**Appendices**

# Appendix A: Patient inclusion and exclusion criteria

**Table A.1:** **Patient inclusion and exclusion criteria**

|  |  |
| --- | --- |
| Inclusion criteria | Patients were included if:   * Age ≥70 * STS Score ≥4 or “intermediate risk” for AVR as determined by heart team * Heart team (comprised at a minimum, of one Interventional Cardiologist and one Cardiac Surgeon) agrees on eligibility including assessment that TAVI is appropriate * Heart team agrees (a priori) on treatment strategy for concomitant coronary disease (if present) * Patient has senile degenerative aortic valve stenosis with echocardiographically derived criteria: mean gradient >40 mmHg, jet velocity greater than 4.0 m/s, an initial AVA of ≤1.0 cm2, or indexed EOA <0.5 cm2/m2. * Qualifying echo must be within 180 days of the date of the procedure. If a qualifying echo falls outside 180 days, the investigator may petition the Sponsor for study consideration * Patient is symptomatic from his/her aortic valve stenosis, as demonstrated by NYHA functional class II or greater * The heart team agrees (and verified in the case review process) that valve implantation will likely benefit the patient * The study patient or the study patient’s legal representative has been informed of the nature of the study, agrees to its provisions and has provided written informed consent as approved by the HREC of the respective clinical site * The study patient agrees to comply with all required post-procedure follow-up visits |
| Exclusion criteria | Patients were excluded if   * Age <70 years * Evidence of an acute myocardial infarction (MI) ≤1 month (30 days) before the intended treatment [(defined as: Q wave MI, or non-Q wave MI with total CK elevation of CK - MB ≥ twice normal in the presence of MB elevation and/or troponin level elevation (WHO definition)] * Aortic valve is a congenital unicuspid or congenital bicuspid valve, or is non-calcified * Evidence of mixed aortic valve disease (AS and aortic regurgitation with predominant aortic regurgitation >3+) * Pre-existing bioprosthetic valve in any position * Complex coronary artery disease: * Unprotected left main coronary artery * Syntax score >32 (in the absence of prior revascularization) * Any therapeutic invasive cardiac procedure resulting in a permanent implant that is performed within 30 days of the index procedure (unless part of planned strategy for treatment of concomitant coronary artery disease). Implantation of a permanent pacemaker is not excluded. * Any patient with a BAV within 30 days of the procedure (unless BAV is a bridge to procedure after a qualifying echocardiogram). * Leukopenia (WBC <3000 cell/mL), acute anemia (Hgb <9 g/dL), thrombocytopenia (platelets <50,000 cell/mL) * Hypertrophic cardiomyopathy with or without obstruction (HOCM) * Severe ventricular dysfunction with left ventricular ejection fraction (LVEF) <20% * Echocardiographic evidence of intracardiac mass, thrombus or vegetation * Active upper gastrointestinal (GI) bleeding within 3 months (90 days) prior to procedure * A known contraindication or hypersensitivity to all anticoagulation regimens, or inability to be anticoagulated for the study procedure * Native aortic annulus size <18 mm or >27 mm as measured by echocardiogram * Clinically (by neurologist) or neuroimaging confirmed stroke or transient ischemic attack (TIA) within 6 months (180 days) of the procedure * Renal insufficiency (creatinine >265 micromol/L) and/or renal replacement therapy at the time of screening * Estimated life expectancy <12 months (365 days) due to carcinomas, chronic liver disease, chronic renal disease or chronic end stage pulmonary disease * Expectation that patient will not improve despite treatment of aortic stenosis * Significant aortic disease, including marked tortuosity (hyperacute bend), aortic arch atheroma [especially if thick (>5 mm), protruding or ulcerated] or narrowing (especially with calcification and surface irregularities) of the abdominal or thoracic aorta, severe “unfolding” and tortuosity of the thoracic aorta * Iliofemoral vessel characteristics that would preclude safe placement of 16F, 18F or 20F introducer sheath such as severe obstructive calcification, severe tortuosity or minimum average vessel size less than <6 mm for the 23 mm system, <6.5 mm for the 26 mm system or <7.0 for the 29 mm system * Currently participating in an investigational drug or another device studya * Active bacterial endocarditis or within 6 months (180 days) of procedure. |

AS = aortic stenosis ; AVA = aortic valve area; BAV = balloon aortic valvuloplasty ; CK = creatine-kinase; CK-MB = creatine kinase-MB isoenzyme; EOA = effective orifice area; F = French; GI = gastrointestinal; Hgb = hemoglobin; HOCM = Hypertrophic cardiomyopathy with or without obstruction ; HREC = human research ethics committee ; LVEF = left ventricular ejection fraction; MI = myocardial infarction; NYHA = New York Heart Association; AVR = aortic valve replacement; STS = Society of Thoracic Surgeons; TAVI = transcatheter aortic valve implantation; TIA = transient ischemic attack; WBC = white blood cell; WHO = World Health organization.

