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STATISTICAL REVIEW(S)



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STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/Serial Number: 20-7987 / S_0000

Drug Name: ABLYSINOLTM (Dehydrated Alcohol Injection, USP)

Indication(s): Improve (b) (4) Exercise Capacity in Patients with Symptomatic, (b) (4), Hypertrophic Obstructive Cardiomyopathy (b) (4)

Applicant: Belcher Pharmaceuticals, LLC

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1. EXECUTIVE SUMMARY

1.1 Conclusions and Recommendations

This is a 505(b) (2) application that relies on published literature to support the efficacy and safety of dehydrated alcohol injection used in percutaneous transluminal septal myocardial ablation (PTSMA) in patients with symptomatic, (b) (4), hypertrophic obstructive cardiomyopathy (HOCM) (b) (4).

The available published literature studies seem to support the proposed indication of improving (b) (4) exercise capacity in HOCM patients; nonetheless, all the analyses and results are exploratory with inherent biases and many statistical issues identified from the published literature studies.

1.2 Brief Overview of Clinical Study

There was no clinical efficacy study conducted. This submission is a 505(b) (2) application that relies on published literature to support the nonclinical profile, clinical pharmacology, safety, and efficacy of Dehydrated Alcohol Injection. Alcohol and Dextrose Injection (NDA 004589 approved 17 January 1946) is the listed drug. The proposed indication is to improve (b) (4) exercise capacity in patients with symptomatic, (b) (4), hypertrophic obstructive cardiomyopathy (HOCM) (b) (4).

The published literature was searched to find clinical studies of PTSMA used in the treatment of HOCM, including initial searches for the pre-IND meeting package and later searches for review of literature published since initial searches. Searches of PubMed using the term PTSMA or its derivatives (e.g., Alcohol Septal Ablation [ASA], Septal Ethanol Ablation [SEA], Nonsurgical Septal Reduction Therapy [NSRT], or Transcatheter Ablation of Septal Hypertrophy [TASH]) were conducted. A total of 38 studies, including 4 randomized, prospective studies, 30 retrospective studies, and 4 meta-analyses were founded and used to support efficacy and safety.

Additionally, a convenience sample of patient-level outcome database (n=100) from a HOCM patient registry (N=180) at Motol University Hospital, Prague, Czech was also provided.

1.3 Statistical Issues and Findings

This NDA relies on published literature and a selected convenience sample of patient-level outcome data to support efficacy claim.

The literature based application shares a common drawback—potential bias, such as publication bias, time lag bias, outcome reporting bias. There are many statistical issues, such as lack of randomization, blinding, controls, pre-defined primary endpoint, and lack of multiplicity adjustment. Among those identified studies, only very few are randomized controlled trials (RCT). The patient-level outcome data is a convenience sample and it does not seem to provide

much useful information due to a potential selection bias. All of these make it difficult to yield a statistically persuasive conclusion for efficacy.

2. INTRODUCTION

2.1 Overview

Dehydrated alcohol, USP is a solution of $\geq$ (b) (4) % by volume of ethanol supplied in a sterile glass ampoule. Dehydrated alcohol is a potent tissue toxin that produces a small, controlled infarction when injected percutaneously into a target septal vessel, which causes the hypertrophied septum to thin. Dehydrated alcohol is used in performing PTSMA. This nonsurgical septal reduction procedure treats obstruction associated with hypertrophic cardiomyopathy (HCM), a genetic disease causing thickening of the heart septum that can obstruct proper blood flow. In the subset of HOCM patients with disabling heart failure symptoms unresponsive to pharmacologic therapy, PTSMA has been shown in studies in the published literature and in clinical use to be a safe and effective alternative to surgical septal myectomy.

2.2 Data Sources

The sponsor's datasets were stored in the directory of [\\cdsesub1\EVSPROD\NDA207987\0000](#) of the Center's electronic document room.

3. STATISTICAL EVALUATION

3.1 Data and Analysis Quality

This is a 505(b) (2) application that relies on published literature. No individual level data is available for the studies identified from the published literature. A convenient sample of patient level outcome data selected from a HOCM patient registry is provided, and the dataset is readable.

