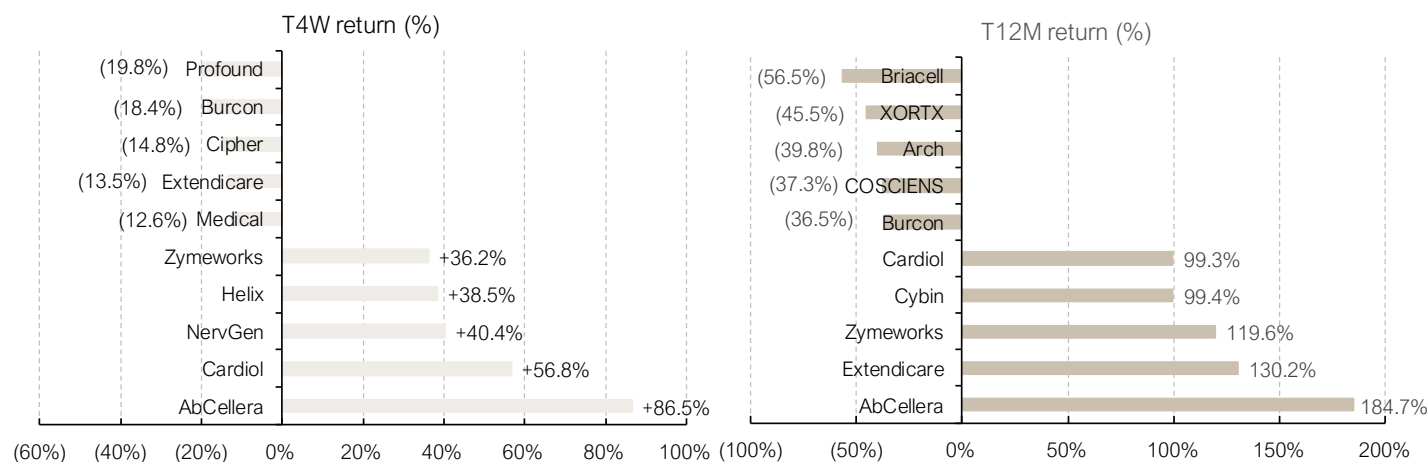


Core Highlights of the Week

Top Movers

Exhibit 1. Top Healthcare/Biotechnology Movers for the Trailing Four-Week & YTD Periods



Source: Leede Financial, Refinitiv

Updates From Our Healthcare Coverage Universe

- Cipher successfully navigates its arbitration proceedings with Absorica marketing partner Sun Pharma.** As we described in a Cipher-specific research comment earlier this week, ON-based dermatology-focused specialty pharmaceutical firm Cipher Pharmaceuticals (CPH-T, Buy, PT C\$19.50) provided a favorable update on its now-resolved arbitration with its US Absorica (CIP-isotretinoin) marketing partner Sun Pharms (SUN-BO, NR), with a New York court ruling in favor of Cipher on all elements that are germane to Cipher's operating risk profile & thus to our investment thesis.
- The arbitration related to Cipher's claim that Sun Pharma leveraged Cipher's existing clinical data in support of its original Absorica NDA filing to support its NDS filing in Canada for Absorica LD, an isotretinoin formulation for cystic acne that resembles the PK profile of Cipher's CIP-isotretinoin brand in Canada, Epuris. Sun launched Absorica LD in Sept/23; we do not have specific Canadian sales data for Absorica LD but we know from Cipher's financial data that Epuris has substantial market share in the Canadian isotretinoin medical market (Epuris FQ226 sales were US\$4.1M & thus at the top end of quarterly sales that Cipher has achieved in the Canadian dermatology market since Epuris' launch in FH213), a market that includes not only Absorica LD but also Roche's (ROG-SW, NR) legacy isotretinoin brand Accutane & Viatris/Mylan's (VRTS-Q, NR) generic isotretinoin brand Clarus.
- Resolution of the Sun Pharma arbitration on Absorica LD is multi-layered & includes cash elements that are positive to Cipher's overall financial risk profile.** The ruling has three directly positive consequences along with a fourth more qualitative consequence that we ourselves believe is key to the US Absorica franchise. But on the ruling itself, there were two elements that directly impact Cipher's balance sheet cash & financial risk, one of which was an overt damages award of C\$4.2M/US\$3.05M & the other was a decision to retrospectively fund Cipher's legal costs incurred during the arbitration in F2024/F2025.

Please see end of report for important disclosures.

- We calculate those legal costs in those two years alone to have been US\$3.2M, 80% of which is US\$2.56M/C\$3.56M. The other positive element is that Cipher will be entitled to a 15% royalty on future Canadian Absorica LD sales out to end-of-F2040 & including retrospective payments for the FQ126-to-FQ326 financial periods. We add this notional cash to our pro forma cash calculation, as represented in Exhibit 3. Our model assumes that near-term arbitration-ascribed legal costs would be minimal in F2027/F2028 & so our EBITDA/EPS forecasts in those fiscal periods are unchanged.
- Absorica LD is similar to Absorica but with distinctive PK profile under fasting conditions & with Cipher already receiving modest economics from US Absorica LD sales.** We have not recently allocated many equity research resources to describing the distinctions between Absorica & Absorica LD at least not since 2019 when Absorica LD's FDA approval was granted, since it did not bear significantly on our royalty revenue forecasts. But recent legal resolution leading to more overt impact on Cipher's business risk going forward motivated us to reflect a bit more directly on this particular isotretinoin formulatin & its development history.

Exhibit 2. Financial Forecast Summary for Cipher

<i>Fiscal year-end Dec 31</i> <i>(US\$000, except EPS)</i>	2018A	2019A	2020A	2021A	2022A	2023A	2024A	2025A	2026E	2027E	2028E
US/RoW, royalty revenue											
Royalty rev, ConZip (US)	552	600	500	430	152	138	33	154	119	188	188
Royalty rev, Lipofen (US)	2,378	2,312	2,400	2,331	2,850	2,175	2,045	1,600	1,841	1,887	1,963
Royalty rev, Absorica (US)	12,942	11,300	9,929	7,648	5,143	6,148	4,545	1,800	2,397	2,185	2,185
Royalty rev, Natroba (RoW)	0	0	0	0	0	0	0	0	554	1,342	1,375
Canada/US, direct Rx sales											
Revenue, Epuris (Cda)	5,813	7,300	8,100	10,885	11,330	10,848	12,980	14,700	15,661	15,242	15,242
Revenue, Vaniqa/Actikerall/ Beteflam/other (Cda)	1,064	939	678	650	1,200	1,753	1,780	2,200	2,137	2,296	2,486
Revenue, Natroba (US)	0	0	0	0	0	0	11,980	29,997	28,267	29,533	30,244
Revenue, Natroba (Cda)	0	0	0	0	0	0	0	0	353	1,477	1,512
Total revenue	\$22,749	\$22,451	\$21,607	\$21,944	\$20,675	\$21,162	\$33,363	\$50,451	\$51,327	\$54,150	\$55,195
Revenue growth (%)	(43.6%)	(1.3%)	(3.8%)	1.6%	(5.8%)	2.4%	57.7%	51.2%	1.7%	5.5%	1.9%
Operational expenses	15,984	9,822	8,116	9,294	8,233	8,712	18,237	24,968	21,438	22,513	22,938
EBITDA	\$6,765	\$12,629	\$13,491	\$12,650	\$12,442	\$12,450	\$15,126	\$25,483	\$29,889	\$31,637	\$32,257
EBITDA growth (%)	(74.5%)	86.7%	6.8%	(6.2%)	(1.6%)	0.1%	21.5%	68.5%	17.3%	5.8%	2.0%
EBITDA margin (%)	29.7%	56.3%	62.4%	57.6%	60.2%	58.8%	45.3%	50.5%	58.2%	58.4%	58.4%
Non-operating expenses	\$3,379	\$4,570	\$6,598	\$1,593	\$1,392	\$2,417	\$9,992	\$7,285	\$9,071	\$8,400	\$8,400
Net interest exp (income)	\$712	\$786	\$291	\$80	(\$464)	(\$1,870)	(\$330)	\$1,165	\$36	\$0	\$0
Tax expense, exc tax loss carry-forward	\$1,922	\$3,071	\$3,554	\$3,413	(\$847)	(\$4,965)	\$54	\$12	\$2,427	\$4,963	\$5,118
Net income, fully-taxed	\$1,201	\$2,639	\$4,386	\$7,759	\$26,636	\$20,383	\$11,546	\$27,329	\$19,884	\$19,853	\$20,473
Fully-taxed EPS (basic)	\$0.04	\$0.10	\$0.16	\$0.29	\$1.06	\$0.81	\$0.45	\$1.08	\$0.78	\$0.78	\$0.81
Fully-taxed EPS (fd)	\$0.04	\$0.10	\$0.16	\$0.28	\$1.01	\$0.78	\$0.43	\$1.03	\$0.75	\$0.75	\$0.78
P/E (basic)	232.0x	106.1x	64.1x	35.5x	9.9x	12.9x	22.9x	9.7x	13.3x	13.3x	12.9x
EV/EBITDA	38.1x	20.4x	19.1x	20.4x	20.7x	20.7x	17.0x	10.1x	8.6x	8.1x	8.0x

Source: Historic data – Cipher financial filings; Forecasts/Estimates – Leede Financial Inc.

- Back when Absorica LD was originally FDA-approved, we described how that isotretinoin formulation was pharmacologically similar to Lidose-based Absorica itself, but with a few formulation distinctions. Whereas Lidose is mostly based on the fatty acids sorbitan monooleate (an eighteen-carbon double-bond-containing fatty acid to which the tetra-hydroxylated sugar alcohol sorbitan is linked – this emulsifying agent is not a unique component of Lidose but it is likely present to improve isotretinoin's bioavailability in the gut), & stearyl polyoxyglyceride (a mixture of glycerol & polyethylene glycol, each with multiple free hydroxyl groups to which a different eighteen-carbon fatty acid, stearic acid, is bound), Absorica LD's core formulation contains the emulsifier polysorbate 80 & the anti-oxidant butylated hydroxy anisole (BHA), neither of which is particularly unique to LD's formulation & are incorporated into multiple drug & food products.

- Both formulations use soybean oil, which is a mixture of long-chain fatty acids bound in triglyceride form as are found in most naturally-occurring processed oils, presumably added for also enhancing isotretinoin's bioavailability. In a May/21 editorial published by Sun Pharma advisor LH Kircik in the *Journal of Drugs In Dermatology*, it was claimed that Absorica LD is actually absorbed more efficiently in the gut than Absorica, not just because of the distinct lipid-based excipients it contains but also from using a micronizing technology that we assume breaks up lipid-encapsulated isotretinoin into small microspheres, increasing the total surface area of all isotretinoin-containing particles in a way that at least notionally could enhance its rate of absorption by intestinal epithelial cells. In a separate publication in the same journal issue, Sun Pharma presented a table showing that Absorica LD's AUC (area-under-curve, a measure of total time-concentration that a drug resides in the body in its active state) & Cmax (the maximum concentration that a drug attains in blood plasma) were higher than for Absorica, but only in fasting patients.
- What has long surprised us (these data were published five years ago & Absorica LD itself was FDA-approved in 2019) is that virtually no peer-reviewed studies on Absorica LD have been published since & Absorica LD's commercial traction seems not to be rivalling levels that Absorica (US) or Epuris (Canada) achieved in peak quarters, even while armed with this comparative PK data in both North American markets. Galephar's Absorica/Lidose patents expired long ago (US#8,367,102 B2; *Pharmaceutical Semi-Solid Composition Of Isotretinoin*) & generic alternatives to Absorica specifically have been available from Teva Pharmaceuticals (TEVA-NY, NR, with acquired firm Actavis actually filing the original ANDA back in Oct/13 but with an agreement with Cipher to allow US launch in FQ420). Sun does have issued US patents that are germane to Absorica LD's formulation that are listed in the FDA's Orange Book including US#9,700,535 B2 (*Oral Pharmaceutical Composition of Isotretinoin*) & US#9,750,711 B2 (*Low Dose Oral Pharmaceutical Composition of Isotretinoin*), both of which expire in 2035.

