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PMN-NASDAQ

Rating:	Speculative Buy
Target:	US$9.50
Price:	US$1.18
Return:	705%
Valuation:	NPV (30% rate), 20x EPS, 15x EV/EBITDA (F2029 ests)

Market Data

Basic S/O (M)	32.7
FD S/O (M)	79.0
Market cap (US$M, basic S/O)	38.6
Ent Val (US$M, basic S/O)	30.2
Pro forma cash (rec Q, US$M)	8.4
LT debt (rec. Q, US$M)	0.0
52 Week Range	$0.38-$2.20
Avg. Daily Volume (M)	8.4709
Fiscal Year End	Dec-31

Financial Metrics

In C$M	2027E	2028E	2029E
PMN310/Alz dis (AD)	0.0	33.4	129.1
Alpha-synuc mAb (PD)	0.0	0.0	9.5
SOD1/TDP43 mAb (ALS)	0.0	2.6	8.4
Royalty revenue, mAbs	0.0	36.0	147.0
EBITDA ($C)	(11.1)	26.6	136.8
Net Inc ($C)	(11.8)	18.0	95.1
EPS (basic)	($0.36)	$0.55	$2.91
EPS (FD)	($0.15)	$0.23	$1.20

Milestones

Lecanumab, Ph III Clarity AD data (Sept/22)	FQ322
Donanemab, Ph III Trailblazer-ALZ2 data (May/23)	FQ223
PMN-310, commence Phase I SAD trial	FQ423
PMN-310, complete Phase I SAD trial	FQ324
PMN-310, Fast Track Designation granted	FQ325
PMN-310, commence Phase I MAD Alz dis trial	FQ425

Company Description

ProMIS is a MA-based mAb developer, with core mAb expertise in targeting con-formational peptide epitopes. Preclinical-stage PMN310 selectively targets amyloid oligo-mers; other mAbs target alpha-synuclein in Parkinson's disease (PMN442) and TBP-43 in ALS (PMN267)

Source: Consensus data- Refinitiv, Forecasts/Estimates - Leede Financial

PMN310 Receives Fast Track Status, A Positive Signal That The US FDA Sees Value In Next-Generation Alzheimer's Disease Therapies Despite Recent Approvals– Speculative Buy

MA-based CNS-targeted biologics developer ProMIS Neurosciences received Fast Track Status from the US FDA for its beta-amyloid oligomer-targeted Alzheimer's disease mAb PMN310. This favorable status was granted even though three other non-oligomer-selective mAbs in Biogen's (BIIB-Q, NR) aducanumab, Eisai's (4523-JP, NR) lecanemab & Eli Lilly's (LLY-NY, NR) donanemab were previously approved by the agency, thus showing us that the FDA sees limitations in the existing Alzheimer's disease therapy hierarchy even after aducanumab/lecanemab/donanemab were made available through recent approvals. One of these mAbs – Biogen's aducanumab – has in fact been withdrawn from the market (announced in Jan/24, marketing formally discontinued in Nov/24).

Fast Track Status does not guarantee that PMN310 will perform well in future Phase II/III Alzheimer's disease studies, but it should facilitate expedited review if/when positive data are generated & filed. If you have read this far, you are probably already aware of just what Fast Track Status actually is, but in brief, it is essentially what is implied by its name, a mechanism by which the US FDA recognizes that approved therapies for treating a disease (in this case, Alzheimer's disease) are limiting in some way, either because existing drugs only work in a defined subpopulation of diseased patients, or because even if existing drugs work acutely, they do not confer chronic benefit even with chronic use, or because existing drugs are just not that effective in comparison to their price or to expectations.

To be candid, we do not conventionally comment on special FDA recognition like this, either Fast Track Status or Orphan Drug Status or Breakthrough Therapy Designation or Accelerated Approval, to name four, just because FDA regard is more or a reflection on medical need than on the ability of the relevant therapy to perform to approvable standard in future Phase II/III studies. But there are a few reasons why we believe Fast Track Status is long overdue recognition of PMN310's medical prospects, even if development of the oligomer-targeted mAb is still in early Phase I testing.

