	2022A	2023E	2024E	2025E
Sales	810	587	643	618	714
% Change	11.1%	-27.5%	9.6%	-3.8%	15.5%
Gross Profit	799	573	634	606	699
% Change	11.5%	-28.3%	10.7%	-4.4%	15.4%
EBITDA	12	(343)	(361)	(421)	(373)
% Change	NM	NM	-5.2%	-16.6%	11.4%
Net Interest & Other Income	0	153	1	(60)	(60)
Net Income (Adjusted)	**(29)**	**(270)**	**(458)**	**(467)**	**(416)**
% Change	**94.0%**	**-821.3%**	**-69.5%**	**-2.0%**	**11.0%**

Free Cash Flow Data (Dec)

(US$ Millions)	2021A	2022A	2023E	2024E	2025E
Net Income from Cont Operations (GAAP)	(29)	(270)	(458)	(467)	(416)
Depreciation & Amortization	42	68	69	69	68
Change in Working Capital	(114)	32	11	(1)	(3)
Deferred Taxation Charge	0	0	0	0	0
Other Adjustments, Net	132	110	100	91	83
Capital Expenditure	(12)	(18)	(19)	(17)	(19)
Free Cash Flow	**19**	**-78**	**-297**	**-325**	**-286**
% Change	**NM**	**NM**	**-281.2%**	**-9.6%**	**12.0%**
Share / Issue Repurchase	12	12	12	550	12
Cost of Dividends Paid	0	0	0	0	0
Change in Debt	251	(50)	(100)	0	0

Balance Sheet Data (Dec)

(US$ Millions)	2021A	2022A	2023E	2024E	2025E
Cash & Equivalents	869	716	294	482	171
Trade Receivables	62	23	26	25	29
Other Current Assets	1,414	1,416	1,379	1,370	1,358
Property, Plant & Equipment	178	184	191	196	203
Other Non-Current Assets	89	89	89	89	89
Total Assets	**2,612**	**2,428**	**1,978**	**2,162**	**1,849**
Short-Term Debt	4	0	0	0	0
Other Current Liabilities	237	253	250	259	268
Long-Term Debt	1,188	1,138	1,038	1,038	1,038
Other Non-Current Liabilities	412	412	412	412	412
Total Liabilities	**1,840**	**1,802**	**1,699**	**1,709**	**1,718**
Total Equity	**772**	**626**	**279**	**453**	**132**
Total Equity & Liabilities	**2,612**	**2,428**	**1,978**	**2,162**	**1,849**

* For full definitions of ***iQ***method℠ measures, see page 24.

Company Sector

Biotechnology

Company Description

Ionis Pharmaceuticals is a biotechnology company focused on discovery and development of RNA-targeted therapeutics. The company's drug platform is called antisense technology which aims to modify/reduce the production of disease-causing proteins by binding/destroying RNA so that the amount of disease-causing protein is dramatically decreased. IONS has three commercial drugs approved in major markets, four drugs in Ph3 of development and over 30 medicines in early to mid-stage development.

Investment Rationale

We rate IONS Buy on favorable stock setup ahead of catalyst-rich path in 2024-1H25. There will be multiple mid-/late-stage clinical readouts that can increase likelihood of success for four assets with $300m-1bn nominal peak revenue estimates (Wainua, donidalorsen, olezarsen, ION582). Approval of Wainua in polyneuropathy with a clean label indicates ION's improved antisense (ASO) platform can mitigate legacy safety issues, effectively validating the safety profile of IONS' broader pipeline.

Stock Data

Average Daily Volume	1,161,780

Quarterly Earnings Estimates

	2022	2023
Q1	NA	NAA
Q2	NA	NAA
Q3	NA	NAA
Q4	NA	NA

Contents

Executive Summary

Ionis is in a Ph1/2 study (HALOS) evaluating an antisense (ASO) candidate ION582 for treating Angelman Syndrome (AS), a rare neurodevelopmental disease. IONS will topline HALOS results around mid-year (expected to include efficacy data) and present detailed data at a medical forum in 2H24. The '582 clinical update will be more important than a typical Ph1 study as it will offer first-in-human efficacy assessment (n=51) with at least 4-month of follow-up. We see upside potential to IONS shares if '582 can establish a safe and clinically active ASO profile; our checks suggest clinical activity will be scrutinized based on biomarker (EEG) and improvement on clinical outcome (Bayley) relative to historical control. ION582 accounts for $2/share in our SOTP, in which we assume 30% POS (likelihood of success) pending de-risking data on ION582 and forecast ~$300m in nominal peak royalty revenue to IONS on ~$2bn peak sales. At current trading level, we believe ION582 is largely priced out of stock given the program is early stage with limited clinical data disclosed. In a Ph1/2 success scenario, we believe a ~$300m peak royalty (100% operating margin) at 30-50% POS could translate to +$2-5/share upside depending on strength of the data.

In this report, we deep dive into the basics of AS, whereas below we condense our findings into 'top 10' takeaways:

- **AS is a sizable market with high unmet need and room for multiple therapeutics**: AS is estimated to affect 60k+ pts across key global markets, which translates into $10bn+ theoretical global opportunity at full penetrance, across genetic alterations and age groups evaluated in IONS' HALOS study. We more conservatively estimate a global market size of $5bn+ as we limit our assumption on TAM (addressable market) to the segment of patients thought to have higher likelihood of success, e.g. deletion subtype and younger patients (we model up to young adults). Looking at the TAM in a different way, the AS market by patient number is at least 2-3x the size of SMA [spinal muscular atrophy], where Spinraza reached $2bn peak sales and total market annualizing at >$3.5bn global sales. There are no approved therapies for AS, and we believe the market is big enough to support more than one player. Five programs across four drug developers are in early-to-mid stage clinical development (Ph1/2), including three ASO programs (Roche, Ultragenyx and Ionis) and two alternative mechanisms (Roche, Neuren).

- **UBE3A is thought to be a key disease driver for AS and a logical therapeutic target**: Ube3a (ubiquitin ligase E3A) targets proteins for degradation and controls synapse communications. AS patients can't produce Ube3a proteins in neurons for normal neurodevelopmental functions, as the paternal copy of the UBE3A gene is naturally silenced by UBE3A-antisense (UBE3A-ATS RNA) while the maternal copy is missing due to chromosome 15 abnormality. Two types of UBE3A alterations (out of 4) representing >80% of AS patients are deletion (~70%) and mutation (~15%). Because there is no other identifiable mutation besides UBE3A in the ~15% AS patients with mutation subtype, UBE3A is thought to be the primary disease driver of AS. That said, deletion subtype generally has more severe disease than mutation thus neighboring genes surrounding UBE3A on chromosome 15 may also contribute to deletion-subtype of AS. Lastly, deleting UBE3A gene in mice can recapitulate Angelman-like symptoms, and restoration of UBE3A can reverse those symptoms.

- **Feasibility of ASO delivery, target engagement, and disease rescue demonstrated in animal models**: multiple preclinical publications have reported that using ASOs can knockdown over 80-90% of target (UBE3A-ATS RNA) at the high end, partially restoring Ube3a protein (range 30-80%) in brain regions, and rescue disease symptoms of AS mice. ASOs could also recapitulate similar range of target knockdown and Ube3a restoration in NHP (non-human primate; a model closer to human than mouse). The therapeutic threshold of Ube3a protein restoration has not yet been established in animal models, but our review of several

literature publications suggests (to us) over 80-90% target (UBE3A-ATS) knockdown and corresponding 50%+ Ube3a protein recovery (more important marker) as possible benchmark in AS mice. Importantly, clinical transability of the above preclinical data is TBD, given 1) UBE3A gene is not conserved from mouse to human, 2) it is unclear to us how good animal models are at predicting ASO delivery to human brain. Right now, the field does not have the tool (e.g. Ube3a protein assay in CSF [cerebrospinal fluid]) to directly gauge target knockdown in human brain but the approvals of Ionis' other brain targeting ASOs (Spinraza and Qalsody) in neurological diseases at least indicate general feasibility of ASO brain delivery. Ionis noted the company has done several studies with other ASO drugs with the same ASO chemistry across preclinical models, NHP, and humans, and these prior experiences gave the company a good understanding of how PK/PD (neuro drug exposure) of its ASOs would translate from preclinical to humans.

- **Ongoing AS studies are exploratory, owing to lack of standardized endpoint:** most AS patients suffer from lack of speech while other relevant disease domains include cognitive, communication, motor skills, behavior, seizure, and sleep disorder. Bayley and Vineland are two outcome measures that have the richest sets of NHS data (collected since 2006). Bayley is a direct assessment of a patient's skills in cognitive, motor, and communication by a clinician and is widely accepted as a validated assessment in AS, but Bayley does not capture all disease domains and has other limitations. Vineland captures additional domains not reflected in Bayley including behavioral and activities of daily living, though scoring bias is a theoretical concern given the test is done by parents/caregivers. Other assessment tools have been introduced to address the shortcomings of Bayley, but these tests have relatively little natural history data for benchmarking and none of them have been standardized. The FDA has yet to define a standard registrational endpoint in AS.

- **Teasing out drug benefit from emerging, uncontrolled Ph1/2 datasets will depend on interpretation of natural history data:** since 2006, the largest AS natural history study (ASNHS) has been collecting longitudinal data to track neurodevelopment on AS patients in the real world. AS children make slower gains in development relative to a typical child, at a pace of 1-2 months development per year based on age-equivalent Bayley score. Given ongoing Ph1/2 trials lack an in-study placebo control, natural history (NHS) data (e.g. Bayley) offer drug developers an indirect benchmark to gauge treatment benefit of their ASOs. For comparison purpose, Bayley raw scores are converted to either a) age equivalent or b) growth scale value (GSV) – reflects changes from baseline over time. Bayley had a version update in 2019 (from 3rd edition to 4th) which incorporated an updated scoring system. Given majority of longitudinal data from ASNHS were collected using Bayley-3, there is a theoretical unknown on comparability between NHS data collected using Bayley-3 (less sensitive to change) and Ph1/2 data derived from Bayley-4 (more sensitive to change). Ionis indicated it has access to Bayley-4 based NHS data for comparison, and we await its Ph1/2 update to interrogate the sample size of its NHS dataset. Our KOL checks suggest Bayley may have limitations for older AS children (e.g. it may be more challenging to motivate a 10-year old AS child to put blocks in a cup vs a 2-year old AS child), though IONS believes Bayley does not have an AS age limit citing untreated patients do not display much developmental change over time.