3.2 Evaluation of Efficacy

3.2.1 STUDY OBJECTIVE

This is a 505 (b)(2) submission for Dehydrated Alcohol Injection, USP. The proposed indication is to improve (b) (4) exercise capacity in patients with symptomatic (b) (4), hypertrophic obstructive cardiomyopathy (HOCM) (b) (4).

3.2.2 THE SPONSOR'S EVALUATION

The efficacy evaluation was based on the published literature studies, including 4 randomized, prospective studies, 30 retrospective studies and 4 meta-analyses, as well as a convenient sample of the patient-level outcome data obtained by Belcher from Dr. Veselka.

3.2.2.1 Published Literature Studies

1. Randomized prospective studies

A total of 206 patients who underwent PTSMA were evaluated in the 4 randomized, prospective studies comparing alcohol doses of ≤ 2 mL vs. > 2 mL (Table 1).

Table 1 Randomized Prospective Studies

Study	Objective	Patient Population	Treatment Group
Veselka 2011	To determine long-term (60 to 138 months) clinical and echocardiographic outcomes of HOCM patients treated with low (1-2 mL) or high (> 2 mL) doses of alcohol during PTSMA	Patients with Symptomatic HOCM with a NYHA class $\geq$ II receiving maximum medical therapy	-Alcohol 1-2 mL, N=37 -Alcohol > 2 mL, N=39
Veselka 2006a	To investigate the impact of ethanol dose on the long-term outcome of PTSMA for HOCM	Patients with drug-refractory symptomatic HOCM (NYHA or CCS class $\geq$ III)	-Alcohol ≤ 2 mL, N=27 - Alcohol > 2 mL, N=27
Veselka 2005a	To determine the relation between ethanol doses used during PTSMA and the short-term course of hemodynamic and morphologic changes	Patients with symptomatic HOCM (NYHA class $\geq$ II)	-Alcohol > 2 mL, N=21 - Alcohol ≤ 2 mL, N=21
Veselka 2004	To compare the high doses (2–4 mL) and lower doses (1–2 mL) of alcohol used during PTSMA in terms of clinical, ECG, and echocardiographic outcome.	Patients with symptomatic HOCM receiving maximum medical therapy	-Alcohol > 2 mL, N=21 -Alcohol 1-2 mL, N=21

(Source: The sponsor's Table 2.7.3-2)

Summary of results:

- Two alcohol doses of ≤ 2 mL vs. > 2 mL were compared.
- Lower dose was associated with smaller infarction sizes.
- Both dose groups demonstrated similar improvement in survival, echocardiographic, hemodynamic, functional outcomes including PG, dyspnea (NYHA class), and angina (CCS class).

2. Retrospective studies

- A. Controlled retrospective studies comparing PTSMA vs. Myectomy: 6 Controlled studies and 3 meta-analyses were evaluated, comparing outcomes after PTSMA with outcomes after myectomy (Table 2).

Table 2 Retrospective Studies (Comparing PTSMA vs. Myectomy)

Study	Objective	Patient Population	Treatment Group
Sorajja 2012	To examine the long-term outcome of PTSMA in patients with obstructive HCM	Patients had severe, drug refractory cardiovascular symptoms (defined as NYHA class III/IV dyspnea, CCS angina class III/IV, or disabling syncope).	-PTSMA: alcohol 1-3 mL, N=177 -Myectomy: N=177 (matched with PTSMA patients)
Ralph-Edwards 2005	To compare outcomes following PTSMA or surgical myectomy in patients with HOCM	Symptomatic adults with HOCM who underwent intervention (either PTSMA or myectomy) for LVOT obstruction	-PTSMA: N=54 -Myectomy: N=48
Van der Lee 2005	To compare PTSMA to septal myectomy combined with mitral leaflet extension in symptomatic HOCM patients with an enlarged anterior mitral valve leaflet	Patients with symptomatic HOCM despite optimal medical treatment who underwent myectomy or PTSMA	-PTSMA: N=43 -Myectomy: N=29
Firoozi 2002	To compare subjective and objective clinical outcomes in patients undergoing surgical myectomy and PTSMA	Patients with HOCM. Patients had a NYHA class ≥ 2 despite optimal therapy. Younger patients were encouraged to undergo surgery	-PTSMA: N=43 -Myectomy: N=29
Qin 2001	To assess the subjective and objective outcomes after PTSMA and surgical septal myectomy	Symptomatic patients with HOCM. PTSMA was performed mostly in elderly patients or patients with other comorbid conditions.	-PTSMA: alcohol 1-3 mL, N=25 -Myectomy: N=26
Nagueh 2001	To compare hemodynamic efficacy at 1 year of PTSMA by intracoronary	Patients who underwent PTSMA with asymmetric LV	-PTSMA: alcohol 2-5 mL, N=41

