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Device Evaluation

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Myval transcatheter heart valve system in the treatment of severe symptomatic aortic stenosis

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The transcatheter aortic valve replacement (TAVR) is an established treatment for patients with severe symptomatic aortic stenosis (AS) at prohibitive risk for surgery. It is an alternative treatment to surgical aortic valve replacement in patients with AS at intermediate- and high-surgical risk. Although regulatory authorities extend the indications of TAVR to treat patients at low-surgical risk, the limitations of earlier-generation transcatheter heart valve (THV) systems accelerate the development of improved newer generation of THV systems. Myval™ THV (Meril Life Sciences Pvt. Ltd., Vapi, Gujarat, India) is a newer-generation, balloon-expandable TAVR system with features that facilitate accurate positioning of the bioprosthetic valve and favorable procedural and clinical outcomes. This review summarizes existing preclinical and clinical data on Myval THV for the intervention of symptomatic native AS and lays out the plan for future research program.

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Severe symptomatic aortic stenosis (AS), if left untreated, has a mortality rate of as high as 50% within 2 years of the disease initiation [1]. The risk of death is even higher in the frail and elderly population [2]. In the USA alone, there were 500,000 patients diagnosed with severe AS with nearly 50% being symptomatic [3]. In Europe as well, severe AS is highly prevalent and serious complication. The proportion of these patients increases with the aging population [4]. Upon extrapolating the western prevalence data, Gupta *et al.* estimated that approximately 250,000 to 300,000 Indians have severe symptomatic AS [5].

According to American College of Cardiology/American Heart Association (ACC/AHA) 2014 guidelines, surgical aortic valve replacement (SAVR) is the class-I recommendation for severe symptomatic AS [6]. However, nearly a third of this population is not recommended for SAVR because of advanced age, multiple comorbidities, left ventricular dysfunction and frailty [2]. Moreover, an increased risk of mortality after SAVR is reported in patients with chronic renal disease and advanced age [7]. Transcatheter aortic valve replacement (TAVR) has been developed as an alternative treatment for this vulnerable patient population. Different randomized controlled trials have established superiority of TAVR over SAVR in patients with AS at high surgical risk as well as noninferiority of TAVR over SAVR in patients with AS at intermediate surgical risk [8–14]. Additionally, TAVR has been reported to be noninferior and/or superior to SAVR in patients at low surgical risk [15–18].

Since the first 'proof-of-concept' case in 2002, TAVR has undergone a paradigm shift in terms of technical advances of transcatheter heart valve (THV) systems that led to broadening of the indications [19]. Earlier-generation

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Table 1. Currently approved newer-generation transcatheter heart valves in USA, Europe and its country of origin.

No.	TAVR device	Genre	Manufacturer	Approval body
1	SAPIEN 3	BE	Edwards Lifesciences	CE, FDA
2	Evolut PRO, Evolut R	SE	Medtronic	CE, FDA
3	Portico	SE	Abbott Laboratories	CE, FDA
4	ACURATE neo/ACURATE TA	SE	Boston Scientific	CE
5	JenaValve	SE	JenaValve Technology	CE, FDA (breakthrough device designation)
6	LOTUS Edge	Controlled expansion	Boston Scientific	CE, FDA
7	Myval THV	BE	Meril Life Sciences	CE, CDSCO (India)
8	Allegra	SE	NVT	CE
9	VitaFlow	SE	MicroPort	NMPA (China)

BE: Balloon expandable; CDSCO: Central Drug Standard Control Organisation; CE: Conformité Européene; NMPA: National Medical Products Administration; SE: Self-expandable; TAVR: Transcatheter aortic valve replacement; THV: Transcatheter heart valve.