- **Early competitor data suggest ASO approach is clinically active in AS**: in updates provided in 4Q23: 1) competitor Ultragenyx's ASO (GTX-102) led to improvements in EEG (electroencephalogram) rhythmics, 3 out of 5 domains from Bayley assessment (vs natural history), as well as directional improvements in sleep and behavior, 2) IONS provided a preliminary and qualitative assessment of initial Ph1/2 data which noted positive impact on EEG, Bayley, and CGI (clinician global impression). While functional outcomes (Bayley, CGI) have shortcomings as

discussed, we believe impacts on EEG indicate that these ASOs are clinically active. EEG is widely accepted as a PD (pharmacodynamic) biomarker in AS, given EEG pattern is disturbed in AS patients and level of disturbance correlates with disease severity (cognitive). Also, EEG offers an indirect means to gauge target engagement in human, given there is no assay to measure Ube3a level in CSF.

- **The optimal 'window to treat' remains unknown, thus a trial risk**: AS is usually not detected until developmental delays become noticeable, which is usually around the age of 6-12 months. Beyond the lack of a validated clinical endpoint, one trial risk is age of treatment intervention. Preclinical data indicate early intervention is needed to drive disease rescue in AS mice, whereas ability to reverse disease domains declines with age of treatment intervention. While it is not entirely understood when it is best to start an ASO in human patients, most ASO developers are defaulting to "earlier the better" (currently) focusing on enrollment of 4–17-year-olds; Ionis will generate some data in patients up to age 50.

- **Interplay of structured intervention is another trial risk:** structured interventions include education and therapist sessions provided to help educate the AS patient on communication and performing tasks, after Ube3a has restored to a more physiological normal state upon ASO treatment. It is unclear whether ASO alone, or ASO + structured interventions will yield better trial results. KOLs cautioned such interventions should be well planned and standardized in trials. For example, parents may be more motivated to see their children succeed on a treatment intervention in open-label trials, which presents a theoretical risk that a trial-enrolled child may receive more educational support thus gain development skills at a faster pace than untreated patients in NHS or in the real world. Ionis does not have specific structured interventions incorporated in its HALOS study.

- **Focus for IONS' 2024E data updates**: KOLs we spoke with were most focused on better characterization of ION582's treatment effect on EEG and Bayley (and/or Vineland), in the context of NHS data. Based on our KOL checks, we believe there could be challenges framing a positive ION582 clinical outcome but improvement in EEG and Bayley (vs. natural history) is thought to offer the most directional support. The KOLs are also curious about impact ION582 has on other disease domains captured in other multi-domain tools (e.g. CGI), though there are relatively limited NHS data to benchmark against those metrics. We will also look to Ultragenyx's update on GTX-102 in mid-part of 1H24 for read-across.

- **2H24 company updates on FDA reg path will be important to valuing AS opportunity**: we look to drug sponsors' alignment with the FDA on a registrational endpoint. Ultragenyx guided to a regulatory update in mid'24 while timing is TBD for Ionis (we assume 2H24E). Bayley is a likely candidate for inclusion in primary endpoint(s). Other possible candidates include multi-domain tools (e.g. CGI, MDRI) though KOLs lament these tools have not been standardized and the FDA may prefer standardized tools with rich NHS data like Bayley over newer (less validated), even though the FDA will very likely require a randomized controlled Ph3 program to support approval.

Background: disease, pipeline, animal data

Angelman (AS) is a rare neuro disorder linked to missing of UBE3A gene

Angelman Syndrome (AS) is a rare genetic and neurological disorder that affects an estimated 1 in 50k to 1 in 10k patients globally, a wide range given imperfect epidemiology data. The disease driver of AS is believed to be a missing copy of the maternal UBE3A gene (DNA inherited from the mother side) due to an aberration on

chromosome (DNA) 15. The paternal copy of UBE3A is naturally silenced (so called "imprinted") in the neurons of the brain (but not in other cell types) in all humans, which means healthy individuals can rely on the maternal copy of UBE3A for normal neurological function but AS patients do not have a maternal copy of UBE3A (Exhibit 1). UBE3A was linked to AS in 1997 thus diagnosed patients skew younger in demographics. There is no FDA-approved treatment for AS and UBE3A has not been incorporated in routine newborn screening, thus the actual patient prevalence remains poorly defined. How silencing of the UBE3A gene leads to manifestation of AS has yet been fully elucidated. We know UBE3A codes for a protein called ubiquitin ligase E3A that targets other proteins for degradation. Further, protein accumulation in neurons in the absence of proper protein degradation is hypothesized to drive over-excitement of the neuron synapses and impair normal synapse communications.

Chromosome 15 deletion is most common AS subtype with severe disease

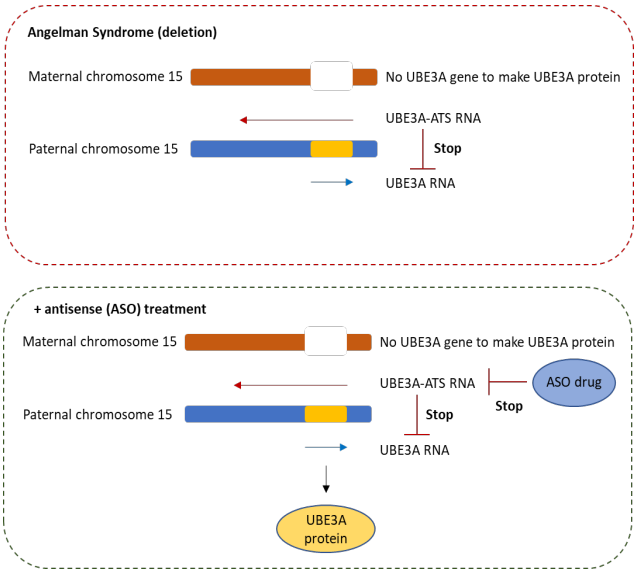
There are 4 key types of chromosome-15 aberrations found in AS patients, and the common theme is missing of the maternal copy of the UBE3A gene (Exhibit 2). Deletion is the most common alteration in AS which accounts for an estimated 65-80% of AS cases, followed by point mutations (5-15% AS). The remainder of AS cases consists of so called uniparental disomy and imprinting defect. Patient data from the natural history studies indicate patients with a deletion subtype have more severe neurodevelopmental impairments than non-deletion subtypes, which suggest other genes near UBE3A on chromosome 15 may also contribute to disease symptoms in patients with deletion AS. Differences in disease severity among non-deletion subtypes are less clear. Deletion and, to a lesser extent, point mutations are currently under clinical trial investigation for treatment intervention. Drug developers are taking a more measured approach by not enrolling patients (currently) with other subtypes (which have more than one copy of paternal UBE3A) given theoretical safety unknowns around over expression of paternal UBE3A on un-silencing more than one copy of UBE3A gene in the neurons.

AS patients have speech and developmental issues since early childhood

AS patients suffer from cognitive and developmental defects which may include universal lack of speech (most common symptom), frequent smiling and laughter, intellectual disability, developmental delays, poor muscle control, fine motor challenges, seizures, and/or sleep issues. While symptoms such as development delays may be noticeable as early as 6-12 months of age, AS is usually diagnosed in early childhood above one year of age when clinical features and characteristic behaviors become more evident. AS patients can have (close to) a normal lifespan, but they are unable to live independently and require life-long care.

In terms of which symptoms are most common in AS, according to a review article (Wheeler et al 2017), almost all AS patients have some level of movement disorders, most individuals do not ever develop speech or more than a few vocalizations though adulthood. Behavioral characteristics are considered "consistent" symptoms of AS patients but more variable in profile and occurrence vs speech and motor disorders. The literature points to an estimated 80%+ of AS patients have seizures, whereas the prevalence of sleep disorders in AS patients is poorly defined with estimates ranging from 20-90% of patients. Opinions vary on rank ordering the most challenging AS symptoms from a parents/caregiver perspective, though speech and communication skills among the most cited domains. FAST (Angelman patient advocacy group) conducted a survey with 332 patients and caregivers, in which speech, followed by communication, seizure, mobility, and learning/memory were ranked as top 5 AS outcomes most impacted (vs 9th for sleep). Our KOL check suggests speech, communication, behavioral, and/or sleep as most challenging domains to manage.