a Trials requiring extended follow-up for products that were investigational, but have since become commercially available, are not considered investigational trials

# Appendix B: Additional results of the SOLACE-AU trial

**Table B.1: Primary endpoint at 30 days (AT-population)**

|  |  |
| --- | --- |
| **Study Endpoint** | **TAVI (N = 199)** |
| Primary Endpoint, KM Estimate as a % [95%CI]  All-cause mortalitya  All strokea  Life-threatening bleedinga  Acute kidney injury – Stage 3 (Including renal replacement therapy)  Coronary artery obstruction requiring intervention  Major vascular complicationa  Valve-related dysfunction requiring repeat procedure | 12.1 [8.3, 17.5]  2.5 [1.1, 5.9]  3.5 [1.7, 7.3]  3.5 [1.7, 7.2]  0.5 [0.1, 3.5]  0.0 [0.0, 0.0]  6.0 [3.5, 10.4]  0.0 |

CI = confidence interval; KM = Kaplan-Meier; TAVI = transcatheter aortic valve implantation

aAdjudicated by CEC

**Table B.2: Site-reported deaths by cause of death through 2 years (AT-population N = 199)**

| **Cause of Death and Relationship** | **KM Estimate [95%CI]** | | | **All Events to End of Reporting Period**  **n (%N)** |
| --- | --- | --- | --- | --- |
| **30 Days** | **1 Year** | **2 Years** |
| All-cause mortality | 2.5 [1.1, 5.9] | 8.7 [5.5, 13.6] | 16.8 [12.2, 23.0] | 50 (25.1) |
| Cardiac | 2.5 [1.1, 5.9] | 4.6 [2.4, 8.6] | 8.8 [5.4, 13.9] | 23 (11.6) |
| Non-cardiac | 0.0 [0.0, 0.0] | 3.8 [1.8, 7.8] | 7.8 [4.7, 12.9] | 19 (9.5) |
| Unknown cause of death | 0.0 [0.0, 0.0] | 0.5 [0.1, 3.8] | 1.1 [0.3, 4.4] | 8 (4.0) |

CI = confidence interval; KM = Kaplan-Meier

**Table B.3: Device success (AT population N = 199)**

| Parameter (m, %n) | TAVI |
| --- | --- |
| Device Success (n = 190)  Successful vascular access device and delivery system (n = 199)  Correct position of the device (n = 199)  Intended performance of the valvea (n = 188)  Only one valve implanted in the proper location (n = 199) | 167/190 (87.9)  194/199 (97.5)  196/199 (98.5)  172/188 (91.5)  196/199 (98.5) |

TAVI = transcatheter aortic valve implantation

a Intended performance of the prosthetic heart valve (mean aortic valve gradient <20 mmHg or peak velocity <3 m/s, without moderate or severe prosthetic valve AR). For the intended performance of the valve, the post procedure echo was used if available. Otherwise, the earliest post-procedure echo was used through 30 days.

[Figure B.1 near here]

**Table B.4: NYHA functional class changes (VI population)**

| **Change** | **NYHA functional class, n/N (%)** | | |
| --- | --- | --- | --- |
| **Improved** | **Same** | **Worsened** |
| Baseline to 30-day visit | 161/186 (86.6) | 23/186 (12.4) | 2/186 (1.1) |
| Baseline to 6-month visit | 149/168 (88.7) | 17/168 (10.1) | 2/168 (1.2) |
| Baseline to 1-year visit | 134/149 (89.9) | 15/149 (10.1) | 0/147 |

NYHA = New York Heart Association

[Figure B.2 near here]

**Table B.5: Mean gradient, peak gradient and effective orifice area through year 2 (VI population)**

| **Variable**, mean ± SD | **Visit** | **Value** | **Change From Baseline** |
| --- | --- | --- | --- |
| Mean Gradient, mmHg | Baseline | 50.0 ± 14.63 | NA |
| Post-Procedure | 10.6 ± 4.13 | -38.8 ± 12.25 |
| 30 Day | 10.4 ± 5.39 | -39.5 ± 13.22 |
| 1 Year | 10.5 ± 4.01 | -39.3 ± 13.66 |
| 2 Years | 10.3 ± 4.39 | -38.6 ± 12.77 |
| Peak Gradient, mmHg | Baseline | 80.8 ± 23.14 | NA |
| Post-Procedure | 19.9 ± 7.87 | -61.2 ± 20.87 |
| 30 Day | 18.9 ± 7.03 | -61.7 ± 21.23 |
| 1 Year | 19.4 ± 7.01 | -60.9 ± 21.80 |
| 2 Years | 18.8 ± 8.14 | -59.7 ± 19.67 |
| EOA, cm2 | Baseline | 0.7 ± 0.21 | NA |
| Post-Procedure | 1.8 ± 0.47 | 1.1 ± 0.43 |
| 30 Day | 1.7 ± 0.46 | 1.0 ± 0.43 |
| 1 Year | 1.7 ± 0.44 | 1.0 ± 0.46 |
| 2 Years | 1.7 ± 0.54 | 1.1 ± 0.5 |