Exhibit 3. Valuation Summary for Cipher

Price/earnings multiple, F2027	5x	10x	15x	20x	25x	30x	35x
Implied share price ^{1,2}	\$3.76	\$7.52	\$11.29	\$15.05	\$18.81	\$22.57	\$26.34
EV/EBITDA multiple, F2027	5x	7x	9x	10x	11x	13x	15x
Implied share price ^{1,2}	\$6.80	\$9.29	\$11.78	\$13.03	\$14.27	\$16.76	\$19.25
One-year Cipher target price (US\$)				\$14.04			
One-year Cipher target price (C\$) ³				\$19.51			

¹ Based on F2027 adj EBITDA forecast of US\$31.6M, F2027 adj fd EPS of US\$0.75, basic S/O 25.4M; fd S/O 26.4M

² Based on 20x EPS, 10x EV/EBITDA (F2027); pro forma cash of US\$14.7M [C\$20.5M] (FQ226 cash of US\$9.1M or C\$12.7M, plus pending payments from Sun arbitration settlement), no LT debt

³ PT in C\$ assumes USD:CAD exchange rate of 1.39x

Source: Leede Financial Inc.

- When we see what the magnitude of that retrospective payment is, we will have a more precise measure of what quarterly Absorica LD royalties could be during F2027, the reference year in our CPH valuation. The 15% royalty rate is interesting to us in that it is identical to the royalty that Sun was paying out collectively on US Absorica sales to Cipher & its Absorica manufacturing partner Galephar PR (private), splitting that royalty evenly between the two parties. Until a few years ago, Galephar PR's share of US Absorica royalties was owned by another ON-based specialty pharmaceutical firm HLS Therapeutics (HLS-T, NR), which returned rights to Galephar PR back in FQ420 after acquiring them in FQ316.
- Absorica US marketing rights revert to Cipher by end-of-FQ426, shifting Absorica economics into an Epuris-like direct sales model.** The fourth positive element, if more indirect than the cash-based arbitration elements are, is that it refocuses our attention on Cipher's pending acquisition of US marketing rights for Absorica at the end-of-FQ426, an action that is long overdue strategically though established contractually long ago to transpire over this time frame. Sun Pharma's US Absorica sales performance in recent quarters has been underwhelming to be charitable, falling from peak royalties to Cipher of US\$9.4M in FQ417 (corresponding to gross sales just in that quarter of US\$125M); admittedly before generic forms were available from Teva Pharmaceuticals (TEVA-NY, NR, originally developed & approved under the stewardship of one of Teva's acquired firms Actavis/Allergan, also from other US generic drug manufacturers like

Upsher Smith Pharmaceuticals [private]) down to an equilibrium royalty revenue level during the FQ118-to-FQ221 period of US\$2.8M, later dropping to an average of US\$0.79M per quarter during the FQ423-to-FQ226 period.

- Though Absorica's market share in the US isotretinoin dermatology market was destined to decline with the introduction of generic Absorica alternatives (so not just generic forms of isotretinoin itself, but generic forms that exhibit the super-bioavailable/super-GI absorption that Absorica's Lidose platform confers), we have long advocated for Sun Pharma (& now Cipher) to drive Absorica market share with more of a branded generic pricing strategy, capturing market share from lower-bioavailable generic isotretinoin formulations (of which there are several, including from Teva) in the process. We await clarity on Cipher's Absorica pseudo-relaunch characteristics in coming quarters, presumably during FH126.

Exhibit 4. Comparable Companies for Cipher

			Shrs	Share	Mkt	Mkt	Ent.	Ent.						
	Filing		Out.	Price	Cap	Cap	Value	Value		EV/EBITDA		Price/Earnings		
Company	Curr.	Sym.	(M)	2-Sep	(\$M)	(C\$M)	(\$M)	(C\$M)	(T12M)	(2026E)	(2027E)	(T12M)	(2026E)	(2027E)
Profitable Canadian healthcare firms														
Apotex	CAD	APTX	228.5	\$32.62	7,454	7,454	12,080	12,080	NA	NA	11.8x	NA	NA	14.9x
Aurinia Pharmaceuticals	USD	AUPH	133.1	\$16.05	2,135	2,135	2,281	2,315	9.4x	8.3x	6.6x	6.7x	17.0x	13.6x
Bausch Health	USD	BHC	374.0	\$6.83	2,554	3,549	31,053	43,138	5.6x	5.6x	6.0x	NA	1.5x	1.6x
BioSyent	CAD	RX	11.5	\$15.87	183	183	167	167	10.9x	10.4x	8.9x	18.2x	17.8x	14.7x
CareRx	CAD	CRRX	63.5	\$3.17	201	201	274	281	8.9x	7.9x	6.9x	7.4x	36.2x	15.6x
Chartwell REIT	CAD	CSH.R	328.3	\$9.36	3,073	3,073	10,109	10,155	22.2x	19.9x	17.8x	NA	NA	NA
DRI Healthcare Trust	CAD	DHT.UN	55.0	\$17.66	971	971	1,537	1,560	6.2x	6.5x	7.3x	NA	7.0x	7.6x
Extendicare REIT	CAD	EXE	95.0	\$29.84	2,836	2,836	3,619	3,563	16.3x	14.3x	12.6x	22.5x	21.8x	19.6x
HLS Therapeutics	CAD	HLS	30.9	\$3.61	112	112	164	162	7.1x	6.0x	5.1x	NA	NA	NA
Jamieson Wellness	CAD	JWEL	41.5	\$45.40	1,884	1,884	2,388	2,359	14.5x	13.3x	11.9x	24.1x	21.1x	18.6x
K-Bro Linen	CAD	KBL	13.0	\$45.18	588	588	897	901	7.7x	8.1x	7.8x	26.8x	22.1x	18.0x
Knight Therapeutics	CAD	GUD	98.2	\$9.67	950	950	818	846	8.3x	9.8x	9.3x	NA	NA	36.4x
Medexus ¹	CAD	MDP	32.0	\$3.76	121	121	204	199	8.5x	9.2x	6.6x	50.0x	NA	23.9x
Medical Facilities ¹	CAD	DR	16.2	\$10.92	177	177	304	277	3.8x	3.7x	8.9x	15.6x	5.9x	14.4x
Microbix Biotech	CAD	MBX	137.0	\$0.29	40	40	40	41	NA	NA	NA	NA	NA	NA
Vital Infrastructure	CAD	VITL.UN	250.0	\$5.23	1,308	1,308	2,712	2,687	13.5x	13.1x	12.6x	NA	NA	NA
Savaria	CAD	SIS	72.1	\$27.43	1,978	1,978	2,283	2,346	11.8x	11.1x	10.1x	22.4x	19.8x	17.4x
Sienna Senior Living	CAD	SIA	110.9	\$20.51	2,274	2,274	3,633	3,627	21.7x	17.8x	15.7x	39.0x	38.0x	32.6x
Viemed	USD	VMD	38.1	\$8.98	342	475	484	682	6.2x	5.4x	4.7x	23.7x	21.7x	16.5x
Vitalhub	CAD	VHI	63.4	\$8.16	517	517	374	359	12.8x	11.0x	9.1x	NA	44.1x	23.9x
Well Health	CAD	WELL	255.5	\$4.25	1,086	1,086	2,004	2,004	NA	10.6x	9.8x	NA	16.7x	11.9x
Average									10.9x	10.1x	9.4x	23.3x	20.8x	17.9x
Profitable specialty pharmaceutical firms														
AbbVie	USD	ABBV	1767.1	\$259.99	459,433	638,405	727,622	1,011,067	16.7x	15.9x	13.9x	NA	18.5x	16.0x
Amgen	USD	AMGN	540.6	\$438.12	236,862	329,131	389,249	540,882	15.7x	12.8x	12.5x	27.0x	19.0x	17.9x
Biogen	USD	BIIB	147.8	\$216.04	31,921	44,356	53,802	74,761	12.4x	13.4x	11.1x	38.0x	17.5x	13.1x
Fresenius	EUR	FREG	563.2	€44.79	25,225	40,629	55,225	76,737	12.4x	12.1x	11.4x	16.1x	12.1x	11.4x
Cardinal Health	USD	CAH	232.6	\$239.35	55,667	77,352	83,158	115,552	19.3x	20.1x	18.4x	32.9x	22.2x	19.0x
Dr. Reddy Labs	INR	500124	833.0	Rp1,161	Rp967,099	14,148	13,973	19,417	23.6x	17.2x	21.2x	30.0x	19.0x	27.0x
Gilead Sciences	USD	GILD	1240.0	\$149.92	185,894	258,309	290,193	403,238	19.6x	NA	17.0x	NA	NA	15.1x
Jazz Pharmaceuticals	USD	JAZZ	64.9	\$243.71	15,820	21,983	24,968	34,695	15.2x	10.6x	10.2x	16.0x	9.7x	9.4x
Neurocrine Biosciences	USD	NBIX	101.6	\$156.76	15,935	22,142	21,596	30,009	24.8x	21.7x	15.7x	22.3x	22.3x	15.4x
Perrigo	USD	PRGO	138.8	\$14.43	2,002	2,782	6,804	9,455	10.6x	9.3x	9.2x	NA	6.6x	6.0x
Sun Pharma/Ranbaxy ²	INR	SUN	2399.3	Rp1,933	Rp4,637,914	67,848	63,632	88,419	35.3x	35.9x	32.3x	39.3x	38.4x	35.6x
Teva Pharmaceuticals ³	USD	TEVA	1165.3	\$36.19	42,172	58,600	77,677	107,936	17.4x	18.1x	13.9x	58.3x	18.2x	11.8x
United Therapeutics	USD	UTHR	42.9	\$512.70	21,990	30,556	26,852	37,312	17.6x	18.3x	16.1x	16.9x	19.5x	17.4x
Vertex Pharmaceuticals	USD	VRTX	253.5	\$547.65	138,808	192,880	181,936	252,810	34.7x	32.0x	27.9x	31.6x	29.1x	25.8x
Viatis ⁴	USD	VTRS	1148.6	\$16.63	19,101	26,542	43,129	59,929	10.8x	9.8x	9.5x	NA	6.6x	6.3x
Average									19.1x	17.7x	16.0x	29.9x	18.5x	16.5x
Cipher Pharma ¹		CPH	25.4	\$10.21	260	361	245	340	12.6x	11.5x	10.0x	8.9x	12.7x	11.4x

¹ Share price converted to USD for stocks reporting financial data in USD but for which share value is reported in CAD

² Cipher's US Absorica marketing partner

³ Generic Absorica competitor (since April-21)

⁴ Cipher's generic isotretinoin competitor in Canada with Clarus

Source: Leede Financial, Consensus Data - Refinitiv

- **Summary & valuation.** We maintained our Buy rating & PT of C\$19.50 in that report, while still basing our valuation on multiples of our F2027 EBITDA/fd EPS financial forecasts (US\$31.6M & US\$0.75/shr, respectively) as shown in Exhibit 2. Our EV calculation incorporates pro forma cash of US\$14.7M/C\$20.4M that we adjusted from our last CPH update based on pending cash payments from Sun Pharma (FQ226 cash balance of US\$9.1M/C\$12.7M adjusted for a C\$4.2M damages award along with 80% retrospective compensation on Cipher's legal costs in F2024/F2025 – US\$1.6M in each of those years, according to Cipher's MD&A documents describing those fiscal years, 80% of which is US\$2.56M/C\$3.56M - to fund its own legal costs during the arbitration). As before, Cipher had no LT debt to incorporate into our EV calculation & we use basic S/O of 25.4M in the denominator of our EV derivation.
- In our report, we reflected on all of the imminent milestones that are on the horizon for Cipher, independent of course of its quarterly financial data through which we will gain insight into how Absorica will impact quarterly royalty revenue in coming periods, with or without Sun's proportionate contribution from Canadian Absorica LD sales. First of all, most Cipher followers are likely more focused on economic impact for the firm's topical head lice/scabies Spinosad A/D formulation Natroba on our valuation, with US sales of that product contributing about 55% of our consolidated F2026-to-F2028 annual revenue forecasts.
- The growth drivers for that drug are unchanged from our last commentary on this theme & include: (1) capturing market share from GSK's (GSK-LN, NR) permethrin/Nix based on superior efficacy (well-documented in Natroba's prescribing information & in the peer-reviewed papers that it cites) & on emergence of permethrin-resistant head lice/scabies strains in most major infectious disease markets; (2) review of Cipher's Health Canada NDS filing for Natroba submitted in Jan/26 should conclude imminently & if as favorably reviewed as we believe it will be, Canadian Natroba launch could transpire during FH127, & (3) royalty revenue from RoW product out-licensing alliances should augment our consolidated royalty revenue forecasts (which for now consist only of Absorica & CIP-fenofibrate/Lipofen) in coming quarters.
- Separately, we are closely monitoring clinical progress for a partnered plaque psoriasis-targeted small-molecule drug – Can-Fite Biopharma's (CANF-TASE-NY) adenosine A3 receptor agonist piclidenoson/CF101 – for which Cipher holds Canadian marketing rights. The drug performed well in an already-completed & published Phase III plaque psoriasis trial (the 426-patient Comfort-1 trial, described in a Jun/24 issue of the *Journal of the European Academy of Dermatology & Venereology*) in which piclidenoson-treated patients out-performed not only placebo patients but also patients treated with an alternative already-approved phosphodiesterase 4 (PDE4)-inhibiting small-molecule apremilast (Amgen's [AMGN-Q, NR] Otezla; FQ226 sales US\$491M but far higher in FQ225 at US\$618M; availability of generic formulations since F2024 likely impacting growth trajectory). Piclidenoson's favorable comparison to Otezla, an orally-active psoriasis drug that competes commercially with the multitude of injectable interleukin-targeted mAbs already approved in this market, give us confidence in piclidenoson's commercial prospects in the plaque psoriasis pharmacopeia if eventually approved. Commencement of a second 705-patient Phase III plaque psoriasis/piclidenoson trial is imminent, with four-month PASI75 efficacy data expected during FH228.