Today's share price ascent, while positive, essentially returns PMN share value to a baseline level at which we believe PMN310's clinical value is still steeply discounted. First of all, until today, PMN was trading at an enterprise value of essentially nil & by any standard that we have used (or observed being used by others) to establish value of clinical-stage assets, PMN's pipeline of conformational epitope-targeted mAbs that includes but is not limited to PMN310 is worth more than that, so says us. The mechanistic rationale for selectively targeting & eliminating beta amyloid oligomers from systemic circulation & cerebrospinal fluid is well-supported in the medical literature in our view (though we would not deny that data from large Phase II/III Alzheimer's disease studies are certainly necessary to confirm this hypothesis), as is PMN310's ability to exhibit superior oligomer-binding selectivity/specificity in comparison to the aforementioned mAbs as well as others that historically advanced to Phase III testing but were never approved.

In fact, the most positive element of PMN310's Fast Track Status in our view is that it signals FDA disappointment in legacy Phase III performance of already-approved anti-amyloid mAbs against which PMN310 is clearly differentiated. By definition, Fast Track Status implies that the US FDA will work more collaboratively with innovators developing therapies to which the new status applies. The relevant condition must be 'serious', a bit of an ambiguous term but one that the agency specifically believes & explicitly states is relevant to Alzheimer's disease, and the status-receiving therapy must fill an unmet medical need. As of this writing, there are actually no shortage of FDA-approved Alzheimer's disease therapies, including but not limited to the three mAbs mentioned above, and so we infer that the existing Alzheimer's disease pharmacopeia is deemed insufficient by the FDA itself to consider the condition to be well-managed. Clearly, the FDA does not assume that lecanemab/donanemab were able to exceed an efficacy threshold in pivotal Phase III testing to therefore assume that they should be ubiquitiously prescribed for treating early-stage Alzheimer's disease. We agree.

Exhibit 1. Financial Forecast Summary For ProMIS Neurosciences

Year-end December 31 (C$M, except per share data)	2023A	2024A	2025E	2026E	2027E	2028E	2029E	2030E	2031E	2032E	2033E
Royalty revenue, by mAb & indication											
PMN310/Alzheimer's disease (AD)	$0.0	$0.0	$0.0	$0.0	$0.0	$33.4	$129.1	$232.6	$319.1	$367.5	$419.2
Parkinson's disease (PD)	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$9.5	$32.3	$56.9	$83.5	$112.2
Amyotrophic lateral sclerosis (ALS)	$0.0	$0.0	$0.0	$0.0	$0.0	$2.6	$8.4	$14.5	$20.9	$27.8	$35.1
Royalty revenue, mAbs	**$0.0**	**$0.0**	**$0.0**	**$0.0**	**$0.0**	**$36.0**	**$147.0**	**$279.4**	**$397.0**	**$478.8**	**$566.4**
Revenue growth (%)	*NA*	*NA*	*NA*	*NA*	*NA*	*NA*	*309%*	*90%*	*42%*	*21%*	*18%*
Cash operating expenses	$14.0	$16.0	$32.4	$33.0	$21.1	$19.4	$20.1	$21.0	$22.0	$23.0	$24.1
Non-cash operating expenses	$0.3	$0.8	$0.7	$0.7	$0.7	$0.7	$0.7	$0.7	$0.7	$0.7	$0.7
Milestone & other revenue	$0.0	$0.0	($10.0)	($10.0)	($10.0)	($10.0)	($10.0)	($10.0)	($10.0)	($10.0)	($10.0)
Operating income	**($14.3)**	**($16.8)**	**($23.1)**	**($23.7)**	**($11.8)**	**$25.9**	**$136.2**	**$267.7**	**$384.4**	**$465.1**	**$551.6**
EBITDA	**($14.0)**	**($16.0)**	**($22.4)**	**($23.0)**	**($11.1)**	**$26.6**	**$136.8**	**$268.4**	**$385.1**	**$465.8**	**$552.3**
EBITDA growth (%)	*NA*	*NA*	*NA*	*NA*	*NA*	*NA*	*414.0%*	*96.1%*	*43.5%*	*21.0%*	*18.6%*
EBITDA margin (%)	*NA*	*NA*	*NA*	*NA*	*NA*	*74.0%*	*93.1%*	*96.1%*	*97.0%*	*97.3%*	*97.5%*
Other non-operating expenses (Interest, income tax, deriv value)	($0.7)	($19.0)	$0.7	$0.7	$0.7	$0.7	$19.7	$81.2	$116.3	$140.5	$166.4
Net income	($13.2)	$2.8	($23.9)	($24.5)	($12.6)	$25.1	$116.3	$186.3	$268.0	$324.6	$385.1
Adjusted net inc, fully-taxed	($14.1)	($16.9)	($23.1)	($23.7)	($11.8)	$18.0	$95.1	$187.2	$268.9	$325.4	$385.9
EPS (fully-taxed, basic)	**($0.75)**	**($0.52)**	**($0.71)**	**($0.72)**	**($0.36)**	**$0.55**	**$2.91**	**$5.73**	**$8.23**	**$9.95**	**$11.81**
EPS (fully-taxed, fd)	**($0.42)**	**($0.21)**	**($0.29)**	**($0.30)**	**($0.15)**	**$0.23**	**$1.20**	**$2.37**	**$3.41**	**$4.12**	**$4.89**
S/O (basic, M)	*18.9*	*32.7*	*32.7*	*32.7*	*32.7*	*32.7*	*32.7*	*32.7*	*32.7*	*32.7*	*32.7*
S/O (fully-diluted, M)	*33.8*	*79.0*	*79.0*	*79.0*	*79.0*	*79.0*	*79.0*	*79.0*	*79.0*	*79.0*	*79.0*
P/E (fd)	*NA*	*NA*	*NA*	*NA*	*NA*	*1.9x*	*0.4x*	*0.2x*	*0.1x*	*0.1x*	*0.1x*
EV/EBITDA (fd)	*NA*	*NA*	*NA*	*NA*	*NA*	*1.0x*	*0.2x*	*0.1x*	*0.1x*	*0.1x*	*0.0x*