EOA = effective orifice area; mmHg = millimeters of mercury; NA = not assessed SD = standard deviation

# Appendix C: Costing Analyses

**Cost analyses**

In the estimation of hospital costs and resource usage for the SOLACE-AU trial, a micro-costing approach using ‘cost-bucket’ data from 1) The Prince Charles Hospital (TPCH) in Brisbane, Queensland and 2) the Fiona Stanley Hospital (FSH) and Royal Perth Hospital (RPH) in Perth, Western Australia (hereafter referred to as FSH/RPH) was considered [24]. These hospitals are the most mature facilities providing TAVI, and account for >50% of the procedures performed in the SOLACE-AU trial.

The average cost per Emergency Department (ED) presentation was estimated using data from Rounds 16-20 of the NHCDC costing reports for admitted and non-admitted patients across Australia [25, 26]. Similarly, the average cost pertaining to the relevant Tier 2 (i.e. specialty) outpatient clinic was used to estimate the costs attributed to the relevant category of outpatient visit accrued at the 30-day, 6-month and 1-year follow-up periods. All costs are reported in AU$2016 values (AU$1 = US$0.72) and were calculated from the perspective of costs to the Australian health care system.

The results of the cost analyses are presented in Tables C1 and C2 and Figure C1 below. These costing analyses were performed to explore the potential drivers for TAVI in the Australian setting.

**Table C1: Comparison of index hospitalization costs, TAVI prostheses costs and procedural costs (as-treated for TPCH and FSH/RPH)**

|  |  |  |
| --- | --- | --- |
| **Cost parametera** | **TPCH and FSH/RPH**  **(N = 99)** | |
| **Mean (SD)** | **95% CI** |
| **Index hospitalization costb**  **Procedure cost**  **Prosthesis cost**  **TAVI costc** | $28,389 ($15,868)  $13,673 ($9,035)  $29,574 ($5,514)  $ 57,963 ($16,835) | $25,224 - $31,554  $11,871 - $15,475  $28,474 - $30,674  $54,606 - $61,321 |

FSH = Fiona Stanley hospital; TPCH = The Prince Charles Hospital; RPH = Royal Perth Hospital; TAVI = transcatheter aortic valve implantation

aAdjusted for inflation to 2016 $AUD

bExcludes prosthesis cost

cCost of index hospitalization and prosthesis

[Figure C1 near here].

**Table C2: Cumulative ED attendances and outpatient visits costs over time (Valve Implant population)**

| **Variable** | **30-day visit** | **6-month visit** | **1-year visit** |
| --- | --- | --- | --- |
| **ED attendances** | | | |
| Cost per patient  Non-admitted patients b  Mean (SD)  Median, [IQR]  Admitted patients c  Mean (SD)  Median [IQR] | $612 ($225)  $506 [$483, $540]  $1,201 ($520)  $1,070 [$1,041, $1,093] | $743 ($474)  $506 [$483, $994]  $1,675 ($1,064)  $1,070 [$1,026, $2,185] | $925 ($619)  $540 [$483, $1,029]  $2,519 ($1,655)  $2,074 [$1,041, $3,072] |
| **Outpatient visits** | | | |
| Cost per patient a  Unadjusted  Mean (SD)  Median [IQR] | $428 ($156)  $337 [$337, $374] | $966 ($522)  $748 [$674, $1,122] | $1,286 ($599)  $1,011 [$1,011, $1,685] |
| Adjusted (lower) d  Mean (SD)  Median [IQR] | $364 ($133)  $286[$286, $318] | $819 ($441)  $636 [$573, $954] | $1,094 ($500)  $859 [$859, $1,432] |
| Adjusted (upper) d  Mean (SD)  Median [IQR] | $491 ($179)  $388[$388, $430] | $1,097 ($595)  $860 [$775, $1,290] | $1,478 ($677)  $1,163 [$1,163, $1,938] |

