A Randomized Comparison of the ACURATE neo versus the SAPIEN 3 Transcatheter Heart Valve System in Patients with Symptomatic Severe Aortic Stenosis


on behalf of the SCOPE I investigators
Disclosure Statement of Financial Interest

I, Jonas Lanz, DO NOT have a financial interest/arrangement or affiliation with one or more organizations that could be perceived as a real or apparent conflict of interest in the context of the subject of this presentation.
Background

• TF TAVR has become an indispensable treatment option for patients with symptomatic severe aortic stenosis across all risk categories.

• The generalizability of outcomes observed in landmark trials comparing TAVR with SAVR to other commercial TAVR systems is limited by differences in device properties and the lack of head-to-head device comparisons.

• Iterations of the balloon-expandable SAPIEN THV system have been extensively investigated in several large-scale, high-quality RCTs and registries setting the current benchmark in terms of safety and efficacy.

• The ACURATE neo is a novel, self-expanding TAVR prosthesis associated with favorable outcomes in non-randomized studies.
Objective

To compare early safety and efficacy of the self-expanding ACURATE neo to the balloon-expandable SAPIEN 3 transcatheter heart valve system in patients with symptomatic severe aortic stenosis undergoing transfemoral TAVR.
# Study Devices

<table>
<thead>
<tr>
<th>Frame</th>
<th>Nitinol</th>
<th>Cobalt-chromium</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leaflets</td>
<td>Porcine pericardium, supra-annular</td>
<td>Bovine pericardium, intra-annular</td>
</tr>
<tr>
<td>Expansion</td>
<td>Self-expanding (top-down)</td>
<td>Balloon-expandable</td>
</tr>
<tr>
<td>Recapturable</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Valve sizes</td>
<td>S (23 mm), M (25 mm), L (27 mm)</td>
<td>23 mm, 26 mm and 29 mm</td>
</tr>
<tr>
<td>Sheath inner diameter</td>
<td>18-French</td>
<td>14- and 16-French expandable</td>
</tr>
<tr>
<td>Paravalvular leakage reduction</td>
<td>Outer &amp; inner skirt</td>
<td>Outer cuff &amp; inner skirt</td>
</tr>
<tr>
<td>CE mark / FDA approval</td>
<td>Sep 2014 / No</td>
<td>Jan 2014 / Jun 2015</td>
</tr>
</tbody>
</table>
Study Design

Patients with severe aortic stenosis requiring intervention

Heart team decision

Screening Log ↔ TF TAVR ↔ SAVR

Randomized controlled trial (730 patients)

1:1 Randomization

ACURATE neo ↔ SAPIEN 3

Follow-up:
at 30-days, 1 and 3 years

Primary endpoint:
Combined early safety & clinical efficacy at 30 days
(VARC-2)
Eligibility Criteria

**Major Inclusion Criteria**
- Age ≥ 75 years
- Aortic valve area < 1 cm²
- Clinical symptoms (> NYHA I, angina, syncope)
- Inoperable *or* at increased risk for SAVR based on risk scores *and/or* heart team recommendation
- Aortic annulus dimensions and peripheral access suitable for either device

**Major Exclusion Criteria**
- Congenital anomaly of aortic valve
- Emergency procedures
- LV-EF< 20%
- Left-sided prosthetic valve
- Concomitant planned procedure (except for PCI)
- Stroke or myocardial infarction (previous 30 days)
- Planned non-cardiac surgery (next 30 days)
Primary Endpoint

Safety & clinical efficacy at 30 days based on VARC-2

- All-cause mortality
- All stroke (disabling and non-disabling)
- Life-threatening or disabling bleeding
- Major vascular complication
- Coronary artery obstruction requiring intervention
- Acute kidney injury (stage 2 or 3)
- Re-hospitalization for valve-related symptoms or worsening CHF
- Valve related dysfunction requiring repeat procedure
- Valve-related dysfunction (echocardiography): mean Gradient $\geq 20$ mmHg and $\text{EOA} \leq 0.9-1.1$ cm$^2$ and/or $\text{DVI} < 0.35$ AND/OR $\geq$ moderate regurgitation
Statistical Methods

