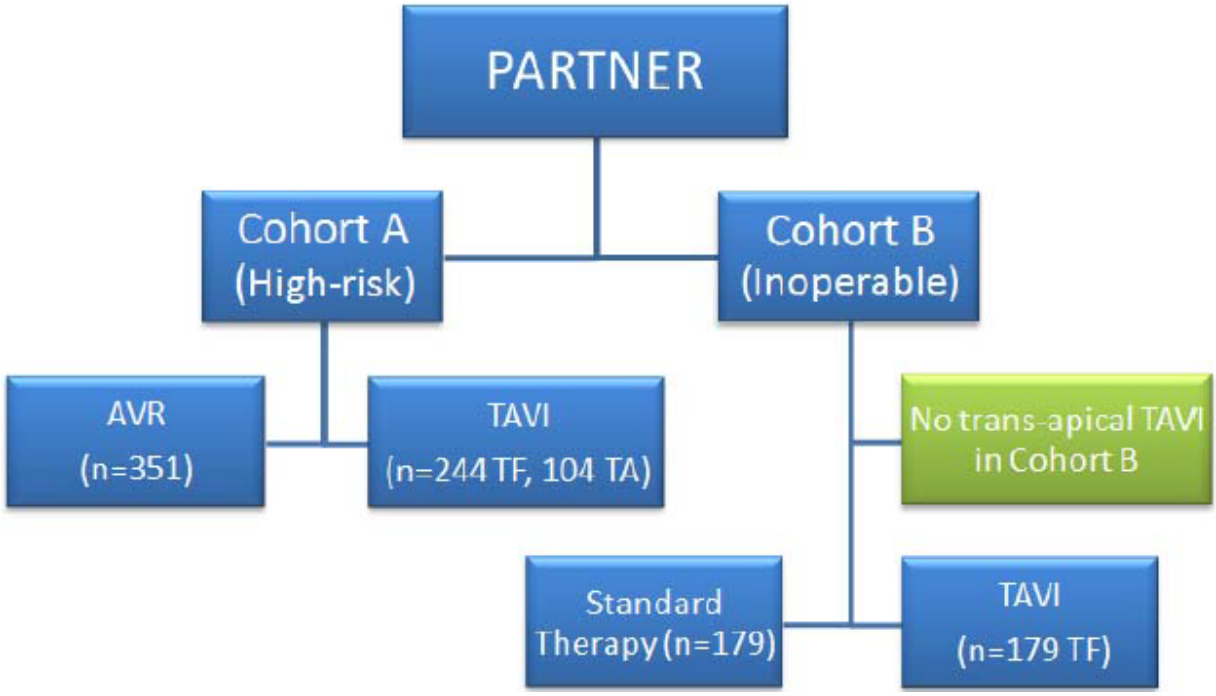
## Supplements

The PARTNER trial is an open-label, randomised study sponsored by Edward Lifesciences and was conducted in 25 centres: 21 in the US, 3 in Canada and 1 in Germany. High-risk patients with symptomatic severe aortic stenosis who were candidates for surgical aortic valve replacement were eligible to participate in the study. After screening, they were stratified into two groups (Figure 4):[1 2]

1. Cohort A included high-risk patients with an estimated operative mortality risk of at least 10% by the STS score, or at least 15% due to other severe problems not included in the STS score.
2. Cohort B included patients considered as inoperable by at least two heart surgeons either due to anatomical factors (thoracic wall malformation, repeated previous thoracic surgeries, significant aortic calcification – so-called porcelain aorta, sequelae of radiotherapy) or due to concomitant severe medical conditions.

**Figure 4: The PARTNER trial design**




AVR: surgical aortic valve replacement; TA: transapical; TAVI: transcatheter aortic valve implantation; TF: transfemoral. Cohort A of the TAVI group was composed of a transfemoral (TF) subgroup and a transapical (TA) subgroup. Only the transfemoral approach was used in cohort B.

Thereafter, the patients underwent a second stratification by whether or not it was technically possible in the patient in question to gain access to the heart with the necessary catheters through a femoral artery.