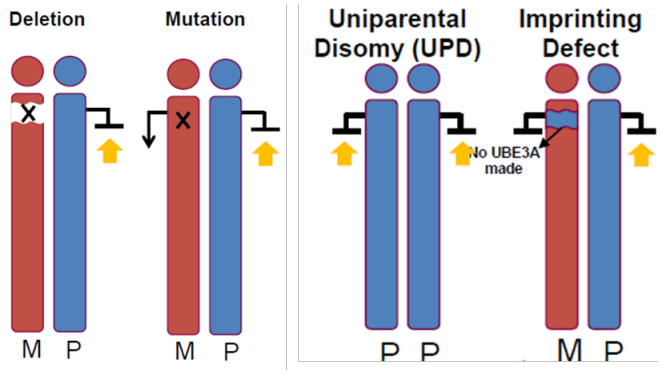
Exhibit 1: Genotype of AS and mechanism of ASO treatment
ASO treatment aims at stopping UBE3A-ATS induced silencing of UBE3A



Source: BofA Global Research

BofA GLOBAL RESEARCH

Exhibit 2: Types of chromosome 15 aberrations in Angelman Syndrome
AS involves loss of maternal UBE3A on chromosome 15



Source: modified from Ionis corporate presentation at FAST 2023

BofA GLOBAL RESEARCH

ASO-induced Ube3a restoration being explored in trials

Current Ph1 strategies are mainly focused on using an antisense oligonucleotide (ASO) to un-silence the paternal copy of UBE3A in the neuron of AS patients. Mechanistically, paternal UBE3A is naturally silenced by an antisense copy of UBE3A (called UBE3A-ATS) in human neurons. Drug developers are exploring an ASO approach to knockdown UBE3A-ATS aimed at loosening the brake on paternal UBE3A silencing (Exhibit 1). Other potential therapeutic approaches include: 1) restoring maternal UBE3A: for example, via gene therapy though no such approaches are in clinical development, 2) modulating downstream targets: for example, modulating GABA (neurotransmitter) involved in synapse communication.

Exhibit 3: Clinical pipeline in Angelman Syndrome
Un-silencing paternal UBE3A via ASO is most common approach in clinical development in Angelman Syndrome

Company	Drug	Modality	Target	Approach	Status	Next clinical milestone
Ionis / Biogen	ION582	ASO	UBE3A-ATS	Un-silencing paternal UBE3A	Active, Ph1/2 ongoing	Ph1/2 dose escalation update mid-24
Roche	Rugonersen	ASO	UBE3A-ATS	Un-silencing paternal UBE3A	Looking for partner as Ph1 data didn't meet internal threshold	TBD
Ultragenyx	GTX-102	ASO	UBE3A-ATS	Un-silencing paternal UBE3A	Active, Ph1/2 ongoing	Ph1/2 dose expansion update mid part of 1H24: at least 20 patients with 6-month data
Roche	Alogabat	Small molecule	GABAA alpha-5 receptor	Targeting downstream target	Active, Ph2a ongoing	Ph2a topline 2025E
Neuren	NNZ-2591	Small molecule	Insulin-like growth factor (IGF-1)	Targeting downstream target	Active, Ph2a ongoing	Ph2a topline 3Q24E

Source: company reports

BofA GLOBAL RESEARCH

ASO passes preclinical feasibility; clinical translation TBD

Multiple published preclinical studies have demonstrated the feasibility of un-silencing paternal UBE3A gene via ASO knockdown of UBE3A-ATS. When treated with an ASO, AS mouse models showed improvement in some of the disease-related symptoms. Given translatability of AS animal model to clinical efficacy in human has yet been established, we largely view preclinical data as directionally supportive of further investigation of an ASO approach in the clinic but ultimately see human data as key to de-risking the AS

treatment mechanism. Caveats aside, preclinical data (while imperfect) suggest to us that different ASOs might perform differently in human depending on how well each ASO knockdowns target in human brain. Below, we framed key preclinical results that may have inform viability of future clinical data and the competitive profile of different ASO candidates:

UBE3A-ATS sequence in mouse is very different from human: majority of the UBE3A-ATS sequence is not conserved from mouse to human, which complicates assessment of treatment benefit in mouse model with an ASO designed to target the human sequence. Ionis and Roche screened ASOs based on human UBE3A-ATS and evaluated for potency (e.g. ability to knockdown UBE3A-ATS) and safety in human-derived neurons, non-human primate (NHP), and/or transgenic mice (human sequence inserted). Ultragenyx's ASO was designed to target a specific region conserved from mouse to human which enabled direct assessment in mouse model. We believe each approach has pro's and con's thus do not see one approach as superior than another.

Significant target knockdown is needed to drive un-silencing of UBE3A: Roche's preclinical work (Jagasia et al. 2022) suggests ~90% target (UBE3A-ATS) knockdown (KD) is needed to drive ~70% increase in UBE3A mRNA (messenger) and ~50% increase in Ube3A protein (most important) in mouse model, and that magnitude of target KD needed to un-silence UBE3A is at least similar magnitude needed in NHP (mid-80% knockdown to drive ~50% increase in UBE3A mRNA) as in mouse. Similarly, Ultragenyx's preclinical publication (Dindot et al. 2023) suggests >90% KD is needed to increase paternal UBE3A mRNA level close to normal level (using ratio of paternal to maternal UBE3A mRNA as a proxy). What level of Ube3a protein recovery is sufficient to drive rescue of disease symptoms in AS models has not yet been clearly defined in the literature, but our review points to >50% restoration of Ube3a protein (which implies >80-90% of target KD) as a possible therapeutic threshold in AS mice (see below).

UBE3A un-silencing is not universal across all brain regions in animal models: based on Roche and Ultragenyx's publications, following delivery of ASOs to NHP via lumbar intrathecal administration, target KD of UBE3A-ATS and/or increases in ube3a protein level in NHP appear most pronounced in the cortex (outer layer of brain) vs more variable / less effective in deeper brain regions including midbrain, thalamus, and hindbrain tissues (cerebellum, medulla, pons). Correlation between dose strength and Ube3a recovery in deeper brain regions seems variable: increasing dose level (or number of doses) and ASO exposure could enhance target KD and/or Ube3a level in some deeper brain regions while other regions seem more resistant to change.

Preclinical data suggest dose response relationship and/or therapeutic window may be best in younger ages: studies using AS mouse model found that most neurological functions require UBE3A reinstatement during late embryonic and early postnatal (birth) period, and the number of disease symptoms that could be improved became fewer the older the mice at time of treatment intervention. Further, cross-study comparisons suggest to us that higher level of Ube3a restoration seems to correlate with reversal in higher number of disease symptoms in younger mice (Exhibit 4). Most of the disease improvement findings were reported at >50% restoration of Ube3a protein in the literature, suggesting that might be a therapeutic threshold in AS mice. Given translability of AS mouse model to clinical efficacy in human has yet been established, it remains to be seen how much of the animal findings will carry over to human AS patients.

More recent preclinical data suggest possible therapeutic benefit in adult: Lee et al. (Elife 2023) found that ASO could lead to improvement of brain (EEG) rhythmic and sleep pattern in adult AS mice, suggesting ASO might have some form of therapeutic benefit in older patients. The improvements in EEG and sleep correlate with level of Ube3a restoration, with EEG rhythms/sleep time closest to normal level observed in wildtype mice at ~50%+ level of Ube3a restoration.

Exhibit 4: Impact of UBE3A un-silencing in AS mice
Restoration of UBE3A protein led to rescue of disease domains in AS mice in a dose- and age-dependent manner

				Cognitive	Motor	Motor / behavioral		Behavioral		Seizure
Publication	**Intervention**	**Mouse age**	**UBE3A restoration**	Fear conditioning	Rotorarod	Forced swim	Open field	Marble burying	Nest building	Audiogenic
Intra-study comparison										
Silva-Santos et al. 2015	Knock-in	Embryonic	~ 80-100%							
Silva-Santos et al. 2015	Knock-in	New born (day1)	~35-65%							
Silva-Santos et al. 2015	Knock-in	Juvenile (3wk)	~ 70-100%							
Silva-Santos et al. 2015	Knock-in	Adolescent (6wk)	~ 70-100%							
Silva-Santos et al. 2015	Knock-in	Adult (3mo+)	~ 70-100%							
Cross-study comparison										
Meng et al. 2015	ASO	Adult (2-4mo)	~ 35-45%							
Silva-Santos et al. 2015	Knock-in	Adult (3mo+)	~ 70-100%							
Silva-Santos et al. 2015	Knock-in	New born (day1)	~35-65%							
Milazzo et al. 2021	ASO	New born (day1)	~ 50-75%							
Milazzo et al. 2021	ASO	Juvenile (3wk)	~ 50-75%		Tests conducted but data not shown					
Silva-Santos et al. 2015	Knock-in	Juvenile (3wk)	~ 70-100%							

Not tested / not reported
No improvement
Minor improvement
Partial improvement
(Near) complete rescue

Source: Nature, J Clin Invest, JCI insight

BofA GLOBAL RESEARCH

Natural history study offers insights to AS progression

AS children make slower gains in development skills relative to a typical child, though regression of skills in AS pts is rare. There have been iterations of NHS studies capturing neurodevelopment progress of AS patients over time (longitudinally) in the real word. Angelman Syndrome Natural History Study (ASNHS) is the largest and longest natural history study that has been enrolling AS patients since March 2006. Other NHS studies include FREESIAS (2018-present) and ASNHS global expansion into countries outside of North America. Drug developers (e.g. Ionis) also have in-house NHS data as part of a pre-competitive collaboration among scientific groups and drug developers to enrich NHS data. There is a central database (LADDER) that houses data collected across multiple sources, including ASNHS, Global Angelman Syndrome Registry, and patient visits to clinics within the LADDER network. Considering ongoing Ph1/2 clinical trials lack an in-study placebo control, NHS data offer drug developers an indirect benchmark to gauge treatment benefit of their ASOs relative to natural gains in skills expected from an AS patient as the patient ages. NHS may also help inform whether safety signals detected in trials are due to drug effect or part of natural history of the disease.

Largest AS NHS has collected data from over 550 patients over 16 years

The ASNHS study was initially funded by the NIH (National Institutes of Health) and had enrolled ~300 patients across 6 study sites from 2006 to 2014 prior to discontinuation of the NIH funding. The study resumed in 2017-22 with funding from the FDA and had sites expanded from 6 US sites to 10 sites in North America (7 in the US and 3 in Canada), followed by current iteration (2022 – present) of the study funded by ABOM (Angelman Biomarkers and Outcome Measure alliance, which includes patient support groups and drug developers). To date, ASNHS has enrolled 550+ patients over 16 years.