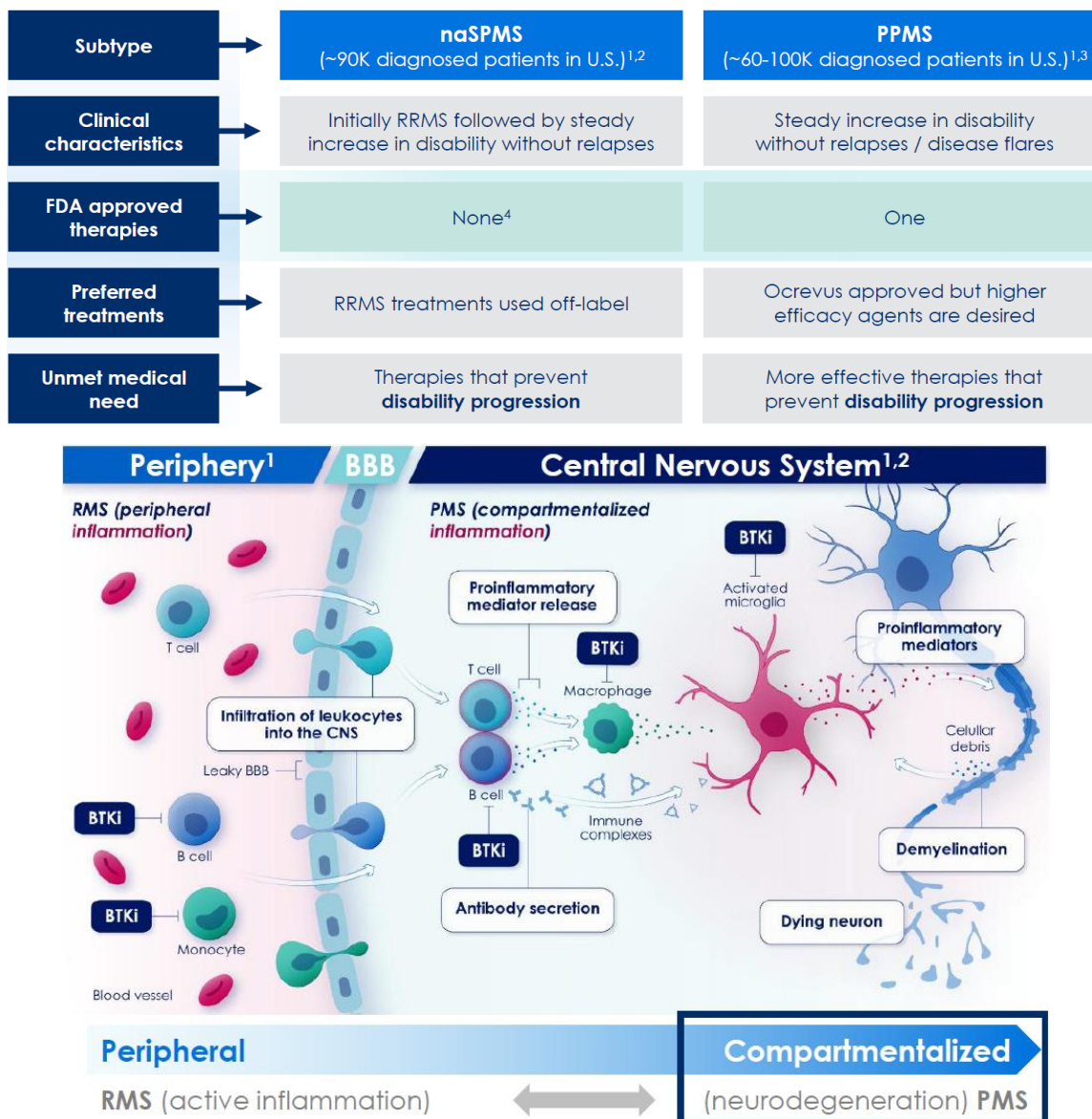
Significant Developments With Relevance To Our Coverage Universe

- **Novartis continues to redefine the multiple sclerosis pharmacopeia with a new positive Phase III data signal.** Swiss pharma giant Novartis (NVS-NY, NR) reported positive Phase III multiple sclerosis data from the 1,000-patient Remodel-1 & the 1,007-patient Remodel-2 trials testing the firm's Bruton's tyrosine kinase (BTK) inhibitor drug remibrulinib/Rhapsido. The drug was actually already FDA-approved last year for treating chronic spontaneous urticaria (skin rash/hives; FQ226 sales for that indication were modest but certainly not trivial at US\$64M, up from US\$37M in FQ126).
- On the data themselves, Novartis showed in both trials that BTK inhibitor remibrulinib/Rhapsido reduced the annual relapse rate in patients with relapsing remitting multiple sclerosis to a far greater degree than patients treated with legacy immune-modulating small-molecule drug teriflunomide (now genericized but originally developed by Sanofi [SNY-NY, NR] & branded as Aubagio) while remibrulinib/Rhapsido patients also exhibited reduction in gadolinium-enhanced brain lesions as visualized by MRI. As pharma firms usually do, Novartis reported remibrulinib/Rhapsido's performance in the trials only on a qualitative level, preserving formal data analysis for a pending medical conference, in this case expected to be the MSToronto2026 conference in late Oct/26. As we found in other multiple sclerosis trials that incorporate an active control & not just a placebo arm, the comparator drug seems usually to be teriflunomide/Aubagio,

probably because the drug is genericized & thus of diminishing commercial significance to innovative drug developers (including Sanofi itself, see below).

- As well, Novartis reported that remibrulinib/Rhapsido exhibited meaningful impact on disease progression at both three- & six-month follow-up (using the well-validated confirmed disability scale [CDS] as a measure of progression mitigation), suggesting that the drug could perform well in future Phase III studies targeting primary progressive or perhaps even secondary progressive disease, two multiple sclerosis markets with incidence/prevalence levels that rival relapsing remitting disease but which until recently have been refractory to therapy. That trend is changing & BTK inhibitors are driving the change in a few circumstances. We will be interested in remibrulinib/Rhapsido's side effect profile, specifically on liver toxicity, for reasons that will be clear as we expand our BTK inhibitor competitive landscape analysis below.

Exhibit 5. On Closer Biochemical Analysis, It Is Clear That BTK Is As Relevant To Multiple Sclerosis Symptoms As It Was Earlier Shown To Be In B-Cell Lymphomas



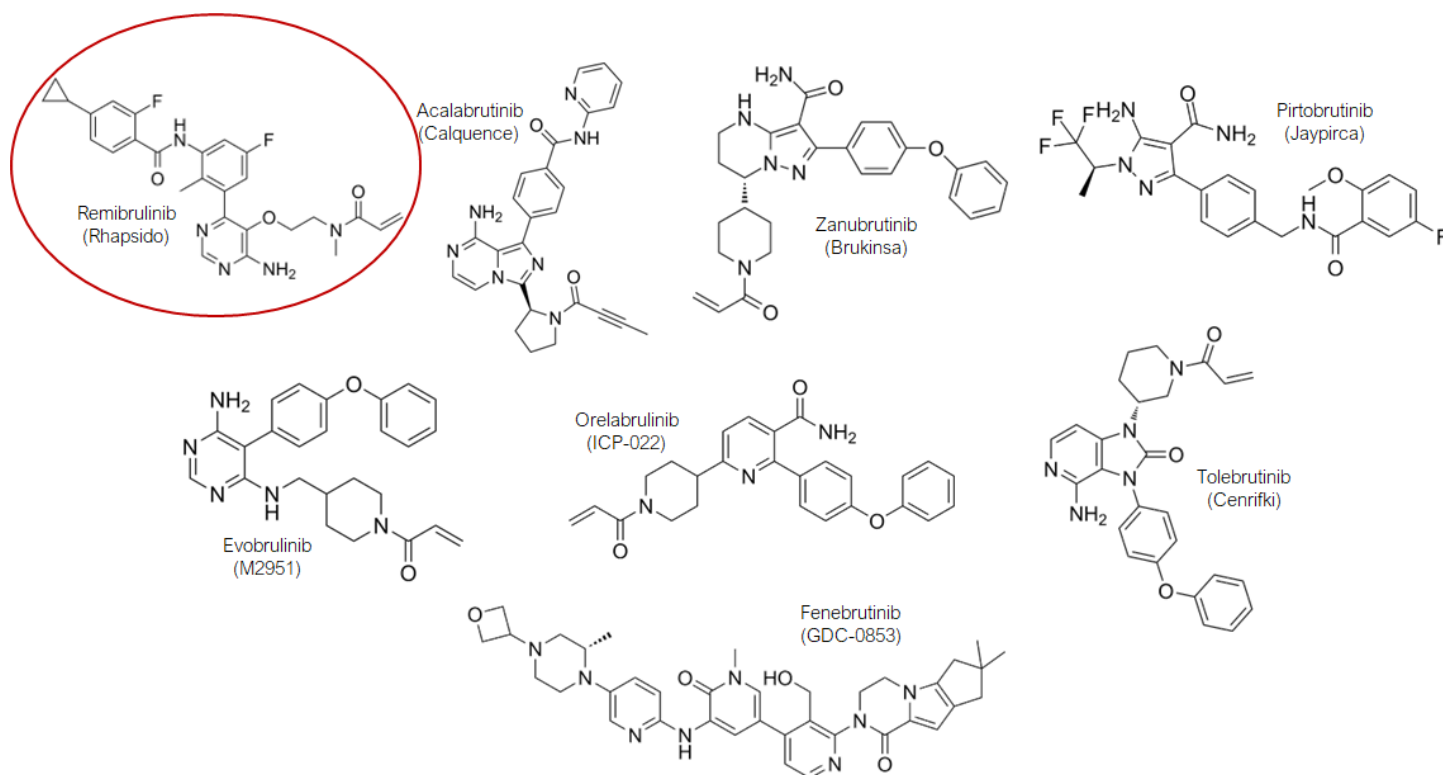
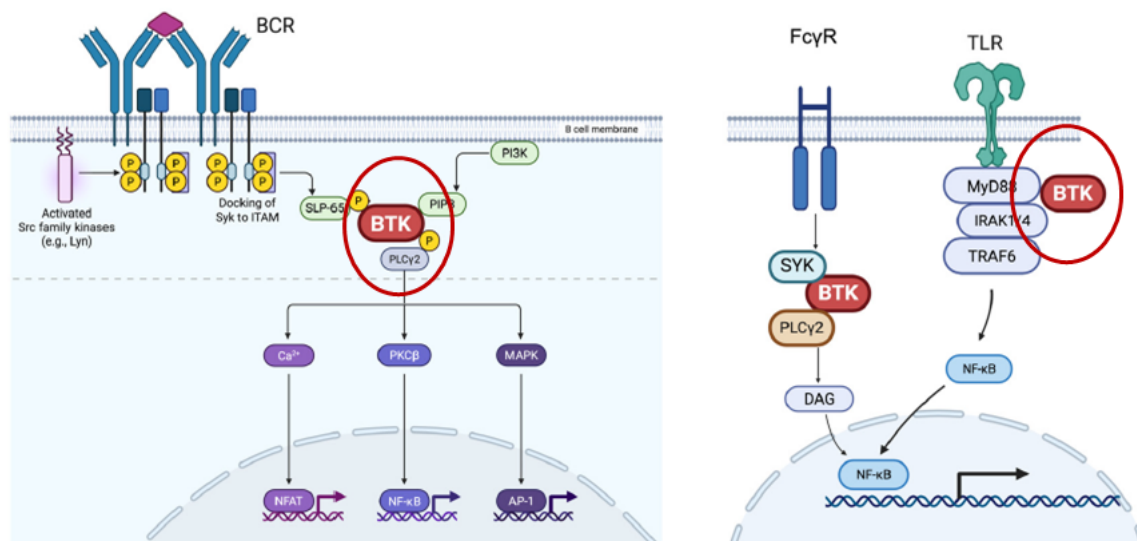
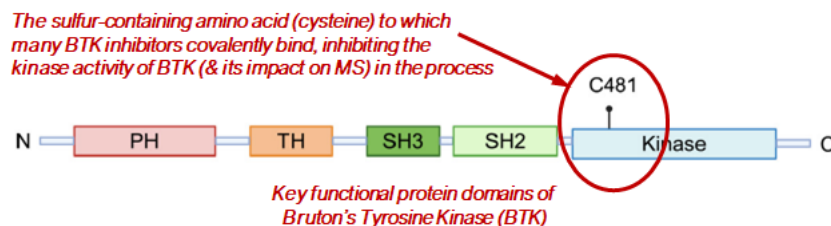
Source: Zenas Biopharma presentation (Sept/26)

- Candidly, the role of BTK inhibitors in the multiple sclerosis pharmacopeia is not exactly a new concept & multiple 'brutinib's' have advanced through Phase III testing to approval before. But Novartis' Remodel-1/Remodel-2 data for remibrulinib/Rhapsido provides us with justification for conducting a deeper dive into this therapeutic realm, based in our view on BTK's increasing mechanistic relevance to future multiple sclerosis drug development but also for its

relevance to our legacy coverage of the indication that in prior years overlapped with our coverage of ON-based cobolamin developer Transition Therapeutics (now part of FL-based Opko Health; OPK-Q, NR) & dirucotide/MDP8298 developer BioMS (ticker was MS-T but it no longer exists as a drug development entity after a Phase III failure in secondary progressive disease back in Jul/09). Secondly, autoimmune disease is a theme that pervades other commentary in our Healthcare Weekly today, so we thought we would get the ball rolling with a review of one of the highest-profile diseases in this category.

