CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

207987Orig1s000

CLINICAL REVIEW(S)

DIVISION OF CARDIOVASCULAR AND RENAL PRODUCTS

Divisional Memo

NDA: 207987 Ethanol (Ablysinol) to improve [redacted] (b) (4) exercise capacity in patients with symptomatic, [redacted] (b) (4) hypertrophic obstructive cardiomyopathy [redacted] (b) (4)

Sponsor: Belcher Pharmaceuticals

Review date: 8 December 2015

Reviewer: N. Stockbridge, M.D., Ph.D., HFD-110

This memo conveys the Division's recommendation to issue a "Complete Response" letter for this application.

This application has been the subject of reviews of CMC (Sarker, Chelliah, Park, Chabrier-Rosello, and Kakhi; 30 October 2015), pharmacology/toxicology (Wu; 30 October 2015), clinical pharmacology (Hinderling; 4 November 2015, and Madabushi; 25 November 2015), clinical effectiveness and safety (Senatore; 1 November 2015) and statistics (Liu; 29 October 2015). There is also a CDTL memo (Targum; 11 November 2015), with which I am in agreement.

Hypertrophy of the cardiac septum below the aortic valve can obstruct left ventricular outflow, resulting in symptoms of reduced cardiac output. This can be treated by myectomy or controlled ablation of some myocardium. Interestingly, both are associated with immediate symptom relief, which indicates that there is a function component to the obstruction, because it does not require time for regression of killed myocardium. This is fortunate, because there are no good studies of the effectiveness of alcohol to achieve ablation, so the review team and senior management were convinced on the basis of clear immediate improvements reported in numerous publications. Descriptions of technique will be briefly abstracted into labeling, but there is no way to document the appropriate use of the product; physicians will learn from one another.

The application is a 505(b)(2) because of its reliance upon literature for nonclinical toxicology and effectiveness.

Approval is pending identification of and our acceptance of a manufacturing site for the drug substance.

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/s/

NORMAN L STOCKBRIDGE
12/08/2015

CLINICAL REVIEW

Application Type	505(b)(2)
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Priority or Standard	Standard
Submit Date(s)	12 FEB 2015
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Division / Office	DCRP / ODE-1
Reviewer Name(s)	Fred Senatore MD, PhD, FACC
Review Completion Date	11 SEP 2015
Established Name	Dehydrated Alcohol
(Proposed) Trade Name	ABLYSINOL
Therapeutic Class	Alcohol
Applicant	Belcher Pharmaceuticals, LLC
Formulation(s)	Dehydrated Ethanol
Dosing Regimen	(b) (4) (> (b) (4) % ethanol)
Indication(s)	Percutaneous Transluminal Septal Myocardial Ablation.
Intended Population(s)	Patients with symptomatic, (b) (4), hypertrophic obstructive cardiomyopathy (b) (4)

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List of Abbreviations

ACCF	American College of Cardiology Foundation
AHA	American Heart Association
AMVL	Anterior Mitral Valve Leaflet
ASA	Alcohol Septal Ablation (synonymous with PTSMA)
CCS	Canadian Cardiovascular Society
CK	Creatinine Kinase
DDD	Dual Chamber Pacing
HCM	Hypertrophic Cardiomyopathy
HOCM	Hypertrophic Obstructive Cardiomyopathy
ICD	Implantable Cardiac Defibrillator
IVRT	Isovolemic Relaxation Time
LVOT	Left ventricular outflow tract
LVOT-PG	Left ventricular outflow tract-pressure gradient
MLE	Mitral Leaflet Extension
MR	Mitral Regurgitation
MV	Mitral Valve
NYHA	New York Heart Association
PTSMA	Percutaneous Transluminal Septal Myocardial Ablation (synonymous with ASA): alcohol assumed to be the ablative agent in all cases
SAM	Systolic Anterior Motion (of mitral valve)
SM	Surgical Myectomy
V_P	Propagation Velocity

1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

I recommend that in patients with refractory symptomatic hypertrophic obstructive cardiomyopathy (HOCM) who are clinically assessed as non-candidates for surgical myectomy (SM), ethanol be approved to induce septal myocardial necrosis when used as an adjunct to percutaneous transluminal septal myocardial ablation (PTSMA) to improve exercise capacity.

My recommendation was based on an assumption that the ethanol described in the publications was equivalent to the ethanol the Applicant will have produced. Despite issues with the evidence provided by the Applicant to support their proposed indication as described in this review, I recommended approval for the following reasons:

- The body of evidence provided in the 38 publications that formed the basis of the Applicant's NDA, although largely retrospective and observational, described consistent PTSMA-mediated improvements in hemodynamic measurement (i.e. Left Ventricular Outflow Tract Pressure Gradient {LVOT-PG}), subjective measures of functional capacity (i.e. New York Heart Association {NYHA} and Canadian Cardiovascular Society {CCS} class) and objective measures of functional capacity (i.e. treadmill exercise testing as described in 8 of the 38 publications).
- Nine publications (5 of which comprised the originally mentioned 8 publications that reported PTSMA-mediated improvements in exercise capacity), came from registries of consecutive patients, thereby attenuating potential bias.
- The benefit of ethanol-based PTSMA outweighed the risk of this procedure in patients with refractory symptomatic HOCM.

1.2 Risk Benefit Assessment

The benefit of ethanol in concert with PTSMA (alcohol-PTSMA) to improve functional capacity in patients with refractory symptomatic HOCM who are not surgical candidates outweighed the risk of alcohol-PTSMA (i.e. complete heart block). This risk was adequately mitigated by pacemaker placement and was therefore acceptable, compared to the risk of not having PTSMA in this high risk patient population. As this review demonstrated, SM is considered to be the gold standard to date. Therefore, the benefit of alcohol-PTSMA for the purpose of a risk-benefit assessment for drug approval centered on those high risk patients who were not surgical candidates.

The ethanol dose yielding the favorable benefit-risk profile was 1-3 mL total for a single PTSMA procedure with an average of 2.3-2.5 mL/septal artery. However, there was one publication (Kuhn, 2008) showing a higher mortality risk in patients who were

administered > 2 mL ethanol, compared to ≤ 2 mL, during PTSMA. This finding was not consistent with the body of evidence. The highest ethanol total dose reported in the publications was 5 mL (Nagueh 2001 and Van der Lee 2005). There was no reported experience of total ethanol doses exceeding 5 mL.

The risk-benefit analysis was performed by assessing:

- Issues identified in this NDA.
- Ethanol dose from both the efficacy and safety perspective.
- PTSMA from both the efficacy and safety perspective.
- Retrospective comparison between PTSMA and SM as reported in the literature.

Issues: Of the 38 publications provided by the Applicant to support their proposed indication, only 4 of the publications described randomized trials. They evaluated 1 mL vs 2 mL total ethanol dose in PTSMA for CK release and improvement of subjective measures of functional capacity. The remaining 34 publications were retrospective observational studies. The following submission quality issues impacted the risk/benefit analysis:

- There were no descriptions of validation techniques for assessing subjective symptoms indicating functional improvement.
- There were no prospective randomized trial data other than the 1 mL vs 2 mL ethanol dose comparison studies.
- There were no trials directly comparing PTSMA to SM.
- There were no trials comparing ethanol to another ablative agent as an adjunct to PTSMA.
- In response to our request for a database, the Applicant provided an incomplete listing of patients (100 of 180) who underwent PTSMA at one institution and explicitly stated in the NDA that the data could be biased. An attempt to retrieve the remainder of the dataset was not successful.
- There was no evidence that the alcohol used in the publications was equivalent to the product manufactured by the Applicant for which approval is being sought.
- The Applicant did not provide a rationale as to why their ethanol product was uniquely suited over other commercially available ethanol products that are used for this procedure.

Ethanol Dose:

- Dose from efficacy perspective:
    - In 4 randomized trials by Veselka et al (see Table 2) doses ranging from 1.1 ± 0.2 mL to 2.5 ± 0.8 mL were evaluated. The key finding in all 4 of these trials was that the release of CK-MB was directly proportional to the alcohol dose (Figure 5), but the outcome at the lower dose (i.e. subjective improvement in functional capacity and LVOT-PG reduction) was similar to that of the higher dose.

Of the 8 of a total of 38 publications that showed PTSMA-mediated improved exercise capacity in concert with improved NYHA and CCS class, 6 publications provided sufficient data to calculate the average dose of

ethanol (mL) per septal artery used during PTSMA: 2.53 mL/septal artery (average total 2.80 mL ethanol) as shown in

  - Table 83.
  - Of the total of 38 publications, 15 that showed improvement in functional capacity (objective or subjective) also provided dosing data allowing for the calculation of the average ethanol dose per septal artery used during PTSMA: 2.25 mL/septal artery (average total 2.49 mL ethanol) as shown in Table 84. These numbers were similar to those from the subgroup of 6 publications showing an improvement in exercise capacity.
- Dose from safety perspective:
  - A higher mortality rate was shown in patients who were treated with > 2 mL ethanol (i.e. 8%) compared to those who were treated with ≤ 2 mL ethanol (i.e. 1%) and that alcohol dose was determined to be an independent predictor of survival (Kuhn, 2008). This finding was the result of evaluating 329 consecutive patients between the years 1995-2001. The total ethanol dose in this patient cohort was 2.2 ± 1.0 mL ranging from 0.93 mL to 2.9 mL per patient (average 2.0 mL/septal artery). This finding was not corroborated by any other data presented in this NDA or independently researched. As an example, Fernandes (2008) showed a mortality rate of 3.9% (n= 619) in the population showing improvement in exercise capacity where the average total ethanol dose was 2.6 mL (2.0 mL/septal artery). In the review of 2959 subjects by Alam (2006) showing improvement in NYHA (n=2808), CCS (n=821) and treadmill exercise capacity (n=720) with an average ethanol dose of 2.9 mL (2.4 mL/artery), the mortality rate was 1.5% within the initial 30 days of PTSMA and an additional all-cause late mortality rate of 0.5%.
  - From the truncated database of 100 patients out of 180 patients who underwent PTSMA at the Motol University Hospital, Prague, Czech Republic, ethanol doses were reported only in the death and heart block narratives that were provided upon our additional request to the Applicant. There were 14 deaths during the 5--6 year mean follow-up period resulting in an annual all-cause mortality rate of 2.5%. This was similar to the published studies. Those patients who died received a total average dose of 1.5 mL ethanol (1.4 mL/septal artery). The rate of permanent pacemaker placement consequent to post-PTSMA development of heart block was 13% (similar to the rate in the publications). Those patients requiring a permanent pacemaker received a total ethanol dose of 1.9 mL (1.4 mL/artery). These data were similar to the cohort of patients in the Veselka database who were reported to have a heart block but did not require a pacemaker.
  - One study suggested that an ethanol bolus induced adverse outcome (i.e. permanent complete heart block) compared to a slow ethanol infusion over 30-60 seconds (Chang, 2003).

Reviewer Comment: Mortality rates from other retrospective studies were not reliable because of small sample sizes. The causes of early mortality in the study by Alam (2006) were LAD dissection, ventricular fibrillation, cardiac tamponade, and cardiogenic shock. I believe these causes of death were procedure related and common with standard percutaneous coronary intervention rather than being intrinsic to PTSMA. I also believe that the results reported by Kuhn (2008) might have been due to chance because of the retrospective nature of the TASH registry and lack of corroborative data from other studies. From the body of evidence, the mortality rate of approximately 1.5%--3.9% appeared to be dose-independent. I have not been able to confidently identify a safety margin for ethanol dosing.

- Estimation of Ethanol Therapeutic Index:
    - A compilation of data showed that an average dose of 2.5 mL ethanol per septal artery, or average total of 2.8 mL ethanol used in PTSMA, resulted in improved exercise capacity. The total ethanol doses mostly varied between 1-3 mL during the PTSMA procedure, but reports of up to 5 mL ethanol was used *(Nagueh 2001; Van de Lee 2005)*. The final dose was based on a titration strategy using instantaneous LVOT-PG as the controlling variable. Other than the Kuhn (2008) analysis of the observational TASH registry, there was no identifiable or stated dose above which a safety signal emerged. The optimal dose and therapeutic index could not be adequately evaluated from the publication data or Veselka database provided by the Applicant.

Reviewer Comment: I recommend a total ethanol dose of 1-3 mL. The dose per artery should be at the discretion of the interventional cardiologist performing the PTSMA. Final dosing should be titrated to LVOT-PG less than 10 mmHg during PTSMA (Sorajja, 2012). A maximum total ethanol dose should be 5 mL because of reported efficacy experience at this dose without a reported safety concern (Nagueh 2001; Van de Lee 2005). There were no published data demonstrating experiences at doses higher than 5 mL.

Efficacy of PTSMA:

- The clinical benefit of PTSMA depended upon features not related to intrinsic drug efficacy: operator experience and adequate septal perforator anatomy that matched with septum anatomy thus permitting adequate septal ablation. The challenge was how to distinguish drug efficacy from procedure efficacy.
- The quality of evidence provided by the Applicant to support efficacy of PTSMA was heterogeneous. The evidence included LVOT-PG data considered to not accurately reflect clinical status (Geske, 2011), subjective measures of functional capacity: NYHA Class and CCS Class that were not validated, and objective measures of functional capacity: exercise tolerance, in a subgroup of the publications provided. Despite these liabilities, the total body of evidence supporting efficacy demonstrated congruence between reduction in LVOT-PG,

improvement in NYHA and CCS class, and improvement in exercise tolerance. This persuasively suggested efficacy of PTSMA with ethanol despite the heterogeneity in data quality and absence of prospective data. Given the natural history of disease progression, the consensus in the cardiology community was that a procedure (either PTSMA or SM) was better than no procedure.

Safety of PTSMA:

- The safety of PTSMA depended upon features not related to intrinsic drug safety: complications of the intervention itself (e.g. arterial dissection, perforation leading to tamponade, embolization leading to infarction). Therefore, drug safety could not be independently evaluated.
- The safety data reported in the publications were focused on complete heart block associated with PTSMA relative to that of SM. Given the nature of the NDA, there was no source validation and no opportunity to conduct an audit for adverse events that may not have been reported. The publications of the 4 randomized trials describing the effect of ethanol dose on outcome following PTSMA were silent on safety issues. Notwithstanding the possibility that the results reported by Kuhn (2008) were due to chance, I further opine that the need for greater than 2 mL ethanol during PTSMA likely implied a mismatch between septal arterial anatomy and location of greatest septal thickness causing obstruction, thereby complicating the safety and effectiveness of PTSMA.
- The annual mortality rate was 2.5% as was similarly reported in the publications and in the Veselka database. The mortality rate was reported to approach that of the general population following PTSMA (Sorajja 2012). The narratives accompanying the Veselka database indicated that most of the patients who died had a complicated medical history. Given the natural history of the disease (see section 2.1 History of Hypertrophic Cardiomyopathy and Treatment Paradigms), the causes of death reported in the Veselka database were consistent with the observed age-related causes of death in patients with HOCM. The duration of time between PTSMA and death suggested that the procedure did not cause the death with the exception of the two patients who died from sudden death.
- There was an age-related safety signal associated with PTSMA (see Table 9). The older patients had a higher propensity towards complete heart block that required placement of a permanent pacemaker. However, the benefit of PTSMA outweighed the risk of a heart block where the risk mitigation was pacemaker placement.

Retrospective Comparisons between PTSMA and SM:

- In the literature, in lieu of a direct comparison between SM and PTSMA, there were attempts to retrospectively compare PTSMA to SM for patients with symptomatic refractory HOCM. Publications compared outcome between an independent series of observational studies of PTSMA with ethanol and an independent series of observational studies of SM. The general findings

suggested that PTSMA was less safe than SM regarding heart blocks, but comparable on efficacy with a trend favoring SM over PTSMA.

- One study suggested that PTSMA was at best similar to SM in improving LVOT-PG, NYHA class and CCS class, but was inferior to SM in measures of peak oxygen consumption and work rate (Firoozi, 2002).
- Both PTSMA and SM showed similar mortality rates (Sorajja, 2012), but another study suggested that SM was superior to PTSMA for mortality (Ralph-Edwards, 2005).
- There was a significant complication rate associated with PTSMA over SM involving complete heart block and pacemaker requirement (Sorajja, 2012; Qin, 2001).
- One study suggested that the requirement of a permanent pacemaker did not adversely affect post-PTSMA improvement of subjective functional capacity (Chang 2003-see Table 8).

Reviewer Comment: Although the overall benefit/risk analysis could not be adequately performed, the body of evidence pointed to a differential benefit of SM over PTSMA regarding both safety and efficacy. Regarding labelling language, two issues for consideration were:

- *Ethanol induced septal myocardial necrosis, but the efficacy of PTSMA was also based on adequate septal perforator coronary anatomy, and the skill of the interventionist. I therefore recommended that ethanol be indicated to induce septal myocardial necrosis in patients undergoing PTSMA* (b) (4)
- *SM was still the gold standard. Therefore, my recommendation placed a caveat specifying that the Applicant's drug should be used in patients who are not SM candidates.*

*The recommended indication would therefore be: "**In patients with refractory symptomatic hypertrophic obstructive cardiomyopathy who are clinically assessed as non-candidates for surgical myectomy, ethanol be approved to induce septal myocardial necrosis when used as an adjunct to percutaneous transluminal septal myocardial ablation to improve exercise capacity**".*

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

No recommendations.

1.4 Recommendations for Postmarket Requirements and Commitments

I recommend a post-approval registry of consecutive patients that would focus on safety measurements. The design of this registry should be patterned after registries normally

in effect in cardiac catheterization laboratories. The purpose of this recommendation is to improve upon the limited safety database in the NDA.

2 Introduction and Regulatory Background

2.1 History of Hypertrophic Cardiomyopathy and Treatment Paradigms

Hypertrophic Cardiomyopathy (HCM) is defined as a thick myocardium (> 1.5 cm) without an identifiable cause (e.g. hypertension, amyloidosis, aortic stenosis). HCM is the most common genetic cardiovascular disorder. It is autosomal dominant with variable penetrance and expressivity. It is thought that a genetic mutation in one of up to twelve sarcomeric and non-sarcomeric proteins causes histological myocyte disarray and fibrosis in HCM. Hypertrophy can occur in any part of the left ventricle, although it is most common in the anterior ventricular septum. Troponin T mutations have an increased risk of sudden death, which can occur without evidence of left ventricular hypertrophy. In a minority of cases, HCM is sporadic and presents as a non-familial form of the disease. The prevalence of HCM is 1 in 500. It is 2.9 times more common in men than women and 2.4 times more common in blacks than in whites (Fananapazir & Epstein, 1995). The obstructive form, HOCM, is seen in 25% of the cases (Fananapazir et al, 1992). Severe, medically refractory HOCM is seen in 10% of the cases (Olivotto et al, 2007). An illustration comparing a normal heart to one with HCM is shown in Figure 1. In a normal heart, there is sufficient distance between the mitral valve leaflet and the septal wall for blood to flow through the outflow tract towards the aortic valve. In HCM, the thick septal wall can abut the mitral valve leaflet thereby creating an outflow tract obstruction (i.e. HOCM). This results in an outflow tract pressure gradient (i.e. LVOT-PG). This condition causes symptoms such as shortness of breath with exertion, chest pain, palpitations, dizziness and syncope. Complications of HOCM are arrhythmias, dilated cardiomyopathy, mitral regurgitation, heart failure, and sudden death from ventricular tachycardia / ventricular fibrillation. The incidence of sudden death is approximately 1%/year, often in people < 30 years of age.

The mode of death as a result of HCM is shown in Figure 2. The mode of death is sudden in young people. The usual paradigm is the young basketball player who had symptoms of dizziness and or palpitations, usually attributed to suboptimal fitness or dehydration, and who then collapsed and died. Middle-aged patients usually die of “burn-out” (i.e. heart failure) as the left ventricle dilates due to continued obstruction throughout life. Elderly patients usually die of stroke that has been attributed to atrial fibrillation associated with HCM-mediated dysrhythmia.

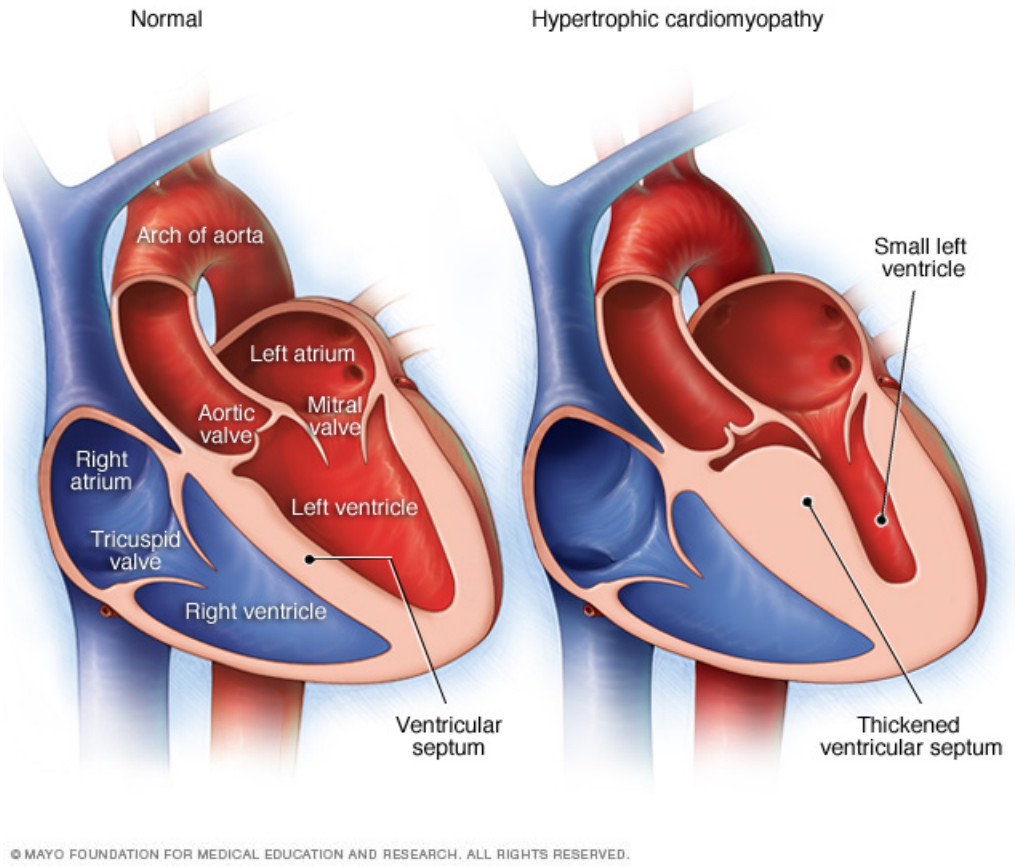
Treatment for HCM / HOCM is illustrated in the algorithm shown in Figure 3. Patients with obstructive physiology and symptoms of heart failure or angina pectoris are initially medically managed with beta blockade, verapamil, and/or disopyramide. If symptoms persist, then invasive therapy is indicated. If the patient is an acceptable surgical

candidate, the guidelines prescribe either SM or PTSMA. If the patient is not an acceptable candidate for SM, then the patient should be considered for PTSMA. If patients are not considered acceptable candidates for PTSMA, then dual chamber pacing should be considered. The key exclusion criteria for PTSMA is bad septal anatomy, defined as insufficient vascular coverage of the thickened septum to adequately perform the procedure, or inability to access the septal perforators due to coronary artery disease. Pacing the right ventricle will induce paradoxical contraction of the septal wall away from the mitral valve leaflet while inducing a left bundle branch block. Generally, SM is the preferred treatment option for most severely symptomatic patients with HOCM, especially in younger relatively healthy adults, whereas PTSMA is preferred in patients for whom surgery is contra-indicated or considered high risk, particularly the elderly (Gersh et al, 2011).

PTSMA with alcohol as the ablative agent was first introduced in 1995 as an alternative to SM (Sigwart, 1995). Alcohol is the only agent used in PTSMA for routine clinical practice. A recent study evaluated microsphere embolization as an alternative for alcohol in PTSMA (Vriesendorp et al, 2013). In two patients, the use of microsphere embolization was reported to result in immediate reduction of LVOT-PG. The extent of experience with microsphere embolization in PTSMA is insufficient at this time to render this product as available for use as an active comparator.

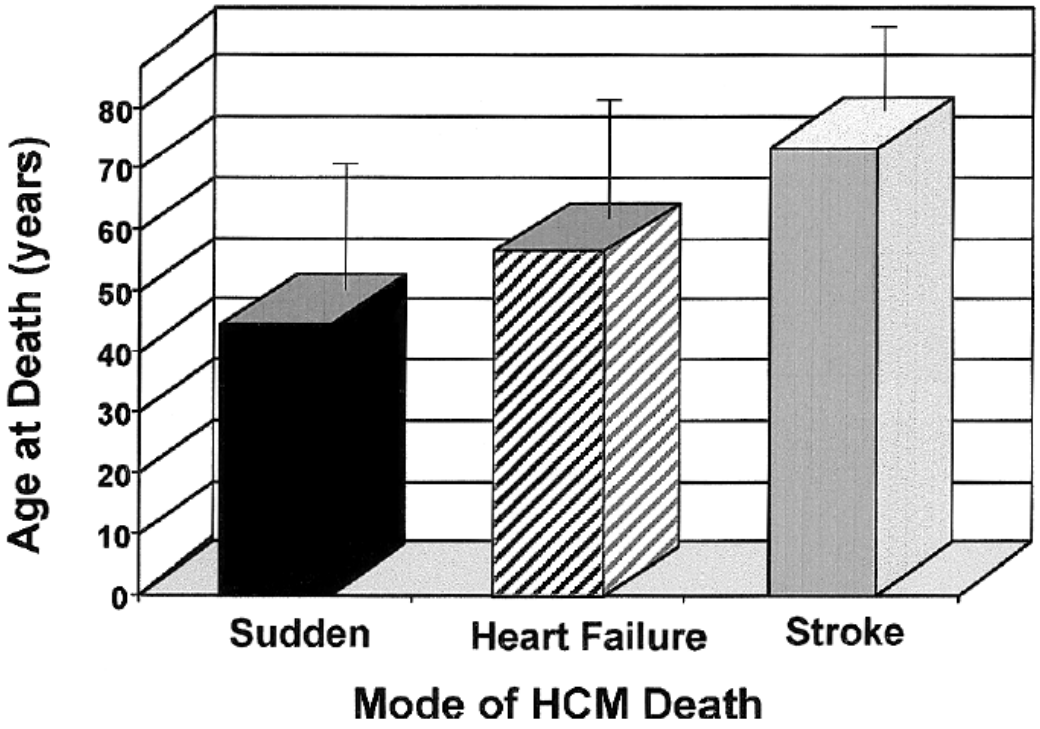
Independent from the evidence provided by the Applicant, characteristics of PTSMA and SM are shown in Table 1. PTSMA was reported to provide some decrease in LVOT-PG instantly, but 6-12 months is required for the full effect. SM, however, was reported to instantaneously and completely reduce LVOT-PG. The success rate of PTSMA was reported to be > 80% compared to a greater than 95% success rate for SM. The LVOT-PG was reported to be < 25 mmHg after PTSMA and < 10 mmHg after SM. The need for a permanent pacemaker was reported to be 12-27% for PTSMA and 3-10% for SM. If there were no pre-existing conduction abnormalities, the need for a permanent pacemaker was reported to be 13% post-PTSMA and 2% post-SM. The predominant post-PTSMA conduction abnormality was reported to be a right bundle branch block, and the predominant post-SM conduction abnormality was reported to be a left bundle branch block. Although there was no direct comparison between these two procedures, it appeared that SM was safer (measured by permanent complete heart blocks and pacemaker requirements) and more effective (measured by LVOT-PG) than PTSMA.

Figure 1. Comparison: Normal Heart vs Hypertrophic Cardiomyopathy



Source: Mayo Clinic Foundation for Medical Education

Figure 2. Mode of Death in Patients with Hypertrophic Cardiomyopathy with Age



Source: Maron et al., 2000

Figure 3. Treatment algorithm for hypertrophic cardiomyopathy

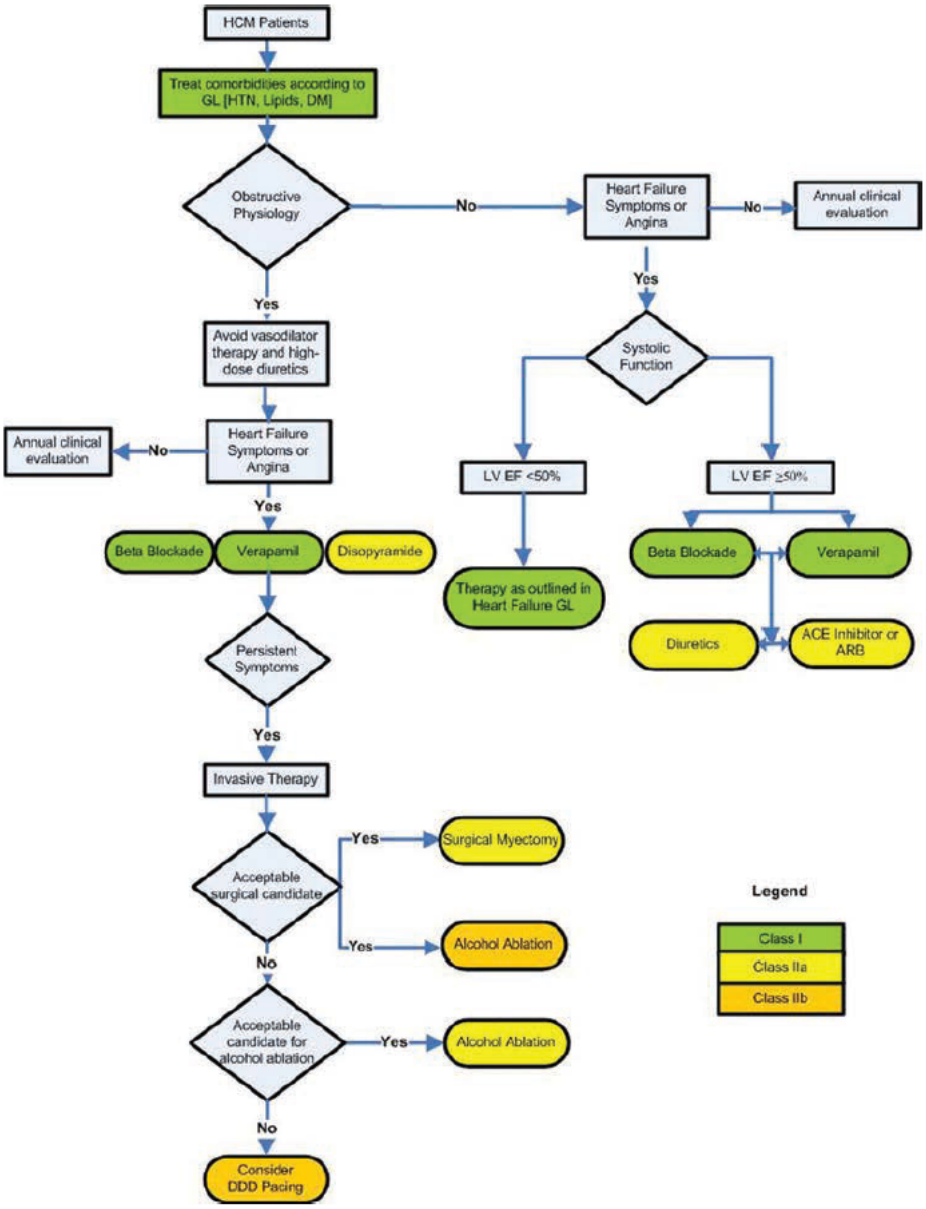


Figure 4. Treatment algorithm. ACE indicates angiotensin-converting enzyme; ARB, angiotensin receptor blocker; DM, diabetes mellitus; EF, ejection fraction; GL, guidelines; HCM, hypertrophic cardiomyopathy; HTN, hypertension; and LV, left ventricular.

Source: Gersh et al, ACCF/AHA Guidelines, 2011

Table 1. Description of PTSMA and SM for Patients with HOCM

Parameter	PTSMA	SM
Invasiveness	Percutaneous groin access	Sternotomy
Onset of reduction in LVOT-PG	Some decrease in gradient instantly, but 6-12 months for full effect	Instantaneous
Success Rate	>80%	>95%
Procedural Mortality	1-2%	0-2%
Recovery Time	2-4 days	1 week
Effect on LVOT-PG	Decreases to < 25 mm Hg	Decreases to < 10 mm Hg
Post-procedure conduction abnormality	RBBB	LBBB
Need for PPM-all patients	12-27%	3-10%
Need for PPM if no preexisting conduction abnormalities	13%	2%
Length of follow-up	6-8 years	30-40 years

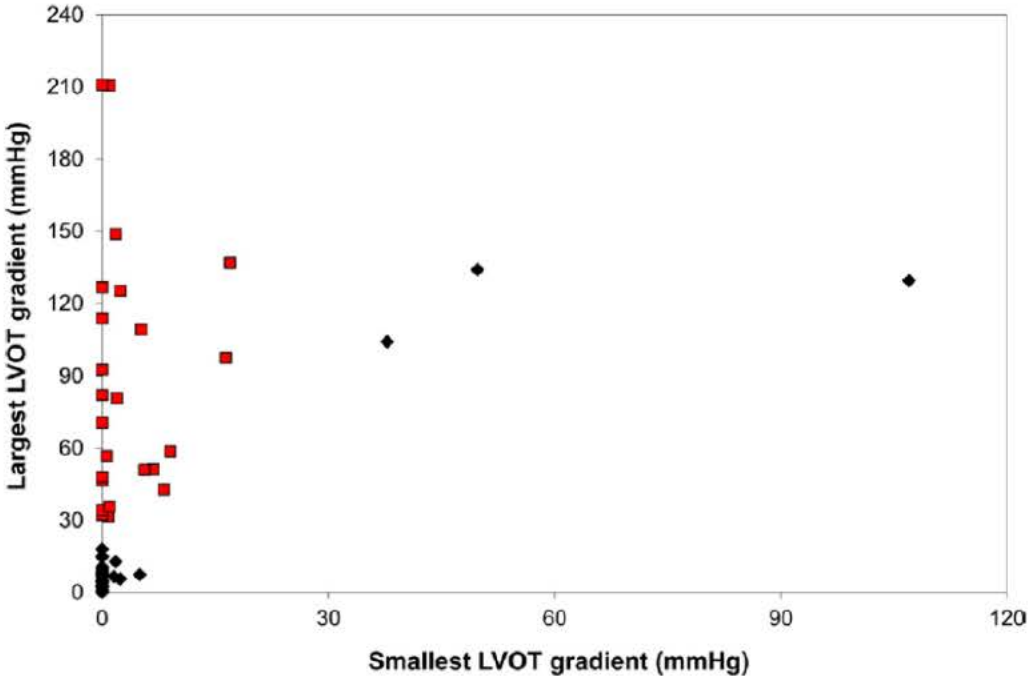
LVOT-PG (Left ventricular outflow tract-pressure gradient); PPM (permanent pacemaker); RBBB (right bundle branch block); LBBB (left bundle branch block). Source: Cleveland Clinic Center for Continuing Education (www.clevelandclinicmeded.com/medicalpubs/diseasemanagement/cardiology/hypertrophic-cardiomyopathy/#bib76)

LVOT-PG has been viewed as a measure of left ventricular outflow tract obstruction and was considered to have clinical utility because it was inherent to symptom etiology and served as an independent predictor of progression to severe symptoms of heart failure and to death (Maron, MS, et al., 2003). In patients with refractory symptomatic HOCM, consideration of septal reduction therapy was guided by LVOT-PG and the success of septal reduction therapy was guided by post-procedural quantification of LVOT-PG (Maron, MS, et al., 2003). However, the correlation between LVOT-PG and severity of obstruction was put into question in a study by the Mayo Clinic that investigated the variability of LVOT-PG during cardiac catheterization in 50 patients with HCM (Geske et

al, 2011). In this study, variability (i.e. difference between the largest and smallest LVOT-PG measurements in the absence of provocative maneuvers or interventions) for all 50 participants was substantial (see Figure 4). All the patients had NYHA class III-IV symptoms. Obstruction was defined as resting LVOT-PG ≥ 30 mm Hg, and severe obstruction was defined as a resting LVOT-PG ≥ 50 mmHg. The spontaneous LVOT-PG variability was 49.0 ± 53.1 mmHg, where the reported highest and lowest LVOT-PG measurements were 54.6 ± 56.4 mmHg and 5.7 ± 17.3 mmHg, respectively. This variability indicated severe and no obstruction in the same cohort. This study illustrated that reliance on LVOT-PG can be misleading and can have an adverse effect on therapeutic decision making.

From the perspective of regulatory decision making, I believe that this study supported our original advice to the Applicant (section 2.3 below) (b) (4)

Figure 4. Spontaneous LVOT-PG Variation for the Study Population



Source: Geske et al, 2011

2.2 Product Information

Dehydrated alcohol is a solution of ≥ (b) (4)% by volume of ethanol supplied in a sterile (b) (4) (b) (4) glass ampule.

2.3 Summary of Presubmission Regulatory Activity Related to Submission

On 11 SEP 2013, the Office of Orphan Products Development granted orphan-drug designation to dehydrated alcohol for the treatment of HOCM pursuant to section 526 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C 360bb).

In correspondence with the Applicant dated 22 May 2013, the Applicant indicated that they intended to submit a 505(b)(2) NDA comprised of published articles supporting (b) (4) (b) (4) their drug for use in PTSMA. The Applicant was advised that the indication should reflect a clinically meaningful benefit, i.e., reducing symptoms such as dyspnea, angina, or syncope; improvement in functional capacity; and/or improved outcomes such as reducing the incidence of heart failure hospitalization or increasing survival. (b) (4) A potentially acceptable indication was suggested:

Improving exercise capacity in patients with symptomatic, hypertrophic cardiomyopathy (b) (4) (b) (4)

The Applicant was also advised (b) (4) The Applicant was further advised that a stronger case for both efficacy and safety could be made if they could obtain study-related information (e.g. protocol, case report forms, datasets, and study report) from a recent outcome study. The Division offered to consider the possibility of using the published literature and a post-approval registry to evaluate safety.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

The 505(b)(2) NDA comprised of 38 publications (34 retrospective studies and 4 randomized trials describing dose-response) that focused primarily on hemodynamic parameters. The publications also generally described follow-up assessment of NYHA heart failure scale focusing on dyspnea and CCS scale for angina pectoris. Publications that reported improvements in dyspnea or chest pain did not describe validation procedures or suitable instruments for obtaining subjective patient assessments. Nine

retrospective studies described follow-up assessment of exercise capacity objectively measured by treadmill testing (8 of these were PTSMA-mediated; 1 showed improvement in exercise capacity after SM was performed as a consequence of a failed PTSMA). There were no prospective trials studies examining clinical primary endpoints.

There were no prospective trials or any published literature comparing the Applicant's drug to an active comparator for use in PTSMA due to lack of alternative available ablation agents. Similarly, there were no prospective trials comparing PTSMA to SM. Four retrospective studies and three meta-analyses paired the results from patients undergoing SM to the results from patients undergoing PTSMA in order to extract a comparison of outcome. The studies describing SM and PTSMA were independent from each other. Also, the patient population undergoing PTSMA had different characteristics from the cohort undergoing SM (Sorajja et al, 2012). Thus, these were not true comparisons.

During pre-NDA communication, the Applicant was advised to provide study-related information in order to strengthen their case for both efficacy and safety. They consequently provided a truncated dataset of patients who underwent a PTSMA at Motol University Hospital in the Czech Republic (i.e. sample size: 100 out of a total cohort of 180). This dataset listed the patients ages, date of PTSMA, follow-up timepoints, left ventricular ejection fraction (LVEF) at last check-up, death if occurred and cause of death, NYHA class, presence of syncopal episode, and presence of heart blocks. The reported criteria for selecting the 100 patients for this listing were: "reliable history", "completed medical reports", and "possible future cooperation of both patients and family members". It was unclear how the patients in the 180 patient dataset were selected for publications by Dr. Veselka (investigator at this institution) and if any of the 80 patients not provided to the Applicant were used for publications. It was also unclear what the outcome was for the 80 patients not provided to the Applicant. The Applicant admitted that the database provided in the NDA could be biased.

Reviewer Comment: The submission quality of this application was sub-optimal for the following reasons:

- *There were no descriptions of validation techniques for assessing subjective symptoms indicating functional improvement.*
- *There were no prospective randomized trial data other than the 1 mL vs 2 mL ethanol dose comparison studies.*
- *There were no trials directly comparing PTSMA to SM.*
- *There were no trials comparing ethanol to another ablative agent as an adjunct to PTSMA.*
- *In response to our request for a database, the Applicant provided an incomplete listing of patients (100 of 180) who underwent PTSMA at one institution and explicitly stated in the NDA that the data could be biased. An attempt to retrieve the remainder of the dataset was not successful.*

- *There was no evidence that the alcohol used in the publications was the product manufactured by the Applicant for which approval is being sought.*
- *The Applicant did not provide a rationale as to why their ethanol product was advantageous over other commercially available ethanol products that can be used for this procedure.*

3.2 Financial Disclosures

The Applicant disclosed that (b) (4)

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

The Applicant has (b) (4) I have deferred to CMC to address this issue.

4.2 Clinical Microbiology

The drug product endotoxins specification (b) (4) EU/mg) could potentially result in an endotoxin exposure that exceeds the USP recommended maximum limit of (b) (4) EU/kg/hr when administered to adult patients at the maximum recommended dose based on the proposed package insert (b) (4) A request was made to the Applicant to revise the endotoxins specification based on the maximum dose delivered within one hour based on the package insert and to provide the revised drug product specification and stability protocol documents reflecting the change. I have deferred to Clinical Microbiology to confirm adherence to their request.

4.3 Preclinical Pharmacology/Toxicology

Section 2.6 was missing from Module 2. The Applicant was requested to add this section for completeness and to reorganize the supportive data based on appropriate sections such as pharmacology (primary, secondary, and safety pharmacology), ADME/pharmacokinetics, general toxicology, genetic toxicology, carcinogenicity, reproductive and developmental toxicology and/or special toxicology studies, which should be summarized in Module 2.4 or 2.6. I have deferred to Pharmacology / Toxicology to assess completion and reorganization of relevant sections pursuant to their review.

4.4 Clinical Pharmacology

The Applicant was asked to provide information on the number of readers, their blinding and how inter-reader differences were dealt with for all reports and publications that determined echocardiographic endpoints in different groups or determined the parameters before and after the septal procedure. The Applicant was also asked to provide information on the strength, volume and injection rate of ethanol for all reports and publications. I have deferred to Clinical Pharmacology to assess receipt of all relevant information pursuant to their review.

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

The Applicant submitted 38 publications to support their NDA. Of these, there were 4 randomized clinical trials (see Table 2), 3 meta-analyses and 1 systematic literature review (see Table 3), 4 retrospective studies published by Veselka et al (see Table 4), 6 retrospective studies comparing PTSMA to Myectomy (see Table 5), 2 retrospective mid-term follow-up studies (see Table 6), 7 retrospective long-term follow-up studies (see Table 7), 4 retrospective studies evaluating PTSMA-mediated complete heart block (see Table 8), 4 retrospective studies evaluating the effect of age (see Table 9), 1 retrospective study evaluating SM after unsuccessful PTSMA (see Table 10), and 2 studies focusing on left ventricular diastolic properties (see Table 11).

Of the 38 publications, 13 listed Dr. Veselka as the primary author and 1 listed Dr. Veselka as a co-author (total of 37% of publications). Therefore, the data to support the NDA was based on considerable weight from a single author. The patient-level dataset from this same author was likely biased as submitted and therefore its utility as an adequate source of support for safety and efficacy of the Applicant's drug was questionable. Furthermore, it was not clear how much of the patient data from this dataset was used in the various publications.

The database submitted by the Applicant was not evaluated for efficacy because it was potentially biased. However, the database and associated narratives for mortality and heart block events were reviewed to support safety of ethanol in PTSMA.

Table 2. NDA-Supporting Publications: Randomized Clinical Trials

Randomized Clinical Trials		
Year	**Author**	**Title**
2011	Veselka, J, et al	Long-term Effects of Varying Alcohol Dosing in Percutaneous Septal Ablation for Obstructive Hypertrophic Cardiomyopathy: A Randomized Study with a Follow-up up to 11 years
2006	Veselka, J, et al	Impact of Ethanol Dosing on the Long-Term Outcome of Alcohol Septal Ablation for Obstructive Hypertrophic Cardiomyopathy: A single-center, prospective and randomized study
2005	Veselka, J, et al	Effects of Varying Ethanol Dosing in Percutaneous Septal Ablation for Obstructive Hypertrophic Cardiomyopathy on Early Hemodynamic Changes
2004	Veselka, J et al	Alcohol Septal Ablation for Hypertrophic Obstructive Cardiomyopathy: Lower Alcohol Dose Reduces Size of Infarction and has Comparable Hemodynamic and Clinical Outcome

Table 3. NDA-Supporting Publications: Meta-Analyses and Systematic Review

Meta-Analyses and Systematic Review		
Year	**Author**	**Title**
2010	Leonardi, R, et al	Meta-Analyses of Septal Reduction Therapies for Obstructive Hypertrophic Cardiomyopathy: Comparative Rates of Overall Mortality and Sudden Cardiac Death after Treatment
2010	Agarwal, S, et al	Updated Meta-Analysis of Septal Alcohol Ablation versus Myectomy for Hypertrophic Cardiomyopathy
2009	Alam, M, et al	Hypertrophic Obstructive Cardiomyopathy- Alcohol Septal Ablation vs. Myectomy: a Meta-analysis
2006	Alam, M, et al	Alcohol Septal Ablation for Hypertrophic Obstructive Cardiomyopathy: A Systematic Review of Published Studies

Table 4. NDA-Supporting Publications: Retrospective Studies: Veselka et al

Retrospective Studies		
Year	**Author**	**Title**
2014	Veselka, J, et al	Early Outcomes of Alcohol Septal Ablation for Hypertrophic Obstructive Cardiomyopathy: A European Multicenter and Multinational Study
2013	Veselka, J, et al	Low Incidence of Procedure-Related Major Adverse Cardiac Events after Alcohol Septal Ablation for Symptomatic Hypertrophic Obstructive Cardiomyopathy
2009	Veselka, J, et al	Alcohol Septal Ablation for Obstructive Hypertrophic Cardiomyopathy: Ultra-low dose of alcohol (1 ml) is still effective
2005	Veselka, J, et al	Effects of Alcohol Septal Ablation for Hypertrophic Obstructive Cardiomyopathy on Doppler Tei Index: a mid-term follow-up

Table 5. NDA-Supporting Publications: Retrospective Studies: Ablation vs Myectomy

Retrospective Studies: Comparison vs Myectomy		
Year	**Author**	**Title**
2012	Sorajja, P, et al	Survival after Alcohol Septal Ablation for Obstructive Hypertrophic Cardiomyopathy
2005	Ralph-Edwards, A, et al	Hypertrophic Obstructive Cardiomyopathy: Comparison of Outcomes after Myectomy or Alcohol Ablation adjusted by Propensity Score
2005	Van der Lee, C, et al	Percutaneous versus Surgical Treatment for Patients with Hypertrophic Obstructive Cardiomyopathy and Enlarged Anterior Mitral Valve Leaflets
2002	Firoozi, S, et al	Septal Myotomy-Myectomy and Transcoronary Septal Alcohol Ablation in Hypertrophic Obstructive Cardiomyopathy
2001	Qin, JX, et al	Outcome of Patients with Hypertrophic Obstructive Cardiomyopathy after Percutaneous Transluminal Septal Myocardial Ablation and Septal Myectomy Surgery
2001	Nagueh, S, et al	Comparison of Ethanol Septal Reduction Therapy with Surgical Myectomy for the Treatment of Hypertrophic Obstructive Cardiomyopathy

Table 6. NDA-Supporting Publications: Retrospective Studies: Mid-Term Follow-Up

Retrospective Studies: Mid-Term Follow-up		
Year	**Author**	**Title**
2012	Veselka, J, et al	Mid-Term Outcomes of Alcohol Septal Ablation for Obstructive Hypertrophic Cardiomyopathy in Patients with Sigmoid versus Neutral Ventricular Septum
2005	Faber, L, et al	Catheter-based Septal Ablation for Symptomatic Hypertrophic Obstructive Cardiomyopathy: follow-up results of the TASH-registry of the German Cardiac Society

Table 7. Retrospective Studies: Long-Term Follow-Up

Retrospective Studies with Long Term Follow-up		
Year	**Author**	**Title**
2014	Veselka, J, et al	Long-term Survival after Alcohol Septal Ablation for Hypertrophic Obstructive Cardiomyopathy: a comparison with general population
2014	Moss, T, et al	Left Ventricular Systolic Function Following Alcohol Septal Ablation for Symptomatic Hypertrophic Cardiomyopathy
2013	Jensen, M, et al	Alcohol septal ablation in patients with hypertrophic obstructive cardiomyopathy: low incidence of sudden cardiac death and reduced risk profile
2013	Krejci, J, et al	Comparison of Long-Term Effect of Dual-Chamber Pacing and Alcohol Septal Ablation in Patients with Hypertrophic Obstructive Cardiomyopathy
2011	Nagueh, S, et al	Alcohol Septal Ablation for the Treatment of Hypertrophic Obstructive Cardiomyopathy: A Multicenter North American Registry
2008	Fernandes, V, et al	Follow-Up of Alcohol Septal Ablation for Symptomatic Hypertrophic Obstructive Cardiomyopathy
2008	Kuhn, H, et al	Survival after Transcoronary Ablation of Septal Hypertrophy in Hypertrophic Obstructive Cardiomyopathy (TASH): a 10 year experience

Table 8. Retrospective Studies: Alcohol Septal Ablation and Complete Heart Block

Retrospective Studies: Septal Ablation and Complete Heart Block		
Year	**Author**	**Title**
2014	Veselka, J, et al	Outcome of Patients after Alcohol Septal Ablation with Permanent Pacemaker Implanted for Periprocedural Complete Heart Block
2007	Faber, L, et al	Percutaneous Septal Ablation for Symptomatic Hypertrophic Obstructive Cardiomyopathy: Managing the risk of procedure-related AV Conduction Disturbances
2007	El-Jack, S, et al	Predictors of Complete Heart Block after Alcohol Septal Ablation for Hypertrophic Cardiomyopathy and the Timing of Pacemaker Implantation
2003	Chang, SM, et al	Complete Heart Block: Determinants and Clinical Impact in Patients with Hypertrophic Obstructive Cardiomyopathy Undergoing Nonsurgical Septal Reduction Therapy

Table 9. Retrospective Studies: Effect of Age

Retrospective Studies: Effect of Age		
Year	**Author**	**Title**
2014	Veselka, J, et al	Survival of Patients $\leq$ 50 Years of Age after Alcohol Septal Ablation for Hypertrophic Obstructive Cardiomyopathy
2013	Leonardi, R, et al	Alcohol Septal Ablation for Obstructive Hypertrophic Cardiomyopathy: Outcomes in Young, Middle-Aged, and Elderly Patients
2006	Veselka, J, et al	Age-related Hemodynamic and Morphologic Differences in Patients Undergoing Alcohol Septal Ablation for Hypertrophic Obstructive Cardiomyopathy
2004	Gietzen, FH, et al	Transcoronary Ablation of Septal Hypertrophy for Hypertrophic Obstructive Cardiomyopathy: feasibility, clinical benefit, and short term results in elderly patients

Table 10. Retrospective Studies: Myectomy after Unsuccessful Septal Ablation

Retrospective Study: Myectomy after Unsuccessful Alcohol Septal Ablation		
Year	**Author**	**Title**
2007	Nagueh, S, et al	Outcome of Surgical Myectomy after Unsuccessful Alcohol Septal Ablation for the Treatment of Patients with Hypertrophic Obstructive Cardiomyopathy

Table 11. Retrospective Studies: Left Ventricular Diastolic Properties

Retrospective Studies: Left Ventricular Diastolic Properties		
Year	**Author**	**Title**
2006	Jassal, D, et al	Sustained Improvement in Left Ventricular Diastolic Function after Alcohol Septal Ablation for Hypertrophic Obstructive Cardiomyopathy
2001	Mazur, W, et al	Regression of Left Ventricular Hypertrophy after Nonsurgical Septal Reduction Therapy for Hypertrophic Obstructive Cardiomyopathy

5.2 Review Strategy

The review strategy was based on the following:

- The indication should reflect a clinically meaningful benefit, i.e., reducing symptoms such as dyspnea, angina, or syncope; improvement in exercise capacity; and/or improved outcomes such as reducing the incidence of heart failure hospitalization or increasing survival.
- (b) (4)

The strategic approach to the review process focused primarily on the database provided by the Applicant in response to our request, and on published studies providing objective measures of improved functional capacity of patients with refractory symptomatic HOCM, such as exercise testing and/or reduced mortality. In the absence of objective evidence, the review focused on evidence of subjective measures of improved functional capacity (NYHA-dyspnea, CCS-angina pectoris) that included descriptions of validation tools for adequate evaluation of subjective evidence. In the absence of evidence describing subjective measures of improvement that included validation tools for such subjective measures, the review searched for any evidence of consistent functional improvement (b) (4) was considered not

acceptable. Improvements in functional capacity were evaluated against possible increases in adverse events, such as mortality or other unacceptable increases in the incidence of adverse events (i.e. ventricular arrhythmias, heart blocks requiring permanent pacemaker placement).