Bayley and Vineland assessments have richest amount of NHS data

Since the inception of ASNHS in 2006, the study has expanded data capture from a few outcome measures to 10+ assessment tools over the years. Among those, Bayley and Vineland are two assessments in which ASNHS has been collecting data since the study inception in 2006. As such, Bayley and Vineland have the richest amount of NHS data

relative to other / newer outcome measures. ASNHS had published natural history data in Bayley and Vineland (Exhibit 5).

- **Bayley**: a direct assessment of skills in cognitive, communication, and motor skills in young children from birth to 42 months old. Bayley is thought to be applicable for AS children older than 3 years old (with caveat – see below) given it is tailored towards the developmental level rather than chronological age. Bayley is conducted on site by a trained investigator who has direct interaction with the AS child. While most AS patients suffer from a lack of speech, the Bayley does not rely heavily on verbal skills for assessment. The Bayley is cited as a "validated" assessment for AS and is the most widely used test across natural history studies and clinical trials. However, Bayley is not without drawbacks based on our KOL checks. First, the test does not capture all possible disease domains of AS (e.g., seizure, sleep, adaptive behavior [Vineland]). Second, Bayley has more limitations the older a child gets (e.g. age 10) as older children (even with AS) may not be motivated to perform tasks that are tailored for <age 4. Lastly, while Bayley an objective/direct assessment of a child's ability to perform a range of tasks, the child's performance at the assessment day/time can be influenced by confounding factors (e.g. structured interventions, surrounding environment, how well rested the child is after traveling).

- **Vineland**: the Vineland Adaptive Behavior Scales (VABS) shares some similarity in measure of disease domains as the Bayley (cognitive, communication and motor skills) and captures additional domains not assessed in Bayley i.e. daily living activities, socialization, and adaptive behavior. Similar to Bayley, Vineland assessment was conducted since the inception of ASNHS (2006-) thus there is relatively rich amount of longitudinal NHS data available (along with Bayley). Per our KOL checks, one concern for using Vineland is potential bias (vs Bayley) given it is an assessment of the child's typical performance by a parent or caregiver and does not require the child to be present at time of the survey. Conversely, a KOL believes Vineland can be complementary or a preferred tool to Bayley if done appropriately (e.g. in conjunction with a clinician assessment), considering Vineland evaluates a patient's typical performance on a day-to-day basis and offers more nuance assessments thus likely more sensitive to detecting change.

Exhibit 5: Natural history studies of Angelman Syndrome
AS Natural History Study is the largest and longest natural history study established to date with multiple longitudinal data publications

Study	Sample size	Age	Study period	Measurement	Trial ID	Publication
AS Natural History Study	236	1 - 12 years old	2006 - 2014	Bayley-3	NCT00296764	Journal of Autism and Developmental Disorders 2023
AS Natural History Study	257	1 - 12 years old	2006 - 2014	Vineland-2	NCT00296764	Journal of Autism and Developmental Disorders 2023
AS Natural History Study	250	1 - 18 years old	2006 - 2014	Bayley-3, Vineland-2, PSL-4, CSS	NCT00296764	Molecular Psychiatry 2021
AS Natural History Study	92	5 - 60 months old	2006 - 2008	Bayley-3, Vineland-2, ABC	NCT00296764	J Dev Behav Pediatr 2010
FREESIAS	55	1 - 12, and ≥18 years old	2019 - 2021	EEG, seizure, sleep, Bayley-3	NCT04507997	Journal of Neurodevelopmental Disorders 2023

Source: company reports. Note: PSL: Preschool Language Scale, CSS: Clinical Severity Scale, ABC: Aberrant Behavior Checklist.

BofA GLOBAL RESEARCH

NHS data offer insights to development delays in AS relative to typical children

Bayley is an assessment on a children's (or AS patient's) ability to perform over 260 items across five domains: 1) cognitive, 2) receptive communication, 3) expressive communication, 4) fine motor, and 5) gross motor. Bayley raw scores for each domain are converted into an age-equivalent score and a growth score equivalent to contextualize the developmental progress of an AS patient. According to ASNHS' modeling of AS progression based on patient-level Bayley-3 data, AS children make slower gains in neurodevelopmental skills at a rate of 1-2 months per year based on age-

equivalent score, and most 6-years old AS children function at the developmental level of a 14- to 27-months old neurotypical child. Gross scale value (GSV) is used to measure an individual's change from baseline in each Bayley domain and has a scale from 200 to 800. ASNHS reported that that AS children gain 1-16 GSV per year depending on AS subtype and disease domains, though there is no GSV from typical population for comparison and the 42-month age limit of Bayley in neurotypical individuals could complicate comparisons between AS and neurotypical individuals.

Exhibit 6 illustrates pace of neurodevelopment of AS patients based on Bayley-3 data from the ASNHS study, but it is not designed for cross-trial comparison vs drug sponsors' Ph1/2 data which are based on Bayley-4 (current version). NHS studies have started to capture Bayley-4 data since around 2020. ASNHS database had fairly limited longitudinal Bayley-4 datapoints based on last reported metrics as of 4Q23, but IONS noted it has access to the broader LADDER database and will have Bayley-4 based NHS data for comparison with its Ph1/2 data update.

Exhibit 6: Modeled change of Bayley-3 scores in AS patients through 12 years of age
According to a developmental growth model derived from on ASNHS-collected data, AS patients gain 1-2 months of developmental age per chronological year and 1-16 growth scale points per year across key AS subtypes

	Modeled change (increase) in age equivalent score per year			Modeled change (increase) in GSV per year		
	Class I deletion	Class II deletion	Mutation	Class I deletion	Class II deletion	Mutation
Cognitive	1.0 months per year	0.9 mo	2.2 mo	7.5 GSV per year	6	11.3
Receptive communication	0.7 mo	0.7 mo	2.5 mo	5.7	5.7	16
Expressive communication	0.3 mo	0.2 mo	1.1 mo	2.3	1.4	9.3
Fine motor	1.0 mo	0.9 mo	3.0 mo	7	5.9	13.3
Gross motor	1.0 mo	0.9 mo	1.8 mo	10.5	9.6	9.7

Source: Journal of Autism and Developmental Disorders 2023

BofA GLOBAL RESEARCH

Some drawbacks with NHS: dropout, age skew, not much data outside of Bayley

There are differences in the type of data captured and how data were collected between natural history studies and ongoing clinical trials. Angelman is a relatively new territory in terms of clinical development, and there are limited studies/data to corroborate the predictive value of NHS to a placebo effect occurring in a randomized controlled trial. As such, we note theoretical caveats that might (or might not) interfere with our/investors' ability to compare drug developers' Ph1 results to natural history data:

- **Evolution of efficacy measurements**: Most of the data published by ASNHS were derived from Bayley-3 and Vineland-2 assessments collected during 2006-2014. Since then, the ASNHS has pivoted to latest edition of Bayley (Bayley-4; 2020) and Vineland (Vineland-3; 2017) and the study has incorporated new outcome measures such as Clinical Global Impressions (CGI) introduced by drug developers, sleep and seizure questionnaires, and quality of life instruments requested by the FDA (per ASNHS investigator at FAST 2023). For new outcome measures introduced in recent years, there are relatively less longitudinal natural history data for drug developers to compare their open-label trial results to (Exhibit 7). As of Nov 5, 2023, there were 25-patient worth of longitudinal Bayley-4 datapoints (2 visits per patient) entered into ASNHS database. However, IONS noted it has access to a broader LADDER database where new Bayley-4 data are added on an ongoing basis thus the company would have Bayley-4 NHS data for comparison. Lastly, the FDA/regulators have not defined an acceptable registrational endpoint for AS.

- **High dropout rate**: the ASNHS had high drop-out rate following initial patient visits, with a median of 2-3 (roughly annual) visits per participant throughout the course of the study (Exhibit 7). Such drop-out rate would still yield 2-3 years worth of patient data (given roughly annual visits) from over 100-200 enrollees in 2006-2014. Conversely, ASNHS did not start capturing new outcome measures until 2020-22 and dropouts could slow down data accrual under those new measures. To

combat visit dropouts, ASNHS has pivoted to a hybrid model utilizing on-site and virtual visits; Bayley, physical and neuro examinations will be conducted in-person.

- **Age group skewed to younger children**: most patients enrolled in ASNHS were children under the age of 13 (85% of enrollees) in North America. While ongoing Ph1 studies from Ionis and Ultragenyx are similarly skewed to younger patients, a risk is that investors may discount the immediate addressable patient number (TAM) accordingly, pending further clinical validation in older AS patients. Another consideration is that adolescence (13-17 years of age) is an age group characterized by changes in AS symptoms (eg improvements in sleep and seizure) and clinical heterogeneity, thus some NHS publications excluded this age group for analysis. Ionis enrolled patients 2-50 years of age across 11 sites in US, EU, and rest of world, though most patients enrolled (42 out of 51) were below 18 years old. Ultragenyx enrolled patients 4-17 years of age in 25 sites across 8 countries including the US, with majority of data derived from ex-US sites.

Exhibit 7: Newer outcome measures completed in ASNHS
ASNHS had high dropout rate and relatively limited longitudinal data on newer outcome measures

	1 visit	2 visits	3 visits	4 visits	Total
Overall retention rate (2006-present; %)	100%	64%	42%	26%	---
Newer outcome measures collected (2017-present; n=number of subjects)					
Bayley-4	122	25	1	0	148
Vineland III	151	53	22	8	234
ORCA	110	32	2	0	144
Ultragenyx CGI	66	6	0	0	72
Roche CGI	70	0	0	0	70
Sleep diary	41	0	0	0	41
Seizure diary	41	0	0	0	41
Home EEG	12	0	0	0	12

Source: FAST 2023. Note: ASNHS database as of Nov 5, 2023.