Source: Forecasts/Estimates – Leede Financial Inc.

But tangibly, Fast Track Status confers clear advantages as compared to other non-status-bearing therapies, including more frequent engagement with the FDA, eligibility for priority review (assuming ProMIS generates positive Phase III data from future PMN310 pivotal studies, the resulting BLA could be reviewed in six months and not twelve months [or longer]), and the potential for undertaking rolling submissions of modules in the BLA that can thus expedite timelines to BLA submission. In theory, Fast Track Status implies that ProMIS could be eligible to submit its BLA for PMN310 based on surrogate endpoint data and not cognition data but we believe that ship sailed with aducanumab/lecanemab & our model assumes that ProMIS will need to document clear reversal of cognitive impairment in a pivotal (and probably 1,500-to-2,000-patient trial, as conducted by Eli Lilly for donanemab & by Eisai for lecanemeb) mild-to-moderate Alzheimer's disease trial. While we stand by our diligence justifying our view that beta-amyloid oligomers are uniquely neurotoxic in Alzheimer's disease patients based on biochemical & population genetics studies we described in our original report, we would not therefore assume that oligomer-mAb binding – and the elimination of oligomer neurotixicity in cerebrospinal fluid that such binding could facilitate - is sufficiently documented so as to eliminate the need for controlled Phase III cognition studies.

Exhibit 2. Valuation Summary for ProMIS Neurosciences

NPV, discount rate		20%	25%	30%	35%	40%	50%
Implied value per share		$23.96	$15.65	**$10.58**	$6.87	$4.55	$1.87
				Discounted share price mid-2026			
Price/earnings multiple, F2029	**P/E**	**20%**	**25%**	**30%**	**35%**	**40%**	**50%**
Implied share price[1]	10	$5.81	$4.93	$4.22	$3.63	$3.14	$2.38
	20	$11.62	$9.86	**$8.44**	$7.26	$6.28	$4.76
	30	$17.43	$14.79	$12.66	$10.89	$9.42	$7.14
EV/EBITDA multiple, F2029		**5x**	**10x**	**15x**	**20x**	**25x**	**30x**
Implied share price[1,2]		$3.07	$6.11	**$9.14**	$12.17	$15.21	$18.24
One-year PMN target price				$9.38			

[1] *Based on F2029 fd fully-taxed EPS forecast of $1.20; EBITDA of $136.8M; 30% discount rate*

[2] *EV incorporates FQ125 cash of US$8.4M, no LT debt, S/O (basic) of 32.7M, S/O (fd; assuming full exercise of pre-funded warrants over time) of 79.0M.*

Source: Leede Financial Inc.

