Takeda’s pivotal trial has suggested that TAK-003 could work in both dengue-naïve and previously infected patients, making Sanofi’s Dengvaxia look irrelevant.

Sanofi was already on shaky ground with its dengue fever vaccine, Dengvaxia. Now the product looks likely to be relegated to the sidelines thanks to impressive data from the pivotal Tides trial of Takeda’s rival candidate, TAK-003.

Dengvaxia was approved by the US FDA in May, but only in children who had previously been infected with the virus, following concerns about its safety in dengue-naïve subjects. Notably, as well as looking good in the overall population, TAK-003 showed signs of efficacy in previously uninfected people, which could help the Takeda project get a broader label.

Still, the findings in the dengue-naïve, or seronegative, population are only exploratory so far, and Takeda will have to wait for more data to confirm TAK-003’s efficacy here.

And Takeda’s vaccine showed a much better performance against some strains of the virus than others, although these data were also exploratory.

**Turning Tides**

The results, from the first part of the 20,000-patient Tides study, were published yesterday in the NEJM. Previously, all Takeda had said was that the trial had met its primary endpoint with no serious safety concerns.

The study enrolled healthy children aged 4-16 in Asia and Latin America, who received either two doses of TAK-003 or placebo three months apart. The primary endpoint was the prevention of Dengue caused by any of the four different serotypes of the virus, known as DENV-1 to 4.

TAK-003’s overall efficacy was 80%, higher than the 59% pooled efficacy rate seen across Dengvaxia’s two phase III trials. The figure for Dengvaxia is skewed by its lack of efficacy in seronegative people; excluding this population, Dengvaxia’s efficacy was 77-81%, according to its US label, putting it in line with TAK-003.
Dengue data: cross-trial comparison of TAK-003 and Dengvaxia

<table>
<thead>
<tr>
<th>Project</th>
<th>Company</th>
<th>Overall</th>
<th>Seronegative at baseline</th>
<th>DENV-1</th>
<th>DENV-2</th>
<th>DENV-3</th>
<th>DENV-4</th>
</tr>
</thead>
<tbody>
<tr>
<td>TAK-003</td>
<td>Takeda</td>
<td>80%</td>
<td>75%</td>
<td>74%</td>
<td>98%</td>
<td>63%</td>
<td>63%**</td>
</tr>
<tr>
<td>Dengvaxia</td>
<td>Sanofi</td>
<td>59%*</td>
<td>38%*</td>
<td>55%</td>
<td>43%</td>
<td>72%</td>
<td>77%</td>
</tr>
</tbody>
</table>

*Pooled from two trials; **Results inconclusive. Source: Tides study, published in NEJM; WHO.

However, Dengvaxia is not just ineffective in the seronegative population – it could actually be harmful. A mass immunisation programme in the Philippines uncovered a link between the vaccine and more severe disease seen in previously uninfected children who went on to contract dengue (More Sanofi dengue setbacks could benefit Takeda, March 8, 2019).

This is where TAK-003 could have the edge: safety analyses have thrown up nothing to worry about so far. A secondary endpoint of Tides is the vaccine’s performance according to baseline infection status, and part one of the study found efficacy of around 75% in the seronegative group. This is only an exploratory finding at present and needs to be confirmed in the second part of the trial, which involves another six months of follow-up.

Another secondary endpoint that will be formally assessed in part two is TAK-003’s performance in the different dengue serotypes. In the exploratory analysis in part one, the vaccine did best against the strain known as DENV-2, but had only modest efficacy in the other serotypes. There were only a handful of cases of infection with the DENV-4 serotype, so these data were inconclusive.

There was also an indication, again not conclusive, that the vaccine might not be effective against the DENV-3 strain in people who were seronegative at baseline.

The picture should soon become clearer: Takeda plans to present data on TAK-003 at the American Society of Tropical Medicine and Hygiene, being held in Maryland on November 20-24, including a formal assessment of the secondary endpoints.

The commercial prospects of a vaccine against dengue, which is endemic in poorer countries, might be another matter. But if Takeda can prove TAK-003’s worth in seronegative subjects the vaccine could presumably have potential in travellers to dengue-afflicted regions, which would open up a broader market.

TAK-003 is forecast to bring in $453m in 2024, according to EvaluatePharma sellside consensus, making it Takeda’s most valuable pipeline asset. Whether it will live up to these expectations is just one of the unanswered questions around the vaccine. On the evidence so far, it has a better chance of making a mark than Dengvaxia.

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