The strategic approach to the review process also focused on any study directly comparing SM to PTSMA, or ethanol to any other ablative agent used in PTSMA. In the absence of such direct comparisons, the review focused on any study that separately evaluated observations from each procedure or other ablative agents in order to indirectly compare the efficacy of each independently studied procedure or ablative agent.

The review proceeded according to the following hierarchy:

1. Evaluation of randomized clinical trials and the Applicant's database.
2. Evaluation of meta-analyses and systematic review
3. Evaluation of retrospective studies

All publications submitted by the Applicant to support their proposed indication were reviewed. The Veselka database was reviewed for safety (i.e. mortality and heart block)

5.3 Discussion of Individual Studies/Clinical Trials

5.3.1 Randomized Clinical Trials

Executive Summary and Reviewer Overall Assessment of Randomized Clinical Trials

There were 4 published prospective randomized clinical trials that compared 1 mL of ethanol to 2 mL of ethanol for use in PTSMA (see Table 2). All were authored by Veselka et al, and focused on the effect of alcohol dose by volume on hemodynamic and clinical outcome following PTSMA. Salient findings from these 4 publications were:

- There was a correlation between alcohol dose and amount of released CK-MB at peak.
- The hemodynamic, septal thickness and patient symptom outcomes were dose-independent. The lower doses of alcohol used in PTSMA resulted in similar outcomes despite the lower infarct size produced by the lower alcohol dose as measured by peak CK-MB.
- There was a decrease in septal thickness and LVOT-PG following PTSMA that persisted for the duration of follow-up time (max 84-85 months).
- There was evidence of symptomatic improvement (dyspnea by NYHA class and angina pectoris by CCS class) that persisted for the duration of follow-up.
- Key caveats from these 4 randomized trials were:

- There was no description of validated tools used to assess dyspnea and chest pain.
- There was no description of quantitative or objective functional assessment or exercise capacity associated with subject symptom assessment (b) (4)
- None of the 4 randomized trials were designed and powered for clinical assessment as the primary endpoint.
- It was not clear if the investigator was blinded to treatment when assessing subjects' symptoms.
- All the trials were conducted by the same investigator from the same site despite the span of years ranging from 2004-2011. This put into question potential site-based bias.

My overall assessment is that the 4 randomized trials demonstrated no difference between a lower and higher alcohol dose in reducing LVOT-PG and septal thickness, and improving patient subjective symptoms. The data from these trials supported subjective functional improvement from baseline.

Veselka et al (2011) conducted a prospective randomized clinical trial designed to evaluate long term (> 60 months) clinical and echocardiographic outcomes of patients with symptomatic HOCM who were treated with low (1-2 mL) or high (> 2 mL) doses of 96% alcohol as measured by volume of injection. Seventy-six patients were randomized in a 1:1 distribution into the low dose vs high dose group. Baseline data is shown in Table 12. The mean low-dose volume was 1.1 mL (1 ml/artery) and the mean high dose volume was 2.5 mL (2.3 mL/artery). Mean follow-up time was 84-85 months ranging from 60-138 months. The baseline characteristics were similar between the two groups.

The correlation between peak CK-MB and alcohol dose is shown in Figure 5. The results demonstrated that the higher the alcohol dose, the greater the infarct. Changes in hemodynamic parameters and dyspnea classification-NYHA for each arm are shown in Table 13. Septal thickness and LVOT-PG significantly decreased from baseline throughout the follow-up period and appeared independent of dose. Similarly, dyspnea-NYHA class significantly fell from baseline throughout the follow-up period and also appeared to be dose-independent. Adverse outcomes (i.e. complete heart block, permanent pacemaker placement, ventricular tachycardia requiring cardioversion, and death) are shown in Table 14. The incidence of arrhythmia and conduction defects was low and empirically comparable in each group.

Table 12. Baseline Characteristics of Alcohol Dose Randomized Trial (Veselka, 2011)

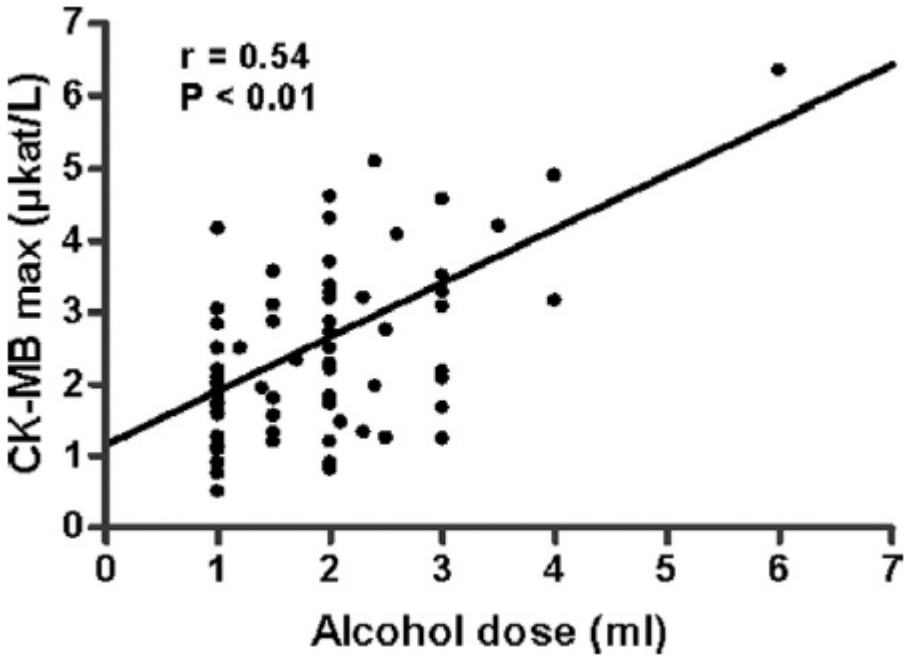
Variable	Low-dose group	High-dose group
Alcohol amount (mL)	1.1 ± 0.2	2.5 ± 0.8
Follow-up duration, median (mo)	84	85
Women/men, *n* (%)	16/21 (43/57)	16/23 (41/59)
Age (y)	57 ± 13	53 ± 13
Pacemaker *n* (%)	2 (5)	8 (21)
LV ejection fraction (%)	82 ± 6	80 ± 7
LV diameter (mm)	42 ± 5	44 ± 5
Septum thickness (mm)	21 ± 3	22 ± 5
LV outflow gradient (mm Hg)	74 ± 36	74 ± 38
Dyspnea (NYHA class)	2.8 ± 0.6	2.8 ± 0.5

Data are presented as mean ± SD except where otherwise noted. Differences between the 2 groups are not significant.

LV, left ventricular; NYHA, New York Heart Association.

Source: Veselka et al, 2011

Figure 5. Alcohol dose and peak CK-MB: early post-PTSMA period (Veselka, 2011)



Source: Veselka et al, 2011

Table 13. Efficacy Outcome at 1-year and Follow-up Period (Veselka, 2011)

Variable	Baseline	1 year	Final
LV ejection fraction (%)			
Low-dose group	82 ± 6	79 ± 6	78 ± 6*
High-dose group	80 ± 7	76 ± 7*	76 ± 9*
LV diameter (mm)			
Low-dose group	42.1 ± 4.8	46.0 ± 5.9*	46.1 ± 5.0*
High-dose group	43.5 ± 4.9	45.9 ± 4.4*	47.4 ± 4.7*
Septum thickness (mm)			
Low-dose group	21.0 ± 3.1	15.2 ± 4.1*	14.2 ± 3.6*
High-dose group	22.4 ± 4.6	14.3 ± 4.8*	13.2 ± 4.6*
LV outflow gradient (mm Hg)			
Low-dose group	74 ± 36	28 ± 35*	24 ± 32*
High-dose group	74 ± 39	19 ± 18*	18 ± 20*
Dyspnea (NYHA class)			
Low-dose group	2.8 ± 0.6	1.5 ± 0.7*	1.6 ± 0.8*
High-dose group	2.8 ± 0.5	1.4 ± 0.5*	1.4 ± 0.5*

Data are presented as mean ± SD.
LV, left ventricular; NYHA, New York Heart Association.
* $P < 0.05$ vs baseline value.

Source: Veselka et al, 2011

Table 14. Adverse Events (Veselka, 2011)

Veselka, J, et al, 2011		
	Low Dose	High Dose
Sample Size	36	40
Temporary Complete Heart Block	5	2
Permanent Pacemaker Placement	2	2
Ventricular Tachycardia requiring cardioversion	2	1
Cardioverter-Defibrillator implantation	2	1
Death (1 year)	1	1
Death (follow-up period: 84-85 months)	2	3

Source: Veselka et al, 2011: tabulated by FDA clinical reviewer from publication content

Reviewer Comment (Veselka 2011): Although not specified in the publication, this study appeared to be a single-center trial. The data from this study showed symptomatic benefit aligned with decreases in both LVOT-PG and septal thickness following PTSMA. The publication did not describe what if any validated tool was deployed to acquire subjective data from patients about dyspnea. The publication did not report whether the investigator evaluating the patient for symptomatic outcome was blinded to randomized treatment at the time of the evaluation. Mechanisms to ensure minimization of loss-to-follow-up to ensure that all mortality events were captured were not described. The follow-up period had a wide range and there was no assurance that the actual follow-up times labeled as "final" in Table 13 were similar between the groups for the individual parameters evaluated. Despite liabilities associated with the reporting of this study, this randomized trial demonstrated that decreases in septal thickness and LVOT-PG, as well as improvement in dyspnea, could be accomplished with a lower dose of alcohol and correspondingly lower infarct size as measured by peak CK-MB. Objective improvement in exercise capacity was not demonstrated.

Veselka et al (2006, Circ. J, 70:1550-1552) conducted a single-center, prospective randomized study designed to evaluate the impact of ethanol dose on the long-term (> 6 months) outcome of alcohol septal ablation for patients with HOCM. Fifty four patients undergoing PTSMA were randomized 1:1 to receive an ethanol dose ≤ 2 mL (low-dose, Group A) or > 2 mL (standard dose, Group B). The low-dose group received 1.5 mL (1

mL/artery) and the high-dose group received 2.6 mL (2.6 mL/artery). Mean follow-up time was 40 months.

Baseline characteristics of patients undergoing PTSMA are shown in Table 15. The baseline characteristics were similar between the two groups. Clinical and echocardiographic characteristics at follow-up (40 months ranging from 6-72 months) are shown in Table 16. There was generally no difference between the groups in echocardiographic characteristics, dyspnea, and chest pain. Adverse outcomes are shown in Table 17. The number of patients requiring re-injection of alcohol due to insufficient decreases in LVOT-PG appeared comparable between the two dose groups. In each of the two dosing groups, there were similar number of patients who experienced ventricular tachycardia requiring cardioversion, new left bundle branch blocks, repeat PTSMA, and death. The number of patients requiring a permanent pacemaker was 4 in the high dose-group and 1 in the low-dose group.

Table 15. Baseline Characteristics of Patients undergoing PTSMA (Veselka, 2006)

	Group A	*Group B*	*p value*
Age, years	*58±15*	*53±14*	*0.15*
Women, n	*17*	*18*	*1*
IVS, mm	*21±4*	*22±4*	*0.44*
LVd, mm	*43±4*	*44±4*	*0.63*
PW, mm	*12±3*	*12±3*	*0.80*
LA, mm	*48±5*	*47±4*	*0.47*
LVEF, %	*80±7*	*81±7*	*0.67*
LV outflow gradient, mmHg	*75±41*	*71±41*	*0.77*
Dyspnea, NYHA class	*2.8±0.6*	*2.8±0.4*	*0.80*
Angina pectoris, CCS class	*2.3±0.7*	*2.3±0.7*	*0.95*
Initially paced patients, n	*2*	*6*	*0.25*

IVS, interventricular septum end-diastolic diameter; LVd, left ventricular end-diastolic diameter; PW, left ventricular posterior wall end-diastolic diameter; LA, left atrial end-systolic diameter; LVEF, left ventricular ejection fraction; LV, left ventricular; NYHA, New York Heart Association; CCS, Canadian Cardiovascular Society.

Source: Veselka et al, 2006, Circ. J, 70:1550-1552

Table 16. Characteristics post-PTSMA at Follow-Up (Veselka, 2006)

	Group A	*Group B*	*p value*
Follow-up duration, months (range)	*40±20 (6–72)*	*39±19 (6–70)*	*0.78*
IVS, mm	*15±4*	*13±5*	*0.11*
LVd, mm	*48±5*	*48±5*	*0.80*
PW, mm	*11±3*	*12±3*	*0.55*
LA, mm	*48±5*	*47±5*	*0.47*
LVEF, %	*79±7*	*75±7*	*0.03*
LV outflow gradient, mmHg	*25±29*	*21±21*	*0.61*
Dyspnea, NYHA class	*1.4±0.9*	*1.2±0.8*	*0.25*
Angina pectoris, CCS class	*0.8±0.8*	*0.6±0.5*	*0.27*
Paced patients, n	*6*	*7*	*1*

Source: Veselka et al, 2006, Circ. J, 70:1550-1552

Table 17. Adverse Events (Veselka, 2006 Circ Journal)

Veselka, J, et al, 2006		
	Low Dose	High Dose
Sample Size	27	27
Actual Dose	1-1.5 mL	2.1-2.5 mL
Additional Ethanol injection because LVOT-PG did not decrease by > 50%	10	9
Permanent Pacemaker Placement	4	1
Ventricular Tachycardia requiring cardioversion	2	2
New Left Bundle Branch Block	13	15
Repeat PTSMA	1	1
Death (follow-up period: 6-72 months)*	1	1

*(one death was described as sudden death and the other described as due to bronchogenic carcinoma. Death causality in which arm was not reported)

Source: Veselka et al, 2006, Circ. J, 70:1550-1552, tabulated by FDA clinical reviewer from publication content

Reviewer Comment (Veselka 2006, Circ. J, 70:1550-1552): I identified the following liabilities during my review of this publication:

- *As in other studies, this publication did not describe what if any tool was deployed to acquire subjective data from patients about dyspnea or chest pain.*
- *The publication did not report if the investigator evaluating patient symptoms was blinded at the time of the evaluation.*
- *The publication did not report on steps taken to minimize loss to follow-up (i.e. whether all deaths and adverse events were accounted for).*
- *The follow-up period was 40 months but the variability was very wide (i.e.6-72 months). The publication did not report on how the follow-up variability distributed between the two groups, potentially making the follow-up period significantly different between the groups.*

This publication suggested no difference between the two doses of alcohol in causing changes in hemodynamic parameters and symptomatic improvement in dyspnea and chest pain.

Veselka et al (2005, American Journal of Cardiology, 95: 675-678) conducted a prospective randomized study designed to evaluate the association between dose and post-procedural hemodynamic changes in 42 patients treated by PTSMA for HOCM. The patients were randomized into 2 groups: 21 receiving > 2 mL (Group A) and 21 receiving ≤ 2 mL (Group B). Mean follow-up time was 3 months. Group A received 2.8 mL (2.5 mL/artery) and Group B received 1.1 mL (1.0 mL/artery).

Baseline characteristics are shown in Table 18. There appears to be no significant difference between the two arms in baseline characteristics except for the number of syncopal events. There was twice the number of syncopal events in the higher dose arm compared to the lower dose arm at baseline. Given 21 patients per arm, the number (percentage) of “pacemaker or implantable cardioverter-defibrillator” reported events in the higher dose arm (3 {44%}) is a typographical error.

Table 18. Baseline Characteristics of Alcohol Dose Randomized Trial (Veselka, 2005)

Variable	Ethanol Amount >2 cm^3	Ethanol Amount ≤2 cm^3
Age (range) (yrs)	53 ± 13 (30–75)	53 ± 10 (24–68)
Women/men	13/8	12/9
Dyspnea, NYHA class	2.6 ± 0.7	2.7 ± 0.6
Angina pectoris, CCS class	2.1 ± 0.9	2.4 ± 0.9
Episodes of syncope	10 (48%)	5 (24%)
Pacemaker of implantable cardioverter-defibrillator	3 (44%)	4 (19%)
LV outflow gradient (mm Hg)	78 ± 47	73 ± 35
LV outflow gradient after isosorbide dinitrate (mm Hg)	120 ± 60	118 ± 40
Basal septum thickness (mm)	22 ± 4	21 ± 4
LV diameter (mm)	44 ± 5	43 ± 5

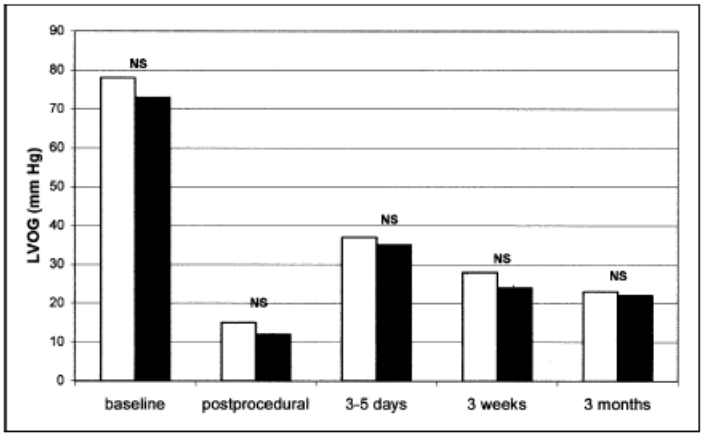
CCS = Canadian Cardiovascular Society; NYHA = New York Heart Association.

Source: Veselka et al, 2005, American Journal of Cardiology, 95: 675-678

There were no differences between the arms for LVOT-PG as shown in Table 19. Immediately post-procedure, the drop in LVOT-PG from baseline appeared considerable for both arms. Following this initial decline, the LVOT-PG rose in each arm by approximately 3-fold 3-5 days post-operatively and it then slowly declined over time for the 3-month follow-up period. Other echocardiographic and electrocardiographic data are shown in Table 20. There appeared to be no difference between the arms for basal septal thickness, left ventricular diameter, and number of patients requiring pacemaker placement. There appeared to a numerically higher incidence of bundle branch blocks in initially non-paced patients in the higher dose arm, but the small sample size attenuates the ability to draw a conclusion.

Adverse events and clinical follow-up are shown in Table 21. The data suggested a correlation between alcohol dose and peak CK-MB. Data on follow-up clinical outcome (NYHA and CCS), as well as repeat PTSMA, were not reported. There were 3 patients who were reported to have experienced sustained ventricular tachycardia induced by injection of echocardiographic contrast medium (2 cases) and ethanol (1 case) into the septal branch for which immediate cardioversion was needed. The arm to which these 3 patients were randomized was not reported.

Table 19. Changes in LVOT-PG during Follow-up (Veselka, 2005)



Source: Veselka et al, 2005, American Journal of Cardiology, 95: 675-678; White Bars: Higher Dose; Black Bars: Lower Dose

Table 20. Echocardiographic and ECG Changes during Follow-Up (Veselka, 2005)

Variable	Baseline	Postprocedural	3 to 5 Days	3 Weeks	3 Months
LV outflow gradient (mm Hg)					
Group A	78 ± 47	15 ± 25*	37 ± 39*†	28 ± 32*†‡	23 ± 26*†‡
Group B	73 ± 35	12 ± 15*	35 ± 26*†	24 ± 5*†‡	22 ± 21*†‡
Basal septum (mm)					
Group A	22 ± 4	—	20 ± 4*	16 ± 3*†‡	14 ± 4*†‡
Group B	21 ± 4	—	18 ± 5*	15 ± 4*†‡	14 ± 3*†‡
LV diameter (mm)					
Group A	44 ± 5	—	45 ± 5	47 ± 5*	47 ± 5*
Group B	43 ± 5	—	44 ± 5	46 ± 5*	47 ± 5*
Bundle branch block in initially nonpaced patients					
Group A	4 (25%)	11 (69%)*	11 (69%)*	11 (69%)*	11 (69%)*
Group B	1 (6%)	8 (47%)*	7 (41%)*	7 (41%)*	7 (41%)*
No. of paced patients					
Group A	3 (14%)	7 (33%)	5 (24%)	5 (24%)	5 (24%)
Group B	4 (19%)	7 (33%)	6 (29%)	6 (24%)	6 (24%)

*p <0.05 versus baseline value; †p <0.05 versus postprocedural value; ‡p <0.05 versus 3 to 5 days value.

Source: Veselka et al, 2005, American Journal of Cardiology, 95: 675-678; Group A: Higher Dose; Group B: Lower Dose

Table 21. Adverse Events and Clinical Follow-Up (Veselka, 2005)

Veselka, J, et al, 2005			
	Group A	Group B	Unknown Arm
Sample Size	21	21	
Actual Dose	2.8 ± 0.6 mL	1.5 ± 0.4 mL	
Peak CK-MB (uKat/L)	3.79 ± 2.42	2.33 ± 0.85	
Permanent Pacemaker Placement	0	1	
Ventricular Tachycardia requiring cardioversion			3
Repeat PTSMA	Not reported	Not reported	
Death (follow-up period: 3 months)*	0	0	
Changes in NYHA / CCS	Not reported	Not reported	

*(the text specified that no deaths occurred during hospital stay and follow-up was completed in all patients. There was no report of death post-hospital stay)

Source: Veselka et al, 2005, American Journal of Cardiology, 95: 675-678; tabulated by FDA clinical reviewer from publication content

Reviewer Comment (Veselka 2005, American J. Cardiol.): This study suggested no difference between the two doses tested for changes in hemodynamic parameters and septal thickness. There was a significant increase in bundle branch blocks compared to baseline for both groups and an empirical trend towards a higher number of blocks in the arm where a higher dose of ethanol was administered. I could not draw any conclusions about the effect of alcohol volume on the induction of bundle branch blocks from the small number of patients studied. There was no clinical outcome data from this trial that would allow me to draw a conclusion on the efficacy of the Applicant's drug (b) (4)

Veselka et al (2004) conducted a 1:1 randomized clinical trial of 34 symptomatic subjects with refractory HOCM presenting for PTSMA. Seventeen subjects were enrolled in Group A (ethanol dose 1-2 mL) and 17 subjects were enrolled in Group B (ethanol dose > 2 mL). Mean follow-up time was 6 months. Group A received 1.6 mL (1.5 mL/artery) and Group B received 3.4 mL (3.1 mL/artery).

Baseline data is shown in Table 22. There were no differences in baseline characteristics between the two dosing arms. Interventional data is shown in Table 23. There were no differences in pressure gradient at start and end of PTSMA between the two dosing groups. Outcome data is shown in Table 24. There were no differences between the two dosing groups in echocardiographic and clinical data. The patients reported significant improvement in symptoms at the 6-month follow-up period in both mean NYHA and mean CCS class from baseline. A persistent right bundle branch block was observed in 6 subjects in the low-dose group and 7 subjects in the high dose group. A persistent left bundle branch block was observed in 1 subject in the low-dose group and 2 subjects in the high dose group. One subject in each group required permanent pacemaker placement.

Table 22. Baseline echocardiographic and clinical data (Veselka, 2004)

Variable	Group A	Group B	*P*
Left ventricular ejection fraction, %	81 ± 8	80 ± 6	NS
Septal thickness, mm	21 ± 3	22 ± 3	NS
Posterior wall thickness, mm	12 ± 2	12 ± 2	NS
Left ventricular dimension, mm	44 ± 5	43 ± 6	NS
Left atrial dimension, mm	47 ± 6	44 ± 6	NS
Left ventricular outflow tract gradient, mm Hg	70 ± 35	66 ± 39	NS
Dyspnea, NYHA class	2.7 ± 0.7	2.5 ± 0.6	NS
Angina pectoris, CCS class	2.3 ± 0.9	2.1 ± 0.9	NS
History of syncope, n	6	7	NS
Number of paced patients, n	3	4	NS

Source: Veselka et al, 2004

Table 23. Interventional Data (Veselka, 2004)

Variable	Group A	Group B	*P*
PG start, mm Hg	66 ± 39	56 ± 32	NS
PG end, mm Hg	11 ± 13	14 ± 12	NS
Ethanol injected, ml	1.6 ± 0.4	3.4 ± 0.9	< 0.001
Number of target vessels	1 ± 0	1.1 ± 0.1	NS

Source: Veselka et al, 2004

Table 24. Echocardiographic and Clinical Data 6 month follow-up (Veselka, 2004)

Variable	Group A	Group B	*P*
Left ventricular ejection fraction, %	75 ± 6	75 ± 5	NS
Septal thickness, mm	13 ± 3	14 ± 4	NS
Posterior wall thickness, mm	11 ± 2	11.3 ± 2	NS
Left ventricular dimension, mm	47 ± 4	47 ± 6	NS
Left atrial dimension, mm	46 ± 5	43 ± 5	NS
Left ventricular outflow tract gradient, mm Hg	16 ± 12	17 ± 15	NS
Dyspnea, NYHA class	1.5 ± 0.8	1.2 ± 0.5	NS
Angina pectoris, CCS class	0.9 ± 0.7	0.8 ± 0.7	NS
Number of paced patients, n	5	5	NS

Source: Veselka et al, 2004

Reviewer Comment (Veselka 2004): Similar to the randomized trials conducted by Veselka et al in the years following this trial, the data suggested that changes in hemodynamic parameters post-PTSMA appeared to be dose-independent for the doses tested. Although the data suggested symptomatic improvement, this study, like the others that followed, did not describe what if any tool was used to acquire subjective data from patients about dyspnea and chest pain. The investigator was likely unblinded because the arms of the study were based on volume. There was no report of time variability in the follow-up period and there was no statement in the publication on whether all the enrolled patients received a follow-up evaluation and how many patients may have been lost to follow-up.

5.3.2 Meta-Analyses

Executive Summary and Reviewer Overall Assessment of Meta-analyses and Systematic Review

The Applicant submitted 3 meta-analyses and 1 systematic review to support their proposed indication for the use of dehydrated alcohol in PTSMA (see Table 3).

- Leonardi et al (2010) meta-analysis was based on 19 PTSMA retrospective publications yielding 2207 patients and 8 SM retrospective publications yielding 1887 patients. Follow-up time ranged from 0.3 years to 11.7 years. None of these publications directly compared PTSMA to SM, but rather respectively evaluated each procedure separately as case studies. The data showed no difference between the data reported for PTSMA and that reported for SM for all-cause mortality, sudden cardiac death, or NYHA improvement. The LVOT-PG improvement was significantly greater for SM over PTSMA.
- Agarwal et al (2010) meta-analysis was based on 12 retrospective studies that evaluated outcomes of PTSMA patients compared to that of SM patients, and yielded 380 patients in the PTSMA group and 326 patients in the SM group.

Follow-up time periods ranged from 3 months to 5 years. There was no difference in mortality between PTSMA and SM. NYHA class improvement trended in favor of SM. There was a significant increase in permanent pacemaker placement for the PTSMA group over the SM group.

- Alam et al (2009) meta-analysis was based on 5 retrospective studies yielding 351 patients (183 undergoing PTSMA and 168 undergoing SM). Follow-up time ranged from an average of 3 months to an average of 2 years. The 5 publications in this meta-analysis retrospectively compared PTSMA to SM in patients with refractory HOCM in case control studies. The data favored SM over PTSMA for reduction of LVOT-PG. The age of patients undergoing PTSMA (54 years) was higher than the age of patients undergoing SM (45 years). This finding that older patients underwent PTSMA and younger patients underwent SM may have label implications.
- Alam et al (2006) systematic review was based on 42 observational studies of PTSMA and case series in patients with refractory HOCM, yielding a total of 2,959 patients. Sample sizes in individual publications ranged from 8 to 337. The mean follow-up time was 12.7 months with a range from 1.5 to 72 months. This review publication was plagued by incomplete reporting of key variables for all the patients in all of the studies. The data, however, suggested an improvement in LVOT-PG, dyspnea, angina pectoris and exercise capacity from baseline. There was no efficacy or safety comparison between PTSMA and SM in this review. Key adverse events included complete heart block requiring permanent pacemaker placement, bundle branch blocks, ventricular fibrillation, persistent symptoms, and the need to perform a repeat procedure: either PTSMA or SM.

The publications referenced in the 3 meta-analyses had considerable overlap. Therefore, I anticipated the following salient common findings from the three meta-analyses:

- There was heterogeneity and bias as specified by the authors.
- There were no differences in the rates of all-cause mortality and sudden cardiac death between patients undergoing PTSMA and SM, respectively (Leonardi, Agarwal).
- LVOT-PG reduction favored SM over PTSMA (Leonardi, Alam). However, in the meta-analysis by Agarwal, there was no difference between SM and PTSMA patients in LVOT-PG reduction.
- NYHA improvement favored SM over PTSMA (Agarwal) but was similar for both procedures in the Leonardi meta-analysis. There was insufficient data to evaluate clinical data (NYHA, mortality) in the Alam meta-analysis.
- There was a higher rate of permanent pacemaker placement (Leonardi, Agarwal, and Alam) and repeat procedure (Alam) in the cohorts receiving a PTSMA compared to the cohorts receiving SM.

In summary, the meta-analyses generally suggested that SM produced better hemodynamic and clinical results than PTSMA, and that PTSMA produced a higher rate of complications requiring permanent pacemaker placement. The systematic review, however, provided retrospective data supportive of improvement in exercise capacity from baseline following PTSMA. Typical of the publications provided by the Applicant, tools to assess NYHA and CCS were not described.

Leonardi et al (2010) conducted a meta-analysis of septal reduction therapies for HOCM in order to compare overall survival and sudden cardiac death rates after PTSMA or SM. The authors conducted an extensive search of PubMed using key phrases such as “alcohol septal ablation” or “transcoronary ablation of septal hypertrophy”, or “nonsurgical septal reduction”. This search yielded a total of 320 references. Similarly, a search using expressions such as “myectomy and hypertrophic” yielded a total of 475 references. Inclusion criteria for PTSMA publications were enrollment of at least 5 patients with medically refractory symptoms of HOCM and follow-up for at least 24 hours. Exclusion criteria for PTSMA publications were lack of reporting of sudden cardiac death during follow-up, use of ablative material other than ethanol (e.g. cyanoacrylate and polyvinyl alcohol foam particles), rescue PTSMA after failed SM, other concomitant procedures such as percutaneous coronary intervention, and high risk of sudden death. Similarly, inclusion criteria for SM publications were enrollment of at least 100 patients with medically refractory symptoms of HOCM. Exclusion criteria for SM publications were lack of reporting of sudden cardiac death during follow-up, rescue SM after failed PTSMA or failed SM, and concomitant procedures. The primary outcome measures were the rates of all-cause mortality and sudden cardiac death. Secondary outcome measures included NYHA functional class, LVOT-PG, septal wall thickness, new permanent pacemaker, and percentage of patients with implanted cardiac defibrillator. Two independent reviewers screened the references. Following consensus amongst the two reviewers, elimination of redundancy, and satisfaction of inclusion / exclusion criteria, 19 PTSMA publications yielding 2207 patients and 8 SM publications yielding 1887 patients were selected for the meta-analysis. Follow-up time ranged from 0.3 years to 11.7 years. In patients undergoing PTSMA, the ethanol dose and the number of septal arteries injected were not specified. None of these publications compared PTSMA to SM, but rather respectively evaluated each procedure separately.

Baseline characteristics in patients undergoing PTSMA and SM were similar in each group of respective publications and are shown in Table 25. Patients undergoing PTSMA were slightly older (55 years) than those undergoing SM (46 years). The primary outcome of this meta-analysis is shown in Table 26. There was no difference in all-cause mortality and in sudden cardiac death between patients undergoing PTSMA and patients undergoing SM. Secondary outcomes are shown in Table 27. There were no differences in NYHA functional class, septal wall thickness, or percentage of patients

with an implanted cardiac defibrillator between subjects undergoing PTSMA and SM, respectively. The LVOT-PG was much higher in patients undergoing PTSMA compared to SM, and there was a much higher incidence of patients requiring a permanent pacemaker who underwent a PTSMA compared to SM. In the cohort of 2207 patients who received PTSMA, the Authors reported a total of 250 all-cause deaths and an additional 45 sudden cardiac deaths. The authors adjusted for available baseline characteristics and concluded that the odds ratios for treatment effect on all-cause mortality and sudden cardiac death were 0.28 (95% CI 0.16-0.46) and 0.32 (95% CI 0.11-0.97), respectively, favoring PTSMA.

Table 25. Baseline characteristics of PTSMA and SM patients (Leonardi, 2010)

Baseline Characteristics: median (interquartile range)							
Procedure	Sample Size	Age	Sex % male	NYHA, mean	LVOT-PG, mm Hg	Septal Wall Thickness, mm	Syncope, %
SM	1887	46.2 (40-50)	53 (52-60)	2.8 (2.5-3.0)	67.3 (67-68)	22.8 (22-24)	31 (24-31)
PTSMA	2207	55 (49-60)	53 (47-60)	2.8 (2.8-3.0)	76.8 (64-88)	21.3 (20-23)	26 (19-36)

Source: Leonardi et al, 2010

SM: Surgical Myectomy; PTSMA: Percutaneous Transluminal Septal Myocardial Ablation

Table 26. Primary Outcome in SM and PTSMA publications (Leonardi, 2010)

	Surgical Myectomy % per Patient-Year, Weighted Mean (95% CI)	ASA % per Patient-Year, Weighted Mean (95% CI)	*P*
All-cause mortality rate	1.8 (1.2–2.6)	2.1 (1.7–2.7)	0.37
SCD rate	0.3 (0.2–0.6)	0.4 (0.3–0.6)	0.36

Source: Leonardi et al, 2010

Table 27. Secondary Outcomes in SM and PTSMA publications (Leonardi, 2010)

	Surgical Myectomy, Median (IQR)	ASA, Median (IQR)
NYHA functional class	1.6 (1.5–1.7)	1.5 (1.3–1.7)
LVOT gradient, mm Hg	3 (2–6)	22 (15–23)
Septal wall thickness, mm	17 (17–19)	16 (15–17)
New permanent pacemaker, %	5 (3–9)	11 (8–15)
Patients with an ICD, %	4 (3–4)	5 (4–8)

IQR indicates interquartile range.

Source: Leonardi et al, 2010

Reviewer Comment (Leonardi 2010): There were several liabilities with this meta-analysis uncovered during the review and as noted by the authors:

- *In SM studies, there was heterogeneity for all-cause mortality ($P<0.01$, $I^2 = 29\%$) as well as publication bias.*
- *In PTSMA studies, publication bias was present for both all-cause mortality and sudden cardiac death.*
- *Follow-up duration was much shorter in the PTSMA studies compared to SM studies.*
- *Prevalence of preprocedural clinical risk factors was inconsistently reported.*
- *Timing of mortality events was not uniformly reported.*
- *Individual patient characteristics were not available thereby resulting in the application of regression models to cohorts rather than individuals and thus attenuating the use of the models to predict individual patient outcomes.*
- *Adjustment for baseline characteristics resulting in an odds ratio favoring PTSMA over SM for mortality could not be independently confirmed.*

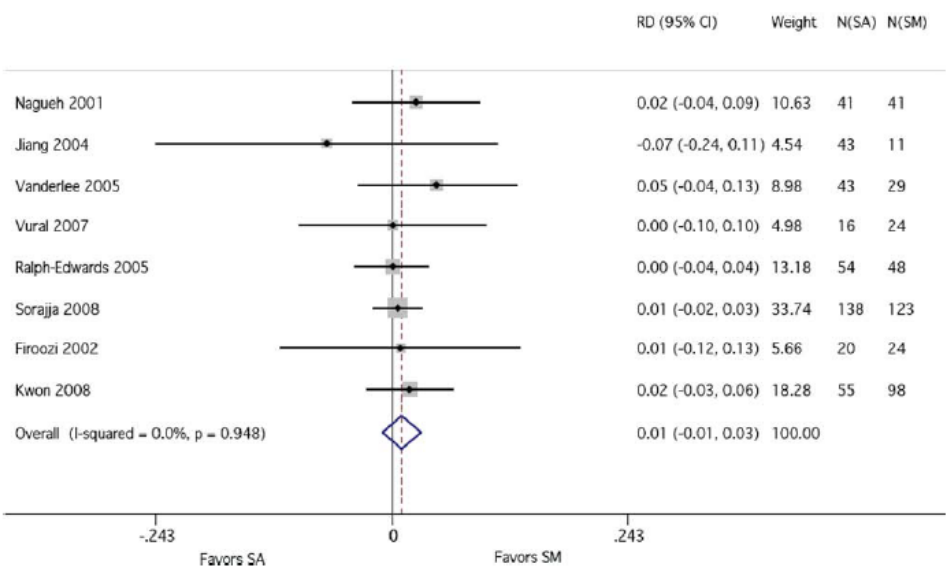
Baseline characteristics appeared similar between PTSMA and SM publications except for age. This meta-analysis showed that there were no differences in change from baseline in all-cause mortality, sudden cardiac death, or NYHA improvement that was reported in ethanol-PTSMA publications and in SM publications, respectively. However, LVOT-PG reduction in SM publications was significantly greater than that reported in PTSMA publications. The incidence of permanent pacemaker placement reported in PTSMA publications were significantly higher than that reported in SM publications. I could not conduct an adequate comparison between PTSMA and SM procedures because none of the publications deployed in this meta-analysis prospectively compared PTSMA to SM.

Agarwal et al (2010) conducted a meta-analysis of studies that retrospectively compared outcomes of PTSMA and SM for the treatment of HOCM. The search strategy retrieved 288 title-abstracts for review using search terms as “septal ablation”,

"non-surgical septal reduction". Of these, 177 lacked a control group; 39 were case reports or case series; and 60 were reviews, consensus articles, or expert opinions. These studies were excluded. The authors' inclusion criteria were any observational studies comparing the outcome of PTSMA with SM in adult patients with refractory HOCM. The result of this selection process was the inclusion of 12 studies eligible for review. The total sample size was not specified in the publication, but summation of the individual sample sizes from the tabulation of publications yielded 380 patients in the PTSMA group and 326 patients in the SM group. The primary outcome was 30-day all-cause mortality. Secondary outcome measures included functional status, re-interventions, pacemaker insertions, ventricular arrhythmias, cardiac dimensions, mitral regurgitation (MR), systolic anterior motion (SAM) of the mitral valve (MV), length of hospital stay, and exercise tolerance. Twelve retrospective cohort studies were selected for this meta-analysis. Follow-up time periods ranged from 3 months to 5 years. In patients undergoing PTSMA, the ethanol dose and the number of septal arteries injected were not specified.

Short-term mortality estimates between PTSMA vs SM patients are shown in Figure 6. The authors reported significant heterogeneity in evaluating long-term mortality. The definition of "short term" was not provided. The results showed no difference between PTSMA and SM for short term mortality.

Figure 6. Short-term mortality: Meta-Analysis (Agarwal, 2010)

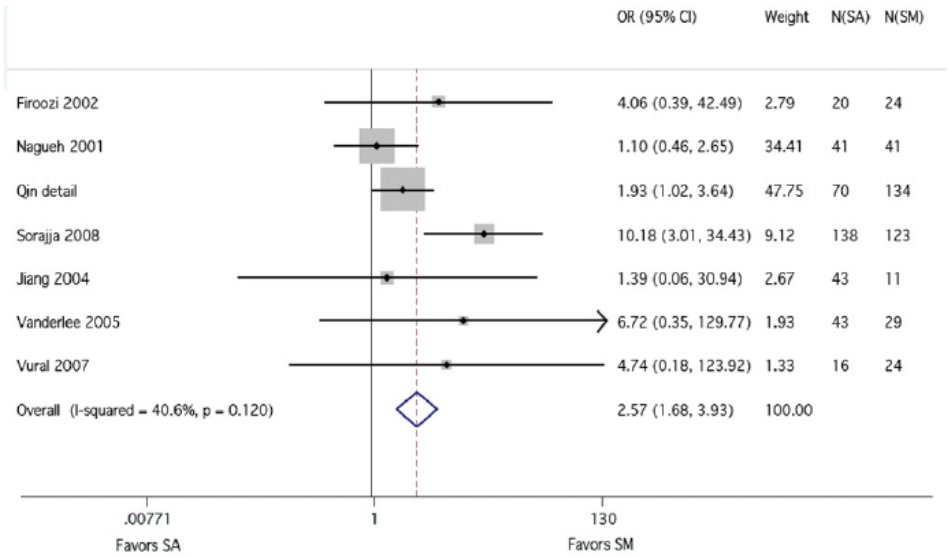


Source: Agarwal et al, 2010

Post-procedure pacemaker placement data is shown in Figure 7. The data indicate that a significantly higher number of pacemaker placement occurred in the PTSMA groups compared to the SM groups. Post procedure NYHA class data is shown in Figure 8. There was a strong trend, bordering on statistical significance, favoring SM over

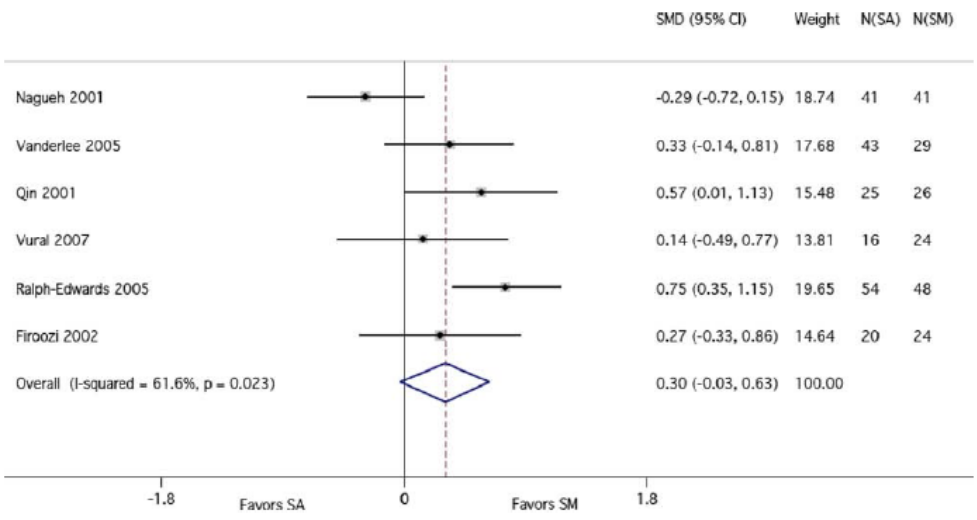
PTSMA in improving NYHA class. The timing of the NYHA assessments relative to the procedures was not described. The authors, however, specified that some of the publications showed an improvement in exercise capacity for both procedures over respective baseline at 1 year follow-up (Firoozi, 2002) and a superior improvement in exercise capacity for patients undergoing SM compared to PTSMA during the immediate post-procedure and 1 year follow-up periods (Nagueh, 2007).

Figure 7. Post-intervention Pacemaker Implantation: Meta-Analysis (Agarwal, 2010)



Source: Agarwal et al, 2010

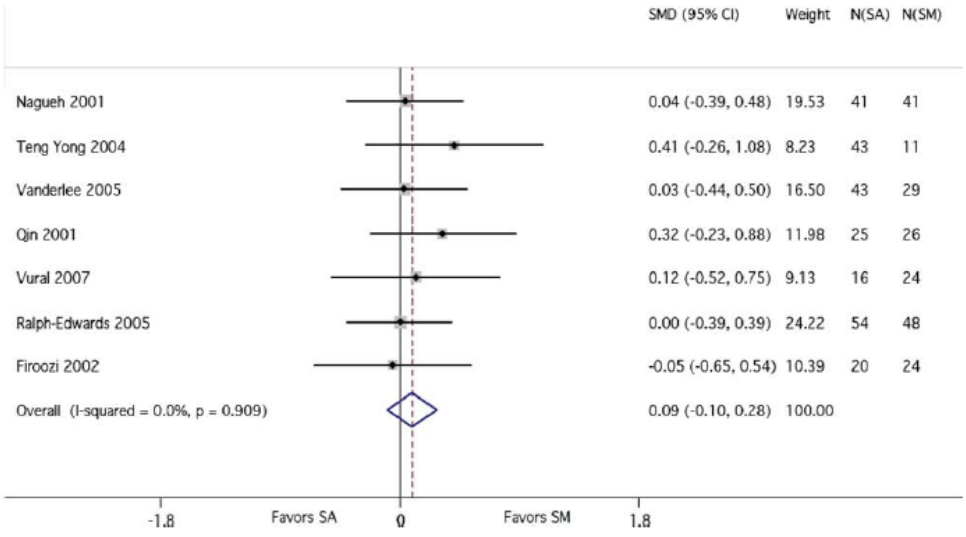
Figure 8. Post procedure NYHA Functional Class: Meta-Analysis (Agarwal, 2010)



Source: Agarwal et al, 2010

Reduction of LVOT-PG following septal reduction procedures is shown in Figure 9. The authors reported significant heterogeneity between the two groups. The data suggested no significant difference between PTSMA and SM in reducing LVOT-PG although there was a trend in favor of SM.

Figure 9. Post-procedure reduction in LVOT-PG: Meta-Analysis (Agarwal, 2010)



Source: Agarwal et al, 2010

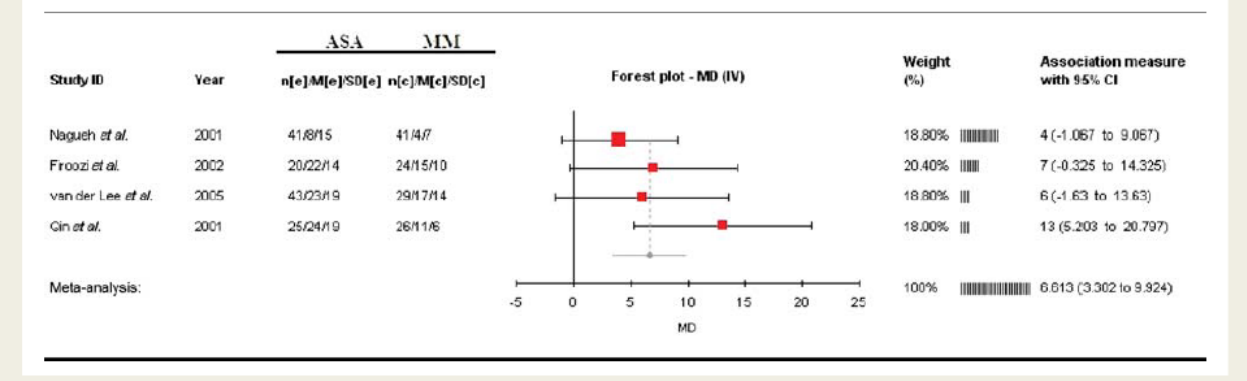
Reviewer Comment (Agarwal 2010): This meta-analysis was plagued by significant heterogeneity when evaluating differential mortality and LVOT-PG reduction between PTSMA and SM. Based on a review of the individual publications used in this meta-analysis, I am in agreement with the authors' comment that patients undergoing PTSMA and SM were inherently different, probably due to different referral patterns for the two procedures at various centers. The direct comparisons between PTSMA and SM in outcome were therefore difficult to interpret. I agree with the authors' assessment that "the meta-regression technique, used to explain heterogeneity, might be fraught with biases attributable to a small number of studies". The data from this study suggested no difference in mortality benefit between PTSMA and SM, a significant increase in the need to implant a permanent pacemaker in the PTSMA group, a strong trend favoring SM over PTSMA for improving NYHA class, and no significant difference between the two groups for reducing LVOT-PG.

