Evaluate Vantage

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Tirzepatide’s time to shine for Lilly

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Tirzepatide’s clinical programme is set to double in size when a huge head-to-head outcome study gets under way. Costs will balloon too.

Lilly confirmed last week that it had huge hopes for its experimental diabetes project tirzepatide. A 12,500-patient cardiovascular outcome trial (CVOT) will start later this year, pitting the dual GIP/GLP-1 agonist against Trulicity, a similarly acting agent that is also the company’s best-selling drug.

Executives are not wrong when they describe the move as “bold”, though with Trulicity losing patent protection in 2027 they presumably feel the risk is worth taking. But the new trial represents a massive financial commitment. *EvaluatePharma Vision*’s R&D cost model* estimates that Trulicity’s CVOT was the most expensive ever run for a GLP-1 agonist. Tirzepatide’s, though, could set a new record.

The Trulicity Rewind trial cost Lilly almost $2bn to run, it is estimated; of the GLP-1 agonist CVOTs Rewind was the longest undertaken, although at almost 10,000 patients enrolment was similar to the outcome studies conducted with Novo Nordisk’s Rybelsus and Victoza, and Glaxosmithkline’s Tanzeum.

Shorter and smaller CVOTs bring down the average in the table below, but the details laid out by Lilly last week indicate that tirzepatide’s test of cardiovascular safety will not come cheap.

Crunching the numbers: the cost of GLP-1 trials	
Mean enrollment in GLP-1 outcome studies	7,747
Estimated mean cost of GLP-1 outcome studies	$868m
Enrollment in Trulicity's Rewind outcome study	9,901
Estimated cost of Rewind	$1.9bn
Enrollment in tirzepatide's Surpass-CVOT outcome study	12,500
Estimated cost of Surpass-CVOT*	???
**Cost will be estimated once trial listed in clinicaltrials.gov. Source: EvaluatePharma Vision.*	

To be called Surpass-CVOT, the study will recruit patients with type 2 diabetes and confirmed atherosclerotic cardiovascular disease. The primary endpoint will be time to the first occurrence of the composite endpoint of CV death, myocardial infarction, or stroke, and will assess both non-inferiority and superiority of tirzepatide versus Trulicity. Lilly estimates that the study will take just over four years to complete.

This trial alone will double the number of patients in whom the company plans to test tirzepatide. However, a look at the clinical programme already running shows that the company's ambitions for this project lie beyond diabetes. Impressive weight loss seen in phase II patients is fuelling hopes in obesity, while a mid-stage programme is also underway in Nash.

It is thought that hitting GIP adds effectiveness to GLP-1 agonism, though this comes at a cost. Tirzepatide's weak spot is likely to be tolerability, with very high rates of nausea, vomiting and diarrhoea having been reported in earlier trials. Lilly believes these can be managed with dose titration but the very long run-in proposed – up to 20 weeks for the highest dose being tested – could limit the project's appeal.

As such, until the Surpass programme starts to read out towards the end of this year, the real potential of tirzepatide is hard to estimate.

Not that this has held the sellside back: consensus forecasts indicate a launch in 2022 and a swift ramp to sales of $1.6bn by 2024. This surely represents a best-case scenario, though after committing billions to this project, Lilly must be expecting nothing less.

Tirzepatide's late-stage clinical programme				
Status	**Acronym**	**N**	**Details**	**Primary completion**
Phase III	Surpass-1	472	In T2D not controlled with diet and exercise	Oct 2020
	Surpass-2	1,872	vs Ozempic + metformin in T2D	Mar 2021
	Surpass-3	1,420	vs Tresiba in T2D	Dec 2020
	Surpass-4	1,878	vs Basaglar in T2D patients with increased cardiovascular risk	May 2021
	Surpass-5	472	vs placebo in T2D inadequately controlled with Basaglar +/- metformin	Jan 2021
	Surpass J-combo	441	In T2D patients on oral antihyperglycaemic medications	Mar 2021
	Surpass J-mono	636	vs dulaglutide in T2D	Apr 2021
	Surpass-AP-combo	956	T2D patients on metformin +/- sulfonylurea	Feb 2022
	Surmount-1	2,400	Obese or overweight patients	Feb 2022
Phase II	Synergy-Nash	196	Nonalcoholic steatohepatitis	Mar 2022
Total in all clinical trials		**12,136**		
Source: EvaluatePharma.				

**EvaluatePharma Vision's R&D cost model estimates the cost of individual clinical programmes using real-world data. Company disclosed product-level spend and clinical trial patient numbers are combined to create cost per patient benchmarks by technology and therapy type. Utilising a matching algorithm, these benchmarks are applied to all commercially relevant clinical trials to estimate their cost, which can then be aggregated by product to estimate the cost of development of all products.*