Though we stand by our view that both aducanumab & lecanemab merited positive FDA regard at the time of their respective reviews in June/21 & July/23, respectively. Recall that both mAbs were conditionally approved under the FDA's accelerated approval pathway, whereby drugs can be approved based on surrogate endpoints (in this case, reduction in amyloid plaques deposited in the brain) and not primary endpoints (which for Alzheimer's disease would of course be medium-to-long-term reversal of cognitive impairment, the magnitude of which would of course be a judgement call based on comparison to alternative therapies, for which only acetylcholinesterase inhibitors or N-methyl-D-aspartate [NMDA]-receptor antagonists were transiently effective).

Exhibit 3. ProMIS' Pipeline of CNS Disease-Targeted Conformational Epitope-Binding mAbs, Led By Alzheimer's Disease-Focused Beta-Amyloid Oligomer-Binding PMN310

Asset	Target protein	Disease indication	Normal physiological role	Clinical Stage: Discovery / Preclinical / I / II / III	Timelines to next milestone
Lead antibodies in formal preclinical/IND-enabling testing					
PMN310	Epitope exposed in beta-amyloid oligomers	Alzheimer's disease	Synaptic plasticity, memory formation in hippocampus		Phase I completed, data in FH224 PRECISE-AD is active; data in FH226
PMN267	TDP-43 (Transactive response DNA-bind protein)	Amyotrophic lateral sclerosis (ALS)	Transcription factor (mRNA homeoasis/processing)		Complete IND-enabling studies, FH225 Commence Phase I ALS trial, FQ127
PMN442	Alpha-synuclein (pre-synaptic tetramer in the brain)	Parkinson's disease, multiple system atrophy	Controls neurotransmitter release, vesicle transport		Complete IND-enabling studies, FH225 Commence Phase I PD/MSA trial, FQ127
Misfolded protein antigens being targeted in discovery					
TBD	RACK1, SOD1	Amyotrophic lateral sclerosis (ALS)	Protein synthesis		Lead mAb generation by F2026
TBD	Tau	Alzheimer's disease Frontotemporal lobar degeneration (FTLD)	Microtubule stabilization neuron generation		Lead mAb generation by F2026
TBD	DISC1	Schizophrenia	Neuron generation mitochondrial transport		Lead mAb generation by F2026
TBD	Beta-amyloid vaccine	Alzheimer's disease prevention	Synaptic plasticity, memory formation in hippocampus		Lead mAb generation by F2026

Source: ProMIS Neurosciences, Leede Financial

And interestingly, Biogen withdrew aducanumab from the US market in Nov/24, citing prioritization of other pipeline Alzheimer's disease therapies and in effect, acknowledging that the mAb was not conferring magnitude of cognitive benefit (about 18%-to-40% cognitive benefit at eighteen-month follow-up, depending on the mode of cognitive assessment). Conversely, Eisai

continues to market lecanemab/Leqembi for which T12M sales to end-of-Mar/25 were US$171M. Eli Lilly's donanemab/Kisunla exhibited some distinct pharmacology to the other two mAbs mentioned above in that it conferred cognitive improvement of up to 35% in the 1,736-patient Phase III TRAILBLAZER-ALZ 2 trial, while conferring cognitive improvement to that degree with limited-duration & not chronic dosing (an average of 84% of brain-residing amyloid plaque was removed after a one-year dosing regimen of monthly infusions). FQ125 sales were US$21M.

Exhibit 4. Comparable Companies For ProMIS Neurosciences. Alzheimer's Disease Drug Developers