Alam et al (2009) conducted a meta-analysis of published studies that retrospectively compared PTSMA to SM in patients with refractory HOCM in case-controlled studies. The authors conducted a search in PubMed covering January 2004 through September 2008 and identified 5 studies. These studies have been independently submitted by the Applicant and are listed in Table 5. The sample size in this meta-analysis of 5 studies was 351 (183 undergoing PTSMA and 168 undergoing SM). The primary outcome

variables included mortality, improvement in NYHA functional class, reduction in LVOT-PG, and reduction in septal thickness. Procedural complications including the incidence of permanent pacemaker implantation were also evaluated. Follow-up time ranged from an average of 3 months to an average of 2 years. In patients undergoing PTSMA, the ethanol dose and the number of septal arteries injected were not specified.

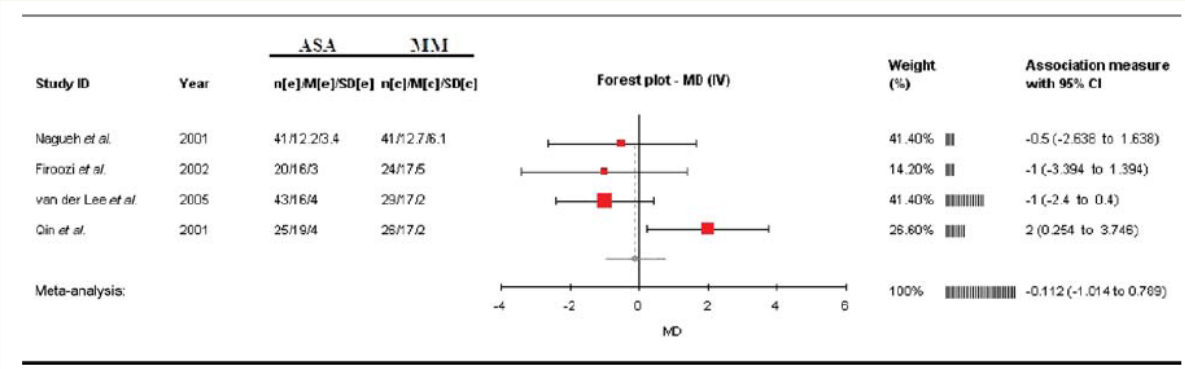
The Forest Plot of follow-up LVOT-PG in patients undergoing PTSMA vs SM is shown in Figure 10.The data showed that patients who were treated with SM had a lower LVOT-PG at follow-up. The mean difference in LVOT-PG was 6.6 mmHg ($p<0.001$). However, there was no difference in follow-up septal thickness as shown in Figure 11. Echocardiographic and outcome data is shown in Figure 12. As already suggested in the Forest Plot figures, the data showed a significant decrease in follow-up LVOT-PG in patients who underwent SM, compared to PTSMA, with no difference in follow-up septal thickness. The authors reported that 3 of the 5 publications did not report NYHA follow-up data. The authors also reported that there was not enough data to conduct a meaningful meta-analysis of mortality. Adverse events that were reported in the meta-analysis are shown in Table 28. The patients who underwent PTSMA were significantly older than patients who underwent SM. The mortality rate was low (3 in the PTSMA group and 1 in the SM group). There was a significantly higher incidence of permanent pacemaker placement and repeat procedure in the PTSMA group. Of the 10 repeat procedures in the PTSMA group, 5 were repeat PTSMA and 5 were SM. The one repeat procedure in the SM group was another SM.

Figure 10. LVOT-PG in PTSMA vs SM patients: Meta-analysis (Alam, 2009)



Source: Alam et al, 2009

Figure 11. Follow-up Septal Thickness in PTSMA vs SM: Meta-analysis (Alam, 2009)



Source: Alam et al, 2009

Figure 12. Echocardiographic and Clinical Outcome: Meta-analysis (Alam, 2009)

Variable	Number of studies	*n*	MD[a] (CI)[b]	Z[c] (*P*-value)	Q[d] (*P*-value)	H[e] (CI)[b]
LVOT gradient (follow-up)	4	249	6.6 (3.3–9.9)	3.9 (<0.001)	3.6 (0.3)	1.1 (1.0–1.7)
IVSd mm (follow-up)	4	249	−0.11 (−1.1–0.8)	0.2 (0.8)	7.82 (0.05)	1.6 (1.0–2.8)
NYHA (mean follow-up)	5	351	N/A	N/A	N/A	N/A
Mortality[f]	5	351	N/A	N/A	N/A	N/A

[a]MD, mean difference between ASA and MM.
[b]CI, 95% confidence interval.
[c]Z, standardized Z-score.
[d]Q, Cochran's Q score for heterogeneity.
[e]H, Higgins's test of heterogeneity.
[f]Not enough data to conduct meaningful meta-analysis on this variable.

Source: Alam et al, 2009

Table 28. Adverse Events: Meta-analysis (Alam, 2009)

Adverse Events: Meta-analysis (Alam, 2009)		
	PTSMA	SM
Sample Size	183	168
Age (SD)	54.4 (6.3)	45.0 (4.4)
Death	3	1
Cause of Death	• LAD Dissection • Cardiac Tamponade • Refractory Ventricular Fibrillation after PTSMA	• Post-SM Congestive Heart Failure
% Permanent Pacemaker (SD)	18.4 (7.9)	3.3 (3.9)
Repeat Procedure: n (%)	10 (5.5%)	1 (0.6%)
Type of Repeat Procedure	• Repeat PTSMA: 5 • SM: 5	• Repeat SM

SD=standard deviation

Source: Alam et al, 2009: tabulated by FDA clinical reviewer from publication content

Reviewer Comment (Alam 2009): This meta-analysis failed to produce clinically meaningful data (b) (4)
Although each procedure yielded similar follow-up septal thickness, reduction in LVOT-PG favored SM over PTSMA. There was a significant difference in mean age between those patients who underwent PTSMA (54 years) compared to those who underwent SM (45 years) thereby suggesting a difference in population characteristics between the two groups despite documented homogeneity for baseline NYHA class, baseline LVOT-PG, and baseline history of syncope or pre-syncope. Of the three causes of death in the PTSMA group, dissection of the left anterior descending artery and cardiac tamponade can reasonably be attributed to operator-based intervention similar to any percutaneous coronary intervention. However, refractory ventricular fibrillation following PTSMA can reasonably be attributed to PTSMA.

Alam et al (2006) conducted a systematic review of published studies on PTSMA for patients with HOCM. After a search of electronic databases (MEDLINE and PubMed), a total of 42 observational studies and case series were included in the final review and have been tabulated in Table 29. Although the authors classified these publications as observational, 2 of the 42 studies were randomized clinical trials (Veselka, 2005,

American Journal of Cardiology, 95: 675-678; Veselka, 2004, Catheterization and Cardiovascular Interventions, 63: 231-235). Of the 42 publications, 9 were independently submitted by the Applicant to support their proposed indication. These publications reported results for a total of 2,959 patients. Sample sizes in individual publications ranged from 8 to 337. The mean follow-up time was 12.7 months with a range from 1.5 to 72 months.

On average, 3 mL absolute ethanol was injected in 1.2 septal perforator arteries (2.5 mL/artery). Serum CK peaked at 964 U/L. Patient-characteristics are shown in Table 30. The mean NYHA classification (dyspnea) for 2,808 patients was 2.9, and the mean CCS classification (angina pectoris) for 821 patients was 1.9. The mean NYHA fell from 2.9 at baseline to 1.2 at 12 months. The mean CCS fell from 1.9 at baseline to 0.4 at 12 months. These results are illustrated in Figure 13. In addition to NYHA and CCS classification, exercise capacity for baseline, 3 months, and 12 months, is shown in Table 31. The mean exercise capacity for 720 patients at baseline was 325 seconds. At 3 months, the exercise capacity reported for 197 patients was 473 seconds. At 12 months, the mean exercise capacity for 391 patients was 438 seconds. Similarly, the exercise capacity measured in watts at baseline for 787 patients was 86. At 3 months post PTSMA, the exercise capacity for 437 patients was 110 watts. At 12 months post PTSMA, the exercise capacity for 45 patients was 123 watts. Coincident with these findings, LVOT-PG (at rest and provoked) decreased from baseline to immediate post-PTSMA. The decrease in LVOT-PG was maintained for up to 24 months. These findings are shown in Figure 14.

Complications of PTSMA as reported in the 42 publications are shown in Table 32. In-hospital mortality was reportedly 1.5% for the cohort of 2,959 patients. This number was also referred to as early mortality (up to 30 days after PTSMA) in the publication text. It was therefore not clear if all deaths occurred in-hospital or post-discharge within the 30 days post-PTSMA. The mean time of late all-cause mortality was not specified, but was defined as occurring after 30 days post-PTSMA. The mean rate of late all-cause mortality for the mean-follow-up time was 0.5% for the cohort of 2, 840 patients. A new right bundle branch block occurred in 46.2% (range 0.0-75.0%) of a cohort of 381 patients. A new left bundle branch block occurred in 6.5% (range 0.0-17.2%) of a cohort of 322 patients. The rate of complete heart block requiring a permanent pacemaker was 10.5% (range 0.0 – 40.0%) in 1,869 patients. Ventricular fibrillation occurred in 2.2% (range 0.0 – 12.5%) of 464 patients. A repeat PTSMA was reported in 6.6% (range 0.3% to 16.2%) of 1,140 patients. A post-PTSMA surgical myectomy occurred in 2.0% (range 0.4% - 6.9%) of 1,044 patients. Symptoms of HOCM persisted in 10.8% (range 5.0% - 25.0%) of 724 patients.

Table 29. Publications selected in systematic review (Alam, 2006)

Publications Selected in Systematic Review (Alam, 2006)							
Abraham 2002	Airoldi 2000	Bhagwandeen 2003	Chang 2004	Chang 2003*	Dokainish 2005	Faber 2004	Faber 2000
Faber 2000	Faber 1998	Faber 1998	Fernandes 2005	Firoozi 2002*	Gietzen 2004*	Gietzen 2002	Gietzen 1999
Guo 2004	Kim 1999	Knight 1997	Kuhn 2004	Lakkis 2001	Lakkis 2000	Lakkis 1998	Li 2004
Mazur 2001*	Mutlak 2002	Nagueh 2001*	Nagueh 1999	Nagueh 1998	Osterne 2003	Park 2002	Ralph-Edwards 2005*
Rivera 2003	Ruzyllo 2000	Seggewiss 2001	Seggewiss 1999	Seggewiss 1998	Tsuchikane 2003	Veselka 2005*	Veselka 2005*
Veselka 2004*	Veselka 2004						

*Separately submitted by Applicant to support NDA. Note: publications by Veselka separately submitted by Applicant: Veselka 2005, American J Cardiology, 95: 675-678; Veselka 2005, American Journal of Cardiology, 95: 675-678; Veselka 2004, Catheterization and Cardiovascular Interventions, 63: 231-235

Source: Alam et al, 2006: tabulated by FDA clinical reviewer from publication content

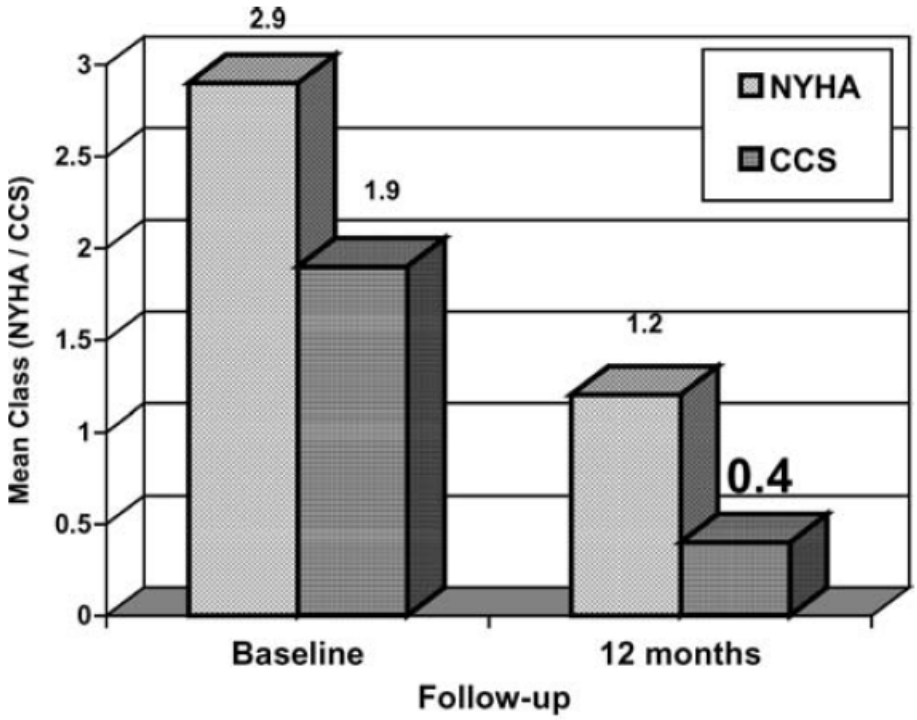
Table 30. Patient Population Characteristics: Systematic Review (Alam. 2006)

	N	Mean ± SEM	Median	Range
Mean age (years)	2,739	53.5 ± 0.1	54.0	35.4–72.0
Mean follow-up (months)	1,770	12.7 ± 0.3	10.6	1.5–43.2
Males (%)	2,489	53.0 ± 0.1	50.9	35.0–75.8
Family history of HOCM (%)	1,105	23.0 ± 0.3	23.6	5.5–40.0
Dyspnea NYHA Class	2,808	2.9 ± 0.01	2.8	2.3–3.5
Angina (CCS)	821	1.9 ± 0.01	2.0	1.6–2.6
Left ventricular failure (%)	453	12.8 ± 0.2	10.7	10.6–24.0
Atrial fibrillation (%)	407	6.9 ± 0.2	6.8	0.0–15.0
Systemic hypertension (%)	594	10.8 ± 0.3	8.5	4.0–27.3
Coronary artery disease (%)	661	6.7 ± 0.2	8.7	0.0–16.6
Supraventricular arrhythmia (%)	764	18.2 ± 0.4	23.7	3.0–40.0
Syncope/Presyncope history (%)	1,645	31.7 ± 0.3	29.4	7.4–62.1
Sudden cardiac death (%)	273	1.8 ± 0.1	1.3	1.3–3.7
Prior defibrillator (%)	632	2.7 ± 0.2	2.3	0.4–19.1
Prior myectomy (%)	986	3.5 ± 0.1	3.0	1.5–12.0
Prior permanent pacemaker (%)	1,712	10.1 ± 0.2	6.3	3.7–34.5
Beta blocker (%)	1,409	51.2 ± 0.6	33.2	27.5–96.9
Calcium channel blocker (%)	1,355	53.4 ± 0.4	54.9	54.9–72.7
Disopyramide (%)	251	29.9 ± 1.5	19.5	6.9–74.1

NYHA = New York Heart Association Class; CCS = Canadian Cardiovascular Society Class; HOCM = hypertrophic obstructive cardiomyopathy.

Source: Alam et al, 2006

Figure 13. Baseline and 12 month follow-up in NYHA and CCS Class (Alam, 2006)



NYHA (New York Heart Association class),
CCS (Canadian Cardiovascular Society class)

Source: Alam et al, 2006

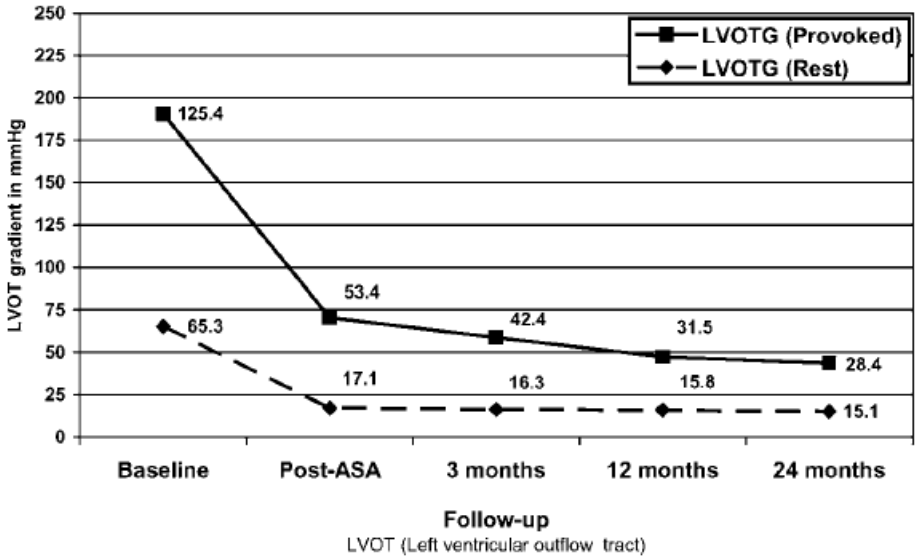
Table 31. NYHA, CCS, and Exercise Capacity at baseline and follow-up (Alam, 2006)

Variable	Baseline	3 Months	12 Months
NYHA Class	2.9 ± 0.003 (2,808)	1.4 ± 0.004 (817)*	1.2 ± 0.01 (583)*
CCS Class	1.9 ± 0.01 (821)		0.4 ± 0.02 (253)*
Peak VO_2 in mL/kg/min	17.8 ± 0.1 (511)	21.4 ± 0.1 (375)*	23.6 ± 0.3 (81)*
Exercise capacity in seconds	325.3 ± 2.6 (720)	472.6 ± 6.4 (197)*	437.5 ± 4.6 (391)*
Exercise capacity in watts	86.2 ± 0.4 (787)	109.6 ± 0.6 (437)*	122.8 ± 1.6 (45)*

*$P < 0.001$; ( ) = number of patients.
NYHA = New York Heart Association Class; CCS = Canadian Cardiovascular Society Class; VO_2 = peak oxygen consumption.

Source: Alam et al, 2006

Figure 14. LVOT-PG at baseline and at follow-up: Systematic Review (Alam, 2006)



Source: Alam et al, 2006

Table 32. Complications of PTSMA: Systematic Review (Alam, 2006)

	N	Mean ± SEM	Range
In-hospital mortality (%)	2,959	1.5 ± 0.03	0.0–5.0
Late mortality (%) all cause	2,840	0.5 ± 0.03	0.0–9.3
Complete heart block requiring permanent pacemaker (%)	1,869	10.5 ± 0.2	0.0–40.0
Coronary dissection (%)	434	1.8 ± 0.1	0.4–4.6
Pericardial effusion (%)	355	0.6 ± 0.02	0.4–1.1
Ventricular fibrillation (%)	464	2.2 ± 0.1	0.0–12.5
Coronary artery spasm (%)	292	1.4 ± 0.2	0.4–12.5
Stroke (%)	361	1.1 ± 0.1	0.0–4.0
New right bundle branch block (%)	381	46.2 ± 0.7	0.0–75.0
New left bundle branch block (%)	322	6.5 ± 0.3	0.0–17.2
Persistence of symptoms (%)	724	10.8 ± 0.2	5.0–25.0
Redo-ASA (%)	1,140	6.6 ± 0.2	0.3–16.2
Post-ASA myomectomy (%)	1,044	2.01 ± 0.1	0.4–6.9

Source: Alam et al, 2006

Reviewer Comment (Alam 2006): The authors of this review article included case series of patient cohorts from tertiary centers over a decade. There was no randomized clinical trial that could be found for inclusion in this systematic review. The authors reported that some of the patients may have been reported multiple times in different studies from

these centers. Not all outcome variables (i.e. exercise capacity, NYHA class, CCS class) were reported for all the patients in all the studies. Thus the cohort size for each variable was different. The data, however, suggested that alcohol-PTSMA was effective in reducing LVOT-PG, improving symptoms of dyspnea and chest pain, and improving exercise capacity. I could not adequately evaluate patient symptoms because assessment tools were not described to assess subjective data. However, I viewed improvement of exercise capacity as an objective measure of alcohol-PTSMA efficacy. I viewed the major risks of this procedure to be complete heart blocks requiring permanent pacemaker placement, bundle branch blocks, ventricular fibrillation, persistent symptoms, and the need to undergo a repeat PTSMA or post-PTSMA SM.

5.3.3 Retrospective Studies: Veselka et al

Executive Summary and Reviewer Overall Assessment of Veselka Retrospective Studies

The Applicant submitted 4 retrospective studies (i.e. registry, database review, pilot study, and echocardiographic study, respectively) as part of the submission package of 38 publications to support their proposed indication (see Table 4). Salient findings from these 4 retrospective studies were:

- There were improvements in symptoms (dyspnea and angina pectoris) in alignment with reductions in LVOT-PG.
- There were high rates of complete heart block and complete heart block requiring permanent pacemaker placement.

These publications did not report on objective functional assessment (i.e. exercise capacity). Similar to the meta-analyses and randomized trials reviewed in this document, tools for the assessment of dyspnea and angina pectoris in order to mitigate subjectivity were not defined. However, a consistent pattern of symptomatic improvement in alignment with reduction of LVOT-PG suggested efficacy of PTSMA using ethanol as the ablative agent.

Veselka et al (2014, Catheterization and Cardiovascular Interventions, 84: 101-107) developed a registry in which data from patients undergoing PTSMA for symptomatic and refractory HOCM were prospectively collected and retrospectively reviewed. From 1999 to 2012, at total of 459 consecutive patients who underwent PTSMA from 9 centers in 6 European countries were followed for 113 ± 40 days post-PTSMA. An average total of 1.5 mL ethanol was injected but the average number of septal arteries was not specified. Baseline and Follow-up characteristics are shown in Table 33. Of the 459 subjects, 23 were lost to follow-up. There was a significant improvement in dyspnea and angina pectoris from baseline, as well as episodes of syncope (presumably by patient report). These results were aligned with a significant reduction in LVOT-PG and basal septal thickness. Adverse events are shown in Table 34. Reported rates of mortality and sustained ventricular tachycardia requiring

cardioversion were low, but there was a high rate of bundle branch block and complete heart block with pacemaker placement.

Table 33. Baseline and Outcome: Retrospective Review (Veselka, 2014)

	Baseline $N=459$	Follow-up $N=436$	P value
Age, years	57 ± 13	57 ± 13	
Dyspnea, NYHA class	3 (2–3)	1 (1–2)	<0.01
Angina, CCS class	2 (1–3)	1 (0–1)	<0.01
Episodes of syncope, %	24	4	<0.01
Left ventricular outflow gradient at rest, mm Hg	88 (58–123)	21 (11–41)	<0.01
Left ventricular diameter, mm—median (IQR)	43 (39–46)	45 (41–48)	<0.01
Left ventricular ejection fraction	70 (60–78)	65 (60–75)	0.88
Basal septum thickness, mm—median (IQR)	21 (19–24)	18 (15–20)	<0.01
Left atrium diameter, mm—median (IQR)	45 (42–50)	44 (40–48)	<0.01

Source: Veselka et al, 2014, Catheterization and Cardiovascular Interventions, 84: 101-107

Table 34. Adverse Events: Retrospective Study (Veselka, 2014)

Retrospective Study: Veselka et al, 2014	
Adverse Event	Number of Subjects
In-hospital mortality	1 (cardiac tamponade)
Three- month mortality	2 (Sudden cardiac death x 2)
Sustained Ventricular Tachycardia requiring cardioversion	3
Complete Heart Block (intra and post PTSMA)	82
Complete Heart Block requiring permanent pacemaker	43
Post-PTSMA Bundle Branch Block (% of patients with right bundle branch block)	189 (80%)
Repeat septal intervention	8 (repeat PTSMA: 5; Endocardial radio-frequency ablation: 3)

Source: Veselka et al, 2014, Catheterization and Cardiovascular Interventions, 84: 101-107: tabulated by FDA clinical reviewer from publication content

Reviewer Comment (Veselka 2014, Catheterization and Cardiovascular Interventions, 84: 101-107): Retrospective studies lack the strength of a prospective randomized trial. Tools for validation of symptom assessment were not described. However, the data suggested an improvement in symptoms aligned with hemodynamic improvement following PTSMA. The incidence of complete heart block (125/426: 29%) was high, as well as the incidence of complete heart block requiring permanent pacemaker placement (43/426: 10%). The data supported efficacy based on symptomatic improvement.

Veselka et al (2013) reviewed institutional databases of 421 patients with symptomatic HOCM who underwent PTSMA in 8 European cardiology departments from 1998 to 2011. Patients were followed for 3-6 months. An average total of 1.5 mL ethanol was injected but the average number of septal arteries was not specified. The results of this retrospective review are shown in Table 35. The key results were the significant reduction in reports of dyspnea and angina pectoris in alignment with a significant reduction in LVOT-PG. Adverse events are shown in Table 36. Of note is the high rate of complete heart block (70/394: 18%), half of which required permanent pacemaker placement.

Table 35. Baseline and Outcome: Retrospective Review (Veselka, 2013)

	Baseline n = 421	Follow-up 3-6 months n = 394	*P* value
Age, y, median (IQR)	59 (48-67)		
Alcohol volume, mL, median (IQR)	1.5 (1-2)		
Peak CK-MB, median (IQR)			
Bielefeld, n = 123; ULN = 15 U/L	117 (81-158)		
Bratislava, n = 21; ULN = 0.42 µkat/L	2.5 (1.8-4.0)		
Brno, n = 25; ULN = 0.42 µkat/L	4 (3.3-6.6)		
Prague, n = 100; ULN = 0.42 µkat/L	2.1 (1.6-3.2)		
Trinec, n = 70; ULN = 0.42 µkat/L	2.1 (1.3-3.0)		
Warsaw, n = 23; ULN = 6 U/L	121 (63-153)		
Peak CK, median (IQR)			
Krakow, n = 26; ULN = 190 U/L	1321 (1002-1713)		
Pleven, n = 33; ULN = 190 U/L	1382 (1124-1550)		
LV outflow gradient, mm Hg	89 (60-130)	21.5 (11-42)	< 0.01
Septal thickness, mm	21 (19-24)	17 (14-20)	< 0.01
LV diameter, mm	43 (39-46)	45 (41-48)	< 0.01
Left atrial diameter, mm	46 (42-50)	44 (41-48)	< 0.01
LV ejection fraction, %	70 (60-78)	65 (60-75)	< 0.01
Dyspnea, class (N)	3 (3-3)	1.5 (1-2)	< 0.01
Dyspnea, class III-IV (NYHA), %	76	6	< 0.01
Angina pectoris, class (CCS)	2 (1-3)	1 (0-1)	< 0.01
Angina pectoris, class III-IV (CCS), %	36	1	< 0.01

ASA, alcohol septal ablation; CCS, Canadian Cardiovascular Society; CK-MB, creatine kinase MB; IQR, interquartile range; LV, left ventricular; NYHA, New York Heart Association; ULN, upper limit of normal.

Source: Veselka et al, 2013

Table 36. Adverse Events: Retrospective Review (Veselka, 2013)

Retrospective Study: Veselka et al, 2013	
Adverse Event	Number of Subjects
Death	3
Complete Heart Block	70
Complete Heart Block requiring Pacemaker	35
Non-sustained ventricular tachycardia	12
Sustained ventricular tachycardia	3

Source: Veselka et al, 2013: tabulated by FDA clinical reviewer from publication content

Reviewer Comment (Veselka 2013): These results were similar to the previous study (Veselka, 2014): improvement in symptoms and reduction of LVOT-PG accompanied by a high rate of complete heart block and pacemaker placement. Based on the review of investigative centers between this publication and the previous publication one year later as well as the overlapping years of data collection, it appeared that both publications may have been derived from a common database although I cannot be certain of this. This might explain the similarity of results.

Veselka et al (2009) performed a pilot study on 70 patients with symptomatic refractory HOCM undergoing HOCM and divided these patients into two groups depending on the dose of alcohol used during PTSMA (Group I: 1.0 ± 0.1 mL [0.9 mL/artery]; Group II: 2.5 ± 0.8 mL [2.3 mL/artery]). Each group comprised of 35 consecutive patients and follow-up time was 6 months. The results of this pilot studied showed an improvement in dyspnea and angina pectoris from baseline to 6 months associated with decreases in septal thickness and LVOT-PG for both groups. The changes from baseline were similar between the groups. Reported adverse events of persistent bundle branch blocks were similar between the groups (11 in Group I and 14 in Group II). This publication reported no deaths. The peak CK-MB was 1.6 ± 0.9 uKat/L in Group I and 2.6 ± 1.2 uKat/L in Group II. There were no other reported adverse events.

Reviewer Comment (Veselka 2009): This pilot study suggested no difference in hemodynamic and symptom outcome between 1 mL and 2-3 mL doses of alcohol in PTSMA. This pilot study was similar to the randomized trials conducted by the same author in 2004, 2005, 2006 and 2011 with similar results.

Veselka et al (2005, ECHOCARDIOGRAPHY, 22 (2): 105-109) performed a study of 27 consecutive patients with symptomatic refractory HOCM. Clinical and echocardiographic data were collected at baseline, 6 and 12 months after PTSMA. The authors specified that only 1 septal artery was injected in the patients, but did not specify the average total dose of alcohol. The purpose of this study was to investigate the effect of PTSMA on the Doppler Tei index (TI) ([Isovolemic Contractile Time + Isovolemic Relaxation Time] / Left Ventricular Ejection Time). The TI is considered to be an index of myocardial performance by characterizing both systolic and diastolic left ventricular function. Shortening of the TI is suggestive of improvement in myocardial performance. The authors reported a significant improvement in the TI 6 months after PTSMA with maintenance of improvement for an additional 6 months. The results also showed improvement in dyspnea and angina pectoris as illustrated in Table 37. The authors stated that the 12 month survival rate was 96% (i.e. 4% mortality) and that 3 patients (11%) required pacemaker implantation for sustained complete heart block after PTSMA.

Table 37. Improvement of Symptoms during Follow-Up (Veselka, 2005)

Improvement of Symptoms during Follow-Up

Parameter	Baseline	6 Months	12 Months
Dyspnea (NYHA class; 27 pts.)	2.5 ± 0.7	1.4 ± 0.6*	1.4 ± 0.6*
Angina pectoris (CCS class; 22 pts.)	2.6 ± 0.9	0.8 ± 0.8*	0.7 ± 0.7*

*$P < 0.01$ between baseline and 6- or 12-month follow-up.

Source: Veselka et al, 2005, ECHOCARDIOGRAPHY, 22 (2): 105-109

Reviewer Comment (Veselka 2005, ECHOCARDIOGRAPHY, 22 (2): 105-109): This publication submitted by the Applicant to support their proposed indication focused on an echocardiographic parameter, but symptomatic improvement from baseline was reported for 12 months post-PTSMA.

5.3.4 Retrospective Studies: Comparison vs Myectomy

Executive Summary and Reviewer Overall Assessment of Retrospective Studies Describing PTSMA vs SM

The Applicant submitted 6 non-randomized retrospective studies designed to compare PTSMA to SM for patients with refractory symptomatic HOCM (see Table 5). Salient findings from these studies included:

- Sorajja (2012): There was no difference between PTSMA and SM for mortality but a similar reduction in mortality rate for each procedure to the level found in the general US population. Patients undergoing PTSMA who had a residual LVOT-PG $\geq$ 10 mm Hg post-PTSMA had a lower survival (free of all-cause mortality) compared to those post-PTSMA patients who had a residual LVOT-PG of < 10 mm Hg. There were considerable procedural complications in PTSMA compared to SM. There was no quantitative assessment of functional or exercise capacity in this study.
- Ralph-Edwards (2005): There was superiority of SM over PTSMA for mortality and freedom from pacemaker placement.
- Van der Lee (2005): There were similar reductions in NYHA class from baseline to follow-up for both PTSMA and SM.
- Firoozi (2002): There was superiority of SM over PTSMA for both peak oxygen consumption and work rate although there were improvements from baseline to follow-up in both exercise test parameters.
- Qin (2001): There was similar effectiveness of both PTSMA and SM for reducing LVOT-PG and NYHA class but a greater need for permanent pacemaker placement for PTSMA.
- Nagueh (2001): PTSMA increased exercise duration, peak oxygen consumption, metabolic equivalents, and percent maximal predicted oxygen consumption similar to SM.

These studies did not compare PTSMA to SM but rather paired an independent series of PTSMA retrospective observational studies to an independent series of SM retrospective observational studies. These studies had small sample sizes. Based on the data presented to me, I assessed that PTSMA may at best be similar to SM for reducing LVOT-PG and NYHA class as well as exercise capacity, but PTSMA causes a considerable increase in complications. However, SM may be superior to PTSMA from both a safety and efficacy perspective as suggested in the studies from this section.

Sorajja et al (2012) performed a retrospective non-randomized evaluation of 177 patients with symptomatic refractory HOCM who underwent PTSMA at the Mayo Clinic. Patient selection criteria included dynamic LVOT obstruction due to SAM of the mitral valve with an LVOT-PG of ~30 mm Hg at rest or ~50 mm Hg with provocation, NYHA class III-IV dyspnea, CCS class III-IV angina pectoris, ventricular septal thickness ~15 mm, no significant intrinsic mitral valve disease, and suitable coronary anatomy amenable to percutaneous coronary intervention and ablation. Follow-up time was 5.7 years (standard deviation 4.9 years, maximum 11.9 years).

The dose of alcohol was 1-3 mL (average 1.8 mL, 1.6 mL/artery). The primary endpoints were all-cause mortality and the combination of all-cause mortality and need for additional septal reduction therapy. In order to compare PTSMA to SM, data from patients who underwent SM were matched by age and sex in 1:1 fashion to those patients who underwent PTSMA. Baseline characteristics are shown in Table 38. The baseline variables were generally balanced between patients who underwent PTSMA and patients who underwent SM. The most notable difference was that all 177 patients undergoing PTSMA had NYHA class III/IV whereas 133 of 177 (75%) of the matched SM patients had NYHA class III/IV. Acute procedural results and 30-day clinical events are shown in Table 39. There was a low incidence of mortality with no difference between those patients undergoing PTSMA and the matched SM patients. There was a significantly higher rate of procedural and in-hospital complications in the cohort of PTSMA patients compared to the matched SM patients driven by pacemaker dependency. However, the rate of permanent pacemaker placement was 1.7%. Clinical events during follow-up beyond 30 days after PTSMA are shown in Table 40. The mortality rate in both the PTSMA and SM cohorts was 13.5%, respectively. A significant number of these deaths were non-cardiac. There was a significantly increased rate of cardiac surgery in the PTSMA cohort driven by surgical myectomy. The observed free of all-cause mortality survival curve for patients having undergone PTSMA, compared to the expected curve calculated from age- and sex-specific mortality rates obtained from the US general population, is shown in Figure 15. The results showed no difference between PTSMA patients and the general population. Figure 16 showed no difference in free of all-cause mortality survival between patients having undergone PTSMA and age- and sex-matched population of patients who underwent SM. When defining survival as the combination of freedom from death or freedom from need for additional septal reduction therapy, age- and sex-matched patients who underwent SM had a higher percentage of survival compared to patients who underwent PTSMA as shown in Figure 17. As shown in Figure 18, patients who had a residual LVOT-PG $\geq$ 10 mm Hg post-PTSMA had a lower survival (free of all-cause mortality) compared to those post-PTSMA patients who had a residual LVOT-PG of < 10 mm Hg.

Table 38. Baseline Characteristics (Sorajja, 2012)

	Ablation Patients (n=177)	Myectomy Patients (n=177)	
Age, y	63±13	62±12	0.17
Women, n (%)	102 (58)	102 (58)	0.99
NYHA class III/IV, n (%)	177 (100)	133 (75)	<0.0001
CCS class III/IV, n (%)	34 (19)	50 (28)	0.07
Syncope, n (%)	27 (15)	30 (17)	0.78
Past medical history, n (%)			
Atrial fibrillation	28 (16)	22 (12)	0.29
Previous stroke	4 (2)	2 (1)	0.23
Hypertension	91 (51)	27 (15)	<0.0001
Diabetes mellitus	13 (7)	3 (2)	0.02
Coronary artery disease	24 (14)	7 (4)	0.002
Previous myectomy	3 (2)	0 (0)	0.08
Previous septal ablation	0 (0)	1 (1)	0.32
Family history of HCM, n (%)	31 (18)	23 (13)	0.18
Family history of sudden death due to HCM, n (%)	10 (6)	17 (10)	0.20
Morphology, n (%)			0.15
Asymmetric hypertrophy	130 (73)	120 (68)	
Concentric hypertrophy	41 (23)	57 (32)	
Maximum ventricular wall thickness, mm	23±5	22±7	0.05
End-diastolic diameter, mm	45±6	45±6	0.07
End-systolic diameter, mm	25±5	24±5	0.53
Resting LVOT gradient, mm Hg	70± 40	67±40	0.41
-50 mm Hg, n (%)	121 (68)	118 (66)	0.73
Internal cardioverter-defibrillator, n (%)	8 (5)	12 (7)	0.40
Permanent pacemaker, n (%)	6 (3)	31 (18)	0.01
Medications, n (%)			
0-receptor antagonist	129 (73)	102 (58)	0.0006
Calcium-channel blocker	66 (37)	86 (49)	0.07
Disopyramide	12 (7)	21 (12)	0.13
Amiodarone	6 (3)	14 (8)	0.08

Coronary artery disease was defined as either a -50% stenosis in the left main or a -70% stenosis in other major epicardial coronary arteries from invasive angiography. Resting gradient from echocardiography. CCS indicates Canadian Cardiac Society; HCM, hypertrophic cardiomyopathy; LVOT, left ventricular outflow tract; and NYHA, New York Heart Association.

Source: Sorajja et al, 2012

Table 39. Acute and 30 Day Results for PTSMA vs SM (Sorajja, 2012)

	Ablation Patients (n=177)	Myectomy Patients (n=177)	
No. septal arteries injected, mean ±SD	1.1 ±0.4		
Volume of ethanol injected, median (IQR), mL	1.8 (0.5)	...	...
Residual LVOT gradient at rest, median (IQR), mm Hg	11 (15)	5 (5)	0.001
Reduction in LVOT gradient, %	85±16	88±19	
Procedural and in-hospital complications, n (%)	51 (28.8)	10 (5.6)	<0.0001
Pacemaker dependency	36 (20.3)	4 (2.3)	
Cardiac tamponade	6 (3.3)	1 (0.6)	
Sustained ventricular tachycardia	3 (1.7)	0	
Cardiac surgery	2 (1.1)	2 (0.6)	
Resuscitated sudden cardiac arrest	2 (1.1)	1 (0.6)	
Pneumothorax	1 (0.6)	2 (1.1)	
Stroke	1 (0.6)	0	
Death	2 (1.1)	1 (0.6)	0.32
Sudden cardiac death	1 (0.6)	0	
Heart failure	1 (0.6)	1 (0.6)	

IQR indicates interquartile range; LVOT, left ventricular outflow tract; and SD, standard deviation.

Source: Sorajja et al, 2012

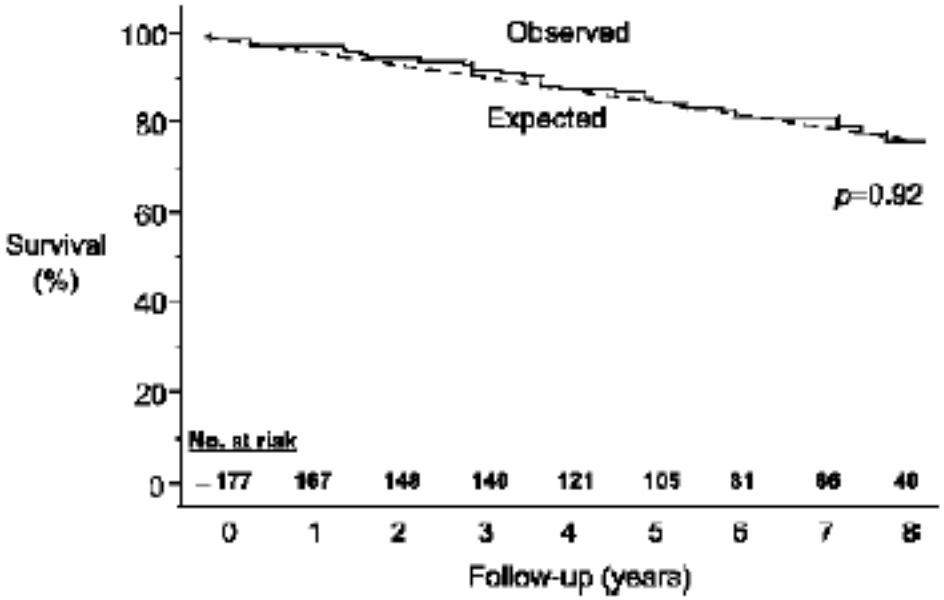
Table 40. Events Beyond 30 days: PTSMA vs SM (Sorajja, 2012)

	Ablation Patients (n=177)	Myectomy Patients (n=177)	*P*
Permanent pacemaker implantation, n (%)	3 (1.7)	2 (4.3)	0.65
ICD discharge for VT or VF, n (%)	1 (0.6)	0 (0.0)	
Septal ablation, n (%)	5 (2.8)	0 (0.0)	
Cardiac surgery, n (%)	15 (8.5)	2 (1.1)	0.0001
Surgical myectomy	10 (5.6)	1 (0.6)	
Coronary artery bypass grafting	1 (0.6)	0 (0.0)	
Ascending aortic aneurysm repair	1 (0.6)	0 (0.0)	
Aortic valve replacement	1 (0.6)	1 (0.6)	
Pericardiotomy	1 (0.6)	0 (0.0)	
Mitral valve repair	1 (0.6)	0 (0.0)	
Death, n (%)	24 (13.5)	24 (13.5)	0.99
Noncardiac cause	11 (6.2)	15 (8.5)	
Unknown cause	12 (6.8)	7 (4.0)	
Sudden cardiac death	3 (1.7)	3 (1.7)	

ICD, implantable cardioverter-defibrillator; VF, ventricular fibrillation; and VT, ventricular tachycardia.

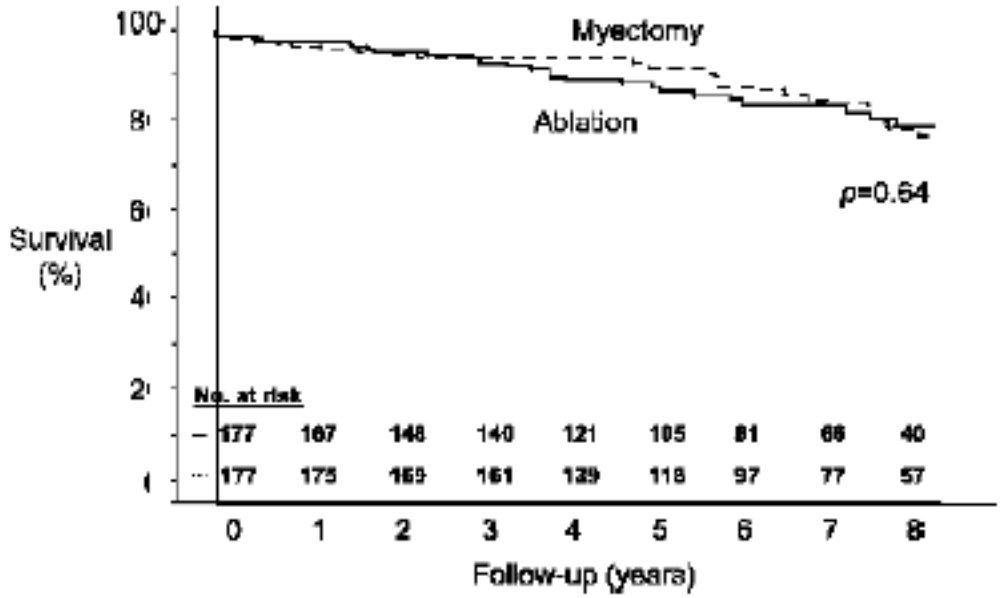
Source: Sorajja et al, 2012

Figure 15. Observed vs Expected Survival (Sorajja, 2012)



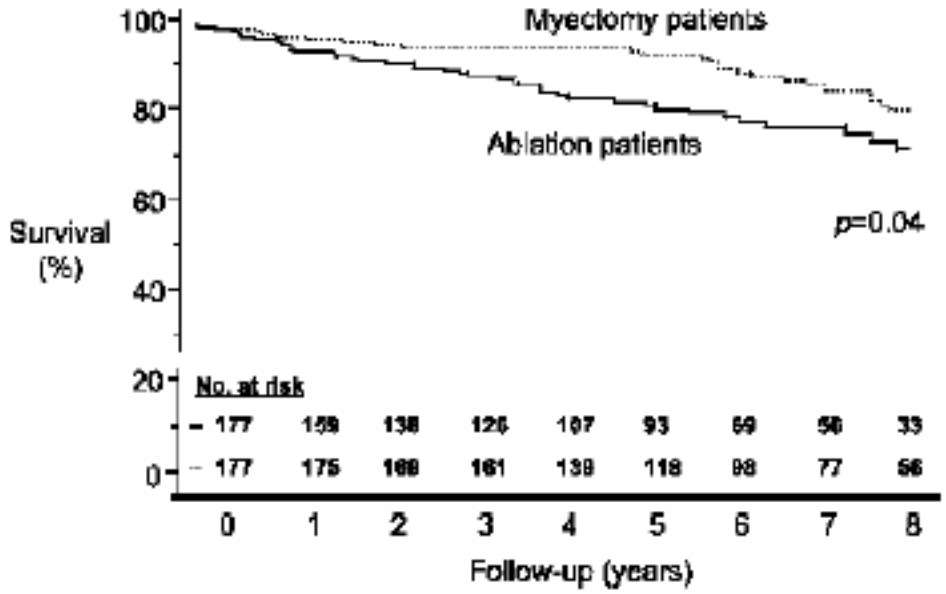
Source: Sorajja et al, 2012

Figure 16. PTSMA vs SM Survival (Sorajja, 2012)



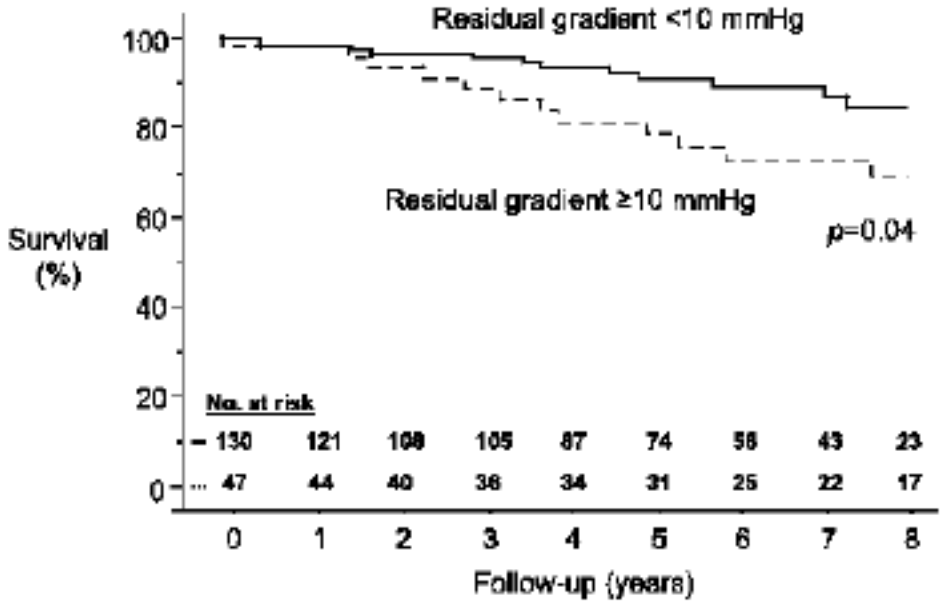
Source: Sorajja et al, 2012

Figure 17. Survival or Additional Septal Reduction (Sorajja, 2012)



Source: Sorajja et al, 2012

Figure 18. Survival as Function of Residual LVOT-PG (Sorajja, 2012)



Source: Sorajja et al, 2012

Reviewer Comment (Sorajja 2012): This was a nonrandomized and retrospective evaluation of PTSMA vs SM with retained potential for selection bias. However, the meticulous description of study methodology (i.e. clearly defined inclusion criteria,

PTSMA technique, follow-up procedures and data analysis that included well defined endpoints) enhanced this publication's qualifications as supportive for an NDA. This study suggested no difference between PTSMA and SM for mortality. Both procedures showed a reduction in mortality to that of the general US population. Compared to SM, PTSMA patients experienced considerable procedural complications, driven by pacemaker dependency and the need for a follow-up SM. This study did not describe changes from baseline in functional capacity for either procedure. A key finding with label implications is that patients with a residual LVOT-PG ≥ 10 mmHg had a lower survival compared patients whose residual LVOT-PG was less than 10 mmHg.

