ROTH Capital Partners

Jotin Marango, M.D., Ph.D., (646) 616-2780
jmarango@roth.com
Sales (800) 933-6830, **Trading** (800) 933-6820

Healthcare

Beyond the Rise and Fall of Amyloid

This past week, a few days before the aducanumab news, we hosted a timely panel discussion on Alzheimer's disease at our 31st Annual Roth Conference titled "Beyond the rise and fall of amyloid". Below, we distill our thoughts around Alzheimer's from the last week, as we all head towards a likely refocusing of investor attention and pharma BD priorities on the new wave of non-amyloid programs in development.

The definition of insanity is doing the same thing over and over and expecting different results. Without much time to heal since the failure of Roche/AC Immune's crenezumab Phase 3 study in January, this past week brought a sudden farewell to Biogen's anti-amyloid antibody aducanumab. The interim analysis of aducanumab's Phase 3 studies (ENGAGE and EMERGE) suggested that the primary endpoint, Clinical Dementia Rating-Sum of Boxes (CDR-SB) score, would likely not be met. As we zoom out from the last few months, and focus on the MoA of all failed anti-amyloid antibodies in late-stage trials, we note that the lack of efficacy in primary endpoint measures (ADAS-Cog, ADCS-ADL, and/or CDR-SB) appears irrespective of: (i) antibody backbone (IgG1, IgG2, IgG4); (ii) antibody recognition epitope (amino acids 1-5, 16-26, or 30-40, etc.); (iii) target amyloid conformations (monomers, oligomers, fibrils); (iv) validated reduction in CSF amyloid and brain PET amyloid plaques; (v) disease stage of intervention (mild-moderate or prodromal Alzheimer's). The data is the data, therefore we must ascribe clinical failure to the common thread among these trials--the target itself (amyloid)--rather than individual agents.

Tidbits from our panel discussion on non-amyloid approaches to Alzheimer's. We returned from our Roth conference with a bullish view on: (i) the multiplication of non-amyloid therapeutic avenues (inflammation, epigenetics, cellular homeostasis, synaptic resilience); and (ii) the evolution of the FDA's thinking around Alzheimer's trial design (new draft guidance from February 2018). Our panelists were supportive of non-amyloid approaches, and expressed optimism around the 2018 NIH Biomarker Initiative in Neuroscience using disease biomarkers to facilitate drug development and to identify biomarker-positive patients most likely to derive the greatest clinical benefit. Moreover, they unanimously acknowledged the historical haphazardness of Alzheimer's trials pointing to an urgent need to improve trial design (disease stage, patient population, clinically meaningful endpoints). Lastly, a common message in our panel was the essential obligation to find correlation between clinical benefit (e.g. cognition, slowing disease progression), target engagement, and modulation of specific biomarkers or molecular pathways being interrogated. In our view, the latter is fundamental to the rise of a new non-amyloid biomarker-centric path to approval, and will serve as a fundamental step in de-risking current programs and re-energizing investors' interest.

What is on our watch list? As we continue to monitor Alzheimer's drug development, we highlight an array of program on our watch list (see Table 1 below). We are certainly aware that investors remain wary of Alzheimer's studies, especially as clinical programs transition from Phase 2 into Phase 3, which has been historically associated with an abrupt disappearance of clinical benefit. Alzheimer's is highly complex and heterogeneous, thus scaling up a study and recruiting all idiopathic Alzheimer's patients likely contributes to significant variability and indirectly to trial failure. Therefore, we are paying special attention to trials with genetically pre-defined or biomarker-selected patients as a way to de-risk late-stage trials and also facilitate a more flexible regulatory path to review and approval. As examples, we highlight clinical programs from Denali Therapeutics (DNLI-NC) and Anavex Life Sciences (AVXL-Buy). Meanwhile, among novel mechanistic avenues we remain intrigued by epigenetics, and guide investors to keep an eye on the rapidly evolving clinical programs at Rodin Therapeutics (private) and Oryzon Genomics (ORY.SM-Buy). Overall, we expect multiple clinical updates from an array of non-amyloid companies towards YE19 and into 2020, which in our view will cumulatively redefine molecular targets and clinical protocols in Alzheimer's therapeutics.

Reason for Report:
Industry Update

Roth Covered Companies Mentioned in this Report:

AVXL	$3.08	Buy
ORY.SM	$3.52	Buy

Stock prices are as of previous day's close, if not otherwise specified

SUMMARY

Table 1. Non-amyloid Alzheimer's programs on our radar.