- **The multiple sclerosis pharmacopeia has advanced considerably since the days when only interferon formulations (& Copaxone) were available to patients & only for relapsing remitting disease.** Trial results were of interest to us not because they impact our existing coverage universe in any overt way, but rather for their historic impact on publicly-traded firms that we did cover in prior years & even more so for our intrinsic interest in how the multiple sclerosis pharmacopeia has transformed in recent years, notwithstanding the moderate commercial success still experienced by long-ago approved/launched multiple sclerosis biologics. Next-generation BTK inhibitors are driving a substantial amount of that transformation, hence our interest in Novartis' recent clinical advances in this realm as announced earlier this week.
- Examples include Israel-based Teva Pharmaceuticals' (TEVA-NY, NR) glatiramer acetate formulation Copaxone (originally FDA-approved in 1996; fairly stable quarterly sales in recent years at/near US\$61M-to-US\$62M, in FQ226 & FQ225 respectively) & three interferon formulations in MA-based Biogen's (BIIB-Q, NR) interferon beta-1a formulation Avonex (also originally FDA-approved in 1996; FQ226 sales US\$170.0M, of which US\$120.9M were US sales) & its PEGylated form Plegridy (much lower FQ226 sales of US\$55.1M, of which US\$25.2M were US sales), Merck KgaA/EMD Serono's (private) interferon beta-1a formulation Rebif (as with Copaxone/Avonex, also FDA-approved in 1996; FQ226 sales €107M) & Bayer Healthcare's (BAYN-DE, NR) analogous interferon beta-1a formulation Betaseron/Betaferon (FQ226 sales were likely <44M, which was the highest revenue level for which Bayer provided product-specific sales data). A first-generation interferon beta-1a branded by Bayer Healthcare & Novartis as Extavia was FDA-approved in 1993 but no longer appears to be aggressively marketed by either firm, though its prescribing information is still updated in some geographies.
- **BTK inhibitors have a mixed history as multiple sclerosis therapies, but more recent clinical studies have been more favorable, including in treating primary progressive disease.** We are intrigued by the fact that a BTK inhibitor drug – BTK is a target enzyme for many anti-cancer agents & specifically anti-B-cell lymphoma agents, the most famous of which is J&J/Pharmaceuticals' (JNJ-NY, NR) imbrutinib/Imbruvica (FQ226 sales US\$599M though down from US\$735M in FQ225), but next-generation BTK inhibitors exhibiting more selective binding to BTK & not to other tyrosine kinases include AstraZeneca's (AZN-LN, NR) acalabrutinib/Calquence (FQ226 sales US\$1.02B, up 17% y/y) & BeOne Medicine's (688235-SS, NR) zanubrutinib/Brukina (FQ226 sales US\$1.3B, of which US\$893 were US sales), followed chronologically by Eli Lilly's (LLY-NY, NR) pirtobrutinib/Jaypirco (FQ226 sales US\$192M, up from US\$123M in FQ225)
- The clinical history for BTK inhibitor drugs in multiple sclerosis is mixed, hence our interest in how Novartis was able to reverse that trend with remibrutinib/Rhapsido in Remodel-1 & Remodel-2. For example, private Swiss pharma firm EMD Serono did not achieve Phase III success with its own BTK inhibitor drug evobrutinib/M2951 in the 267-patient Phase III evolutionRM1 & evolutionRM2 relapsing remitting multiple sclerosis trials, failing to show superiority to dimethyl fumarate/Tecfidera; these data were published in Nov/24 in *Lancet Neurology* (liver toxicity was deemed intolerably as well, leading to a partial hold on the trials in Apr/23).
- But then offsetting this clinical setback was the clinical success that Swiss pharma giant Roche (ROG-SW, NR) reported in Feb/26 for its own more BTK-specific inhibitor drug fenebrutinib in the Phase III FENTrepid trial, in this case targeting primary progressive multiple sclerosis for which few if any FDA-approved therapies exist. Data from that 985-patient trial showed that fenebrutinib-treated patients performed better on reduced risk of disease progression as early as at a six-month timepoint as compared to patients treated with an alternative immunologically-active agent, Roche/Genentech's own anti-CD20 mAb ocrelizumab/ Ocrevus (Roche's best-selling Rx therapy with FH126 sales of CHF3.47B/US\$2.82B; ocrelizumab is the only FDA-approved therapy for treating primary progressive multiple sclerosis, targeting the same CD20 B-cell target as does Novartis' ofatumumab/Kesimpta, which we describe below).

Exhibit 6. Molecular Structures Of BTK Inhibitors For Which Phase III Multiple Sclerosis Testing Is Either Completed Or FDA Approvals Are Granted Already



Source: Adapted from *Molecules* (2026). Vol. 31, pp. 1272-1301; MedChemExpress

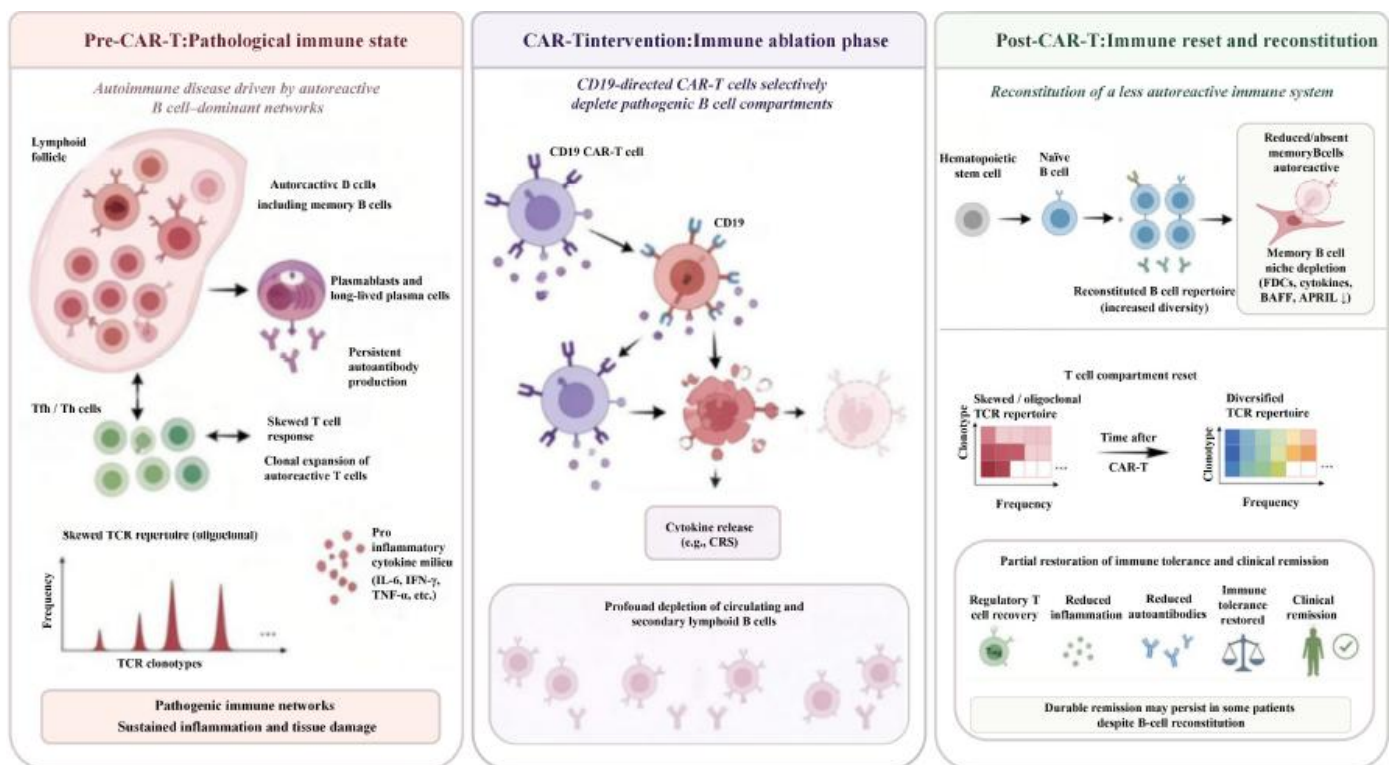
- Moreover, fenebrutinib performed well in relapsing remitting multiple sclerosis as well in the Phase III FENhance 1 & FENhance 2 trials as reported by Roche/Genentech in Apr/26. In those trials, fenebrutinib-treated patients exhibited reduced relapse rate & reduced brain lesions over 96-week follow-up by 51.1% in comparison to patients treated with an alternative multiple sclerosis drug, Sanofi/Genzyme's (SNY-NY, NR) dihydro-orotate dehydrogenase (an enzyme that is part of the pathway that generates pyrimidine nitrogenous bases that are incorporated into DNA/RNA) inhibitor teriflunomide/Aubagio (no longer one of Sanofi's best-selling Rx therapies, multiple generics approved since Nov/18). Foundational Phase II clinical data in a 106-patient relapsing remitting multiple sclerosis trial (the FENopta trial) were published in Aug/24 in *Lancet Neurology*, showing that fenebrutinib-treated patients exhibited far fewer new gadolinium-enhanced MRI-visualized brain lesions from baseline in comparison to placebo patients, hence explaining Roche's enthusiasm now known to be justified for funding fenebrutinib Phase III clinical testing in at least two multiple sclerosis forms.
- The private MA-based drug developer Zenas Biopharma (ZBIO-Q, NR) is developing its own BTK inhibitor drug orelabrutinib in multiple oncology clinical trials but in parallel, it is also funding a sizable 990-patient placebo-controlled Phase III secondary progressive multiple sclerosis trial, assessing progression over 120 weeks using the conventional expanded disability status scale (EDSS) as most multiple sclerosis trials do. Simultaneously, Zenas is funding a 705-patient placebo-controlled Phase III primary progressive multiple sclerosis trial. Final data for both studies are expected by FH230.
- **Independent of Novartis' recent Phase III remibrulinib/Rhapsido clinical success, Sanofi's tolebrutinib continues to feature prominently in its pipeline despite regulatory hurdles.** The most recent clinical success in BTK inhibitor testing in multiple sclerosis was clearly achieved by EU-based pharma giant Sanofi (SNY-NY, NR) with tolebrutinib, for which EU approval as a therapy in secondary progressive multiple sclerosis was just granted in Jun/26 based on progression data reported in the 1,131-patient Phase III HERCULES trial. FDA approval has not yet transpired however & indeed the drug was subjected to a Complete Response Letter back in late Dec/25. These data were published last year in Apr/25 in the *New England Journal of Medicine*, showing therein that tolebrutinib-treated patients exhibited a smaller proportion of patients experiencing confirmed disability progression over six-month follow-up vs placebo patients (22.6% vs 30.7%, a gap that does not on superficial inspection appear to be that large but it was statistically-significant according to the paper).
- A modest but seemingly manageable level of liver toxicity (as assessed by the amount of circulating alanine aminotransferase in blood plasma, an enzyme that normally resides in healthy liver cells & release into circulation is deemed a measure of liver cell damage) was observed in 4% of tolebrutinib patients vs 1.6% of placebo patients. Yet our review of commentary on the negative FDA review indicated above is that liver toxicity was deemed to be a limiting factor in mitigating the agency's view on tolebrutinib's approvability, a surprisingly rigid interpretation of HERCULES data in our view when considering that virtually all BTK inhibitors (many of which are FDA-approved though mostly for treating B-cell malignancies where side effect profile is held to a different standard) exhibit liver toxicity to some degree, but at least one other multiple sclerosis-targeted BTK inhibitor (EMD Serono's [private] evobrutinib/M2951, see above) was not approved not just because it underperformed teriflunomide/Aubagio but also for its liver toxicity profile.
- But a suite of next-generation immune-modulating agents have been FDA-approved specifically for treating relapsing remitting disease, which we will describe below. Other disease forms like primary progressive & secondary progressive multiple sclerosis have more limited treatment options even though one small-molecule drug - mitoxantrone/Novantrone - was actually approved for use in secondary progressive disease by Immunex (now part of Amgen; AMGN-Q, NR) & now overseen by EMD Serono. Medical evidence for its effectiveness was sufficient to support FDA approval back in 2000, based on data from a placebo-controlled 191-patient trial showing superior outcomes on the widely used EDSS measure of disease severity. EDSS is short for Kurtzke Expanded Disability Status Scale, a ten-point questionnaire that assesses muscle & neurological function & changes therein for diseased patients.
- **At its core, multiple sclerosis is a myelin sheath disruption disorder, either through autoimmune attack on the myelin sheath or through inability to repair damaged myelin sheath, or both.** At a physiological level, multiple sclerosis is a demyelination disease, a fancy way of stating that it results from absence of or damage to the myelin sheath that surrounds neurons in the body, damaging the ability of neurons to transmit electrical signals that govern multiple body functions, including muscle movement & nerve signal transmission, but also mental acuity & sensory perception (vision,