Company	Filing Curr	Sym	Shares Out (M)	Share price 21-Jul	Mkt cap ($M) (curr)	Mkt cap ($M) (C$)	Ent val ($M) (curr)	Ent val ($M) (C$)	Status of lead program
Comparable AD drug developer targeting beta-amyloid, tau, and other signalling pathways									
Acumen Pharmaceuticals Inc	USD	ABOS	60.6	$1.50	$90.9	$124.7	($28.8)	($39.5)	Lead mAb is ACU193 (sabirnetug), targeting amyloid oligomers. 62-patient Phase I AD trial (INTERCEPT-AD) reported 28-week safety-MR imaging-ECG-Columbia-Suicide Severity Rating Scale data at AAIC in July/23
AC Immune SA	USD	ACIU	100.4	$2.07	$207.8	$285.2	$26.1	$35.8	ACI-24, vaccine based on pyroglutamate-modified N-terminal beta amyloid fragment; positive interim Phase I safety/immunogenicity data in Jan/23 from 140-patient ABATE trial, final data in 2026
Alpha Cognition Inc	USD	ACOG	16.0	$9.99	$160.0	$160.0	$114.5	$114.5	Lead AD drug ALPHA-1062 is enteric-coated benzoyl ester prodrug of acetylcholinesterase inhibitor galantamine (Razadyne); FDA-approved in Jul/24 as Zunveyl; licensed in Jan/25 with China Medical System Holdings (867-HK), US$6M upfront, US$44M total deal value
Alzinova AB	SEK	ALZ	104.3	1.94 kr	202.4 kr	$28.7	199.6 kr	$28.3	ALZ-101, vaccine formulations specifically targeting beta amyloid oligomers and not monomer or fibril forms; ALZ-201, mAb selected against disulfide-bridged stabilized beta-amyloid oligomers; 33-pt Phase I AD trial ongoing, interim data in Q424
Anavex Life Sciences Corp	USD	AVXL	85.4	$10.98	$937.4	$1,286.2	$821.6	$1,127.3	ANAVEX2-73 (blarcamesine), 508-pt Phase III trial, 48-week ADAS-Cog data generated in Sept/23, reduced serum amyloid & reduced MR-confirmed brain atrophy; 96-week open-label extension ongoing
Annovis Bio Inc	USD	ANVS	19.5	$2.65	$51.6	$70.9	$29.4	$40.3	Buntanetap (Translational Inhibitor of Neurotoxic Aggregation Protein, TINAPs, potentiates binding of iron responsive elements to iron binding protein), improved axonal transport. Reduced levels of neurotoxic proteins (tau, amyloid precursors) in CSF in 14-pt Phase I trial
Athira Pharma Inc	USD	ATHA	39.0	$0.41	$15.9	$21.9	($20.7)	($28.5)	ATH-1017/fosgonimeton (HGF-MET neurotrophic system modulator); 300-pt Phase III AD trial (LIFT-AD) ongoing, Six-month ADAS-Cog/ADCS-CGIC data by end-of-2022
BioArctic AB	SEK	BIOA B	74.1	194.00 kr	14,380.9 kr	$2,036.3	13,495.2 kr	$1,910.9	Original developer of Eisai's Phase III-stage protofibril-targeted lecanemab (FDA approved, denied EU approval in Jul/24)
BioVie Inc	USD	BIVI	1.9	$9.00	$16.7	$22.9	($6.4)	($8.8)	Lead orally-active anti-inflammatory beta-androstenetriol drug NE3107 in 439-patient Phase III AD trial, 30-week CDR-SB data insufficiently powered (258 patients excluded due to protocol deviation)
Cassava Sciences Inc	USD	SAVA	48.3	$2.21	$106.8	$146.5	($10.6)	($14.5)	Lead AD drug simufilam/PTI-125 alters shape/function of altered filamin A in the brain. 52-week 750-patient Phase III RETHINK-ALZ trial & 78-week 1,000-patient Phase III REFOCUS-ALZ trial both ongoing. Slowed cognitive decline by 38% at six-month follow-up in 157-patient Phase II mild-to-moderate AD trial (July/23)
Cognition Therapeutics Inc	USD	CGTX	62.0	$0.65	$40.5	$55.6	$24.1	$33.1	Lead AD drug CT1812 (Elayta), binds to TMEM97 subunit of sigma-2 receptor, displaces amyloid oligomer binding to neurons. 540-patient Phase III AD trial is ongoing, data in 2027. Separate 130-patient Phase II Lewy Body Dementia trial ongoing, data in Q424
MorphoSys AG	EUR	MOR	37.7	€ 67.25	€ 2,532.8	$4,039.6	€ 2,294.1	$3,658.9	Gantenerumab developer, partnered with Roche. Underperformed in Phase III GRADUATE I/II AD trials
INmune Bio Inc	USD	INMB	26.6	$2.42	$64.3	$88.3	$45.0	$61.7	DN-TNF, selective protein-based inhibitor of soluble tumor necrosis factor (TNF), Xpro; preserves activity of membrane-bound TNF; inhibits neuroinflammation caused by glial cell activation. 201-pt Phase II AD trial started in Q122, 24-wk cognition data by H223.
Vaccinex Inc	USD	VCNX	2.7	$0.91	$2.4	$3.3	$3.0	$4.1	Anti-semaphorin 4D mAb pepinemab (VX15); enrolling 50-pt Phase I SIGNAL-AD trial, 40-wk brain metabolism/PET data by H224
Vivoryon Therapeutics NV	EUR	VVY	26.1	€ 1.44	€ 37.5	$59.9	€ 28.5	$45.4	Lead glutaminyl cyclase inhibitor drug varoglutamstat (PQ912), inhibits formation of pyroglutamyl beta-amyloid. Negative data from 414-pt Phase II AD trial (VIVIAD trial, discontinuing AD testing as of Mar/24
Average								**$464.6**	
ProMIS Neurosciences Inc	**USD**	**PMN**	**32.7**	**$1.18**	**$39**	**$39**	**$30**	**$30**	**mAb drug developer, targets disease-relevant conformational epitopes, including in Alzheimer's disease with Phase I-stage PMN310, also targeting ALS & Parkinson's disease.**