ED = emergency department; IQR = interquartile range; SD = standard deviation

aCumulative mean visits per patient or outpatient at 0-30 days, 0 days – 6 months and 0 days - 1 year

bNon-admitted patients include patients discharged to home, nursing home or died

cPatients discharged to medical ward, ICU, CCU, surgical ward or operation theatre

dAdjusted by up to 15% to account for temporal trends

# Appendix D: Comparison of adverse events over time between SOLACE-AU, Partner 2A and the NRCA study

**Table D.1: Comparison of adverse events over time between SOLACE-AU, Partner 2A and the NRCA study**

| **Outcome, n (%) or mean ± SD** | **SOLACE-AU**  **TF-TAVI**  **(N=199)** | | **Partner 2A Leon (2016)a** | | **NRCA** | | **PARTNER 1B**  **Leon (2010)** | | **PARTNER 1Ab (Smith 2011)** | | **Adams (2014)c** | |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **30 day** | **1 year** | **30 day** | **1 year** | **30 day** | **1 year** | **30 day** | **1 year** | **30 day** | **1 year** |
| **30 day** | **1 year** | **TF-TAVI**  **N=755** | **TF-TAVI**  **N=755** | **TF-TAVI (n = 1,023)** | | **TF-TAVI**  **N=179** | **TF-TAVI**  **N=179** | **TF-TAVI**  **N=244** | **TAVI**  **N= 244** | **TAVI**  **N=390** | **TAVI**  **N=390** |
| Death any cause | 5 (2.5) | 17 (8.7) | 23 (3.0) | 77 (10.0) | 44 (4.3) | 192 (19.0) | 9 (5) | 55 (30.7) | 8 (3.3) | 54 (22.2) | 13 (3.3) | 55 (14.2) |
| Death from CV cause | 5 (2.5) | 9 (4.6) | 21 (2.7) | 46 (6.0) | 33 (3.2) | 81 (8.4) | 8 (4.5) | 35 (19.6) | 8 (3.3) | 29 (12.6) | 12 (3.1) | 40 (10.4) |
| Repeat hospitalizations | - | - | 42 (5.5) | 97 (13.1) | 70 (7.1) | 185 (19.6) | 10 (5.6) | 40 (22.3) | 11 (4.6) | 42 (18.5) | - | - |
| Stroke or TIA | 7 (3.5) | 9 (4.7) | 39 (5.1) | 69 (9.2) | 42 (4.2) | 60 (6.2) | 12 (6.7) | 19 (10.6) | 12 (5.0) | 15 (6.4) | 22(5.7) | 39 (10.4) |
| MI | 2 (1.0) | 3 (1.5) | 5 (0.6) | 14 (1.9) | 6 (0.6) | 14 (1.5) | 0 | 1 (0.6) | 0 | 1 (0.5) | 3(0.8) | 7 (1.9) |
| Vascular complications | 62 (31.2) | NA | - | - | 160 (15.7) | 169 (16.6) | 55 (30.7) | 58 (32.4) | 55 (22.7) | 57 (23.5) | - | - |
| Major vascular complications | 12 (6.0) | NA | 66 (8.5) | 68 (8.8) | 82 (8.0) | 85 (8.4) | 29 (16.2) | 30 (16.8) | 34 (14.0) | 35 (14.4) | 23 (5.9) | 24 (6.2) |
| Acute kidney injury d | 1 (0.5) | 8 (4.2) | 4 (0.5) | 16 (2.2) | - | - | 0 | 2 (1.1) | 4 (1.7) | 12 (5.4) | 23 (6.0) | 23 (6.0) |
| Major bleeding | 7 (3.5) | 16 (8.3) | 52 (6.7) | 84 (11.1) | 69 (6.8) | 125 (12.9) | 30 (16.8) | 40 (22.3) | 23 (9.5) | 38 (16.2) | 109 (28.1) | 114 (29.5) |
| Repeat TAVI | - | - | - | - | - | - | 3 (1.7) | 3 (1.7) | - | - | 3 (0.8) | 7 (1.9) |
| New PPM | 16 (8.0) e | | 62 (8.1) | 73 (9.6) | - | - | 6 (3.4) | 8 (4.5) | 9 (3.7) | 13 (5.5) | 76 (19.8) | 85 (22.3) |
| Days from procedure, mean, SD | 398.7 ± 423.24 | | - | - | - | - | - | - | - | - | - | - |

aBased on supplementary data on TF-TAVI group of the PARTNER 2A trial

bBased on supplementary data on TF-TAVI group of the PARTNER 1A trial

cIncluded both transfemoral and transapical approaches and used CoreValve self-expanding devices

CV = Cardiovascular; MI= Myocardial Infraction; NA = not assessed; NRCA = Non-randomized Continued Access Registry; PPM = permanent pacemaker; TAVI = transfemoral transcatheter aortic implantation; TF= transfemoral; TIA= Transient Ischemic attack

dStage 3 (including renal replacement therapy)

eBased on the total incidence of permanent pacemaker implantation in the SOLACE-AU trial