hearing, touch). The disease is frequently described as an autoimmune disorder, meaning that it arises from an individual's immune system attacking its own myelin-enwrapped neurons; while our interpretation of the autoimmune thesis is that it is only half of a diagnosis (what is causing the immune system to recognize self-myelin as a foreign body justifying attack is the other half in our view), it is nonetheless true that the vast majority of approved (& at least partially effective) therapies are immunologically active to some degree. But malfunctioning of cells that produce the myelin sheath in the first place (such cells are called oligodendrocytes) & thus could replace it when damaged is a parallel mechanism of multiple sclerosis onset – it just turns out to be easier to impede immunological pathways that break down the myelin sheath rather than to stimulate oligodendrocytes to product more myelin sheath components that have broken down. The existing multiple sclerosis pharmacopeia reflects that reality.

- **Legacy multiple sclerosis therapies sustain surprisingly robust medical traction despite emergence of novel therapies, of which BTK inhibitors is one such category.** Interferon-based Avonex/Rebif clearly are intrinsic to the immune system, released whenever the body is subjected to viral attack (they 'interfere' with viral replication, hence their name) & glatiramer acetate/Copaxone (which is a repeat sequence of the naturally-occurring amino acids glutamate, lysine, alanine & tyrosine) was designed years ago by Teva as a mimic for an amino acid sequences found within a myelin protein called myelin basic protein (MBP), diverting the immune system to target extraneously-administered glatiramer acetate instead of neuron-attached protein antigens that it was designed to imitate. Our intention here is not to dive too deep into glatiramer acetate's mechanism of action, but in brief, it has been shown in long-ago-published biochemical & preclinical murine studies that glatiramer acetate (variations on this peptide polymer were called Cop-1 in some of the early literature, from which we assume Copaxone derives its brand name) activates a category of T-cells called suppressor T-cells while competing with MBP itself for binding to the cell-surface proteins (called MHC class II proteins, short for major histocompatibility complex) that are responsible for self-recognition that would otherwise recognize MBP as self & not foreign.
- **Dimethyl fumarate (Tecfidera, Vumerity; Biogen [BIIB-Q, NR]).** Virtually all FDA-approved multiple sclerosis therapies that have been developed since have been immunologically-active to some degree & by some mechanism that either overlaps with or secondarily influences pathways through which interferon beta-1a/glatiramer acetate exert pharmacologic effects. These include Biogen's own dimethyl fumarate/BG-12 formulation Tecfidera & its next-generation prodrug form Vumerity for which total FQ226 sales were US\$287.4M (US\$196.5M of which were Vumerity global sales & US\$172M of that Vumerity's total sales were US sales). Tecfidera's mechanism of action in multiple sclerosis is a bit more indirect than the other drugs we describe above & will describe below, seemingly working through activating a protein called erythroid-derived nuclear factor-like 2 (Nrf2) that modulates oxidative stress, a mechanism that does not seem to us to be overly neuron-specific but yet the drug performed well in two separate Phase III studies, both published in Sept/12 in the *New England Journal of Medicine* showing lower proportion of dimethyl fumarate-treated patients experiencing a relapse during two year follow-up in comparison to placebo patients (26%-to-27% of drug-treated patients vs 46% of placebo patients in one of these trials).
- Dimethyl fumarate exhibited no limiting side effects in elderly MS patients in the Phase IV ESTEEM trial or the Phase III PROCLAIM trials as summarized in a 2025 paper in *Advances In Therapy*, a dataset that we suspect contributes to its sustained revenue stability. Dimethyl fumarate had no impact on primary progressive MS as shown in a 96-week 33-patient Phase II trial published in Feb/23 in the journal *Multiple Sclerosis & Related Disorders*, which is actually consistent with observations in the aforementioned Phase III studies in which relapse frequency was mitigated by drug but pace of disability progression was not.
- **Natalizumab (Tysabri; Biogen [BIIB-Q, NR]).** Biogen anti-integrin $\alpha 4$ -subunit-targeted mAb natalizumab/Tysabri (FDA-approved in 2004; FQ226 sales US\$450.8M, of which US\$270.5M were US sales) impacts immunological mechanisms in multiple sclerosis by binding to the $\alpha 4$ subunit of two different integrins called $\alpha 4\beta 1$ & $\alpha 4\beta 7$, both of which are found on all white blood cells (leukocytes) except for neutrophils. In doing, that integrin-mAb binding impedes the ability of leukocytes to bind to cells expressing integrin receptor proteins. In multiple sclerosis, this inhibition of integrin-mediated leukocyte migration impedes the ability of those cells to exert pro-inflammatory action in the brain & elsewhere that neurological function is compromised.

- **Ofatumumab (Kesimpta; Novartis [NVS-NY, NR]).** Novartis anti-CD20 mAb ofatumumab/Kesimpta (FDA-approved in 2009; FQ226 sales US\$1.4B, of which US\$942M were US sales) proposed mechanism is that by binding to CD20, a well-characterized B-cell surface marker that many anti-cancer mAbs like Roche/Genentech's (ROG-SW, NR) rituximab/Rituxan also targets, it mitigates the ability of such B-cells to attack other antigens, including those within the neuronal myelin sheath & perhaps MBP specifically. The sphingosine 1-phosphate inhibitor drug fingolimod/Gilenya was once prominent in Novartis' commercial portfolio but the firm no longer provides market commentary on the drug & it seems not to be part of its own commercial Rx portfolio for multiple sclerosis (like teriflunomide/Aubagio, fingolimod/Gilenya is genericized by multiple vendors).
- **Pharma giants Novartis (NVS-NY, NR) & Bristol Myers Squibb (BMY-NY, NR) have both paused autoimmune CAR-T cell therapy programs following serious safety events, marking the most significant setback for the extension of this already-approved genetically engineered T-cell platform from oncology into autoimmune disease.** Novartis halted eight clinical trials of rapcabtagene autoleucel (rap-cel; YTB323), its autologous CD19-directed CAR-T, on August 24 following three patient deaths attributed to immune effector cell-associated hemophagocytic syndrome (IEC-HS). BMS separately paused enrollment across its CD19 CAR-T program, zolacabtagene autoleucel (zola-cel; BMS-986353), citing "transient & reversible inflammatory events." The simultaneous pauses across two major programs, both built on rapid manufacturing platforms designed to preserve less differentiated, more proliferative T cells, raise a platform-level safety question at a moment when over 100 clinical trials are competing for overlapping autoimmune indications with functionally similar CD19-directed products.
- CAR-T cell therapy was first developed as a form of engineered immunotherapy for hematologic malignancies. A patient's T lymphocytes (white blood cells) are collected via leukapheresis, genetically modified in a laboratory to express a synthetic chimeric antigen receptor on their surface, & reinfused after a preparative course of lymphodepleting chemotherapy. The chimeric receptor combines an extracellular domain that recognizes a specific protein on the surface of target cells with intracellular signaling components that activate the T cell upon binding. Upon encountering target cells, the engineered T cells activate, proliferate, & kill through direct cytotoxic mechanisms including perforin & granzyme release.

Exhibit 7. Model Of Immune-Reset-Like Remodeling After CD-19-Directed CAR-T Therapy In Autoimmune Diseases



Source: Adapted from *Frontiers In Immunology* (2026). Vol. 17, pp. 1853170-1853177

- The platform was first validated in B-cell malignancies, where CD19, a surface protein expressed broadly across the B-cell lineage, provided a tractable target: tisagenlecleucel (Kymriah) received FDA approval in 2017 for relapsed or refractory pediatric B-cell acute lymphoblastic leukemia, & six CAR-T products directed against either CD19 or BCMA are now approved across B-cell lymphomas, leukemias, & multiple myeloma. These oncology programs established the core proof of concept: engineered T cells could be directed to eliminate an entire antigen-defined cell population with durable clinical effect.
- The extension from oncology to autoimmune disease follows a similar rationale. Many autoimmune conditions, including systemic lupus erythematosus (SLE), inflammatory myopathies, & systemic sclerosis, are driven in part by autoreactive (self-targeting) B cells that produce pathogenic autoantibodies targeting the body's own tissues. If CD19-directed CAR-T cells can eradicate malignant B-cell populations in cancer, the same approach should be capable of depleting the autoreactive B cells & antibody-secreting plasmablasts that sustain autoimmune pathology. Mougiakakos & colleagues first tested this logic in a single patient with refractory SLE (Mougiakakos & coworkers, *NEJM*, 2021), & Mackensen & coworkers subsequently demonstrated drug-free remission lasting up to 17 months in five patients treated under compassionate use, with only mild cytokine release syndrome (CRS) & no dose-limiting toxicity (Mackensen & coworkers, *Nature Medicine*, 2022).
- A follow-up case series confirmed durable responses across SLE, myositis, & systemic sclerosis (Müller & coworkers, *NEJM*, 2024). A notable observation from these early reports was that clinical remission persisted even after B cells repopulated, & that the reconstituting B-cell compartment was skewed toward naive phenotypes lacking autoreactive properties, suggesting that a single CAR-T infusion may achieve a broader immune "reset" rather than simply transient B-cell depletion. Consequently, the substantially lower infusion burden in autoimmune patients relative to hematologic malignancies was expected to translate into a more favorable safety profile, an assumption the fatal outcomes directly challenge.
- The Novartis pause covers Phase II studies of rap-cel in lupus nephritis, systemic sclerosis, ANCA-associated vasculitis, & idiopathic inflammatory myopathies, & Phase I/II studies in rheumatoid arthritis, Sjögren's disease, generalized myasthenia gravis, & multiple sclerosis. Screening, randomization, & dosing have been halted across all eight trials; patients already treated will continue protocol monitoring. The company stated that its oncology CAR-T programs, including its Phase I/II trial in CLL/SLL & DLBCL, are unaffected. BMS has provided less detail, characterizing its pause as voluntary & precautionary, with the company focused on completing its evaluation & resuming enrollment.
- The mechanism behind the observed toxicity, immune effector cell-associated hemophagocytic syndrome (IEC-HS), is distinct from the more common cytokine release syndrome (CRS). CRS typically occurs within days of CAR-T infusion, as activated CAR-T cells rapidly release inflammatory cytokines & is generally managed with tocilizumab & corticosteroids. IEC-HS tends to develop later & involves a broader, self-reinforcing immune response. According to the American Society for Transplantation & Cellular Therapy, prolonged activation of engineered T cells can strongly stimulate macrophages, another type of immune cell, which then release additional inflammatory signals including IFN- γ , IL-6, IL-18 & TNF- α (Hines & coworkers, *Transplant Cell Ther*, 2023).
- This creates a feedback loop in which T cells & macrophages continue activating one another. In severe cases, hyperactivated macrophages begin engulfing the body's own blood cells, a process called hemophagocytosis, leading to coagulopathy, liver dysfunction, & multi-organ failure. Molecular profiling of CAR-T products from oncology patients who developed the syndrome has identified upregulated interferon signaling & chromatin changes at NF- κ B & NFAT loci, suggesting that susceptibility may be partly encoded in the infused CAR-T cells even prior to administration (Frank & coworkers, *Lancet*, 2024; Frank & coworkers, *ASH*, 2024). IEC-HS is a recognized, rare, & potentially fatal class effect across approved oncology CAR-T products (Ayoobkhan & coworkers, *Blood*, 2024), but it was not expected to be a meaningful risk in autoimmune disease. CAR-T expansion is antigen-driven: each encounter with a target cell triggers activation & proliferation, so the massive malignant B-cell populations in hematologic cancers provide sustained proliferative stimulus. Autoimmune patients carry a physiologically normal or modestly elevated B-cell compartment, orders of magnitude smaller, which is depleted more rapidly & removes the proliferative stimulus earlier. Early clinical data were consistent with this logic, showing mild toxicity across the initial autoimmune case series. There also exists a risk-tolerance asymmetry; in refractory malignancy, rare fatal toxicity is weighed against near-certain death without

treatment. In contrast, the autoimmune conditions being studied, though serious & debilitating, are generally not imminently life-threatening, & existing immunosuppressive regimens offer disease control for most patients.