1. Cohort A patients were randomised to transfemoral or transapical TAVI depending on whether or not transfemoral access was possible versus the classical surgical treatment (aortic valve replacement - AVR). In the analysis of the primary endpoint of the trial (all-cause mortality), both TAVI variants together were compared with surgery.
2. Cohort B patients with the possibility of a transfemoral access were randomised to transfemoral TAVI versus a standard therapy which, in addition to medication, generally involved balloon aortic valvuloplasty, a technique where the narrowed aortic valve is dilated with a balloon. The study sponsor opted not to include cohort B patients without a transfemoral access in the study, though this was originally asked by the FDA.

According to the study protocol,[11] quality of life was also measured with the EQ-5D questionnaire that allows mapping of health status to population-level utility weights. This is an important metric for cost-effectiveness analysis. No further information is provided on the mapping of the health states to utility weights. The EQ-5D results are not published. These data were requested directly from the study sponsor and provided in Table 3.

**Table 3: EQ-5D values for inoperable patients.**

| EQ-5D Utilities | TAVI | Standard therapy |
|---|---|---|
| **Baseline** | 0.59 ± 0.23 | 0.57 ± 0.23 |
| **1 month** | 0.71 ± 0.23 | 0.64 ± 0.22 |
| **6 months** | 0.72 ± 0.26 | 0.66 ± 0.24 |
| **12 months** | 0.72 ± 0.24 | 0.62 ± 0.23 |

Source: information provided by the study sponsor.

These variables were modeled as beta distributions with the same mean and standard deviation.

The percentage of observed events after 30 days and one year in high-risk operable and inoperable patients of the PARTNER trial (Table 4) are used in the economic model.

