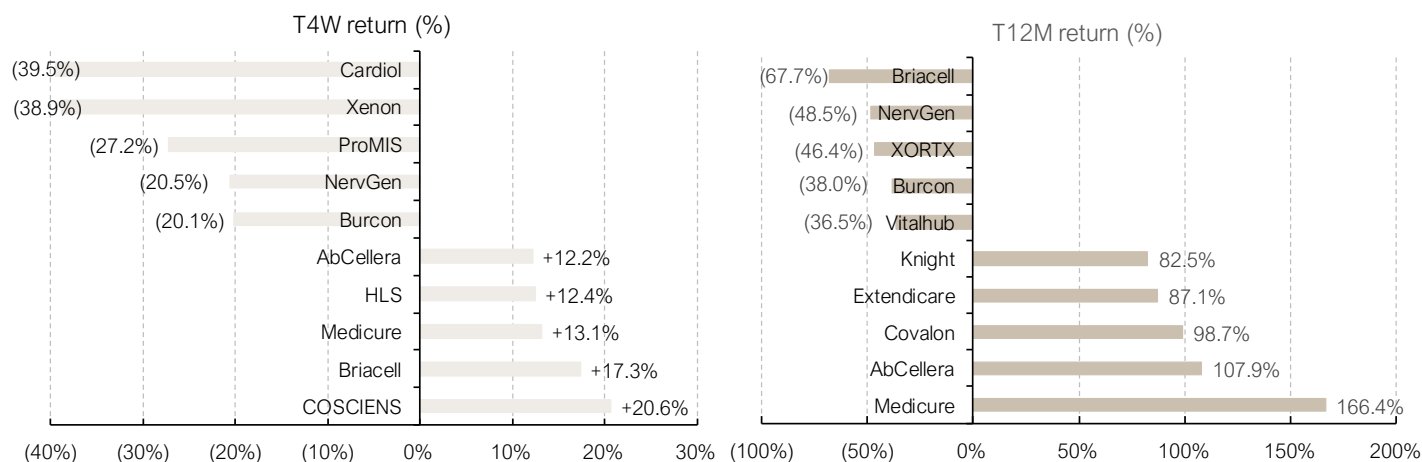


Core Highlights of the Week

Top Movers

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



Source: Leede Financial, Refinitiv

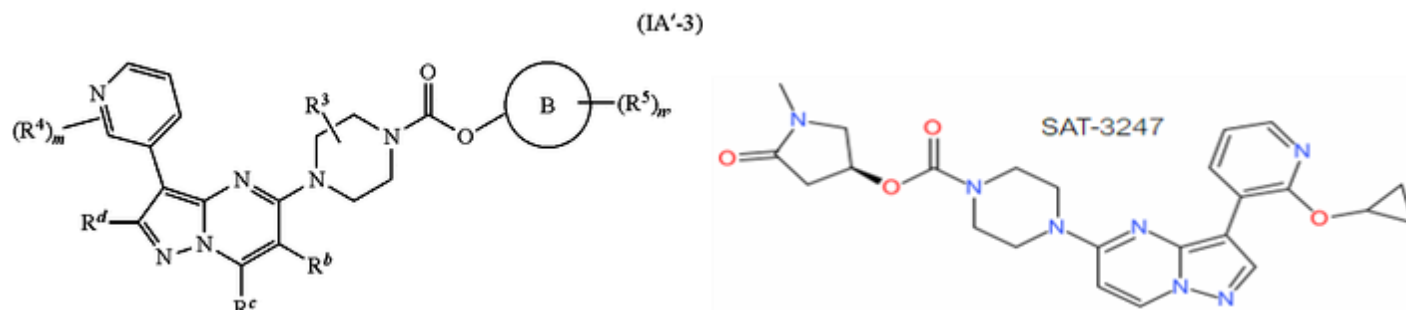
Updates From Our Healthcare Coverage Universe

- Satellos receives formal issuance of a flagship US patent describing composition of matter for SAT-3247.** ON-based muscle regeneration-focused small-molecule developer Satellos Bioscience (MSCL-T/MSLE-Q, Spec Buy, PT US\$16.00) was just issued a new US patent (US#12,745,245) entitled 'AP2 Associated Kinase 1 Inhibitors & Uses Thereof' that describes the molecular structure (or at least, the range of possible molecular structures based on a foundational nitrogen heterocycle backbone) of the firm's lead AAK1 inhibitor drug SAT-3247. The structural details of what SAT-3247 could be were already described in an earlier US patent application filed in Sept/24 that we assume forms the basis for the US patent now formally issued.
- In our original report, we described that patent filing & the insights we could glean on SAT-3247 plausible pharmacology, with those details now a bit clearer in our conceptualization of SAT-3247's molecular details. In an earlier Healthcare Weekly, we formally published SAT-3247's specific structure as put into the public domain by a chemistry information website, but to our knowledge, Satellos has not yet formally presented SAT-3247's structure (or details for any of the related compounds that it may have tested pharmacologically in the process of selecting SAT-3247 as a lead AAK1-inhibiting, muscle progenitor cell asymmetric division-driving molecular entity) in the peer-reviewed medical literature.
- A new patent issuance does not typically move the needle on our investment thesis or valuation of a clinical-risk equity & we will not be revising our valuation for Satellos in this circumstance either. But it is certainly positive for the firm to receive formal issuance of a composition of matter patent since it sets in motion the duration over which the molecule if eventually FDA-approved will be protected from generic competition – the patent was originally filed in Sept/24 (we described structural details that we could infer from this filing in our original Satellos report) & so its duration of exclusivity extends to Sept/44 (twenty years after patent filing), independent of any other supplemental patents that Satellos may file in coming quarters either in the US or other geographies where the firm (or its notional acquirers) could conceivably launch SAT-3247 into the Duchenne muscular dystrophy (DMD) medical market (or perhaps the related facio-

Please see end of report for important disclosures.

scapulohumeral muscular dystrophy [FSHD] medical market) in time. Our model assumes that SAT-3247 could conclude pivotal Phase III DMD testing by end-of-FH229 & be FDA-approved/launched by FH230. The molecule was most recently described in an abstract published this month in the journal *Neuromuscular Disorders*, but no structural information was provided therein.

Exhibit 2. Molecular Structure For SAT-3247, Both As Conceptualized In Satellos' Newly-Issued US Patent & As Archived From Secondary Sources To Which We Referred In Prior Healthcare Weeklies



Source: US Patent & Trademark Office; IUPHAR/BPS Guide to Pharmacology

- As shown in Exhibit 2, the core backbone of nitrogen-containing cyclic organic moieties is preserved in the described chemistry in the issued US patent & in SAT-3247, with the R4 component known to be a cyclopropane oxide group while the R5 component is a tertiary five-membered nitrogen-containing cyclic ketone.

Exhibit 3. Income Statement & Financial Forecast Data For Satellos Bioscience, F2026E-to-F2035E

Year-end December 31 (US\$000, exc share data)	2027E	2028E	2029E	2030E	2031E	2032E	2033E	2034E	2035E	2036E	2037E	2038E
SAT-3247 royalty revenue, US	\$0	\$0	\$0	\$31,455	\$63,287	\$84,889	\$106,748	\$128,866	\$151,246	\$163,021	\$174,933	\$186,981
SAT-3247 royalty revenue, EU	\$0	\$0	\$0	\$0	\$39,635	\$80,063	\$107,818	\$136,120	\$164,978	\$194,399	\$210,367	\$226,635
Total SAT-3247 revenue	\$0	\$0	\$0	\$31,455	\$102,922	\$164,952	\$214,566	\$264,986	\$316,223	\$357,420	\$385,300	\$413,616
Revenue growth (%)	NA	NA	NA	NA	227%	60%	30%	23%	19%	13%	8%	7%
R&D, clinical expenses	\$22,500	\$22,500	\$15,000	\$14,155	\$12,351	\$8,248	\$7,510	\$7,420	\$7,906	\$7,148	\$6,935	\$6,204
G&A, marketing expenses	\$5,250	\$5,500	\$6,000	\$8,176	\$9,547	\$10,287	\$10,112	\$11,194	\$11,705	\$12,322	\$12,611	\$12,803
Other expenses	\$0	\$0	\$0	\$0	\$0	\$0	\$0	\$0	\$0	\$0	\$0	\$0
EBITDA	(\$27,750)	(\$28,000)	(\$21,000)	\$9,124	\$81,025	\$146,417	\$196,944	\$246,372	\$296,612	\$337,949	\$365,753	\$394,609
EBITDA growth (%)	NA	NA	NA	NA	788%	81%	35%	25%	20%	14%	8%	8%
EBITDA margin (%)	NA	NA	NA	29%	79%	89%	92%	93%	94%	95%	95%	95%
Non-operating expenses	\$1,260	\$1,260	\$1,260	\$1,260	\$1,260	\$1,260	\$1,260	\$1,260	\$1,260	\$1,260	\$1,260	\$1,260
EBIT	(\$29,010)	(\$29,260)	(\$22,260)	\$7,864	\$79,765	\$145,157	\$195,684	\$245,112	\$295,352	\$336,689	\$364,493	\$393,349
Other non-oper expenses	(\$1,538)	(\$1,576)	(\$1,615)	(\$1,656)	(\$1,697)	(\$1,740)	(\$1,783)	(\$1,828)	(\$1,873)	(\$1,920)	(\$1,968)	(\$2,017)
EBT	(\$27,473)	(\$27,684)	(\$20,645)	\$9,519	\$81,462	\$146,897	\$197,467	\$246,940	\$297,226	\$338,609	\$366,462	\$395,367
Tax expense, other	\$0	\$0	\$0	\$2,380	\$20,365	\$36,724	\$49,367	\$61,735	\$74,306	\$84,652	\$91,615	\$98,842
Net income, fully-taxed	(\$27,473)	(\$27,684)	(\$20,645)	\$7,140	\$61,096	\$110,173	\$148,100	\$185,205	\$222,919	\$253,957	\$274,846	\$296,525
Fully-taxed EPS (basic)	(\$1.32)	(\$1.28)	(\$0.95)	\$0.33	\$2.82	\$5.09	\$6.84	\$8.55	\$10.29	\$11.72	\$12.69	\$13.69
Fully-taxed EPS (fd)	(\$1.19)	(\$1.16)	(\$0.87)	\$0.30	\$2.56	\$4.62	\$6.21	\$7.76	\$9.34	\$10.64	\$11.52	\$12.43
P/E (basic)	NA	NA	NA	19.1x	2.2x	1.2x	0.9x	0.7x	0.6x	0.5x	0.5x	0.5x
EV/EBITDA	NA	NA	NA	2.9x	0.3x	0.2x	0.1x	0.1x	0.1x	0.1x	0.1x	0.1x
S/O, basic (M)	20,831	21,665	21,665	21,665	21,665	21,665	21,665	21,665	21,665	21,665	21,665	21,665
S/O, fd (M)	23,026	23,859	23,859	23,859	23,859	23,859	23,859	23,859	23,859	23,859	23,859	23,859

Source: Satellos Bioscience financial filings; Leede Financial

- Summary & valuation.** We are maintaining our Speculative Buy rating & one-year PT of US\$16.00 on MSCL/MSLE, with our valuation still based on NPV (30% discount rate, comparable to the rate we embed in clinical-risk coverage stocks at Phase II stage of development) & multiples of our F2031 EBITDA/fd EPS forecasts (US\$81.0M & US\$2.56/shr, respectively). Our EV calculation incorporates FQ226 cash of US\$61.8M, excluding the US\$5.0M grant funding announced last week from FSHD Canada Foundation funding that we expect to be paid to Satellos not as an upfront payment but on a more protracted payment schedule, no LT debt, & fd S/O of 23.0M.

Exhibit 4. Comparable Companies In The Duchenne Muscular Dystrophy Drug Development Universe For Satellos

Company	Curr	Sym	Shares out (M)	Share price 8-Oct	Mkt Cap (\$M)		Ent Val (\$M)		Company description
					(curr)	(C\$)	(curr)	(C\$)	
Duchenne Muscular Dystrophy-focused therapy developers - Exon-Skipping Or RNA/Antisense Technologies									
BioMarin Pharmaceutical Inc.	USD	BMRN	193.6	\$55.20	\$10,685	\$15,231	\$19,952	\$28,439	CA-based rare disease-focused drug developer; lead DMD antisense drug BMN 351 in Italy-based 18-patient Phase II testing, data expected by H127
Sarepta Therapeutics, Inc.	USD	SRPT	105.6	\$17.50	\$1,848	\$2,635	\$2,719	\$3,876	Three approved antisense therapies targeting genetic variants of DMD (Exondys 51, Vyondys 53, Amondys 45); Roche-partnered approved adenovirus-based gene therapy (Elevidys); FQ226 sales US\$328.7M
Wave Life Sciences Ltd.	USD	WVE	197.0	\$3.54	\$698	\$994	\$295	\$420	Exon 53-skipping antisense therapy WVE-N531; 48-week Phase II (Forward-53 trial) data in Mar/25; dystrophin express up 7.8%, 88% of pts over threshold of 5%; final data in H127
Duchenne Muscular Dystrophy-focused therapy developers - Adenovirus (AAV)-Based Gene Delivery Technologies									
Hansa Biopharma AB	SEK	HNSA	101.8	SEK 33.38	SEK 3,397	\$506	SEK 552	\$82	SRP-9001-104 trial; Sarepta-partnered pre-treatment with imlifidase/Ideferix (cleaves IgG, mitigates immune response to adenovirus vectors) prior to gene therapy with SRP-9001/Elevidys; Phase I testing is ongoing
REGENXBIO Inc.	USD	RGNX	66.0	\$7.60	\$501	\$715	\$823	\$1,173	AAV-based gene therapy RGX-202 encodes C-terminal domain of micro-dystrophin; Phase I/II data from five patients (Nov/24) in 15-patient AFFINITY DUCHENNE trial, data by mid-2028
Solid Biosciences Inc	USD	SLDB	107.2	\$6.85	\$734	\$1,047	\$509	\$725	AAV-based gene therapy SGT-003 in 43-patient Phase I/II INSPIRE DUCHENNE trial, data by mid-2027, microdystrophin expression observed in mdx mouse, targets cardiac & skeletal muscle with minimal liver targeting; proprietary capsid AAV-SLB101 is vector
Average					\$3,521		\$5,786		
Duchenne Muscular Dystrophy-focused therapy developers - Small Molecule Or Other Technologies									
Capricor Therapeutics, Inc.	USD	CAPR	58.1	\$8.10	\$471	\$671	\$332	\$473	Deramiciol (CAP-1002; exosome-secreting allogeneic cardio-sphere-derived cell therapy); 106-patient Phase III HOPE-3 trial (Lancet, Jul/26), negative FDA advisory committee vote in Jul/26
Dyne Therapeutics, Inc.	USD	DYN	186.7	\$15.97	\$2,982	\$4,251	\$3,278	\$4,673	DYNE-251 (z-rostudirsén) in 86-patient Phase II (DELIVER) trial, projects early BLA filing by Q226
Edgewise Therapeutics, Inc.	USD	EWTX	108.6	\$39.57	\$4,297	\$6,126	\$5,469	\$7,795	CO-based sevasesmen (EDG-5506) developer, in Phase II testing for Becker/Duchenne muscular dystrophy; Phase II LYNX trial, data in early F2027
PTC Therapeutics, Inc.	USD	PTCT	83.5	\$63.23	\$5,277	\$7,522	\$8,505	\$12,123	Emflaza/deflazacort (corticosteroid; FQ226 sales US\$24.6M vs US\$36.4M last year), Translarna/ataluren (RNA therapy; FQ226 sales US\$42.2M vs US\$59.5M last year)
Santhera Pharmaceuticals	CHF	SANN	15.9	CHF 14.14	CHF 225	\$391	CHF 431	\$748	Developed corticosteroid vamorolone/Agamree (Catalyst holds US rights, Kye Pharma holds Cdn rights)
Rare Disease Drug Developers									
BridgeBio Pharma, Inc.	USD	BBIO	195.5	\$66.50	\$13,000	\$18,531	\$22,299	\$31,786	Rare diseases; Nulibry (2021; molybdenum cofactor deficiency Type A), Attruby (2024; ATTR-cardiac amyloidosis)
Traverse Therapeutics, Inc.	USD	TVTX	94.3	\$53.44	\$5,037	\$7,180	\$7,342	\$10,465	Filspari/sparesentan FDA-approved in Sept/24 for kidney disease (IgA Nephropathy); endothelin-angiotensin II receptor antagonist
Ultragenyx Pharmaceutical Inc.	USD	RARE	98.6	\$14.89	\$1,468	\$2,092	\$3,313	\$4,722	Five product approvals in rare diseases, including Dojolvi (trihexetanoin; long-chain fatty acid oxidation disorders), Mepsevii (recombinant beta-glucuronidase/vestronidase; mucopolysaccharidosis VII)
Average					\$3,315		\$5,220		
Satellos Bioscience Inc.	USD	MSLE	20.8	\$7.63	\$159	\$227	\$149	\$212	Lead AAK1 inhibitor drug SAT-3247 in Phase I/II testing for Duchenne muscular dystrophy (DMD)
Amicus Therapeutics	USD	FOLD	Targets Fabry disease (Galafold/migalastat; chaperones alpha-galactosidase A to lysosomes; approved in 2018) & Pompe disease (Pombiliti-Opfolda/ miglustat; recombinant glucosidase alpha enzyme stabilizer; approved in 2023); acquired by BioMarin for US\$4.8B in Dec/25						
Apellis Pharmaceuticals	USD	APLS	Empaveli/pegcetacoplan (PEGylated pentadecapeptide); complement C3 inhibitor, targets paroxysmal nocturan hemoglobinuria (PNH); acquired by Biogen for US\$5.6B in May/26						