	ethanol with surgical myectomy for the treatment of HOCM in patients matched for age and LVOT gradient	hypertrophy with a septal thickness of at least 1.5 cm and LV outflow obstruction with a resting gradient ≥ 40 mmHg.	-Myectomy: N=41 (matched with PTSMA patients)
Leonardi 2010	Meta-analysis, to compare overall survival and SCD rates after PTSMA or surgical myectomy	Symptomatic patients with HOCM.	-PTSMA: 19 publications, N=2207 -Myectomy: 8 publications, N=1887
Agarwal 2010	Meta-analysis, to compare outcomes of PTSMA with septal myectomy for treatment of HOCM	Symptomatic patients with HOCM.	-PTSMA: 12 publications, N=380 -Myectomy: 12 publications, N=326
Alam 2009	Meta-analysis, to compare PTSMA and myectomy for treatment of HOCM	Symptomatic patients with HOCM.	-PTSMA: 5 publications, N=183 -Myectomy: 5 publications, N=168

(Source: The sponsor's Tables 2.7.3-3, 2.7.3-6)

Summary of results:

- Both procedures showed similar survival, reduction of LVOT PG, and functional improvement (e.g. NYHA class).
- After PTSMA, improvement in exercise capacity was showed, and survival is comparable with survival in a comparable general population.
- All cause and sudden mortality rates were nearly identical weighted for patient-years of follow-up for both procedures.
- Rates of new pacemaker implantation and residual LVOT gradients were higher after PTSMA than after myectomy.
- Prevalence of implantable cardioverter-defibrillator therapy was similar for both procedures.
- PTMSA is often performed in elderly patients, or patients with other comorbid condition.

B. Uncontrolled retrospective studies: 27 uncontrolled studies assess outcomes of patients who underwent PTSMA, including 9 studies by Dr. Veselka, 15 additional studies (including long-term follow up, PTSMA and CHB, LV diastolic properties, effect of age, myectomy performed after PTSMA, and contrast echocardiographic approach versus pressure-guided-fluoroscopy approach) and 1 meta-analyses (Table 3).

Table 3 Uncontrolled Retrospective Studies

Study	Objective	Patient Population	Treatment Group
Studies by Veselka			
9 Studies	To determine outcomes in patients who underwent PTSMA.	Symptomatic (NYHA or CCS class >II) adult patients with HOCM	-PTSMA:alcohol 1-3 mL, N=1260
Studies with Long-term Follow-up			
6 Studies	To determine the long-term outcomes of PTSMA, including mortality and survival, incidence of SCD and risk factors for SCD after PTSMA, clinical status and echocardiographic parameters,	Symptomatic (NYHA class II or CCS class >II) adult patients with HOCM	-PTSMA: mean infusion of 0.8- 4.1 mL, N=2828
Studies Examining PTSMA and Complete Heart Block			
3 Studies	To provide tools for predicting the course of AV conduction disturbances; to define ECG changes; to identify the determinants of CHB and its clinical impact	Symptomatic (NYHA class ≥ II) adult patients with HOCM	-PTSMA: 1 to 3 mL alcohol use, N=466
Studies Assessing LV Diastolic Properties			
2 Studies	To determine if PTSMA provides long-term improvement in LV diastolic function using both conventional and novel Doppler echocardiographic measurements of diastolic function	Patients with symptomatic HOCM and documented LVOT obstruction gradient	-PTSMA: N=56
Studies of Effect of Age			
2 Studies	To compare the efficacy and safety of PTSMA for HOCM in different age group patients	HOCM patients with drug-refractory severe symptoms who underwent PTSMA	-PTSMA: N=157
Studies Assessing Myectomy Performed after PTSMA			
1 Study	To determine the effect of failed PTSMA on the outcome of subsequent	Patients who subsequently needed surgical	-PTSMA: N=20

