Evaluate Vantage

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The cost to Astrazeneca of building Brilinta

Amy Brown

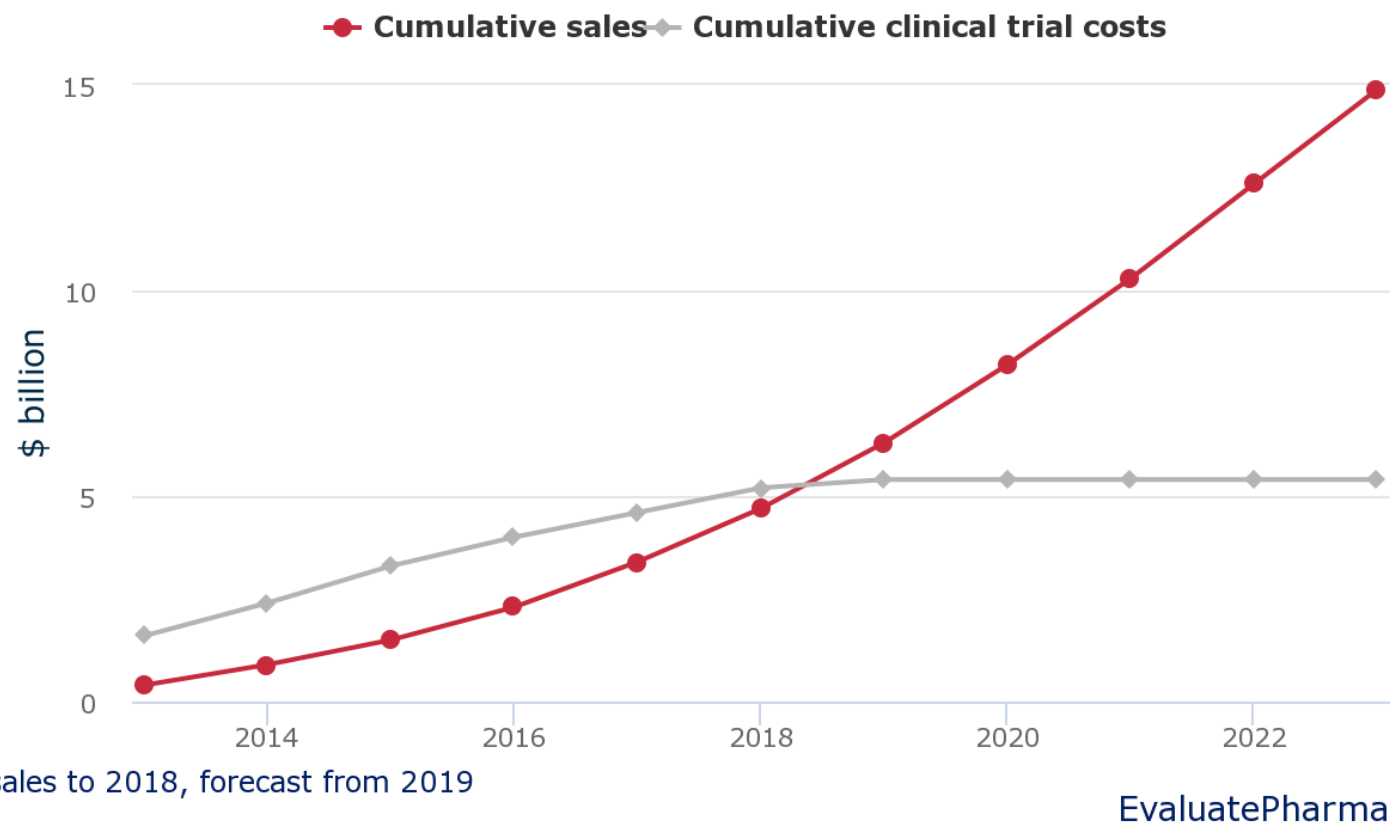
Thales, the final Brilinta outcome trial in Astrazeneca's huge Parthenon programme, has hit – but the UK group's vast investment in its blood thinner has yet to pay off.

Outcome studies designed to prove that a particular drug can help patients live longer are not a cheap undertaking. Therefore Astrazeneca's Parthenon series, which involved six such trials of Brilinta, represented a massive investment commitment.

How big? Total Parthenon costs are likely to reach $3.7bn, according to *EvaluatePharma Vision*'s R&D cost model*, a figure that does not include the expense of running the 80-odd other studies that have been conducted with the product. Some of these are investigator-sponsored, but the vast majority will have had Astrazeneca involvement: *EvaluatePharma* estimates that the total clinical trial costs associated with Brilinta will reach $5.4bn.

Companies risk these sums for the rewards of owning a life-saving drug, but it is hard to argue that in this case the spend was worth it. Plotting cumulative clinical trial costs against sales, below, suggests a breakeven point for Brilinta in 2018. However, this does not factor in the cost of actually selling the drug, which will push profitability further out. The final twist here is the arrival of generics, which are expected in late 2024.

Brilinta: cumulative clinical trial costs and sales



Brilinta has long been a commercial disappointment, largely because of the bleeding risk that the Parthenon programme has arguably laid bare. The 11,000-patient Thales trial, which was toplined today, is a case in point.

The study recruited patients who had suffered a minor acute ischaemic stroke or high-risk transient ischaemic attack, and Astra said Brilinta plus aspirin yielded a statistically significant and clinically meaningful reduction in its primary endpoint, a composite of the risk of stroke and death, at 30 days. This came at the expense of an increased bleeding rate, which has bedevilled the project before.

Stroke is a notoriously tough setting with substantial unmet need, but given Brilinta's bleeding risk it is hard to handicap the product's chance of approval here without knowing the magnitude of the benefit. That data remain under wraps for a medical conference.

Of the Parthenon programme only two studies have made it into the drug's label so far, while two have been clear failures. Astra told *Vantage* that it was still talking to regulators about the Themis data, which showed the clearest benefit in a prespecified subgroup of patients.

Astra's head of biopharmaceuticals R&D, Mene Pangalos, spoke to *Vantage* at the ESC meeting last September about the Themis trial, and his remarks summed up the crucial point with Brilinta: "The bleeding risk isn't any different to what we've seen before. The key is finding the population where we're going to see the optimal benefit/risk."

Astrazeneca has spent an awful lot of money finding that population. And in the meantime predictions of $3.5bn in peak Brilinta sales, made when Astra was fending off Pfizer, have looked increasingly unachievable. Even if Thales reveals an unequivocal benefit, the expensive decision to double down on Brilinta trials looks questionable.

Acropolypse: Astrazeneca's Parthenon programme				
Trial	**N**	**Cost per patient ($; estimated)**	**Total trial cost ($m; estimated)**	**Outcome**
Plato	18,624	34,544	643	Demonstrated benefit over Plavix in patients with ACS on background aspirin.
Pegasus	21,379	36,398	778	Brilinta plus aspirin demonstrated long-term benefit in heart attack patients, but with heightened bleeding risk.
Socrates	13,307	31,433	418	Failed to show benefit in secondary prevention setting in stroke patients, versus aspirin, at three months.
Euclid	13,885	40,357	560	Failed to show benefit over Plavix in PAD patients.
Themis	19,271	48,047	926	Hit primary endpoint in patients with CV disease and type 2 diabetes, but with heightened bleeding risk.
Thales	11,000	30,375	335	Brilinta plus aspirin hit primary endpoint in secondary stroke prevention, but with heightened bleeding risk.
		Total	**3,661**	

ACS=acute coronary syndrome. PAD=peripheral arterial disease. TIA=transient ischaemic attack. Source: EvaluatePharma Vision.

**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.*