Source: Refinitiv, Leede Financial

- As before, we base our forecasts on notional fd S/O of 23.9M which assumes that Satellos could consummate supplemental equity offerings to fund SAT-3247 to FDA approval in pediatric/adult Duchenne muscular dystrophy. Satellos intention to commence testing in a related but the distinct muscle degeneration disorder FHSD (fasio-scapulohumeral muscular dystrophy) is a positive advance in our view & SAT-3247 certainly has a scientific rationale

for being relevant to FHSD muscle regeneration, but for now, our PT/valuation are exclusively focused on DMD as a flagship indication. As indicated above, our investment thesis is now squarely focused on TRAILHEAD/BASECAMP final data, for which we have high visibility on timelines to data at least for BASECAMP in F2027.

Exhibit 5. Valuation Scenarios for Satellos Bioscience

NPV, discount rate		20%	25%	30%	35%	40%
Implied value per share		\$35.77	\$22.70	\$14.55	\$9.04	\$5.46
Price/earnings multiple, 2031E		20%	25%	30%	35%	40%
Implied share price ^{1,2}	10	\$12.35	\$10.49	\$8.97	\$7.71	\$6.67
	20	\$24.70	\$20.98	\$17.93	\$15.42	\$13.33
	30	\$37.05	\$31.47	\$26.90	\$23.13	\$20.00
EV/EBITDA multiple, 2031E		7.5x	10x	12.5x	15x	17.5x
Implied share price ^{1,2}		\$9.83	\$12.80	\$15.77	\$18.74	\$21.72
One-year MSCL target price (US\$) ^{1,2}				\$16.08		

¹ Based on F2031 fd fully-taxed EPS of US\$2.56; EBITDA of US\$81.0M, discounted at 30%, current basic S/O post-consol, post Feb/26 equity offering of 20.8M, FD S/O of 23.0M (excluding pre-funded warrants)

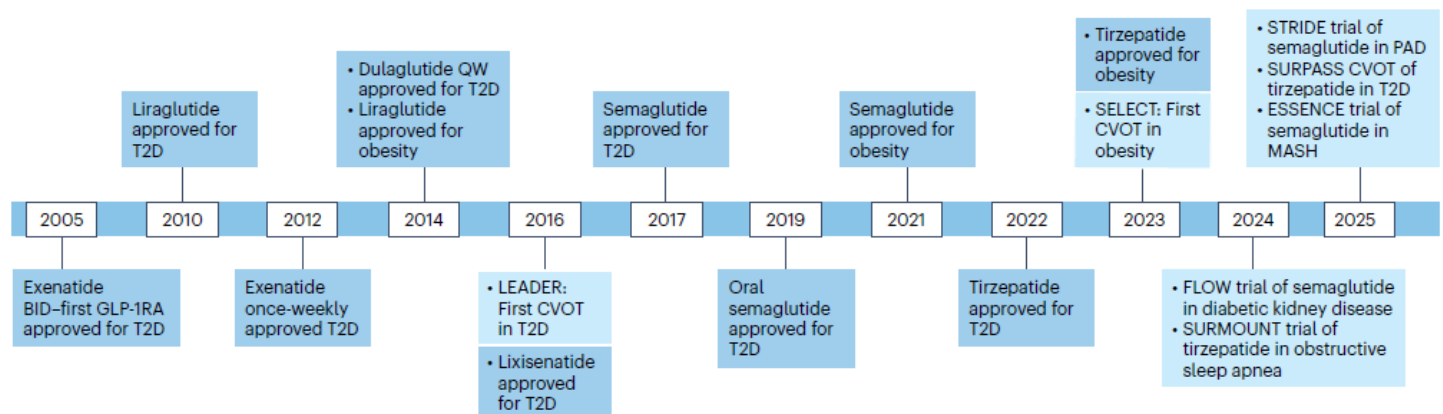
² Enterprise value based on notional fd S/O of 23.9M (assumes supplemental equity capital raise during our forecast period); FQ226 cash of US\$61.8M, no LT debt

Source: Satellos Bioscience financial filings; Leede Financial

Significant Developments With Relevance To Our Coverage Universe

- **Still more updates on the GLP-1 universe – status of clinical evidence for longer-term secondary side effects/benefits.** In the last two editions of our Healthcare Weekly, we provided analysis of the ever-growing GLP-1 pharmacopeia, focusing both on business development events combining next-generation GLP-1 analog developers with commercial-stage GLP-1 marketers as well on the clinical evidence supporting how the category has gone mainstream on its weight loss clinical activity.

Exhibit 6. Timeline Of Major Trials & Approvals For GLP-1 Medicines



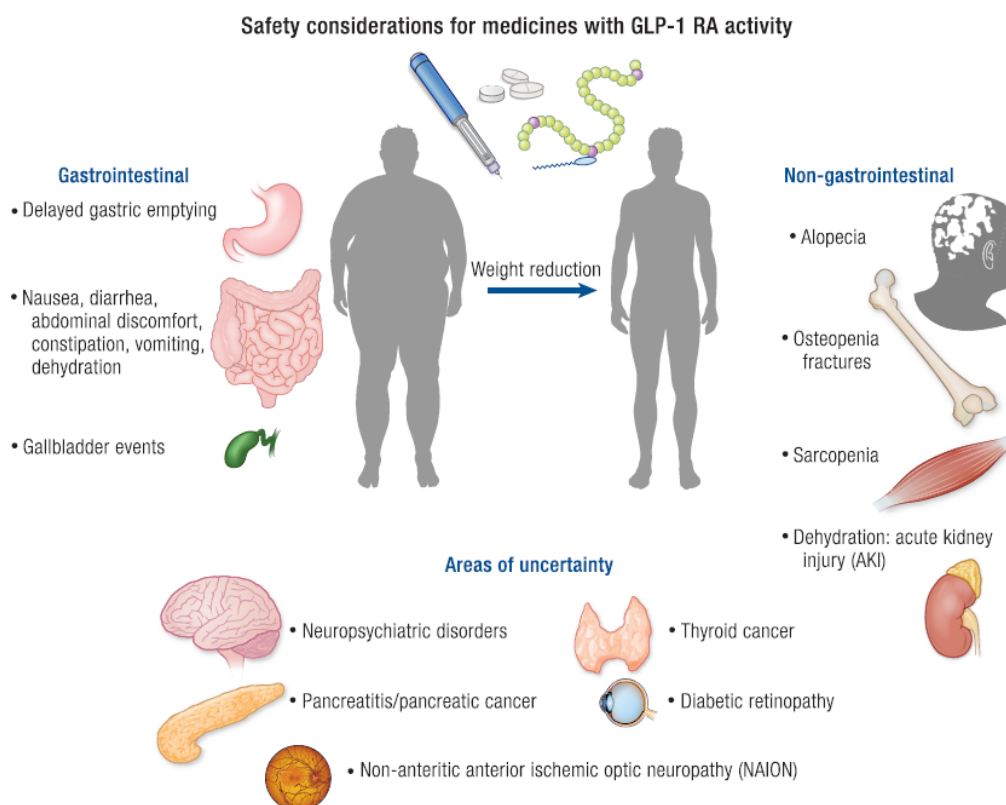
Source: Adapted from *Nature Medicine* (2026). Vol. 32, pp. 47-57

- We are not pretending that the broader population is not well aware of GLP-1 as a weight loss agent – the public advertisements are everywhere & brand awareness is high in our view – but we are interested from a capital markets perspective on just how much traction that market-leading Eli Lilly (LLY-NY, NR) & Novo Nordisk (NVO-NY, NR) believe is still to be achieved in this already-multi-blockbuster endocrinology market, as indicated through their respective partnership activities with earlier-stage GLP-1 developers. Cumulative sales for all GLP-1 formulations for which weight loss is an FDA-approved indication as sold primarily by Eli Lilly/Novo Nordisk (so for Mounjaro/Zepbound & Ozempic/Wegovy/Rybelsus) totalled

US\$23.8B just in FQ226 alone. The GLP-1 weight loss pharmaceutical category is generating more global sales in a quarter than virtually all other FDA-approved pharmaceuticals (other than Merck's [MRK-NY, NR] anti-PD1 mAb cancer-targeted pembrolizumab/Keytruda; FQ226 sales US\$8.4B) generate in a year & by a wide margin at that.

- As followers of our commentary on this market may recall, we were not originally enamored with the broader adoption of GLP-1s as weight loss agents just because the longer-term side effects were not as well-characterized as we would have liked at the time of Ozempic/Wegovy launch & we were mindful from our early days of covering QC-based ConjuChem (ticker was CJC-T, which in the early 2000s was developing its *in vivo* albumin-binding DAC conjugation chemistry for its Phase II-stage DAC-GLP-1 platform) & following its main peer firm exenatide/Byetta/Bydureon developer Amylin Pharmaceuticals (part of AstraZeneca [AZN-LN, NR] since 2014) that acute pancreatitis was a notable side effect of GLP-1 longer-term dosing.

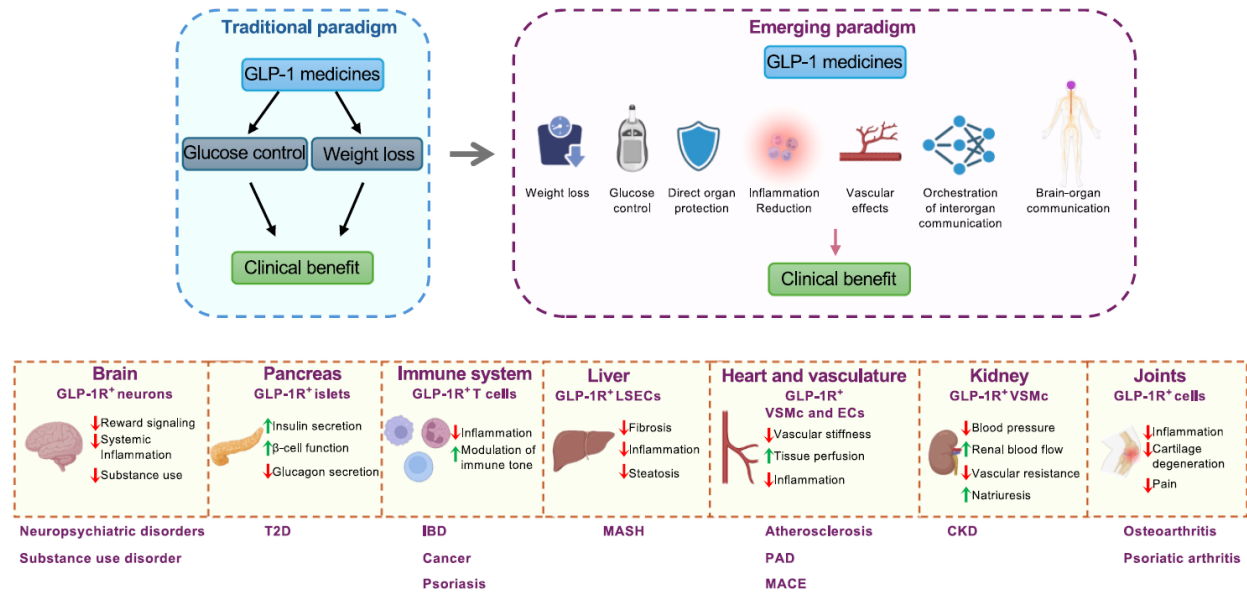
Exhibit 7. There Is No Denying That GLP-1 In All Of Its Approved Forms Has Substantial Endocrinologic Activity Specifically On Weight Loss, But The Medical Literature Is Clear That As With Virtually All Rx Therapies, Safety Considerations Do Exist



Source: Adapted from *Endocrine Reviews* (2026). On line.

- As an aside, GLP-1 followers may not be aware that the Canadian life sciences community is a substantial contributor to our understanding of GLP-1 pharmacology, with notable publications by University of Toronto researcher DJ Drucker dating back to the early 1990s – Drucker's first GLP-1-relevant study was in fact published in Oct/92 in the *Journal of Biological Chemistry*, actually focusing in that paper on the role of glucagon processing in a transgenic murine model of glucagon expression but with GLP-1 expression simultaneously quantified due to its independent impact on blood glucose homeostasis. Dr. Drucker has published 292 GLP-1-relevant peer-reviewed studies since then & we assume that supplemental contributions to the GLP-1 literature from his laboratory are in process.
- Our inspiration for extending our GLP-1 review to include secondary effects of chronic GLP-1 administration coincides with the timing of three peer-reviewed papers on this topic - a Jan/26 review published by Drucker in the journal *Nature Medicine*, a more recent review on the same theme published in Aug/26 by Drucker & collaborators in the journal *Cell Metabolism* & a third that was just published online in the journal *Endocrine Reviews*, with all three reviews including summaries of many of the Phase IV clinical trials demonstrating broader-spectrum organ/tissue effects beyond blood glucose regulation & weight loss.