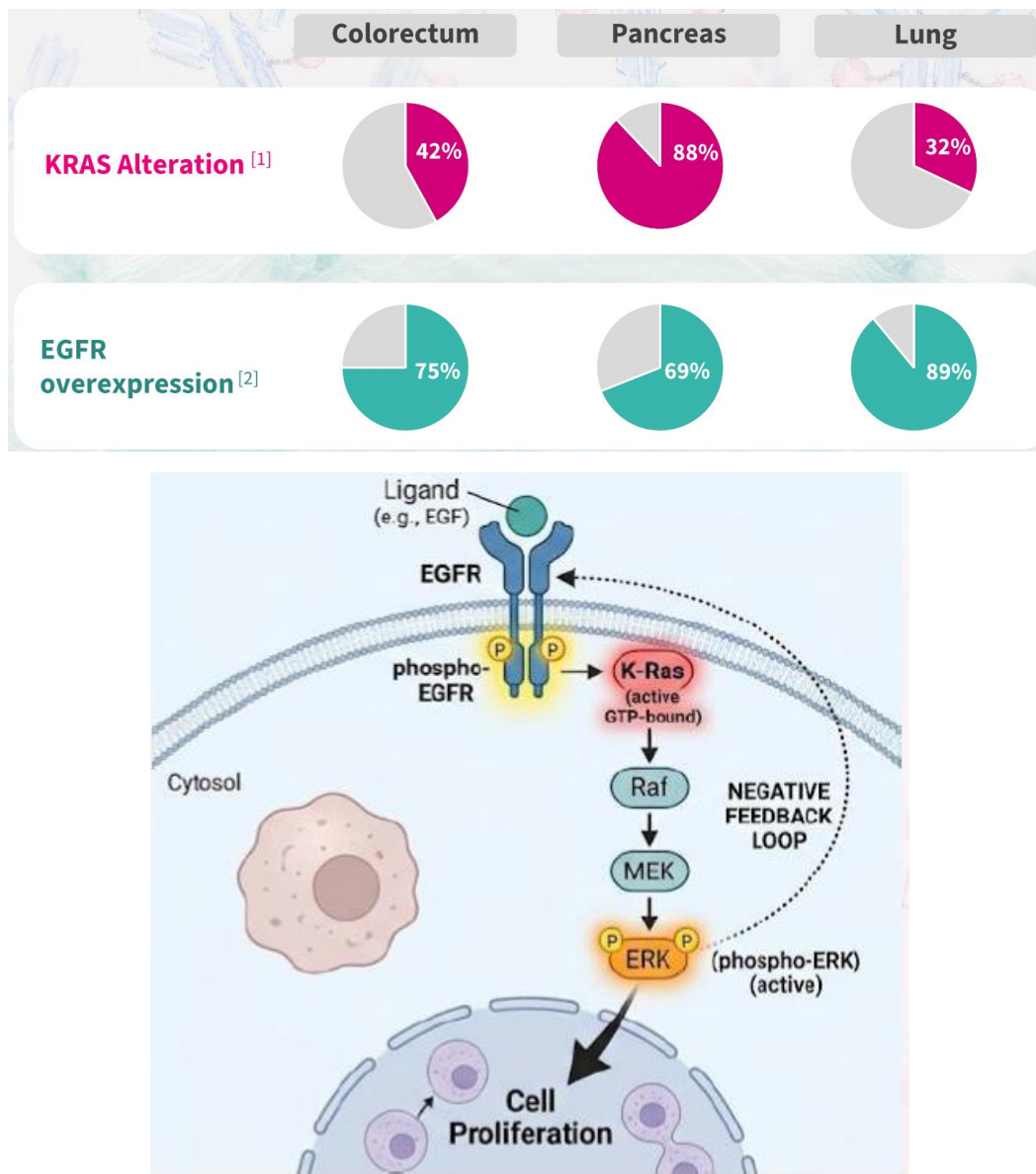
- One possible explanation for the emergence of these safety signals is the way these CAR-T products are manufactured. Novartis's T-Charge platform produces rap-cel in less than two days, minimizing the time that the cells are grown outside the body & preserving a younger, more stem-like population of T cells. These cells are designed to expand strongly after they are infused into the patient. BMS's NEX-T platform follows a similar principle, using a shortened manufacturing process intended to produce more potent T cells. The fact that both rapidly manufactured products have now shown inflammatory safety signals raises the possibility that very strong CAR-T expansion could contribute to IEC-HS. This would be consistent with oncology studies showing an association between greater CAR-T expansion & IEC-HS. However, the relationship remains speculative. Rapidly manufactured CAR-T products have also produced substantial expansion in oncology patients without frequent severe IEC-HS, suggesting that manufacturing alone is unlikely to explain the events & that the underlying disease or patient immune environment may also be important. Worth noting, leading competitors (Kyverna's miv-cel, Cabaletta's rese-cel) use conventional manufacturing.
- These safety concerns arise at a moment of significant crowding in autoimmune CAR-T development. Chen & coworkers mapped 358 trial-indication entries across 11 autoimmune diseases from an April 2026 Trialtrove snapshot, with CD19-directed programs representing the vast majority of activity (*Chen & coworkers, Frontiers in Immunology, 2026*). The most clinically advanced program is Kyverna Therapeutics' (KYTX-Q, NR) mivocabtagene autoleucel (miv-cel), which achieved statistically significant improvement across all endpoints in the registrational KYSA-8 trial in stiff person syndrome, with BLA submission planned for H1 2026 & a pathway to become the first FDA-approved CAR-T for an autoimmune indication. Cabaletta Bio (CABA-Q, NR) is targeting a 2027 BLA for its fully human CD19 CAR-T, rese-cel, in myositis following RMAT designation & FDA alignment on registrational design elements. Notably, Kyverna's lead indication, stiff person syndrome, is a genuinely underserved condition with no approved therapy & a population that historically lacked a viable treatment paradigm; the decision to pursue a registrational path in SPS rather than compete directly in the crowded SLE/SSc/myositis space illustrates how indication selection can create clinical & commercial differentiation in an otherwise saturated field.
- From a commercial standpoint, the crowding itself is the larger risk. With over 100 programs pursuing functionally similar CD19-directed approaches in overlapping indications, any class-wide safety signal disproportionately pressures the undifferentiated middle of the pack, where product differentiation is minimal & the path to market requires competing against both established immunosuppressive regimens & dozens of other CAR-T entrants simultaneously. Programs with clearer regulatory paths, including those targeting indications with no approved therapies, are better positioned to absorb a safety setback of this nature.
- **Eli Lilly (LLY-NY, NR) agreed to acquire privately held Merida Biosciences for up to US\$2.9B in cash, adding an early-stage platform designed to remove the specific antibodies that cause autoimmune & allergic diseases while leaving the rest of the antibody response intact.** Merida was seeded by Third Rock Ventures (private) in 2022 & formally launched in Apr/25 with a US\$121M Series A offering co-led by Third Rock & a syndicate of dedicated life sciences investors with which we are familiar (Bain Capital Life Sciences [BCSF-Q, NR], BVF Partners [private], Perceptive Xontogeny Venture Funds [private], GV [private]). Under the agreement, Lilly will make an undisclosed upfront payment with additional clinical, regulatory & commercial milestones bringing total potential consideration to US\$2.9B; closing is expected in Q4/26. Merida's pipeline is led by MER511 in Phase I for Graves' disease, with additional IND-enabling programs targeting IgE in allergic diseases (MER769) & PLA2R autoantibodies in primary membranous nephropathy (MER683).
- Merida's founding scientists have published minimally if at all on MER511 & its mechanism of action but we were able to glean some foundational insights from the firm's website & cross-compare details to what is published about Graves' disease pathology in general. Merida's approach is built around a relatively intuitive "decoy & dispose" mechanism. Their lead asset focuses on Graves' disease, a condition where pathogenic autoantibodies bind & activate the thyroid-stimulating hormone receptor (TSHR) on thyroid cells, driving excess thyroid hormone production.
- MER511 is engineered to mimic the part of TSHR recognized by these autoantibodies, effectively acting as a decoy that captures them in circulation before they can stimulate the thyroid. MER511 then uses a second engineered component, its Fc domain, to dispose of the captured antibodies. The Fc has been modified to preferentially bind FcγRIIB, an

inhibitory receptor highly expressed on specialized liver sinusoidal endothelial cells (LSECs) that normally clear antibody-containing immune complexes from the blood.

- Once MER511 has bound a pathogenic anti-TSHR antibody, its Fc engages FcγRIIB on these liver cells, causing the entire MER511-autoantibody complex to be internalized & broken down in lysosomes. In mice, Ganesan & colleagues found that roughly 75% of FcγRIIB was located in the liver, predominantly on LSECs, supporting the liver as a major site of FcγRIIB-mediated immune-complex clearance (*Ganesan & coworkers, Journal of Immunology, 2012*). Merida has also engineered MER511 to engage FcγRIIB on the B cells producing anti-TSHR antibodies, with the aim of suppressing production of new pathogenic antibodies. The result is a potential dual mechanism: selectively remove the existing disease-causing antibodies while also reducing their continued production, without broadly depleting protective IgG. MER511 itself is a monomeric TSHR-IgG Fc fusion protein combining the TSHR ectodomain with a mutated Fc engineered for increased FcγRIIB affinity (*Duvvuri & coworkers, Journal of the Endocrinology Society, 2025*)
- The Graves' disease landscape increasingly supports pathogenic antibody depletion as a therapeutic strategy, but competing approaches differ in how selectively they achieve it. FcRn (involved in antibody recycling) inhibitors such as Immunovant's (IMVT-Q, NR) imeroprubart & argenx's (ARGX-Q, NR) efgartigimod block the receptor that normally rescues IgG from lysosomal degradation & recycles it back into circulation. This is essentially the opposite of Fc-engineering approaches such as YTE modifications, which enhance FcRn-mediated recycling to extend antibody half-life (recall Apogee's [APGE-Q, NR] YTE modified anti-IL-13). FcRn blockade instead lowers the broader IgG pool, including protective antibodies alongside pathogenic anti-TSHR antibodies. Biohaven's (BHVN-N, NR) BHV-1300 is more selective, degrading IgG1, IgG2 & IgG4 while sparing IgG3, & has advanced into Phase III after early data showed >80% mean reduction in TSHR-IgG1. MER511 takes the selectivity thesis a step further by targeting the anti-TSHR autoantibody itself. The key question whether this greater precision can deliver comparable or deeper pathogenic antibody depletion without the broader immunoglobulin lowering inherent to FcRn or subclass-directed approaches.
- The strategic value extends beyond MER511 itself. Merida's platform is designed to pair a disease-specific "decoy" that captures a pathogenic antibody with a reusable FcγRIIB-directed clearance mechanism, theoretically allowing the same architecture to be retargeted across antibody-mediated diseases. The company is already applying this approach beyond Graves' disease to IgE in allergic disease & PLA2R autoantibodies in membranous nephropathy.
- **GSK enters a new Kras-relevant alliance with Hutchmed.** UK-based pharma giant GSK (GSK-LN, NR) just signed a US\$1.3B alliance (US\$110M in upfront cash) with Hong Kong-based drug developer Hutchmed (0013-HK, NR), ostensibly to gain rights to Hutchmed's HMPL-A830, a preclinical-stage antibody-drug conjugated targeted cytotoxic drug that targets Kras- & epidermal growth factor receptor (EGFr)-overexpressing cancer forms. The drug is comprised of an antibody component that binds to EGFr along with a small-molecule inhibitor of the Kirsten rat sarcoma (Kras) oncogene. The partners specifically identify colorectal, lung & pancreatic cancer as plausible target markets for HMPL-A830, with pancreatic cancer representing an obvious candidate indication when considering the profound clinical success from the Phase III RASolute 302 trial (data published in Apr/26) & more recent regulatory approval (in late Aug/26) success of Revolution Medicine's (RVMD-Q, NR) orally-active daraxonrasib/Rasonque, on which we have commented in prior Healthcare Weeklies.
- Hutchmed is funding an ongoing China-based 147-patient Phase II solid tumor trial for which response rate/survival data over a two-year follow-up period are expected by end-of-F2028. Hutchmed has footprints all over the medical literature with regard to Kras & associated proteins in the pathways that Kras influences, so it appears to be a solid participant in the Kras drug development universe. But at present we have no specific details on the mechanism of action of the attached cytotoxin to HMPL-A830 other than a peripheral understanding that the mAb component is EGFr-targeted & the small-molecule drug attached to it is specific for impeding Kras action. Preclinical/Phase I data on HMPL-A830 are not published, at least not by that name.
- On competitive landscape, another Asia-based drug developer Jacobia Pharmaceuticals (1167-HK, NR) is developing JAB-BX600, itself an EGFr-targeted mAb to which the Kras inhibitor drug JAB-22G82 is covalently linked. JAB-22G82 is specifically designed to inhibit only the Kras form that is dysregulated through a point mutation (a glycine-to-aspartic acid alteration at position #12 in Kras' amino acid chain). Preclinical data for this construct were published in Jul/26 in abstract form in the journal *Clinical Cancer Research*, showing tight binding specifically to mutated Kras G12D while exhibiting potent tumor shrinkage in two animal models of disease, one in colorectal cancer & another in pancreatic cancer. A formal IND filing is contemplated for end-of-F2026.