	surgical myectomy	myectomy after PTSMA	
Study of Contrast Echocardiographic Approach versus Pressure-guided-fluoroscopy Approach			
1 Study	To evaluate the acute and mid-term course of all patients treated with PTSMA comparing the pressure-fluoroscopy-guided and contrast echocardiographic approaches	Patients with symptomatic HOCM	-PTSMA: N=242
Uncontrolled Meta-Analyses			
1 meta-analysis	To examine outcomes and complications after PTSMA	Patients with symptomatic HOCM	-PTSMA: 42 publications, N=2959

(Source: The sponsor's Tables 2.7.3-4,5,6)

Summary of results:

- Studies consistently showed improvement in LVOT PG, symptoms (e.g., as measured by NYHA or CCS class) and exercise capacity when reported after PTSMA.
- Survival after PTSMA is comparable with survival in a comparable general population.

3.2.2.2 Patient-Level Database

A convenient sample of patient-level outcome database was available (Table 4). The database includes 100 patients selected from the HOCM patient registry (N=180) at Motol University Hospital, Prague, Czech Republic (May 1998 -- December 2013). The patient level outcome data from the registry was used in many studies published in literature.

Table 4 Patient-level Database

Parameter	Overall	
Number of Patients	100 (43 males; 57 females)	
Mean Age (range) (years)	58 (25 to 86)	
Mean Alcohol Dose (range) (mL)	1.43 (0.6 to 4 mL)	
Mean Follow-up (years)	5.61	
Total Deaths during Follow-up	14	
	Before PTSMA	After PTSMA
Mean CCS Class	1.95	0.59 (last check-up)
Total with Syncope	14	9 (during follow-up)
Mean NYHA Class	2.88	1.39 (last check-up)
Mean Interventricular Septal Diameter	21.16	13.32 (last check-up)
Mean Pressure Gradient (mmHg)	64.59	18.53 (last check-up)
Mean Pressure Gradient after Provocation (mmHg)	108	23.06 (last check-up)

CCS = Canadian Cardiovascular Society; NYHA = New York Heart Association; PTSMA = percutaneous transluminal septal myocardial ablation

(Source: Sponsor's Table 2.5-5)

Summary of results:

- PTSMA became the first-choice therapy of highly symptomatic HOCM patients refractory to medical therapy in Motol University Hospital and in nearby parts of Europe.
- Long-term outcomes are considered acceptable, with survival comparable to the sex- and age-matched general population in the Czech Republic as shown in a published study.

3.2.3 STATISTICAL REVIEWER'S EVALUATION

3.2.3.1 Review Strategy and recommendation

This NDA is a literature based application, there is no new clinical efficacy study conducted and individual level data is not available for the identified published literature studies. Therefore, no formal statistical analysis was conducted, and the study results were not verified. This reviewer recommends that all analyses and results be considered exploratory and proper interpretation of results is necessary.

3.2.4 CONCLUSION

The identified studies from published literature and a convenient sample of patient level outcome data seem to support the proposed indication of dehydrated alcohol injection used in PTSMA. However, from statistical standard point of view, no statistical inference should be drawn from these study results, and all study results should be interpreted with caution.

3.3 Evaluation of Safety

Please refer to Dr. Senatore's review for safety assessment.

4. SUMMARY AND CONCLUSIONS

4.1 Statistical Issue and Collective Evidence

This NDA relies on published literature and a selected convenience sample of patient-level outcome data to support efficacy claim.

The literature based application shares a common drawback—potential bias, such as publication bias, time lag bias, outcome reporting bias. There are many statistical issues, such as lack of randomization, blinding, controls, pre-defined primary endpoint, and lack of multiplicity adjustment. Among those identified studies, only very few are randomized controlled trials (RCT). The patient-level outcome data is a convenience sample and it does not seem to provide much useful information due to a potential selection bias. All of these make it difficult to yield a statistically persuasive conclusion for efficacy.

4.2 Conclusions and Recommendations

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