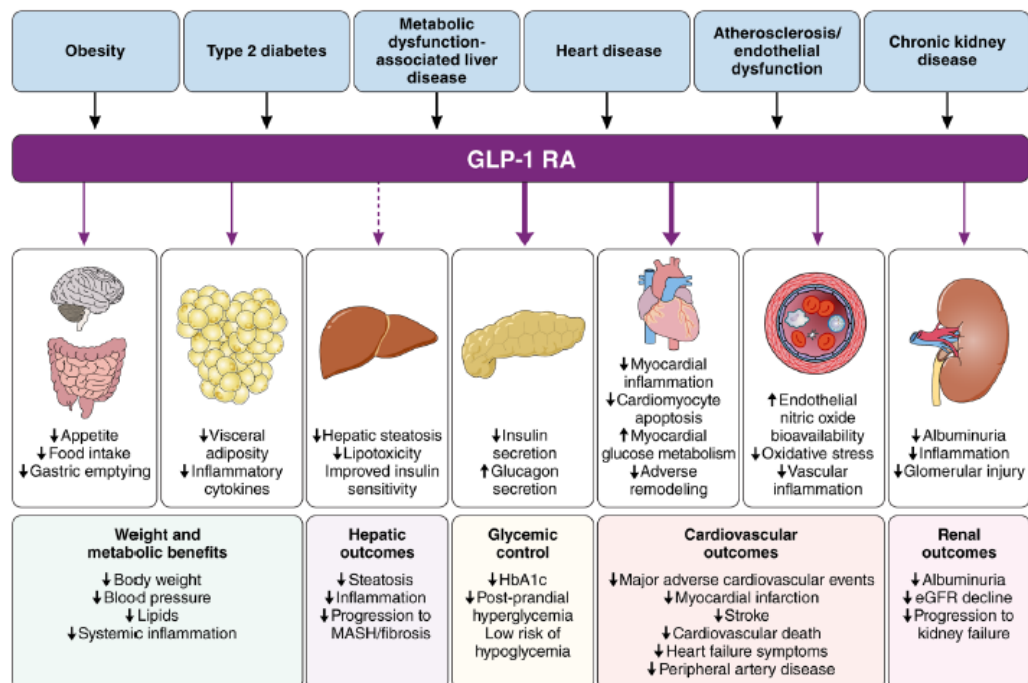
Exhibit 8. Multiple Mechanisms Have Been Proposed For How GLP-1 Exhibits Multi-Organ Effects Independent Of Weight Loss



Source: Adapted from *Cell Metabolism* (2026). Vol. 38, pp. 1535-1539.

- More recent meta-analyses of GLP-1 side effect profile published last month by Case Western Reserve University researchers in the *Journal of Personalized Medicine* claimed that acute pancreatitis risk was historically overstated & the evidence presented for this assertion, at least when comparing GLP-1 to alternative endocrinology therapies that may be administered to type II diabetes patients (for example, small-molecule dipeptidyl peptidase IV inhibitor drugs like Merck's [MRK-NY, NR] sitagliptin/Januvia or sodium-glucose cotransporter II inhibitors like Boehringer Ingelheim's [private] empagliflozin/Jardiance) in a retrospective analysis of 291,152 patients, was strong in our view.

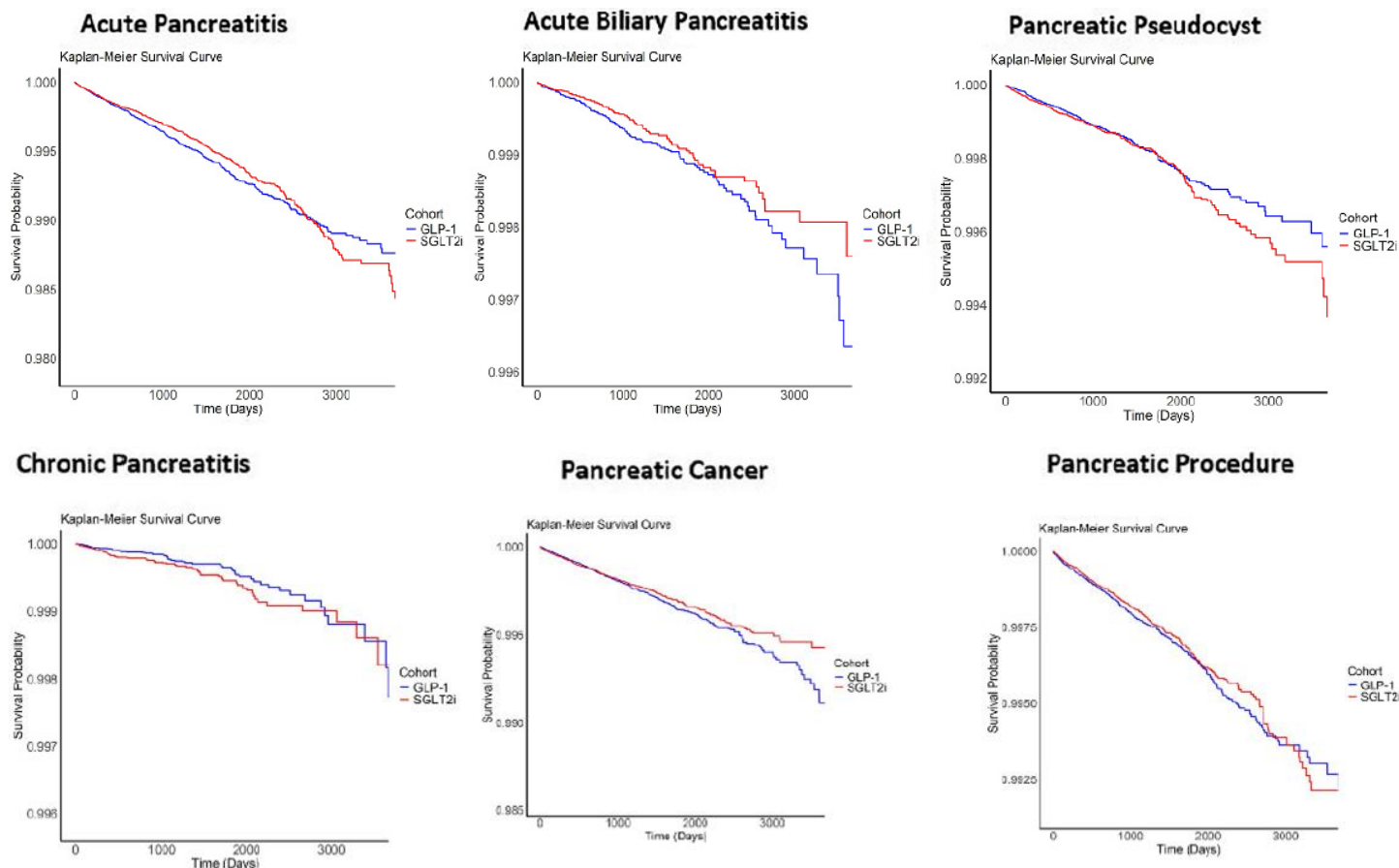
Exhibit 9. But It Is Conversely Well-Documented That GLP-1s Have Favorable Secondary Effects On Endocrinology That Are Related To But Independent From Weight Loss



Source: Adapted from *Circulation* (2026). Vol. 154, pp. 66-73.

- We believe however that as with all chronic therapies, GLP-1 adverse event signals should be closely monitored, especially with the number of weight loss & type II diabetics on GLP-1 support already representing a sizable proportion of the overall population in the US & western Europe. Accordingly, our attention was drawn to a study published in May/26 by Chicago-based researchers in the journal *Cureus* in which the incidence of ketoacidosis in non-diabetic patients (which we read as patients receiving therapy but without blood glucose dysregulation) was relatively high in patients on either semaglutide or tirzepatide support.

Exhibit 10. Acute Pancreatitis Was An Early Risk Factor Identified Both During & After Exenatide & Liraglutide Were Originally Tested/Launched, But More Recent Meta-Analysis Suggests That This Risk Factor Could Be Overstated



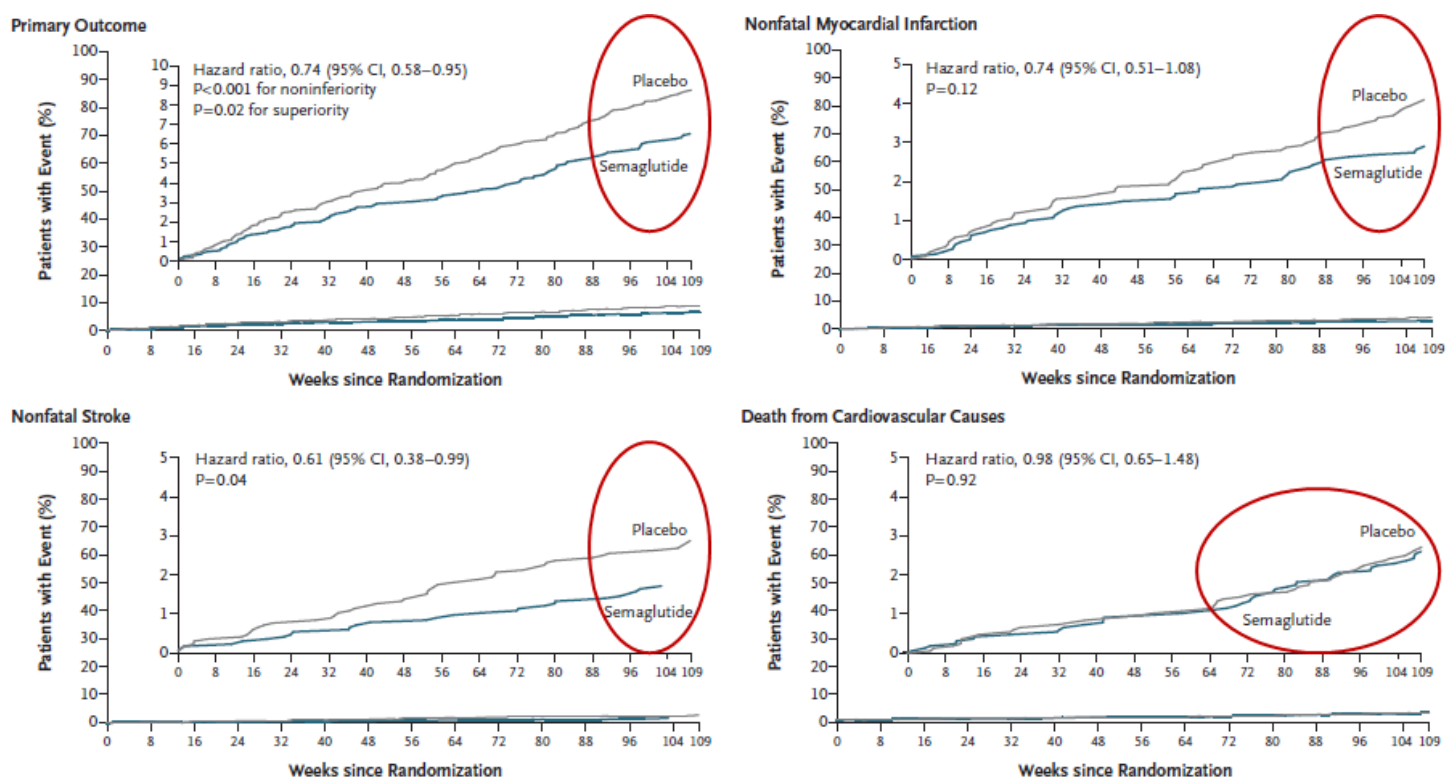
Source: Adapted from *Journal of Personalized Medicine* (2026). Vol. 16, pp. 478-489

- Ketoacidosis is a condition whereby afflicted individuals do not produce enough insulin (initially as C-peptide by pancreatic islet cells) to drive glucose uptake by muscle or other tissues, driving the individual's metabolic activity toward burning fat instead of glucose to produce biological energy. This condition is caused by accumulation of a category of carbon-based organic compounds called ketones (defined as compounds having a carbon-oxygen double bond & with that carbon atom bound to two other carbon atoms & not to any other atomic entity) that if produced in excess can make blood in circulation more acidic than it normally is.
- Ketones as a chemical class are not 'acidic' as such, but one of the relevant by-products of ketoacidosis is a small-molecule called beta-hydroxybutyrate (which is not actually a ketone by the way) & in so doing, compromise function of the organs through which acidic blood circulates. The condition is certainly reversible if properly diagnosed early but can be life-threatening if not, a key concern for us especially with GLP-1's more frequently being prescribed for high-BMI patients for which no other endocrinologic conditions are recognized by GLP-1-prescribing physicians.
- A University of Ottawa/University of Toronto study was published earlier this year in the journal *Clinical Nutrition* that explored the frequency with which patients on GLP-1 support reported symptoms of muscle atrophy, essentially reviewing data from Q423-to-Q124 submitted to the FDA Advisory Event Reporting System & in so doing, identifying

142 cases of muscle atrophy recorded in that database. Interestingly, once-weekly semaglutide (probably Ozempic/Wegovy, although orally-active Rybelsus could have been the semaglutide form incorporated into the database) was associated with a disproportionately high reporting rate when compared to patients treated with alternative once-daily GLP-1 forms, either exenatide (Amylin/Astra's [AZN-LN, NR] Byetta/Bydureon) or liraglutide (Novo Nordisk's [NVO-NY, NR] Victoza/Saxenda).

- The authors were sufficiently observant in our view to comment that the FDA's FAERS database is a signal detection platform rather than evidence of causality & while the loss of muscle mass/function is a widely-reported side effect of chronic GLP-1 administration (we will directly comment on muscle mass loss below, but this GLP-1 effect as part of its overall impact on caloric restriction & weight loss is well-described in several studies, including a Nov/24 paper published in the journal *The Lancet Diabetes & Endocrinology*). In that paper, the researchers state that 25%-to-39% of total weight loss over a nine-to-eighteen-month dosing period (independent of GLP-1 formulation); muscle mass loss from caloric restriction alone tends to be lower though it does overlap with the lower end of the GLP-1 range at 10%-to-30%, at least according to a 2007 review published in the *International Journal of Obesity*, but this range is clearly wide & undoubtedly influenced by multiple factors independent of caloric restriction if considered in isolation.

Exhibit 11. Cardiovascular Side Effect Profile Data For Semaglutide In Type II Diabetics In The SUSTAIN-6 Trial

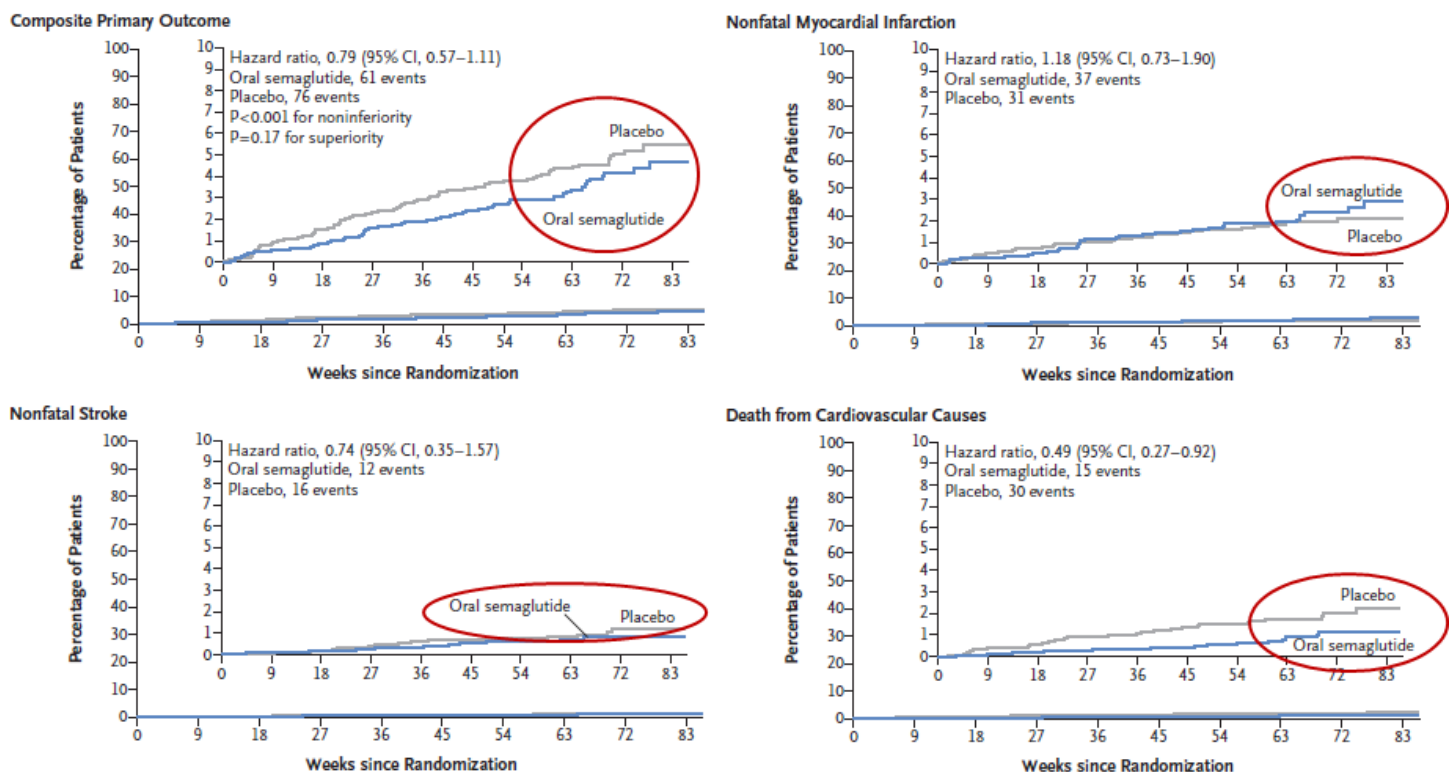


Source: Adapted from *The New England Journal of Medicine* (2016). Vol. 375, pp. 1834-1844.