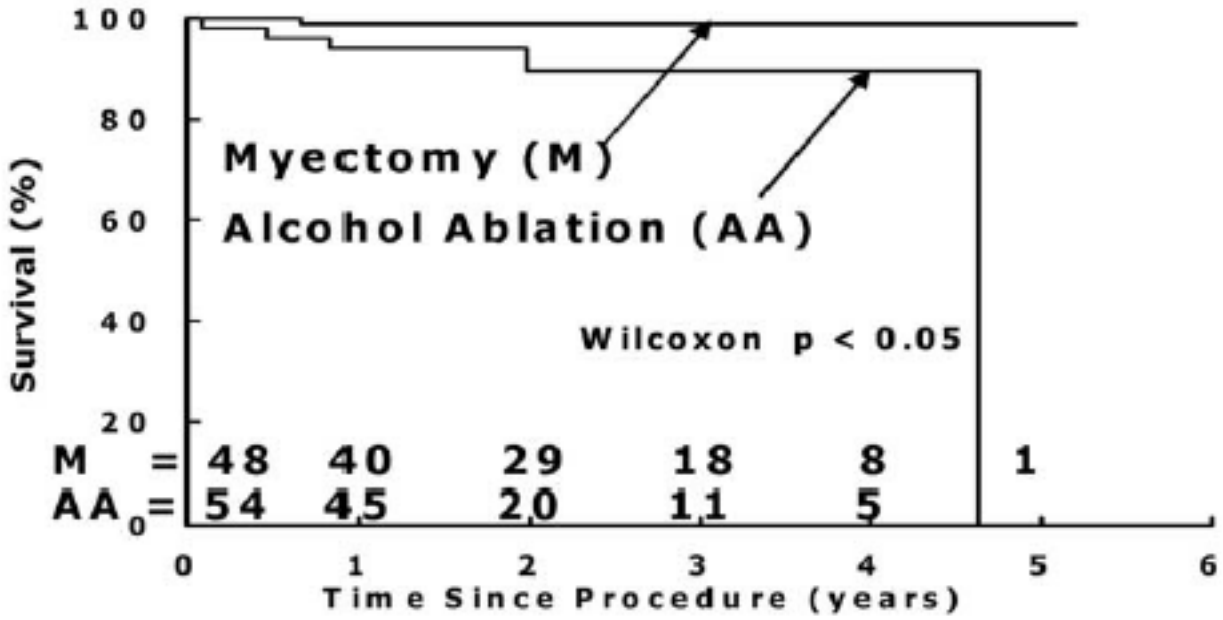
Ralph-Edwards (2005) conducted a non-randomized study of 150 patients undergoing PTSMA (intended N=60) vs SM (intended N=90) based on referrals for these procedures. The objective of this study was to compare the effects of these two treatment modalities on symptoms and hemodynamics. Mean follow-up time was 2.0 ± 1.3 years. Neither the ethanol dose nor the average number of septal arteries injected was specified. Patients undergoing PTSMA were reported to be significantly older, had higher resting systolic blood pressure, were less likely to have angina pectoris or pre-syncope/syncope, had better NYHA class, were more likely to have coronary artery disease, and had decreased ventricular septal thickness and posterior wall relative to patients undergoing isolated SM. The authors admitted that the comparing the performance of these two procedures was attenuated by differing patient referral patterns, non-randomization, short follow-up, and small sample size. Furthermore, SM was reported to be an established procedure at the investigator's institution, whereas the indications, technique, and care of PTSMA patients were new and evolving.

Figure 19 shows the Kaplan-Meier survival curve for patients undergoing PTSMA and SM. The authors reported 5 deaths in the PTSMA cohort (2 sudden, 1 congestive heart failure, 1 malignancy, and 1 after liver implantation) vs no deaths in the SM cohort. Figure 20 shows the Kaplan-Meier curve for freedom from pacemaker in both cohorts. Inspection of this figure suggested that approximately 40% of the PTSMA patients versus approximately 15% of SM patients required a permanent pacemaker. Survival free from pacemaker placement was greater in the SM cohort compared to the PTSMA cohort. Table 41 shows the echocardiographic variables between those undergoing PTSMA vs isolated SM. Of note was the finding that after adjusting for older age and better NYHA class in the PTSMA group, resting post-procedure LVOT-PG was reported to be significantly higher in the PTSMA group (adjusted difference 14 mm Hg, $p < 0.001$).

The authors specified that an optimal composite outcome at follow up was defined as survival, NYHA class I, no post-procedure pacemaker placement, and a follow-up resting LVOT-PG of less than 20 mm Hg. This was reported to be noted in 12 (22%) patients in the PTSMA group and 35 (73%) patients in the isolated SM group ($p<0.001$).

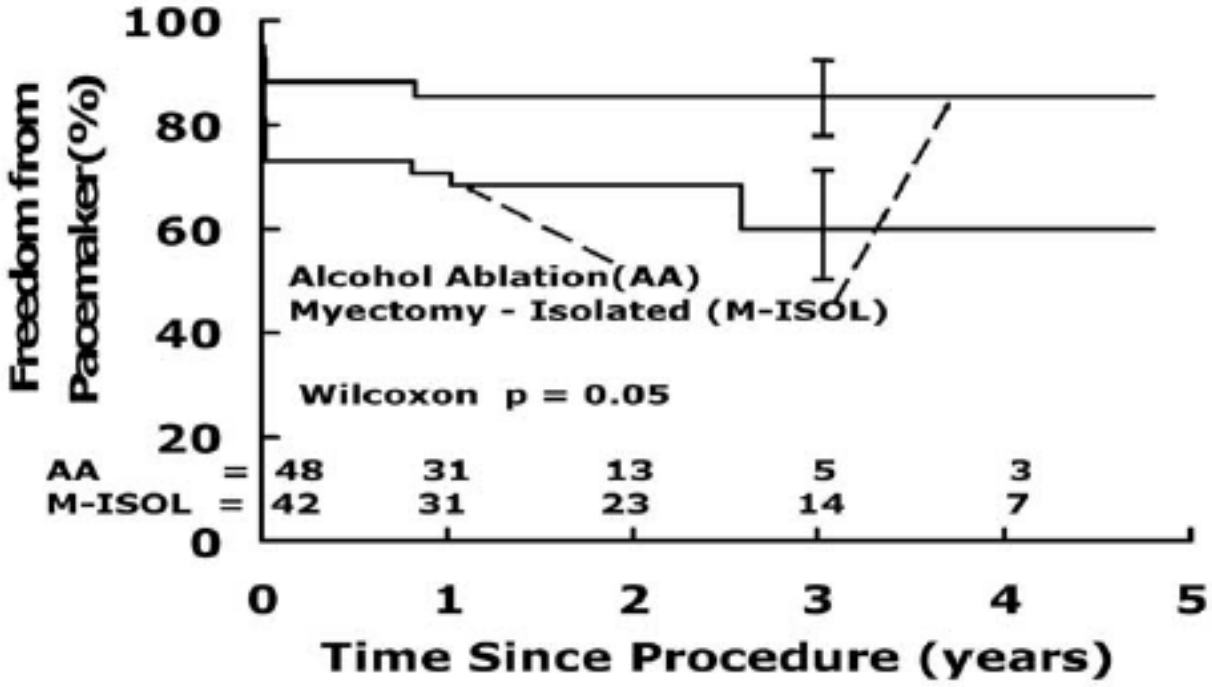
The authors stated several study liabilities, such as general applicability because SM was an established procedure at the institution whereas PTSMA was not. There were different referral patterns for each procedure. Without randomization, the different referral patterns, especially with small sample sizes, impacted interpretation of the data. The authors suggested a prospective multicenter trial of SM vs PTSMA.

Figure 19. Survival after Septal Reduction Procedure (Ralph-Edwards, 2005)



Source: Ralph-Edwards et al, 2005

Figure 20. Freedom from Pacemaker (Ralph-Edwards, 2005)



Source: Ralph-Edwards et al, 2005

Table 41. Echocardiographic Variables post Septal Reduction (Ralph-Edwards, 2005)

	Alcohol ablation (n = 54)	Surgical myectomy (n = 46)	*P* value*	*P* value†	*P* value‡
Mean interval to echocardiography (y)	1.8 ± 1.1	2.3 ± 1.5	.07		
Resting LV outflow gradient (mm Hg)	15 (0, 96)	5 (0, 17)	<.001	<.001	.002
Provoked LV outflow gradient (mm Hg)	42 (0, 125), n = 50	14 (0, 42), n = 27	<.001	<.001	.004
Presence of systolic anterior motion of the mitral valve	32/48 (67%)	12/41 (29%)	<.001	.006	.01
Presence of moderate or more severe mitral valve regurgitation	8/53 (15%)	6/45 (13%)	.84	.96	.65

LV, Left ventricular.
*Unadjusted.
†Adjusted for significant baseline variables.
‡Adjusted for significant baseline variables and propensity score.

Source: Ralph-Edwards et al, 2005

Reviewer Comment (Ralph-Edwards 2005): Although I am cognizant of the liabilities of this study as described by the authors, the results suggested that SM was superior to PTSMA for survival and for freedom from pacemaker placement. Based on the study by Sorajja et al (2012) reviewed previously, we learned that a post-PTSMA residual LVOT-PG ≥ 10 mm Hg adversely affected all-cause mortality relative to a post-PTSMA residual LVOT-PG < 10 mm Hg, and that a post-procedure residual LVOT-PG was an independent predictor for mortality. The residual LVOT-PG in this study was

considerably higher in the PTSMA group (15 mmHg) compared to the SM group (5 mmHg). The 5 deaths in the PTSMA group vs no deaths in the SM group in light of the higher residual LVOT-PG in the PTSMA group created a suspicion that PTSMA might not have been as effective as SM in reducing LVOT-PG, thereby placing patients at higher risk of death. Of the 5 deaths, the causes of 3 deaths (2 sudden and 1 congestive heart failure) were associated with complications or failure of the procedure (sudden death probably due to ventricular dysrhythmia) or natural history of the disease (heart failure due to "burn-out").The results in this study therefore suggested that PTSMA might have placed the patient at a higher risk of death compared to SM due to the significantly higher residual LVOT-PG in the PTSMA cohort relative to that in the SM cohort. There was no functional data presented in this publication. (b) (4) *However, I believe this publication is useful for providing statements in the label referring to the risk associated with a residual LVOT-PG ≥ 10 mmHg.*

Van der Lee et al (2005) studied medically refractory symptomatic HOCM patients with an enlarged anterior mitral valve leaflet (AMVL) who underwent SM and combined mitral leaflet extension (MLE) (N=20) or PTSMA (N=43). The objective was to determine if surgical correction of an enlarged AMVL attenuates residual SAM. SM with MLE was reported to be superior to SM alone, but the benefit of SM/MLE compared to PTSMA was not known. This was a non-randomized study where SM/MLE was performed on patients between 1986 and1999, and PTSMA was performed on patients after August 1999. Follow-up time was 1 year. An average total of 1→5 mL ethanol was injected into an average of 1 septal artery. The authors did not provide specific doses of ethanol. The clinical and echocardiographic data at baseline and at 1-year follow-up is shown in Table 42. The results showed similar reductions in NYHA class and LVOT-PG between SM/MLE and PTSMA. Mitral Regurgitation grade was more severe in the SM/MLE group, but the combined surgical procedure was thought by the authors to produce a residual grade similar to PTSMA. There was a greater decrease in SAM grade in the SM/MLE arm vs the PTSMA arm. The authors stated that after PTSMA, 4 patients died and 4 required a permanent pacemaker for a complete heart block.

Table 42. Clinical and Echocardiographic Data (Van der Lee, 2005)

	Preprocedure		One-Year Follow-Up	
	Myectomy (n=29)	PTSMA (n=43)	Myectomy (n=29)	PTSMA (n=41)
Clinical data				
Mean age, y	44±12*	52±17		
NYHA class	2.8±0.4	2.4±0.5	1.3±0.4†	1.5±0.7†
No. of drugs‡	1.5±0.7	1.5±0.9	0.8±0.9	0.9±0.8
Echocardiographic data				
Septal thickness, mm	23±4	21±4	17±2†	16±4†
LVOT gradient, mm Hg	100±20	101±34	17±14†	23±19†
MR grade	2.1±1.1*	1.5±0.8	0.6±0.6†	0.8±0.8†
SAM grade	2.9±0.3	2.8±0.5	0.5±0.7*†	1.3±0.9†
Left atrium, mm	47±9	47±7	46±11	45±6
LV EDD, mm	43±5	43±6	44±8	44±8
LV ESD, mm	27±5	25±5	28±7	30±8†
LV ejection fraction, %	72±6	71±5	70±8	69±7
MLA, cm^2	16.7±3.4	15.9±2.7		

n indicates number of patients; EDD, end-diastolic diameter; ESD, end-systolic diameter; and MLA, mitral valve leaflet area.
*$P<0.05$ vs PTSMA; †$P<0.05$ vs baseline value.
‡β-Blocker and/or calcium antagonist.

Source: Van der Lee et al, 2005

Reviewer Comment (Van der Lee 2005): The result of this study showed the same trend as other studies reviewed thus far: PTSMA reduced LVOT-PG and NYHA class. The tool to evaluate NYHA class was not described. Dyspnea, or any other symptom such as fatigue or palpitation, was not mentioned as the variable associated with NYHA class. This study provided by the Applicant did not provide exercise capacity data. Despite standard liabilities of retrospective studies, I have concluded that this study added to the growing body of evidence supporting the use of PTSMA to improve functional capacity.

Firoozi et al (2002) conducted a non-randomized single-center cohort study in order compare subjective and objective clinical outcomes in patients undergoing PTSMA or SM. The cohort comprised of 44 patients with refractory HOCM and a resting LVOT-PG of at least 50 mm Hg who were referred to the cardiomyopathy clinic at the St George Hospital Medical School, London, UK, between 1990 and 2000. Twenty-four patients underwent SM between April 1990 and September 2000. Twenty patients underwent PTSMA between May 1997 and May 2000. The decision to proceed with SM or PTSMA was based on individual patient choice and physician guidance. The mean follow-up

time in the SM cohort was 45.6 ± 25.1 months, and the mean follow-up time in the PTSMA cohort was 27.7 ± 15.3 months. The average ethanol dose was 3.0 mL into 1 septal artery (3.0 mL/artery).

Baseline characteristics are shown in Table 43. The data showed equipoise between the PTSMA and SM cohorts with the exception that the cohort undergoing PTSMA was older than that undergoing SM. Changes in NYHA class following SM or PTSMA are shown in Figure 21. At follow-up, 13 of 23 patients in the SM were in Class I, 8 were in Class II, and 2 were in Class III. Five patients reported no improvement. At follow-up, 10 of 19 patients in the PTSMA group were in Class I, 7 were in Class II, and 2 were in Class III. Seven patients reported no improvement. There was 1 death in each cohort (heart failure in the SM group and sudden death in the PTSMA group). The authors reported an improvement in NYHA class from 2.4 ± 0.6 to 1.5 ± 0.7 in the SM cohort, and an improvement in NYHA class from 2.3 ± 0.5 to 1.7 ± 0.8.

Metabolic exercise testing was accomplished by cycle ergometry using a ramp protocol of 10 to 15 watts per minute. Patients were required to cycle at a rate of 60 to 70 revolutions per minute to the point of exhaustion or symptom limitation. Respiratory gases were continuously sampled. The results are shown in Figure 22. Mean peak oxygen consumption increased from 16.4 ± 5.8 to 23.1 ± 7.1 mL / (kg-min) to 23.1 ± 7.1 mL / (kg-min) following SM, and increased from 16.2 ± 5.2 to 19.3 ± 6.1 mL / (kg-min) following PTSMA, indicating greater improvement in peak oxygen consumption favoring SM ($p<0.05$ favoring SM over PTSMA). Following SM, the work rate increased from 130 ± 57 watts at baseline to 161 ± 60 watts at follow-up. Following PTSMA, the work rate increased from 121 ± 53 watts at baseline to 137 ± 51 watts at follow-up. The authors reported that the change in work rate favored SM over PTSMA ($p<0.05$). The authors concluded that the improvement observed with SM was superior to that with PTSMA.

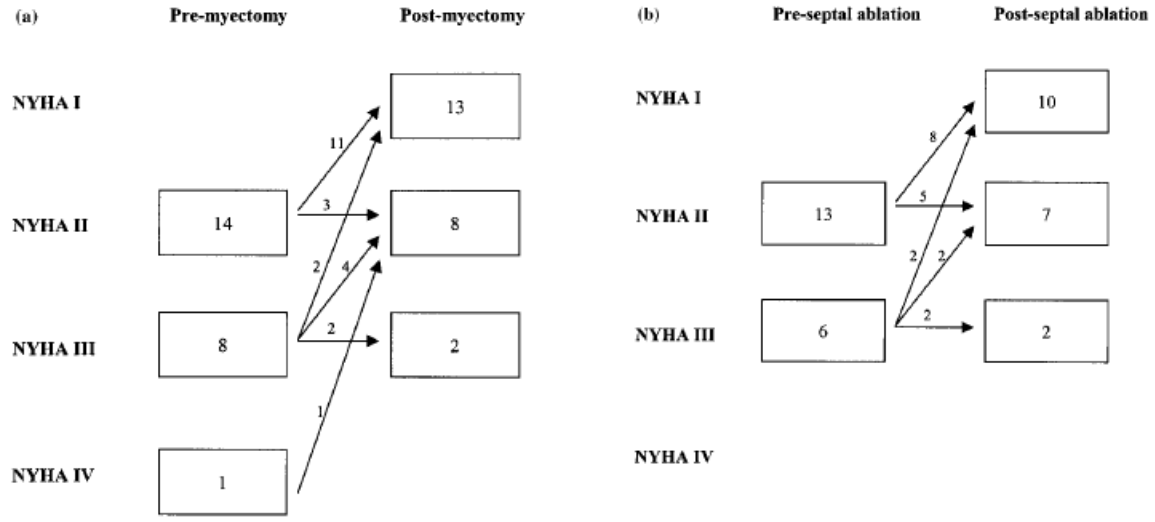
Table 43. Baseline characteristics: retrospective PTSMA vs SM (Firoozi, 2002)

	Myectomy group (n=24)	Septal ablation group (n=20)	*P*-value
Age (years)	38 ± 16	49 ± 13	0·02
Male sex	54%	60%	0·39
Drugs (%)			
β-blockers	8 (33)	9 (45)	0·43
CCA	4 (17)	6 (30)	0·29
Disopyramide	6 (25)	6 (30)	0·71
Amiodarone	4 (17)	3 (15)	0·88
Permanent AF	1	2	0·44
Paroxysmal AF	2	1	0·66
NYHA (%)			
Class II	15 (63)	14 (70)	0·61
Class III	8 (33)	6 (30)	0·81
Class IV	1 (4)	0	0·36
Exertional chest pain (%)	12 (50)	9 (45)	0·74
Syncope (%)	5 (21)	2 (10)	0·33
MLVWT (mm)	23 ± 6	21 ± 4	0·27
LA (mm)	48 ± 8	47 ± 11	0·76
LVEDD (mm)	40 ± 7	42 ± 4	0·43
LVESD (mm)	20 ± 6	23 ± 5	0·14
FS (%)	50 ± 10	45 ± 6	0·06
LVOTG (mmHg)	83 ± 23	91 ± 18	0·41
Work (watts)	130 ± 57	121 ± 53	0·29
Peak VO_2 (ml . kg^{-1} min^{-1})	16·4 ± 5·8	16·2 ± 5·2	0·9
% Predicted peak VO_2	50·2 ± 13·6	54·5 ± 15·1	0·4

AF=atrial fibrillation, CCA=calcium channel antagonist, FS=fractional shortening, LA=left atrium, LVEDD=left ventricular end-diastolic diameter, LVOTG=left ventricular outflow tract gradient, MLVWT=maximal left ventricular wall thickness, NYHA=New York Heart Association, VO_2=oxygen consumption rate.

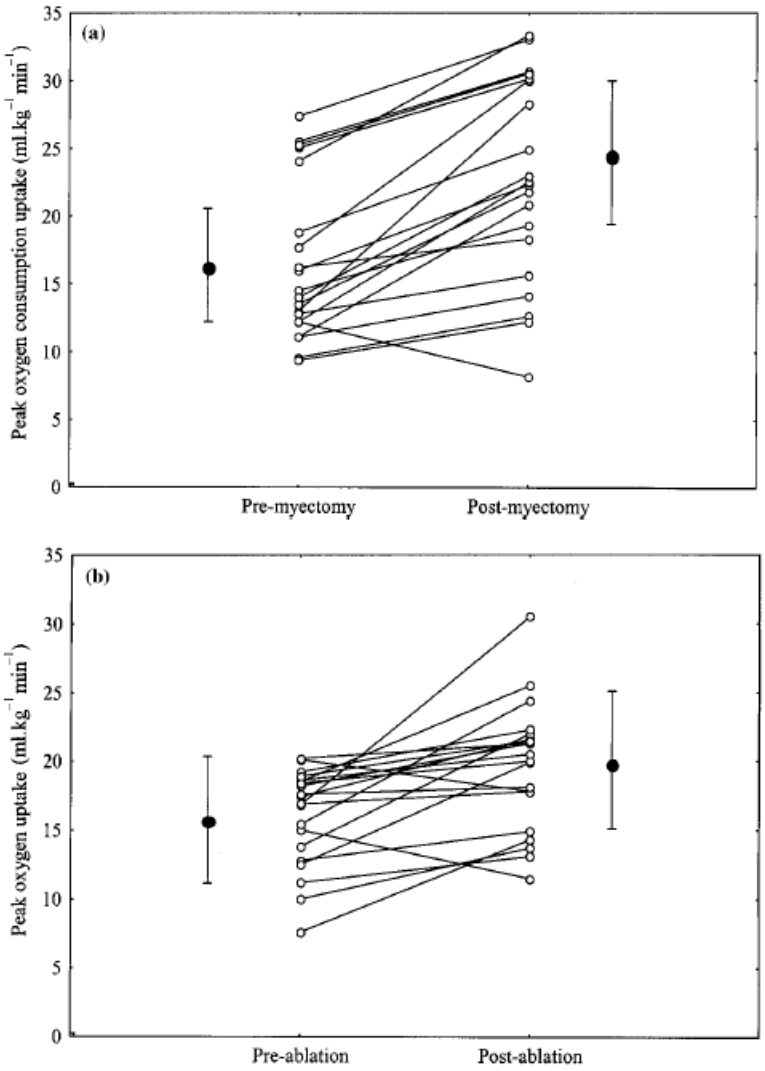
Source: Firoozi et al, 2002

Figure 21. NYHA Shift data: retrospective PTSMA vs SM (Firoozi, 2002)



Source: Firoozi et al, 2002

Figure 22. Exercise-peak oxygen update: retrospective PTSMA vs SM (Firoozi, 2002)



Source: Firoozi et al, 2002

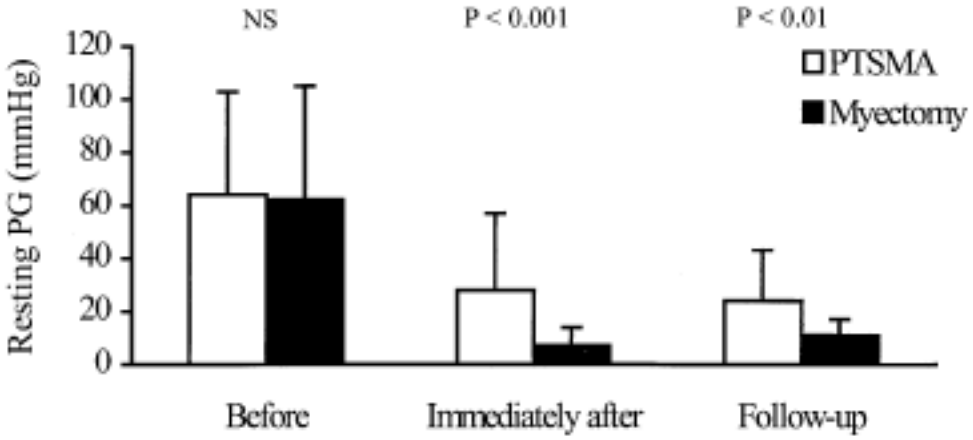
Reviewer Comment (Firoozi 2002): This non-randomized study had different follow-up time periods between the PTSMA (28 months) and SM cohort (46 months) thus placing into question the adequacy of the comparison. Despite the inherent liabilities associated with a non-randomized study, this study provided exercise data supportive of the Applicant's proposed indication. Based on the data from this study, I have concluded that PTSMA significantly increased peak oxygen consumption but did not have a significant effect on work rate. SM, on the other hand, significantly increased both peak oxygen consumption and work rate. I agreed with the authors' conclusion that although PTSMA improved subjective exercise limitation in appropriately selected patients, SM was superior to PTSMA on both peak oxygen consumption and work rate, and thus

remained the gold standard against which other treatment modalities should be compared.

Qin et al (2001) conducted a retrospective follow-up study to evaluate results in 51 patients with symptomatic HOCM who underwent either PTSMA (N=25) or SM (N=26). Patients selected for PTSMA were usually elderly and had comorbid conditions that could increase the risk of surgery. If there was a need for concomitant valvular surgery or if severe coronary artery disease was present, the patient was excluded from PTSMA. Echocardiographic and NYHA functional class was obtained at baseline and at follow-up. The follow-up period was 128 ± 84 days for SM and 117 ± 36 days for PTSMA. The average ethanol dose was 2.7 mL injected into 1 septal artery (2.7 mL/artery).

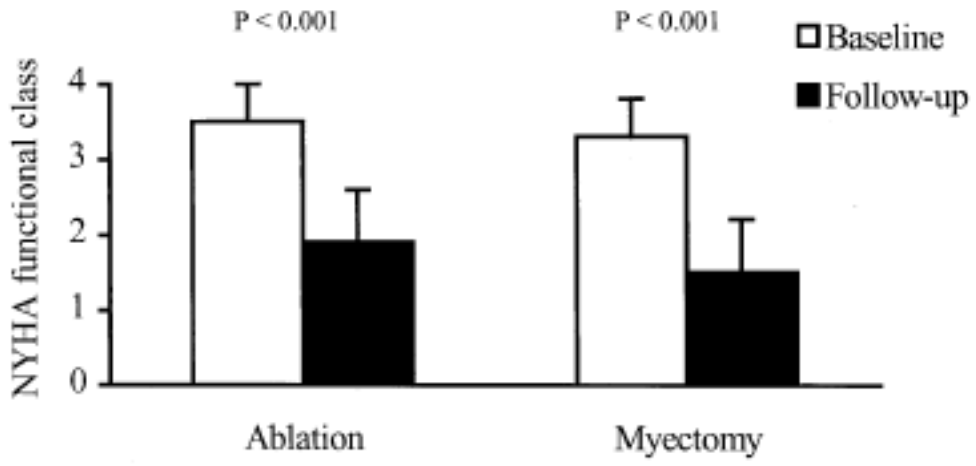
Resting LVOT-PG for both PTSMA and SM at baseline, immediately after the procedure, and at respective follow-up, is shown in Figure 23. Both procedures reduced resting LVOT-PG, but SM appeared more effective than PTSMA. NYHA data for both procedures at baseline and respective follow-up is shown in Figure 24. Each procedure significantly reduced NYHA class from baseline. The adverse events profile is shown in Table 44. The authors reported no deaths in the follow-up period. There were 9 right bundle branch blocks in the PTSMA group and no right bundle branch blocks in the SM group. However, there were 14 left bundle branch blocks in the SM group and 2 left bundle branch blocks in the PTSMA group. There were 6 vs 2 permanent pacemaker placements in the PTSMA vs SM groups, respectively. There were 6 re-do procedures at a 15 month follow-up (5 SM and 1 PTSMA). All 5 SM re-do procedures had permanent pacemaker placement because of complete heart blocks. Re-do procedures in the SM group were not reported.

Figure 23. LVOT-PG data: retrospective PTSMA vs SM (Qin, 2001)



Source: Qin et al, 2001

Figure 24. NYHA data: retrospective PTSMA vs SM (Qin, 2001)



Source: Qin et al, 2001

Table 44. Adverse Events: retrospective PTSMA vs SM (Qin, 2001)

Adverse Events		
	PTSMA	SM
Death	0	0
Right Bundle Branch Block	9	0
Left Bundle Branch Block	2	14
Permanent Pacemaker Placement	6	2
15 month late follow-up		
Re-do procedure (SM)	5*	Not reported
Re-do procedure (PTSMA)	1	Not reported

*All 5 patients undergoing re-do procedure with SM had permanent pacemaker placement because of complete atrio-ventricular block.

Source: Qin et al, 2001: tabulated by FDA clinical reviewer from publication content

Reviewer Comment (Qin 2001): This study demonstrated similar effectiveness of both PTSMA and SM for reducing LVOT-PG and NYHA class. PTSMA resulted in a greater

need for permanent pacemaker placement. A tool for NYHA evaluation was not described. There were no objective exercise data. This publication added support to the Applicant's proposed indication.

Nagueh et al (2001) conducted a non-randomized trial of 41 consecutive patients undergoing PTSMA at the Baylor College of Medicine with a 1-year follow-up. An average total of 2→5 mL ethanol was injected into an average of 1 septal artery. The authors did not provide specific doses of ethanol. These patients were compared to age and LVOT-PG matched SM patients from the Mayo Clinic. Baseline characteristics of the two cohorts at each respective institution were generally similar and are shown in Table 45. One year results are shown in Table 46. The data indicated a similar improvement in NYHA class and Angina class from baseline to 1-year follow-up for the two groups. Exercise data is shown in Table 47. Both SM and PTSMA increased exercise duration, peak oxygen consumption, metabolic equivalents, and percent maximal predicted oxygen consumption.

Table 45. Baseline Characteristics: Retrospective PTSMA vs SM (Nagueh, 2001)

	NSRT (n = 41)	Surgery (n = 41)
Age (yrs)	49 ± 17	49 ± 16
LVOT gradient (mm Hg)	76 ± 23	78 ± 30
NYHA class		
I and II		9 (22%)
II	4 (10%)	
III and IV	37 (90%)	32 (78%)
Angina class		
I	16 (39%)	16 (39%)
II	15 (37%)	10 (24%)
III	10 (24%)	15 (37%)
Presyncope	24/41 (59%)*	23/41 (56%)†
Permanent pacemaker‡	9/41 (22%)	16/41 (39%)
Cardiac medications		
Beta-blockers	31/41 (76%)	26/41 (63%)
Calcium antagonists	19/41 (46%)	18/41 (44%)
Disopyramide	8/41 (20%)	4/41 (10%)
Amiodarone	3/41 (7%)	4/41 (10%)
Sotalol	3/41 (7%)	None

*18 with syncope. †6 with syncope. ‡In both groups, pacemakers were placed as therapy for HOCM and not for heart block. There were no statistically significant differences between the two groups ($p > 0.1$).

HOCM = hypertrophic obstructive cardiomyopathy; LVOT = left ventricular outflow tract; NSRT = nonseptal surgical reduction therapy; NYHA = New York Heart Association.

Source: Nagueh et al, 2001

Table 46. One year Results: retrospective PTSMA vs SM (Nagueh, 2001)

	NSRT (n = 41)	Surgery (n = 41)
LVOT gradient (mm Hg)	8 ± 15	4 ± 7
NYHA class		
I	36 (88%)	32 (78%)
II	5 (12%)	8 (20%)
III		1 (2%)
Angina class		
I	41 (100%)	38 (93%)
II		3 (7%)
Presyncope	2/41 (5%)	7/41 (17%)
Permanent pacemaker	18/41 (44%)	17/41 (41%)
Due to heart block	9/41	1/41*
Cardiac medications		
Beta-blockers	7/41 (17%)	24/41 (59%)*
Calcium antagonists	1/41 (2%)	8/41 (20%)*
Disopyramide	3/41 (7%)	1/41 (2%)
Amiodarone	None	3/41 (7%)
Sotalol	2/41 (4%)	None

*$p < 0.05$ vs. NSRT.
Abbreviations as in Table 1.

Source: Nagueh et al, 2001

Table 47. Exercise Tolerance: retrospective PTSMA vs SM (Nagueh, 2001)

	Pre-NSRT	Post-NSRT	Pre-Surgery	Post-Surgery
Exercise duration (s)	289 (188–422)	417* (301–589)	330 (294–525)	480* (393–600)
Peak Vo_2 (ml/kg/min)	20.8 ± 4.9	26.2 ± 6.5*	18.9 ± 5.7	22.2 ± 5.3*
METS	5.9 ± 1.4	7.5 ± 1.9*	5.3 ± 1.7	6.5 ± 1.5*
% Maximal predicted Vo_2	55 ± 15	72.5 ± 18.4*	57 ± 11.5	69 ± 17*

*$p < 0.05$ vs. baseline.
METS = metabolic equivalents; NSRT = nonsurgical septal reduction therapy; Vo_2 = oxygen consumption.

Source: Nagueh et al, 2001

Reviewer Comment (Nagueh 2001): I agreed with the authors on the study limitations: non-randomized study, possibly not generalizable due to the experienced nature of the two institutions, different exercise protocols between the two institutions, use of regression equations in the PTSMA group for peak oxygen consumption and metabolic equivalents achieved. Despite this, objective exercise capacity data corroborated NYHA assessment. This study in my opinion supported the Applicant's proposed indication by demonstrating that PTSMA increased exercise duration, peak oxygen consumption, metabolic equivalents, and percent maximal predicted oxygen consumption similar to SM. The only caveat is that authors of this paper felt that the results might not be generalizable because not all centers would be similarly experienced.

5.3.5 Retrospective Studies: Mid-Term Follow-Up

Executive Summary and Reviewer Overall Assessment of Retrospective Studies Describing Mid-Term Follow-Up

The Applicant submitted 2 retrospective studies described as mid-term follow-up (see Table 6):

- Veselka (2012): The effect of myocardial septum morphology (neutral vs sigmoid) on hemodynamic efficacy and safety of PTSMA was evaluated. The authors found that post-PTSMA resting and provoked LVOT-PG were similar for both septum morphologies.
- Faber (2005): The 3-6 month follow-up on the German Cardiac Society multicenter registry of symptomatic HOCM patients undergoing PTSMA (Transcoronary Ablation of Septal Hypertrophy {TASH} registry) was reported. The findings showed a reduction in post-PTSMA LVOT-PG and NYHA class and a suggested correlation between these two variables. The findings also showed a more pronounced decrease in post-PTSMA LVOT-PG with corresponding higher levels of peak-CK-MB in a subgroup of patients who died at follow-up, compared to those who had survived at follow-up. This findings were in contradistinction to other findings (Chang et al, 2004) suggesting a requisite peak CK as high as > 1300 U/L for hemodynamic efficacy.

I assessed the publication by Veselka et al (2012) (b) (4) as having insufficient sample size to adequately assess safety of alcohol-PTSMA as a function of septum morphology.

I assessed the publication by Faber et al (2005) as suggestive for clinical efficacy because of NYHA class reduction in alignment with LVOT-PG reduction post-PTSMA. If the findings of increased mortality in association with a higher CK-MB and more pronounced reduction of LVOT-PG were correct, we would need to identify the optimal degree of septal necrosis required to affect an improved mortality approaching that of the general population and an improved functional capacity However, I believe it was more reasonable to opine that these counter-intuitive results could have been by chance because it was a subgroup analysis of retrospective registry data.

Veselka et al (2012) evaluated mid-term outcomes of PTSMA for HOCM in patients with sigmoid versus neutral ventricular septum. The objective of this study was to determine whether differences in the baseline septum morphology influenced outcomes of patients after PTSMA. A total of 100 consecutive symptomatic HOCM patients (74 patients with a neutral septum and 26 patients with a sigmoid septum) who underwent PTSMA were followed for a mean of 44 ± 36 months (median 30 months for patients

with a neutral septum and median 24 months for patients with a sigmoid septum). The ethanol doses reported in this publication were embedded in icons that were not responsive when attempting to gain access. Neutral septum morphology was defined as generally a straight or slightly convex septum toward the left ventricular cavity. Sigmoid septum morphology was defined as generally an ovoid left ventricular cavity with protrusion of the left septal endocardium into the LVOT (i.e. basal septal bulge) and qualitatively determined as the most thickened area of the basal septum.

The results of this study showed that at baseline, neutral septum morphology was associated with a thicker basal septum and a higher resting LVOT-PG compared to sigmoid septum morphology, but each type of septum had a similar provoked LVOT-PG. After PTSMA, both resting and a provoked LVOT-PG were similar for both septum morphologies. There were 2 deaths in each cohort. A cardioverter-defibrillator was prophylactically implanted in 7 patients in the neutral septum group vs 0 in the sigmoid septum group because of pre-procedural assessment of sudden cardiac death (i.e. not worsening ventricular arrhythmias following PTSMA). Repeat PTSMA was necessary in 4 patients (i.e. 3 from the neutral group and 1 from the sigmoid group). One of these patients who had a repeat PTSMA (cohort not specified but probably neutral group based on specified 1%) was later sent for SM. The authors stated that permanent pacemakers were implanted in 3 patients. The authors concluded that PTSMA was safe and effective in patients with either neutral or sigmoid septum morphology.

Reviewer Comment (Veselka 2012): This study did not evaluate exercise capacity or other function capacity. The sample size was too small to adequately assess safety of the Applicant's drug based on septum morphology. (b) (4)

Faber et al (2005) reported on the German Cardiac Society multicenter registry 3-6 month follow-up of 242 patients who underwent PTSMA for symptomatic HOCM. Follow-up was 92% complete (n=222) with a mean follow-up time-period of 4.9 $\pm$ 2.3 months. The average total ethanol dose was 2.8 mL but the average number of septal arteries was not specified. Echocardiographic and LVOT-PG data at baseline, at discharge post-PTSMA, and at follow-up are shown in Table 48. The data showed a significant reduction in LVOT-PG at rest and with provocation at discharge post-PTSMA with a continued reduction at follow-up. NYHA distribution at baseline and at follow-up is shown in Figure 25. A total of 168 of 222 patients (76%) were reported to have NYHA III or IV symptoms at baseline and 54 of 222 patients (24%) were reported to have NYHA I or II symptoms. At follow-up, 195 of 222 patients (88%) were reported to have NYHA I or II symptoms, and 27 of 222 patients (12%) were reported to have Class III or IV symptoms. The authors referred to patients achieving NYHA class I or II as a clinical success compared to those who were referred to as having residual symptoms (NYHA III or IV) and were therefore considered non-successful. As Table 49 shows, those patients who were classified as a clinical success had a lower LVOT-PG both at rest and with provocation as determined either by echocardiography or catheterization.

However, as Table 50 shows, patients who survived had a trend towards a higher LVOT-PG (both resting and with provocation) at follow-up compared to those who had died. Those who survived at follow-up also had a lower peak-CK (477 ± 254 U/L) and peak CK-MB (68 ± 40 U/L) compared to those who had died (peak-CK 721 ± 307 U/L; peak CK-MB 118 ± 49 U/L). The authors stated that the mortality rate for the 4.9 month follow-up period was 2.5% and the rate of permanent pacemaker placement was 9.6%.

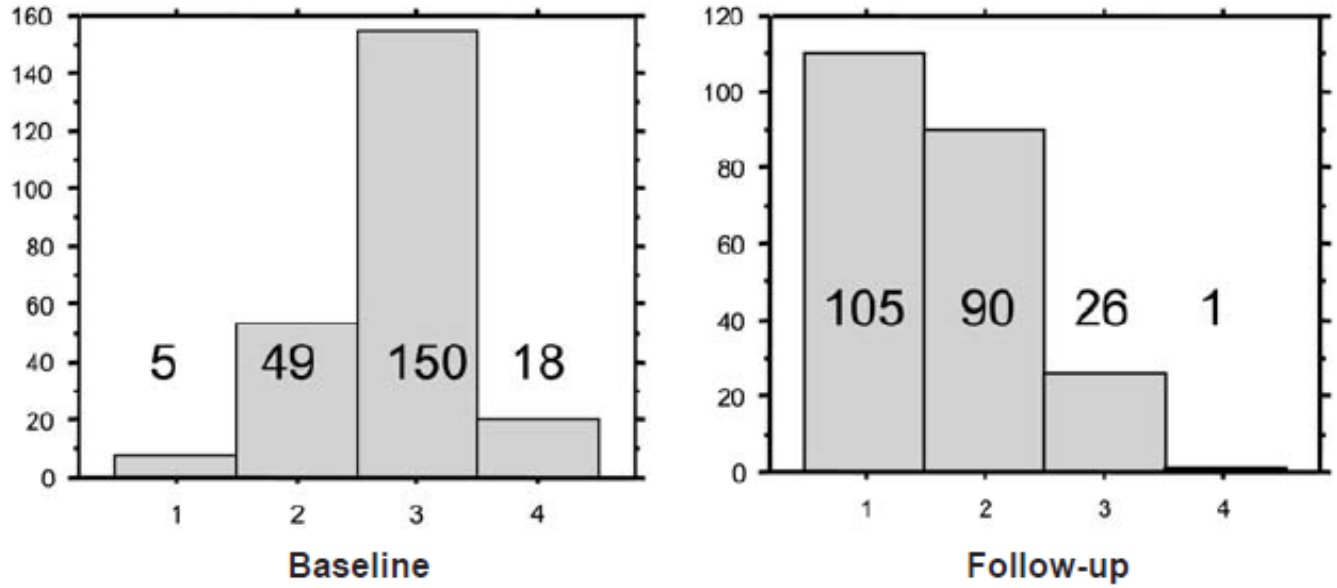
Table 48. Echocardiographic and LVOT-PG data (Faber, 2005)

	Baseline	At discharge	Follow-up	p value (vs baseline)
LA diameter (mm)	46±8		44±7	<0.001
Septum (mm)	20±5		15±5	<0.001
LVOT gradient at rest (Echo, mmHg)[b]	57±31	25±25[a]	20±21	<0.001
LVOT gradient with stress (Echo, mmHg)[b]	107±53	49±40[a]	44±40	<0.001
LVOT gradient at rest (catheter, mmHg)[c]	60±39	15±20[a]	7±17	<0.001
LVOT gradient with stress (catheter, mmHg)[c]	109±61	48±44[a]	34±52	<0.001
LVOT gradient post-ES (catheter, mmHg)[c]	143±47	40±41[a]	29±42	<0.001

[a] Numbers taken from the analysis of the acute results [17]; [b] data available for 207 patients; [c] data available for 129 patients

Source: Faber et al, 2005

Figure 25. NYHA Distribution at Baseline and Follow-up (Faber, 2005)



Source: Faber et al, 2005

Table 49. LVOT-PG with NYHA improvement vs residual symptoms (Faber, 2005)

	Clinical success (class I–II)	Residual symptoms III–IV	p value
LVOT gradient at rest (Echo, mmHg) [a]	18 ± 19	33 ± 30	< 0.001
LVOT gradient with stress (Echo, mmHg) [a]	41 ± 36	65 ± 62	0.04
LVOT gradient at rest (catheter, mmHg) [b]	5 ± 11	18 ± 28	< 0.001
LVOT gradient with stress (catheter, mmHg) [b]	26 ± 39	51 ± 62	0.04

[a] Data available for 207 patients; [b] data available for 129 patients

Source: Faber et al, 2005

Table 50. LVOT-PG in Survivors vs Non-Survivors (Faber, 2005)

	Survived until follow-up	Death until follow-up	p value
Post-intervention LVOT gradient at rest (Echo, mmHg)	48 ± 40	18 ± 33	0.08
Post-intervention gradient with stress (Echo, mmHg)	49 ± 44	19 ± 12	0.09
Ethanol dose (ml)	2.9 ± 2.3	3.3 ± 6.8	0.55
Peak CK (U/l)	477 ± 254	721 ± 307	0.03
Peak CK-MB (U/l)	68 ± 40	118 ± 49	0.01

Source: Faber et al, 2005

Reviewer Comment (Faber 2005): Data from this Transcoronary Ablation of Septal Hypertrophy (TASH) registry is consistent with other findings from the Applicant's submission package that PTSMA lowers LVOT-PG and improves NYHA class. The data also suggested that there might be a correlation between LVOT-PG and NYHA class. Patients with residual symptoms classified as NYHA class III-IV had a higher residual LVOT-PG compared to those patients considered a clinical success (NYHA class I-II). I have no explanation for the counter-intuitive finding that patients who died had a more pronounced decrease in LVOT-PG as well as a higher peak CK-MB compared to those who survived at follow-up. These results led me to speculate that baseline morbidity might have affected mortality outcome. These findings also suggested that a peak CK as high as > 1300 U/L as a prerequisite for hemodynamic efficacy (Chang et al, 2004) might not be related to a mortality benefit. There was no difference in ethanol dose between those who survived at follow-up and those who did not survive. These results from the Faber (2005) publication could have been by chance because it was a subgroup analysis of registry data. I have assessed this TASH registry mid-term follow-up report as suggestive for clinical efficacy because of NYHA class reduction in alignment with LVOT-PG reduction post-PTSMA.

5.3.6 Retrospective Studies: Long-term Follow-up

Executive Summary and Reviewer Overall Assessment of Retrospective Studies Describing Long-Term Follow-Up

The Applicant submitted 7 retrospective studies described as long-term follow-up (see Table 7). Mean follow-up times ranged from 3.1 ± 2.3 years (Moss, 2014) to 8.4 ± 4.1 years (Krejci, 2013). Sample sizes ranged from 24 patients (Krejci, 2013) to 874 patients (Nagueh, 2011). There was an additional long-term follow-up paper by Veselka (2011) that was also a randomized clinical trial. Consequently, that paper was listed under Randomized Clinical Trials as shown in Table 2. Key findings from this set of publications were:

- Veselka (2014-Eu Heart Journal): n=178, follow-up time 5.2 ± 3.7 years (maximum 15 years). The ethanol dose was 1.7 ± 0.8 mL; the number of septal arteries injected was not specified. There was an improvement in NYHA and CCS class and a reduction in LVOT-PG. The observed mortality rate approximated that of the general population. The number of pacemaker placement cases was not specified.
- Moss (2014): n=167, follow-up time 3.1 ± 2.3 years (maximum 9.7 years). The ethanol dose was 4.1 ± 1.7 mL; the number of septal arteries injected was 1.1. There were improvements in NYHA class and a reduction in LVOT-PG. The death rate was 11% and incidence of complete heart block was 27%. The rate of repeat PTSMA was 15%.
- Jensen (2013): n=470, follow-up time 8.4 ± 4.0 years (maximum years not reported). The ethanol dose was 0.1 mL / mm septum; the number of septal arteries injected was not specified and the total volume of alcohol injected was

not specified. There was a decrease in LVOT-PG from baseline. Cardiac mortality post-PTSMA approximated that of the general population. There was a decrease in the number of risk factors for sudden death post-PTSMA. The incidence of permanent pacemaker placement was 10%. There was no assessment of clinical benefit.

- Krejci (2013): n=24, follow-up time 8.4 ± 4.1 years for dual pacemaker placement for HOCM; 7.3 ± 1.9 years for PTSMA (maximum years not reported). The ethanol dose was 1-4 mL; the number of septal arteries injected was 1. Both dual chamber pacing and PTSMA decreased LVOT-PG and improved NYHA class from baseline thus making dual chamber pacing a viable alternative to PTSMA. Pacemaker requirements in the PTSMA population were not reported.
- Nagueh (2011): n=874, follow-up time ~ 2 years (standard deviation and maximum years not reported). The ethanol dose was 2.9 ± 1.5 mL; the number of septal arteries injected was 1 in 78% of the patients, 2 in 20% of the patients, 3 in 1.4% of the patients, and 4 in 0.4% of the patients. There were decreases in LVOT-PG and improvements in NYHA and CCS classes. The incidence of pacemaker requirement was 8.9%. A noteworthy finding was that the smaller number of septal arteries injected with alcohol was an independent predictor of mortality. This finding was counter-intuitive to me unless it was not independent but rather associated with insufficient ablation and consequent residual higher LVOT-PG.
- Fernandes (2008) n=619, follow-up time 4.7 ± 2.5 years (range 3 months to 10.2 years). The ethanol dose was 2.6 ± 1.0 mL; the number of septal arteries injected was 1.3 ± 0.5. There was a significant increase in exercise time as an objective measure in alignment with the subjective improvements in NYHA class and CCS class. The incidence of pacemaker requirement was 8.2%. A considerable number of patients were lost-to-follow-up beyond 5 years.
- Kuhn (2008): n=644, follow-up time 1.4 years (standard deviation and maximum years not reported). The ethanol dose in “Group A” (early cohort) was 2.2 ± 1.0 mL ranging from 0.93 mL to 2.9 mL per patient. The ethanol dose in “Group B” (later cohort defined as “low dose era”) was 0.8 mL ± 0.4 m ranging from 0.3 mL to 1.5 mL. The number of septal arteries injected was 1.1. There appeared to be a mortality-alcohol dose direct relationship. The authors suggested that a dose of ethanol exceeding 2 mL was associated with a higher mortality. These results were inconsistent with findings from other studies (i.e. Veselka Randomized Trials –see Table 2; Sorajja 2012; Chang 2004; Faber 2005).

I assessed these publications as supportive of efficacy because of improvement in subjective functional capacity as well as in exercise time (Fernandes 2008 and Alam 2006). The complication rate associated with permanent pacemaker placement was consistent amongst the studies reporting these data. The Kuhn study raised a question about the optimal ethanol dose. In all the long-term follow-up studies, the approximate average dose was 2 mL/artery injected. This included “Group A” of the Kuhn study. The

average dose in “Group B” of the Kuhn study was 0.7 mL/artery injected. I believe the association between doses > 2 mL ethanol and greater mortality might have been by chance because of the retrospective nature of the study and the temporal asynchrony of the two doses.

Veselka et al (2014, Eur Heart Journal, 35: 2040-2045) evaluated the long-term survival of 178 symptomatic HOCM patients who underwent PTSMA between 1998 and 2013 at 2 institutions in the Czech Republic. Mean follow-up time was 5.2 ± 3.7 years with a median of 4.8 years and a maximum of 15.1 years. The ethanol dose was 1.7 ± 0.8 mL (1.6 mL/artery).