• Stratified randomization (by STS-PROM category and site)

• Non-inferiority design
  ➢ Assumed primary endpoint event rate: 22%
  ➢ Non-inferiority margin: 7.7% (risk-difference)
  ➢ Power: 80%
  ➢ Type I error (α) = 0.05 (one-sided)
  ➢ 365 patients per group

• Primary analysis in intention-to-treat cohort, risk difference pooled over STS strata by Mantel-Haenszel (M-H) method
Trial Organization

• **Sponsor**
  - Clinical Department of Cardiology, University Hospital Bern, Switzerland

• **Data management & Monitoring**
  - University Hospital & Clinical Trials Unit, University of Bern, Switzerland

• **Statistics**
  - Clinical Trials Unit, University of Bern, Switzerland

• **Clinical Events Committee**
  - Cardiovascular European Research Center (CERC), Massy, France

• **Echocardiography Core Laboratory**
  - Medical Research Development, Hospital La Zarzuela, Madrid, Spain

• **Funder**
  - Boston Scientific, Marlborough, Massachusetts, USA
## Study Sites

### 20 European sites, 4 Nations: Switzerland (3), Germany (15), Netherlands (1), UK (1)

<table>
<thead>
<tr>
<th>Study Site</th>
<th>Local Principal Investigator</th>
</tr>
</thead>
<tbody>
<tr>
<td>Klinikum Augsburg</td>
<td>Christian Thilo, MD</td>
</tr>
<tr>
<td>Zentralklinik, Bad Berka</td>
<td>Stefan Richter, MD</td>
</tr>
<tr>
<td>Heart and Vascular Center, Bad Bevensen</td>
<td>Christof Burgdorf, MD</td>
</tr>
<tr>
<td>Kerckhoff Heart and Thorax Center, Bad Nauheim</td>
<td>Won-Keun Kim, MD</td>
</tr>
<tr>
<td>Cardio-vascular Center Bad Neustadt, St.-Johannes-Hospital</td>
<td>Sebastian Kerber, MD</td>
</tr>
<tr>
<td>Heart Center, Dortmund</td>
<td>Axel Linke, MD</td>
</tr>
<tr>
<td>Helios Klinik, Karlsruhe</td>
<td>Lars Conzelmann, MD</td>
</tr>
<tr>
<td>St. Vincentius-Kliniken, Karlsruhe</td>
<td>Alexander Würth, MD</td>
</tr>
<tr>
<td>Städtisches Klinikum, Karlsruhe</td>
<td>Gerhard Schymik, MD</td>
</tr>
<tr>
<td>University Heart Center, Cologne</td>
<td>Stephan Baldus, MD</td>
</tr>
<tr>
<td>Heart Center, Leipzig</td>
<td>Holger Thiele, MD</td>
</tr>
<tr>
<td>German Heart Centre, Munich</td>
<td>Michael Joner, MD</td>
</tr>
<tr>
<td>University Medical Center, Regensburg</td>
<td>Michael Hilker, MD</td>
</tr>
<tr>
<td>University Medical Center, Utrecht</td>
<td>Pieter Stella, MD</td>
</tr>
<tr>
<td>St Thomas’ Hospital, London</td>
<td>Simon Redwood, MD</td>
</tr>
<tr>
<td>Bern University Hospital, Bern</td>
<td>Thomas Pilgrim, MD</td>
</tr>
<tr>
<td>Lucerne Cantonal Hospital, Lucerne</td>
<td>Stefan Toggweiler, MD</td>
</tr>
<tr>
<td>University Hospital Zurich, Zurich</td>
<td>Maurizio Taramasso, MD</td>
</tr>
</tbody>
</table>
Patient Flow Chart

739 patients with severe, symptomatic aortic stenosis selected for TF TAVR by the Heart Team

Randomization

372 allocated to ACURATE neo

369 TF TAVR initiated
  363 received ACURATE neo
    11 multiple valve implantation
    2 conversion to SAVR
    6 received SAPIEN 3