- But the literature on GLP-1-impacted muscle loss is mixed, with more recent reviews on the topic concluding that chronic GLP-1 administration is less impactful on muscle loss than originally thought. In a meta-analysis published in Apr/26 also in the *International Journal of Obesity* by EU-based researchers concluded from analysing 1,032 patients in twenty-four different studies that GLP-1 administration over three-to-twelve months & in various forms (dulaglutide-semaglutide-liraglutide-exenatide) generated reductions in fat mass & visceral adipose tissue that were far greater than the magnitude of muscle mass loss across most of the evaluable trials (most of which were published since 2018).
- As we documented in two of our most recent Healthcare Weeklies, many of the clinical-stage GLP-1 formulations, including dual-acting & triple therapies simultaneously incorporating GIP's insulin-secreting activity & glucagon's liver glucose-releasing activity, have documented secondary effects that are more positive to endocrinologic health than the side effects that we describe above.

- Many of the relevant studies supporting GLP-1 broad-spectrum positive impact on multi-organ health in ways that are independent of the hormone's blood glucose-modulating activity were nicely described in a recent review in the journal *Cell Metabolism*, with the following trials providing supporting evidence for GLP-1 utility on these non-weight loss indications. Many of these studies were characterized in the medical literature during F2022-to-F2026 when once-weekly GLP-1 analogs were ascending in the weight loss/endocrinology medical market & thus increasingly prescribed for patients presenting with no other pathologies (specifically type II diabetes) other than high BMI index.
- To be clear, the studies to which we will refer below that were published during the earlier years in the aforementioned range are not exactly new, but with GLP-1 Rx volumes expected to grow in coming years in part from availability of generic alternatives, we believe that more intense scrutiny of secondary medical effects is warranted. As will be apparent in the clinical summary that follows, the *New England Journal of Medicine* has become a seminal consolidator of many of the key clinical studies in this realm.

Exhibit 12. Cardiovascular Side Effect Profile Data For Semaglutide In Type II Diabetics In The PIONEER-6 Trial – Orally-Active Formulation Shows Itself To Confer Minimal-If-Any Negative Impact On Cardiovascular Adverse Events In Early Clinical Testing



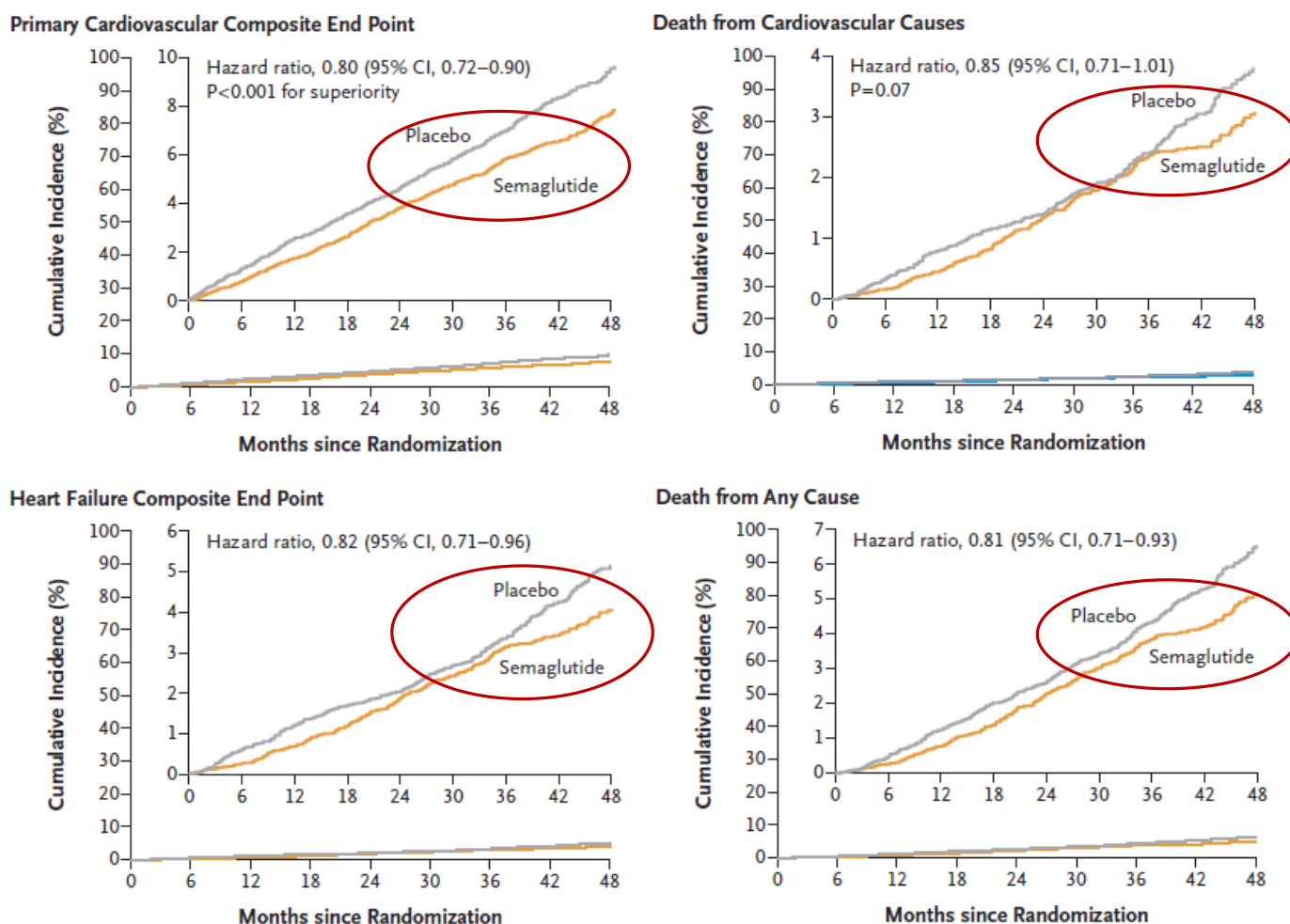
Source: Adapted from *The New England Journal of Medicine* (2019). Vol. 381, pp. 841-851.

- ♦ **Cardiovascular disease risk/benefit – the PIONEER 6, SUSTAIN 6 & SELECT trials, among others.** We were drawn to a Jul/26 review published in the journal *Circulation* by McMaster University researchers who authored a self-described clinical primer on the cardiovascular impact of chronic GLP-1 administration, concluding that GLP-1 & its long-acting analogs actually support cardiovascular risk reduction, consistent with many specific clinical studies that we reviewed for this exercise. To be clear, one of semaglutide's three approved indications is mitigating risk of adverse cardiovascular events (the others are improvement of glycemic control of course as well as reducing risk of sustained glomerular filtration rate decline by the kidneys, an indication that we will explore below). But we ourselves had not extensively reviewed the medical literature in support of semaglutide/GLP-1 secondary effects & we are doing so in this analysis.
- ♦ With specific regard to the aforementioned review, the McMaster University team assimilated data from published trials for which patient enrollment was focused on type II diabetes patients, patients with high BMI at enrollment but without type II diabetes symptoms & on a smaller number of patients presenting with HFpEF (diastolic heart failure, or heart failure with preserved ejection fraction), with overall data set exceeding 100,000 patients in the analysis.

Not only did that meta-analysis not identify any major cardiovascular adverse event rates that could limit chronic deployment of once-weekly GLP-1 formulations (usually but not exclusively semaglutide) but that cardiovascular benefit was clearly documented, specifically in the Phase IV trials that we summarize below.

- Similar to our analysis of ON-based **Medexus Pharmaceuticals (MDP-T, Buy, PT C\$8.00)** & its lead bone marrow-conditioning agent Treosulfan, whereby we extensively surveyed the medical literature & could not find any definitive justification for denying FDA approval of the drug (we were proven correct just a few months after launching coverage on the firm), we were striving in our GLP-1 analysis to find definitive studies showing that analogs of the hormone should be limited in its deploying for chronic use as a weight loss therapy, both for diabetic & non-diabetic patients. The weight of evidence on the benefit side of the medical ledger is vastly more substantive than on the risk side, at least based on the studies we reviewed for this analysis.

Exhibit 13. Cardiovascular Side Effect Profile Data For Semaglutide In The SELECT Trial – Mitigation Of Adverse Cardiovascular Events In Non-Diabetic But High BMI patients

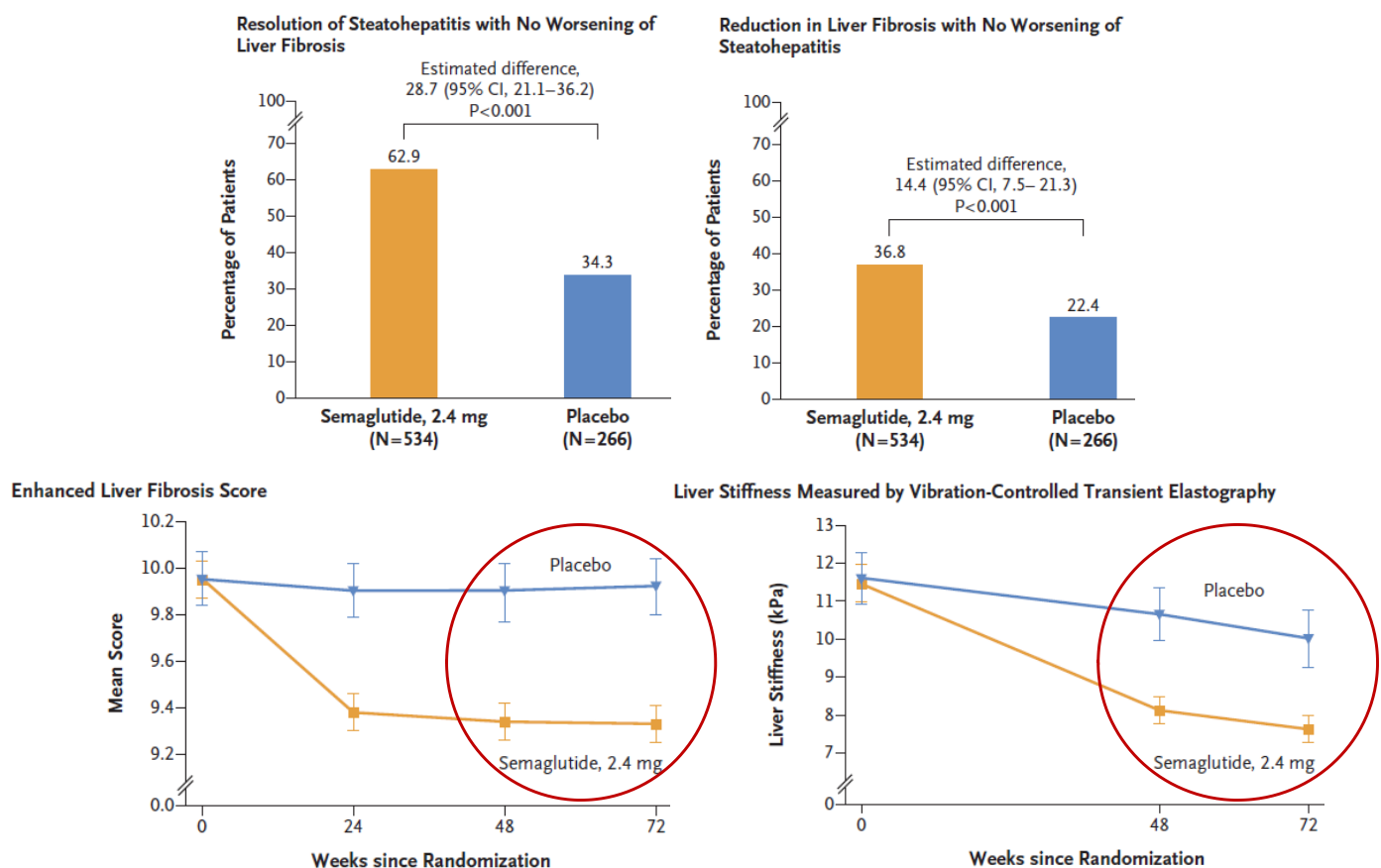


Source: Adapted from *The New England Journal of Medicine* (2023). Vol. 389, pp. 2221-2232.

- But we reflect specifically on three cardiovascular risk event rate trials that were specific to semaglutide. First of all, we feature the 17,604-patient Phase IV SELECT trial published in Dec/23 in the *New England Journal of Medicine* by Novo Nordisk & collaborators, showing in their data analysis that the primary composite endpoint (frequency of cardiovascular-related death, myocardial infarction or stroke) favored semaglutide-treated patients (event rate of 6.5% vs 8.0% for placebo patients) & virtually all cardiovascular/hematological secondary endpoints favored semaglutide-treated patients as well, almost without exception, notably improvements in systolic blood pressure & reduction in circulating levels of the systemic inflammation biomarker C-reactive protein.

- ♦ Unsurprisingly & not overly impactful on our assessment of GLP-1-associated cardiovascular risk/benefit, there were more drop-outs in the semaglutide arm of the trial, with virtually all of the drop-out imbalance related to GI discomfort, an inevitable consequence of one of GLP-1's core intestinal effects (it slows gastric emptying). In a separate study published back in 2016 also in the *New England Journal of Medicine* by Novo & collaborators, the 3,297-patient SUSTAIN-6 trial, data showed in that trial that semaglutide performed similarly but with the study focused exclusively on type II diabetics & not high BMI patients as have become the target patient population for this drug in recent years. Semaglutide-treated type II diabetic patients exhibited far fewer cardiovascular or renal adverse events over the two-year dosing period than placebo patients – primary event rate was 6.6% in the semaglutide arm as compared to 8.9% in the placebo arm.
- ♦ Frequency of nonfatal myocardial infarction was lower but not to a significant degree for semaglutide patients (2.9% of semaglutide patients vs 3.9% of placebo patients) but all other key endpoints did favor semaglutide to a significant degree (nonfatal stroke – 1.6% vs 2.7% for semaglutide vs placebo patients, for example) & rates of new or worsening kidney disease were lower for semaglutide patients (3.8% for semaglutide vs 6.1% of placebo patients), but interestingly the rate of retinopathy complications – a well-documented side effect of the vascular degeneration that diabetic patients experience over time (indeed, 84% of patients presented with retinopathy at enrollment) – was overall quite low but still higher for semaglutide (3.0% vs 1.8% of placebo patients) & this formed the basis for subsequent clinical testing as we describe below.

Exhibit 14. Renal Side Effects (Or Lack Thereof) For Semaglutide In The ESSENSE Trial – Improvements On Liver Fat Reduction & Liver Fibrosis Clearly Documented In Semaglutide-Treated Patients



Source: Adapted from *The New England Journal of Medicine* (2025). Vol. 392, pp. 2089-2099.