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Exploratory Ph1: multiple endpoints due to lack of FDA standardized endpt

While Bayley is a validated assessment for AS, the test does not capture all possible disease domains of AS. Drug developers are exploring additional clinical and biomarker measures (in addition to Bayley and Vineland) in ongoing Ph1/2 which could help inform therapeutic potential of their drug candidates and facilitate future discussions with the FDA on a registrational endpoint to support potential drug approval. The list below is not intended to be exhaustive but contains key measures captured in clinical programs:

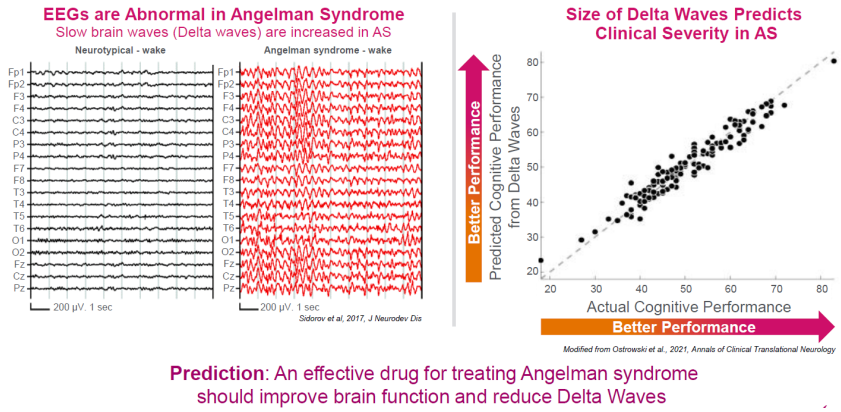
- **UBE3A level (or lack thereof)**: a measure of knockdown of UBE3A-ATS (antisense) and/or restoration of Ube3a protein level in CSF (cerebral spinal fluid) would help inform target engagement in the brain. There is no good assay for quantifying UBE3A-ATS or Ube3a protein level (difficult to measure) in human CSF. Ionis is working on developing an assay for Ube3a protein, but the company does not see the assay as a prerequisite for Ph3 advancement. A quantitative Ube3a assay would help inform dose response in humans relative to preclinical data which suggest (to us) >50% restoration of Ube3a protein level is needed to drive a therapeutic benefit in AS mice.

- **Brain EEG**: AS patients have abnormal brain waves as measured by EEG vs healthy individuals. Increased rhythmicity of a slow-frequency brain wave called delta wave is a prominent phenotype AS (est. ~80%+ of patients) (Exhibit 8). The increase in delta activity seems more pronounced in deletion vs non-deletion subgroups, but the correlation is inconclusive per the literature. Studies found the size of delta

waves correlates with cognitive function in AS, supporting EEG as a PD (pharmacodynamic) biomarker in AS. Whether EEG is a predictive biomarker for other AS symptoms is less clear; Hipp et al. reported directional but not statistically significant correlations between EEG and motor / communication domains of Bayley. KOLs we spoke with view EEG is an objective measure and good biomarker if EEG measurement is standardized and done with consistency to minimize noise and cofounders (eg timing/procedure of the EEG measurement).

Exhibit 8: Role of EEG as a biomarker in AS

EEG is thought to be a biomarker is AS given 1) AS patients have abnormal EEG pattern (increased delta activity) vs neurotypical individuals, 2) delta activity correlates with severity of cognitive function in AS



Source: Ionis presentation at FAST 2023

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- **Bayley-4**: ongoing Ph1 clinical trials capture Bayley scores using the latest (4th) edition, as opposed to NHS which collected data under Bayley-3 up until 2020. Relative to the 3rd edition, Bayley-4 has fewer items to assess per disease domains, takes less time to conduct, and incorporates a questionnaire to caregivers. More importantly, Bayley-4 is based on a polytomous scoring system (0= not present, 1=emerging, 2=mastery) which offers better sensitivity at detecting changes vs dichotomous used in Bayley-3 (0=did not meet criteria, 1=met criteria). For example, a child demonstrates some evidence of a skill would score a 0 for that item under Bayley-3 but a 1 under Bayley-4. Otherwise, raw scores from both editions can be converted into GSV (range: 200 to 800). Given majority of historical NHS data were collected under Bayley-3, there are two approaches for drug sponsors to presenting NSH data: 1) convert Bayley-3 scores to Bayley-4 (post-hoc): KOLs we spoke with think this is an acceptable practice given scarcity of Bayley-4 data in ASNHS, but we flag a theoretical unknown when comparing data initially collected using Bayley-3 and then making B-4 conversion might under-capture subtle changes in NHS; 2) leverage newer Bayey-4 based NHS data, though at a smaller sample size relative to Bayley-3 NHS database. Ultragenyx converted its NHS data from Bayley-3 to Bayley-4 for comparison with its Ph1 results (Bayley-4). Ionis noted it has access to Bayley-4-based NHS data thus no conversion would be needed for comparing its NHS data with its Ph1/2 results.

- **ORCA**: Observer-Reported Communication Ability (ORCA) is an assessment administered to parents/caregivers that evaluates expressive, receptive, and pragmatic forms of communication of the patient. The ORCA was originally developed for AS in response to parents/caregivers' strong desire to see improvements in speech and communication in their children but there lacked a parent/caregiver-reported measures of communication ability that can be used in clinical trials for AS. ORCA was introduced in 2018 thus there is less longitudinal NHS data vs Bayley. Both Ionis and Ultragenyx collect ORCA data in ongoing Ph1/2.

- **Sleep and seizure questionnaires**: seizure and sleep are two potential disease domains of interest. We note factors that may interfere with interpretation of sleep/seizure data: 1) age – studies have found that sleep disorders and seizures may improve as patients become older (adolescence / adulthood); 2) background therapy – Ionis' and Ultragenyx's Ph1 trial enrolled patients who already had seizure controlled with anti-epileptic medication, and it is unclear (to us) whether and to what extent background medication will interfere with the ability to detect a treatment benefit in seizure reduction / elimination. Ultragenyx does not expect to see significant change in seizure given patients must have stable seizure count on medication coming into the study, thus the company is tracking seizure for safety (not for efficacy) and that it has not observed meaningful changes in seizure in Ph1/2. On the other hand, Ionis does not expect background medication to preclude the company from tracking changes, given most drugs help patients manage seizure but do not completely control / eliminate seizures.

- **Clinical Global Impression (CGI)**: CGI is a disease-agnostic scale designed to assess overall severity of a disease and change, and it has been used in conjunction with disease-specific rating scales. For example, Acadia's Daybue was approved for Rett Syndrome based on co-primary endpoints in CGI and a disease-specific rating scale (RSBQ). In AS, CGI was a primary endpoint for Ovid's failed Ph3 trial of OV101 (GABAA agonist). Other drug developers have introduced their own versions of CGIs to interrogate disease domains beyond those captured in Bayley (Exhibit 9). CGI is rated on a scale of 7 ranging from very much worse (7) to no change (4) to very much improved (1). There is currently very limited longitudinal CGI data from ASNHS (Exhibit 7). Further, it is unclear how open-label nature of Ph1 studies may impact (bias) CGI scoring of clinical improvement in AS patients. KOLs we spoke with view CGI as a good tool (along with multi-domain rating scale) and more sensitive at detecting changes vs Bayley, but would like to see a unified CGI scale as opposed to having three versions (Roche's, Ultragenyx's, and Ionis'). Ionis noted 1-point improvement in CGI is generally considered meaningful based on the literature.

Exhibit 9: Clinical assessment of Angelman Syndrome
Bayley was widely used in natural history studies, and drug developers assess disease domains not captured by Bayley

	Bayley	Vineland	CGI-C/S/I-AS (Roche, Ultragenyx)	SAS-CGI-C (Ionis)
Cognitive	x			x
Receptive communication	x	x	x	
Expressive communication	x	x	x	x
Fine motor	x	x	x	x
Gross motor	x	x	x	x
Behavior		x	x	x
Seizure				x
Sleep			x	x
Social relationships		x		
Activities of daily living		x		x
Global / overall			x	x

Source: company reports

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Exhibit 10: Clinical assessment of AS used in ongoing clinical trials
Both Ionis and Ultragenyx are capturing a wide variety of AS disease domains beyond Bayley (list is not exhaustive)

	Ionis	Ultragenyx
Cognitive	Bayley-4, SAS-CGI-C	Bayley-4
Overall communication		CGI-C/S/I-AS
Receptive communication	Bayley-4, ORCA	Bayley-4, ORCA
Expressive communication	Bayley-4, SAS-CGI-C, ORCA	Bayley-4, ORCA
Fine motor	Bayley-4, SAS-CGI-C	Bayley-4, CGI-C/S/I-AS
Gross motor	Bayley-4, SAS-CGI-C	Bayley-4, CGI-C/S/I-AS
Behavior	SAS-CGI-C	ASA-behavior, CGI-C/S/I-AS
Seizure	SAS-CGI-C	Diary, EEG
Sleep	SAS-CGI-C	ASA-Sleep, CGI-C/S/I-AS
Activities of daily living	SAS-CGI-C	Vineland
Global / overall	SAS-CGI-C	CGI-C/S/I-AS

Source: company reports

BofA GLOBAL RESEARCH

2024 is a critical juncture for ION582

ASO approach is clinically active but data benchmarking is challenging

Cumulative clinical updates from Ultragenyx (RARE) and Ionis (IONS) have so far suggest un-silencing UBE3A via ASO is clinically active in AS patients and may be a promising approach worth further clinical investigation. However, we would argue there is still work to do to establish the clinical benefit of the class (and ION582) considering Ph1/2 studies are open-label (potential bias) and lack a placebo control. Criteria for clinical meaningfulness in AS has not yet been defined though work is ongoing per our KOL checks. FDA has yet to set a registrational endpoint in AS, pending sponsors post-data discussions with the Agency (in 2024). Further complicating the story is Roche's decision to de-prioritize its ASO program and the company has yet to present the Ph1/2 results that underlie its decision. That said, there were signs of meaningfulness from IONS' and RARE's prior updates based on trial investigator assessments and threshold of significance defined by the Bayley manual. Below, we summarize key findings from clinical ASO programs in AS:

- **Roche's rugonersen**: in June 2023, Roche announced it would look for a partner to develop its ASO rugonersen instead of pursuing the program alone, based on interim analysis of its Ph1/2 study (TANGELO). Roche noted the drug showed an acceptable safety profile and some encouraging effects in EEG in Ph1/2 (n=70+), but the observed level of clinical improvements explored relative to NHS data did not meet the company's internal criteria for advancement. Roche plans to shut down its Ph1 study in 1H24, although the company had more recently at FAST (Nov'23) signaled a possibility of keeping the Ph1 active for enrolled patients beyond 1H24. RARE does not see read-through from Roche's de-prioritization, citing stronger potency of RARE's GTX-102 vs rugonersen. Reflecting another unknown in cross-trial comparison, we note Roche explored less frequent maintenance dosing regimen (every 4- to 6-months) than competitors (every 3-months) in Ph1/2, and a trial investigator from TANGELO speculated that Roche wanted a 6-month dosing schedule. Roche continues to evaluate its small molecule candidate alogabat (GABA(A) alpha-5 receptor modulator) in an open-label Ph2a.