Source: Refinitiv

Seminal Phase Ib testing in PRECISE-AD trial is underway, from which our first insights into PMN310 clinical efficacy & impact on disease-associated biomarkers should be available next year. ProMIS has already completed Phase I PMN310 in its single-ascending-dose & multiple-ascending dose studies, nicely showing Phase I study and we are thus some time away from completing pivotal Phase III Alzheimer's disease trials to which accelerated review could apply. But the firm is advancing well in its Phase Ib PRECISE-AD trial that will be testing efficacy in Alzheimer's disease patients in the 128-patient trial, enrolling its first patient in Feb/25 & completing enrollment in the first patient cohort by mid-FQ225. The firm predicted that interim six-month data should be available by H126 (which we assume means by June/26) and that final one-year data should be available by end-of-F2026. We would not expect meaningful impact on cognitive impairment with six-month PMN310 dosing but trends on biomarker reduction & on plaque deposition in the brain should be apparent by that time point.

The trial is testing three distinct PMN310 IV dosage strengths ranging from 350-mg-to-1,400-mg as a single one-hour infusion & one-year data on safety/tolerability & biomarker analysis (specifically the phosphorylated tau protein p-tau217 & changes in amyloid deposition in the brain as assessed by PET imaging) should be available by end-of-F2026. One-year follow-up may be too brief to observe any statistically-significant impact on cognition but we expect to see trends on cognitive improvement over this time frame, with cognition being measured conventionally by the well-characterized CDR-SB, MMSE, ADAS-Cog14 & ADCS-ADL questionnaires that Biogen-Eisai-Eli Lilly and most other Alzheimer's disease drug developers conventionally use in their independent clinical studies.

ProMIS previously showed that PMN310 binds minimally to amyloid monomers or to higher-order amyloid aggregates/plaques, which we believe actually dampens the efficacy of mAbs that bind to these amyloid forms to a greater degree than PMN310 does. Limited binding to brain-residing amyloid plaques is actually the key feature of PMN310 that we believe should enhance its side effect profile, particularly on limiting the localized brain swelling/edema that mAb binding to amyloid plaques in the brain (ARIA-E) can cause.

Exhibit 5. Comparable Companies For ProMIS Neurosciences. ALS/Parkinson's Disease Drug Developers