3 TF TAVR not initiated
  (2 deaths, 1 infection)

5 withdrawal of consent
0 lost-to-follow-up

367 allocated to SAPIEN 3

363 TF TAVR initiated
  362 received SAPIEN 3
    2 multiple valve implantation
    1 received ACURATE neo

4 TF TAVR not initiated
  (2 deaths, 1 withdrawal, 1 planned TA TAVR)

3 withdrawal of consent
0 lost-to-follow-up

367 (99%) Clinical endpoints assessed
361 (97%) Echocardiography performed and analyzed

364 (99%) Clinical endpoints assessed
363 (99%) Echocardiography performed and analyzed
### Baseline Characteristics *(intention-to-treat)*

<table>
<thead>
<tr>
<th>Demographics</th>
<th>ACURATE neo (N = 372)</th>
<th>SAPIEN 3 (N = 367)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age - years <em>(mean ± SD)</em></td>
<td>82.6 ± 4.3</td>
<td>83.0 ± 3.9</td>
</tr>
<tr>
<td>Female sex</td>
<td>218 (59%)</td>
<td>202 (55%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>ACURATE neo (N = 372)</th>
<th>SAPIEN 3 (N = 367)</th>
</tr>
</thead>
<tbody>
<tr>
<td>NYHA classification III or IV</td>
<td>287 (77%)</td>
<td>268 (73%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Risk assessment</th>
<th>ACURATE neo (N = 372)</th>
<th>SAPIEN 3 (N = 367)</th>
</tr>
</thead>
<tbody>
<tr>
<td>STS-PROM score - median <em>(interquartile range)</em></td>
<td>3.7 (2.6, 4.9)</td>
<td>3.4 (2.6, 5.2)</td>
</tr>
<tr>
<td>STS-PROM score categories</td>
<td></td>
<td></td>
</tr>
<tr>
<td>low STS-PROM (&lt; 3%)</td>
<td>134 (36%)</td>
<td>136 (37%)</td>
</tr>
<tr>
<td>intermediate STS-PROM (≥ 3% and &lt; 8%)</td>
<td>207 (55%)</td>
<td>203 (55%)</td>
</tr>
<tr>
<td>high STS-PROM (≥ 8%)</td>
<td>31 (8%)</td>
<td>28 (8%)</td>
</tr>
</tbody>
</table>
## Baseline Imaging Characteristics *(intention-to-treat)*

<table>
<thead>
<tr>
<th></th>
<th>ACURATE neo (N = 372)</th>
<th>SAPIEN 3 (N = 367)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Echocardiography</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aortic valve mean gradient - mmHg <em>(mean ± SD)</em></td>
<td>42.9 ± 17.2</td>
<td>41.5 ± 15.1</td>
</tr>
<tr>
<td>Aortic valve area - cm² <em>(mean ± SD)</em></td>
<td>0.7 ± 0.2</td>
<td>0.7 ± 0.2</td>
</tr>
<tr>
<td>Left ventricular ejection fraction - % <em>(mean ± SD)</em></td>
<td>56.4 ± 11.1</td>
<td>57.1 ± 10.7</td>
</tr>
<tr>
<td><strong>Computed tomography</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aortic annulus perimeter - mm <em>(mean ± SD)</em></td>
<td>75.7 ± 5.2</td>
<td>75.9 ± 5.1</td>
</tr>
<tr>
<td>Aortic annulus area - mm² <em>(mean ± SD)</em></td>
<td>439.1 ± 59.6</td>
<td>442.9 ± 60.3</td>
</tr>
<tr>
<td>Aortic valve calcification, moderate or severe</td>
<td>286 (77%)</td>
<td>286 (78%)</td>
</tr>
<tr>
<td>LVOT calcification, moderate or severe</td>
<td>94 (25%)</td>
<td>99 (27%)</td>
</tr>
</tbody>
</table>
Procedural Characteristics

**Procedure Time**

- ACURATE neo: 47 min
- SAPIEN 3: 40 min

**Contrast Volume**

- ACURATE neo: 128 mL
- SAPIEN 3: 100 mL

Significance levels:
- Procedure Time: $p = 0.0002$
- Contrast Volume: $p < 0.0001$
Procedural Characteristics