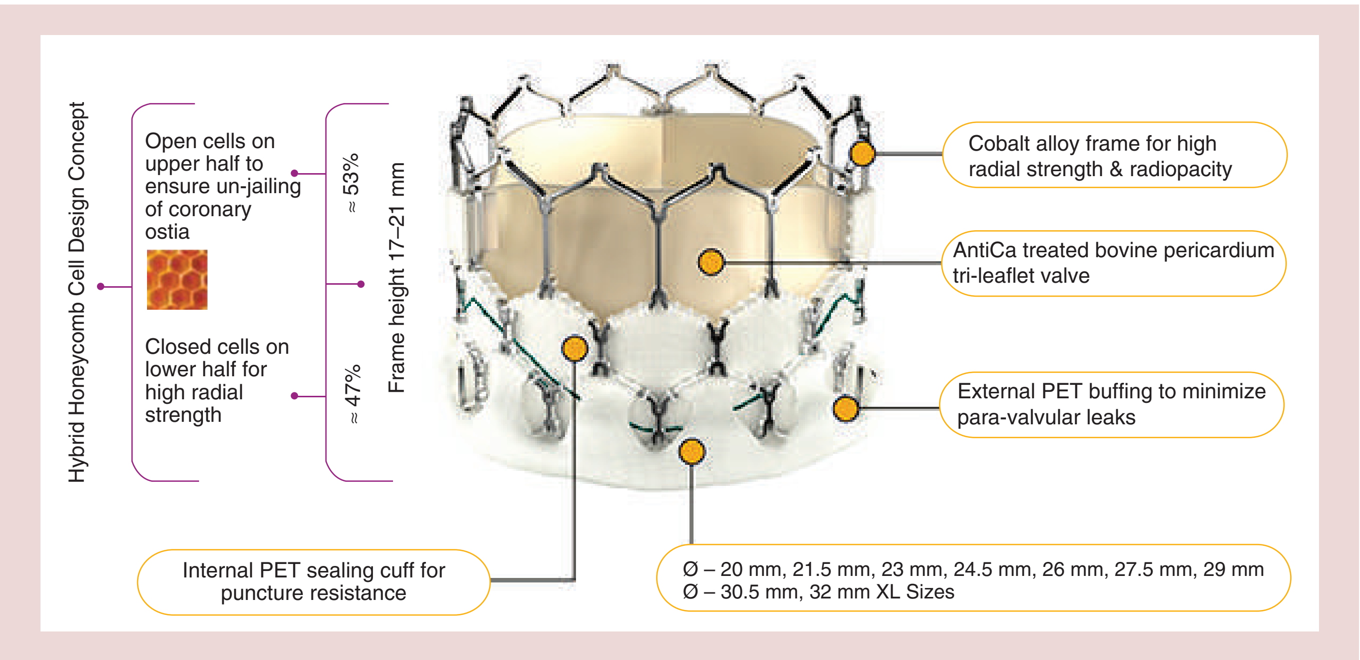

Figure 1. Design of Myval™ transcatheter heart valve.
AntiCa is Meril's proprietary anti-calcification treatment technology. All Myval THV sizes are currently CE approved and 30.5 mm is currently awaiting CDSCO approval (data on file).
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THVs are associated with periprocedural complications, including paravalvular aortic regurgitation (PAR), vascular complications, stroke and conduction disturbances leading to new permanent pacemaker implantation (PPI). Subsequently, newer-generation THVs are developed with an aim to overcome these limitations. The newer-generation THVs are featured with the use of smaller delivery sheaths, controlled deployment techniques and circumferential cuffs and skirts. Real-world registries comparing earlier-generation THVs with newer-generation THVs demonstrated reduced PAR rate and favorable hemodynamics with newer-generation devices [20–24]. Evidences revealed that in addition to reducing the events of PAR, the newer-generation THVs have improved patient and procedural outcomes [9,25]. To name a few, the currently approved newer-generation THVs are enlisted in Table 1.

Myval™ THV (Meril Life Sciences Pvt. Ltd., India) is a newer-generation balloon-expandable THV (Figure 1). It was developed with a fundamental intent of deploying the bioprosthetic valve at the orthotopic position, the annulus. This precise orthotopic positioning of the diameter-matched THV ensures optimal, large effective orifice area (EOA); restoration of normal hemodynamics postimplantation, in other words, low gradients and velocity;