Clinical and Echocardiographic characteristics at baseline and follow-up are shown in Table 51. After 5 years post-PTSMA, the data showed a significant decrease in dyspnea NYHA class and angina pectoris CCS class. There was also a significant decrease in syncopal episodes between baseline and follow-up. This was in alignment with a significant decrease in basal septum thickness and LVOT-PG.

There were 19 deaths (11%) reported in this publication during 925 patient-years. The overall mortality rate was estimated to be 2.1% per year. The causes of death are shown in Table 52. The main causes of death were stroke (42%), sudden death (21%), and cancer (21%). In these patients who died, the mean survival was 4.5 ± 3.9 years. The authors reported that 9 patients underwent implantation of a cardiac defibrillator. The Kaplan-Meier survival curve is shown in Figure 26. This curve included the 95% confidence interval and a superimposed line representing the survival profile expected in the general population after adjustment for sex and age. The observed mortality was reported to be comparable with the expected survival for age- and sex-comparable general population.

Table 51. Baseline Characteristics: Long-term Survival (Veselka, 2014)

	Baseline	Follow-up	*P*-value
Age, years	58 ± 12	63 ± 12	<0.01
Dyspnoea, NYHA class	2.9 ± 0.5	1.6 ± 0.8	<0.01
Angina, CCS class	1.9 ± 1 0.1	0.5 ± 0.7	<0.01
Episodes of syncope, %	15	5	<0.01
Left ventricular outflow gradient, mmHg	68 ± 42	20 ± 25	<0.01
Left ventricular diameter, mm	43 ± 5	47 ± 5	<0.01
Left ventricular ejection fraction, %	77 ± 9	72 ± 10	<0.01
Basal septum thickness, mm	21 ± 4	14 ± 4	<0.01

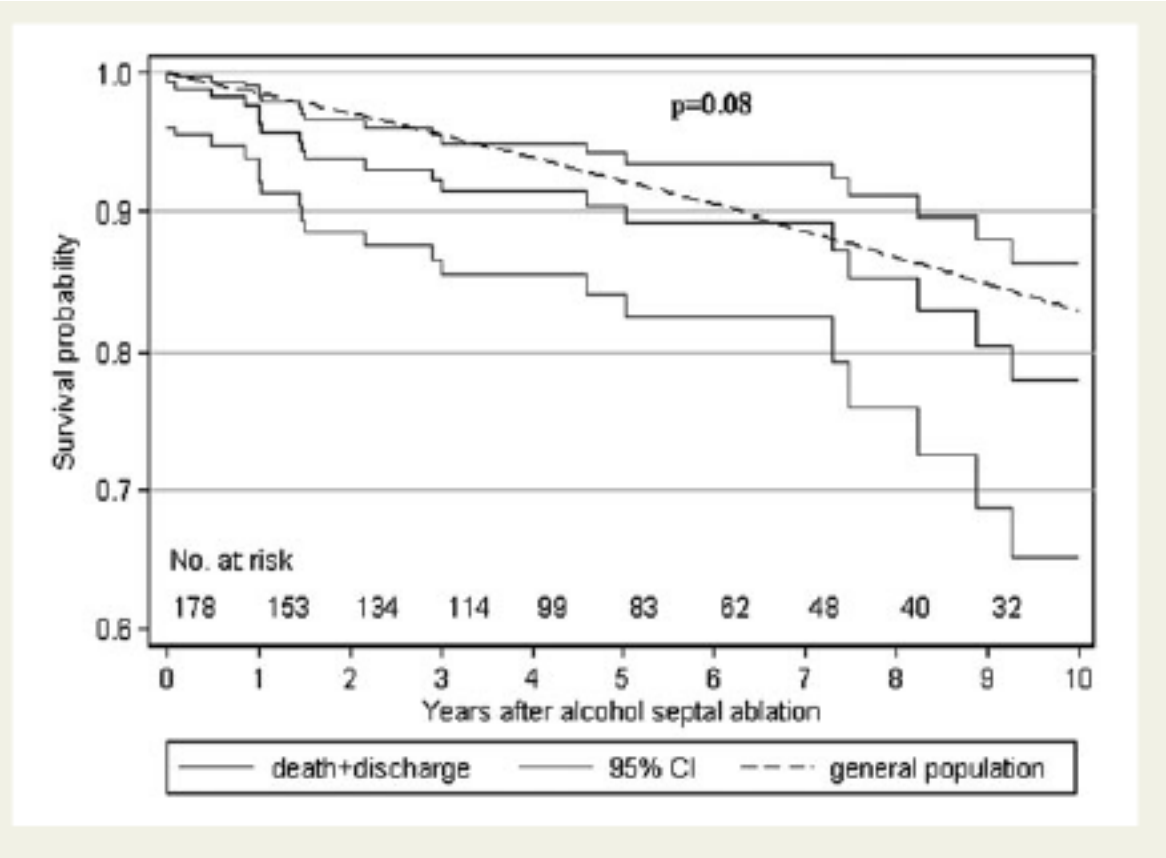
Source: Veselka et al, 2014 (Eur Heart Journal, 35:2040-2045)

Table 52. Causes of Death during Follow-up: Long-term Survival (Veselka, 2014)

Patient	Age at ASA, years	Length of follow-up, years	Cause of death
1	70	0.01	Post-procedural pulmonary embolism
2	49	0.1	Sudden cardiac death
3	76	0.8	Sudden death
4	72	1.0	Stroke
5	49	1.0	Cancer
6	75	1.0	Infective endocarditis
7	63	1.4	Stroke
8	84	1.5	Stroke
9	78	2.2	Stroke
10	48	3.0	Stroke
11	73	4.6	Bowel obstruction (cancer)
12	74	5.0	Sudden death
13	62	7.3	Sudden death
14	62	7.5	Stroke
15	56	8.3	Stroke
16	55	8.9	Stroke
17	70	9.3	Cancer
18	76	10.2	Cancer
19	68	12.5	Heart failure

Source: Veselka et al, 2014 (Eur Heart Journal, 35:2040-2045)

Figure 26. Kaplan-Meier Survival Curve: Long-term Survival (Veselka, 2014)



Source: Veselka et al, 2014 (Eur Heart Journal, 35:2040-2045)

Reviewer Comment (Veselka 2014, Eur Heart J): This study retained the standard liabilities associated with retrospective non-randomized studies. The authors did not report if any of the 9 patients who underwent implantation of a cardiac defibrillator died, or if such implantation was due to an adverse event or as a prophylactic measure. There were no reports of heart blocks, ventricular dysrhythmias, or pacemaker implantation. I have assessed the results of this study to be similar to that conducted by Sorajja (2012) regarding the similarity of the post-PTSMA mortality rate to that of the general population. Caveats from both sets of authors have cautioned that these retrospective data supportive of PTSMA were carried out at a tertiary center by staff familiar with HOCM and experienced with PTSMA.

Moss et al (2014) conducted an observation cohort study of 167 patients who underwent a PTSMA at the Denver Health Medical Center from 2002 to 2011. The mean follow-up time was 3.1 years ± 2.3 years (maximum 9.7 years). The ethanol dose was 4.1 ± 1.7 mL; the number of septal arteries injected was 1.1 (3.7 mL/artery). The results of this observational study are shown in Table 53. The death rate was 11% and incidence of complete heart block was 27%. However, only 2 patients were reported to

require a permanent pacemaker. The rate of repeat PTSMA was 15%. There was a significant reduction in LVOT-PG from baseline to follow-up at rest, with Valsalva, and with amyl nitrate. There was also a significant reduction in mean NYHA class from 2.9 at baseline to 1.3 at follow-up.

Table 53. Results of Longitudinal Cohort Study (Moss, 2014)

Results of Longitudinal Observational Cohort Study (Moss et al, 2014)	
Original Sample Size	167
Follow-Up Sample Size	139
Mean Age (standard deviation)	57.5 ± 15.5 years
Follow-Up Time (standard deviation)	3.1 ± 2.3 years
Mean volume of alcohol injected	4.1 ± 1.7 mL
Death (percentage)	16 (11%)
Complete Heart Block (percentage)	39 (27%)
Re-do PTSMA	22 (15%)
• Baseline mean LVOT-PG at rest ± standard deviation (mm Hg) • Follow-up mean LVOT-PG at rest ± standard deviation (mm Hg)	75.4 ± 44.9 mm Hg 18.6 ± 23.3 mm Hg
• Baseline mean peak LVOT-PG with Valsalva ± standard deviation (mm Hg) • Follow-up mean peak LVOT-PG with Valsalva ± standard deviation (mm Hg)	101.5 ± 43.7 mm Hg 33.5 + 36.4 mm Hg
• Baseline mean peak LVOT-PG with amyl nitrate ± standard deviation (mm Hg) • Follow-up mean peak LVOT-PG with amyl nitrate ± standard deviation (mm Hg)	98.1 ± 28.2 mm Hg 33.6 ± 26.4 mm Hg
Baseline mean NYHA class (standard deviation)	2.9 ± 0.4
Follow-up NYHA class (standard deviation)	1.3 ± 0.5

Source: Moss et al (2014): tabulated by FDA clinical reviewer from publication content

Reviewer Comment (Moss 2014): The study results are similar to the other retrospective studies reviewed thus far in the Applicant's NDA package. PTSMA reduced LVOT-PG and NYHA class from baseline.

Jensen et al (2013) conducted an observational cohort study (follow-up 8.4 ± 4 years) of 470 consecutive patients who underwent PTSMA for refractory HOCM at 2 tertiary referral centers (Germany, Denmark) from 1996 to 2010. The average age was 56 ± 14 years. The objective was to assess survival, incidence of sudden cardiac death after PTSMA, and the effects of PTSMA on the traditional risk factors for sudden cardiac death. Risk factors for sudden cardiac death were defined by Gersh et al (2011) as: 1) family history of sudden cardiac death in a close relative before the age of 40 years, 2) abnormal blood pressure response during exercise in patients < 50 years of age (systolic increase ≤ 20 mm Hg or systolic drop ≥ 15 mm Hg), 3) non-sustained ventricular tachycardia, 4) maximum septum wall thickness ≥ 30 mm, and 5) unexplained syncope occurring within 1 year of evaluation.

The ethanol dose was 0.1 mL / mm septum; the number of septal arteries injected was not specified and the total volume of alcohol injected was not specified. LVOT-PG at rest and during Valsalva at baseline and at follow-up is shown in Table 54. The data indicated a significant reduction in LVOT-PG both at rest and during Valsalva. Prevalence of risk factors for sudden cardiac death in 470 patients with HOCM before and after PTSMA is shown in Table 55. Key findings from this table suggested a significant decrease in modifiable risk factors (i.e. abnormal blood pressure response to exercise, non-sustained ventricular tachycardia, syncope, and maximum septum wall thickness). The overall survival and survival free of sudden cardiac death (reportedly including appropriate implanted cardioverter defibrillator discharge and aborted cardiac arrest) in the cohort of 470 patients having undergone PTSMA, compared with the overall survival of an age- and sex-matched background population, are shown in Figure 27. This figure indicates a decreasing sample size as a function of time for the mean 8.4 ± 4 years of follow-up time. The authors reported that 5 patients died during the in-hospital period and an additional 42 patients died during the follow-up period (3921 patient-years) for an estimated annual death rate of 1.2%. The 1-, 5-, and 10-year mean survival data after PTSMA were 98%, 93%, and 88%, respectively. These rates appeared to be the same as age- and sex-matched background population. Forty-three percent of the patients developed transient or permanent complete heart block during the procedure and in 10% of the patients permanent pacing was needed.

Table 54. Hemodynamic Results following PTSMA (Jensen, 2013)

Hemodynamic Characteristics (Jensen, 2014)			
LVOT-PG mm Hg	Before PTSMA	Follow-Up	Reported P-Value
-At Rest	60 (35-80)	1 (1-9)	< 0.0001
-During Valsalva	114 (90-140)	11 (1-4)	<0.0001

Source: Jensen et al, 2013: tabulated by FDA clinical reviewer from publication content

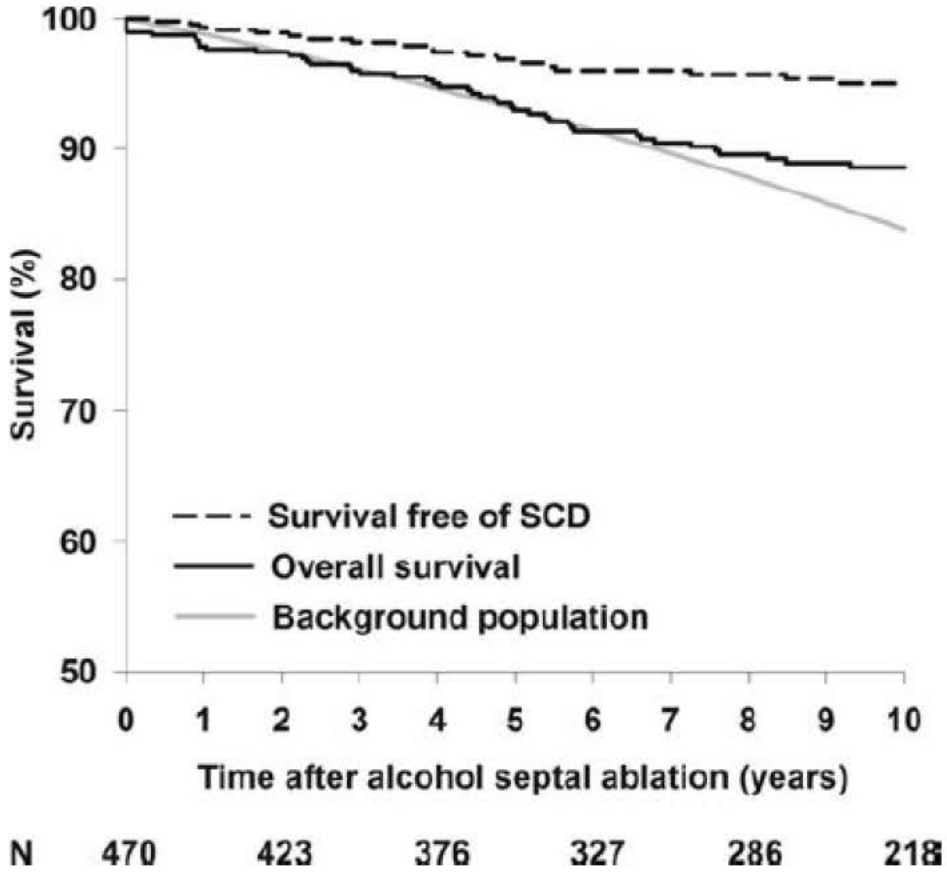
Table 55. Pre/Post PTSMA Risk Factors for Sudden Death (Jensen, 2013)

Risk factors	Before ablation % (n/N)	After ablation % (n/N)	p Value (N)*
Major risk factors for SCD			
Abnormal blood pressure response	23 (79/341)	9 (29/307)	<0.001 (245)
Non-sustained VT	23 (83/367)	17 (56/325)	0.047 (273)
Syncope	26 (123/465)	2 (10/444)	<0.001 (444)
Maximal wall thickness ≥30 mm	7 (34/460)	2 (10/447)	<0.001 (445)
Family history of SCD	19 (90/465)	–	–
0 Risk factors	41 (93)	60 (134)	<0.001 (225)#
1 Risk factor	34 (77)	32 (71)	
2 Risk factors	18 (44)	8 (19)	
3 Risk factors	6 (18)	0.4 (1)	
4 Risk factors	0.4 (1)	0 (0)	
Sum of major risk factors ≥2†	25 (89/361)	8 (23/278)	<0.001 (225)

*Uncorrected probabilities (p) of paired comparison between pre- and post-ablation prevalence of risk factors (McNemar's test).
†Abnormal blood pressure response only counted as a risk factor in patients younger than 50 years of age.
N, number of patients analysed; SCD, sudden cardiac death; VT, ventricular tachycardia.
#The p values relate to Ficher's exact test of risk factor groups (0–4) before and after alcohol septal ablation.

Source: Jensen et al, 2013

Figure 27. Survival Curve post PTSMA (Jensen, 2013)



Source: Jensen et al, 2013

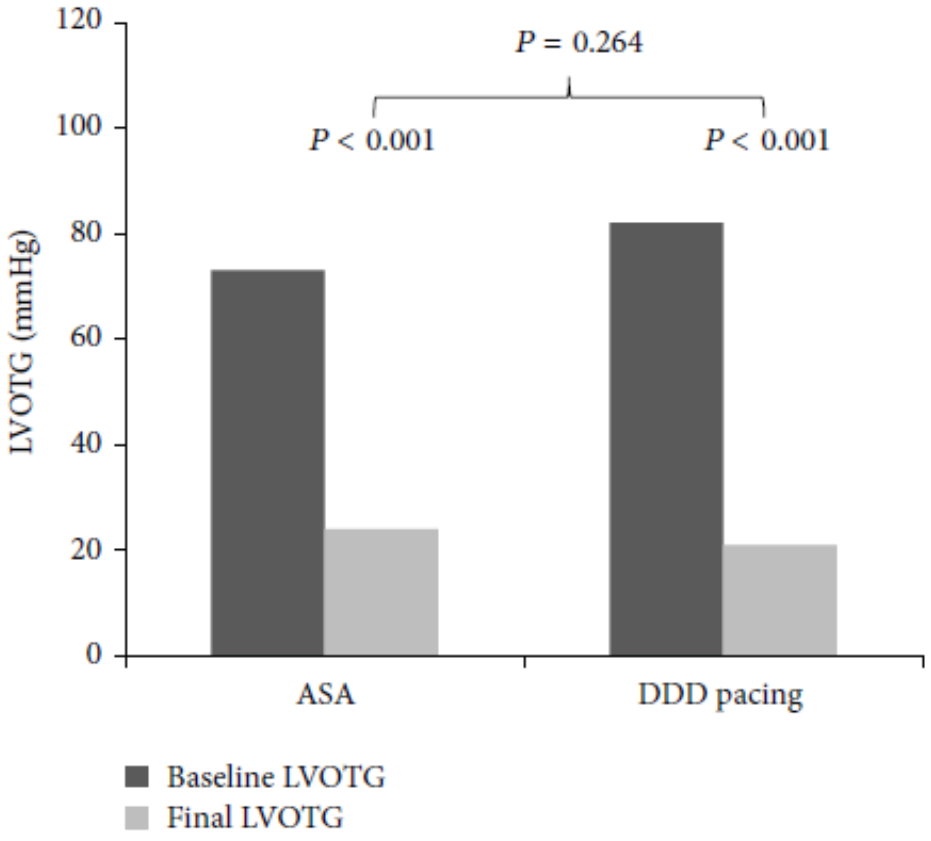
Reviewer Comment (Jensen 2013): My assessment of this observational cohort study was that PTSMA performed in patients with HOCM decreased LVOT-PG and decreased the prevalence of risk factors for sudden cardiac death. The overall survival rate appeared to be similar to the matched general population. The survival numbers quoted in the publication content (1-, 5-, and 10- year survival of 99%, 93%, and 88%, respectively) did not appear to be the empirically observed numbers for the same timepoints shown in Figure 27*. This did not alter the overall assessment, however.*

(b) (4)

Krejci et al (2013) retrospectively analyzed data from 3 centers from the Czech Republic who were engaged in 2 non-pharmacologic treatment approaches for HOCM: dual chamber pacing (DDD) and PTSMA. Twenty-four patients were treated with DDD and were followed for 101 ± 49 months. Fifty-two patients were treated with PTSMA and were followed for 87 ± 23 months. The objective was to evaluate the effectiveness of each procedure in reducing LVOT-PG and NYHA. The ethanol dose was 1-4 mL; the

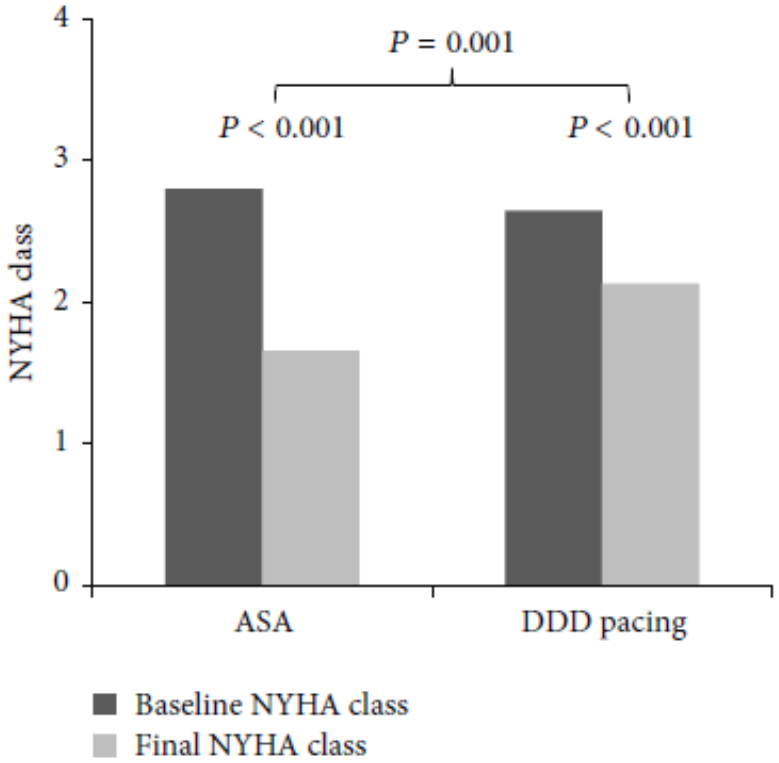
number of septal arteries injected was 1. Data on LVOT-PG is shown in Figure 28. With DDD pacing, the LVOT-PG decreased from 82 ± 44 mm Hg to 21 ± 21 mm Hg. With PTSMA, the LVOT-PG decreased from 73 ± 38 mm Hg to 24 ± 26 mm Hg. NYHA data is shown in Figure 29. With DDD pacing, NYHA class improved form 2.7 ± 0.5 to 2.1 ± 0.6. With PTSMA, NYHA class improved from 2.8 ± 0.5 to 1.7 ± 0.8. Changes in LVOT-PG and NYHA class were similar between the two groups. The authors stated that one patient required a permanent pacemaker 7 years after PTSMA. The authors concluded that DDD pacing could be considered an alternative to PTSMA or SM.

Figure 28. LVOT-PG Data for PTSMA and Dual Chamber Pacing (Krejci, 2013)



Source: Krejci et al, 2013

Figure 29. NYHA Data for PTSMA and Dual Chamber Pacing (Krejci, 2013)



Source: Krejci et al, 2013

Reviewer Comment (Krejci 2013): Consistent the standard liabilities of a retrospective study, I could not identify criteria for the selection of intervention (i.e. DDD vs PTSMA). Although this study suggested efficacy in reducing NYHA class from baseline for both DDD and PTSMA, the suggestion that DDD pacing could be an alternative to PTSMA raised the question about the advantage of PTSMA over other procedures. I believe a statement on DDD as an alternate effective strategy should be placed in the label.

Nagueh et al (2011) developed a multicenter North American registry of 874 patients who underwent PTSMA for refractory symptomatic HOCM. The primary objective was to identify the predictors of clinical outcome following PTSMA defined as mortality and freedom of repeat septal reduction procedures). Patients undergoing PTSMA in this registry were selected by clinical evaluation, discussion of options with the patients, and patient decision. The authors noted that during the period of registry (beginning year 2000—ending year not specified), 320 patients underwent SM as the primary treatment of symptomatic refractory HOCM. The follow-up time was approximately 2 years.

The ethanol dose was 2.9 ± 1.5 mL; the number of septal arteries injected was 1 in 78% of the patients, 2 in 20% of the patients, 3 in 1.4% of the patients, and 4 in 0.4% of the patients (average 2.3 mL/artery). Efficacy outcome data from this publication are shown in Table 56. The data indicated a shift in NYHA class and CCS class from baseline to follow-up signifying improvement in symptoms. This was aligned with a reduction in resting LVOT-PG between baseline and follow-up. The variation in LVOT-PG data was expressed as a standard deviation at baseline and as 1st and 3rd quartile values at follow-up. The LVOT-PG with provocation at follow-up was not reported. Adverse events are shown in Table 57. The incidence of death for the follow-up period was 9.3%. The authors noted that the time-dependent survival rate was 96.8% (Confidence Interval –presumed 95% 95.5%-98.1%) at 1 year, 85.6% (80.9%-90.6%) at 5 years, and 74.2% (63.8%-86.3%) at 9 years. The incidence of ventricular fibrillation and ventricular tachycardia during the follow-up period was 1.6% and 3.9%, respectively. Seventy-eight patients (8.9%) required a permanent pacemaker because of high grade heart block. One hundred and Twelve patients (12.8%) required a repeat PTSMA and 25 patients (2.9%) had a SM after PTSMA.

The authors identified the following predictors of mortality after PTSMA: lower baseline left ventricular ejection fraction, worse baseline NYHA functional class, smaller number of septal arteries injected with alcohol, larger number of ablation procedures per patient, higher septal thickness post-PTSMA, and use of beta-blockers post-PTSMA.

Table 56. Outcome in North American Registry (Nagueh, 2011)

	Baseline	Follow-Up (776 ± 26 days)
N	874	857 (based on content statement that there was 2% loss to follow-up)
Age (years)	55 ± 16	
Resting LVOT-PG mm Hg (sd)	70 ± 38	35 (1st -3rd quartile: 16-46)
Provoked LVOT-PG mm Hg (sd)	99 ± 55	Not reported
NYHA Class (% of cohort)	III-IV (78%)	III-IV (~5%)
CCS Class (% of cohort)	III-IV (43%)	III (1%-based on report of 8 patients with CCS III)

sd = standard deviation

Source: Nagueh et al, 2011: tabulated by FDA clinical reviewer from publication content

Table 57. Adverse Events in North American Registry (Nagueh, 2011)

Adverse Events *Follow-Up (776 ± 26 days)*	n (% of total N=874)
Death	81 (9.3)
Ventricular Fibrillation	14 (1.6%)
Ventricular Tachycardia	35 (3.9%)
High grade heart block requiring permanent pacemaker	78 (8.9%)
Implantable Cardioverter Defibrillator	94 (10.8%)
Repeat PTSMA	112 (12.8%)
SM after PTSMA	25 (2.9%)

Source: Nagueh et al, 2011: tabulated by FDA clinical reviewer from publication content

Reviewer Comment (Nagueh 2011): This registry had a relatively substantial number of patients in the cohort thus rendering greater credibility to the safety and efficacy data. I felt that the lower number of septal arteries injected with alcohol as an independent predictor of mortality was counter-intuitive, unless it was associated with insufficient ablation. This was not fully explored in the publication. I agreed with the authors' description of study limitations about cause and effect regarding the factors identified as predictors of death in the PTSMA setting, versus the possibility that the identified variables were markers of a higher risk group. The etiology of death was not adjudicated. I assessed the data from this registry as being consistent with the symptomatic improvement post-PTSMA that was observed in the other retrospective and observational studies. The incidence of permanent pacemaker placement appeared to be similar to that reported elsewhere [i.e. Leonardi 2010 (11%); Alam 2009 (8%); Alam 2006 (11%); Veselka 2006 (8%); Sorajja 2012 (3%)]. (b) (4)

Fernandes et al (2008) conducted a prospective non-randomized study at the Medical Center of South Carolina and Methodist-DeBakey Heart Center to determine the long-term outcome of PTSMA for refractory symptomatic HOCM. Six hundred and twenty nine patients were enrolled consecutively between 1998 and 2007 of which 619 underwent PTSMA with 579 patients (92%) followed-up in 2007. The ethanol dose was 2.6 ± 1.0 mL; the number of septal arteries injected was 1.3 ± 0.5 (2.0 mL/artery). Mean follow-up time was 4.6 ± 2.5 years (range 3 months to 10.2 years).

Baseline characteristics are shown in Table 58. The key finding in this table is the similarity in baseline characteristics between the "intention to treat" population and those who were not followed up. NYHA, CCS and Treadmill time data are shown in Figure 30. The authors reported marked early improvement of heart failure symptoms and angina pectoris at 3 months, with persistence of improvement at follow-up. There was a corresponding improvement in exercise time. These results were aligned with LVOT-PG reduction as shown in Figure 31 for both resting and provoked gradients. Mortality data is shown in Table 59. There were a total of 45 deaths, 24 that were cardiac deaths and 21 that were non-cardiac deaths. Of the cardiac deaths, 6 were procedure related as described the by the authors in Table 60. These deaths appeared to this reviewer as being associated with percutaneous coronary intervention as compared to complications intrinsic to PTSMA. The authors reported 6 deaths of unknown cause, but it was not clear to this reviewer if this represented additional deaths not listed in Table 59. Repeat septal ablation data is shown in Table 61. There were 91 (14%) repeat PTSMA procedures and 25 (4%) surgical procedures following PTSMA. There were 52 patients (8.2%) that required placement of a permanent pacemaker.

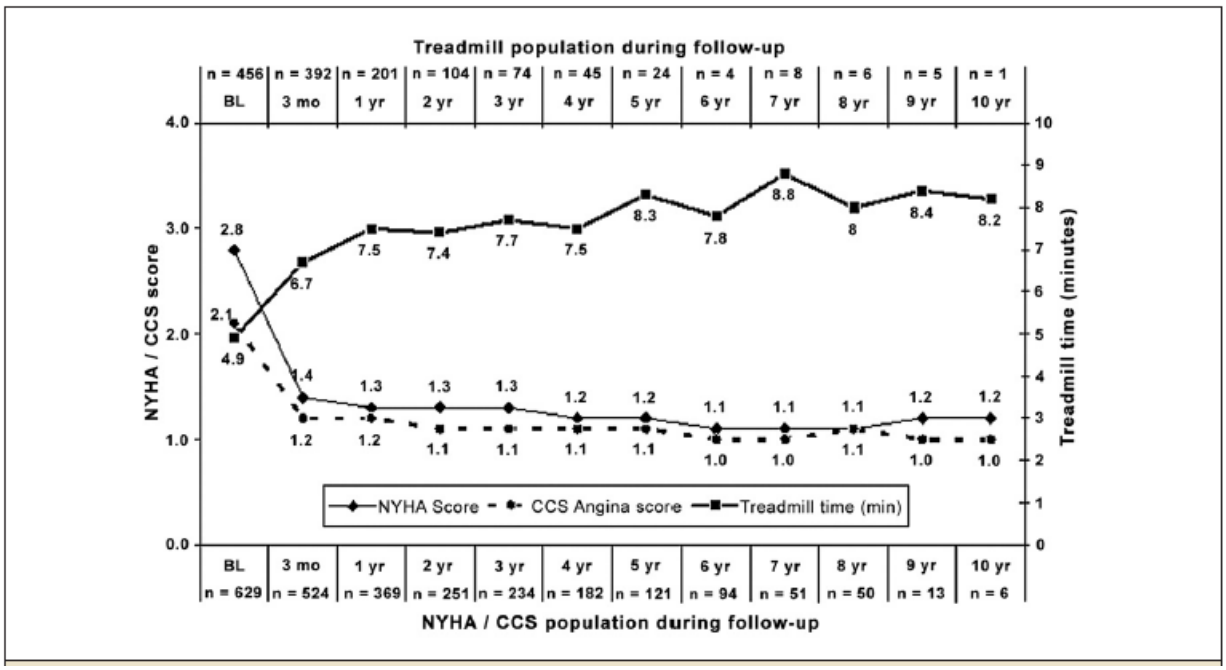
Table 58. Baseline Characteristics (Fernandes, 2008)

Baseline	All Patients at Entry	No Follow-Up in 2007
Total	629	50
Age (yrs)	53.9 ± 15.0	48 ± 18
Male/female	318/311	25/25
Prior pacemaker/ICD	98 (15.6%)	6 (12%)
CCS angina score	2.1 ± 0.9	2.3 ± 0.8
NYHA score	2.8 ± 0.6	2.9 ± 0.6
Treadmill time (min)	4.6 ± 3.4	4.6 ± 3
Rest gradient (mm Hg)	(n = 497) (79%) 78 ± 30	(n = 41) (82%) 72 ± 25
Provoked gradient (mm Hg)	(n = 132) (21%) 72 ± 34	(n = 9) (18%) 79 ± 45
Septal thickness (cm)	2.1 ± 0.5	2.2 ± 0.5
Ejection fraction, %	68 ± 9	68 ± 12
Number of septal arteries injected	1.2 ± 0.5	1.4 ± 0.6
Amount of alcohol injected (ml)	2.6 ± 1.0	2.9 ± 1.3
Peak CK (U)	1,221 ± 716	1,285 ± 615

CCS = Canadian Cardiovascular Society; CK = creatine kinase; ICD = implantable cardioverter-defibrillator; NYHA = New York Heart Association.

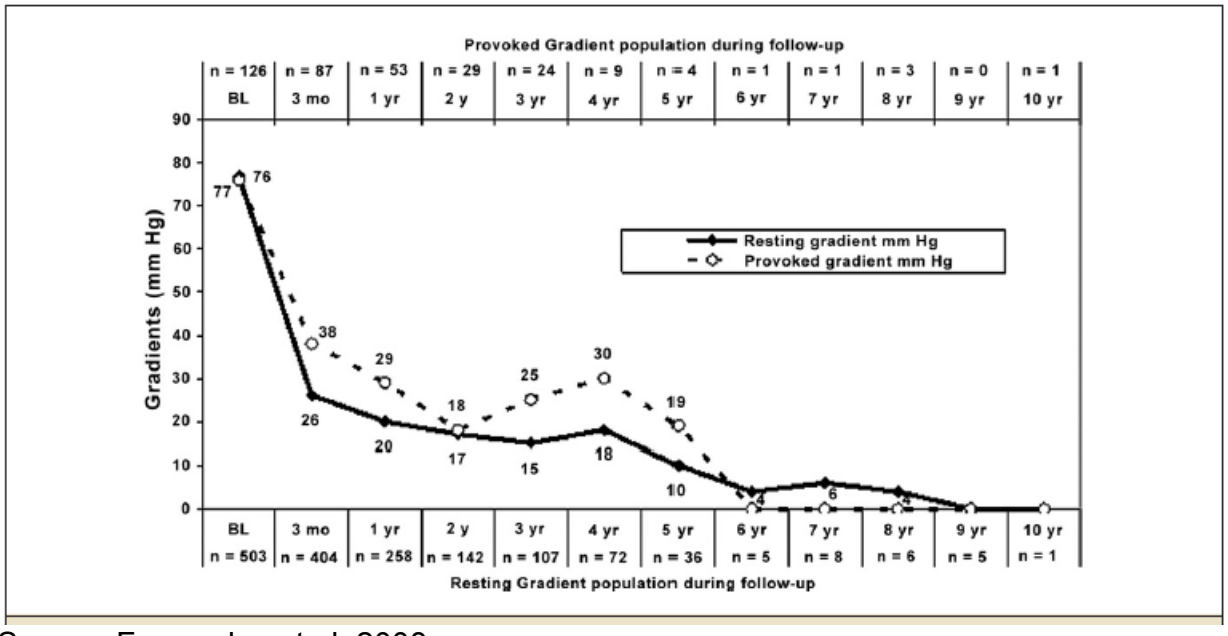
Source: Fernandes et al, 2008

Figure 30. Symptom and Functional Outcome (Fernandes, 2008)



Source: Fernandes et al, 2008

Figure 31. LVOT-PG Data post-PTSMA (Fernandes, 2008)



Source: Fernandes et al, 2008

Table 59. Mortality Data (Fernandes, 2008)

Cardiac Deaths (n = 24)	Noncardiac Deaths (n = 21)
Procedure related, n = 6	Lung disease, n = 7
Post-operative, n = 8	Infection and sepsis, n = 4
CHF (EF >60%), n = 3	Cancer, n = 3
SCD, n = 7	CVA, n = 4
	Other causes, n = 3

There were 6 deaths with unknown causes.
CHF = congestive heart failure; CVA = cerebrovascular accident; EF = ejection fraction; SCD = sudden cardiac death.

Source: Fernandes et al, 2008

Table 60. Causes of PTSMA-related cardiac deaths (Fernandes, 2008)

	Cause of Death
1	LAD dissection and ventricular fibrillation during ASA, died during surgery (acutely in the catheter laboratory)
2	Retroperitoneal bleeding from femoral vascular access (within 24 h of septal ablation)
3	Acute septal perforation (VSD) in a patient with mild calcific aortic stenosis (within 24 h of septal ablation)
4	Left main dissection (acutely in the catheter laboratory)
5	Sudden death 10 days after ASA
6	Late inferior wall with RV infarction (10 days after ASA)

RV = right ventricle; VSD = ventricular septal defect; other abbreviations as in Table 2.

Source: Fernandes et al, 2008

Table 61. Repeat Septum Ablation Procedures post-PTSMA (Fernandes, 2008)

Repeat Procedures post-PTSMA *Follow-Up (4.59 ± 2.47 years)*	Number of repeat procedures (% of total N=629)
Repeat PTSMA	91 (14%)
SM post PTSMA	25 (4%)

Source: Fernandes et al, 2008: tabulated by FDA clinical reviewer from publication content

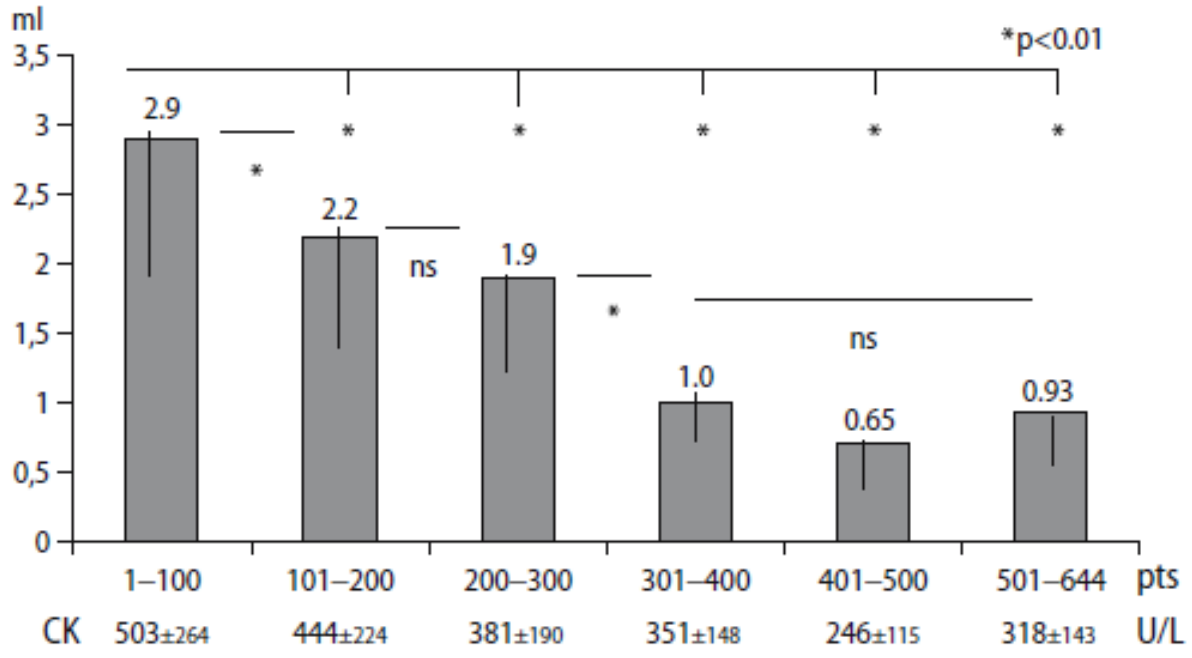
Reviewer Comment (Fernandes 2008): This study provided by the Applicant was supportive of the proposed indication because it contained exercise time data. This objective measure of functional improvement following PTSMA was aligned with subjective NYHA and CCS data in concert with LVOT-PG data. Mean exercise time increased from a baseline of 4.9 minutes (n=629) to 6.7 minutes at 3 months (n=524) to 7.5 minutes at 1 year (n=369). Sample size decreased as a function of time to a level that jeopardized data interpretation for long-term outcome (i.e. beyond 5 years). At the mean follow-up period of approximately 4.6 years, there were approximately 121-182 patients under review from the original 629 patients. Despite the lack of a comparator arm, the decreasing sample size as a function of follow-up time, and the paucity of objective data after 5 years, I assessed this study as supportive of the Applicant's proposed indication because of the concatenation of objective, subjective, and hemodynamic data with a reasonable sample size at 3 months-1 year follow-up.

Kuhn et al (2008) sought to determine the impact of PTSMA (i.e. transcoronary ablation of septal hypertrophy, TASH) on the survival of all patients with HOCM treated at 1 institution (Klinikum Bielefeld-Mitte, Germany) between 1995 and 2005. The total sample size was 644 consecutive patients. The authors focused on the effect of alcohol dose on survival. The total sample size was studied as two sequential groups. Group A was the first series of 329 patients who were treated in a dose finding strategy with decreasing amounts of ethanol until December 2001. The ethanol dose was 2.2 ± 1.0 mL ranging from 0.93 mL to 2.9 mL per patient (average 2.0 mL/artery). Group B was the second series of 315 patients who were treated during what the authors described as the "low alcohol dose era" where the mean ethanol dose 0.8 ± 0.4 mL ranging from 0.3 to 1.5 mL (average 0.7 mL/artery). The mean follow-up period for all patients was 1.4 years. The mean follow-up period for patients in Group A was 2.1 years with a maximum of 6.2 years. The mean follow-up period for patients in Group B was 7.3 months.

The relationship between ethanol dose and CK release is shown in Figure 32. The data shows that the amount of CK release is correlated with the dose of alcohol. Based on

the authors' description, I inferred that the 1.0 mL dose (n=310-400) bar in the figure incorporated both Group A and Group B patients. Mortality data is shown in Table 62. There was a discrepancy in follow-up time between Group A and Group B. Follow-up time was much longer in Group A (2.1 years) than in Group B (7.3 months). The prevalence of in-hospital mortality and the annual cardiac mortality rates were higher in patients of Group A compared to patients of Group B. Cumulative mortality in Group A patients stratified for ethanol doses > 2 mL or ≤ 2 mL is shown in Figure 33. The data indicated that patients treated with high amounts of ethanol (> 2.0 mL) showed a higher total mortality (8% at 70 months) than patients treated with small amounts (≤ 2.0 mL) (1% at 70 months). The authors stated that alcohol dose turned out to be an independent predictor of survival. The post-PTSMA pacemaker implantation rate was 17%. The authors concluded that the TASH registry data represented the largest available database on survival after PTSMA for HOCM from a single center with a large experience, and that evolution of this procedure over 10 years with increasing procedural experience included the pronounced reduction of ethanol quantity.

Figure 32. Alcohol dose-CK profile (Kuhn, 2008)



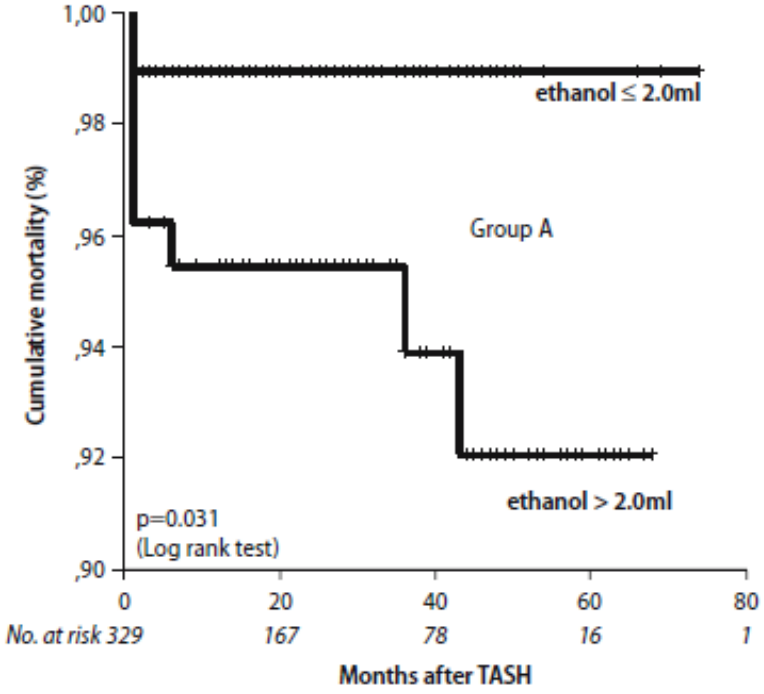
Source: Kuhn et al, 2008

Table 62. TASH Registry Mortality Data (Kuhn, 2008)

TASH Registry Mortality Data (Kuhn et al, 2008)			
	Total	Group A	Group B
Sample Size	644	329	315
Age: years (standard deviation)	58 ± 15	58 ± 15	57 ± 14
Mean Follow-Up Time	1.4 years (max not reported)	2.1 years (maximum 6.2 years)	7.3 months (maximum not reported)
All-cause mortality: n (%)	33 (5.1%)	29 (8.8)	Not reported
Annual all-cause mortality: n (%)	21 (3.2%)	14 (4.3%)	Not reported
In-hospital mortality: n (%)	8 (1.2%)	6 (1.8%)	2 (0.6%)
Annual cardiac mortality: n (%)	6 (0.7%)	5 (1.5%)	0

Source: Kuhn et al, 2008: tabulated by FDA clinical reviewer from publication content

Figure 33. Cumulative Mortality for Ethanol Dose > or ≤ 2mL (Kuhn, 2008)



Source: Kuhn et al, 2008

Reviewer's Comment (Kuhn 2008): The label in Figure 33 appeared incorrect. I believe it should have read "survival" rather than cumulative mortality because of the report that mortality was higher in patients administered > 2.0 mL ethanol. The safety issue with a higher ethanol dose as described here appeared to contradict other data. Based on the publications of randomized trials authored by Veselka et at, lower alcohol doses had a similar outcome as higher doses despite the higher CK release with higher alcohol doses. Nagueh et al (2011) identified a smaller number of arteries injected with alcohol as an independent predictor of mortality. This implied a lower dose of alcohol. Although not discussed in the publication, I believe that this finding might be associated with insufficient septal ablation and a consequent higher residual LVOT-PG. Faber et al (2005) observed from the same TASH registry a higher mortality rate for more pronounced reductions of LVOT-PG and increased levels of CKMB. The alcohol doses between those that survived (2.9 ± 2.3 mL) and those that did not survive (3.3 ± 6.8 mL) were not considered significantly different from each other (see Table 50). This finding by Faber et al (2005) in itself was counter-intuitive to the concept that a significant release of CKMB was necessary for hemodynamic efficacy (Chang et al, 2004). In the study that evaluated a series of PTSMA procedures and an independent series of SM procedures (Sorajja et al, 2012), the doses of alcohol reported were from 1-3 mL for a mortality benefit. My assessment of this uncertain set of findings in the setting of retrospective studies and registries has led me to speculate that hemodynamic efficacy and symptomatic improvement may not be an adequate surrogate for a mortality benefit

and that a well powered randomized trial is required to address these uncertainties. The results reported by Kuhn might also have been due to chance because of the retrospective nature of the TASH registry and the temporal asynchrony between the two doses. This study focused on the 10 year PTSMA experience aimed at understanding the impact of the procedure on mortality. (b) (4)

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5.3.7 Retrospective Studies: Septal Ablation and Compete Heart Blocks

Executive Summary and Reviewer Overall Assessment of Retrospective Studies Describing Septal Ablation and Complete Heart Blocks

The Applicant submitted 4 retrospective studies (Veselka, 2014, Int. J. Cardiol.; Faber, 2007; El-Jack, 2007; and Chang, 2003) assessing the risk of PTSMA-related complete heart block and subsequent need for permanent pacemaker, as well as predictors and management of this risk. Key findings from this set of publications were:

- Veselka (2014, International J Cardiology): n=167. Pacemaker requirement rate was approximately 10%. Improvements in symptoms (NYHA, CCS) were similar between post-PTSMA patients who required a pacemaker and those who did not.
- Faber (2007): n=155. Pacemaker requirement rate was approximately 7%. A risk factor scoring system for a complete heart block requiring a permanent pacemaker categorized the risk as low (<8), intermediate (8-12) and high (> 12). If all the risk factors for a complete heart block that can be measured prior to PTSMA were found in a patient undergoing evaluation, the total score would be 8, categorized as intermediate (low: < 8; intermediate: 8-12; high: ≥12). The authors recommended placement of a permanent pacemaker for the presence of baseline left bundle branch block. It appeared reasonable to opine that the post-PTSMA risk factors for a complete heart block that can be identified prior to PTSMA would likely not change the decision to perform the procedure with the possible exception of a baseline left bundle branch block. There were no data to show the effect of post-PTSMA pacemaker placement on outcome. However, both subjective (NYHA class) and objective (exercise tolerance) measures of functional capacity showed improvement at 3 months over baseline for the entire combined cohort, thus supporting the Applicant's proposed indication.
- El-Jack (2007): n=50. Pacemaker requirement rate was 18% Baseline left bundle branch block was a predictor of post-PTSMA complete heart block requiring a permanent pacemaker.
- Chang (2003): n=224. Pacemaker requirement rate was 14%.There was improvement in treadmill exercise time from baseline, and that the improvement appeared comparable between the group requiring a pacemaker and the group that did not. The development of a permanent complete heart block requiring pacemaker placement did not appear to compromise patient outcome following PTSMA. Unique to this publication was the finding that a bolus of ethanol was an independent risk factor for complete heart block compared to a gradual injection.

I assessed these findings as being consistent with each other regarding the pacemaker placement rate for post-PTSMA permanent complete heart block (7%-18%) with variations attributable to low sample sizes in retrospective studies. I also assessed these findings as showing clinical improvement both subjectively (NYHA, CCS) and objectively (exercise tolerance). The requirement for a post-PTSMA pacemaker did not appear to adversely affect outcome, and I believe that the risk of a permanent pacemaker requirement should not impact the decision to perform a PTSMA on symptomatic refractory HOCM patients.