- **Ultragenyx's GTX-102**: RARE provided an interim Ph2 update in 4Q23 which featured extension cohort data of 15 ex-US patients who received 4 monthly loading doses of GTX-102 at 3.3–7.5mg followed by maintenance dose every 3 months at 10-14mg dose range, with roughly 1-2 years of follow-up. RARE showed GTX-102 led to improvements in 3 out of 5 domains in Bayley-4 (cognitive, gross motor, receptive communication), at levels exceeding NHS data and a "threshold of significance" according to the Bayley-4 manual. GTX-102 also led to improvements in EEG, sleep and behavior relative to baseline though there were no NHS data to draw comparisons with. On safety, 3 patients discontinued treatment for non-serious adverse events (AE) and there were no unexpected AEs or safety concerns. In an earlier datacut (2022), RARE also observed directional improvements based on CGI-change scores at patient-level data. Early in Ph1 development (2020), high dose of GTX-102 (20mg+) led to serious AE in lower extremity weakness in patients (n=5 out of 5). RARE noted patients who received high-dose GTX102 had lost skills after treatment discontinuation but those patients had regained those skills following re-treatment with a lower dose. RARE has not observed a single case of lower extremity weakness since moving to lower dose range (up to 14mg).

- **Ionis' ION582**: at FAST 2023 (Nov), IONS provided preliminary data from Part 1 MAD (multi-ascending dose) portion of Ph1/2. The datacut was as of Oct'23 and captured 4 months of patient follow-up (3-month MAD plus 1-month follow-up). The update was mostly qualitative in nature. Nonetheless, IONS observed early signs of EEG improvement: ~70% of subjects showed a reduction in EEG delta activity vs baseline, at a magnitude exceeding levels observed in NHS. IONS indicated most patients showed some level of improvement in overall CGI-change score (as rated

by clinicians) and that the overall improvement in AS symptoms was considered "meaningful" to the clinicians. Lastly, IONS noted the majority of subjects showed improvement in total Bayley score beyond changes observed from NHS over the same time period. IONS indicated the drug was well-tolerated at all dose levels tested, and there were no trends in safety labs (CSF, blood, urine) and no concerning safety trends from independent safety monitoring committee. Given RARE reported serious AE in lower extremity weakness early in drug exposure (within 1-5 months) from initial high-dose cohort, risks of ION582 running into similar serious AE appears low to us at current juncture given its study remains ongoing (no clinical hold) at minimum follow-up of over 7 months (our est.) as of Feb'24.

2024 clinical updates offer de-risking opportunity

Given early promising data, we look to 2024 updates from IONS and RARE for broader de-risking of the class and ION582 and alignment with the FDA on Ph3 registrational endpoint. Below, we frame milestones expected for clinical ASO programs in 2024:

- **Ionis**: in mid-2024, IONS will provide a detailed data analysis on Part 1 MAD portion of its HALOS Ph1/2 study as well as data from a cut (portion) of the Part 2 LTE (long-term extension; 12-month additional follow-up). As of Oct 2023 datacut, the Part 1 MAD was fully enrolled and had followed patients for at least 4 months, thus current timing suggests to us that by mid-2024 most enrollees should have a minimal follow-up of around a year. Therefore, we expect IONS' mid-year update will help inform safety on longer term dosing and better characterization of efficacy vs preliminary update provided at FAST 2023 which was fairly high-level and qualitative in nature. IONS expects the mid-year update to help inform end-of-Ph2 FDA meeting, but Ph3 timing is TBD (could spill into 2025E). Partner Biogen can opt-in for '582 development within a predefined period of time after the Ph1/2 update, not contingent on timing of IONS' end-of-Ph2 meeting with the FDA.

- **Ultragenyx**: RARE's next update in middle part of 1H24 will include dose expansion data in at least 20 patients with at least 6 months of follow-up, including around 10 patients with longer follow-up through Day 250, as well as a data update of the overall Ph1/2 patient population. Given loading dose from the expansion cohort will be higher than the loading dose strengths tested prior (3.3-7.5mg), RARE expects to observe a bigger treatment effect in loading dose period vs prior data. RARE expects to have an end-of-Ph2 meeting with the FDA in mid-year, and RARE's commentary at FAST 2023 suggests Ph3 may start as early as 2H24E.

- **Roche**: Roche is actively looking for a partner to advance rugonersen in clinical trials and plans to reserve data disclosure until the company has identified a partner.

Competitive positioning: difficult to peg with existing data

Among the three clinical ASO programs, RARE's GTX-102 is most advanced on timeline, followed by IONS which is about 3-6 months behind by our estimate. Roche's status is TBD pending identification of a R&D partner. In terms of profile comparisons, we have not found sufficient preclinical data in the public domain to draw comparisons across ASO candidates. Key challenges in such exercise include: 1) there were no head-to-head preclinical comparisons published, 2) UBE3A is not conserved from mouse model to human which would caveat comparison of ASO data using mouse models, 3) preclinical data may not reflect effectiveness of ASO delivery to the human brain, 4) IONS have not published antisense sequence or preclinical data of ION582. We summarize differences in molecule profile, Ph1/2 study design, and clinical data across the clinical ASO programs in Exhibit 11 and Exhibit 12.

RARE framed GTX-102 is more potent than competitor molecules based on its LNA (locked nucleic acid)-based ASO backbone and GTX-102's target binding region on UBE3A-ATS (vs regions patented by Roche and Ionis). Citing higher potency of GTX-102, the company can afford to administer lower dose range to achieve clinical efficacy despite higher risk of toxicity with LNA-based ASO. From IONS perspective, the efficacy and safety profiles of its approved neuro ASO portfolio (ie Spinraza and Qalsody) validate MOE (methoxyethylribose) as a backbone of choice for ION582. IONS has also explored LNA-based ASOs in preclinical testing but could not find a candidate that meets its internal (safety) threshold for advancement.

Although initial Ph1 update of ION582 at FAST 2023 were highly preliminary and caveated by dose escalating nature of the study (ie mix of low/high dose strengths), we are encouraged with IONS commentary around improvement in EEG pattern (ie decreases In delta activity) for a couple of reasons. First, EEG is an objective measure and higher EEG delta activity correlates with more severe disease in cognitive domain of Bayley. Second, IONS noted impact on EEG over a 4mo period exceeded changes observed in untreated patients from NHS. The commentary on EEG was encouraging to us, considering competitor's GTX-102 led to minimal change from baseline in mean delta power over similar time period (day 128) in Ph1 dose escalation data. With that said, we believe it is too early to draw conclusion on competitive positioning between the two molecules, in the absence of placebo-controlled data on a Ph3 dose. Nonetheless, at a minimum, IONS' preliminary data provides a basis for ION582 potential to be a competitive agent vs GTX-102. Ultimately, we see AS a market large enough to accommodate more than one player.

Exhibit 11: Comparison of clinical-stage ASO programs in AS
We note Ph1 trial design and ASO differences among clinical stage programs

	Ionis / Biogen	Ultragenyx	Roche
Drug			
Drug	ION582	GTX-102	Rugonersen
Backbone	MOE	LNA	LNA
Antisense region	Not disclosed	Upstream region of UBE3A-ATS	Downstream region of UBE3A-ATS
ASO identification	IONS screened >3,000 ASOs for good binding to human UBE3A-ATS RNA in cell culture and effective in transgenic AS mouse model (human UBE3A inserted) and iPSC neurons, and select safest and most effective ASOs in NHPs. (FAST 2023)	Given UBE3A-ATS gene is different between mouse and human, inventor designed an ASO from a region of UBE3A-ATS conserved from mouse to human, enabling assessment of efficacy in mouse model which helped inform human ASO candidate selection. (Dindot et al 2023)	Roche conducted a library screen of ~2500 LNA-ASOs based on upregulation of UBE3A mRNA in AS-patient derived neurons. Rugonersen was selected based on potent and selective unsilencing of UBE3A in iPSC and NHPs. (Jagasia et al 2022)
Dose range explored	Dose range: not disclosed, but IONS noted dose consistency with approved portfolio (12mg Spinraza to 100mg Qalsody); Dose interval: not fully disclosed, but Part 1 tested 3 doses over 3 mo, and Part 2 tested dosing every 3mo	Most recent update in 4Q23: Loading dose 3.3 - 7.5mg every 1mo Maintenance dose 10 - 14mg every 3mo	Dose level not disclosed; Dose interval: Part 1: up to 3 doses in 8-week Part 2: every 16wk to every 24 wk
Ph1/2 trial			
Study size	51	74	74
Trial start	December, 2021	February, 2020	August, 2020
Age group	Range: 2 - 50 years old 27% 2-5 years old 55% 4-17 years old 18% 18-50 years old	Range: 4-17 years old	Range: 1-12 years old
Subtype	84% deletion, 16% mutation	Deletion only	Deletion and mutation
Location	11 sites in 6 countries	25 sites in 8 countries	12 sites in 4 countries
Next update	Final MAD data (3-month) and a cut of LTE data (up to 12-month)	Dose expansion data from 20+ patients at 6-month+ follow-up in 1H24. Previous update included dose escalation data from 15 patients with up to 506 days of follow-up	TBD - Roche is looking to partner Rugonersen citing clinical improvements observed in P1/2 vs natural history data did not meet internal threshold.