- ♦ And going back a few years, the focus on semaglutide's cardiovascular event rate status was originally explored in the 3,183-patient type II diabetes PIONEER-6 trial, in this case testing orally-active semaglutide instead of its injectable form (so Rybelsus instead of Ozempic/Wegovy) & comparing cardiovascular/renal event rate in this patient population over a sixteen-month dosing period. Data were published in Aug/19 in the – you guessed it –

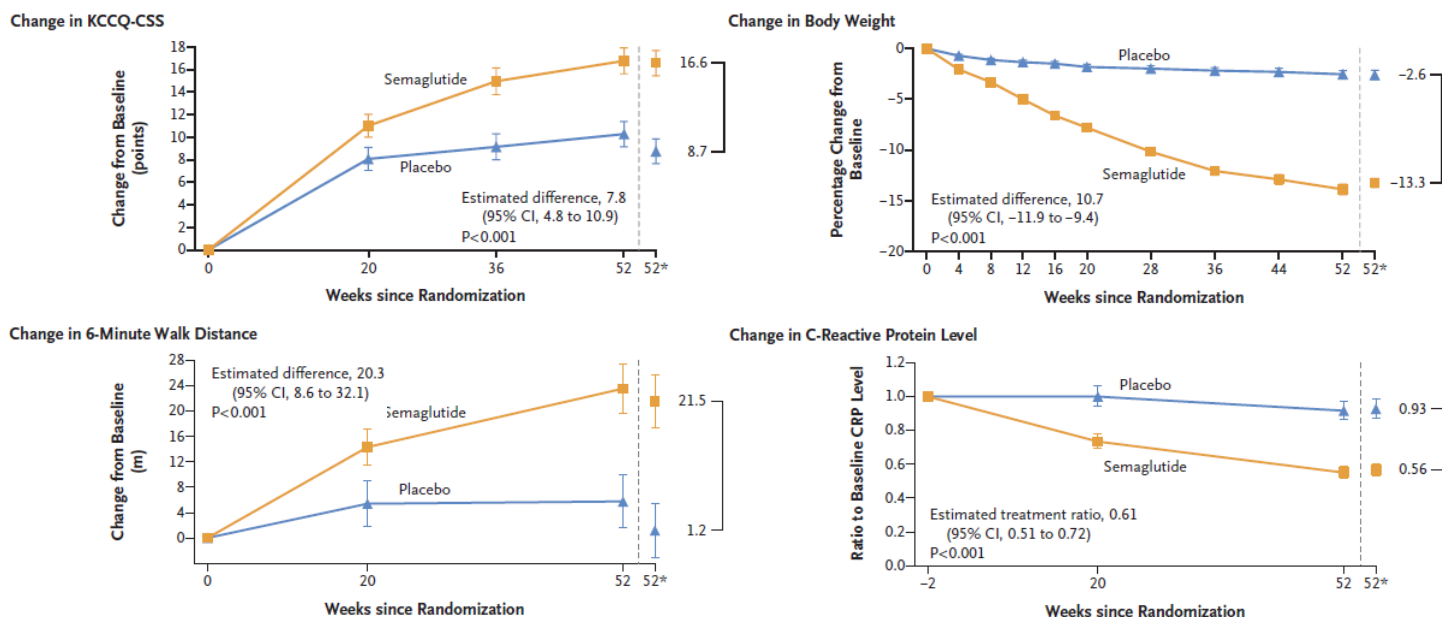
New England Journal of Medicine. The goal of this trial was to assess non-inferiority of oral semaglutide & not to quantify cardiovascular/renal benefits that we now know are demonstrable with subsequent clinical testing.

- ♦ But as a signpost for establishing that semaglutide conferred no cardiovascular/renal risk with chronic administration to type II diabetic patients (for whom cardiovascular risk is high anyway because of the longer-term vascular damage that the disease inevitably causes through blood glucose dysregulation, however well-managed it is through exogenous insulin administration), we believe that PIONEER-6 data have predictive value.
- ♦ As with the other semaglutide cardiovascular/renal risk stratification studies that came after, PIONEER-6 data showed that oral semaglutide-treated patients exhibited lower cardio-vascular event rate of 3.8% vs 4.8% for placebo patients, though the delta was smaller for some cardiovascular measures than for others (event rate for non-fatal stroke or non-fatal myocardial infarction were virtually identical over the sixteen-month dosing period). But at this juncture in semaglutide's clinical/regulatory/commercial activities, it was deemed to be positive on balance that the drug when orally-administered exhibited no limiting cardiovascular side effects while the drug was impacting weight loss as intended.
- ♦ Data from the semaglutide-specific 9,650-patient Phase IV SOUL trial were illustrative on this theme, with Novo Nordisk & its medical collaborators reporting in a 2025 *New England Journal of Medicine* paper that primary outcome events (six different measures of adverse cardiovascular or renal events; Exhibit 17) over the four-year dosing period were at a lower frequency in semaglutide-treated patients (3.1 events per 100 person-years, or 12.0% of patients) as compared to placebo patients (3.7 events per 100 person years, or 13.8% of patients), with this difference deemed to be statistically significant.
- ♦ In a separate 13,299-patient Phase IV cardiovascular risk stratification trial (the SURPASS-CVOT trial) published also in 2025 in the *New England Journal of Medicine* this time by Australia-based Monash University researchers, data showed that Eli Lilly's (LLY-NY, NR) once-weekly injectable GLP-1/GIP dual agonist tirzepatide (Mounjaro/ Zepbound) was non-inferior to an alternative once-weekly injectable GLP-1/IgG4 Fc region fusion protein dulaglutide (not exactly a placebo but a control without complementary GIP insulinotropic activity). Non-inferiority was defined by multiple measures of cardiovascular event rate, including cardiac-related death, heart attack & stroke.
- ♦ In a 731-patient heart failure/obesity hybrid Phase IV trial (the SUMMIT trial) published last year in the *New England Journal of Medicine* by Eli Lilly & collaborators, data showed that tirzepatide treated patients reported far fewer heart failure-worsening events over a two-year dosing period – 8.0% of tirzepatide-treated patients reported heart failure worsening (as quantified by the Kansas City Cardiomyopathy Questionnaire clinical summary score) as compared to 14.2% of placebo patients; the tirzepatide-placebo gap remained relatively stable on an absolute basis if cardiovascular-related deaths (eight on tirzepatide vs five on placebo) were included in the event rate analysis (9.9% of tirzepatide-treated patients experienced heart failure worsening or death [or both in succession] as compared to 15.3% of placebo patients).
- ♦ As for the other cardiovascular risk stratification studies described above, this two-year event-rate gap was deemed to be statistically significant & thus a seminal component of tirzepatide's overall medical profile. Tirzepatide is of course not a purely GLP-1-based therapy & thus its pharmacology is simultaneously augmented by its GIP-based activity, but at its core, the drug is still a weight loss-mediating endocrinologic agent for which side effect profile is still relevant we believe to the overall GLP-1 pharmacopeia.
- ♦ **Metabolic dysfunction-associated steatohepatitis (MASH) – the ESSENSE trial.** The 1,197-patient ESSENSE trial that was published in Apr/26 in the *New England Journal of Medicine* assessed impact of once-weekly semaglutide dosing on patients presenting with biopsy-confirmed MASH symptoms at enrollment along with stage two/three liver fibrosis. The placebo-controlled trial is still ongoing, but sponsor Novo Nordisk (NVO-NY, NR) & its academic collaborators published data in the paper from the first 800 enrolled subjects for whom seventy-two week follow-up data were already available.
- ♦ Semaglutide-treated patients responded favorably on disease resolution, with 62.9% of 534 semaglutide-treated patients experiencing resolution of fatty liver (steatohepatitis) symptoms without any worsening of liver fibrosis after seventy-two weeks of once-weekly semaglutide dosing, whereas only 34.2% of 266 placebo patients experienced

the same outcome. Conversely, researchers showed that 36.8% of semaglutide-treated patients experienced a reduction in liver fibrosis without worsening of liver fat deposition as compared to 22.4% of placebo patients experiencing the same response characteristic. Novo Nordisk's Wegovy/semaglutide is specifically indicated as a MASH therapy among its approved indications while Ozempic is not, at least not yet.

- ♦ Taking both liver fat reduction & liver fibrosis reduction as a single composite endpoint, researchers showed that symptomatic relief on both of these liver pathologies transpired in 32.7% of semaglutide-treated patients as compared to 16.1% of placebo patients, with all three of these data scenarios exhibiting statistically-significant benefit favoring semaglutide. Unsurprisingly, semaglutide-treated patients exhibited mean change in body weight from baseline of 10.5% as compared to 2.0% for placebo patients, a predictable observation that is of course independent of semaglutide's now-documented impact on liver steatohepatitis & fibrosis; ESSENCE results if sustained over the entire 240-week dosing period for the trial could certainly support positive regulatory regard for the liver-based indication but probably not until the study concludes (projected to be in H129).
- ♦ **Heart failure with preserved ejection fraction – the STEP-HFpEF trial.** One of the earlier cardiovascular indications for which GLP-1 (specifically semaglutide) safety/efficacy profile was explored was heart failure, specifically diastolic heart failure (also called heart failure with preserved ejection fraction) whereby the left ventricle does not fill with oxygenated blood from the left atrium through the mitral valve as efficiently as it should. This is a related but distinct pathology to systolic heart failure (or HFrEF, heart failure with reduced ejection fraction) for which the left ventricle does not efficiently pump out oxygenated blood – the result of these two conditions is the same (poor pumping efficiency, low oxygenated blood flow to peripheral organs) but the underlying cardiac pathologies clearly differ.
- ♦ Recall that diastolic heart failure/HFpEF is a key secondary cardiovascular market that ON-based **Cardiol Therapeutics (CRDL-T, Spec Buy, PT C\$7.00)** is targeting with its preclinical-stage subcutaneously injectable cannabidiol formulation CRD-38, for which the firm has published its own heart failure data in 2025 in the *Journal of the American College of Cardiology Basic Translational Science*. We described those data in our Cardiol-specific reports & can send those documents to interested readers.

Exhibit 15. Cardiovascular Side Effect Profile Data For Semaglutide In Type II Diabetics As Described In The STEP-HFpEF Trial – Mitigation Of Heart Failure Risk Simultaneous To Weight Loss

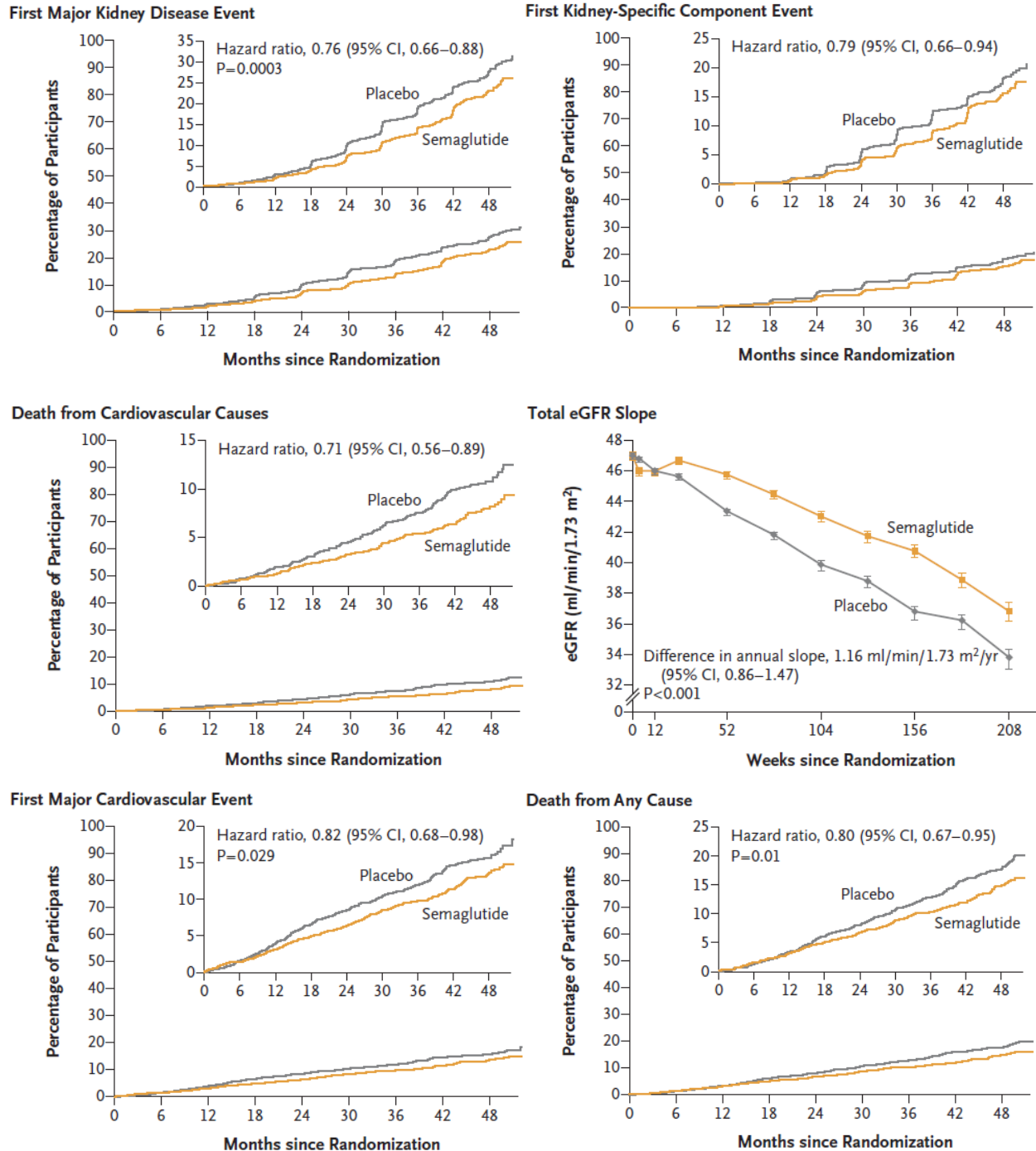


Source: Adapted from *The New England Journal of Medicine* (2023). Vol. 389, pp. 1069-1084.

- ♦ But shifting back to semaglutide, its utility in treating diastolic heart failure was explored by Novo in the 529-patient Phase IV STEP-HFpEF trial that was published in Sept/23 in the *New England Journal of Medicine*, with data showing that a one-year semaglutide dosing period was associated with a substantial improvement from baseline in the so-called Kansas City Cardiomyopathy Questionnaire clinical summary score (KCCQ-CSS) as compared to placebo

patients (16.6 points for semaglutide, 8.7 points for placebo patients) for patients simultaneously presenting both with high BMI & diastolic heart failure at enrollment. Additionally, semaglutide-treated heart failure patients experienced dramatic improvement in six-minute walking distance (21.5 meters vs 1.2 meters for placebo patients) while circulating levels of the systemic inflammation biomarker C-reactive protein were dramatically reduced in semaglutide patients at one-year follow-up (by 43.5% for semaglutide, by 7.3% for placebo patients).