Veselka et al (2014, International J Cardiology, 171:e37-e38) investigated the outcome of patients who required permanent pacemaker placement because of peri-PTSMA complete heart block compared to those PTSMA patients who did not require permanent pacemaker placement. Of 167 consecutive patients with symptomatic HOCM who underwent PTSMA, 17 sustained a complete heart block requiring pacemaker implantation. Follow-up time was 4.0 years (interquartile range 2.5-8.3 years) for patients who were given a pacemaker, and 4.8 years (interquartile range 2.1-7.2 years). Neither the ethanol dose nor the number of septal arteries injected was specified. Baseline characteristics are shown in Table 63. There were no differences between the patient cohort that ultimately required a pacemaker and the cohort that did not require a pacemaker. Patient characteristics at follow-up are shown in Table 64. The data showed no differences between the patient cohort that ultimately required a pacemaker and the cohort that did not require a pacemaker. Each group showed empirically similar reductions in LVOT-PG as well as symptomatic improvements in NYHA and CCS class. Survival curves (i.e. free from all-cause mortality) for both paced and non-paced cohorts are shown in Figure 34. There were no significant differences in survival between the cohorts.

Table 63. Baseline Patient characteristics (Veselka, 2014 Int. J. Cardiol)

	Baseline non-paced pts.	Baseline paced pts.	P value
Age, years	59 ± 12	59 ± 11	0.97
Women, %	52	65	0.44
Dyspnea, NYHA class	2.9 ± 0.4	2.9 ± 0.3	0.89
Angina, CCS class	1.8 ± 1.1	2.3 ± 0.9	0.09
Episodes of syncope, %	13	12	1.00
Left ventricular outflow gradient, mm Hg	69 ± 43	62 ± 39	0.46
Left ventricular diameter, mm	42 ± 5	43 ± 6	0.48
Left ventricular ejection fraction, %	77 ± 9	73 ± 10	0.17
Basal septal thickness, mm	21 ± 4	20 ± 2	0.26
Left atrium diameter, mm	47 ± 6	47 ± 4	0.54

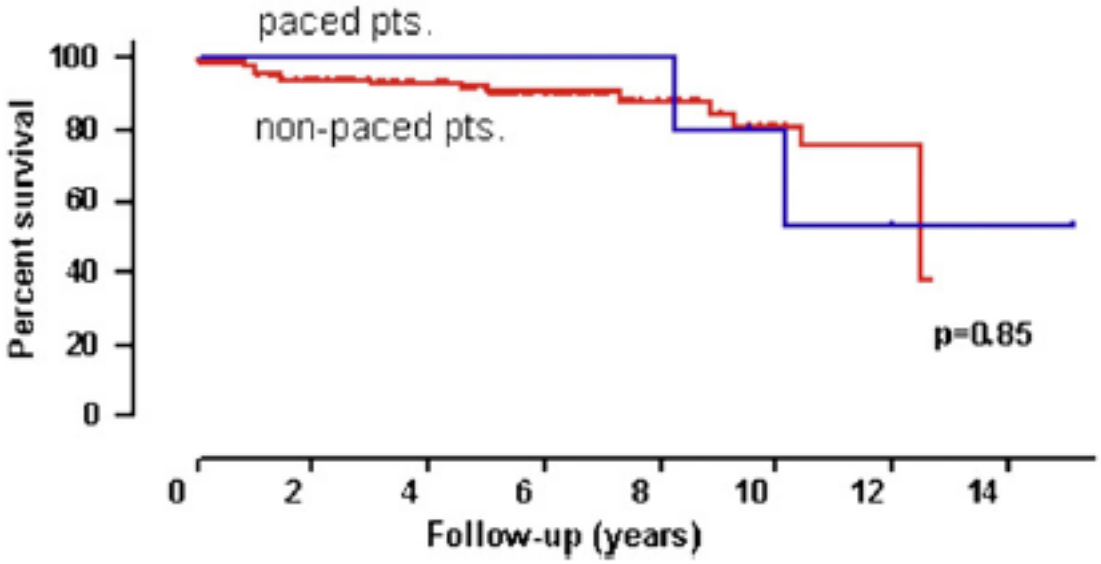
Source: Veselka et al, 2014 (International J Cardiology, 171:e37-e38)

Table 64. Patient Characteristics at Follow-up (Veselka, 2014 Int. J. Cardiol)

	Follow-up non-paced pts.	Follow-up paced pts.	P value
Age, years	64 ± 12	65 ± 11	0.84
Dyspnea, NYHA class	1.7 ± 0.8	1.6 ± 0.8	0.60
Angina, CCS class	0.5 ± 0.7	0.5 ± 0.5	0.95
Episodes of syncope, %	3	12	0.15
Left ventricular outflow gradient, mm Hg	21 ± 26	15 ± 13	0.31
Left ventricular diameter, mm	47 ± 5	48 ± 5	0.08
Left ventricular ejection fraction, %	73 ± 10	71 ± 13	0.74
Basal septal thickness, mm	14 ± 4	13 ± 3	0.41
Left atrium diameter, mm	48 ± 6	48 ± 4	0.75

Source: Veselka et al, 2014 (International J Cardiology, 171:e37-e38)

Figure 34. Survival Curve (paced vs non-paced) (Veselka, 2014 Int. J. Cardiol)



Source: (Veselka, 2014 Int. J. Cardiol)

Reviewer Comment (Veselka 2014, Int. J. Cardiol): This study showed a pacemaker requirement incidence of approximately 10% that is consistent with the remainder of the data observed thus far in this NDA review. The data in this study suggested that patients who experienced a peri-PTSMA complete heart block and required a permanent pacemaker had similar results compared to those PTSMA patients who did not require a permanent pacemaker. There was no report of heart blocks that did not require a permanent pacemaker.

Faber et al (2007) developed a scoring system in 1996-1998 to predict the risk of permanent atrio-ventricular block following PTSMA. This scoring system, shown in Table 65, was used to assess 155 consecutive HOCM patients between1999-2004. Follow-up time was 3 months. The average ethanol dose was 2.1 mL injected into 1 septal artery (2.1 mL/artery). Key risk factors included baseline PQ interval, baseline minimal heart rate, baseline LVOT-PG, presence of 3rd degree AV block at any time, no recovery after 12-48 hours, maximum QRS width during the 1st 48 hours post-PTSMA, and timing of peak enzyme GOT (U/L). The distribution of patients and pacemaker implantations in the different risk groups is shown in Figure 35. Three sets of bars respectively represented low risk, intermediate risk, and high risk scores for permanent heart block. A total of 116 patients were scored in the low risk category and none of these patients required a permanent pacemaker. A total of 31 patients were categorized as intermediate risk of which 4 (13%) received a permanent pacemaker. A total of 8 patients were deemed high risk, of which 7 (87.5%) received a permanent pacemaker. Of the total cohort of 155 patients, 11 (7.1%) received a permanent pacemaker. The authors also noted that a new right bundle branch block was the most frequent ECG finding after PTSMA. However, of the 11 recipients of a permanent pacemaker, 4 had a

baseline left bundle branch block. The authors suggested that candidates for PTSMA with a baseline left bundle branch block should undergo dual chamber pacemaker implantation. Clinical, echocardiographic, and hemodynamic results of PTSMA in the total cohort of 155 patients are shown in Table 66. The data showed both significant subjective (NYHA, CCS) and objective (exercise tolerance) improvement at 3 months from baseline in concert with significant decreases in both resting and provoked LVOT-PG at 3 months from baseline. The authors documented a mean peak total CK release of 466 U/L and a mean peak CK-MB release of 53 U/L.

Table 65. Post-PTSMA Risk Factors for Pacemaker Dependency (Faber, 2007)

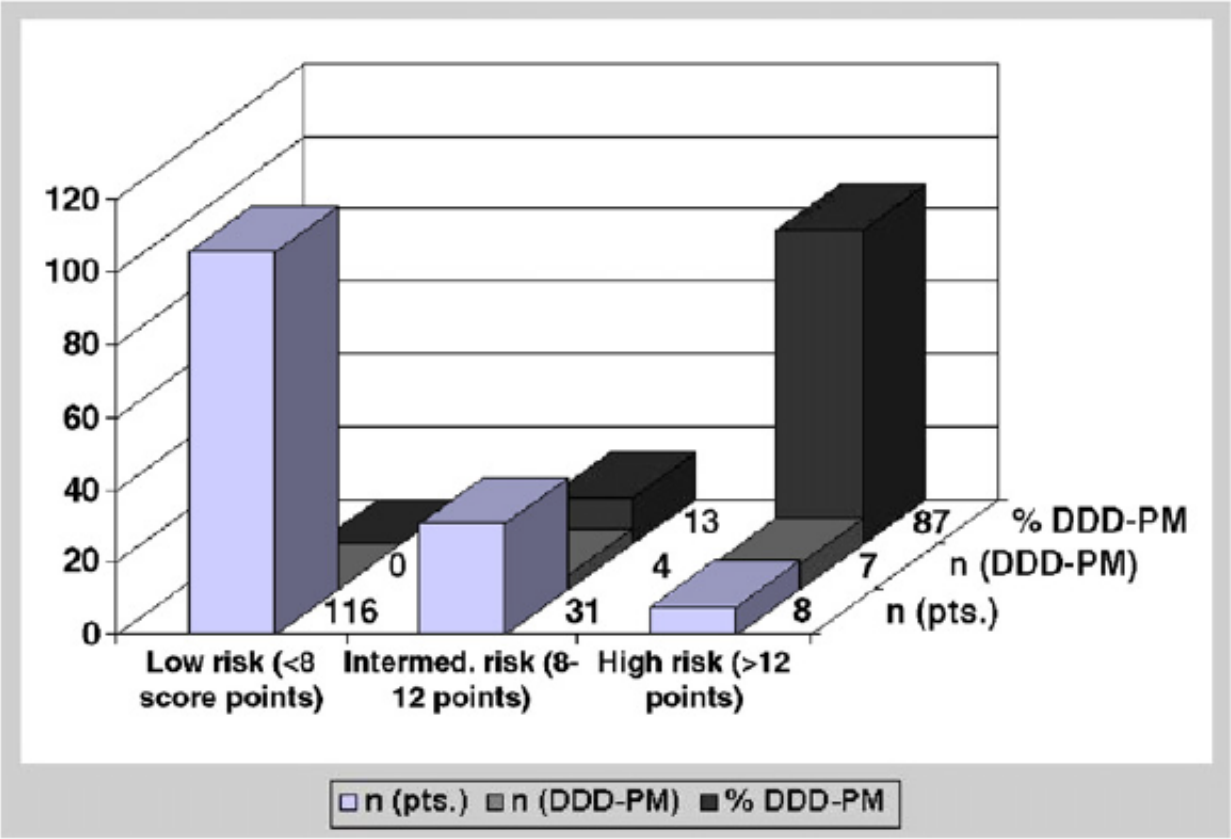
Score-system to predict the risk of pacemaker dependency after percutaneous septal ablation

#	Parameter	Cutoff value	Score points
1	Baseline PQ interval (ms)	>160	+2
2	Baseline minimal heart rate (Holter, 1/min)	<50	+2
3	Baseline LVOT gradient (Echo, mm Hg)	>70	+2
4	AV block III during PTSMA (any time)	Yes	+2
5	AV block III at CCU admission	Yes	+2
6	Recovery of AV conduction at 12 h	Yes	−2
7	No recovery after 12 h	Yes	+1
8	No recovery after 24 h	Yes	+2
9	No recovery after 48 h	Yes	+3
10	Maximum QRS width during the first 48 h (ms)	>155	+3
11	Timing of GOT peak (h)	>16	+1
		>20	+3

Risk group	Score points	Procedure
Low	<8	Discharge from monitoring
Intermediate	8–12	Prolonged monitoring
High	>12	Prepare for early PM implantation

Source: Faber et al, 2007

Figure 35. Heart Block Risk- Pacemaker Placement profile (Faber, 2007)



Source: Faber et al, 2007

Table 66. Baseline and Follow-up Characteristics (Faber, 2007)

Clinical, echocardiographic, and hemodynamic result of PTSMA in 155 patients

	Baseline	3 months	*p* value
NYHA class	2.8±0.4	1.6±0.6	<0.0001
Pts. in class III and IV	128 (83%)	12 (8%)	<0.0001
Exercise tolerance (watts)	94±46	119±44	<0.01
LA Diameter (mm)	49±6	46±6	<0.001
Septum thickness (mm)	20±4	16±4	<0.001
LVOT gradient (rest, mm Hg)	58±29	11±19	<0.0001
LVOT gradient (stress, mm Hg)	113±27	38±38	<0.0001

Source: Faber et al, 2007

Reviewer Comment (Faber 2007): I believe this study supported the Applicant's proposed indication because of the clinical data showing significant improvement of exercise tolerance (94 ± 46 watts at baseline → 119 ± 44 watts at 3 months) in alignment with subjective clinical and hemodynamic improvement. The overall pacemaker placement rate of 7% was generally consistent with the results of other studies. I believe that pre-PTSMA identification of risk for complete heart block will not change the decision to perform the procedure because all baseline risk factors added up to 8, placing the maximum pre-PTSMA risk estimation at the boundary between low and intermediate (8-12). The risk factors for a post-PTSMA complete heart block have mostly been identified during or after the procedure. The authors recommended placement of a permanent pacemaker for the presence of baseline left bundle branch block. Although this publication submitted by the Applicant focused on risk for permanent pacemaker placement, its importance was additionally derived from the data showing improvement of exercise tolerance after PTSMA although there was no data evaluating the relationship between pacemaker requirement and outcome. I believe that the risk of a permanent pacemaker should not attenuate performing a PTSMA.

El-Jack et al (2007) investigated the predictors of complete heart block after PTSMA for HOCM in 50 patients. An average total ethanol dose of 4.4 ± 1.5 mL was injected into 1 septal artery in 33 patients (66%), and into 2 septal arteries in 17 patients (34%). The weighted average dose per septal artery was 3.7 mL/artery. The authors did not provide specific doses of ethanol. Among 50 patients studied, 9 required a permanent pacemaker (18%). The authors found that a right bundle branch block was the most common new ECG after PTSMA, and that baseline left bundle branch block was strongly associated with the development of persistent complete heart block. The

authors suggested that patients undergoing PTSMA for HOCM with a baseline left bundle branch block would probably be most effectively treated by early pacemaker implantation if the complete heart block persists beyond the first 24 hours.

Reviewer Comment (El-Jack 2007): The findings here corroborated those findings from Faber et al (2007) regarding left bundle branch block as a predictor of complete heart block.

Chang et al (2003) performed a retrospective study to examine the incidence and determinants of permanent complete heart block after PTSMA, and to evaluate the clinical impact of permanent pacemaker placement. The database included 261 consecutive patients at Baylor College of Medicine who underwent PTSMA for refractory symptomatic HOCM. The average ethanol dose was 2.9 mL injected into 1.2 septal arteries (2.4 mL/artery). Of these patients, 37 had pre-PTSMA pacemaker placement. Of the remaining 224 patients, 31 (14%) developed complete heart block after the procedure. The authors concluded from a multivariate logistic regression analysis that female gender, bolus injection of ethanol (i.e. compared to gradual injection), injecting more than 1 septal artery, presence of baseline left bundle branch block, and presence of baseline first degree AV block were independent predictors of complete heart block following PTSMA. The baseline characteristics for those 31 patients who required a pacemaker due to complete heart block, vs those 193 patients, who did not require a permanent pacemaker, are shown in Table 67. There were no differences between the two groups in baseline LVOT-PG, NYHA class, and treadmill exercise time. The mean peak total CK level was reported to be 1335 U/L. There were no differences in the volume of ethanol use, but there was a significant difference in bolus administration, compared to a slow infusion over 30 to 60 seconds, in the group that required a permanent pacemaker. The authors claimed that bolus injection of ethanol, in addition to injecting more than one septal artery, the presence of a left bundle branch block on baseline ECG, and 1st degree AV block on baseline ECG, are independent predictors of complete heart block after PTSMA. Comparison of clinical and echocardiographic outcome of patients who required a permanent pacemaker, compared to those who did not, are shown in Table 68. Improvements in NYHA class and exercise time, in alignment with reductions in LVOT-PG, appeared comparable between the group requiring and the group not requiring a permanent pacemaker.

Table 67. Baseline Characteristics: paced vs non-paced (Chang, 2003)

	PPM (n = 31)	No PPM (n = 193)	p Value
Age (yrs)	58 ± 14	52 ± 16	0.06
Female gender (%)	19 (59%)	81 (42%)	0.045
No MCE (%)	3 (10%)	3 (1.5%)	0.001
Bolus injection (%)	7 (23%)	5 (3%)	<0.001
≥2 septals (%)	13 (42%)	49 (25%)	0.05
Ethanol (cc)	2.9 ± 1.6	2.9 ± 1.3	NS
LVOTG (mm Hg)	67 ± 40	60 ± 39	0.45
NYHA CHF class	2.85 ± 0.5	2.65 ± 0.6	0.25
IVS (cm)	2.06 ± 0.43	2.04 ± 0.5	0.80
EF %	74 ± 7	73 ± 6	0.87
Treadmill exercise time (s)	278 ± 197	296 ± 202	0.55

CHF = congestive heart failure; IVS = interventricular septal thickness (cm); LVOTG = left ventricular outflow tract gradient (mm Hg); MCE = myocardial contrast echocardiography; NS = non significant; NSRT = nonsurgical septal reduction therapy; NYHA = New York Heart Association; PPM = permanent pacemaker.

Source: Chang et al, 2003

Table 68. Outcome Data: paced vs non-paced (Chang, 2003)

	PPM n = 31	No PPM n = 193	p Value
NYHA class improvement	1.76 ± 0.63	1.47 ± 0.74	0.09
IVS reduction	0.82 ± 0.67	0.56 ± 0.54	0.063
% IVS reduction	37 ± 20	27 ± 26	0.003
Rest LVOTG reduction	56 ± 42	40 ± 37	0.07
Increase in exercise duration(s)	68 ± 149	102 ± 138	0.35

IVS = interventricular septal thickness; LVOTG = left ventricular outflow tract gradient (mm Hg); NYHA = New York Heart Association. Other abbreviations as in Tables 2 and 3.

Source: Chang et al, 2003

Reviewer Comment (Chang 2003): The most important finding in this publication was the improvement in treadmill exercise time from baseline, and that the improvement appeared comparable between the group requiring a pacemaker and the group that did

not. I agreed with the authors' conclusion that the development of a complete heart block did not appear to compromise patient outcome following PTSMA. I also agreed with the authors' acknowledgement of this study's liabilities that included its retrospective nature, non-evaluation of the impact of septal artery anatomy on outcome, and modest sample size. I did not understand the mechanism by which a bolus of ethanol, compared to a slow injection, was found to be an independent risk factor for a complete heart block requiring a permanent pacemaker. I have found no other corroborative data suggesting the mode of ethanol administration (i.e. bolus vs gradual injection) as a determinant of outcome.

5.3.8 Retrospective Studies: Effect of Age

Executive Summary and Reviewer Overall Assessment of Retrospective Studies Describing the Effect of Age

The Applicant submitted 4 retrospective studies that examined the effect of age on outcome of PTSMA for HOCM. The salient findings from these studies were:

- Veselka (2014, Canadian J Cardiol., 30: 634-638): PTSMA improved subjective functional capacity in the young population (age ≤ 50 years; n=75). The mortality rate was worse than that of the general population. There was no comparative mortality data in this population who have undergone SM. The pacemaker placement rate was 6.7% (similar to the rate in other retrospective studies). Significant improvements in NYHA and CCS classifications were noted.
- Leonardi (2013): PTSMA caused symptomatic improvement from baseline that was similar amongst three age groups (< 45 years, n=110; 45-64 years, n=159; ≥ 65 years, n=120). The complication rate was significantly higher in the elderly cohort.
- Veselka (2006, Circ. J, 70: 880-884): PTSMA was evaluated in three age groups: Group A (n=14; ages 24-48 years), Group B (n=14; ages 49-60 years), and Group C (n=16; ages 61-81 years). Left ventricular septal thickness, at baseline and over the course of follow-up time, was more pronounced in the younger population, and earlier reduction of LVOT-PG was observed in the elderly group. In the lumped patient population, symptomatic improvement and reduction in LVOT-PG was observed but there was no clinical data for individual age groups.
- Gietzen (2004): PTSMA was evaluated in two age groups (< 60 years, average age 44 years, n=80; ≥ 60 years, average age 69 years, n= 77). The data suggested that the older group had worse symptoms and lower exercise capacity than the younger group. PTSMA outcome for symptomatic and objective functional improvement were similar for both age groups and respectively significant from baseline. However, the older age group had a higher complication rate, particularly complete heart block and pacemaker placement.

My overall assessment is that the retrospective studies evaluating age suggested symptomatic improvement and LVOT-PG reduction regardless of age with evidence

from one study showing increased exercise capacity regardless of age. However, there were safety signals that caught my attention that would warrant a description in the label:

- Higher mortality rate compared to the general population in the ≤ 50 years age group that might have been ameliorated by offering SM.
- An expectedly higher complication rate in the elderly (≥ 65 years).

Veselka et al (2014, Canadian J Cardiol., 30: 634-638) evaluated the long-term of patients ≤ 50 years of age after PTSMA for refractory symptomatic HOCM. The purpose of this study was to address ongoing debate about the outcome of younger patients who should be treated with SM according to ACC/AHA guidelines. A total of 290 consecutive patients with HOCM who underwent PTSMA retrospectively were identified at 3 cardiovascular centers, of which 75 patients ≤ 50 years of age. Median duration of follow-up was 5.1 years (range 0.1-15.4 years). The average total ethanol dose was 1.8 mL but the average number of septal arteries injected was not specified. Outcome data is shown in Table 69. The mean age at baseline was 42 years. Significant improvements in NYHA and CCS classifications were noted. The CK-MB peak was 2.6 ± 1.4 uKat/L (upper limit of normal for CK-MB was 0.42 uKat/L). Procedure-related complications are shown in Table 70. The incidence of complete heart block was 8.0% and the incidence of permanent pacemaker placement was 6.7%. The Kaplan-Meier survival curve for all-cause mortality, including the 95% confidence interval and juxtaposed with the all-cause mortality curve expected in the general sex- and age-matched population is shown in Figure 36. The observed all-cause mortality was significantly worse than the expected survival for the general sex- and age-matched population. Long-term survival free of all-cause mortality was approximately 95%, compared to approximately 98% for the general sex- and age-matched population. A similar Kaplan-Meier curve combining all-cause mortality with the first appropriate implanted cardiac defibrillator showed similar results: significantly worse outcome compared to the general sex- and age-matched population. The authors concluded that the younger population undergoing PTSMA for refractory symptomatic HOCM had a low risk of all-cause death or appropriate implantable cardioverter-defibrillator discharge in the long-term follow-up.

Table 69. Outcome: Baseline and Follow-up (Veselka 2014, Canadian J Cardiol.)

Variable	Baseline	Follow-up	*P*
Age (range), years	42 ± 7 (24-50)	48 ± 8 (29-65)	<0.01
Dyspnea, NYHA class	2.8 ± 0.5	1.6 ± 0.7	<0.01
Dyspnea, NYHA class I-II, %	19	89	<0.01
Angina, CCS class	1.7 ± 1.3	0.3 ± 0.6	<0.01
Episodes of syncope, %	25	7	<0.01
Left ventricular outflow gradient, mm Hg	73 ± 38	16 ± 14	<0.01
Left ventricular end-diastolic diameter, mm	43 ± 6	47 ± 6	<0.01
Left ventricular ejection fraction, %	75 ± 9	70 ± 8	<0.01
Basal septal thickness, mm	23 ± 6	14 ± 5	<0.01
Patients with pacemaker, %	11	20	0.11

Data are mean ± SD, except where otherwise noted.

CCS, Canadian Cardiovascular Society; NYHA, New York Heart Association; SD, standard deviation.

Source: Veselka et al, 2014 (Canadian J Cardiol., 30: 634-638)

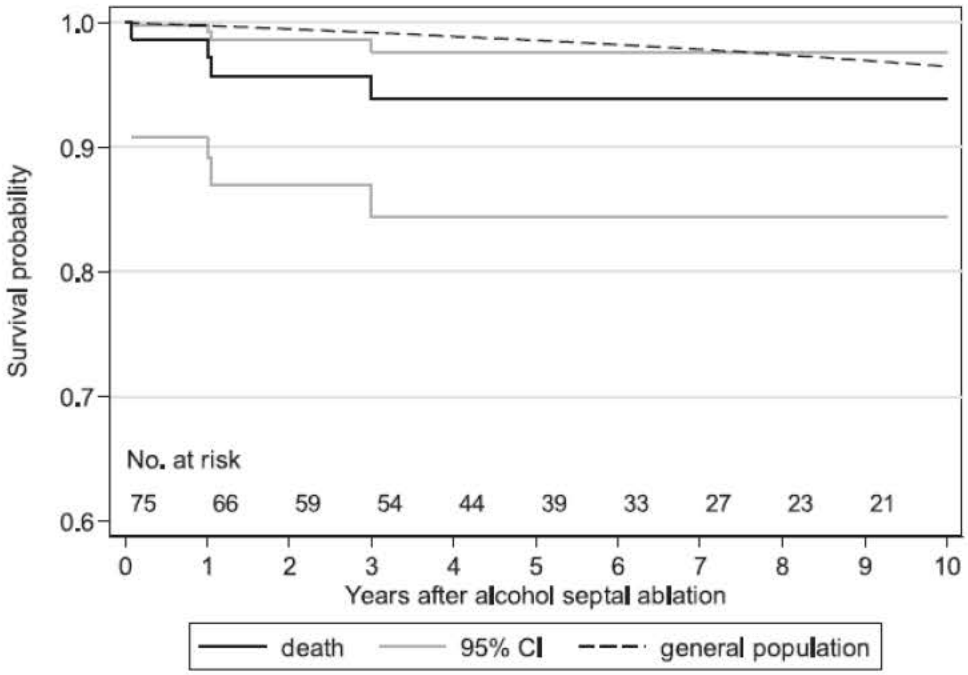
Table 70. Procedure-related Complications (Veselka 2014, Canadian J Cardiol.)

Complication	Value, %
Complete heart block	8.0
Transient AV block II	2.7
Pacemaker implantation for complete heart block	6.7
Post-interventional sustained ventricular tachycardia/ fibrillation requiring defibrillation	2.7

AV, atrioventricular.

Source: Veselka et al, 2014 (Canadian J Cardiol., 30: 634-638)

Figure 36. Kaplan-Meier Survival Curves (Veselka 2014, Canadian J Cardiol.)



Source: Veselka et al, 2014 (Canadian J Cardiol., 30: 634-638)

Reviewer Comment (Veselka 2014- Can. J. Cardiol.): The results of this retrospective study were similar to the retrospective studies thus far reviewed: there appeared to be a significant improvement in subjective functional capacity (NYHA and CCS). The incidence of pacemaker requirement was within the range empirically observed in other retrospective studies. The original question driving this study was the use of PTSMA in a younger patient population who would otherwise qualify for SM. This study did not provide comparative results between PTSMA and SM in this population and I therefore could not render an adequate assessment pursuant to the authors' stated objective. Mortality was observed to be considerably worse than that of the general population. I cannot rule out that if these patients were given a SM, the mortality rate might have been better and therefore more aligned with the general population.

Leonardi et al (2013) prospectively collected and retrospectively analyzed data on 360 consecutive patients undergoing 389 PTSMA procedures according to age: young (< 45 years), middle aged (45-64 years), and elderly (≥ 65 years). The mean ethanol dose was 2.3 mL into 1.1 septal arteries (2.1 mL/artery). Baseline characteristics of the three age groups are shown in Table 71. There was some variability amongst the three age groups. The prevalence of hypertension, coronary artery disease, atrial fibrillation, and other comorbidities appeared to increase with age. The mean NYHA functional class and CCS class appeared numerically similar in all three age groups but were considered to be statistically significantly different between the young and elderly, and

middle-aged and elderly groups. Resting LVOT-PG by echocardiography at baseline, immediately after PTSMA, at 3 months, and at 12 months post-PTSMA for the 3 age groups are shown in Figure 37. The authors reported that data were available for 98%, 69%, 78% and 47% of the procedures at baseline, immediately after, 3 months after, and 12 months after PTSMA, respectively. Compared to baseline, there appeared to be a significant reduction in LVOT-PG from baseline that was sustained for up to 12 months for all 3 age groups. The mean peak total CK release was reported to be 1221 U/L for the young group, 1123 U/L for the middle-aged group, and 1183 U/L for the elderly group. Similarly, there were NYHA symptom improvements from baseline at 3 and 12 months post-PTSMA for all age groups, as shown in Figure 38. Mortality data for all age groups are shown in Figure 39. In-hospital death occurred in 1 young patient (left main coronary dissection), 1 middle-aged patient (end-stage interstitial lung disease for whom PTSMA was palliative), and 4 elderly patients (retroperitoneal bleed, right ventricular perforation, iatrogenic ventricular septal defect, and anterior MI). Post-discharge mortality through 12 months occurred in 3 young patients (all sudden cardiac death), 3 middle-aged patients (sudden cardiac death, post-PTSMA liver transplant complication, and post-PTSMA SM), and 7 elderly patients (post-PTSMA SM, 6 unknown causes). The mortality rates were not significantly different amongst the three age groups. Procedural complications are shown in Table 72. The complication rate for any complication was significantly higher in the elderly group compared to the other groups. The rate of complete heart block requiring a permanent pacemaker was 8.2%, 5.0%, and 12.5% for the young, middle-aged, and elderly cohorts, respectively. The authors concluded that patients undergoing PTSMA had significant and similar improvements in LVOT-PG and symptoms regardless of age, but with complication rates increased in the elderly cohort.

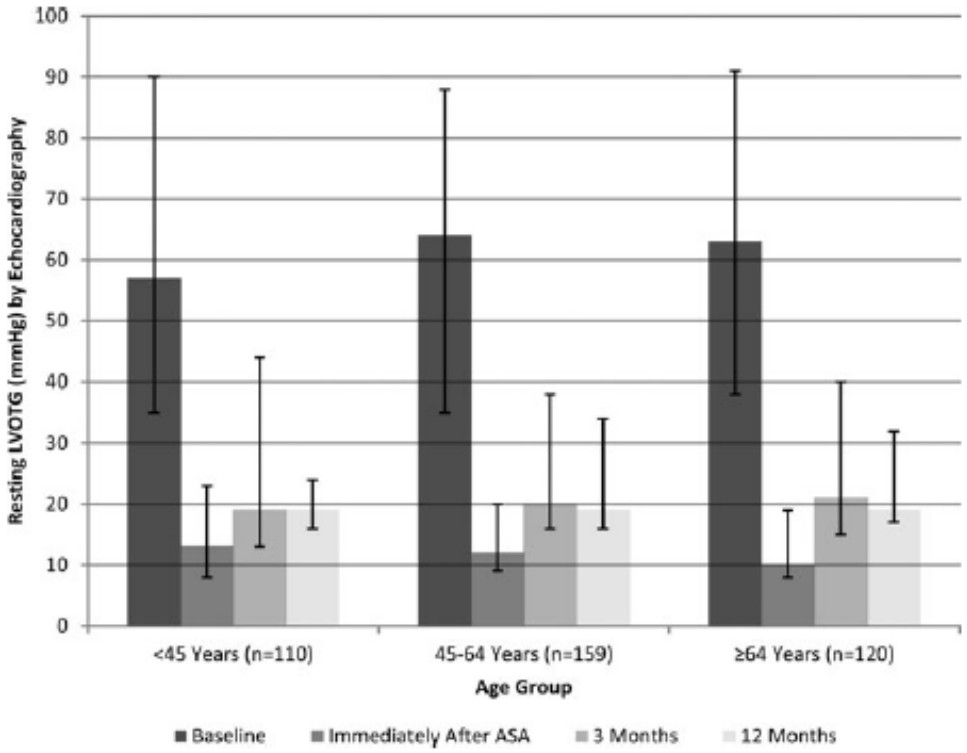
Table 71. Baseline Characteristics (Leonardi, 2013)

	Age (years)			*P* value		
Characteristic	<45 (n = 101)	45–64 (n = 145)	≥65 (n = 114)	<45 vs. 45–64	<45 vs. ≥65	45–64 vs. ≥65
Female sex	46 (45.5)	69 (47.6)	78 (68.4)	0.752	<0.001	<0.001
Hypertension	17 (16.8)	55 (37.9)	72 (63.2)	<0.001	<0.001	<0.001
Diabetes	2 (2.0)	17 (11.7)	14 (12.3)	0.005	0.004	0.891
CAD	3 (3.0)	9 (6.2)	33 (28.9)	0.246	<0.001	<0.001
Chronic kidney disease	2 (2.0)	5 (3.4)	4 (3.5)	0.496	0.497	0.979
Peripheral arterial disease	2 (2.0)	5 (3.4)	8 (7.0)	0.496	0.080	0.192
Atrial fibrillation	6 (5.9)	15 (10.3)	23 (20.2)	0.224	0.002	0.026
Other major comorbidities	8 (7.9)	17 (11.7)	24 (21.1)	0.331	0.007	0.041
Prior sternotomy	4 (4.0)	2 (1.4)	8 (7.0)	0.192	0.338	0.059
Prior surgical myectomy	3 (3.0)	1 (0.7)	1 (0.9)	0.308	0.344	1.000
Prior ASA	1 (1.0)	8 (5.5)	4 (3.5)	0.062	0.221	0.438
Pre-existing ICD	16 (15.8)	9 (6.2)	4 (3.5)	0.014	0.002	0.318
Tobacco abuse/dependence	16 (15.8)	7 (4.8)	4 (3.5)	0.004	0.002	0.601
Family history of HCM	47 (46.5)	47 (32.4)	22 (19.3)	0.048	<0.001	0.015
Family history of SCD	34 (33.7)	33 (22.8)	18 (15.8)	0.085	0.002	0.127
Beta receptor blockers	76 (75.2)	104 (71.7)	83 (72.8)	0.762	0.751	0.976
Non-dihydropyridine CCBs	47 (47.5)	54 (37.2)	51 (44.7)	0.192	0.831	0.265
Disopyramide	10 (9.9)	17 (11.7)	10 (8.8)	0.605	0.790	0.498
Amiodarone	3 (3.0)	4 (2.8)	10 (8.8)	0.948	0.073	0.037
ACE inhibitor or ARB	3 (3.0)	32 (22.1)	32 (28.1)	<0.001	<0.001	0.300
Diuretic	18 (17.8)	49 (33.8)	51 (44.7)	0.004	<0.001	0.089
NYHA functional class (mean)	2.8	2.8	3.0	0.921	0.019	0.004
CCS angina class (mean)	2.4	2.3	2.1	0.6356	0.018	0.081

Data are absolute numbers with (percentages) except as indicated. CAD = coronary artery disease. ASA = alcohol septal ablation. ICD = implantable cardioverter-defibrillator. HCM = hypertrophic cardiomyopathy. SCD = sudden cardiac death. CCBs = calcium channel blockers. ACE = angiotensin converting enzyme inhibitor. ARB = angiotensin receptor blocker. NYHA = New York Heart Association. CCS = Canadian Cardiovascular Society.

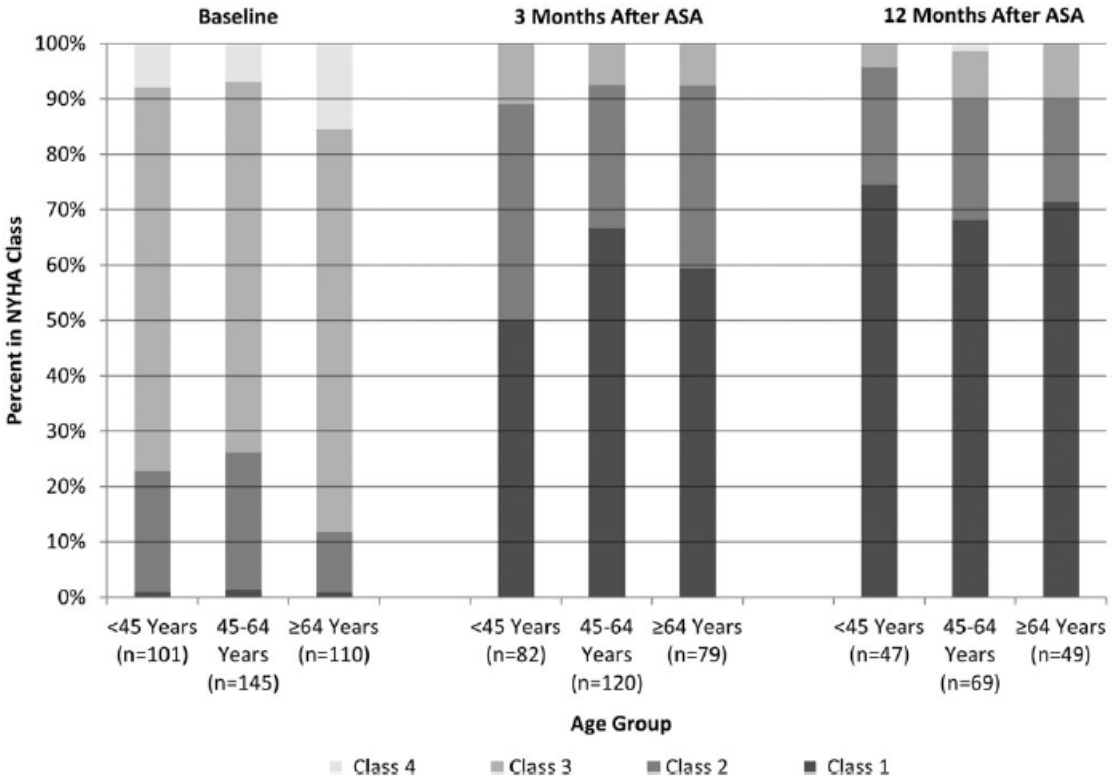
Source: Leonardi et al, 2013

Figure 37. Resting LVOT-PG by Echocardiography: age/outcome (Leonardi, 2013)



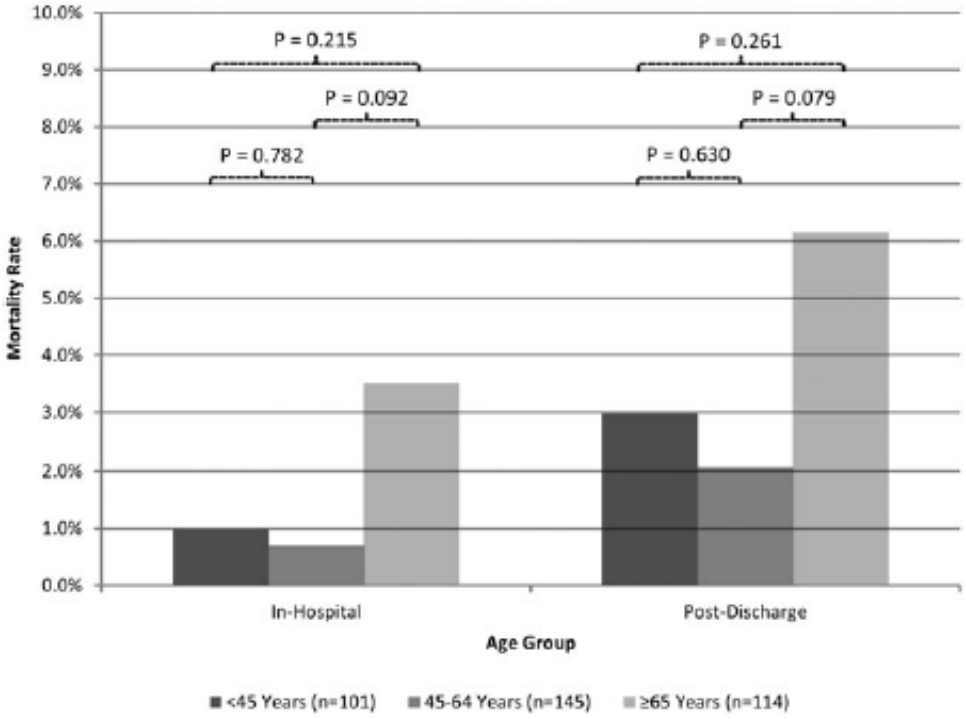
Source: Leonardi et al, 2013

Figure 38. NYHA Class: age/outcome (Leonardi, 2013)



Source: Leonardi et al, 2013

Figure 39. Mortality Rate (per 100 pts) by age group (Leonardi, 2013)



Source: Leonardi et al, 2013

Table 72. Procedural Complications by Age Group (Leonardi, 2013)

	Age (years)			*P* value		
Complication	<45 (n = 110)	45–64 (n = 159)	≥65 (n = 120)	<45 vs. 45–64	<45 vs. ≥65	45–64 vs. ≥65
Alcohol-related Anterior MI	0 (0.0)	0 (0.0)	3 (2.5)	1.000	0.248	0.078
Heart block requiring PPM	9 (8.2)	8 (5.0)	15 (12.5)	0.446	0.271	0.029
VT/F requiring treatment	2 (1.8)	1 (0.6)	0 (0.0)	0.569	0.228	1.000
LMCA or LADCA dissection	1 (0.9)	0 (0.0)	1 (0.8)	0.409	1.000	0.430
Access site bleeding	0 (0.0)	0 (0.0)	5 (4.2)	1.000	0.061	0.014
Acute mitral regurgitation	0 (0.0)	0 (0.0)	1 (0.8)	1.000	1.000	0.430
Procedure-related VSD	0 (0.0)	0 (0.0)	1 (0.8)	1.000	1.000	0.430
Right ventricular perforation	0 (0.0)	1 (0.6)	1 (0.8)	1.000	1.000	1.000
Any complication	10 (9.1)	10 (6.3)	25 (20.8)	0.480	0.016	<0.001

Data are absolute numbers with (percentages). Abbreviations as in Table I. MI = myocardial infarction. PPM = permanent pacemaker. VT/F = ventricular tachycardia/fibrillation. LMCA = left main coronary artery. LADCA = left anterior descending coronary artery. VSD = ventricular septal defect.

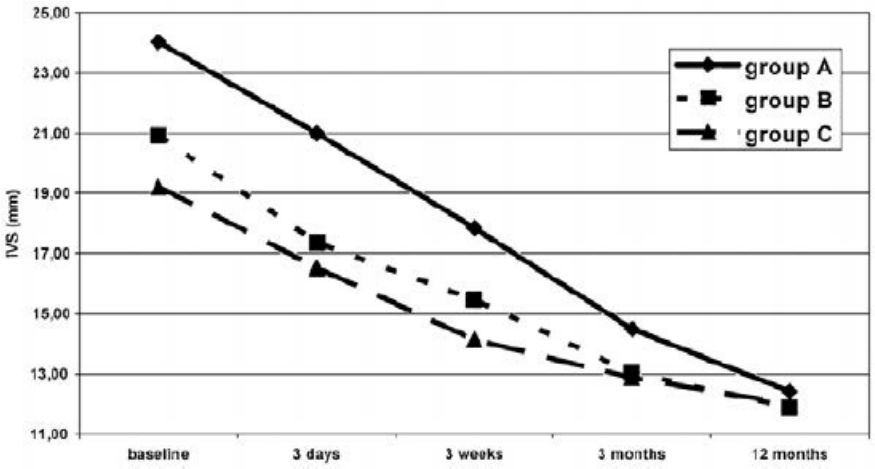
Source: Leonardi et al, 2013

Reviewer Comment (Leonardi 2013): The Applicant misquoted the publication year. Publication date was 2013 rather than 2012. I agree with the authors' assessment that PTSMA caused similar symptomatic improvement regardless of age, but the complication rate was significantly higher in the elderly cohort. This should be described

in the label. I recognize that this study was observational and retrospective, and conducted at a single center. Consequently, the data interpretation was constrained by study limitations: limited completeness of non-mortality follow-up, follow-up outcome frequently performed at other institutions, clinical events adjudicated by the same physicians who performed the procedure.

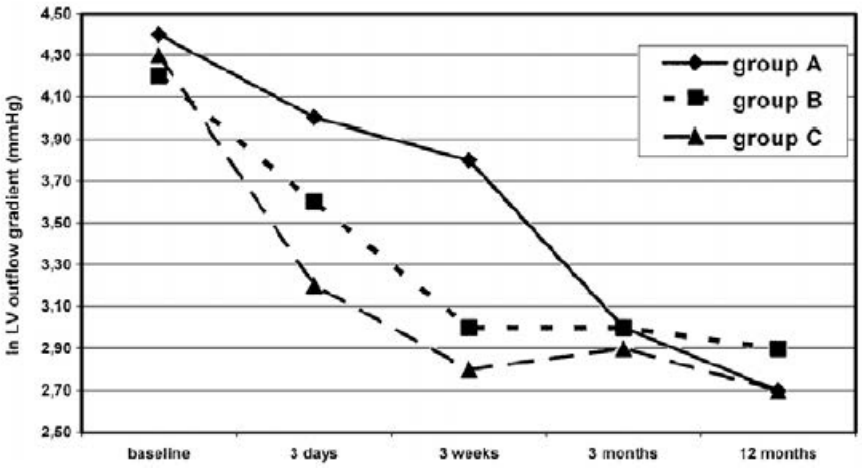
Veselka et al (2006, Circ J, 70: 880-884) retrospectively evaluated age-related hemodynamic and morphologic differences in patients undergoing PTSMA for HOCM in 44 consecutive patients (ages 24-81 years). The 44 patients were subdivided into three age categories: Group A (n=14; ages 24-48 years), Group B (n=14; ages 49-60 years), and Group C (n=16; ages 61-81 years). The average total dose of ethanol was 2.3 mL in Group A, 2.2 mL in Group B, and 2.4 mL in Group C, respectively. The average number of septal arteries was not specified. Interventricular septal thickness for the three age groups at baseline and points in time following PTSMA is shown in Figure 40. The data indicated that younger people (Group A) had greater septal thickness both at baseline and during the 12 month time course following PTSMA, but with all groups (i.e. A, B, and C) converging at 12 months. Logarithmic transformation of the LVOT-PG in the age-related groups during follow-up is shown in Figure 41. All three groups had similar baseline LVOT-PG. The data indicated that older patients (Group C) had earlier reduction of LVOT-PG, but all groups converged at 12 months. The authors stated that the influence of gender, presence of pacing at baseline, and left ventricular ejection fraction at baseline did not significantly influence LVOT-PG reduction. Outcome data is shown in Table 73. There were significant improvements in symptomatic functional capacity (NYHA and CCS) between baseline and 12-month follow-up for the entire cohort in alignment with reduction of LVOT-PG for the same follow-up period. Clinical outcome data was not presented for individual age groups. The authors stated that the mean peak CK-MB values were 2.99 uKat / L for Group A; 2.27 uKat / L for Group B, and 2.97 uKat / L for Group C, respectively (i.e. no difference between the groups).

Figure 40. Age-related septum thickness (Veselka, 2006, Circ. J, 70:880-884)



Source: Veselka et al, 2006, Circ. J, 70:880-884

Figure 41. Age-related LVOT-PG (Veselka, 2006, Circ. J, 70:880-884)



Source: Veselka et al, 2006, Circ. J, 70:880-884

Table 73. Outcome data (Veselka, 2006, Circ. J, 70:880-884)

	Baseline	12-month follow-up	p value
Age, years	54±13	–	–
DDD pacing, n	9	12	0.62
LV ejection fraction, %	80±7	75±7	0.001
LV diameter, mm	43±8	48±4	<0.001
Basal septal thickness, mm	21±4	12±3	<0.001
Left atrium dimension, mm	45±5	46±6	0.41
LV outflow tract gradient, mmHg median (IQR)	69 (41–97)	11 (8–17)	<0.001
Dyspnea, NYHA class	2.7±0.6	1.5±0.6	<0.001
Angina, CCS class	2.3±0.9	0.9±0.8	<0.001

Data are mean ± SD.
LV, left ventricular; IQR, interquartile range; NTHA, New York Heart Association; CCS, Canadian Cardiovascular Society.

Source: Veselka et al, 2006, Circ. J, 70:880-884

Reviewer Comment (Veselka 2006, Circ. J, 70:880-884): This retrospective data showed symptomatic improvement and reduction in LVOT-PG in patients who underwent PTSMA in a lumped population not separated by age group. Left ventricular septal thickness, at baseline and over the course of follow-up time, was more pronounced in the younger population, and earlier reduction of LVOT-PG was observed in the elderly group. There was no data shown on complications (i.e. complete heart block and permanent pacemaker placement). There was no clinical data for each age group. I agreed with the authors' assessment of study limitations: no prospective data, small sample size, confusion about selection criteria for PTSMA and modification of PTSMA technique due to the age of the patient. I could not assess age-specific subjective or objective clinical efficacy, or safety.

Gietzen et al (2004) evaluated short-term results of PTSMA in elderly patients from the Transcoronary Ablation of Septal Hypertrophy (TASH) registry. A total of 157 consecutive patients who underwent PTSMA from 1995 to 1999 were retrospectively reviewed. The average ethanol dose was 3.2 mL (3.2 mL/artery). The average age [standard deviation] was 56 [16 years]. These patients were divided into 2 groups: Group 1 (n=80; age < 60 years, average age 44 [11]) and Group 2 (n=77; age ≥ 60 years, average age 65 [5]). The mean peak total CK was 596 U/L in Group 1 and 491 U/L in Group 2. In addition to hemodynamic measurements and symptom assessment, exercise right heart catheterization was performed for continuous monitoring of pulmonary artery pressures and cardiac output evaluation by direct Fick method while the patient was on a supine bicycle exercising at an initial workload of 25 W to a maximum capacity stepwise increase by 25 W every three minutes. Baseline characteristics for each age group are shown in Table 74. The older group had worse NYHA symptoms, exercise capacity, and cardiac index at baseline. PTSMA procedural data are shown in Table 75. The incidence of permanent complete heart block was

significantly higher in the older group (17%) compared to the younger group (5%). The incidence of pacemaker implantation was also higher in the older group (34%) compared to the younger group (18%). PTSMA outcome at the median follow-up time of 7 months is shown in Table 76. Between the two age groups, there were similar and significant subjective improvements in NYHA class, LVOT-PG reduction, and exercise workload from baseline.