Pre-dilatation
- 88.0% for ACURATE neo (n = 361)
- 23.0% for SAPIEN 3 (n = 363)

Post-dilatation
- 52.0% for ACURATE neo (n = 361)
- 13.0% for SAPIEN 3 (n = 363)

p < 0.0001
## Procedural Adverse Events *(intention-to-treat)*

<table>
<thead>
<tr>
<th>Event</th>
<th>ACURATE neo (N = 369)</th>
<th>SAPIEN 3 (N = 363)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Valve mal-positioning</td>
<td>5 (1%)</td>
<td>2 (1%)</td>
<td>0.26</td>
</tr>
<tr>
<td>Implantation of multiple valves</td>
<td>11 (3%)</td>
<td>2 (1%)</td>
<td>0.0119</td>
</tr>
<tr>
<td>Coronary artery obstruction requiring intervention</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>1.00</td>
</tr>
<tr>
<td>Peri-procedural myocardial infarction</td>
<td>1 (0.3%)</td>
<td>1 (0.3%)</td>
<td>0.96</td>
</tr>
<tr>
<td>Cardiac tamponade</td>
<td>4 (1%)</td>
<td>5 (1%)</td>
<td>0.72</td>
</tr>
<tr>
<td>Annular rupture</td>
<td>2 (1%)</td>
<td>1 (0.3%)</td>
<td>0.57</td>
</tr>
<tr>
<td>Left ventricular perforation</td>
<td>1 (0.3%)</td>
<td>0 (0%)</td>
<td>0.32</td>
</tr>
<tr>
<td>Conversion to open heart surgery</td>
<td>3 (1%)</td>
<td>0 (0%)</td>
<td>0.08</td>
</tr>
<tr>
<td>SAVR</td>
<td>2 (1%)</td>
<td>0 (0%)</td>
<td>0.50</td>
</tr>
<tr>
<td>Immediate procedural death</td>
<td>3 (1%)</td>
<td>1 (0.3%)</td>
<td>0.32</td>
</tr>
</tbody>
</table>
Primary Endpoint Rates at 30 days

*Intention-to-treat*

<table>
<thead>
<tr>
<th>ACURATE neo</th>
<th>SAPIEN 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>87/367 (23.7%)</td>
<td>60/364 (16.5%)</td>
</tr>
</tbody>
</table>
Primary Endpoint

Primary analysis at 30 days (intention-to-treat)

Non-inferiority margin: 7.7%

Upper limit of one-sided 95% CI: 12%
P value for non-inferiority: 0.42

ACURATE neo 23.7%  SAPIEN 3: 16.5%

Risk difference (M-H)
# Primary Endpoint - Secondary Analyses at 30 days

<table>
<thead>
<tr>
<th></th>
<th>ACURATE neo</th>
<th>SAPIEN 3</th>
<th>Risk difference % (95%-CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary endpoint (superiority analysis)</strong></td>
<td>87/367 (23.7%)</td>
<td>60/364 (16.5%)</td>
<td></td>
<td>0.0156</td>
</tr>
<tr>
<td><strong>Single components of primary endpoint</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All-cause death</td>
<td>9/367 (2.5%)</td>
<td>3/364 (0.8%)</td>
<td></td>
<td>0.09</td>
</tr>
<tr>
<td>Stroke (any)</td>
<td>7/367 (1.9%)</td>
<td>11/364 (3.0%)</td>
<td></td>
<td>0.33</td>
</tr>
<tr>
<td>Life-threatening or disabling bleeding</td>
<td>14/367 (3.8%)</td>
<td>9/364 (2.5%)</td>
<td></td>
<td>0.30</td>
</tr>
<tr>
<td>Major vascular complications</td>
<td>29/367 (7.9%)</td>
<td>20/364 (5.5%)</td>
<td></td>
<td>0.21</td>
</tr>
<tr>
<td>Coronary artery obstruction requiring intervention</td>
<td>0/367 (0%)</td>
<td>0/364 (0%)</td>
<td></td>
<td>n/a</td>
</tr>
<tr>
<td><strong>Acute kidney injury, stage 2 or 3</strong></td>
<td>11/367 (3.0%)</td>
<td>3/364 (0.8%)</td>
<td></td>
<td>0.0340</td>
</tr>
<tr>
<td>Re-hospitalization for valve-related dysfunction or CHF</td>
<td>4/367 (1.1%)</td>
<td>5/364 (1.4%)</td>
<td></td>
<td>0.72</td>
</tr>
<tr>
<td>Valve-related dysfunction requiring repeat procedure</td>
<td>3/367 (0.8%)</td>
<td>1/364 (0.3%)</td>
<td></td>
<td>0.32</td>
</tr>
<tr>
<td>Valve-related dysfunction (echocardiography)</td>
<td>35/361 (9.7%)</td>
<td>17/363 (4.7%)</td>
<td></td>
<td>0.0084</td>
</tr>
</tbody>
</table>
Primary Endpoint - Per Protocol Analyses