Exhibit 16. FLOW Trial Data For Semaglutide Clearly Show Simultaneous Benefit For Mitigating Cardiac & Renal Pathologies



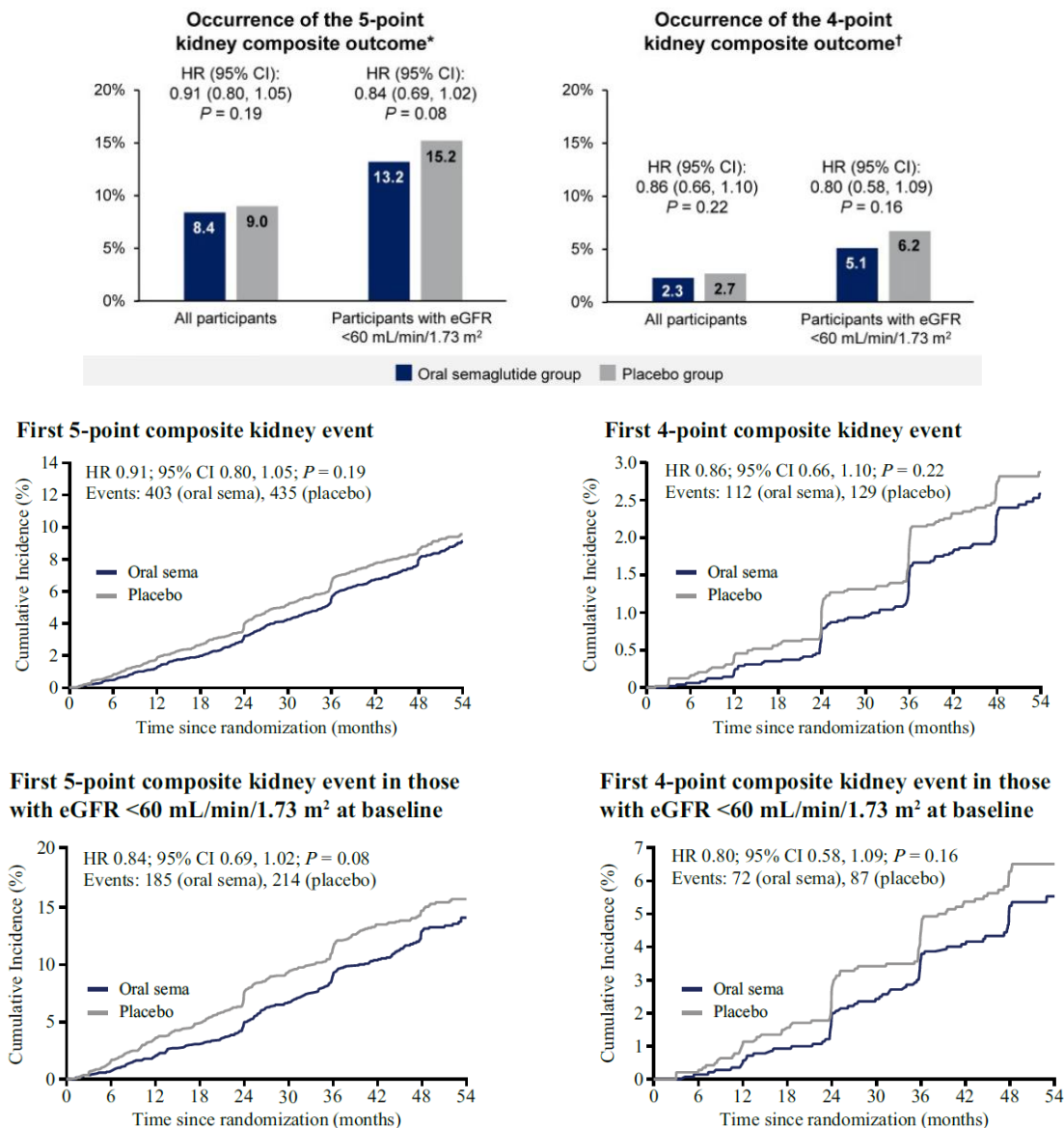
Source: Adapted from *New England Journal of Medicine* (2024). Vol. 391, pp. 109-121.

- ♦ **Kidney disease – the FLOW & SOUL trials.** As indicated above, reduced risk of future kidney pathology (specifically risk of reduced glomerular filtration rate) is already an approved indication for semaglutide (though not yet for tirzepatide) & below we summarize the published clinical data in support of this secondary renal activity. But for

our own diligence, we reviewed the relevant medical literature on GLP-1 impact on kidney function, taking away a largely positive view not just on the minimal-to-no relevant kidney toxicity signals that could impede GLP-1 adoption, but a documentable benefit from chronic GLP-1 dosing specifically on mitigating onset of future kidney failure.

- On this theme, we observe that the 3,533-patient Phase III FLOW trial that was published by Novo & collaborators in Jul/24 in the *New England Journal of Medicine* nicely showed that semaglutide-treated patients experienced far fewer adverse renal events over a 3.4 year dosing period (24% fewer, as shown in Exhibit 16), even though they presented with chronic kidney disease at enrollment. Cardiorenal results were most dramatic for rate of estimated glomerular filtration rate (eGFR) decline, but also for risk of major cardiovascular events (18% lower for semaglutide patients) & for all-cause mortality (20% lower for semaglutide patients). It is no surprise based on FLOW data alone that semaglutide specifically as Ozempic incorporates risk of eGFR decline as one of its approved indications.

Exhibit 17. In The Semaglutide Cardiovascular Outcomes Trial (The SOUL Trial), Oral Semaglutide Did Not Reduce Adverse Renal Events To A Statistical Degree But It Did Slow Down Estimated Glomerular Filtration Rate (eGFR) Decline



Source: Adapted from *Diabetes Care* (2026). Vol. 49, pp. 257-265.

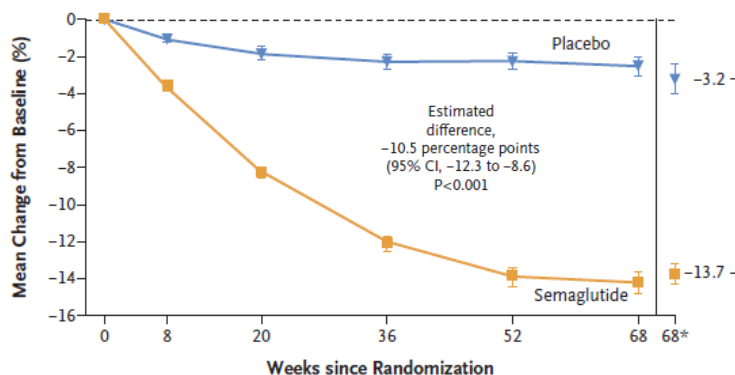
- Shifting to the 9,650-patient SOUL trial that was published by Novo & international clinical collaborators earlier this year in the journal *Diabetes Care* (Exhibit 17), this trial focused on oral semaglutide as the active GLP-1 formulation in patients co-presenting with type II diabetes, atherosclerosis & chronic kidney disease at enrollment (so not

healthy patients, to state the obvious). Data showed at final analysis after four-year follow-up that on two distinct composite measures of cardiorenal function, oral semaglutide only modestly outperformed placebo (8.4% of oral semaglutide patients reported a negative event of some type vs 9.0% of placebo patients on a five-point measure of cardiorenal health; the gap was similar for a separate four-point cardiovascular health measure separately described in the paper) but impact on mitigating glomerular filtration rate decline was far more dramatic & close to statistically-significant (Exhibit 17, upper left panel). Commentary in the discussion section of the paper was predictably cautious on the medical claims for which oral semaglutide could be relevant in this extensively diseased population, but impact on slowing kidney function decline was certainly emphasized & could form the basis for how GLP-1 formulations are prescribed to kidney disease patients in coming years.

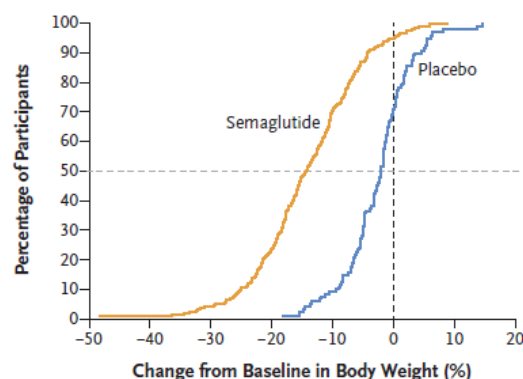
- ◆ **Knee osteoarthritis pain – the STEP-9 trial.** Even before reviewing published clinical data on GLP-1 impact on knee osteoarthritis pain, there seemed to us to be two distinct mechanisms by which pharmacologic impact on this chronic indication could materialize. One mechanism of course is through mitigating the pro-inflammatory impact that sustainably high circulating blood glucose levels can have on joint inflammation, even though strictly speaking, osteoarthritis is a consequence of joint cartilage erosion more than it is an inflammatory condition as such. But the other is that weight loss itself could have a biophysical impact on knee osteoarthritis symptoms just by reducing the force imposed on joints through movement. Regardless, knee osteoarthritis pain (& perhaps hip osteoarthritis pain or lower back pain could be separately explored in future Phase III studies) seems like a plausible indication to explore & as Novo & its collaborators discovered from the 407-patient STEP-9 trial (published in Oct/24 in the *New England Journal of Medicine*), investment in clinical activity for this indication appears warranted.

Exhibit 18. Impact On Knee Osteoarthritis Pain Symptoms From Chronic Semaglutide Dosing - The STEP-9 Trial

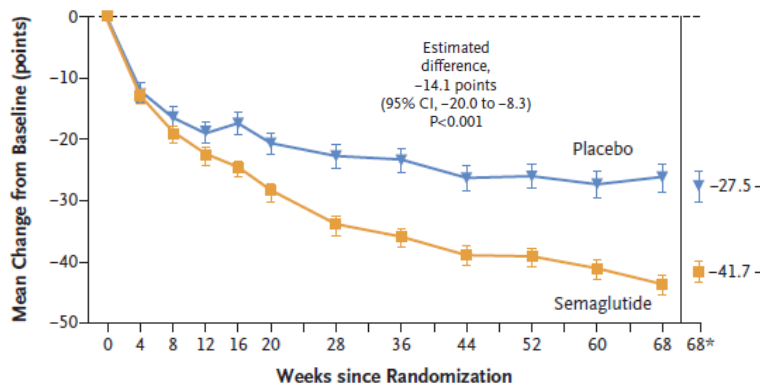
Change in body weight



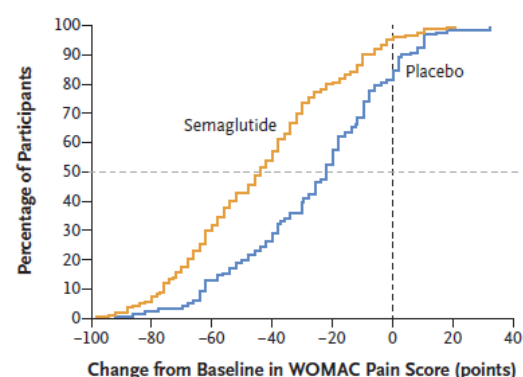
Cumulative frequency of change from baseline in body weight



Change in WOMAC pain scores



Cumulative frequency of change from baseline in WOMAC pain scores

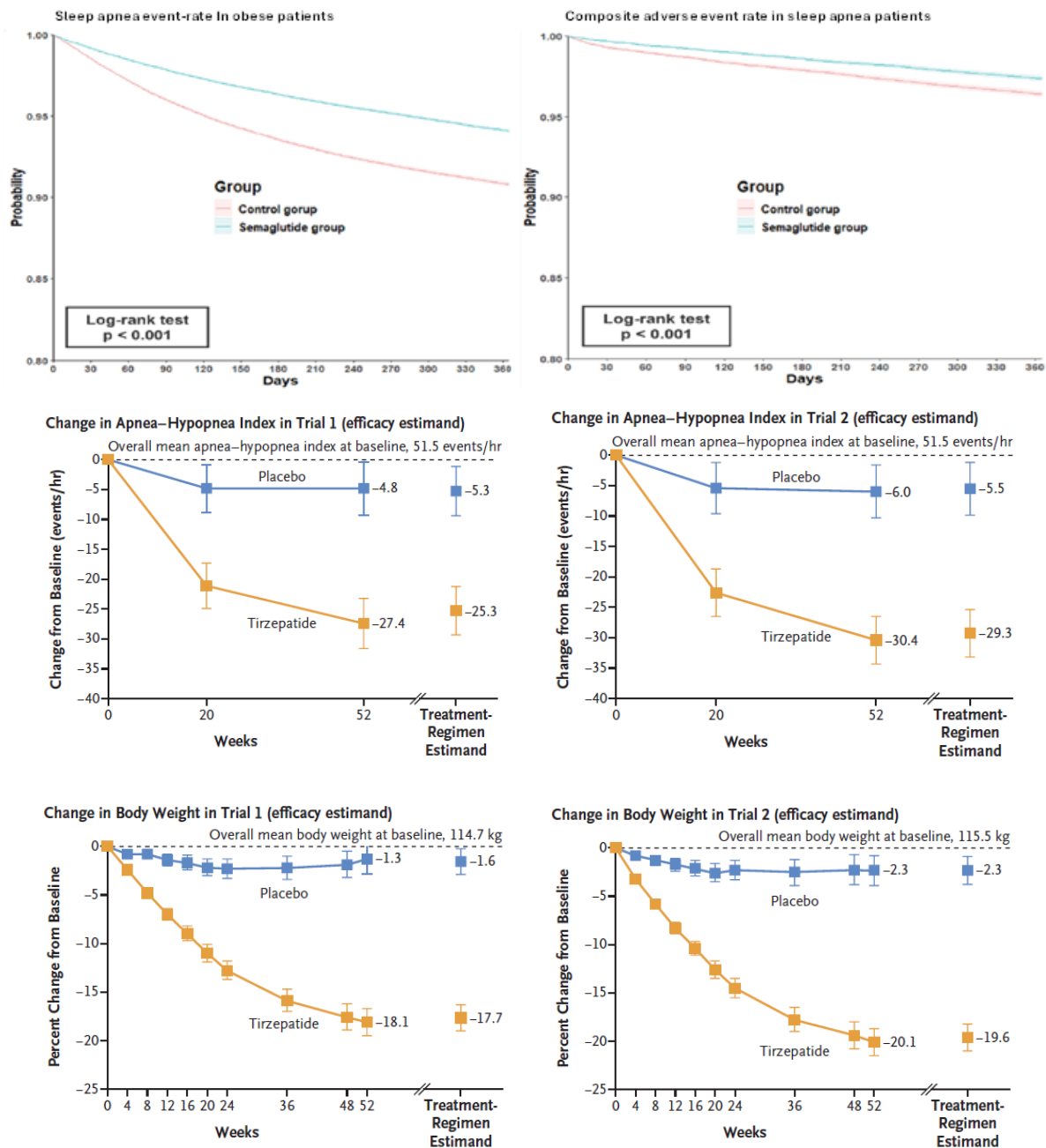


Source: Adapted from *The New England Journal of Medicine* (2024). Vol. 391, pp. 1573-1583.

- ◆ As shown in Exhibit 18, the impact that semaglutide had on weight loss was both predictable & profound, about 10.5% of placebo-adjusted body weight reduction from baseline, & we mention that outcome solely to indicate that we believe that body weight reduction alone could itself have an impact on knee osteoarthritis pain independent of

any other pharmacologic mechanisms that could be involved. Secondly, the impact on joint pain over the sixty-eight week dosing period was correspondingly high in favor of semaglutide, with pain intensity (as measured by the well-characterized WOMAC pain scale that we have reviewed many times before in our coverage history of pain therapy developers) reduction of 41.7 points for semaglutide patients far exceeding 27.5 points for placebo patients (the placebo effect specifically for pain drugs is notoriously high). A separate measure of joint function called the SF-36 physical-function score also favored semaglutide (12.0-point improvement vs 6.5-point improvement for placebo patients; not shown in the above exhibit). As usual, there were a few more drop-outs in the semaglutide arm, but almost always for the same GI discomfort reasons that are intrinsic to GLP-1's impact on slowing gastric emptying; accordingly, there were no unanticipated side effects in STEP-9 that should impede semaglutide/GLP-1 deployment into the joint pain medical market.