Candidate	Sponsor	Target	Stage	Estimated Readout
AGB101	AgeneBio	SV2A	Phase 3	2H22
Elenbecestat	Eisai, Biogen	BACE	Phase 3	mid-2021
LMTX	TauRx Therapeutics	tau	Phase 3	mid-2020
Masitinib	AB Scinece	TKI	Phase 3	**mid-YE19**
ALZT-OP1	AZTherapies	Inflammation	Phase 3	**YE19/1H2020**
CNP520	Novarti AG	BACE	Phase 2/3	mid-2024
Trigriluzole	Biohaven Pharmaceuticals	Glutamate	Phase 2/3	**interim futility analysis 4Q19**
Anavex 2-73	Anavex	Sigma-1 receptor	Phase 2b/3	YE20/early 2021
PXT864	Pharnext	NMDA. GABA	Phase 2b	initiate in FY19
T3D959	T3D Therapeutics	PPARg/d	Phase 2b	planned
ORY-2001	Oryzon Genomics	LSD1-MAO B	Phase 2a	**2H19**
Bryostatin	Neurotrope	PKC	Phase 2	**2H19**
CT1812	Cognition Therapeutics	Sigma-2	Phase 2	**YE19/1H20**
Neflamapimod	EIP Pharma	p38 MARK	Phase 2	**mid-2019**
AADVAC1	Axon Neuroscience	tau	Phase 2	**mid-2019**
GRF6019	Alkahest, Grifols	Blood plasma	Phase 2	2H20
AMX0035	Amylyx Pharmaceuticals	mitochondria	Phase 2	2H20
AR1001	AriBio	PDE5	Phase 2	2H20
ACI-35	AC Immune, Janssen	tau	Phase 2	initiate in 1H19
RG6100	AC Immune, Roche	tau	Phase 2	2H20
ABBV-8E12	AbbVie	tau	Phase 2	2H20
BIIB092	Biogen	tau	Phase 2	2H21
PTI-125	Pain Therapeutics	Flamin A	Phase 2	mid-2019
SUVN-502	Suven Life Sciences	Serentonin 5-HT6	Phase 2	mid-2019
Xanamem	Actinogen Medical	11b-HSD1	Phase 2	2Q19
DNL747	Denali Therapeutics	RIPK1	Phase 1b	**4Q19**
RDN-929	Rodin Therapeutics	HDAC-CoREST	Phase 1	**YE19/1H20**
SDI-118	Syndesi Therapeutics	SV2A	Phase 1	initiate near-term
AL002	Alector, Abbvie	TREM2	Phase 1	**YE19/1H20**
AL003	Alector, Abbvie	SIGLEC-3	Phase 1	mid-2020

Source: Roth Capital Partners research.

Anavex Life Sciences Corp. (AVXL - Buy - $10PT)

Valuation. Our 12-month price target of $10/share ($4/share for Anavex 2-73 in Rett syndrome + $6/share for Anavex 2-73 in Alzheimer's disease) is based on a DCF-NPV analysis covering 2019-2032 using a 12% discount rate. Factors which could impede the achievement of our target price include, but are not limited to: (1) failure and/ or setbacks of the drug in clinical studies; (2) failure of the drug to gain regulatory approval; and (3) smaller than projected commercial opportunity due to changes in market size, competitive landscape, and drug pricing and reimbursement.

Experimental therapeutic product risk. The company's risk profile is based primarily, in our belief, on the company's thesis being based on the clinical and commercial prospects of pipeline candidates. Current funding at the company is being directed toward these programs and should there be any missteps, negative trial data or delays, this could impact the stock negatively. Adding additional risk to both programs is their early stage nature. Drug development is fraught with failures and this risk is increased significantly during the earlier stages of development.

Development timeline risk. The company's shares could be subject to increased volatility, in our belief, based on the time frame required to get meaningful proof of concept data from the planned clinical program. Positive clinical data could yield a potential accelerated path toward approval, however we currently project that our modeled drug candidate Anavex 2-73 may only reach the market around 2021 in Rett and 2023 in Alzheimer's. Investors may choose to delay investment in the company, despite potential excitement, until meaningful clinical data is generated.

Financing risk. As with a majority of development-stage biotechnology companies, the ability to maintain sufficient funding is critical to the progress of pipeline candidates. Should the company experience problems raising sufficient capital, its development programs' progress could be significantly impeded, leading to both delays in development timelines as well as potential negative effects on investor confidence. Each of these could have a negative impact on share price.

Oryzon Genomics SA (ORY.SM - Buy - €15PT)

Valuation. Our 12-month price target of €15/share (rounded: €4/share for ORY-1001 in AML + €10/share for ORY-2001 in AD + €1/share in cash) is based on a DCF-SoP analysis using a 12% discount rate and 1% growth rate. Factors which could impede the achievement of our target price include, but are not limited to: (1) failure and/ or setbacks of the drugs in clinical studies; (2) failure of the drugs to gain regulatory approval; and (3) smaller than projected commercial opportunity due to changes in market size, competitive landscape, and drug pricing and reimbursement.

Experimental therapeutic product risk. The company's risk profile is based primarily, in our belief, on the company's thesis being based on the clinical and commercial prospects of pipeline candidates. Current funding at the company is being directed toward these programs and should there be any missteps, negative trial data or delays, this could impact the stock negatively. Adding additional risk to both programs is their early stage nature. Drug development is fraught with failures and this risk is increased significantly during the earlier stages of development.