Source: company reports

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Exhibit 12: Clinical results in Angelman Syndrome
We look to Ionis mid-2024 update for better assessment of ION582 efficacy given limited disclosure in Oct 2023 datacut

	NHS benchmark of measures (from ASNHS data unless noted otherwise)	GTX-102 (4Q23 dose escalation)	ION582
Bayley - cognitive	RARE-curated NHS data from LADDER database (Bayley-3 converted to Bayley-4 GSV): ~ +2 at Day 365 ~ +3 at Day 730	Bayley-4 GSV: ~ +4.5 at Day 128 ~ +8.5 at Day 254 ~ +10 at Day 338 ~ +14 at Day 506	TBD (Bayley-4)
Bayley - receptive communication	RARE-curated NHS data (converted Bayley-4 GSV): ~ +2 at Day 365 ~ +3 at Day 730	Bayley-4 GSV: ~ +2.5 at Day 128 ~ +6.5 at Day 254 ~ +8 at Day 338 ~ +8 at Day 506	TBD (Bayley-4)
Bayley - expressive communication	Most data captured in Bayley-3 prior to ASNHS pivoting to Bayley-4 in 2020+	Data not yet presented (Bayley-4)	TBD (Bayley-4)
Bayley - gross motor	RARE-curated NHS data (converted Bayley-4 GSV): ~ +1 at Day 365 ~ +1.5 at Day 730	Bayley-4 GSV: ~ +2 at Day 128 ~ +2.5 at Day 254 ~ +3 at Day 338 ~ +6 at Day 506	TBD (Bayley-4)
Bayley - fine motor	Most data captured in Bayley-3 prior to ASNHS pivoting to Bayley-4 in 2020+	Data not yet presented	TBD (Bayley-4)
Bayley - overall	---	---	Majority of subjects showed some level of improvement in total Bayley score after 4 months. The change is beyond levels observed in NHS over the same time period
ORCA - communication	Captured 2018-present	Data not yet presented	TBD (ORCA)
Sleep	SNAKE questionnaire (2017-2022) Sleep diary (2022-present)	ASA Sleep: ~ -1 at Day 254 ~ -1 at Day 506	TBD (SAS-CGI-C)
Behavior	Behavioral history, Aberrant Behavior Checklist (2017-present)	ASA Behavior: ~ -0.6 at Day 254 ~ -1 at Day 506	TBD (SAS-CGI-C)
Seizure	Seizure diary (ASNHS 2022-present, FREESIAS 2018-present), at-home EEG (2022-present)	Data not yet presented (diary, EEG)	TBD (SAS-CGI-C)
Activities of daily living	Vineland-2, Vineland-3 (2006-present)	Data not yet presented (Vineland)	TBD (SAS-CGI-C)
EEG	Captured 2006-present	~ -2% in delta power at Day 128 ~ -10% in delta power at Day 254 No data shown beyond Day 254	~70% subjects showed reduced delta wave vs baseline after 4 months (FAST 2023). Early analyses suggest magnitude of delta reduction over 4mo exceeds level observed in NHS.
Quality of life	Captured 2017-present	---	---

Source: company reports, FAST 2023. Note: fields with data are highlighted in gray.

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Our focus for '24: EEG/Bayley, Ph3 reg path, Biogen opt-in

For upcoming IONS' Ph1/2 update of ION582 in AS, based on KOL feedback, an impact on both EEG and Bayley (or Vineland) can be viewed as encouraging. While Bayley is a validated assessment in AS, KOLs also see value in evaluating benefit with multi-domain measures such as CGI given limitations with Bayley (eg Bayley does not capture all relevant disease domains). IONS will topline results in a press release mid-year (expected to include efficacy assessment but level of details TBD) followed by detailed data presentation at a medical meeting in 2H. Another key update is IONS' alignment with the FDA on registrational endpoint, presumably sometime in 2H (our est). Lastly, Biogen has can opt-in within a predefined period of time after IONS' mid-year update (we assume decision sometime by 2H24E). Below, we frame additional considerations:

- **Improvements in EEG**: in lieu of a Ube3a protein measurement assay in CSF (proxy for brain) to gauge target engagement, we look to improvements in EEG as next best PD biomarker for target engagement. We acknowledge that clinical efficacy (not biomarker) is most important at getting a drug approved. However, in

early (Ph1/2) data, we believe there is value at (indirectly) confirming target engagement with an objective biomarker that has some predictive value in clinical outcome (ie Bayley cognitive), considering open-label nature of Ph1/2 studies may introduce bias at scoring benefits in clinical outcomes. Our KOL checks suggest that EEG can be a good and reliable biomarker if done consistently to minimize potential noise/cofounder. We are encouraged IONS has proactively established a longitudinal EEG model from NHS data (for comparison with ION582 data) and published its work in a peer-reviewed journal (Spencer et al).

- **Dose response relationship**: IONS' Ph1/2 is a dose escalation study, thus ideally we would want to see dose response from mid-year update to corroborate target engagement (i.e. drug dose) with clinical efficacy, which would further support any clinical efficacy observed is likely due to drug as opposed to open-label trial bias.

- **Improvements across multiple domains of Bayley-4**: we would want to see a treatment benefit in Bayley-4 given it is a direct measure by a trained investigator of patients' ability to perform tasks (thus considered more objective) and that it has relatively rich amount of NHS data available for comparison. Based on drug sponsors' commentary and feedback from our KOL checks, the FDA would likely want to include Bayley in at least part of the primary assessment for similar reasons, though we note FDA will very likely require a randomized controlled Ph3 program to support approval (as opposed to relying on NHS).

- **Drug impact outside of Bayley**: Bayley does not capture all of the relevant disease domains in AS. We are most focused on treatment benefit on speech, behavioral, seizure, and/or sleep. Further, the FDA has yet to define a registrational endpoint in AS, thus it is possible the FDA may want to incorporate additional efficacy measures beyond Bayley for approval consideration. Drug sponsors' and KOLs also see value in CGI or multi-domain responder index (MDRI) as efficacy measures, though whether and how either of these would be incorporated in Ph3 assessment (eg which disease domains will be captured in CGI or MDRI) remains TBD. Ovid conducted a Ph3 study (OV101; GABAA receptor) in AS using CGI as a primary endpoint, though the trial failed to meet the primary endpoint (2020). While there's limited to no historical data to compare CGI results to, Ionis noted 1-point improvement in CGI is generally considered meaningful based on the literature.

- **Treatment benefit by age subgroup**: preclinical data found disease reversals were most pronounced when treatment was administered to infant mice and magnitude of treatment benefit declined the later the treatment intervention occurred. Similarly, KOLs we spoke with think early intervention is theoretically best for any neurodevelopmental disease in general. Ionis' Ph1/2 trial has three cohorts by age group: 27% patients in age 2-5, 55% in age 4-17, and 18% in age 18-50.

- **Kinetics of disease improvement; implementation of structured intervention**: KOLs we spoke with want to better understand duration of assessment needed to detect a treatment effect in a clinical trial, as they noted time to initial observation of treatment benefit appears relatively slow/gradual based on current Ph1/2 clinical datasets. Ionis noted the company has observed positive impact on EEG and clinical outcome measures by 4 months of treatment (FAST 2023). Beyond time to response, KOLs also want to see structured intervention to be standardized in trials. Once Ube3a protein level is restored, KOLs would not expect the kids to magically learn how to speak or perform tasks without being taught. On the flip side, parents/caregivers enrolled in a clinical trial may be more motivated or have the (financial) means to push the kids with more interventions (eg teaching, training, therapist sessions) which may skew treatment benefit higher than real world scenario regardless of treatment benefit (or not) with

an ASO. Ionis does not have specific structured interventions incorporated in the HALOS study.

- **Clinical meaningfulness**: we have heard drug sponsors framed their datasets as "meaningful" in some way and form. For instance, GTX-102 led to increases in GSV in the ~mid-single digit to mid-teens range in 3 Bayley domains (cognitive, receptive communication, and gross motor) after patients had been treated for 1-1.5 years. These increases compare favorably to low-single digit increases observed from RARE-curated NHS data (age-match + deletion subtype) from LADDER database over similar period of time and exceed a threshold of significance defined by the Bayley manual. Nonetheless, our KOL checks indicate a consensus view on clinical meaningfulness in AS has yet been established, though work is ongoing (near completion) to establish threshold of clinical meaningfulness in Bayley (with community, parents, and caregivers) which may help inform regulatory interactions.

- **Registrational endpoint**: we look to two updates that will inform the registrational endpoint(s) for AS, notably RARE's end-of-Ph2-meeting with the FDA in mid-2024, followed by IONS' own meeting with the Agency presumably in 2H24E.