Table 74. Baseline characteristics stratified by age (Gietzen, 2004)

	Age <60 years	Age ≥60 years	p Value
Number of patients	80	77	
Age (years)	44 (11) (21–59)	69 (5) (61–83)	<0.001
Male sex	49 (61%)	27 (35%)	0.001
FHCM	22 (28%)	15 (19%)	0.237
Hypertension	4 (5%)	7 (9%)	0.315
NYHA functional class	2.7 (0.5)	3.1 (0.4)	<0.001
IV	2	10	
III	55	62	
II	23	5	
Syncope	23 (29%)	25 (32%)	0.613
Pre-implanted DDD pacemaker	7 (9%)	7 (9%)	0.960
IVS thickness (mm)	23 (4) (16–38)	22 (3) (15–34)	0.010
Left heart catheterisation	80	77	
LVOT gradient			
Rest (mm Hg)	52 (37) (0–140)	57 (47) (0–158)	0.815
Post-ES (mm Hg)	144 (44) (40–236)	150 (56) (30–250)	0.413
LVEDP (mm Hg)	20 (6) (8–38)	19 (6) (8–35)	0.292
LVEF	0.72 (0.07) (0.60–0.87)	0.73 (0.07) (0.60–0.90)	0.318
Right heart catheterisation	75	69	
Workload (W)	91 (30) (0–175)	57 (28) (0–125)	<0.001
PAP (mm Hg)	40 (9) (20–59)	43 (10) (20–69)	0.025
$\dot{V}O_2$max (ml/kg/min)	17.4 (4.5) (9.5–28.1)	12.3 (4.6) (3.9–24.3)	<0.001
$\dot{V}O_2$max (% predicted)	52 (12) (28–82)	49 (17) (17–92)	0.363
CI (l/m^2/min)	6.4 (1.3) (3.5–9.8)	5.0 (1.7) (1.6–9.7)	<0.001

*Data are mean (SD) (range) or numbers (%).
CI, cardiac index at maximum workload; FHCM, familial hypertrophic cardiomyopathy; IVS, interventricular septal; LVEDP, left ventricular end diastolic pressure; LVEF, left ventricular ejection fraction; LVOT, left ventricular outflow tract; NYHA, New York Heart Association; PAP, pulmonary artery mean pressure at pretreatment workload; Post-ES, post-extrasystolic gradient; Rest, resting gradient; $\dot{V}O_2$max, oxygen consumption at maximum workload.

Source: Gietzen et al, 2004

Table 75. PTSMA procedural data stratified by age (Gietzen, 2004)

	Age <60 years	Age ≥60 years	p Value
Number of patients	80	77	
Ethanol 96% injected (ml)	3.2 (2.1) (1.0–10.0)	3.2 (2.1) (0.5–11.0)	0.870
Peak CK activity (U/l)	596 (339) (202–2166)	491 (331) (133–1831)	0.051
TASH procedures per patient	1.1 (0.3) (1–2)	1.1 (0.3) (1–2)	0.931
Septal vessels occluded per patient*	1.1 (0.5) (0.5–3.0)	1.1 (0.5) (0.5–3.0)	0.823
Permanent total AV block	4 (5%)	13 (17%)	0.015
PM implantation	14 (18%)	26 (34%)	0.014

Data are mean (SD) (range) or number (%).
*Occlusion of only a small side branch of the septal target vessel was counted as occlusion of 0.5 septal vessels.
AV, atrioventricular; CK, creatine kinase; PM, dual chamber pacemaker.

Source: Gietzen et al, 2004

Table 76. PTSMA outcome at 7 months (Gietzen, 2004)

	Age <60 years				Age ≥60 years				
	Baseline	Follow up	Change	p Value	Baseline	Follow up	Change	p Value	Change in p value
Clinical evaluation	n=77				n=69				
NYHA functional class	2.7 (0.4)	1.3 (0.5)	−1.4 (0.6)	<0.001	3.0 (0.4)	1.7 (0.7)	−1.3 (0.7)	<0.001	0.636
Subjective improvement			91%				94%		0.453
Haemodynamic function at rest	n=70				n=58				
LVOT gradient									
Rest (mm Hg)	51 (37)	15 (16)	−62 (46)%	<0.001	53 (47)	12 (17)	−61 (49)%	<0.001	0.574
Provocation (mm Hg)	144 (44)	49 (44)	−67 (26)%	<0.001	149 (56)	39 (46)	−72 (29)%	<0.001	0.276
LVEDP (mm Hg)	20 (6)	15 (6)	−24 (24)%	<0.001	19 (6)	14 (4)	−23 (32)%	<0.001	0.852
LVEF	0.71 (0.07)	0.73 (0.07)	3 (12)%	0.263	0.72 (0.08)	0.67 (0.09)	−6 (11)%	0.002	0.001
IVS thickness (mm)	23 (4)	12 (4)	−46 (20)%	<0.001	22 (3)	12 (3)	−41 (18)%	<0.001	0.170
Right heart catheterisation	n=67				n=48				
Workload (W)	93 (30)	112 (32)	23 (31)%	<0.001	60 (30)	75 (28)	33 (48)%	<0.001	0.863
PAP (mm Hg)	41 (8)	33 (9)	−18 (19)%	<0.001	43 (10)	−38 (9)	−9 (27)%	<0.001	0.060
$\dot{V}O_2$max (ml/kg/min)	17.7 (4.6)	19.8 (5.7)	13 (27)%	0.002	12.6 (4.3)	14.1 (3.9)	19 (36)%	0.022	0.434
$\dot{V}O_2$max (% predicted)	53 (13)	59 (16)	13 (27)%	0.004	50 (17)	56 (15)	19 (36)%	0.024	0.434
CI (l /m^2/min)	6.5 (1.3)	7.1 (2.0)	12 (30)%	0.009	5.2 (1.7)	5.3 (1.2)	10 (36)%	0.627	0.822

Data are mean (SD).
Change in p value compares the change in patients <60 years of age versus the change in patients ≥60 years of age.

Source: Gietzen et al, 2004

Reviewer Comment (Gietzen 2004): The data suggested that the older group had worse symptoms and lower exercise capacity than the younger group. PTSMA outcome for symptomatic and objective functional improvement were similar for both age groups and respectively significant from baseline. However, the older age group had a higher complication rate, particularly complete heart block and pacemaker placement. I could not assess whether the pacemakers were permanent because there were respectively lower incidences of permanent complete heart block in each group. I suspect that a majority of the pacemakers were transient. The publication did not address this.

(b) (4)

5.3.9 Retrospective Studies: Myectomy after Unsuccessful Septal Ablation

Executive Summary and Reviewer Overall Assessment of Retrospective Studies Describing Myectomy after Unsuccessful Ablation

This section of the NDA review was populated by only 1 study (Nagueh et al, 2007). As described immediately below, the study showed that SM can be successfully performed after failed PTSMA, defined as post-PTSMA symptoms of dyspnea and angina along with dynamic obstruction despite adequate medical therapy. The reasons for PTSMA failure focused on anatomic distribution of the septal perforators relative to target areas on the septum, resulting in incomplete necrosis and residual LVOT-PG. This study inferred that SM was still the gold standard for septal reduction therapy.

Nagueh et al (2007) sought to determine the outcome of SM after unsuccessful PTSMA. The medical records of 375 patients who underwent PTSMA at the Methodist Hospital in Houston were reviewed. Twenty patients (5.3%, mean age 53 years $\pm$ 18 years) subsequently needed SM. The characteristics of these patients are shown in Table 77. Of these 20 PTSMA patients who ultimately had SM for failed PTSMA, 9 had a repeat PTSMA prior to ultimately proceeding to SM. There was an average of 1.4 septal arteries that were injected in all PTSMAs with an average volume of 2.9 mL ethanol in the original PTSMA (2.1 mL/artery) and 2.3 mL ethanol in those 9 patients who had a repeat PTSMA. The mean peak CK was 1,199 U/L for the index PTSMA and 736 U/L in those patients undergoing a second PTSMA. There were significant reductions in LVOT-PG following both the 1st and 2nd PTSMA. The mean duration of time between the original PTSMA and the 2nd PTSMA was 14 months. The mean duration of time after any PTSMA (1st or 2nd) to when failure was noted was 19 months. Failure was defined as dyspnea or angina along with dynamic obstruction despite adequate medical therapy, thus prompting the option to proceed to SM. Those patients who did not have a 2nd PTSMA and rather proceeded to SM had no target arteries. The original PTSMA occluded the only artery supplying the culprit septal segment. The reasons for unsuccessful PTSMA were based on anatomical distribution of the septal arteries. In 5 of the 20 patients, the target septal segments were supplied by two septal perforators, and ethanol was injected only in one of these perforators with the expectation that this would be sufficient to induce an effective amount of septal necrosis. In the other 15 patients, the distribution of the perforators did not cover the whole septal area involved with dynamic obstruction. Residual septal thickness just distal to the site of ablation led to residual obstruction. Clinical and hemodynamic data after PTSMA and after SM are shown in Table 78. In those cases of failed PTSMA, there were no differences in NYHA class, CCS class, exercise duration, and septal thickness between baseline and post-PTSMA. After SM, there were significant improvements in both subjective and objective measures of functional capacity as well as LVOT-PG. The authors concluded that SM can be performed successfully after failed PTSMA.

Table 77. Characteristics from 1st and 2nd PTSMA prior to SM (Nagueh, 2007)

	Original PTSMA	Repeat PTSMA	Not undergoing repeat PTSMA
N	20*	9	11
Number of Septal Arteries Injected: mean (SD)	1.4 (0.5)	1.4 (0.5)	
Average volume of ethanol (mL): mean (SD)	2.9 mL (1 mL)	2.3 mL (0.7 mL)	
Mean peak CK (U/L): mean (SD)	1,199 U/L (467 U/L)	736 U/L (259 U/L)	
Pre-PTSMA LVOT-PG (mm Hg): mean (SD)	90 (20)	70 (26)	
Post-PTSMA LVOT-PG (mm Hg): mean (SD)	30 (16)	35 (16)	
Number of patients with residual LVOT-PG ≥ 25 mm Hg	13		
Time from original PTSMA to repeat PTSMA (months): mean (SD)		14 (11)	
Reason for not undergoing repeat PTSMA			No target arteries. Original PTSMA occluded only artery supplying culprit septal segment
Duration of time after PTSMA (1st or 2nd) when failure was noted (months): mean (SD)	19 (15)		

*all 20 patients failed PTSMA either on 1 or 2 attempts and subsequently underwent SM.
SD = standard deviation.

Source: Nagueh et al, 2007: tabulated by FDA clinical reviewer from publication content

Table 78. Outcome after PTSMA and subsequent SM (Nagueh, 2007)

	Baseline	After Alcohol Septal Ablation	After Myectomy
NYHA functional class	3 (3–3)*	2.5 (2–3)†	1 (1–1)
CCS angina class	2 (1–3)*	1.6 (1–2)†	1 (1–1)
Exercise duration (s)	171 ± 124†	168 ± 148†	423 ± 171
LVOT gradient (mm Hg)	93 ± 23*	71 ± 26†	6 ± 11
Septal thickness (cm)	2.3 ± 0.4*	1.9 ± 0.3†	1.3 ± 0.3
LVEF (%)	74 ± 6	71 ± 6	70 ± 5
Mitral regurgitation	1.5 (1–2)*	1.25 (1–1.5)†	0 (0–1)

Data are shown as mean ± SD or median (25th to 75th percentiles). *$p < 0.05$ for baseline versus post-alcohol septal ablation and versus post-myectomy. †$p < 0.05$ versus post-myectomy.
CCS = Canadian Cardiovascular Society; LVEF = left ventricular ejection fraction; LVOT = left ventricular outflow tract; NYHA = New York Heart Association.

Source: Nagueh et al, 2007

Reviewer Comment (Nagueh 2997): I assessed this publication as demonstrating the utility of SM in ensuring clinical improvement. However, a less invasive technique such as PTSMA might be initially preferable with resort to the more invasive SM in the event of PTSMA failure that would occur at a rate of approximately 5%. An observation by the authors that caught my attention was the estimated CK release associated with a probability of PTSMA failure. Peak CK values < 1,300 U/L after PTSMA and a residual LVOT-PG of > 25 mm Hg were usually observed in cases of PTSMA failure. This peak CK value was the same as observed by Chang (2004) as the target value above which PTSMA was predicted to be successful. However, in the study by Alam (2006) [see 5.3.2 Meta-Analyses*], both subjective and objective improvements in functional capacity following PTSMA were achieved with an average peak CK of 964 U/L. The study by Faber et al (2005) in review of the German TASH registry showed that the higher the CK value, the more pronounced was the reduction in LVOT-PG, but the mortality rate was higher. Finally, the randomized trials by Veselka (see Table 2) showed that the higher dose of ethanol caused a higher release of CK but no difference in symptomatic outcome between the two alcohol doses and subsequent levels of CK release. This has led to confusion about the optimal alcohol dose and optimal CK release. The Kuhn study also raised a question about the optimal ethanol dose. In all the long-term follow-up studies, the average dose was 2.25 mL/artery injected. Based on the total body of evidence from these studies, I will suggest a dose of 2-3 mL per artery injected as the recommended ethanol dose in the label. I remain uncertain what the optimal CK release is, and it probably should not be specified in the label in lieu of a recommended cap on the residual LVOT-PG.*

5.3.10 Retrospective Studies: Left Ventricular Diastolic Properties

Executive Summary and Reviewer Overall Assessment of Retrospective Studies Describing Left Ventricular Diastolic Properties

The Applicant submitted 2 retrospective studies assessing left ventricular diastolic properties in patients who underwent PTSMA for HOCM. Key findings were:

- Jassal et al (2006): Thirty patients who underwent PTSMA were assessed for echocardiographic parameters of diastolic function. Evaluations occurred at baseline and at 1- year and 2- year follow-up. Compared to baseline, there were significant reductions in NYHA class, LVOT-PG, interventricular septal thickness, and left atrial volume. There were significant improvements in E-wave deceleration time, isovolemic relaxation time, early diastolic mitral lateral annular velocity, mitral flow propagation velocity (Vp), E/E' ratio ([trans-mitral early left ventricular filling velocity]/[early diastolic Doppler tissue imaging of mitral annulus]), and E/Vp at 1 year and persistent to 2 years for whom 2-year data were available.
- Mazur et al (2001): Twenty-six patients who underwent PTSMA for HOCM were assessed for left ventricular size, function, and LVOT-PG by echocardiography at baseline, and at 1 and 2 years after the procedure. The mean age was 53 ± 15 years. There were significant improvements in NYHA, angina class, exercise duration, and LVOT-PG both resting and provocable. There were decreases in left ventricular end systolic and diastolic dimension. The authors reported a 50% decrease in septal thickness (from 20 mm at baseline to 10 mm at 2 years) and an overall regression of left ventricular hypertrophy.

The article by Jassal et al (2006) focused on echocardiographic indices of diastolic function and included data on subjective measures of functional capacity. I assessed this article as suggestive but not conclusive regarding functional capacity. The article by Mazur et al (2001) included data showing improvements of NYHA class, angina class, objective measures of exercise capacity, and LVOT-PG. (b) (4)

Jassal et al (2006) studied the impact of PTSMA on left ventricular diastolic function at baseline, at 1 year and 2 years in 30 patients following successful PTSMA for HOCM. Findings at 1 year for all 30 patients are shown in Table 79. The mean age was 58 years. Neither the ethanol dose nor the average number of septal arteries injected was specified. Compared to baseline, there were significant improvements in NYHA and LVOT-PG at 1 year. There were significant reductions in interventricular septal thickness and left atrial volume. There was no significant change in E/A ratio (i.e. no improvement in diastolic dysfunction). However, E deceleration time (i.e. time from

maximum E to baseline: time from maximum ventricular filling velocity to point immediately prior to atrial contraction) and isovolemic relaxation time (IVRT) were significantly shorter and normalized at 1 year. The 2- year follow-up for 21 of the original 30 patients is shown in Table 80. The data showed sustained improvements in NYHA class and LVOT-PG from baseline. There was still no improvement in diastolic function (i.e. E/A ration remained the same). The E deceleration time continued to improve, but the IVRT showed no further improvement between 1 and 2 years. Diastolic tissue imaging of the mitral annulus showed that the parameters of diastolic function were abnormal in all patients at baseline and were improved up to 2 years following PTSMA. Following PTSMA, both the lateral mitral annular velocity (E') and flow propagation velocity (V_P) improved at 1 year without further improvement at 2 years. The authors concluded that in patients with HOCM, echocardiographic indices of diastolic function improved after PTSMA and that it may contribute to improved functional status.

Table 79. Clinical and Echocardiographic Findings-1 year (Jassal, 2006)

($n = 30$)

Characteristics	Baseline	1 year follow-up	*P*-value
Age (years)	58 ± 15		
Male gender (%)	22 (73)		
NYHA	3.0 ± 0.5	1.5 ± 0.7	<0.0001
HR (bpm)	76 ± 12	74 ± 10	0.6527
SBP (mmHg)	126 ± 13	132 ± 22	0.4531
Cardiac medications			
Beta-blockers (%)	25 (83)	23 (77)	0.6525
Calcium antagonists (%)	15 (50)	13 (43)	0.5448
Disopyramide (%)	3 (10)	4 (13)	0.6845
Left heart dimensions			
IVS (mm)	19 ± 2	14 ± 2	<0.0001
PWT (mm)	13 ± 1	12 ± 2	0.5343
LAVI (mL/m^2)	26 ± 5	20 ± 4	0.0002
LVEDVI (mL/m^2)	57 ± 10	72 ± 11	<0.0001
EF (%)	68 ± 5	66 ± 7	0.6232
Doppler-derived pressure measurements			
LAP (mmHg)	21 ± 5	14 ± 3	<0.0001
LVOT (mmHg)	76 ± 37	19 ± 12	<0.0001
Doppler echocardiography			
MR grade	2.6 ± 0.5	1.4 ± 0.5	<0.0001
Mitral E velocity (cm/s)	91 ± 18	90 ± 21	0.8073
Mitral A velocity (cm/s)	96 ± 36	92 ± 36	0.7980
E/A ratio	1.04 ± 0.4	1.01 ± 0.4	0.5324
E deceleration time (ms)	238 ± 17	168 ± 18	<0.0001
IVRT (ms)	122 ± 20	89 ± 6	<0.0001
Doppler tissue imaging			
Lateral E' (cm/s)	6.5 ± 1.8	8.7 ± 2.3	<0.0001
V_p (cm/s)	34 ± 6	63 ± 12	<0.0001
E/E' (lateral)	15 ± 4	10 ± 2	<0.0001
E/V_p	2.7 ± 0.7	1.5 ± 0.5	<0.0001

Values are mean ± SD. HR, heart rate; SBP, systolic blood pressure; IVRT, isovolumic relaxation time; LAVI, left atrial volume indexed to body surface area; LAP, estimated left atrial pressure; LVEDVI, left end-diastolic volume indexed to body surface area; LVOT, LV outflow tract gradient; MR, mitral regurgitation.

Source: Jassal et al, 2006

Table 80. Clinical and Echocardiographic Findings- 2 years (Jassal, 2006)

follow-up ($n = 21$)

Characteristics	Baseline	1 year follow-up	2 year follow-up
Age (years)	58 ± 16		
Male gender (%)	17 (81)		
NYHA	3.0 ± 0.5	1.6 ± 0.7*	1.1 ± 0.4*
HR (bpm)	75 ± 10	70 ± 12	76 ± 15
SBP (mmHg)	125 ± 12	130 ± 21	134 ± 11
Cardiac medications			
Beta-blockers (%)	16 (76)	15 (71)	13 (62)
Calcium antagonists (%)	10 (48)	9 (43)	9 (43)
Disopyramide (%)	2 (10)	3 (14)	2 (10)
Left heart dimensions			
IVS (mm)	19 ± 2	14 ± 1*	14 ± 1*
PWT (mm)	13 ± 1	12 ± 2	12 ± 3
LAVI (mL/m^2)	23 ± 5	20 ± 5*	20 ± 5*
LVEDVI (mL/m^2)	60 ± 10	74 ± 12*	78 ± 13*
EF (%)	67 ± 5	65 ± 8	66 ± 7
Doppler-derived pressure measurements			
LAP (mmHg)	20 ± 6	15 ± 3*	15 ± 3*
LVOT (mmHg)	75 ± 34	19 ± 12*	18 ± 13*
Doppler echocardiography			
MR grade	2.4 ± 0.5	1.3 ± 0.5*	1.3 ± 0.5*
Mitral E velocity (cm/s)	89 ± 19	98 ± 22*	91 ± 24
Mitral A velocity (cm/s)	101 ± 44	104 ± 45	99 ± 41
E/*A* ratio	1.04 ± 0.5	1.06 ± 0.5	1.01 ± 0.6
E deceleration time (ms)	238 ± 18	165 ± 20*	154 ± 32*
IVRT (ms)	118 ± 21	89 ± 6*	91 ± 5*
DTI			
Lateral *E*′ (cm/s)	6.8 ± 1.8	8.4 ± 2.4*	8.2 ± 2.7*
V_p (cm/s)	36 ± 7	63 ± 11*	68 ± 14*
E/*E*′ (lateral)	15 ± 4	10 ± 2*	10 ± 2*
E/V_p	2.6 ± 0.7	1.5 ± 0.6*	1.1 ± 0.4*

Values are mean ± SD. *P*-values were calculated by ANOVA.
*$P < 0.0001$ vs. baseline.

Source: Jassal et al, 2006

Reviewer Comment (Jassal 2006): Although this publication nicely demonstrated improvement of echocardiographic indices of diastolic function, (b) (4)

(b) (4) *As was common throughout this NDA, references to improvement in subjective measures of functional capacity were not accompanied by a description of validation procedures for subjective assessment.*

Mazur et al (2001) evaluated left ventricular size, function, and LVOT-PG of 26 HOCM patients who underwent PTSMA by echocardiography at baseline, and at 1 and 2 years after the procedure. The mean age was 53 ± 15 years. Ethanol was infused at a rate of 1-1.5 ml/min, but the average total dose and the average number of septal arteries were not specified. Outcome data is shown in Table 81. There were significant improvements in NYHA and angina class as well as exercise duration in alignment with significant improvements in both resting and provocable LVOT-PG. There were decreases in left ventricular end systolic and diastolic dimension. The authors reported a 50% reduction in septal thickness (from 20 mm at baseline to 10 mm at 2 years) and an overall regression of left ventricular hypertrophy. The authors stated that post-PTSMA peak CK levels were 2009 U/L and the rate of permanent complete heart block was 26.9%.

Table 81. Outcome data after PTSMA (Mazur, 2001)

	Baseline	1 Year After NSRT	2 Years After NSRT
NYHA class	3 (3–3)	1 (1–1)*	1 (1–1)*
Angina class	2 (0–2)	0 (0–0)*	0 (0–0)*
Exercise duration, seconds	320 (219–598)	547 (330–721)*	548 (365–728)*
Resting LVOT gradient, mm Hg	36 (15–64)	0 (0–0)*	0 (0–0)*
Provocable LVOT gradient, mm Hg	81 (80–107)	25 (0–64)*	0 (0–31)*†
Left atrium maximum volume, mL	90±37	64±20*	60±16*
LV end-diastolic dimension, mm	36±5	44±6*	46±6*
LV end-systolic dimension, mm	20±6	27±6*	29±7*
LV long axis, mm	81 (76–85)	79 (75–85)	80 (78–85)
LVEDV, mL	96±19	117±23*	124±26*
LVEF, %	72.5±8	70.3±10	68±9*

Values are mean±SD or median (25th–75th percentile).
*$P<0.05$ vs baseline; †$P<0.05$ vs 1 year.

Source: Mazur et al, 2001

Reviewer Comment: (b) (4)

6 Review of Efficacy

Efficacy Summary

The Applicant's proposed indication is: (b) (4) is indicated to improve (b) (4) exercise capacity in patients with symptomatic, (b) (4) hypertrophic obstructive cardiomyopathy (b) (4) The (b) (4) indication should reflect a clinically meaningful benefit, i.e., reducing symptoms such as dyspnea, angina, or syncope; improvement in functional capacity; and/or improved outcomes such as reducing the incidence of heart failure hospitalization or increasing survival. (b) (4)

There were 38 publications provided by the Applicant to support their proposed indication and are shown in Table 82. Of the 38 studies, 4 were randomized trials examining two doses of ethanol in a 1:1 randomization scheme. The remainder of the studies was retrospective and observational. Thirty-one of the 38 publications reported measures of functional capacity (NYHA and / or CCS) as indicated in the table. The 7 publications that did not report functional data were:

- El-Jack (2007): predictors of complete heart block
- Veselka (2005, Am J Cardiol): LVOT-PG data only
- Jensen (2013): risk factors for sudden cardiac death
- Kuhn (2008): alcohol dose-mortality correlation
- Sorajja (2012): SM vs PTSMA: no data on functional capacity. No difference between SM and PTSMA for mortality; superiority of SM for LVOT-PG reduction
- Ralph-Edwards (2005): SM vs PTSMA: no data on functional capacity. Superiority of SM over PTSMA for mortality and LVOT-PG reduction
- Veselka (2012): effect of septal shape on hemodynamic effect

Of the 31 publications reporting functional data, 30 reported significant improvement from baseline in NYHA and CCS class following PTSMA. Only one publication (Nagueh, 2007) reported significant improvement in NYHA and CCS following SM performed as a consequence of failed PTSMA, where there was no improvement in subjective measures of functional capacity from baseline following the index PTSMA. Of these 31 publications, 9 additionally reported improvement in objective measures of functional capacity (i.e. exercise time or workload) as shown in Table 85. Eight of these studies

were PTSMA-mediated and 1 study (Nagueh, 2007) reported improved exercise capacity due to SM performed consequent to a failed PTSMA.

Table 82. Studies that reported functional capacity: NYHA or CCS class

Study	Significant Improvement in NYHA from baseline	Significant Improvement in CCS from baseline		Study	Significant Improvement in NYHA from baseline	Significant Improvement in CCS from baseline
Veselka 2011	yes	NR		Faber 2005	yes	NR
Veselka 2006 (Circ. J 70:1550-2)	yes	yes		Veselka 2014 (Eu Heart J)	yes	yes
Veselka 2005 (Am. J Cardio.)	NR	NR		Moss 2014	yes	NR
Veselka 2004	yes	yes		Jensen 2013	NR	NR
Leonardi 2010	Yes	NR		Krejci 2013	yes	NR
Agarwal 2010***	NR	NR		Nagueh 2011	yes	yes
Alam 2009	NR	NR		Fernandes 2008*	yes	yes
Alam 2006*	yes	yes		Kuhn 2008	NR	NR
Veselka 2014 (Cath Cardio. Int)	yes	yes		Veselka 2014 (Int. J Cardiol)	yes	yes
Veselka 2013	yes	yes		Faber 2007*	yes	NR
Veselka 2009	yes	yes		El-Jack 2007	NR	NR
Veselka 2005 (Echocardiography.)	yes	yes		Chang 2003*	yes	yes
Sorajja 2012	NR-but no diff bet. SM and PTSMA for mortality	NR		Veselka 2014 (Can. J Cardio)	yes	yes
Ralph-Edwards 2005	NR-but higher mortality in PTSMA vs SM	NR		Leonardi 2013	yes	NR
Van der Lee 2005	yes	NR		Veselka 2006 (Circ J 70:880-84)	yes	yes
Firoozi 2002*	yes	NR		Gietzen 2004*	yes	NR
Qin 2001	yes	NR		Nagueh 2007*,**	no	NR

Nagueh 2001*	yes	yes		Jassal 2006	yes	NR
Veselka 2012****	NR	NR		Mazur 2001*	yes	yes

*Exercise data reported; ** Data from Nagueh (2007) reported on failed PTSMA where there was no difference from baseline in NYHA or exercise capacity. Improvements in both occurred after post-PTSMA SM; *** There was no data showing functional improvement from baseline, but odds ratios from PTSMA studies and SM studies were used to draw a comparison between the two procedures; ****LVOT-PG data only when performing PTSMA on Sigmoid vs neutral septum; NR = not reported

Source: FDA reviewer compilation of data from Applicant's NDA submission publications

6.1 Dose

In 4 randomized trials by Veselka et al (see Table 2), doses ranging from 1.1 ± 0.2 mL to 2.5 ± 0.8 mL were evaluated. The key finding in all 4 of these trials was that the release of CK-MB was directly proportional to the alcohol dose (Figure 5), but the outcome at the lower dose (i.e. subjective improvement functional capacity and LVOT-PG reduction) was similar to that of the higher dose.

The finding that subjective outcome and hemodynamic response were independent of ethanol dose-related CK-MB release was contradicted by other findings. Peak CK values < 1,300 U/L after PTSMA and a residual LVOT-PG of > 25 mm Hg were usually observed in cases of PTSMA failure defined as post-procedure continuation of obstruction and symptoms (Nagueh, 2007). This peak CK value was the same as that observed by Chang (2004) as the target value above which PTSMA was predicted to be successful. These findings implied a dose-response in order to produce an adequate CK-release for hemodynamic and symptomatic improvement. However, in the study by Alam (2006), both subjective and objective improvements in functional capacity following PTSMA was achieved with an average peak CK of 964 U/L rather than the stated 1300 U/L. This raised a question about the published predictive value of 1,300 U/L that must be exceeded to produce a successful PTSMA outcome.

From the 9 publications that showed improvement in exercise capacity, 7 provided sufficient data (i.e. total dose of ethanol and average number of septal arteries injected) to allow calculation of the average dose of ethanol per septal artery. This compiled data is shown in

Table 83. Two of the 9 studies (Nagueh 2001 and Mazur 2001) did not report a specific total dose of ethanol. Nagueh (2001) reported a dose range (i.e. 2-5 mL) injected into a single target septal artery. Mazur (2001) reported an ethanol infusion rate of 1-1.5 mL/min into an unspecified number of septal arteries for an unspecified period of time. Another study (Nagueh 2007) reported a total dose and number of septal arteries injected, but the PTSMA failed and the results were SM-mediated. After eliminating these three studies, the average dose of ethanol/septal artery that demonstrated

PTSMA-mediated objective functional efficacy from the residual 6 publications was calculated to be 2.53 mL ethanol per septal artery (average total 2.80 mL ethanol). In a similar exercise, the average dose of ethanol per septal artery queried or reported from all 38 publications submitted by the Applicant in support of their NDA is shown in Table 84.

The data provided in these publications, thus allowing for the determination of ethanol dose per septal artery, were distributed as follows:

- 15 of the 38 submitted publications showed improvement in functional capacity (i.e. exercise or NYHA or CCS) and allowed for the calculation of the average ethanol dose per septal artery.
- 13 of the 38 publications showed improvement of functional capacity but did not contain data allowing for the determination of the average ethanol dose per septal artery.
- 5 of the 38 publications allowed for the determination of the average ethanol dose per septal artery but did not report functional capacity.
- 5 of the 38 publications had neither functional capacity data nor data that would allow for the determination of the average ethanol dose per septal artery.

Based on the data from the 15 studies showing improvement in functional capacity and allowing for the calculation of the average ethanol dose per septal artery, the average dose was 2.25 mL ethanol per septal artery (average total 2.49 mL ethanol). These numbers were similar to those from the subgroup of publications showing an improvement in exercise capacity.

The Applicant provided a truncated database of 100 patients out of 180 patients who underwent PTSMA at the Motol University Hospital, Prague, Czech Republic. The database did not provide ethanol doses or the number of arteries injected. This attenuated an attempt to understand a dose-response relationship for efficacy in this database. However, the adverse event narratives from this database delivered by the Applicant upon our request provided information on dose and number of arteries injected. As explained in the next section (see section 7.4 Death and Other Complications from Veselka Database), the dose per artery delivered to patients who ultimately died was on the average lower than that identified as producing improvements in objective measures of functional capacity. There was no noticeable dose-dependent safety signal. The general duration of time between PTSMA and death made it unlikely that PTSMA or ethanol was the cause of death.

Reviewer Comment: There was an approximate 0.3 mL higher ethanol dose (mL)/septal artery and a 0.3 mL higher total dose of ethanol (mL) in those studies showing improvement in 3 parameters: exercise tolerance, NYHA and CCS class, and LVOT-PG, compared to those who showed improvement only in NYHA and CCS class, and LVOT-PG. I did not think this difference was significant. From the labelling perspective, I recommend a total ethanol dose of 1-3 mL. The dose per artery should be at the

discretion of the interventional cardiologist performing the PTSMA. Final dosing should be titrated to LVOT-PG less than 10 mmHg during PTSMA (Sorajja, 2012). A maximum total ethanol dose should be 5 mL because of reported efficacy experience at this dose without a reported safety concern (Nagueh 2001; Van de Lee 2005). There were no published data demonstrating experiences at doses higher than 5 mL.

Table 83. Ethanol Dose per Septal Artery from Trials reporting improved Exercise Capacity

Dose Data from Trials Showing Objective Measures of Functional Capacity						
Study	Sample Size	Mean Age (yrs)	Follow-up time	Ethanol Dose (mL) mean (SD)	Mean Number of Septal Arteries Injected	Mean Ethanol Dose per Septal Artery
Fernandes 2008	619	54	4.7 yrs	2.6 (1.0)	1.3	2.0
Nagueh 2007 (*)	20	53	19 mos	2.9 (1.0)	1.4	2.1
Faber 2007**	155	53	3 mos	2.1 (0.5)	1	2.1
Alam 2006	2808(NYHA) 821 (CCS) 720 (ET)	54	12.7 mos	3.0 (NS)	1.2	2.5
Chang 2003	224	52	Up to 4 yrs	2.9 (1.3)	1.2***	2.4
Gietzen 2004	80 (< 60 yrs) 77 (≥ 60 yrs)	44 69	7 mos	3.2 (1.1)	1****	3.2
Firoozi 2002	19	49	46 mos	3.0 (NS)	1	3.0
Nagueh 2001	41	49	1 yr	2—5 (NS)^	1	2—5
Mazur 2001	26	53	2 yrs	1-1.5mL/min # arteries NS	NS	Unknown

NS = Not Specified; * Nagueh (2007): study involved patients who had failed PTSMA and subsequently required SM. The final improvements observed in follow-up exercise capacity and subjective symptoms followed SM; ** Faber 2007 (2007): the publication referred to the "culprit septal perforator artery". I therefore assumed 1 artery; *** Chang 2003: the mean number of septal arteries (1.2) was specified only in patients who were matched for age (57 years) and LVOT-PG who did and did not require a permanent pacemaker (n = 31 for each subgroup). The mean number of septal arteries injected for the entire cohort of 224 was not specified; ****Gietzen 2004: the publication referred to "a small septal branch supplying the area of obstruction. I therefore assumed 1 artery; ^Nagueh 2001: the volume of alcohol injected was dependent upon the vascular territory of the cannulated septal artery.

Source: FDA Reviewer Compilation of Data

Table 84. Ethanol Dose per Septal Artery from All Studies Submitted by Applicant

Dose Data from All Studies Submitted by the Applicant to Support their NDA						
Study	Significant Improvement in NYHA or CCS from baseline	Ethanol Dose (mL)/#Arteries (Dose/artery)		Study	Significant Improvement in NYHA or CCS from baseline	Ethanol Dose (mL)/#Arteries (Dose/artery)
Veselka 2011[V]	yes	2.5/1.1 (2.3) 1.1/1.1 (1.0)		Faber 2005	yes	2.8/NS
Veselka 2006 (Circ. J 70:1550-2)[V]	yes	2.6/1 (2.6) 1.5/1 (1.5)		Veselka 2014 (Eu Heart J)	yes	1.7/1.1 (1.6)
Veselka 2005 (Am. J Cardio.)[V]	NS	2.8/1.1 (2.5) 1.1/1.1 (1.0)		Moss 2014	yes	4.1/1.1 (3.7)
Veselka 2004[V]	yes	3.4/1.1 (3.1) 1.6/1.1 (1.5)		Jensen 2013	NS	0.1/mm artery (NS)
Leonardi 2010	Yes	NS		Krejci 2013	yes	[1—4]/1 (1—4)
Agarwal 2010	NS	NS		Nagueh 2011	yes	2.9/1[78%pts] 2.9/2[20%pts] 2.9/3[1.4%pts] 2.9/4[0.4%pts] (2.3)
Alam 2009	NS	NS		Fernandes 2008*	yes	2.6/1.3 (2.0)
Alam 2006*	yes	3.0/1.2 (2.5)		Kuhn 2008	NS	2.2/1.1[Grp A] 0.8/1.1[Grp B] (2.0) (0.7)
Veselka 2014 (Cath Cardio. Int)	yes	1.5/NS		Veselka 2014 (Int. J Cardiol)	yes	NS/NS
Veselka 2013	yes	1.5/NS		Faber 2007*	yes	2.1/1 (2.1)
Veselka 2009	yes	2.5/1.1(2.3) 1.0/1.1(0.9)		El-Jack 2007	NS	4.4/1 [66%pts] 4.4/2 [34%pts] (3.7)
Veselka 2005 (Echocardiography.)	yes	NS/1		Chang 2003*	yes	2.9/1.2 (2.4)
Sorajja 2012	NS-but no diff bet. SM and PTSMA	1.8/1.1 (1.6)		Veselka 2014 (Can. J Cardio)	yes	1.8/NS

	for mortality					
Ralph-Edwards 2005	NS-but higher mortality in PTSMA vs SM	NS/NS		Leonardi 2013	yes	2.3/1.1 (2.1)
Van der Lee 2005	yes	1—5/1 (1-5)		Veselka 2006 (Circ J 70:880-84)	yes	2.3/ NS(Grp A) 2.2/ NS(Grp B) 2.4/ NS(Grp C)
Firoozi 2002*	yes	3.0/1 (3.0)		Gietzen 2004*	yes	3.2/1 (3.2)
Qin 2001	yes	2.7/1 (2.7)		Nagueh 2007*,**	*no*	2.9/1.4 (2.1)
Nagueh 2001*	yes	2—5/1 (2—5)		Jassal 2006	yes	NS/NS
Veselka 2012***	NS	Not readable		Mazur 2001*	yes	1-1.5mL/min # arteries NS

NS= Not Specified; *Alam 2006, Firoozi 2002, Nagueh 2001, Fernandes 2008, Faber 2007, Chang 2003, Gietzen 2004, Nagueh 2007, Mazur 2001: Exercise data reported; ** Nagueh (2007): publication reported on failed PTSMA where there was no difference from baseline in NYHA or exercise capacity. Improvements in both occurred after post-PTSMA SM; ***Veselka 2012: Data on dose and number of arteries injected were not readily available. Icons representing figures and tables were not expandable and therefore not reviewable; (V) Veselka studies: these were randomized trials comparing 1 mL to 2 mL ethanol doses for reduction of LVOT-PG and symptomatic improvement

Source: FDA Reviewer Compilation of Data

6.2 Efficacy of PTSMA in improving functional capacity

In those 9 publications showing both subjective and objective functional capacity (Table 85), the average age ranged from 44 to 69 years. The sample sizes ranged from 19 to 720 and the follow-up time ranged from 3 months to 4.7 years. The baseline exercise time ranged from 171 seconds to 325 seconds. Follow-up exercise time ranged from 417 seconds to 548 seconds. From individual observational studies, the largest increase in exercise time was 3.8 minutes (Mazur, 2001) and the shortest increase in exercise time was 1.7 minutes (Chang, 2003). In the most recent publication reporting exercise time (Fernandes, 2008), the exercise time increased by 3.6 seconds. Baseline workloads ranged from 60 Watts to 121 Watts. Follow-up workloads ranged from 75 Watts to 137 Watts. From individual observational studies, the largest workload

increase was 25 Watts (Faber, 2007). This study was the most recent study reporting workload. The smallest workload increase was 15 W in patients ≥ 60 years of age (Gietzen, 2004).

Table 85. Studies that showed Objective Measures of Functional Capacity

Study	Sample Size	Mean Age (yrs)	Follow-up time	Exercise Capacity		NYHA Class		CCS Class	
				Baseline	Follow-up	Baseline	Follow-up	Baseline	Follow-up
Fernandes 2008	619	54	4.7 yrs	4.6 min	8.2 min	2.8	1.2	2.1	1.0
Nagueh 2007 (*)	20	53	19 mos	171 sec	168(SA) 423(SM) (sec)	3	2.5 (SA) 1.0(SM)	2	1.6(SA) 1.0(SM)
Faber 2007	155	53	3 mos	94 W	119 W	2.8	1.6	---	---
Alam 2006	2808(NYHA) 821 (CCS) 720 (ET)	54	12.7 mos	325 sec	438 sec	2.9	1.2	1.9	0.4
Chang 2003	224	52	Up to 4 yrs	296 sec	398 sec	2.7	1.5	----	----
Gietzen 2004	80 (< 60 yrs) 77 (≥ 60 yrs)	44 69	7 mos	93 W 60 W	112 W 75 W	2.7 3.0	1.3 1.7	----	----
Firoozi 2002	19	49	46 mos	121 W	137 W	1 (0) 2 (68%) 3 (32%)	1 (53%) 2 (54%) 3 (11%)	----	----
Nagueh 2001	41	49	1 yr	289 sec	417 sec	2 (10%) 3/4(90%)	1 (88%) 2 (12%)	1 (39%) 2 (37%) 3 (24%)	1(100%)
Mazur 2001	26	53	2 yrs	320 sec	548 sec	3	1	2	0

ET = exercise time; W=watts; Yrs=years; (*) = Nagueh (2007) studied patients who had failed PTSMA and subsequently required SM. The final improvements observed in follow-up exercise capacity and subjective symptoms followed SM

Source: FDA reviewer compilation of data from Applicant's NDA submission publications

With the exception of the 9 publications cited in Table 85, efficacy of PTSMA was defined mostly by improvement in subjective measures of functional capacity and reductions in LVOT-PG. There were no reported validation tools for subjective assessment that are generally required for drug approval when using subjective endpoints as the basis of an NDA.

The 100-patient Veselka database out of 180 patients who underwent PTSMA at the Motol University Hospital, Prague, Czech Republic was assessed as potentially biased by the Applicant. The patient information submitted by the principal investigator (Prof Dr. Veselka) to the Applicant was judged to have "reliable history", "complete medical reports", and had a high probability of "future cooperation of both patients and family members". I inferred that the patients whose data were not submitted did not satisfy at least one of these judgment criteria. Despite the Applicant's assessment of potential bias, I reviewed efficacy data. Of the 100 patients (43 men, 57 women), the average age 58 $\pm$ 12 years, the median follow-up time was 53 months and the mean follow-up time was 67.4 $\pm$ 49 months. The investigator reported a decrease in NYHA class from 2.9 $\pm$ 0.5 to 1.4 $\pm$ 0.6 and a corresponding decrease in LVOT-PG from 65 $\pm$ 39 mmHg to 19 $\pm$ 23 mmHg. These results were similar to the data from publications provided by the Applicant that served as the body of evidence for efficacy

Failure of PTSMA thus requiring a second procedure was defined as post-procedural dyspnea, angina, and dynamic obstruction despite adequate medical therapy. The reasons for unsuccessful PTSMA were based on anatomical distribution of the septal arteries (Nagueh, 2007). In 5 of the 20 patients, the target septal segments were supplied by two septal perforators, and ethanol was injected only in one of these perforators with the expectation that this would be sufficient to induce an effective amount of septal necrosis. In the other 15 patients, the distribution of the perforators did not cover the whole septal area involved with dynamic obstruction. Residual septal thickness just distal to the site of ablation led to residual obstruction. The efficacy of PTSMA was therefore based on factors other than alcohol efficacy, namely, coronary artery distribution relative to hemodynamic obstructive segments of the hypertrophic septum, and clinical judgment of the operator in deciding the number of injections and number of septal arteries in which injections would occur in order to optimize outcome of the procedure.

Although there was no trial directly comparing PTSMA to SM, a series of studies were conducted that retrospectively compared outcome from observational studies in patients who underwent PTSMA to outcome from observational studies in patients who underwent SM for refractory symptomatic HOCM.

Sorajja (2012) observed no difference between survival in PTSMA patients and survival in age- and sex specific cohorts from the general US population (Figure 15). There were no observed differences between the two procedures in survival based on mortality

(Figure 16). However, there were notable differences favoring SM when combining survival based on mortality and freedom from additional septal reduction (Figure 17). This was due to the finding that PTSMA patients experienced considerable procedural complications driven by pacemaker dependency and need for follow-up SM. Patients who had a residual LVOT-PG $\geq$ 10 mm Hg post-PTSMA had a lower survival (free of all-cause mortality) compared to those post-PTSMA patients who had a residual LVOT-PG of < 10 mm Hg (Figure 18). Volumes of alcohol ranged from 1-3 mL.

Ralph-Edwards et al (2005) suggested that SM was superior to PTSMA based on the definition of optimal composite outcome: survival + NYHA class I + no post-procedure pacemaker placement + a follow-up resting LVOT-PG of less than 20 mm Hg. This composite efficacy endpoint was reported to be noted in 12 (22%) patients in the PTSMA group and 35 (73%) patients in the isolated SM group ($p<0.001$).

Van der Lee et al (2005) noted no difference between the combined operation of SM and mitral valve leaflet extension vs. PTSMA for hemodynamic and subjective symptom improvement.

Firoozi et al (2002) noted that although PTSMA improved subjective exercise limitation in appropriately selected patients, SM was superior to PTSMA on both peak oxygen consumption and work rate, and thus remained the gold standard against which other treatment modalities should be compared.

Qin et al (2001) noted no difference between PTSMA and SM for reduction in LVOT-PG and improvement in NYHA class although there was a greater need for permanent pacemaker placement in those patients who underwent a PTSMA. Nagueh et al (2001) noted that the suggested similarity of efficacy between PTSMA and SM extended to exercise duration.

In summary, there was retrospective evidence that PTSMA improved both subjective and objective measures of functional capacity in alignment with improvement in LVOT-PG. None of these trials directly compared SM to PTSMA, but the results of these retrospective observational studies examining independent case evaluations for each procedure suggested that the efficacy of PTSMA might at best be similar to SM but is likely to be inferior to SM. There were no studies, either presented by the Applicant or researched independently during the review process that compared alcohol with another ablative agent for use in PTSMA.

The success of PTSMA was weighted equally between ablative agent efficacy, distribution of the septal perforators relative to those areas of the septum producing the hemodynamic obstruction, and operator judgment. Associated with operator judgment was the suggestion that success of PTSMA was impacted by the experience of the institution, usually a tertiary referral center (Sorajja, 2012).

Reviewer Comment: Regarding labelling language, two issues for consideration were 1) ethanol induced septal myocardial necrosis, but the efficacy of PTSMA was also based on adequate septal perforator coronary anatomy, and the skill of the interventionist. I therefore recommended that ethanol be indicated to induce septal myocardial necrosis in patients undergoing PTSMA ((b) (4) *Although the SM vs PTSMA publications were not randomized comparisons, the totality of evidence suggested that SM was still the gold standard. Therefore, my recommendation placed a caveat specifying that the Applicant's drug should be used in patients who are not SM candidates: "**In patients with refractory symptomatic hypertrophic obstructive cardiomyopathy who are clinically assessed as non-candidates for surgical myectomy, ethanol be approved to induce septal myocardial necrosis when used as an adjunct to percutaneous transluminal septal myocardial ablation to improve exercise capacity**".*

6.3 Potential bias in publication selection for efficacy evaluation

The data from publications that were submitted by the Applicant to support the NDA may have been inherently biased. I could not rule out the possibility that unsuccessful PTSMA outcomes were not published. Nagueh et al (2007) showed that the PTSMA failure rate was 5.3%. Failure was defined as continued post-procedure symptoms and continued outflow tract obstruction. This failure rate was retrieved from the database of PTSMA patients at the Methodist Hospital, Houston, from 1996 to 2006. It was not clear whether other publications reporting functional improvement and reduction in LVOT-PG incorporated failed procedures in measuring the extent of improvement. I have assumed that all the publications reported only successful outcomes and that the failure rate requiring post-PTSMA surgery approximated that reported by Nagueh et al (2007). I did not consider complications of PTSMA (e.g. pacemaker dependency, pneumothorax, sustained ventricular tachycardia, and cardiac tamponade) as PTSMA failures.

Thirteen of the 38 publications contained data from consecutive patients and are shown in Table 86. Retrospective studies involving consecutive subjects attenuated the concern about reporting bias. Five of these 13 consecutive patient publications also had exercise capacity data. The sample sizes of the individual retrospective consecutive patient studies ranged from 41 (Nagueh, 2001) to 644 (Kuhn, 2008). The sample sizes considered substantial from other studies evaluating consecutive subjects were: 619 (Fernandes, 2008), 470 (Jensen, 2013), 459 (Veselka, 2014, Cath and Cardiovascular Intervention), and 290 (Veselka, 2014, International J of Cardiology). These studies with consecutive subjects showed improvement in NYHA and CCS classifications as well as improvements in exercise capacity. The congruence of various measures of functional capacity suggesting an improvement post-PTSMA in studies evaluating consecutive subjects has reduced the concern about potential bias.