- Importantly, Jacobia has its own high-profile pharma partnership, in this case with AstraZeneca in a US\$2.0B alliance (US\$100M in upfront cash) as ascribed to a different Kras-targeted therapy called JAB-23E73. Jacobia has actually been focused for many years on Kras-targeted agents, receiving approval in China last year for glecirasib, a Kras inhibitor but one that targets a different mutated form (a glycine-to-cysteine alteration at position #12 in Kras is the relevant target protein) for which use in treating non-small cell lung cancer is the most likely medical application. Glecirasib was described in detail in a Jul/26 review in the *International Journal of Molecular Science* that we surveyed for this Kras analysis, along with another review article just published last month in the journal *Medical Oncology* in which all of these Kras molecules were described.

Exhibit 8. Mode Of Action For HMPL-AA830



Source: Adapted from GSK-Hutchmed corporate presentation (Sept/26)

- Kras is of course relevant to our investment thesis for CA-based Oncolytics Biotech (ONCY-Q, Spec Buy, PT US\$3.00) that is developing the reovirus formulation pelareorep as a therapy for solid tumors, with a legacy emphasis on metastatic breast cancer & pancreatic cancer (Phase II data are available for both indications) but with a recent strategic shift toward conducting Phase II/III testing in second-line Kras-mutated microsatellite-stable metastatic colorectal cancer for which a 60-patient Phase II trial testing pelareorep in combination with the small-molecule combination therapy FOLFIRI (nucleoside analog 5-fluorouracil, folic acid analog leucovorin, DNA topoisomerase I inhibitor

irinotecan) & bevacizumab/Avastin commenced last quarter & for which final response rate/survival data are expected in early F2030. Second line anal cancer is a plausible secondary market for the firm to pursue based on pelareorep's clinical history in the indication & its sparing suite of therapeutic options at present. First-line advanced pancreatic cancer testing still ongoing in the firm's Phase II 122-patient GOBLET trial, combining pelareorep with Roche's anti-PD-L1 mAb atezolizumab/Tecentriq. Our ONCY investment thesis & valuation are unchanged.

- **Novartis (NVS-NY, NR) enters licensing agreement with South Korea's Alteogen (196170-KQ, NR) for rights to ALT-B4 (berahyaluronidase alfa), a proprietary recombinant human hyaluronidase used for converting intravenous drugs into subcutaneously-deliverable drugs.** Under the terms of the US\$3.2B deal Novartis obtains multiple options to acquire exclusive rights to develop & commercialize subcutaneous (SC) formulations across several Novartis products using ALT-B4. The headline figure includes option exercise fees, development & commercial milestone payments, & royalties on net sales of commercialized products. Alteogen's press release discloses no upfront payment, consistent with the option-based structure; for reference, comparable single-product Alteogen deals with GSK/Tesaro & Biogen earlier this year each carried US\$20M upfronts
 - The deal reflects a broader industry push to convert intravenously administered biologics (usually performed at infusion clinics or hospitals) into subcutaneous formulations. As biologic therapies have grown in popularity, particularly in oncology & immunology, the practical limitations of IV infusion are a growing friction point: infusions require dedicated clinical settings, trained nursing staff, & 30 minutes to several hours of chair time per administration cycle, all of which constrain throughput, drive healthcare costs, & burden patients with repeated facility visits. SC delivery compresses administration to minutes, opens the door to home-based or community clinic settings, & in principle improves treatment compliance. SC injections are typically limited to roughly 1.5 to 2 mL in volume, & many biologic doses require protein concentrations that, in conventional aqueous formulation, produce viscosities too high for practical injection. Solving this constraint, whether by enzymatic tissue modification or formulation engineering, has become a high-value platform opportunity.
 - We have touched on the drug delivery sector in previous weeklies through our coverage of Halozyme Therapeutics (HALO-Q, NR) & its Elektrofi acquisition; the Novartis-Alteogen deal adds a significant competitive dimension to that landscape. ALT-B4 & Halozyme's rHuPH20 (ENHANZE platform) address the same biophysical barrier. Hyaluronan (HA) is a major structural component of the subcutaneous extracellular matrix, where it limits bulk fluid dispersion & restricts the volume of drug that can be administered by injection. Both platforms employ recombinant human PH20-class hyaluronidases that temporarily depolymerize HA by hydrolyzing the beta-1,4 glycosidic linkage between N-acetylglucosamine & glucuronic acid, transiently increasing tissue permeability & enabling large-volume SC delivery of biologics that would otherwise require IV infusion.
 - The enzymatic effect is local & reversible, with tissue HA fully reconstituted within 24 to 48 hours (Frost as published in *Expert Opinion In Drug Delivery*, 2007). Although both enzymes derive from the same human PH20 gene product, Alteogen maintains that ALT-B4 is structurally & patentably distinct from Halozyme's modified hyaluronidases, something that is actually in the center of active litigation. Halozyme sued Merck (MRK-NY, NR) in April 2025 in the U.S. District Court for the District of New Jersey, alleging Keytruda SC (Keytruda Qlex, which uses ALT-B4) infringes 15 patents in Halozyme's MDASE portfolio. The patent dispute remains unresolved.
 - The commercial case for SC reformulation is strong. Keytruda Qlex, approved in September 2025 & the highest-profile product utilizing Alteogen's ALT-B4, generated US\$463 million in Q2 2026 sales, a 3.6-fold sequential increase that brought the SC formulation to a double-digit share of U.S. Keytruda volume within less than a year of launch. Merck CFO Caroline Litchfield indicated the company targets 30% to 40% SC adoption by end of 2027. That uptake curve is commercially significant: it demonstrates that prescribers & payers are willing to adopt SC alternatives rapidly when the PK bridging data supports non-inferior systemic exposure, even at price parity. For oncology specifically, the shift from 30-minute IV infusions to 1- to 2-minute SC injections compresses chair time, reduces infusion-related resource utilization, & opens additional care settings, all of which support payer & institutional preference.
 - **Read-through to Eupraxia Pharmaceuticals (EPRX-Q, Buy, PT US\$15.50).** The Novartis-Alteogen transaction provides yet another datapoint in support for the premium valuations that cash-contributing partners are ascribing to differentiated drug delivery platforms. Eupraxia's Diffusphere technology is mechanistically distinct from the SC reformulation platforms discussed above: where Alteogen & Halozyme solve the problem of converting IV biologics to

SC systemic delivery, Diffusphere enables sustained, tissue-targeted local release of active pharmaceutical ingredients (beginning with EP-104GI, a budesonide formulation in eosinophilic esophagitis). The investment thesis is different in kind, but the valuation signal from the broader delivery sector is directionally relevant. Multi-billion-dollar deal values for platform-stage delivery companies (Alteogen, Elektrofi, Lindy, Capstan Therapeutics) confirm that pharma acquirers & licensees are willing to pay substantial premiums for technologies that improve the therapeutic index through better delivery, whether that takes the form of convenience (IV-to-SC conversion), targeting (tissue-specific release), or both. Eupraxia currently pursues a proprietary development model rather than a licensing strategy, which concentrates risk & reward differently than Alteogen's or Halozyme's royalty-driven business models, but the sector-wide deal flow does establish a favorable operating environment for delivery-focused companies advancing toward pivotal data.

Capital Markets Summary

Exhibit 9. EBITDA Or EPS-Positive Canadian Healthcare Stocks

Company	Filing Curr.	Sym.	Shrs Out. (M)	Share Price 3-Sep	Mkt Cap (M)	Mkt Cap (C\$M)	Ent. Value (M)	Ent. Value (C\$M)	EV/EBITDA			Price/Earnings		
									(T12M)	FY1	FY2	(T12M)	FY1	FY2
Profitable Canadian healthcare firms - specialty services ^{2,4}														
DRI Healthcare Trust	CAD	DHT.UN	55.0	\$17.66	971	971	1,503	1,503	6.1x	6.3x	7.1x	NA	7.0x	7.6x
Jamieson Wellness	CAD	JWEL	41.5	\$45.74	1,898	1,898	2,379	2,379	14.4x	13.2x	12.0x	24.3x	21.2x	18.8x
K-Bro Linen	CAD	KBL	13.0	\$45.12	587	587	880	880	7.6x	8.0x	7.6x	26.7x	22.1x	18.0x
Medical Facilities ¹	CAD	DR	16.2	\$10.96	178	246	317	438	5.5x	5.3x	12.8x	15.7x	6.0x	14.4x
Microbix Biosystems	CAD	MBX	137.2	\$0.29	39	39	38	38	NA	NA	NA	NA	NA	NA
Savaria	CAD	SIS	72.1	\$28.25	2,038	2,038	2,193	2,193	11.3x	10.7x	9.7x	23.1x	20.4x	17.9x
Profitable Canadian healthcare firms - specialty pharmaceuticals development/sales ²														
Apotex	CAD	APTX	228.5	\$32.62	7,454	7,454	11,940	11,940	NA	NA	11.7x	NA	NA	14.9x
Aurinia Pharma	USD	AUPH	133.1	\$16.17	2,151	2,979	2,297	3,179	9.5x	NA	NA	6.8x	17.1x	13.7x
Bausch Health	USD	BHC	374.0	\$6.89	2,577	3,567	31,187	43,169	5.6x	5.6x	6.0x	NA	1.5x	1.7x
BioSynt	CAD	RX	11.5	\$14.75	170	170	172	172	13.3x	10.8x	9.2x	18.4x	16.6x	13.7x
Cipher Pharma ¹	CAD	CPH	25.4	\$10.50	267	370	420	581	15.2x	14.1x	12.0x	9.2x	13.0x	10.9x
HLS Therapeutics ¹	CAD	HLS	30.9	\$2.61	81	112	173	239	10.3x	8.7x	7.5x	NA	NA	NA
Knight Therapeutics	CAD	GUD	98.2	\$9.82	965	965	836	836	8.5x	10.0x	9.5x	NA	NA	40.5x
Medexus Pharma ¹	CAD	MDP	32.0	\$3.78	121	167	181	250	10.5x	11.4x	8.4x	50.2x	NA	13.8x
Profitable Canadian healthcare firms - eldercare services or infrastructure developers														
CareRx	CAD	CRRX	63.5	\$3.17	201	201	268	268	8.7x	7.8x	6.8x	7.4x	36.2x	15.6x
Chartwell Retirement	CAD	CSH.UN	328.3	\$21.08	6,920	6,920	10,087	10,087	22.2x	19.8x	17.8x	NA	NA	NA
Extendicare	CAD	EXE	95.0	\$31.39	2,984	2,984	3,516	3,516	15.9x	13.9x	12.2x	23.7x	22.9x	20.7x
Vital Infrastructure	CAD	VITL.UN	250.0	\$5.50	1,375	1,375	2,569	2,569	12.8x	12.1x	12.1x	NA	NA	NA
Nova Leap Health	CAD	NLH	87.3	\$0.50	43	43	47	47	13.4x	NA	NA	32.1x	NA	NA
Sienna Senior Living	CAD	SIA	110.8	\$21.78	2,413	2,413	3,599	3,599	21.5x	17.7x	15.6x	41.5x	40.3x	34.6x
Profitable Canadian healthcare firms - medical equipment distribution/sales ³														
Covalon Technologies	CAD	COV	27.6	\$2.05	57	57	65	65	13.2x	10.6x	9.3x	12.9x	12.1x	10.3x
Viemed Healthcare	USD	VMD	38.1	\$11.88	452	452	468	648	6.0x	5.1x	4.4x	31.4x	28.0x	20.0x
Profitable Canadian healthcare firms - healthcare IT or digital IT services firms ⁵														
Healwell AI	CAD	AIDX	304.6	\$0.80	244	244	288	288	NA	38.9x	20.0x	NA	NA	NA
Hydreight	CAD	NURS	53.7	\$3.91	210	210	194	194	39.6x	8.5x	5.3x	46.3x	13.0x	7.7x
Vitalhub	CAD	VHI	63.4	\$7.91	502	694	368	368	12.5x	10.7x	8.9x	NA	42.1x	22.6x
Well Health	CAD	WELL	255.5	\$4.51	1,152	1,152	2,022	2,022	9.6x	10.7x	9.8x	NA	17.8x	12.6x
Average									12.7x	11.8x	10.2x	24.6x	19.8x	16.5x
Recently-acquired Canadian healthcare firms														
Andlauer	CAD	AND	39.2	\$54.97	2,152	2,152	2,165	2,165	13.4x	NA	NA	32.0x	NA	NA
Dentalcorp Holdings	CAD	DNTL	192.0	\$11.00	2,112	2,112	3,112	3,112	10.9x	NA	NA	NA	NA	NA
Kneat.com	CAD	KSI	96.7	\$6.50	628	868	604	604	NA	34.1x	22.4x	NA	NA	NA
Quipt Home Medical	USD	QIPT	44.5	\$3.65	162	223	235	323	5.4x	NA	NA	2.1x	NA	NA
Theratechnologies	CAD	TH	46.0	\$4.47	206	206	238	238	12.3x	NA	NA	NA	NA	NA