Sales forecast: est. $2bn+ for ION582

We forecast ION582 will reach global net (nominal) product sales of $2-2.2bn at peak level by 2034E, which assumes ~65k global patients, 12% penetration rate for ION582, and $200-300k net cost per patient per year. We assume IONS will receive up to 15% royalty on net sales reported by Biogen (assuming opt-in), similar to partnership terms for Spinraza (SMA), or $300m+ royalty revenue to IONS at peak level by 2034E. Our est. of ~65k patients would imply 2-3x larger market vs SMA (est. 20-45k patients), thus we believe our forecast of '582 (~$2bn nominal peak) conservatively factors in competitive risks and variability in epidemiology and demographics data vs SMA drugs annualizing at >$3.5bn in global net sales. Below, we frame key market model assumptions:

- **65k global patient population**: there is a wide range of prevalence estimate in the literature ranging from roughly 1:50k to 1:10k. Within that range, we model a prevalence of 1:15k (as opposed to midpoint), given majority of publications cites a higher range estimate (1:20k to 1:10k) and a pilot newborn screening study of 16k+ newborns (Australia/EU/US; published on JAMA journal 2022) points a prevalence of ~1:8k. Our estimate factors in mostly Western countries population given diagnosed patients skew Caucasians in publications and compares to Ultragenyx's estimate of ~60k patients. We model ~22k patients in the US and ~43k patients ex-US.

- **20k addressable population**: we model market penetration mainly in patients from 2 years old to young adulthood who have a chromosome 15 deletion, collective of which represents ~30% of the 65k total patient number (or 20k patients). Our assumptions are guided by preclinical data, which suggest therapeutic potential in AS is likely best with early intervention, as well as current body of clinical data which is skewed to younger demographics. We note IONS' Ph1/2 has broader enrollment criteria than our assumptions, such as inclusion of mutation subtype and age group up to 50 years old, which represents potential upside in TAM if clinical efficacy of ION582 can be validated in those patient subgroups. Including mutation subtype and age groups through 50 years-old would increase TAM from 20k to 36k.

- **40% market share**: we model equal market share split between ION582 and GTX-102, pending further clarity on clinical profile differences between the two molecules, and remainder 20% of TAM receive no/other treatment (eg additional pipeline competition). Overall, we model ~12% penetration rate for ION582 vs our estimate of ~65k global patient population.

- **Net price**: we model $300k / $200k net cost per patient per year in the US / ex-US markets based on rare orphan analogs (eg Spinraza).
- **Likelihood of success (POS)**: 30% for ION582, with room for upside pending further clinical validation in 2024E+ updates.

Price objective basis & risk

Ionis (IONS)
Our $62 price objective (PO) is based on a risk-adjusted DCF analysis, in which we assume: (1) risk-adjustment to pipeline programs based on abundance and strength of supportive clinical data, with <30% POS generally assigned to early-stage programs vs. >50% POS for mid-to-late stage assets, (2) the biggest value drivers in our DCF valuation are Wainua, Olezarsen, and Spinraza, (3) we assign marginal value to more speculative, early-stage program, (4) we assume 9.5% discount rate and 0% terminal growth rate.

Downside risks to our PO: 1) key product sales underperform relative to our forecast, 2) failure of key clinical trials, 3) competitor clinical data outperform vs. our expectation.

Upside risks to our PO: 1) delay to regulatory approval of competitors' drug products, 2) failure of competitors' clinical trials, 3) better than expected clinical data readouts

Analyst Certification

I, Jason M. Gerberry, hereby certify that the views expressed in this research report accurately reflect my personal views about the subject securities and issuers. I also certify that no part of my compensation was, is, or will be, directly or indirectly, related to the specific recommendations or view expressed in this research report.

US - Specialty Pharma & Biotechnology Coverage Cluster

Investment rating	Company	BofA Ticker	Bloomberg symbol	Analyst
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	Arrowhead Pharmaceuticals	ARWR	ARWR US	Jason M. Gerberry
	bluebird bio	BLUE	BLUE US	Jason M. Gerberry
	Exelixis	EXEL	EXEL US	Jason M. Gerberry
	Immunovant, Inc.	IMVT	IMVT US	Jason M. Gerberry
	Intra-Cellular Therapies	ITCI	ITCI US	Jason M. Gerberry
	Ionis	IONS	IONS US	Jason M. Gerberry
	Jazz Pharmaceuticals	JAZZ	JAZZ US	Jason M. Gerberry
	Lyra Therapeutics	LYRA	LYRA US	Jason M. Gerberry
	Oculis Holding AG	OCS	OCS US	Jason M. Gerberry
	Relay Therapeutics	RLAY	RLAY US	Jason M. Gerberry
	Tarsus Pharmaceuticals	TARS	TARS US	Jason M. Gerberry
	Teva Pharmaceuticals	TEVA	TEVA US	Jason M. Gerberry
	Vaxcyte Inc	PCVX	PCVX US	Jason M. Gerberry
	Xenon Pharmaceuticals	XENE	XENE US	Jason M. Gerberry
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	Axsome Therapeutics	AXSM	AXSM US	Jason M. Gerberry
	Galapagos	GLPG	GLPG US	Jason M. Gerberry
	ProKidney Corp	PROK	PROK US	Jason M. Gerberry
	Roivant	ROIV	ROIV US	Chi M. Fong
UNDERPERFORM				
	Bausch Health Cos Inc	BHC	BHC US	Jason M. Gerberry
	FibroGen Inc.	FGEN	FGEN US	Jason M. Gerberry
	Harmony Biosciences	HRMY	HRMY US	Jason M. Gerberry
	Organon	OGN	OGN US	Jason M. Gerberry
	Viatris Inc.	VTRS	VTRS US	Jason M. Gerberry

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Business Performance	Numerator	Denominator
Return On Capital Employed	NOPAT = (EBIT + Interest Income) × (1 − Tax Rate) + Goodwill Amortization	Total Assets − Current Liabilities + ST Debt + Accumulated Goodwill Amortization
Return On Equity	Net Income	Shareholders' Equity
Operating Margin	Operating Profit	Sales
Earnings Growth	Expected 5 Year CAGR From Latest Actual	N/A
Free Cash Flow	Cash Flow From Operations − Total Capex	N/A

Quality of Earnings	Numerator	Denominator
Cash Realization Ratio	Cash Flow From Operations	Net Income
Asset Replacement Ratio	Capex	Depreciation
Tax Rate	Tax Charge	Pre-Tax Income
Net Debt-To-Equity Ratio	Net Debt = Total Debt − Cash & Equivalents	Total Equity
Interest Cover	EBIT	Interest Expense

Valuation Toolkit	Numerator	Denominator
Price / Earnings Ratio	Current Share Price	Diluted Earnings Per Share (Basis As Specified)
Price / Book Value	Current Share Price	Shareholders' Equity / Current Basic Shares
Dividend Yield	Annualised Declared Cash Dividend	Current Share Price
Free Cash Flow Yield	Cash Flow From Operations − Total Capex	Market Cap = Current Share Price × Current Basic Shares
Enterprise Value / Sales	EV = Current Share Price × Current Shares + Minority Equity + Net Debt + Other LT Liabilities	Sales
EV / EBITDA	Enterprise Value	Basic EBIT + Depreciation + Amortization

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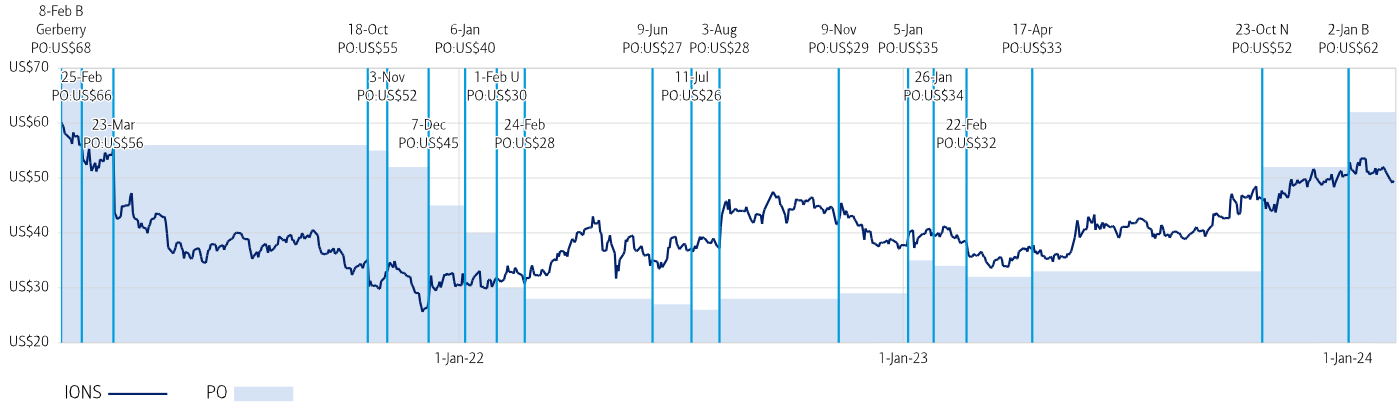
Ionis (IONS) Price Chart



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The Investment Opinion System is contained at the end of the report under the heading "Fundamental Equity Opinion Key". Dark grey shading indicates the security is restricted with the opinion suspended. Medium grey shading indicates the security is under review with the opinion withdrawn. Light grey shading indicates the security is not covered. Chart is current as of a date no more than one trading day prior to the date of the report.

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Coverage Universe	Count	Percent	Inv. Banking Relationships [R1]	Count	Percent
Buy	234	60.94%	Buy	115	49.15%
Hold	80	20.83%	Hold	36	45.00%
Sell	70	18.23%	Sell	29	41.43%

Equity Investment Rating Distribution: Global Group (as of 31 Dec 2023)

Coverage Universe	Count	Percent	Inv. Banking Relationships [R1]	Count	Percent
Buy	1895	53.62%	Buy	1083	57.15%
Hold	832	23.54%	Hold	454	54.57%
Sell	807	22.84%	Sell	383	47.46%

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Investment rating	Total return expectation (within 12-month period of date of initial rating)	Ratings dispersion guidelines for coverage cluster[R2]
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