Table 86. Retrospective Studies Reviewing Consecutive Patients

Studies Reviewing Consecutive Patients						
Study	Sample Size	Mean Age (years)	Follow-up Time	Exercise Capacity	NYHA Class	CCS
Veselka 2014[1]	459	57	113 days	----	3→1	2→1
Veselka 2014[2]	150 –PPM 17 +PPM	59 59	4.0 yrs 4.8 yrs	---- ----	2.9→1.7 2.9→1.6	1.8→0.5 2.3→0.5
Veselka 2014[3]	290	42	5.1 yrs	----	2.8→1.6	1.7→0.3
Jensen 2013	470	56	8.4 yrs	-----	-----	---LVOT-PG only
Leonardi 2013[4]	**101 (<45yrs) 145 (45-64yr) 114 (≥65 yrs)**	**NR NR NR**	**12 mos**	-----	**2.8→1.3 2.8→1.4 3.0→1.4**	**2.4→NR 2.3→NR 2.1→NR**
Veselka 2012	100	NR	44 mos	----	----	--- LVOT-PG only
Fernandes 2008	619	54	4.7 years	4.6→8.2 min	2.8→1.2	2.1→1.0
Kuhn 2008	644	58	1.4	----	----	--mortality only
Faber 2007	155	53	3 mos	94W→119W	2.8→1.6	----
Veselka 2006[5]	14 14 16	24-48 49-60 61-81	12 mos	----	2.7→1.5	2.3→0.9
Veselka 2005[6]	27	54	12 months	----	2.5→1.4	2.6→0.7
Gietzen 2004	157	44 69	7 mos	93W→112W 60W→75W	2.7→1.3 3.0→1.7	----
Chang 2003[7]	261	52	Up to 4 years	296 s→398 s	2.7→1.5	----
Nagueh 2001	41	49	1 year	289 s→417 s	2(10%)-3/4(90%)→1(88%)-2(12%) (shift analysis)	1(39%)-2(37%)-3(24%)→1(100%) (shift analysis)

Source: FDA reviewer compilation of data. 1: Catheterization and Cardiovascular Intervention; 2: International Journal of Cardiology; 3: Canadian Journal of Cardiology; 4: NYHA and CCS values at 12 months were calculated by FDA reviewer from bar graph 5: Circulation Journal, 70:880-884; 6: Echocardiography; 7: Of the 261 consecutive patients, 37 had pre-PTSMA pacemaker placement and were excluded in the PPM vs no PPM study; W=watts; s = seconds; NR Not reported

7 Review of Safety

Safety Summary

Safety issues unique to PTSMA were the induction of complete heart block requiring placement of a permanent pacemaker, and ventricular dysthymias. Additionally, safety issues pertinent to percutaneous coronary intervention were applicable to PTSMA (e.g. coronary dissection, tamponade, myocardial infraction, etc.). For the purpose of this NDA, safety data was defined as the development of complete heart block and cardiovascular mortality. Safety data from studies reporting objective measures of functional capacity are shown in Table 87. CK levels and ethanol dosing were included in the collation of data from the published studies because of questions that emerged regarding the optimal CK release and ethanol dosing to produce an adequate response to PTSMA while maintaining patient safety. From the available data:

- The peak CK-total ranged from 596 U/L (Gietzen 2004) to 1331 U/dL (13,310 U/L) (Chang 2003), with an average of approximately 2833 U/L. If it is assumed that the report by Chang (2003) was erroneous and was actually 1331 U/L, then the average CK release was 1121 U/L.
- The all-cause mortality ranged from 1.5% (Alam 2006) to 3.9% (Fernandes 2008) with an average of 1.8%.
- The permanent pacemaker requirement rate ranged from 7.0% (Faber 2007) to 34% (Gietzen 2004 in patients > 60 years of age) for an average of approximately 16%. From the table, the study by Nagueh (2007) recorded a 10% pacemaker requirement, but only after SM. This was not included in the calculation of the overall average.

A more complete compilation of the safety data from the entire set of publications provided by the Applicant is shown in Table 88. From the available data:

- The peak CK-total ranged from 466 U/L (Veselka 2013) to 1331 U/dL (13,310 U/L) (Chang 2003), with an average of approximately 1898 U/L. If it is assumed that the report by Chang (2003) was erroneous and was actually 1331 U/L, then the average CK release was 1043 U/L
- The all-cause mortality ranged from 0 (Veselka 2005) to 13.4% (Leonardi 2010) with an average of approximately 4%.
- The permanent pacemaker requirement ranged from 0.85% (Jensen, 2014) to 35% (Veselka, 2009) for an average of approximately 11%. It was not clear from the Veselka (2009) publication whether the pacemaker placement rate of 35% represented permanent or transient placement.

The all-cause mortality rate was driven by an unusually high number reported by Leonardi (2010). Chang (2003) reported an unusually high CK release level (unless there was a typographical error in using dL rather than L). Calculating averages was subject to liabilities, such as wide variation in follow-up time amongst the various

observational studies, non-reporting in many of the studies, use of different units for CK values, and lack of specificity in some cases of whether the pacemaker placement was permanent due to sustained complete heart block.

The data available from the publications did not readily point to an optimal CK release or a dose dependency above which the patient would be at increased risk of mortality.

Table 87. Safety Data from Studies reporting Objective Functional Capacity

Study	Sample Size (N)	Mean Age (yrs)	Volume of Alcohol (mL) [# of arteries]	Follow-up time	Peak CK	Mortality	PPM
Fernandes 2008	619	54	2.6± 1.0 mL [1.3±0.5]	4.7 yrs	1,285 U/L	3.9%	8.2%
Nagueh 2007 (*)	20	53	2.9± 1.0 mL [1.4±0.5]	19 mos	1,199 U/L	0	10% (after myectomy)
Faber 2007	155	53	2.1± 0.5 mL [NR] –implied single branch	3 mos	466 U/L	0	7.0%
Alam 2006	2808(NYHA) 821 (CCS) 720 (ET)	54	3(0.6-4.8) mL [1.2(1.0-1.7)]	12.7 mos	964 U/dL	1.5%	10.5%
Chang 2003	224	52	2.9± 1.3 mL [25% >2] No PPM 2.9± 1.6 mL [42% > 2] PPM	Up to 4 yrs	1331 U/dL	NR	14%
Gietzen 2004	80 (< 60 yrs) 77 (≥ 60 yrs)	44 69	3.2± 2.1 mL [1.1±0.5] 3.2± 2.1 mL [1.1±0.5]	7 mos	596 U/L 491 U/L	2.5%(<60yr) 2.6%(≥60yr)	18%(< 60 yrs) 34 %(≥ 60 yrs)
Firoozi 2002	19	49	3 (max 5)mL [1: major proximal sept perforator]	46 mos	NR	NR	NR
Nagueh 2001	41	49	2-5 mL [1: target septal perforator]	1 yr	NR	2.4%	22%
Mazur 2001	26	53	NR [NR]	2 yrs	2009 U/L	NR	26.9%

(*) = Nagueh (2007) studied patients who had failed PTSMA and subsequently required SM. The final improvements observed in follow-up exercise capacity and subjective symptoms followed SM; N = number; PPM = permanent pacemaker; NR = not reported

Source: FDA reviewer compilation of data from Applicant's NDA submission publications

Table 88. Pacemaker Placement, Mortality, and Peak CK from NDA articles

Study	Permanent Pacemaker Placement	Mortality (follow-up time)	Peak CK 1 (tot. CK) 2 (CK-MB)	Study	Permanent Pacemaker Placement	Mortality (follow-up time)	Peak CK 1 (tot. CK) 2 (CK-MB)
Veselka 2011	5.3%	9.2% (85 mos)	6.5 uKat/L (2)	Faber 2005	9.6%	2.5% (4.9 mos)	477 U/L (survivors) (1) 721 U/L (non-survivors) (1) 68 U/L (survivors) (2) 118 U/L (non-survivors) (2)
Veselka 2006 (Circ. J 70:1550-2)	9.3%	3.7% (40 mos)	NR	Veselka 2014 (Eu Heart J)	NR	11% (5.2 yrs)	2.6 uKat/L (2)
Veselka 2005 (Am. J Cardio.)	2.4%	0 (3 mos)	3.8 uKat/L (2)	Moss 2014	1.4% (CHB 27%)	11% (3.1 yrs)	NR
Veselka 2004	5.9%	NR (6 mos)	NR	Jensen 2014	0.85%	10% (8.4 yrs)	NR
Leonardi 2010*	11%	13.4% (0.3-11yr)	NR	Krejci 2013	1.9%	NR (87 mos)	NR
Agarwal 2010**	NR	NR (3mos-5 yrs)	NR	Nagueh 2011	8.9%	9.3% (2 yrs)	NR
Alam 2009	8%	1.6% (0.3-2yrs)	NR	Fernandes 2008	8.2%	3.9% (4.7 yrs)	1,285 U/L (1)
Alam 2006	10.5%	1.5% (12.7mos)	964 U/L (1)	Kuhn 2008	17%	5.1% (1.4 yrs)	503 U/L (1)
Veselka 2014 (Cath Cardio. Int)	9.4%	0.4% (3 mos)	NR	Veselka 2014 (Int. J Cardiol)	10%	~5% (from KP curve)	NR

Veselka 2013	8.3%	0.7% (3-6 mos)	1382 U/L (1) 121 U/L (2)	**Faber 2007**	7.1%	0 (3 mos)	466 U/L (1) 53 U/L (2)
Veselka 2009* **	35%	NR (6 mos)	2.6 uKat/L (2)	**El-Jack 2007**	18%	NR (follow-up time not stated)	NR
Veselka 2005 (Echocardiography.)	11%	4% (12 mos)	NR	**Chang 2003**	14%	NR (up to 4 yrs)	1331 U/dL (1)
Sorajja 2012	1.7%	2.8% (5.7 yrs)	NR	**Veselka 2014 (Can. J Cardio)**	6.7%	5% (5.1 yrs)	2.6 uKat/L (2)
Ralph-Edwards 2005	25%	5% (2 yrs)	NR	**Leonardi 2013**	12.5%	6% (12 mos)	1221 U/L-young (1) 1123 U/L-middle aged (1) 1183 U/L-elderly (1)
Van der Lee 2005	9.3%	4.6% (1 yr)	NR	**Veselka 2006 (Circ J 70:880-84)**	6.8%	0 (12 mos)	2.99 uKat/L-Group A (2) 2.27 uKat/L-Group B (2) 2.97 uKat/L-Group C (2)
Firoozi 2002	NR	NR (45.6 mos SM cohort) (27.2 mos PTSMA cohort)	NR	**Gietzen 2004**	18% (< 60 yrs) 34% (≥ 60 yrs)	2.5% (< 60 yrs) 2.6% (≥ 60 yrs)	596 U/L (< 60 yrs) (1) 491 U/L (≥ 60 yrs) (2)
Qin 2001	24%	0 (128 days)	NR	**Nagueh 2007**	10% (after myectomy)	0 (19 mos)	1331 U/L-1st PTSMA (1) 736 U/L-2nd

							PTSMA (1)
Nagueh 2001	22%	2.4% (1 year)	NR	**Jassal 2006**	NR	NR (1 yr)	NR
Veselka 2012	3%	4% (44 mos)	2.4 uKat/L (2)	**Mazur 2001**	26.9%	NR (2 yrs)	2009 U/L (1)

*Leonardi 2010: calculated by FDA reviewer: (250 all cause deaths + 45 sudden cardiac deaths)/2207 (total sample size); ** Agarwal 2010: no data but Forest plots show no difference for mortality and significance favoring SM for PPM over PTSMA; ***Veselka 2009: it is not clear if the number of patients paced = permanent pacemaker

Source: FDA reviewer compilation of data from Applicant's NDA submission publications

7.1 Risk Factors for Complete Heart Block

A key adverse safety feature of PTSMA over SM was the development of a sustained complete heart block necessitating the implantation of a permanent pacemaker. Faber (2007) developed a scoring system to predict the risk of a complete heart block during the PTSMA (see Table 65). The risk factors for the development of a complete heart block included baseline PQ interval > 160 ms, baseline minimum heart rate <50, baseline LVOT-PG 70 mmHg, development of 3rd degree AC block, no recovery, maximum QRS width during the first 48 hours > 155ms, and timing of peak enzyme GOT (U/L) > 16 hours (+1 score) or > 20 hours (+3 score). Of the 11 parameters in the scoring system, many have been identified after the procedure was started. Baseline hemodynamics and PQ interval on the baseline ECG were identified as risk factors that could be identified before the procedure.

The incidence of complete heart block requiring a permanent pacemaker for 3 age stratifications defined by Leonardi (2013) were: 8.2% (n=110, < 45 years-young), 5.0% (n=159, 45-64 years-middle-aged), 12.5% (n=120, ≥ 65 years-elderly). The difference between the young and elderly group, and between the middle-aged and elderly group, was considered significant.

Reviewer Comment: Based on the body of evidence, the label should describe age, as well as baseline ECG and hemodynamic parameters described by Faber (2007), as risk factors for a complete heart block requiring a permanent pacemaker.

7.2 Effect of Age

In a study by Veselka et al (2014, Canadian J Cardiol., 30: 634-638; n=75), PTSMA improved subjective functional capacity in the young population (age ≤ 50 years). However, the mortality rate was worse than that of the general population.

Sorajja et al (2012) reported that patients who underwent PTSMA had an 8 year survival indistinguishable from that of the general US population (average age 62 ± 13 years, see Figure 15). There was no comparative mortality data in this population who have undergone SM. The pacemaker placement rate was 6.7% (similar to the rate in other retrospective studies).

Leonardi (2013) reported that PTSMA caused symptomatic improvement from baseline that was similar amongst three age groups (< 45 years, n=110; 45-64 years, n=159; ≥ 65 years, n=120). However, the complication rate was significantly higher in the elderly cohort.

Veselka et al (2006, Circ. J, 70: 880-884) evaluated PTSMA in three age groups: Group A (n=14; ages 24-48 years), Group B (n=14; ages 49-60 years), and Group C (n=16; ages 61-81 years). Left ventricular septal thickness, at baseline and over the course of follow-up time, was more pronounced in the younger population, and earlier reduction of LVOT-PG was observed in the elderly group. In the lumped patient population, symptomatic improvement and reduction in LVOT-PG was observed but there was no clinical data for individual age groups.

Gietzen (2004) evaluated PTSMA outcome in 2 age groups (< 60 years, n=80; ≥ 60 years, n= 77 years). The data suggested that the older group had worse symptoms and lower exercise capacity than the younger group. PTSMA outcome for symptomatic and objective functional improvement were similar for both age groups and respectively significant from baseline. However, the older age group had a higher complication rate, particularly complete heart block and pacemaker placement.

Reviewer Comment:

- *Veselka et al (2014, Canadian J Cardiol., 30: 634-638; n=75): The younger population (age ≤ 50 years) were not normalized for mortality to the general population following PTSMA and there was no data on SM with this population. Because of the retrospective nature of this data, the age-related findings could be by chance alone.*
- *Gietzen (2004): Symptomatic and objective improvements were similar amongst all age groups although the complication rate was higher in the elderly population.*

7.3 Dose Dependency for Adverse Events

A safety concern about a dose-dependent therapeutic index was raised by the data published from the German TASH registry. The study by Faber et al (2005) showed that the higher the CK value, the more pronounced was the reduction in LVOT-PG, but the mortality rate was higher. Mean peak CK values were 477 U/L in survivors and 721 U/L in those who died. Using the same TASH registry, Kuhn (2008) concluded that patients treated with high amounts of ethanol (> 2.0 mL) showed a higher total mortality than patients treated with small amounts (≤ 2.0 mL), and that a lower alcohol dose turned was determined to be an independent predictor of survival. Also, one study suggested that a bolus induced adverse outcome compared to a slow infusion (Chang, 2003). The dose of ethanol optimizing the therapeutic index for PTSMA in refractory symptomatic HOCM patients has not been clearly defined.

Reviewer Comment: I have no explanation for the counter-intuitive finding that patients who died had a more pronounced decrease in LVOT-PG as well as a higher peak CK-MB compared to those who survived at follow-up. I can only hypothesize that a potentially excessive MI causing a more pronounced LVOT-PG reduction might have been due to procedural complications requiring a higher volume of ethanol in order to achieve the desired reduction in LVOT-PG. There might have been ethanol spillage into a more proximal artery (i.e. LAD) that was not reported or published, resulting in an infarct that precipitated subsequent adverse clinical outcomes ending in death. In the Faber (2005) study, there was no difference in ethanol dose between those who survived at follow-up and those who did not survive. An alternative hypothesis is that these observations from the Faber (2005) publication could have been due to chance because it was a subgroup analysis of registry data. These data were not corroborated by independent publications. I propose mentioning the TASH registry observations by Faber (2005) and Kuhn (2008) in the label as part of the body of evidence provided by the Applicant.

7.4 Death and Other Complications from Veselka Database

The 100-patient Veselka database was reviewed for safety assessment. An information request was submitted to the Applicant for patient narratives involving death and procedure-related complications. We received this information on August 27, 2015. The Applicant did not verify if the safety profile of the 80 patients whose data were not submitted was equivalent to that of the 100 patients whose safety profile was made available for review.

Of these 100 patients, there were 14 deaths for the mean follow-up period of 67.4 months resulting in an annual all-cause mortality rate of 2.5%. This was similar to the published studies. In addition to the 14 deaths, there were 35 non-fatal adverse events (i.e. 13 with complete heart block requiring a permanent pacemaker, 16 with heart

blocks that did not require a permanent pacemaker, and 6 with other complications such as placement if an implantable cardiac defibrillator (ICD), patent foramen ovale closure during the PTSMA, pseudoaneurysm and pleural effusion, inadequate ICD discharge, and non-sustained ventricular tachycardia).

A listing of the 14 patients who died is shown in Table 89. Individual patients are identified by number ranging from 1 to 100. The average age of the patients who died was 64.3 years and ranged from 44.1 years to 84.1 years. The median age of the patients who died was 62.1. Of these, 5 died of stroke, 3 died of heart failure, 2 died of sudden death, 1 died of sepsis, 1 died of pulmonary embolism, 1 died of pulmonary fibrosis while awaiting a lung transplant during which time a PTSMA for HOCM was performed, and 1 cause of death was unknown but probably heart failure. The mean time between the PTSMA and death was 3.7 years, ranging from 1 year to 9 years. Of these, 5 patients died within 1→1.5 years since their PTSMA, representing the shortest time period between procedure and death. The causes of death in those patients who died in this shorter time period were pulmonary fibrosis x 1, stroke x 2, sepsis x 1, and sudden death x 1. The average age of the patients who died with 1→1.5 years since their PTSMA was 70 and ranged from 53 years to 84 years.

Reviewer Comment: there was no difference in age between those patients who died following PTSMA regardless of time to death and those patients who died within 1→1.5 years post-PTSMA.

The total dose of alcohol ranged from 1 mL to 2.5 mL. Only 2 patients received alcohol doses greater than 2 mL (patient (b) (6) who received 2.3 mL alcohol and died of sudden death, and patient (b) (6) who received 2.5 mL alcohol and died of stroke).

A summary and my independent assessment of the death narratives are found in Table 90. An independent calculation derived directly from narratives, as opposed to the data provided by the Applicant, showed that the average age of the patients who died was 64 years, ranging from 44 years to 84 years. The median age of the patients who died was 62 years, thus corroborating what was shown in Table 89. The average total dose of alcohol and the average dose of alcohol per septal artery administered to patients who died were 1.5 mL and1.4 mL/septal artery, respectively. The narratives indicated that most of the patients who died had a complicated co-medical history (i.e. pulmonary fibrosis: patient (b) (6) hypertension/polycythemia vera: patient (b) (6) meningioma/seizure/atrial fibrillation/stroke: patient (b) (6) chronic renal insufficiency/nephrotic syndrome due to polycystic kidney disease/kidney transplant: patient (b) (6) chronic obstructive pulmonary disease/atrial fibrillation/ papillary thyroid cancer/recto-sigmoid carcinoma: patient (b) (6) breast cancer/abdominal aortic aneurysm/end stage renal disease/ventricular fibrillation/heart failure: patient (b) (6) (b) (6) rheumatic mitral and aortic valve disease/paroxysmal atrial fibrillation: patient peptic ulcer disease/gastrointestinal hemorrhage: patient (b) (6) ischemic heart disease/resistant hypertension: patient (b) (6) breast cancer/hypothyroidism/atrial

fibrillation/ischemic stroke with residual hemiparesis/chronic interstitial nephritis: patient (b) (6) chronic obstructive pulmonary disease/thyroidectomy followed by hypothyroidism /hypertension /dyslipidemia/hyperuricemia: patient (b) (6) atrial fibrillation/sick sinus syndrome/ amiodarone-induced thyrotoxicosis/heart failure: patient (b) (6) Only 2 patients who died had an innocuous medical history: patient (b) (6) (moderate mitral regurgitation-implied asymptomatic and insignificant patent foramen ovale), and patient (b) (6) (hypertension and dyslipidemia).

Based on peri-procedural reduction of LVOT-PG and improvement of NYHA class, PTSMA was largely successful in those patients who died. However, two patients were reported to have suboptimal results. In patient (b) (6) who died of stroke 2 years after PTSMA, LVOT-PG was reduced post-PTSMA but the NYHA class remained unimproved. In patient (b) (6) who died of heart failure 3 years after PTSMA, there was post-PTSMA pulmonary edema despite significant reduction of LVOT-PG and improvement in NYHA class.

In patient (b) (6) the cause of death was sepsis which I believe was iatrogenic due to infection of the temporary pacemaker electrode placed as a consequence of complete heart block induced by PTSMA. In the 2 cases of sudden death (patient (b) (6) and patient (b) (6) the narratives suggested that sudden death was an iatrogenic complication of ventricular arrhythmia associated with PTSMA.

Reviewer Comment: Given the natural history of the disease as described in section 2.1 of my review, the causes of death were consistent with the observed age-related causes of death. The duration of time between PTSMA and death suggested that the procedure did not cause the death with the exception of the two patients who died from sudden death. In these two cases, I believe that iatrogenic conduction disturbance due to PTSMA was the cause of death despite the 7 year timespan between PTSMA and sudden death in patient (b) (6) and the 1 year timespan between PTSMA and sudden death in patient (b) (6) I saw no dose-dependent or age-dependent mortality safety signal in this database. The mortality rate in this database was similar to that reported in the body of publications provided by the Applicant.

Table 89. Patients who died after undergoing PTSMA

Patient No.	Age at PTSMA[a]	Sex	Date of PTSMA[a]	Alcohol Dose (mL)[a]	Date of Death	Cause of death
(b) (6)	44.1	Female	(b) (6)	1	(b) (6)	Unknown; probably heart failure
	53.0	Male		1		Respiratory failure due to pulmonary fibrosis
	69.1	Female		1.5		Pulmonary embolism
	54.6	Female		1		Stroke
	58.1	Male		1		Heart failure
	62.1	Female		2.3		Sudden death
	73.8	Female		1.5		Heart failure
	48.8	Female		2.5		Stroke
	74.7	Female		1.2		Severe pneumonia resulting in sepsis
	63.1	Male		1.5		Stroke
	78.4	Female		1		Stroke
	84.1	Female		1		Stroke
	75.5	Female		2		Sudden death
	61.2	Female		1		Heart failure

[a] Some patients had more than 1 PTSMA procedure. The patient age, date, and alcohol dose are presented for the first procedure. Details of subsequent procedures when applicable are presented in the narratives.

Source: Patient Narratives Document received from Applicant August 2015

Table 90. FDA Review of Veselka Database Death Narratives

Patient # (age at initial PTSMA; race-gender)	Cause of Death (Applicant)	Cause of Death (Reviewer Assessment of Narratives)	Reviewer Comment
(b) (6)	Unknown: probably HF	Agree with Applicant	Dx HCM unknown; hx mod MR; Two failed PTSMA (b) (6) -1mL EtOH/1 SA, (b) (6) 2mL EtOH /1 SA complicated by CHB with PPM in (b) (6) SM (b) (6) died of HF (b) (6)
	Pulmonary Fibrosis	Agree with Applicant	Dx HCM (b) (6) hx pulmonary fibrosis awaiting lung transplant; successful PTSMA (b) (6) -1mL EtOH/1 SA; died of pulmonary fibrosis (b) (6)
	Pulmonary Embolism	Agree with Applicant	Dx HCM unknown; hx arterial HTN and PCV; successful PTSMA (b) (6) 1.5 mL EtOH/1 SA complicated by CHB with TPM followed by sepsis 2° infection of TPM electrode; died of PE (b) (6)
	Stroke	From narrative, cause of death appeared to be MI one year after stroke, unless the patient had a second stroke (b) (6) wording unclear	Dx HCM unknown; hx arterial HTN, dyslipidemia, obesity, PUD; successful PTSMA (b) (6) 1 mL EtOH/1 SA; removal meningioma complicated by PE and seizure (b) (6) ; AF put on Warfarin (b) (6) Stroke (b) (6) died of MI (b) (6)
	HF	Agree with Applicant	Dx HCM unknown; hx CRI 2° PCKD and nephrotic syndrome; successful PTSMA (b) (6) 1 mL EtOH/1 SA; kidney transplant (b) (6) died of HF (b) (6)
	Sudden Death	Agree with applicant. I believe death was likely a complication of ventricular arrhythmia associated with PTSMA.	Dx HCM unknown; hx COPD, AF, papillary thyroid cancer s/p radioiodine Rx (b) (6) successful PTSMA (b) (6) 2.3 mL EtOH/1 SA complicated by CHB →IMI→Arrhythmic Storm requiring defib x 6→still CHB with junctional escape→discharged AMA; follow-up (b) (6) : NSR with RBBB and treated for recto-sigmoid carcinoma; died sudden death (b) (6)
	HF	Agree with Applicant	Dx HCM unknown; no significant medical history; successful PTSMA 2005- 1.5 mL EtOH/1 SA; Vfib during follow-up but no PPM / ICD; breast cancer (b) (6) endovascular Rx for AAA complicated by CRI requiring HD (b) (6) admitted after CPR for Vfib Aug (b) (6) ; died of HF Oct (b) (6)
	Stroke	Agree with Applicant	Dx HCM unknown; hx dyslipidemia, rheumatic MV and AV disease; successful PTSMA (b) (6) 2.5 mL EtOH/1 SA complicated by transient CHB s/p day 3 post-PTSMA with no PPM; PAF with warfarin Rx (b) (6) died of stroke (b) (6)

(b) (6)	Pneumonia-Sepsis	Agree with Applicant	Dx HCM unknown; hx arterial HTN, PUD, GI Bleed (b) (6) and (b) (6) successful PTSMA (b) (6) 1.2 mL EtOH/1 SA complicated by transient CHB with temporary PM →good health at 1 year follow-up; died of pneumonia and sepsis (b) (6)
	Stroke	Agree with Applicant	Dx HCM unknown; hx IHD and resistant arterial HTN; successful PTSMA (b) (6) 1.5 mL EtOH/1 SA complicated by development of RBBB; good condition 1 year follow-up (b) (6) died of stroke (b) (6)
	Stroke	Agree with Applicant	Dx HCM 2006 Rx' d with PPM; hx breast cancer, hypothyroidism, AF, ischemic stroke (b) (6) with residual left hemiparesis, chronic interstitial nephritis; successful PTSMA (b) (6) 1 mL EtOH/2 SA (LVOT-PG improved but NYHA remained at III even last follow-up (b) (6); died of stroke (b) (6)
	Stroke	Agree with Applicant	Dx HCM unknown; hx arterial HTN and dyslipidemia; successful PTSMA (b) (6) 1 mL EtOH/1 SA; 1 month follow-up pt asx with optimal echo; died of stroke (b) (6)
	Sudden Death	Agree with Applicant. I believe death was likely a complication of ventricular arrhythmia associated with PTSMA.	Dx HCM unknown; hx COPD, smoking, hypothyroidism s/p thyroidectomy, arterial HTN, dyslipidemia, and hyperuricemia; successful PTSMA (b) (6) 2 mL EtOH/2 SA complicated by polymorphic VT requiring defib, then sustained RBBB; non-sustained SVT / VT 7 days after PTSMA →refused ICD and was dismissed in SR and RBBB; died sudden death (b) (6)
	HF	Agree with Applicant	Dx HCM (b) (6); hx arterial HTN, AF, and PPM for sick sinus syndrome (b) (6) successful PTSMA (b) (6) 1 mL EtOH/1 SA but initial results suboptimal 2° post-PTSMA HF and pulmonary edema despite significant reduction in LVOT-PG and improvement in NYHA from class IV to class III-rx' d conservatively; ICD implanted for primary prevention of sudden cardiac death at follow-up (b) (6); AF / amiodarone-induced thyrotoxicosis undergoing electric cardioversion (b) (6) died of HF (b) (6)

Note: Reviewer judgment of "successful PTSMA" was based on LVOT-PG reduction and NYHA class improvement; AAA = Abdominal Aortic Aneurysm; AF = Atrial Fibrillation; AMA = Against Medical Advice; asx = asymptomatic; AV = Aortic Valve; CHB= Complete Heart Block; COPD = Chronic Obstructive Pulmonary Disease; CRI = Chronic Renal Insufficiency; HD = Hemodialysis; HF = Heart Failure; HTN = Hypertension; ICD = Internal Cardiac Defibrillator; IHD = Ischemic Heart Disease; IMI = Inferior Myocardial Infarction; MR = Mitral Regurgitation; MV = Mitral Valve; NSR =

Normal Sinus Rhythm; PAF = paroxysmal atrial fibrillation; PCKD = Polycystic kidney disease; PCV = Polycythemia Vera; PE = Pulmonary Embolism; PPM = permanent pacemaker; PUD = Peptic Ulcer Disease; Rx = treatment; SA = Septal Artery; s/p = status post; SR = sinus rhythm; SVT = supraventricular tachycardia; TPM = temporary pacemaker; VT = ventricular tachycardia

Source: FDA Reviewer Compilation

A listing of the 13 patients (4 male and 9 female) in the Veselka database who experienced a heart block and who required a pacemaker shortly after PTSMA is shown in Table 91. The narratives for these patients were reviewed, compiled, and are shown in Table 92. The average age of this subgroup was 57 years, ranging from 45-73 years, and the median age was 54 years. The average total amount of ethanol used was 1.9 mL. The average dose of ethanol per septal artery was 1.4 mL/artery. The rate of permanent pacemaker requirement was 13% which was similar to the rate reported in the publications provided by the Applicant.

There were some discrepancies in the information between the listing from the Applicant (Table 91) and the data from the narratives (Table 92). For example, the listing from the Applicant specified that patient (b) (6) sustained a 1º atrial-ventricular block and transient left bundle branch block, leading me to believe that this complication was the cause of the placement of a pacemaker. Based on the narrative, the patient had a syncopal episode accompanied by a right bundle branch block and left anterior hemiblock one year after PTSMA that precipitated the placement of a pacemaker. In patient (b) (6) the patient had a right bundle branch block, paroxysmal supraventricular tachycardia, and non-sustained ventricular tachycardia. The patient was electrically cardioverted and went into asystole due to a complete heart block. Cardiopulmonary resuscitation was required and ultimately a pacemaker was placed. These events were not captured in the Applicant's listing of complications (i.e. supraventricular tachycardia and complete heart block) associated with the placement of a pacemaker.

Of the 13 cases where a pacemaker was placed, 8 were due to periprocedural development of complete heart block (patient # (b) (6)). The remaining 5 cases did not appear to be related to PTSMA because of substantial durations of time between the procedure and the pivotal event that precipitated the placement of a pacemaker:

- Patient (b) (6) complete heart block 11 years after a 2nd PTSMA.
- Patient (b) (6) syncope 1 year after PTSMA.
- Patient (b) (6) 2º atrial-ventricular block 2 years after the initial PTSMA and 4 years prior to the 2nd PTSMA.
- Patient (b) (6) recurrence of LVOT-PG 3 years after PTSMA resulting in pacemaker placement. I defined this as a failed PTSMA rather than a procedural complication.
- Patient (b) (6) 1º atrial-ventricular block with left bundle branch block occurring 1 year after SM performed as a consequence of failed PTSMA 7 years earlier.

A listing of the 16 patients (7 male, and 9 female) in the Veselka database who experienced either a heart block or dysrhythmia but did not require a permanent pacemaker or ICD after PTSMA is shown in Table 93. The narratives for these patients were reviewed, compiled, and are shown in Table 94. The average age of this subgroup was 59.5 years, ranging from 25-81 years, and the median age was 61 years. The average total amount of ethanol used was 1.4 mL. The average dose of ethanol per septal artery was 1.2 mL/artery.

The information provided by the Applicant (Table 93) was consistent with that compiled from the narratives (Table 94) with the one exception involving patient (b) (6) The Applicant listed this patient as having experienced a ventricular tachycardia and right bundle branch block after PTSMA. Based on the narrative, the patient had polymorphic ventricular tachycardia and loss of consciousness requiring electric cardioversion followed by additional runs of non-sustained ventricular tachycardia. This patient had a normal electrophysiology study and was dismissed without a permanent pacemaker or ICD. The seriousness of the complication was not captured in the Applicant's listing.

The course of the post-PTSMA patients, who had a heart block or ventricular arrhythmia but did not require a pacemaker or ICD, was uncomplicated with two exceptions: patient (b) (6) just described and patient (b) (6) Patient (b) (6) was a 25 year old while male who had two PTSMAs because of a failed initial procedure. The patient had prophylactic placement of an ICD after the initial PTSMA that subsequently discharged, leading to the 2nd PTSMA. The patient experienced a left anterior hemiblock after the 2nd PTSMA and several ICD discharges. The patient had a stroke 4 years after the 2nd PTSMA and an infected ICD mandating its removal. There was no further follow-up reported by the Applicant.

A comparison of patient and procedural characteristics between those patients who developed a heart block and required a pacemaker versus those patients who developed a heart block and did not require a pacemaker is shown in Table 95. The age of the patients and the total ethanol dose, as well as the dose of ethanol per septal artery, were similar between both groups. There was no outstanding characteristic available in the Veselka database that would that would serve as prognostic indicator for a pacemaker requirement post-PTSMA. Based on the work of El-Jack (2007), the strongest prognostic indicator of a complete heart block following PTSMA was a pre-existing left bundle branch block.

Table 96 lists 6 patients with complications other than a complete heart block. Three of these patients had adverse events that may have been related to PTSMA (i.e. ICD placed: patient (b) (6) ICD discharges: patient (b) (6) and non-sustained ventricular tachycardia: patient (b) (6)

Reviewer Comment: The rate of pacemaker placement consequent to complete heart blocks observed in the Veselka database was similar to that observed in the published

literature. The adverse events associated with dysrhythmia were expected in the PTSMA population. I cannot rule out that the rate of pacemaker placement or mortality or dysrhythmia might have been much higher if the entire database, rather than approximately half of the database, was provided by the Applicant.

Table 91. Patients with Heart Block who had Pacemakers Placed after PTSMA

Patient No.	Age at ASA[a]	Sex	Date of ASA[a]	Alcohol Dose (mL)[a]	Complete AV block after ASA	Complication
(b) (6)			(b) (6)	1.5	Yes	Complete heart block
				3	Yes	Complete heart block after second PTSMA procedure (b) (6)
				3	Yes	Complete heart block considered not related to PTSMA; results of procedure were suboptimal
				2	No	1st degree AV block and transient left bundle branch block
				1	No	Uncomplicated PTMSA procedures; in (b) (6) the patient was given a PM for syncope and 2nd degree AV block
				1	Yes	Transient complete heart block during PTSMA; results of procedure were suboptimal; PM
				1.2	Yes	Procedure results suboptimal; later received PM after myectomy
				1	Yes	Transient complete heart block; incomplete right bundle branch block and left anterior hemi-block
				0.6	Yes	Complete heart block
				1	Yes	Complete heart block
				1.5	Yes	Supraventricular tachycardia and complete heart block
				1	Yes	Complete heart block
				1.5	Yes	Complete heart block

[a] Some patients had more than 1 PTSMA procedure. The patient age, date, and alcohol dose are presented for the first procedure. Details of subsequent procedures when applicable are presented in the narratives.

Source: Patient Narratives Document received from Applicant August 2015

Table 92. Narrative Review of Patients Requiring Pacemaker from Veselka Database

Patients with Heart Block Requiring Pacemaker: from Narratives			
Patient #	Age at PTSMA race-sex	Total Alcohol Dose (mL) [Alcohol Dose/Artery]	Past Medical History (PMH)
(b) (6)		1.5 [1.5]	HTN, dyslipidemia; CHB during PTSMA (b) (6) →PPM
		4 [2]	Hyperthyroidism; 2 PSTMAs (b) (6): 3 mL/1 SA→1 mL/1 SA; CHB s/p 2nd PTSMA→PPM
		6.5 [3.25]	Peptic Ulcer Disease; 2 PTSMAs (b) (6) 3 mL/1 SA→3.5 mL/1 SA; CHB (b) (6)→ PPM
		2 [2]	PSVT, HTN, dyslipidemia; PTSMA (b) (6) syncope with RBBB and LAHB (b) (6)→PPM
		1.5 [0.75]	HTN; 2 PTSMAs (b) (6) 1 mL/1 SA→0.5 mL/1 SA; syncope with 2nd degree AVB (b) (6)→PPM
		1 [1]	HTN; dyslipidemia; actinotherapy 2° adenocarcinoma; PTSMA (b) (6) LVOT re-obstruction (b) (6) but NYHA class 1→PPM (b) (6)
		1.2 [1.2]	No PMH; PTSMA (b) (6) suboptimal→ SM (b) (6) followed by LBBB and 1° AVB and pre-syncope→PPM (b) (6)
		1 [1]	Dyslipidemia; hyperuricemia; PTSMA (b) (6) (b) (6) with transient CHB→CPR 2° CHB (b) (6) (b) (6)→PPM (b) (6)
		0.6 [0.6]	HTN; hypothyroidism; asthma; PTSMA (b) (6) with CHB during procedure→PPM
		1 [1]	HTN; T2DM; PTSMA (b) (6) with CHB 3 days s/p procedure→PPM
		1.5 [0.75]	HTN; chronic venous insufficiency; PTSMA (b) (6) complicated by RBBB/NSVT/PSVT requiring electro-cardioversion/asystole 2° CHB with need for CPR→PPM
		1 [1]	HTN; dyslipidemia; "aortic valve disease"; GERD; PTSMA (b) (6) with CHB s/p day 2→PPM
		1.5 [1.5]	No PMH; PTSMA (b) (6) immediately followed by CHB→PPM

AVB=atrial-ventricular block; CHB=complete heart block; GERD=gastro-esophageal reflux disease; HTN=hypertension; LAHB=left anterior hemiblock; NSVT=non-sustained ventricular tachycardia; PPM=permanent pacemaker; PSVT=paroxysmal supraventricular tachycardia; RBBB=right bundle branch block; s/p=status post; T2DM=type 2 diabetes mellitus

Source: FDA Reviewer Compilation of data from Narratives

Table 93. Patients with Heart Block who did not require a pacemaker

Patient No.	Age at ASA[a]	Sex	Date of ASA[a]	Alcohol Dose (mL)[a]	Complete AV block after ASA	Complication
(b) (6)				1.7	Yes	Ventricular tachycardia during PTSMA; transient complete heart block after the procedure
				2.5	Yes	Transient complete heart block during procedure; sinus rhythm with right bundle branch block on discharge
				1	No	Right bundle branch block; ICD placed
				1	Yes	Transient complete heart block
				1	Yes	Asymptomatic bifascicular block then intermittent complete heart block; sinus rhythm was restored
				1	Yes	Transient complete heart block; sinus rhythm and left anterior hemi-block after PTSMA
				2	No	Right bundle branch block with a left anterior hemi-block
				1	No	Ventricular tachycardia; right bundle branch block after procedure
				1	Yes	Transient complete heart block
				2	No	Right bundle branch block and non-sustained ventricular tachycardia
				1	No	Right bundle branch block and non-sustained ventricular tachycardia
				1	Yes	Transient complete heart block
				1.5	No	Right bundle branch block with a left anterior hemi-block
				1.5	No	Focal atrial tachycardia, asymptomatic right bundle branch block, left posterior hemi-block, and first degree AV block
				1.5	No	Right bundle branch block with a first degree AV block
				0.8	Yes	Transient complete heart block

[a] Some patients had more than 1 PTSMA procedure. The patient age, date, and alcohol dose are presented for the first procedure. Details of subsequent procedures when applicable are presented in the narratives.

Source: Patient Narratives Document received from Applicant August 2015

Table 94. Narrative Review of Patients not requiring a pacemaker

Patients with Heart Block Not Requiring Pacemaker: from Narratives			
Patient #	Age at PTSMA race-sex	Total Alcohol Dose [Alcohol Dose/Artery] mL	Past Medical History (PMH)
(b) (6)		1.7 [1.7]	Osteoporosis; anxiety; PTSMA (b) (6) with torsade de pointe during PTSMA followed by transient CHB 2 days after procedure → temporarily paced x 3 days
		2.5 [2.5]	Dyslipidemia; T2DM; hypothyroidism; PTSMA (b) (6) complicated by transient CHB and did not require pacing. Discharged with NSR and RBBB.
		2 [0.67]	No PMH; 2 PTSMAs (b) (6); 1 mL/1 SA →1 mL/2 SA; RBBB after 1st PTSMA; prophylactic ICD placement 2006 discharged (b) (6) resulting in 2nd PTSMA; LAHB after 2nd PTSMA→ICD discharges; AF (b) (6); stroke (b) (6) ICD explanted 2° infection.
		1 [1]	Hypothyroidism; PTSMA (b) (6) complicated by transient CHB and did not require pacing
		1 [1]	Ischemic stroke (b) (6); BPH; dyslipidemia; PTSMA (b) (6) complicated by asymptomatic bifascicular block→intermittent CHB→ temporary pacing; dismissed in NSR and asymptomatic bifascicular block without need for permanent pacing
		1 [1]	Hyperthyroidism; ischemic heart disease; PAF; emphysema; PTSMA (b) (6) complicated by transient heart block and transient pacing; dismissed with NSR and LAHB without need for permanent pacing.
		2 [2]	Smoker; obesity; HTN; PTSMA (b) (6) complicated by asymptomatic RBBB and LAHB.
		1 [1]	HTN; GERD; PTSMA (b) (6) complicated by sustained torsade de pointe and loss of consciousness→electric cardioversion →additional runs of non-sustained ventricular tachycardia→ normal EPS; no PPM or ICD
		1 [1]	Ischemic heart disease; PAF; HTN; obesity; PTSMA (b) (6) complicated by CHB with junctional rhythm1 week post-PTSMA→temporary pacing not required and NSR restored after 4 days.
		2 [1]	No PMH; PTSMA (b) (6) complicated by non-sustained ventricular tachycardia during procedure followed by RBBB and several runs of non-sustained ventricular tachycardia→ PPM / ICD not indicated
		1 [1]	Hypertension; dyslipidemia; ischemic heart disease; PTSMA (b) (6) complicated by RBBB; 4short runs of asymptomatic non-sustained ventricular tachycardia 4 days post-PTSMA. PPM / ICD not indicated
		1 [1]	Hypertension; dyslipidemia; non-ST elevated anterior myocardial infarction s/p PCI of LAD; PTSMA (b) (6) complicated by transient CHB during procedure which

(b) (6)		did not require pacing.
	1.5 [1.5]	Dyslipidemia; 1° AVB; PTSMA (b) (6) complicated by asymptomatic RBBB and LAHB→ pacing not required.
	1.5 [0.75]	PAF; PTSMA (b) (6) complicated by simultaneous PCI of diagonal branch and focal atrial tachycardia requiring electrical cardioversion→ RBBB and LPHB and 1° AVB. PPM not indicated.
	1.5 [1.5]	Hypertension; hypothyroidism; glaucoma; PTSMA (b) (6) complicated by RBBB and 1° AVB. Pacing not indicated.
	0.8 [0.8]	Hypertension; hypothyroidism; dyslipidemia; PTSMA (b) (6) complicated by transient complete heart block during procedure. Permanent pacing not indicated.

AVB=atrial-ventricular block; AF=atrial fibrillation; Benign Prostatic Hyperplasia; CHB=complete heart block; EPS= electrophysiology study; GERD=gastro-esophageal reflux disease; HTN=hypertension; ICD=implantable cardiac defibrillator; LAD=left anterior descending artery; LAHB=left anterior hemiblock; LPHB=left posterior hemiblock; NSR=normal sinus rhythm; PAF= paroxysmal atrial fibrillation; PCI=percutaneous coronary intervention; PPM= permanent pacemaker; s/p=status post; T2DM=type 2 diabetes mellitus

Source: FDA Reviewer Compilation of data from Narratives

Table 95. Characteristics of Veselka Patients Requiring vs Not Requiring Pacemakers

	Heart Blocks Requiring PPM	Heart Blocks not Requiring PPM
Sample Size	13	16
Average Age (years)	57.5	59.5
Age range	45-73	25-81
Median Age	54	61
Average Total Ethanol Dose (mL)	1.9	1.4
Average Dose (mL) per Septal Artery	1.4	1.2

Source: FDA Reviewer Compilation of Data from Narratives

Table 96. Patients with Complications Other Than Complete Heart Block

Patient No.	Age at ASA[a]	Sex	Date of ASA[a]	Alcohol Dose (mL)[a]	Major complication
(b) (6)				2	ICD placed
				2	Patent foramen ovale closure during the procedure; suffered from bleeding from the puncture site after the procedure; ICD placed
				1.5	Pseudoaneurysm; pleural effusion due to heart failure
				1.2	Several inadequate ICD discharges during follow-up due to runs of AV nodal re-entrant tachycardia
				0.7	Non-sustained ventricular tachycardia
				1	Pseudoaneurysm

[a] Some patients had more than 1 PTSMA procedure. The patient age, date, and alcohol dose are presented for the first procedure. Details of subsequent procedures when applicable are presented in the narratives.

Source: Patient Narratives Document received from Applicant August 2015

8 Appendices

8.1 Literature Review/References

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8.2 Labeling Recommendations

The following is a preliminary sketch of the recommended label:

(1) Indication: In patients with refractory symptomatic hypertrophic obstructive cardiomyopathy (HOCM) who are clinically assessed as non-candidates for surgical myectomy (SM), ethanol be approved to induce septal myocardial necrosis when used as an adjunct to percutaneous transluminal septal myocardial ablation (PTSMA) to improve exercise capacity.

(2) Dosing and Administration: The usual dosage is a total of 1-3 mL dehydrated alcohol. The dose per septal artery is at the discretion of the interventional cardiologist. Final dosing should be titrated to LVOT-PG less than 10 mmHg during PTSMA. The highest total ethanol dose reported was 5 mL. There is no published use of ethanol exceeding 5 mL.

(3) Dosage Form and Strength: defer to CMC

(4) Contraindications: Dehydrated alcohol is contraindicated in patients who do not have suitable septal perforator branches for a successful PTSMA.

(5) Warnings and Precautions:

- Cardiac abnormalities that would increase the risk of procedure related complications, such as discreet sub-aortic stenosis, mitral valve redundant leaflets or anomalous papillary muscles, severe coronary artery disease.
- Coronary dissection associated with percutaneous coronary procedures.
- Persistent complete heart block requiring placement of a permanent pacemaker (approximately 10% incidence). Risk factors for pacemaker dependency after PTSMA are shown in the following table

Score-system to predict the risk of pacemaker dependency after percutaneous septal ablation

#	Parameter	Cutoff value	Score points
1	Baseline PQ interval (ms)	>160	+2
2	Baseline minimal heart rate (Holter, 1/min)	<50	+2
3	Baseline LVOT gradient (Echo, mm Hg)	>70	+2
4	AV block III during PTSMA (any time)	Yes	+2
5	AV block III at CCU admission	Yes	+2
6	Recovery of AV conduction at 12 h	Yes	−2
7	No recovery after 12 h	Yes	+1
8	No recovery after 24 h	Yes	+2
9	No recovery after 48 h	Yes	+3
10	Maximum QRS width during the first 48 h (ms)	>155	+3
11	Timing of GOT peak (h)	>16	+1
		>20	+3

Risk group	Score points	Procedure
Low	<8	Discharge from monitoring
Intermediate	8–12	Prolonged monitoring
High	>12	Prepare for early PM implantation

Source: Faber et al, 2007, International Journal of Cardiology, 119: 163-167

- Arrhythmias requiring electrical cardioversion.
- Suboptimal results such as residual left ventricular outflow tract pressure gradient and post-procedural signs and symptoms, requiring either a second PTSMA or referral for surgical septal myectomy.

(6) Adverse Reactions:

- Mortality: average 1.8% ranging from 1.5% (Alam 2006) to 3.9% (Fernandes 2008).
- Permanent Pacemaker requirement: average 16% ranging from 7% (Faber 2007) to 34% Gietzen (2004, in patients > 60 years old)
- Right Bundle Branch block very common following PTSMA
- Ventricular tachycardia / ventricular fibrillation requiring electric cardioversion: approximately 1% (0.68%: Veselka 2014; 1.6%: Nagueh 2011)

(7) Drug Interactions: none

(8) Specific Populations:

- Pregnancy: postpone PTSMA until after delivery and breastfeeding to avoid fetal / neonatal toxicity.
- Elderly: the rate of complications (i.e. cardiac blocks and dysrhythmia) increase with age.
- Pediatric: has not been evaluated.

(10) Overdosage: there is a direct correlation between the volume of alcohol and size of iatrogenic myocardial infarction. One study (Kuhn, 2008) suggested that a total volume exceeding 2 mL was associated with a higher mortality rate, but there were no other corroborating data. There are no publications that reported total doses in excess of 5 mL and 5 mL/septal artery. A total dose exceeding 5 mL is considered an overdose. The procedure should stop if there is failure to reduce LVOT-PG to less than 10 mmHg when reaching a total dose of 5 mL.

(11) Description: defer to CMC.

(12) Clinical Pharmacology: defer to OCP.

(13) Nonclinical Toxicology: defer to Pharm Tox.

(14) Clinical Studies: There were 38 publications of which 4 were randomized trials examining two doses of ethanol in a 1:1 randomization scheme and the remaining publications were retrospective observational studies. Thirty of the 38 publications reported improvement in New York Heart Association dyspnea symptom score and Canadian Cardiovascular System chest pain score following PTSMA. In these 30 publications, 8 also reported improvement in treadmill exercise stress testing following PTSMA.

(Studies could be listed in a table)

8.3 Advisory Committee Meeting

There will be no Advisory Committee Meeting

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/s/

FORTUNATO F SENATORE
10/29/2015

SHARI L TARGUM
11/01/2015