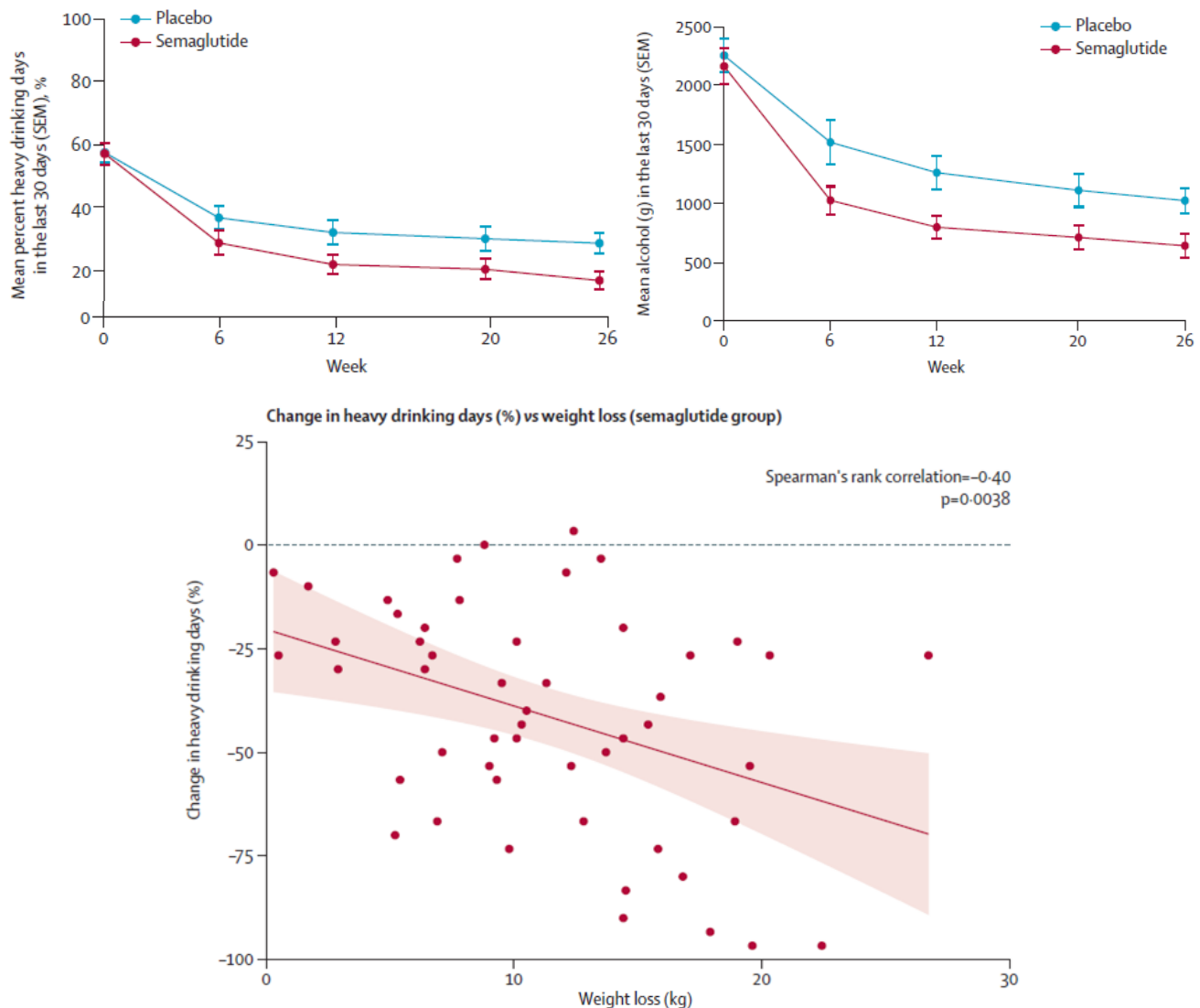
Exhibit 19. Both Semaglutide & Tirzepatide Exhibit Favorable Impact On Mitigating Sleep Apnea Episodes, Probably As A Secondary Consequence Of Weight Loss & Not A Novel Mechanism Unique To Respiratory Function



Source: Adapted from *Annals Of The American Thoracic Society* (2026). Vol. 23, pp. 584-596 (semaglutide; upper panel); *New England Journal of Medicine* (2024). Vol. 391, pp. 1193-1205 (tirzepatide, SURMOUNT-OSA trial; lower panel).

- ♦ **Sleep apnea – the SURMOUNT-OSA trial.** As for our preliminary assessment of knee osteoarthritis pain as a plausible GLP-1 medical market, so too were we favorable to a role for GLP-1s in sleep apnea, if only because of the documented association between sleep apnea symptoms & BMI – the connection is correlative & not causative, but obesity as a risk factor in sleep apnea exacerbation is widely described in the medical literature (references abound, but readers can start with a May/25 review in the *Lancet* journal *eClinicalMedicine*). Interestingly, mitigating sleep apnea symptoms is already an approved indication for tirzepatide/Zepbound & sleep apnea moderation could be a key secondary driver for this GLP-1 formulation in the near-term, at least until other GLP-1 developers seek similarly positive regulatory regard for this indication.

Exhibit 20. Semaglutide Had A Measurable Impact On Reducing Alcohol Consumption In Patients Co-Presenting With Alcohol Use Disorder & Co-Morbid Obesity – Data From A University Of Copenhagen Trial

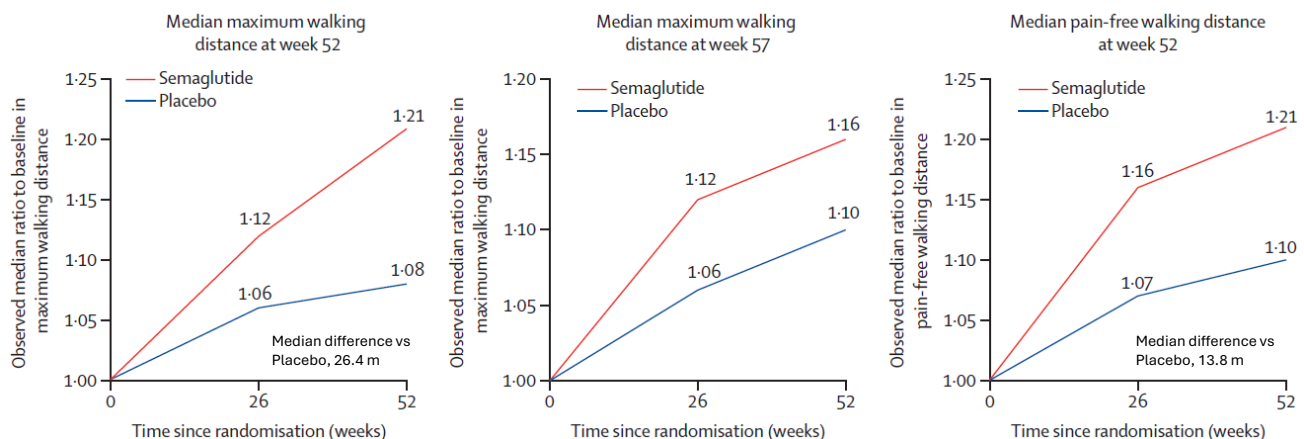


Source: Adapted from *The Lancet* (2026). Vol. 407, pp. 1687-1698.

- ♦ We were thus optimistic that GLP-1 in one or more of its forms could impact sleep apnea symptoms & that was clearly shown in the SURMOUNT-OSA trials (two separate placebo-controlled trials totalling 469 patients) as published in Oct/24 in the *New England Journal of Medicine*. Importantly, this study was funded by Eli Lilly & thus tested tirzepatide as the GLP-1 formulation, a formulation for which its simultaneous GIP activity could clearly play a distinctive role from other pure GLP-1 formulations.

- ♦ SURMOUNT-OSA data clearly showed that tirzepatide-treated patients over the one-year dosing period scored better on the apnea-hypopnea index (AHI, the number of apnea episodes over a one-hour monitoring period) at 49.5-to-51.5 events per hour at enrollment dropping by 25.3 events on average for tirzepatide vs only 5.3 events for placebo patients for one of the trials. In the other trial of similar size, data were similar at 29.3 event drop for tirzepatide vs 5.5 event drop for placebo patients. All secondary endpoints, including improved systolic blood pressure & reduced circulating levels of C-reactive protein, all favored tirzepatide.
- ♦ In a separate retrospective analysis of electronic health records for semaglutide patients that was published by Taiwan-based researchers earlier this year in the *Annals of the American Thoracic Society*, archived data showed a reduced risk of new onset sleep apnea in patients with high BMI at enrollment, while independently showing a reduced number of apnea events in patients co-presenting with high BMI & sleep apnea at the time of commencing semaglutide dosing. These retrospective data probably require more rigorous placebo-controlled clinical testing before Novo could claim sleep apnea as a secondary indication but the rationale for assuming that weight loss for high BMI patients would be a parallel positive outcome for semaglutide dosing, independent of a label claim for the indication.
- ♦ **Alcohol use disorder.** We will not dwell on this indication as a major GLP-1 prescription volume driver, but we observe that data from a six-month 108-patient alcohol use disorder trial was published earlier this year in *The Lancet*, with Novo & its Copenhagen-based clinical collaborators showing that once-weekly semaglutide dosing was associated with a reduction in so-called heavy drinking days (Exhibit 20), clearly a positive outcome for patients presenting with this condition for whom no other compensatory therapy was previously effective. Novo was obviously motivated to test GLP-1 utility in this indication for reasons that we assume were based on medical need & we will see if the firm chooses to emphasize the indication as a regulatory activity or as a commercial driver for semaglutide adoption in future financial updates.

Exhibit 21. Semaglutide-Treated Patients That Co-Presented With Peripheral Artery Disease (PAD) Exhibited Measurable Improvement On Symptoms In The 792-Patient STRIDE Trial

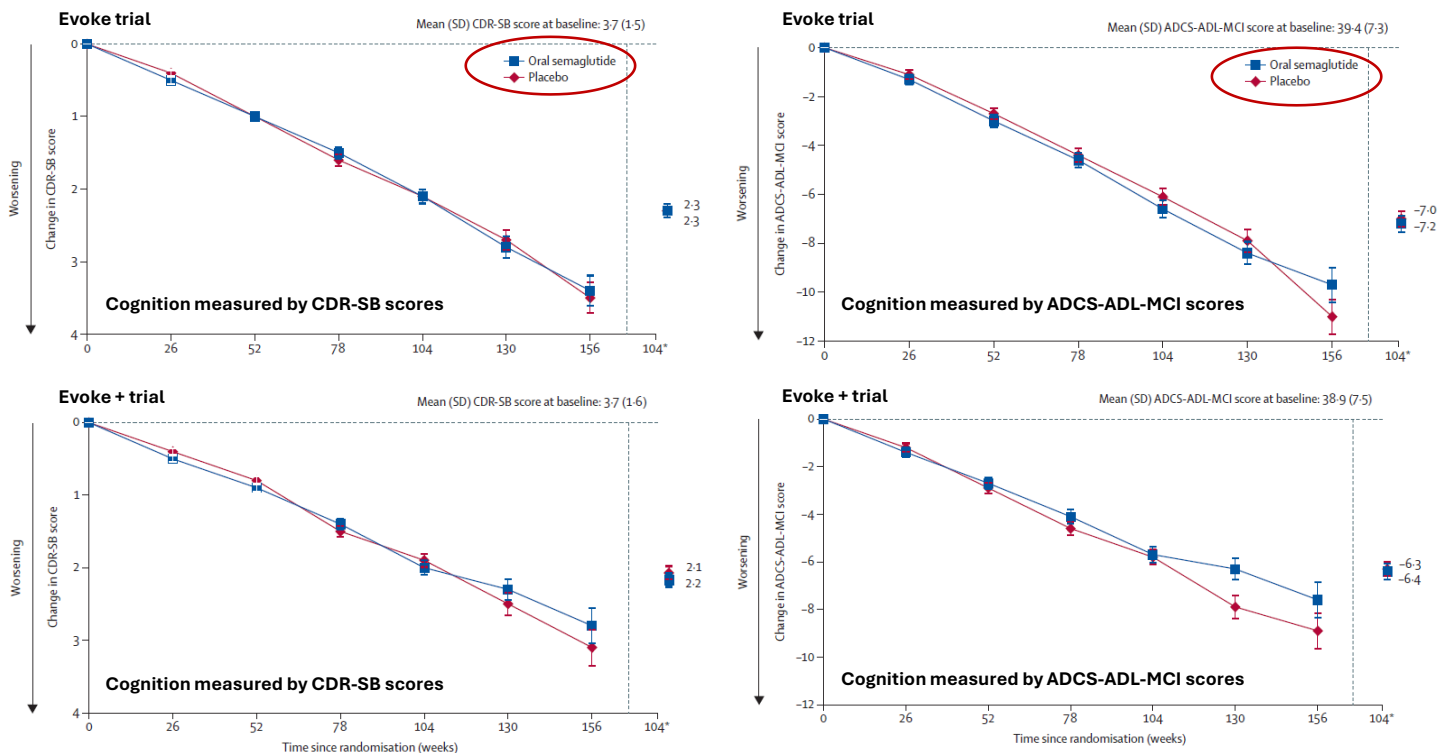


Source: Adapted from *The Lancet* (2025), Vol. 405, pp. 1580-1593 & *Diabetes Care* (2025), Vol. 49, pp. 1529-1535.

- ♦ **Peripheral artery disease – the STRIDE trial.** Novo Nordisk tested semaglutide as a therapy for peripheral artery disease in the 792-patient Phase III STRIDE trial, testing once-weekly semaglutide over a one-year monitoring period. Data were published in 2025 in *The Lancet*; Novo separately tested described STRIDE data in a 2025 paper in the journal *Diabetes Care*. In both papers, Novo showed that patients co-presenting with type II diabetes, high BMI & peripheral artery disease who were treated with once-weekly semaglutide dosing exhibited significantly improved maximum walking distance & pain-free walking distance at the end of the one-year dosing period (Exhibit 21). Peripheral vascular disease is a large & growing market in our view & we will be interested to see if Novo (or Eli Lilly with tirzepatide & its next-generation variations) will choose to more aggressively target this vascular disease with more clinical & commercial focus in coming quarters.

- ♦ **Alzheimer's disease – the Evoke & Evoke+ trials.** Novo's interest in funding a sizable Alzheimer's disease clinical program intrigues us for mechanistic reasons, since a role for dysregulated glucose metabolism in the brain & associated insulin resistance has often been featured as a risk factor in Alzheimer's disease progression (there are multiple review articles on this theme, one of which is a 2020 paper in the *International Journal of Molecular Science*). If semaglutide has impacted cognitive decline in patients presenting with Alzheimer's disease symptoms at enrollment, such data would have been transformational on the field & on its largely-beta-amyloid-targeted & acetylcholinesterase-targeted pharmacopeia.