**Table 4: Overview of events.**

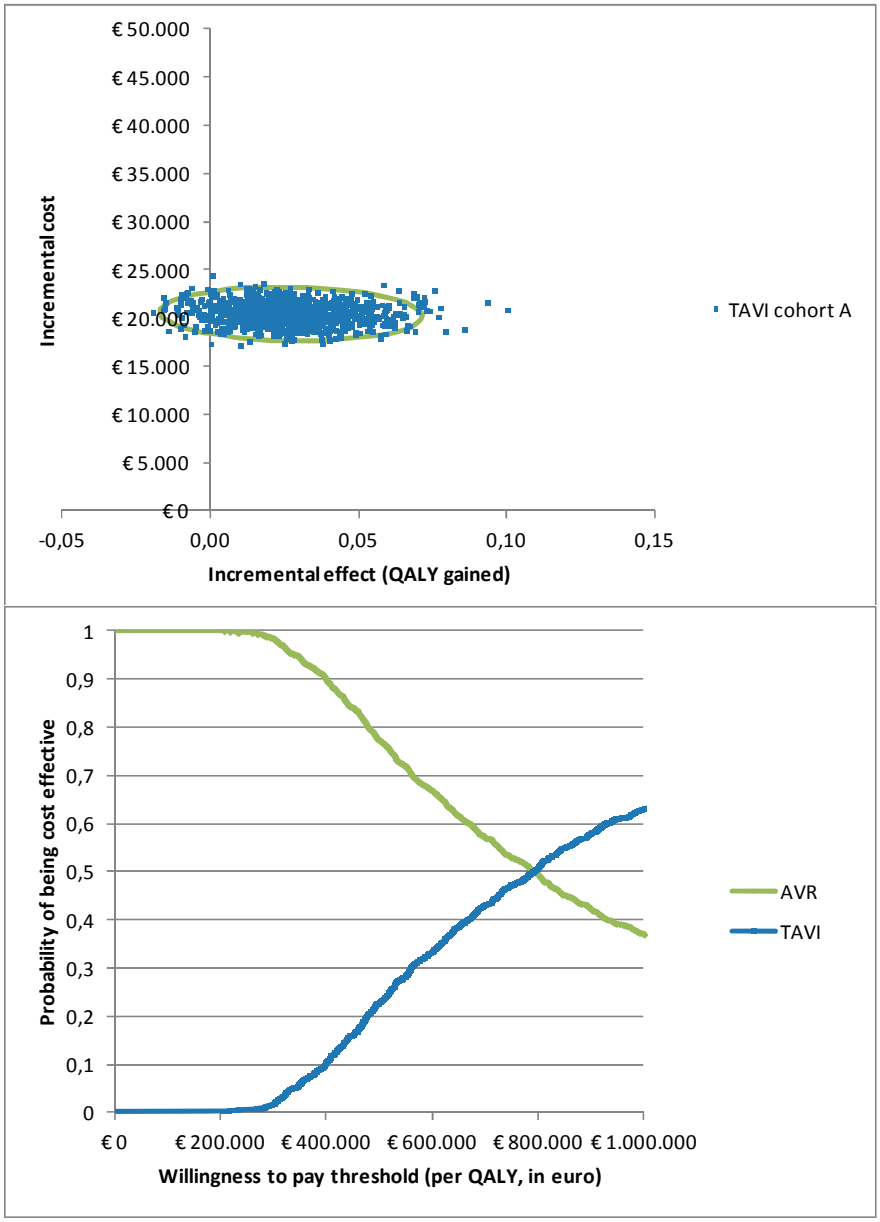
| Event | High-risk operable patients | | Inoperable patients | |
|---|---|---|---|---|
| | TAVI | AVR | TAVI | Standard |
| **Repeat hospitalization** | | | | |
| 30 days | 4.4% | 3.7% | 5.6% | 10.1% |
| 1 year | 18.2% | 15.5% | 22.3% | 44.1% |
| **Major stroke** | | | | |
| 30 days | 3.8% | 2.1% | 5.0% | 1.1% |
| 1 year | 5.1% | 2.4% | 7.8% | 3.9% |
| **Minor stroke** | | | | |
| 30 days | 0.9% | 0.3% | 1.7% | 0.6% |
| 1 year | 0.9% | 0.7% | 2.2% | 0.6% |
| **TIA** | | | | |
| 30 days | 0.9% | 0.3% | 0% | 0% |
| 1 year | 2.3% | 1.5% | 0.6% | 0% |
| **Repeat TAVI** | | | | |
| 30 days | | | 1.7% | |
| 1 year | | | 1.7% | |
| **Aortic-valve replacement** | | | | |
| 30 days | | | 0% | 1.7% |
| 1 year | | | 1.1% | 9.5% |
| **Valvuloplasty** | | | | |
| 30 days | | | | 63.7% |
| 1 year | | | | 83.8% |

Source: High-risk operable patients: Smith et al.,[2] Inoperable patients: Leon et al.[1]

Remark: results were not published for the Continued Access trial and could not be included in the model.

Based on the results in high-risk operable patients of the PARTNER trial, the incremental effects of TAVI in comparison with AVR are on average 0.03 (95%CI -0.01 – 0.07) quality-adjusted life-years (QALYs). In combination with substantial incremental costs (on average €20,397; 95%CI 18,278 - 22,617), this results in relatively very high ICERs of about €750,000 per QALY. This contrast between minimal gains and substantial expenses is also shown on the cost-effectiveness plane (Figure 5). The cost-effectiveness acceptability curve (Figure 5) indicates that a willingness-to-pay for a QALY gained of more than €750,000 is needed to have about 50% chance the intervention is considered cost-effective.

**Figure 5: Cost-effectiveness plane (top) and cost-effectiveness acceptability curve (bottom) for TAVI in high-risk operable patients.**




The green curve on the cost-effectiveness plane is the 95% confidence ellipse.

Only including results of the pivotal trial, without taking into account the conflicting mortality results of the smaller Continued Access trial results in a more favorable ICER of €37,400 per QALY gained (Table 5). Since detailed information was only available for the pivotal trial, sensitivity analyses are based on this analysis. Together with the other scenarios, the base case scenario (mortality pivotal trial + Continued Access) is presented on the tornado graph (Figure 6).