Company	Filing Curr	Sym	Shares Out (M)	Share price 21-Jul	Mkt cap ($M) (curr)	Mkt cap ($M) (C$)	Ent val ($M) (curr)	Ent val ($M) (C$)	Status of lead program
Comparable drug developers targeting Parkinson's disease, amyotrophic lateral sclerosis (ALS), or other forms of dementia									
Alector Inc	USD	ALEC	100.0	$1.59	$159.0	$218.1	($186.1)	($255.3)	TREM2-targeted AL002, 265-pt Phase II AD trial, 48-96-week CDR-SB data expected by Q124; separate Phase II AL001 program targeting TDP-43 in FTD, includes pts with progranulin mutations; partnered with GSK & AbbVie
Alnylam Pharmaceuticals Inc	USD	ALNY	130.4	$320.53	$41,793.4	$57,344.7	$40,186.7	$55,140.2	Diversified siRNA portfolio (includes TTR-amyloidosis drug Onpattro, but also ALN-APP (amyloid precursor protein, mutations lead to ceregral amyloid angiopathy)
Amylyx Pharmaceuticals Inc	USD	AMLX	89.1	$8.34	$743.4	$1,020.1	$539.4	$740.1	Lead ALS drug is AMX0035, a combination of sodium phenylbutyrate & taurursodiol, positive 6-mo ALSFRS-R data from the 137-patient Phase II CENTAUR trial (publ in Sept/20 in *NEJM*), NDA filed in Nov/21, negative FDA Advisory Panel vote in Mar/22
Biohaven Ltd	USD	BHVN	102.1	$14.05	$1,434.7	$1,968.5	$1,111.9	$1,525.7	CNS-focused drug developer, targets diseases related to glutamate dysregulation. Phase III ALS drug is verdiperstat. Collaborating with Artizan Biosciences to explore role of gut microbiome in PD
Denali Therapeutics Inc	USD	DNLI	145.3	$14.00	$2,033.9	$2,790.7	$1,221.5	$1,676.1	Targeting frontotemporal dementia through associated mutations in the GRN granulin gene; lead drug is recombinant BBB-translocating progtranulin DNL593, in 106-pt Phase I/II testing, 18-mo data (Columbia-Suicide Severity Rating Scale) in Q425
Prothena Corporation PLC	USD	PRTA	53.8	$6.26	$337.0	$462.3	($81.0)	($111.1)	Prasinezumab (alpha-synuclein C-terminus-targeted mAb) in Phase II PADOVA trial; also PRX012 (amyloid beta N-terminus-targeted mAb) in Phase I AD testing; dual-acting amyloid-tau vaccine in development. AFFIRM-AL trial targeting light chain amyloidosis with birtamimab
Average								**$9,785.9**	
ProMIS Neurosciences Inc	**USD**	**PMN**	**32.7**	**$1.18**	**$39**	**$39**	**$30**	**$30**	**mAb drug developer, targets disease-relevant conformational epitopes, including in Alzheimer's disease with Phase I-stage PMN310, also targeting ALS & Parkinson's disease.**

Source: Refinitiv

PMN310 Phase I/PK data were sufficiently positive in our view to justify advancing into the PRECISE-AD trial. As we commented in prior PMN reports & Healthcare Weekly updates, PMN310 was well-tolerated at all five test doses tested in the firm's 40-patient healthy volunteer trial, with PK analysis of all doses tested in the 2.5mg/kg-to-40mg/kg range suggesting that once-monthly dosing could be sufficient to sustain mAb levels in plasma & cerebrospinal fluid at predicted therapeutic levels. mAb half-life in cerebrospinal fluid was 25 days & even at the lowest dose tested, PMN310 accumulated in cerebrospinal fluid to a level that ProMIS predicts would be >100x higher than would be necessary to bind all beta-amyloid oligomers conferring cognitive impairment. Interestingly, ProMIS showed that PMN310 was able to cross the blood brain barrier without any transferrin receptor-mediated transcytosis mechanism that Acumen (ABOS-Q, NR) believes could be necessary for its ACU193 mAb through its recently-announced alliance with JCR Pharmaceuticals (4552-JP, NR) & its J-Brain Cargo platform.

The seminal population genetic studies conducted by Tomiyama's team on the Osaka mutation that was published in 2008 in *Annals of Neurology* & described by us in our original report still provides the best evidence in our view for the uniquely neurotoxic role for oligomers in cognitive impairment. PMN310 is well differentiated from other FDA-approved amyloid-binding mAbs on its ability to exhibit selective/specific oligomer binding (ProMIS published binding selectivity/specificity data on this theme in a 2019 paper in *Scientific Reports*).

As we observed in an earlier PMN report, we were encouraged to see the value ascribed to an early-stage ProMIS peer by US-based drug development giant AbbVie (ABBV-N, NR) when it acquired one of ProMIS' AD drug development peers in Aliada Therapeutics in a deal valuing Aliada and its pipeline (specifically Phase I-stage anti-pyroglutamate beta-amyloid mAb ALIA-1758) at US$1.4B. ALIA-1758 is like PMN310 in Phase I testing, with a 53-patient Phase I SAD study on pace to generate final safety/PK data imminently (data were expected during Q225). Though it seems probable to us that AbbVie is ascribing supplemental value to Aliada's transferrin receptor-mediated blood brain barrier translocating Modular Delivery platform (similar conceptually to JCR's J-Brain Cargo platform), it is nonetheless true that ALIA-1758 was the most advanced mAb asset in Aliada's pipeline. That said, it seems plausible to assume that AbbVie will leverage newly-acquired blood-brain barrier-crossing technology to enhance CNS update of its own pyroglutamate amyloid-targeted mAb ABBV-916, its synaptic vesicle glycoprotein 2A (SV2A)-targeted mAb ABBV-552 & its Triggering Receptor Expressed on Myeloid Cells 2 (TREM2)-targeted Alector-licensed (ALEC-Q, NR) mAb AL002, with the latter mAb already undergoing testing in a 150-patient Phase I/II Alzheimer's disease trial (data in late FQ425).