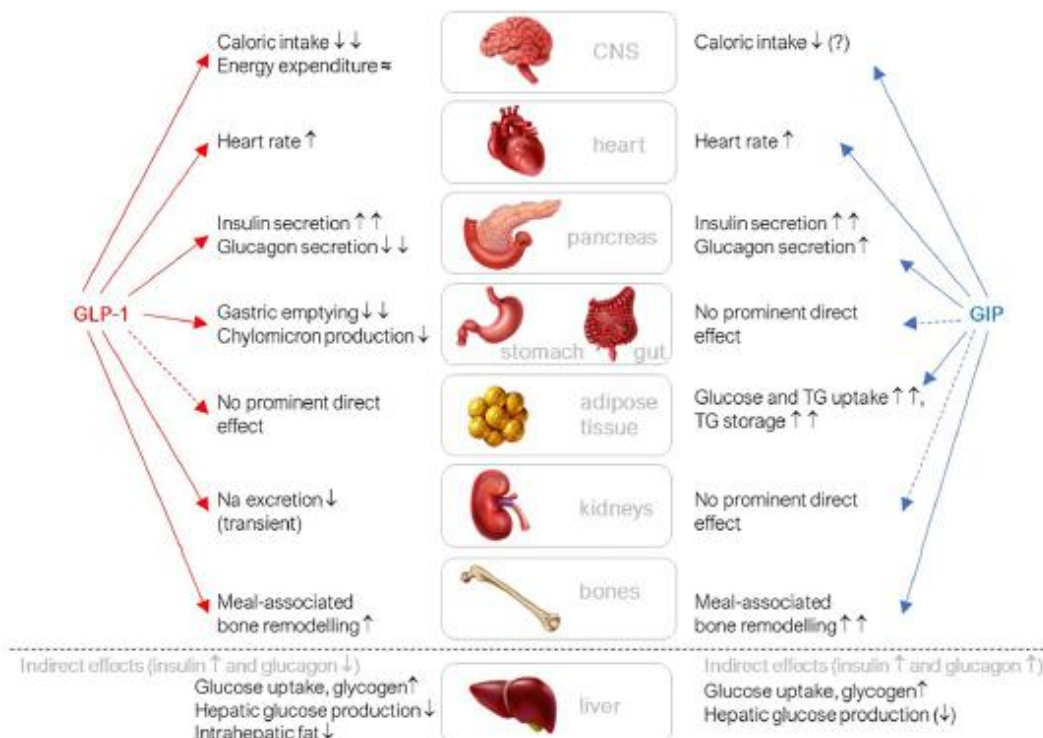
Exhibit 22. Plausible Rationale For Exploring Semaglutide's Blood Glucose-Modulating Insulinotropic Activity As A Cognition-Impacting Therapy, But No Signal Was Observed In Two Relatively Large Phase III Studies – The Evoke/Evoke+ Trials



Source: Adapted from *The Lancet* (2026). Vol. 407, pp. 2167-2179.

- ♦ Unfortunately, data from the 3,808-patient Phase III evoke & evoke+ trials failed to show impact on slowing cognitive decline in Alzheimer's disease, as shown in Exhibit 22. Neither of the two major measures of cognition (the CDR-SB scoring method & the ADCS-ADL-MCI scoring method) showed any significant impact from chronic semaglutide once-weekly dosing. If you squint, we believe one can see a modest benefit in the semaglutide arms during the third year of follow-up, but commentary in the paper thought not to emphasize this point, presumably because absence of benefit over the first two years of dosing clearly would limit semaglutide's commercial & clinical utility for the indication. But we reflect positively on Novo's decision to test the long-standing speculation on just how blood glucose brain chemistry could be impacted by endocrinologic agents like GLP-1, especially when prescription volumes for the entire GLP-1 category suggest that impact on cognition is a variable that could be closely monitored in longitudinal Phase IV studies anyway.

Exhibit 23. In Summary, There Are Multiple Favorable Benefits At The Organ/Tissue Level From Glucose-Dependent Insulinotropic Polypeptide (GIP) & Glucagon-Like Peptide-1 (GLP-1) Administration – All Arrows Point Upward On Rx Adoption



Source: Adapted from *Diabetes Obesity & Metabolism* (2021). Vol. 23 (Supplement 3), pp. 5-29.

Capital Markets Summary

Exhibit 24. EBITDA Or EPS-Positive Canadian Healthcare Stocks

Company	Filing Curr.	Sym.	Shrs Out. (M)	Share Price 8-Oct	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 ^{2,3}														
DRI Healthcare Trust	CAD	DHT.UN	55.0	\$18.25	1,003	1,003	1,554	1,554	6.3x	6.3x	6.0x	NA	7.2x	6.6x
Jamieson Wellness	CAD	JWEL	41.5	\$45.45	1,886	1,886	2,386	2,386	14.5x	13.3x	11.9x	24.1x	21.1x	18.2x
K-Bro Linen	CAD	KBL	13.0	\$40.74	530	530	828	828	7.1x	7.5x	7.2x	24.1x	21.1x	16.5x
Medical Facilities ¹	CAD	DR	16.2	\$10.45	169	241	307	438	5.5x	5.2x	5.2x	14.9x	5.9x	13.8x
Microbix Biosystems	CAD	MBX	136.7	\$0.32	43	43	43	43	NA	NA	NA	NA	NA	NA
Savaria	CAD	SIS	72.2	\$29.16	2,105	2,105	2,282	2,282	11.7x	11.1x	10.1x	23.8x	21.1x	18.7x
Profitable Canadian healthcare firms - specialty pharmaceuticals development/sales ²														
Apotex	CAD	APTX	228.5	\$32.47	7,419	7,419	11,940	11,940	NA	NA	11.7x	19.8x	NA	15.0x
Aurinia Pharma	USD	AUPH	133.1	\$16.01	2,130	3,037	2,297	3,274	9.5x	8.3x	6.6x	6.7x	17.0x	13.6x
Bausch Health	USD	BHC	374.1	\$6.15	2,301	3,280	31,187	44,454	5.6x	5.5x	5.9x	NA	1.3x	1.4x
BioSynt	CAD	RX	11.5	\$16.90	194	194	172	172	11.2x	10.8x	9.2x	19.4x	19.0x	15.6x
Cipher Pharma ¹	CAD	CPH	25.3	\$9.58	243	346	420	599	15.7x	14.6x	12.2x	8.4x	11.8x	10.9x
HLS Therapeutics ¹	CAD	HLS	30.4	\$2.98	91	129	173	246	10.6x	9.2x	7.7x	NA	NA	NA
Knight Therapeutics	CAD	GUD	98.2	\$10.71	1,052	1,052	836	836	8.5x	9.9x	9.5x	NA	NA	40.3x
Medexus Pharma ¹	CAD	MDP	32.0	\$3.42	109	156	181	257	10.8x	11.7x	8.4x	45.4x	NA	21.7x
Profitable Canadian healthcare firms - eldercare services or infrastructure developers														
CareRx	CAD	CRRX	63.4	\$3.25	206	206	274	274	8.9x	7.9x	6.9x	7.6x	37.1x	16.0x
Chartwell Retirement	CAD	CSH.UN	328.5	\$19.44	6,387	6,387	9,620	9,620	21.1x	18.9x	17.0x	NA	NA	NA
Extendicare	CAD	EXE	95.0	\$27.79	2,641	2,641	3,203	3,203	14.4x	12.6x	11.1x	21.0x	19.9x	18.2x
Vital Infrastructure	CAD	VITL.UN	250.0	\$5.20	1,300	1,300	2,503	2,503	12.4x	12.0x	11.6x	NA	NA	NA
Nova Leap Health	CAD	NLH	87.3	\$0.47	41	41	45	45	12.8x	NA	NA	30.2x	NA	NA
Sienna Senior Living	CAD	SIA	111.2	\$19.33	2,149	2,149	3,359	3,359	20.1x	16.5x	14.5x	36.8x	35.8x	30.7x
Profitable Canadian healthcare firms - medical equipment distribution/sales ⁴														
Covalon Technologies	CAD	COV	27.6	\$2.05	57	57	88	88	17.9x	14.4x	12.6x	12.9x	12.1x	10.3x
Viemed Healthcare	USD	VMD	38.1	\$11.88	452	452	506	722	6.5x	5.6x	4.9x	31.4x	28.7x	21.9x
Profitable Canadian healthcare firms - healthcare IT or digital IT services firms ⁵														
Healwell AI	CAD	AIDX	304.8	\$0.75	229	229	274	274	NA	36.9x	19.1x	NA	NA	NA
Hydreight	CAD	NURS	53.7	\$3.43	184	184	174	174	22.6x	8.9x	5.0x	25.3x	11.4x	7.2x
Vitalhub	CAD	VHI	63.4	\$7.25	460	655	328	328	11.2x	9.6x	7.9x	NA	39.2x	23.6x
Well Health	CAD	WELL	256.0	\$4.27	1,093	1,093	1,966	1,966	9.4x	10.4x	9.6x	NA	16.8x	12.0x
Average									11.9x	11.6x	9.7x	22.0x	19.2x	16.6x
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

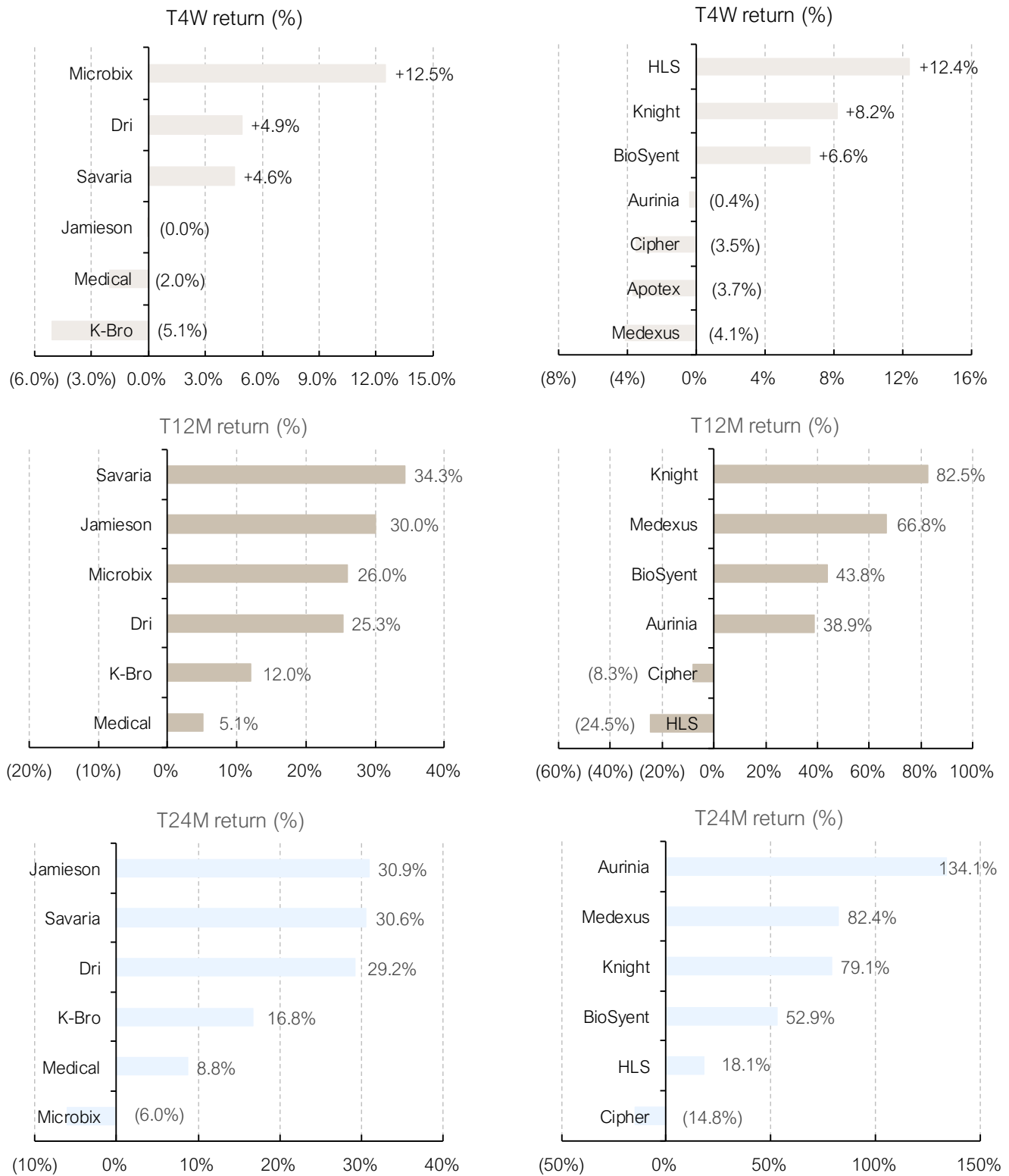
³ Dentalcorp Holdings was acquired by US private equity firm GRRCR LLC in Sept/25 for an EV of C\$3.3B (market value C\$2.1B); transaction closed in Jan/26

⁴ Quipt Home Medical was acquired by Kingswood Capital & Forager Capital for US\$3.65/shr in Dec/25, transaction closed in Mar/26

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

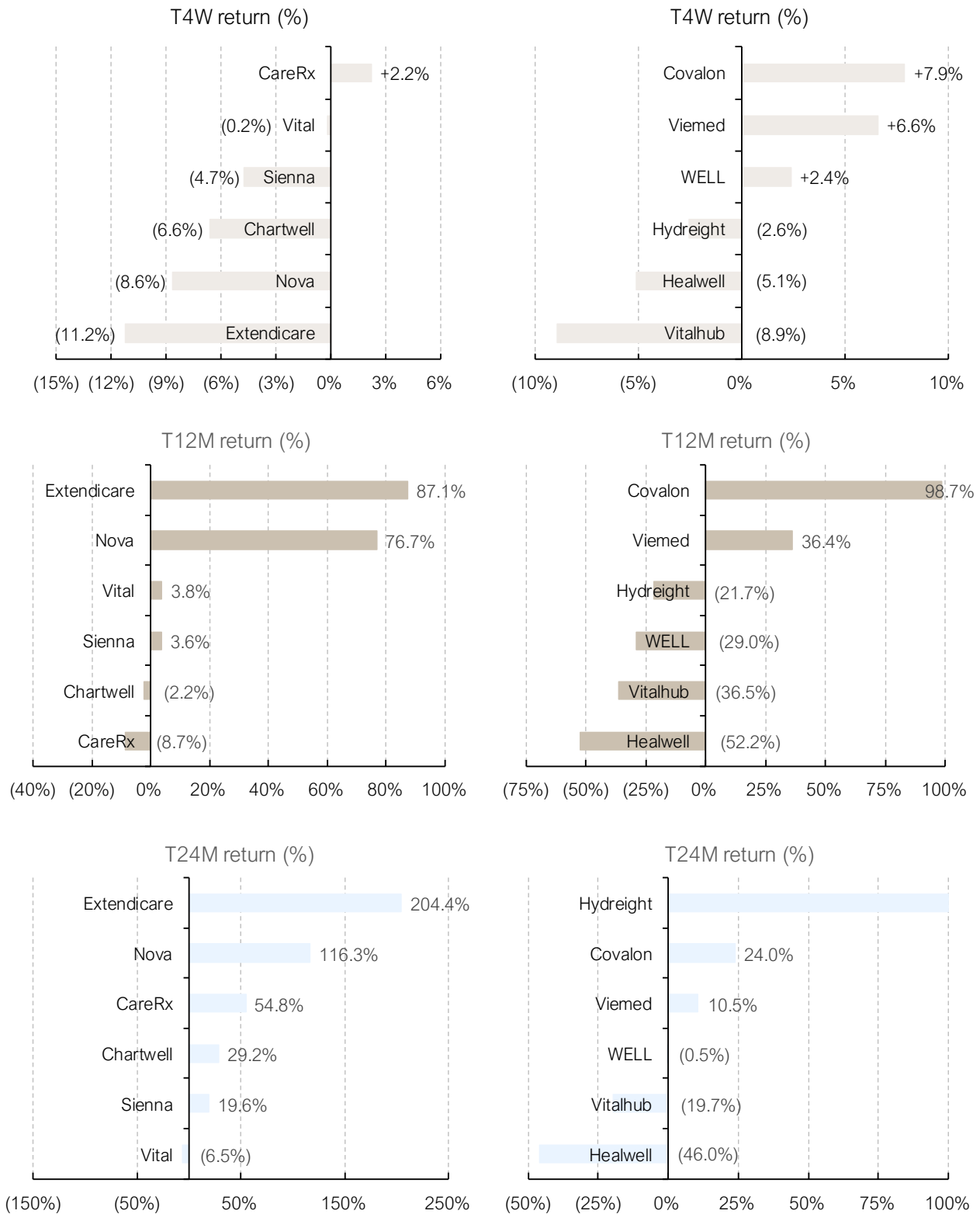
Source: Refinitiv, company reports, Leede Financial

Exhibit 25. 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 26. 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 (Hydreight's T24M return is 1,007%)

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Speculative Buy	The security is considered a BUY but carries an above-average level of risk.
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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