Myval THV size matrix & technical specification	Area 314 mm^2 17.35 mm 20 mm	Area 415 mm^2 17.85 mm 23 mm	Area 531 mm^2 18.85 mm 26 mm	Area 661 mm^2 20.35 mm 29 mm
Perimeter	62.83 mm	72.26 mm	81.68 mm	91.11 mm
Native annulus area	270 – 330 mm^2	360 – 440 mm^2	460 – 560 mm^2	570 – 700 mm^2
Area-derived diameter	18.5 – 20.5 mm	21.4 – 23.7 mm	24.2 – 26.7 mm	26.9 – 29.9 mm
Native annulus size by TEE	16 – 19 mm	18.0 – 22 mm	21 – 25 mm	24 – 28 mm

Myval THV size matrix & technical specification	Myval intermediate size			Myval XL size	
	Area 363 mm^2 18.35 mm 21.5 mm	Area 471 mm^2 18.75 mm 24.5 mm	Area 594 mm^2 19.25 mm 27.5 mm	Area 731 mm^2 20.9 mm 30.5 mm	Area 804 mm^2 21.14 mm 32.0 mm
Perimeter	67.54 mm	76.97 mm	86.39 mm	95.82 mm	100.53 mm
Native annulus area	314 – 380 mm^2	410 – 500 mm^2	510 – 630 mm^2	630 – 770 mm^2	700 – 840 mm^2
Area-derived diameter	20.0 – 22.0 mm	22.8 – 25.2 mm	25.5 – 28.3 mm	28.3 – 31.3 mm	29.9 – 32.7 mm
Native annulus size by TEE	17.5 – 20.5 mm	19.5 – 23.5 mm	22.5 – 26.5 mm	25.5 – 29.5 mm	27 – 31 mm

Figure 2. Size matrix of Myval transcatheter heart valve.
All Myval THV sizes are currently CE approved and 30.5 mm is currently awaiting CDSCO approval. 14 Fr Python Expandable Introducer Sheath can be used for all Myval THV diameter sizes ranging from 20 to 32 mm.
CE: Conformité Européene; THV: Transcatheter heart valve.
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and sound anchoring of the THV at the annulus. Owing to the external skirting in the Myval THV's design and appropriate deployment at the orthotopic position, the development of Myval THV aimed at minimizing the paravalvular leaks. Minimal learning curve is required for precise positioning of the THV prior to deployment that ensures marginal interaction of Myval THV system with the patient's anatomy including left ventricular outflow tract, membranous septum and conduction system. With these features, Myval THV was developed indigenously with an aim to provide the global population a THV that can be implanted at the orthotopic position and provides a wide range of sizes including the traditional size THV and intermediate-size THV (Figure 2). The broad size matrix helps in providing THV for patients with different sizes without compromising the geometry of the bioprosthetic valve and respecting the patient's native anatomy. With these features, we expect to increase the longevity of younger patients and patients at low surgical risk. In addition to Myval THV, the entire Myval THV system was developed to yield better procedural and clinical outcomes. The unique design of Navigator™ THV balloon-catheter delivery system (Meril Life Sciences Pvt. Ltd., Vapi, Gujarat, India) (Figure 3) minimizes the inadvertent dislocation of Myval THV during navigation and the Python sheath of 14 Fr (Meril Life Sciences Pvt. Ltd., Vapi, Gujarat, India) through which the undelivered Myval THV can be retrieved.