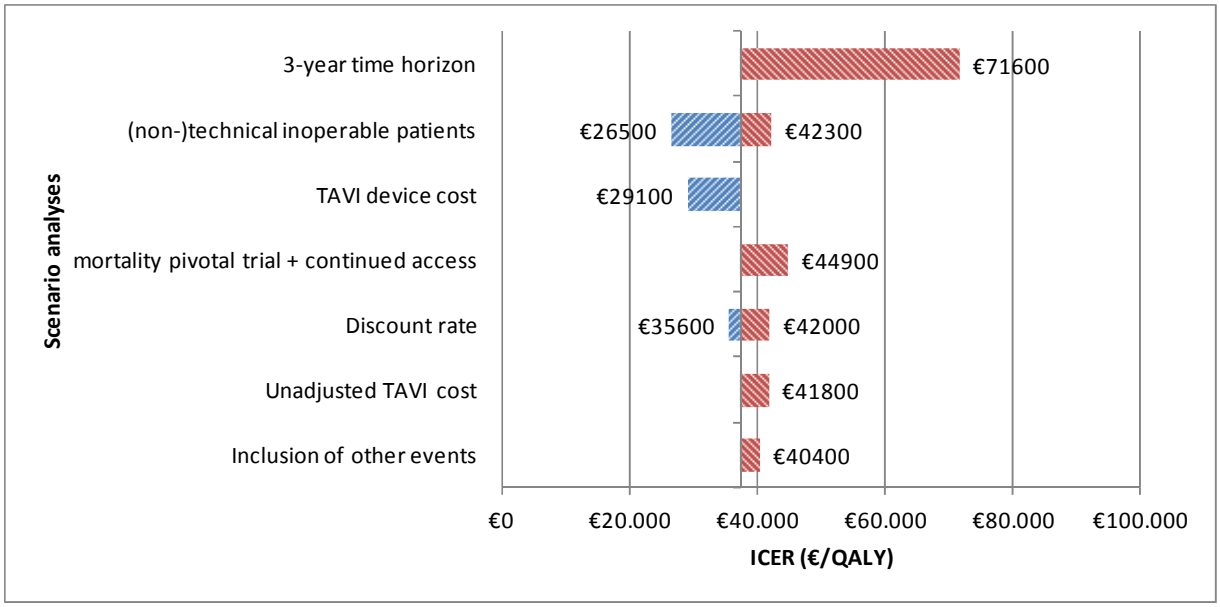
**Table 5: Incremental costs, incremental effects and incremental cost-effectiveness ratio for inoperable patients (based on combined and pivotal trial results).**

| Inoperable patients | Combined | | Pivotal | |
|---|---|---|---|---|
| **IC** | €33,243 | | €34,590 | |
| | €27,452 | €37,773 | €29,881 | €38,631 |
| **IE (LYG)** | 0.88 | | 1.16 | |
| | 0.39 | 1.41 | 0.65 | 1.75 |
| **IE (QALY)** | 0.74 | | 0.92 | |
| | -0.44 | 1.69 | -0.29 | 1.90 |
| **ICER (€/LYG)** | €42,647 | | €31,856 | |
| | €23,655 | €86,311 | €20,259 | €51,554 |
| **ICER (€/QALY)[a]** | ***€44,932*** | | ***€37,432*** | |

IC: incremental cost; ICER: incremental cost-effectiveness ratio; IE: incremental effect; LYG: life-year gained; QALY: quality-adjusted life-year.

a: The probabilistic average and 95%CI are mentioned where appropriate. This approach is not reliable in case the simulated ICERs are spread over several quadrants of the cost-effectiveness plane. As an alternative (in italics), in these cases, the presented ICERs are calculated by dividing the mean incremental cost by the mean incremental benefit.

**Figure 6: Tornado graph one-way sensitivity analyses for inoperable patients (based on data from the pivotal PARTNER trial).**



As noted by FDA, there are limited data beyond 2 years from the PARTNER trial and the long-term mortality benefit of the SAPIEN remains unclear. The shape of the survival curve indicates that the survival benefit might reduce after two years (Figure 7). Long-term follow-up is needed to further evaluate this.

**Figure 7: Published survival curves for inoperable patients (top: Leon et al.[1]; bottom: FDA analysis[4])**