Development timeline risk. The company's shares could be subject to increased volatility, in our belief, based on the time frame required to get meaningful proof of concept data from the planned clinical program. Positive clinical data could yield a potential accelerated path toward approval, however we currently project that our modeled drug candidates ORY-1001 and ORY-2001 may only reach the market in 2023 and 2024, respectively. Investors may choose to delay investment in the company, despite potential excitement, until meaningful clinical data is generated.

Financing risk. As with a majority of development-stage biotechnology companies, the ability to maintain sufficient funding is critical to the progress of pipeline candidates. Should the company experience problems raising sufficient capital, its development programs' progress could be significantly impeded, leading to both delays in development timelines as well as potential negative effects on investor confidence. Each of these could have a negative impact on share price.

Regulation Analyst Certification ("Reg AC"): The research analyst primarily responsible for the content of this report certifies the following under Reg AC: I hereby certify that all views expressed in this report accurately reflect my personal views about the subject company or companies and its or their securities. I also certify that no part of my compensation was, is or will be, directly or indirectly, related to the specific recommendations or views expressed in this report.

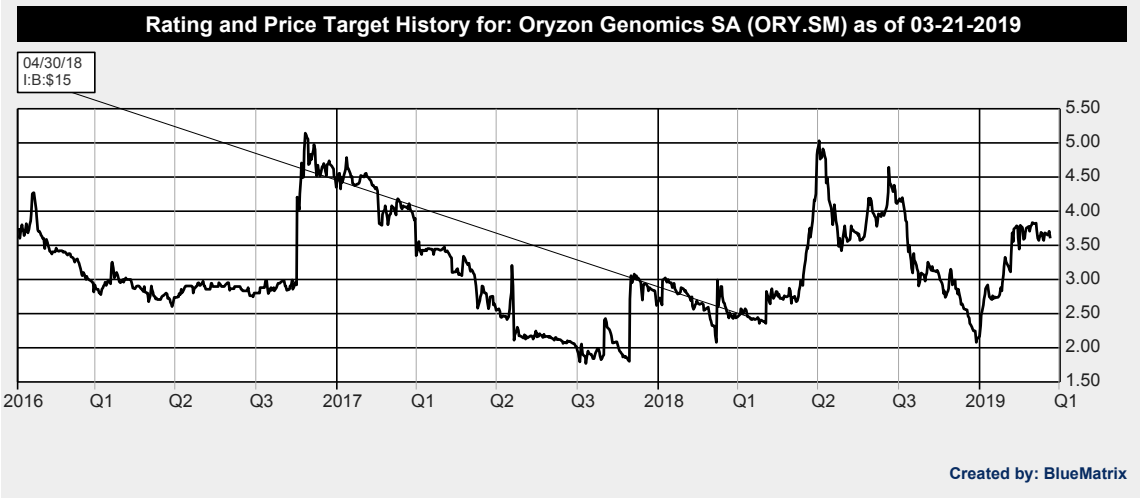
For important disclosure information regarding the companies in this summary report, please contact: The Director of Research at (800) 678-9147 or write to: ROTH Capital Partners, LLC, Attention: Director of Research, 888 San Clemente Drive, Newport Beach, CA 92660

Disclosures:

ROTH makes a market in shares of Anavex Life Sciences Corp and as such, buys and sells from customers on a principal basis.

Shares of Anavex Life Sciences Corp and Oryzon Genomics SA may be subject to the Securities and Exchange Commission's Penny Stock Rules, which may set forth sales practice requirements for certain low-priced securities.

Within the last twelve months, ROTH has received compensation for investment banking services from Oryzon Genomics SA.



Each box on the Rating and Price Target History chart above represents a date on which an analyst made a change to a rating or price target, except for the first box, which may only represent the first note written during the past three years. **Distribution Ratings/IB Services** shows the number of companies in each rating category from which Roth or an affiliate received compensation for investment banking services in the past 12 month.

Distribution of IB Services Firmwide

Rating	Count	Percent	IB Serv./Past 12 Mos. as of 03/24/19 Count	Percent
Buy [B]	266	76.44	143	53.76
Neutral [N]	52	14.94	30	57.69
Sell [S]	3	0.86	1	33.33
Under Review [UR]	26	7.47	12	46.15

Our rating system attempts to incorporate industry, company and/or overall market risk and volatility. Consequently, at any given point in time, our investment rating on a stock and its implied price movement may not correspond to the stated 12-month price target.

Ratings System Definitions - ROTH employs a rating system based on the following:

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Neutral: A rating, which at the time it is instituted and or reiterated, that indicates an expectation of a total return between negative 10% and 10% over the next 12 months.

Sell: A rating, which at the time it is instituted and or reiterated, that indicates an expectation that the price will depreciate by more than 10% over the next 12 months.

Under Review [UR]: A rating, which at the time it is instituted and or reiterated, indicates the temporary removal of the prior rating, price target and estimates for the security. Prior rating, price target and estimates should no longer be relied upon for UR-rated securities.

Not Covered [NC]: ROTH does not publish research or have an opinion about this security.

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