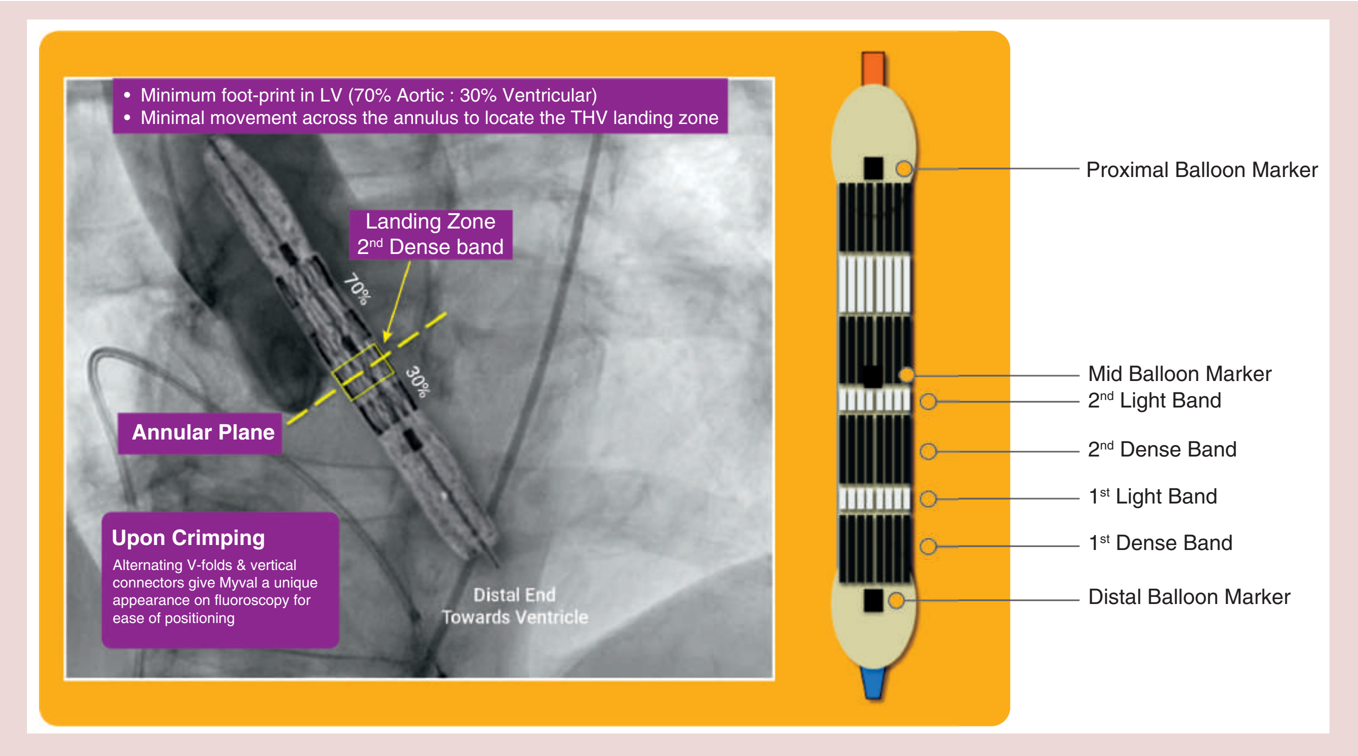

Figure 3. Schematic of crimped Myval transcatheter heart valve on Navigator™ balloon. Minimum footprint in LV (70% aortic: 30% ventricular). Minimal movement across the annulus to locate the transcatheter heart valve (THV)-landing zone. Upon crimping, alternating V-folds and vertical connectors give Myval THV a unique appearance on fluoroscopy for ease of positioning and deployment. The characteristic bands may not be visible in-case Myval THV system is not coaxial to the annular plane. In this case, THV-landing zone must be referenced using mid-balloon marker that has to be kept at 3 mm above the annular plane.
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To date, the device has been implanted in more than 800 patients across 26 countries spanning Europe, South America and Asia with very low MACCRE, low new PPI, low PAR rate and low vascular complication. This review aims to upgrade budding interventional cardiologists' knowledge related to the salient clinical features of Myval THV as well as preclinical and clinical experiences of Myval THV. Additionally, the review also reveals the ongoing trials/registries.

Regulatory approval

Myval THV has been approved by the Central Drugs Standard Control Organization (CDSCO; October 2018) and is commercially available in India since January 2019. Subsequently, the device received the Conformité Européenne (CE) certificate in April 2019 and is available for marketing in the European Union. The device received Class D medical device status as per the global harmonization task force (GHTF) guideline (GHTF/SG1/N15:2006: Principles of Medical Devices Classification).

Introduction to Myval THV system: device design & preclinical testing

Myval THV is indigenously developed at Meril Life Sciences Pvt. Ltd., Vapi, Gujarat, India. Myval THV is characterized by a nickel–cobalt alloy frame composed of a single element – hexagon arranged in a hybrid honeycomb fashion. This unique structure of hybrid honeycomb allows 53% of the frame to have large open cells toward the aortic end, which preserves the coronary flow, and 47% of the frame to have closed cells with higher annular radial force toward the ventricular end (Figure 1). This novel design geometry on crimping gives rise to a unique alternative dark-light band-like pattern allowing precise positioning of the THV at predetermined orthotopic position such that 70% of bioprosthetic THV lies within aorta and remaining 30% in the ventricle. Following the positioning of the valve, it can be deployed across the native annulus by deflating the Navigator

Figure 4. Navigator-THV balloon-catheter delivery system.
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THV balloon-catheter delivery system (Figure 4). This helps in avoiding the excessive deep throating within left ventricular outflow tract, thereby reducing the risk of new left/right bundle block and excitation of conduction system eliminating the need for a new PPI.