Non-inferiority

Non-inferiority margin = 7.7%

Upper-limit one-sided 95%-CI: 12.1%

P value for non-inferiority: 0.39

Superiority

ACURATE neo
n = 298
23.8%

SAPIEN 3
n = 339
16.8%

Risk-difference (M-H): 6.8%
95%-CI: 0.6 to 13.1%, P = 0.0325
New Pacemaker Implantation

Numbers refer to the cohort at risk (patients with pacemaker at baseline excluded)

P = 0.68

ACURATE neo
n = 323
11.5%

SAPIEN 3
n = 327
10.3%
Echocardiographic Valve Performance

**Paravalvular Aortic Regurgitation**

- ACURATE neo: n = 361
  - ≥ moderate: 9.4%
  - mild: 50.1%
  - none: 40.4%
- SAPIEN 3: n = 363
  - ≥ moderate: 2.8%
  - mild: 31.1%
  - none: 66.1%

\[P < 0.0001\]

**Mean Gradient ≥20 mmHg AND EOA ≤ 0.9-1.1 cm² and/or DVI < 0.35**

- ACURATE neo: n = 361
  - yes: 0.6%
  - no: 99.4%
- SAPIEN 3: n = 363
  - yes: 2.2%
  - no: 97.8%

\[P = 0.06\]
Limitations

• Not powered for individual clinical endpoints
• Early primary endpoint limits evaluation of device differences in terms of long-term clinical outcomes
• Single-blinded trial
  - visible differences in the stent frame precluded blinding of echocardiography core laboratory
• Lack of assessment of aortic root CT angiographies by a central core laboratory at baseline
Summary of Major Results

- Non-inferiority of ACURATE neo versus SAPIEN 3 with respect to composite safety and efficacy endpoint at 30 days **not met**

- **Superiority of SAPIEN 3** with regard to composite safety and efficacy endpoint at 30 days in secondary analyses, driven by lower rates of paravalvular regurgitation and acute kidney injury (stage 2 or 3)

- Higher rates of multiple valve implantation with ACURATE neo

- Lower transvalvular gradients and larger effective orifice area with ACURATE neo

- Low mortality, stroke and pacemaker rates with both devices
Conclusions

• **ACURATE neo** did not meet non-inferiority compared to the SAPIEN 3 device regarding the primary composite safety and efficacy endpoint at 30 days.

• Differences between the two TAVR devices were driven by moderate or severe paravalvular regurgitation and stage 2 or 3 acute kidney injury in favor of the SAPIEN 3 device.

• An early composite safety and efficacy endpoint proved useful in discriminating the performance of different TAVR systems.
Simultaneous Publication in *The Lancet*


Jonas Lanz*, Won-Keun Kim*, Thomas Walther, Christof Burgdorf, Helge Möllmann, Axel Linke, Simon Redwood, Christian Thilo, Michael Hilker, Michael Joner, Holger Thiele, Lars Conzelmann, Lenard Conradi, Sebastian Kerber, Gerhard Schymik, Bernard Prendergast, Oliver Husser, Stefan Stortecky, Dik Heg, Peter Juni, Stephan Windecker, Thomas Pilgrim, for the SCOPE I investigators†
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