Summary & valuation. We are maintaining our Speculative Buy rating and one-year PT of US$9.50 on PMN, with our valuation still based on NPV (30% discount rate) and multiples of our F2029 EBITDA/fd EPS forecasts, as shown in Exhibit 2. Our EV calculation is based on FQ125 cash of US$8.4M (no LT debt) & fully-diluted pro forma S/O of 79.3M that assumes full-exercise of previously-issued warrants that were part of the firm's equity offering in July/24. On the milestone watch, we are still laser-focused on PMN310 & timelines to data from the PRECISE-AD trial, but the firm does have two other attractive mAb assets for which binding to disease-relevant conformational epitopes is already established, including for binding to misfolded alpha-synuclein by PMN442 (Parkinson's disease) & to misfolded TDP43 by PMN-267 (amyotrophic lateral sclerosis) & we assume preclinical IND-enabling studies are ongoing for both mAbs as of this writing. Our model does ascribe value to both of these preclinical mAbs, though with commencement of formal clinical testing likely awaiting final Phase Ib data from PRECISE-AD.

As indicated above, we are encouraged by the ricochet exhibited in PMN share value from what we believe were trough levels for both share value & enterprise value ascribed predominantly to PMN310. At current levels, our PT corresponds to a one-year return of 705%, a seemingly aggressive notional return but one that we believe is achievable if PMN310 performs as well clinically on cognitive impairment reversal & biomarker profile improvement in PRECISE-AD as all preclinical/Phase I data generated so far predicts that it could.

Disclosures 2

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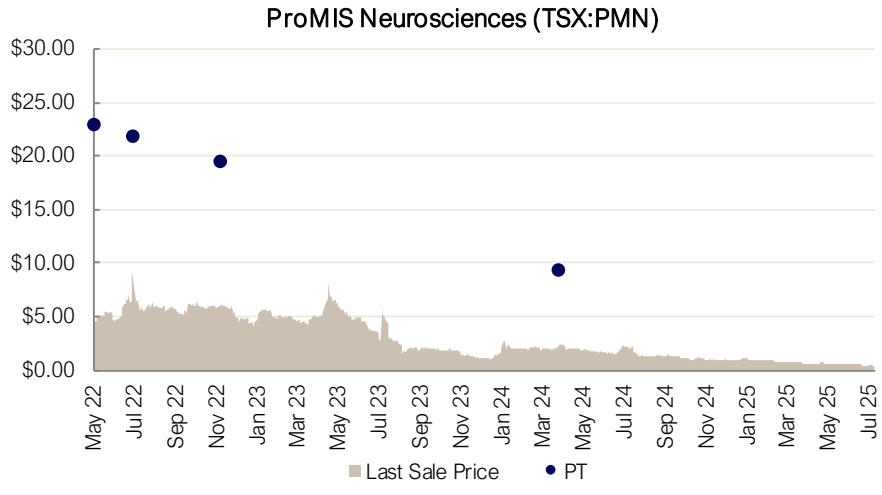
RECOMMENDATION	NO. OF COMPANIES	%
Buy	7	39%
Speculative Buy	8	44%
Hold	2	11%
Sell	-	-
Tender	1	6%
Under Review	-	-

Historical Target Price



Date	Target (C$)	Rating
11 May 2022	C$30.00	Spec Buy
6 Jul 2022	C$28.50	Spec Buy
14 Nov 2022	C$26.00	Spec Buy
2 Apr 2024	US$9.50	Spec Buy

Coverage Initiated: May 11, 2022

Data sourced from: Refinitiv

Historical PTs reflect CAD on the firm's prior TSX listing; adjusted for USD equivalent