The trileaflet THV consists of decellularized bovine pericardium tissue, which receives an anticalcification treatment known as AntiCa™ (Meril Life Sciences Pvt. Ltd., Vapi, Gujarat, India) during the manufacturing of Myval THV. The tissue is procured from Australia and fixed with glutaraldehyde at the site. At Meril, the procured tissue undergoes extensive quality checks to ensure consistency of the tissue. The glutaraldehyde-fixed tissue is cut using femto laser as per prespecified design and then treated with a cocktail of cross-linking agent, denaturant and surfactant to chemically extract phospholipids from the cellular components of pericardial tissue and to inactivate glutaraldehyde-resistant microorganisms. This process reduces bioburden and renders the tissue resistant to calcification.

The lower closed cells of Myval THV are covered externally with a sealing cuff, made of polyethylene terephthalate, to form an external buffing that minimizes or eliminates paravalvular leak. Myval THV is available in various sizes (Figure 3): traditional (20, 23, 26 and 29 mm), intermediate (21.5, 24.5 and 27.5 mm) and extra-large (30.5 and 32 mm; all Myval THV sizes are currently CE approved and 30.5 mm is currently awaiting CDSCO approval). A device to annular size ratio (DAR) should ideally be 10–15%. DAR outside the ideal range may lead to complications including PAR, conduction abnormalities, device migration and annular rupture. The availability of intermediate-size Myval THV broadens the size matrix allowing the heart team to implant a THV without compromising DAR.

Myval THV is recommended to be crimped on its novel, specially designed, hi-flex, over-the-wire Navigator THV balloon-catheter delivery system (Figure 4), before the insertion of the valve within the vessel. The Navigator balloon-expandable THV delivery system has a unique design characterized by proximal deep flexion handle and a distal balloon with two counter-opposing soft stoppers within that create a shallow, low-profile crimping zone and thus a snug fit that prevents any inadvertent dislocation of Myval THV during negotiation through the sheath or thereafter. Additionally, the delivery system allows flexion of the distal catheter system that ensures trauma-free negotiation across the aortic arch and minimizes or eliminates risk of a periprocedural stroke during arch navigation. The balloon has two internal expansion ports that facilitate simultaneous expansion distally and proximally (similar to a dog bone) stabilizing the valve during deployment thereby ensuring precise placement. The crimped THV is inserted via specially designed 14 Fr Python sheath. In case of unavoidable circumstances, the unique sheath design allows the valve retraction within the sheath.

Preclinical experience of Myval THV

Preclinical models for assessing THV systems are difficult to set up owing to absence of any disease in native valves in animals. Additionally, surgical deployment of THV is not feasible in animals due to short height of ascending aorta that prevents convenient cross-clamping for surgeons [26]. One of the commonly used models is mitral position where the valve is surgically implanted at ovine mitral position.

Buszman *et al.* evaluated Myval THV in ovine aortic-banding model. Our study has successfully implanted 11 Myval THVs (either 20 or 33 mm) in sheep using a 22 Fr delivery system via transcarotid approach and there were no device-related mortality. A total of 11 Myval THVs (20 and 23 mm) were successfully implanted in 11 sheep using a 22 Fr delivery system via transcarotid approach. In all surviving sheep, transthoracic echocardiography showed that all valves were functional with no significant regurgitation, calcification, thrombi or vegetation. Healing was advanced, with no instances of excessive cusp calcification. On histopathology, full and stable integration and healing through endothelialization and microcellular neointima without valve thrombosis were observed [27].