¹ Share price converted to USD for stocks reporting financial data in USD but for which share value is reported in CAD

² Theratechnologies (TH-T) acquired in Sept/25 by CB Biotechnology/Future Pak for US\$4.20/shr; Andlauer's acquisition by UPS (UPS-NY, NR) closed in Nov/25

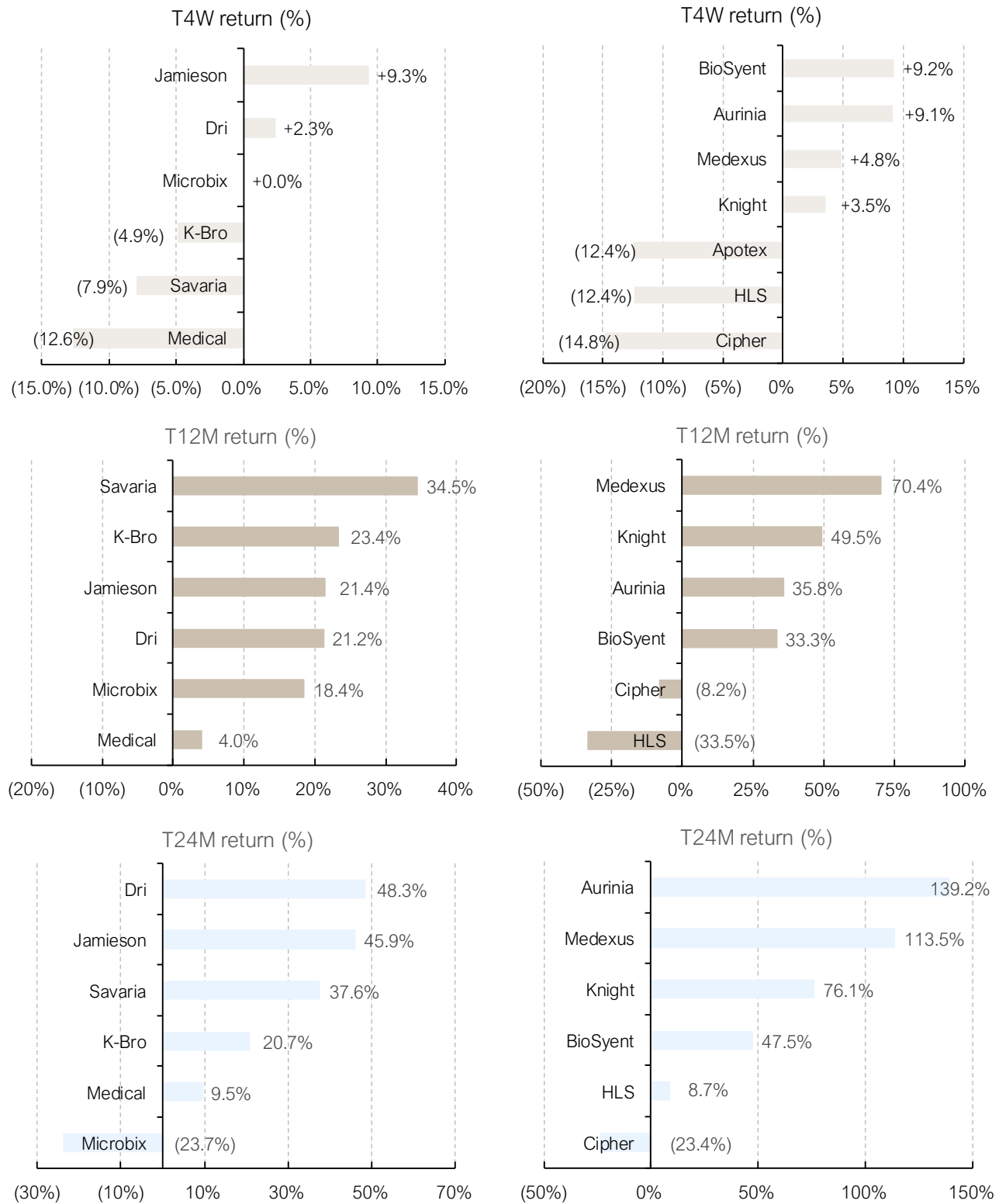
³ Quipt Home Medical was acquired by Kingswood Capital & Forager Capital for US\$3.65/shr in Dec/25, transaction closed in Mar/26

⁴ Dentalcorp Holdings was acquired by US private equity firm GRRCR LLC in Sept/25 for an EV of C\$3.3B (market value C\$2.1B); transaction closed in Jan/26

⁵ Kneat.com was bid to be acquired in Jun/26 by Thoma Bravo LP for C\$650M; transaction closed in Aug/26

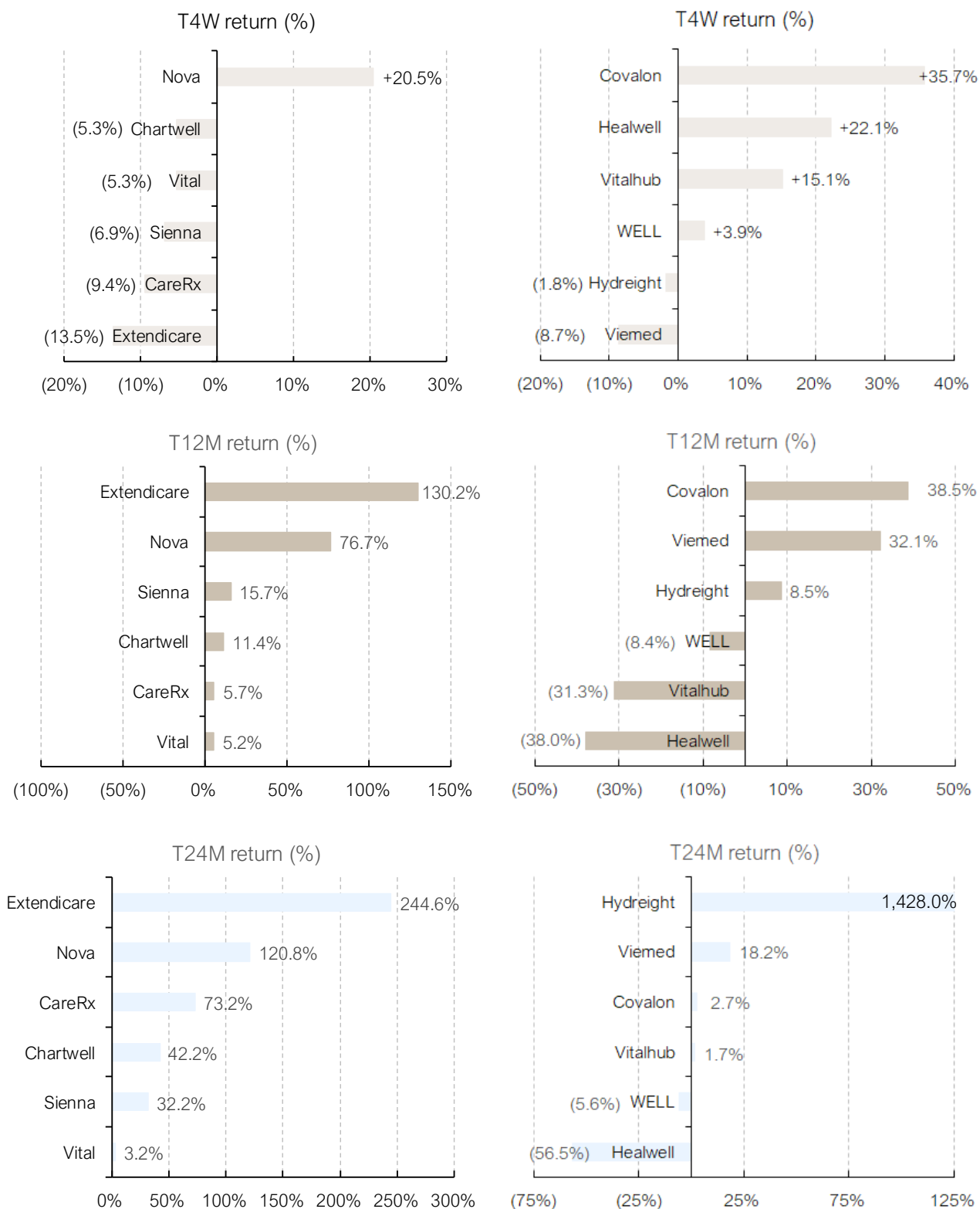
Source: Refinitiv, company reports, Leede Financial

Exhibit 10. Trailing Four-Week, One-Year & Two-Year Relative Share Price Performance For EBITDA/EPS-Positive Canadian Healthcare Equities – Specialty Services & Specialty Pharmaceutical Firms



Source: Refinitiv, company reports, Leede Financial

Exhibit 11. Trailing Four-Week, One-Year & Two-Year Relative Share Price Performance For EBITDA/EPS-Positive Canadian Healthcare Equities – Eldercare Services & Medical Technology Distribution/Healthcare IT Services



Source: Refinitiv, company reports, Leede Financial

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RECOMMENDATION	NO. OF COMPANIES	%
Buy	9	60%
Speculative Buy	4	26%
Hold	1	7%
Sell	-	-
Tender	-	-
Under Review	1	7%

Historical Target Price

Appili Therapeutics APLI-TSXV	None
Cardiol Therapeutics CRDL-TSX, NASDAQ	None
CareRx CRRX-TSX	None
Cipher Pharmaceuticals CPH-TSX	None
Eupraxia Pharmaceuticals EPRX-TSX, NASDAQ	None
Extendicare EXE-TSX	None
K-Bro Linen KBL-TSX	None
Medexus Pharmaceuticals MDP-TSX	None
Medical Facilities DR-TSX	None
Nanalysis Scientific NSCI-TSXV	None
Oncolytics Biotech ONCY-NASDAQ	None
Perimeter Medical Imaging PINK-TSXV	None
Profound Medical PRN-TSX, PROF-NASDAQ	None
ProMIS Neurosciences PMN-NASDAQ	2
Satellos Biosciences MSCL-TSX	2