Clinical testing of Myval THV: first-in-human (MyVal-1) study results & future randomized LANDMARK trial design

Following preclinical work, we assessed safety and efficacy of Myval THV in humans. The MyVal-1 study was the first-in-human, prospective, multicentre, single-arm, open-label, feasibility study conducted to evaluate safety and efficacy in intermediate or high-risk patients with severe symptomatic native AS. The study has recruited 100 patients from over 30 sites across India with an average age of 73.6 years (consisted of 80 males) and with mean Society of Thoracic Surgeons (STS) score of 5.11%**.** All procedures were performed through femoral access with low rate of periprocedural major vascular complications. The outcomes of the study were Kaplan–Meier survival, New York Heart Association (NYHA) functional classification, EOA and six-minute walk test at 30 days, 6 and 12 months after the procedure. The 30-day postprocedural outcomes of 100 patients showed excellent clinical and hemodynamic outcomes in terms of high survival, low incidence of stroke, low-rate of new PPI, precise orthotopic valve positioning, high procedural and device success, and significant improvement in quality of life. Additionally, there was a significant ($p < 0.001$) improvement in the six-minute walk test and Kanas City Cardiomyopathy Questionnaire (KCCQ) score at postprocedure compared with baseline. The echocardiographic findings immediately and 30 days after the procedure showed significant improvement ($p < 0.0001$) in EOA and the mean aortic valve gradient was maintained low [28].

Like most first-in-human studies, the MyVal-1 study was associated with limitations such as smaller sample size and inadequate power to validate the 12-month outcomes. Hence, to elucidate the shortcomings, a multinational randomized trial has been planned in 768 patients, the LANDMARK trial. The study is expected to enroll the first patient in the year 2020. The study population will be randomized in a 1:1 ratio to receive either Myval THV or contemporary THV series (Sapien THV series of Edwards Lifesciences, CA, USA [50%] and Evolut THV series of Medtronic, Dublin, Ireland [50%]). The primary end points at 30-day include all-cause mortality, stroke, major bleeding complications, vascular complications, acute kidney injury, paravalvular leak and requirement of a new permanent pacemaker. The electrocardiogram and echocardiograph follow-up are planned up to 5 and 10 years, respectively.

Conclusion

Indigenously developed Myval THV technology is India's first and globally second-generation balloon-expandable valve characterized by clever design changes that facilitate precise positioning of the valve and ensure accurate orthotopic valve deployment. So far, the real-world experience in more than 800 cases has been exceptionally promising. The planned randomized LANDMARK trial will further support the safety and effectiveness of the device, which will allow broadening the usage and increase confidence on Myval THV.

Author contributions

SK Sharma, RS Rao, M Chopra, A Sonawane, J Jose and G Sengottuvelu were responsible for the conceptualization, writing, reviewing and editing of the article.

Financial & competing interests disclosure

SK Sharma is an external scientific advisor to Meril Life Sciences Pvt. Ltd., Vapi, Gujarat, India. RS Rao, M Chopra, A Sonawane, J Jose and G Sengottuvelu are the proctors for Myval THV Technology. All the authors have received honoraria from Meril Life Sciences Pvt. Ltd., Vapi, Gujarat, India. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

No writing assistance was utilized in the production of this manuscript.

Executive summary

Background

- The transcatheter aortic valve replacement has been rapidly evolving to serve as a therapeutic alternative to surgical aortic valve replacement in high- and intermediate-surgical risk patients with aortic stenosis (AS); earlier-generation transcatheter heart valve (THV) systems were associated with periprocedural complications including paravalvular aortic regurgitation, vascular complications, strokes, and conduction disturbances.
- The newer-generation THV demonstrated reduced paravalvular aortic regurgitation rate and favorable hemodynamics over earlier-generation THV.

Introduction to Myval THV system: device design & preclinical testing

- Myval THV, a balloon-expandable transcatheter aortic valve replacement system developed indigenously, showed high performance and chronic safety in the ovine model of AS.

Clinical testing of Myval THV: first-in-human (MyVal-1) study results & future randomized LANDMARK trial design

- The 30-day outcomes of the first-in-human MyVal-1 study of 100 patients strengthen the safety and effectiveness of Myval THV.
- The complete analysis of the MyVal-1 study and planned LANDMARK trial will further establish the performance of Myval THV in patients with severe symptomatic native AS.

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