The efficacy and safety of Crataegus extract WS® 1442 in patients with heart failure: The SPICE trial

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Abstract

Background: Crataegus preparations have been used for centuries especially in Europe. To date, no proper data on their efficacy and safety as an add-on-treatment are available. Therefore a large morbidity/mortality trial was performed.

Aim: To investigate the efficacy and safety of an add-on treatment with Crataegus extract WS® 1442 in patients with congestive heart failure.

Methods: In this randomised, double-blind, placebo-controlled multicenter study, adults with NYHA class II or III CHF and reduced left ventricular ejection fraction (LVEF ≤ 35%) were included and received 900 mg/day WS® 1442 or placebo for 24 months. Primary endpoint was time until first cardiac event.

Results: 2681 patients (WS® 1442: 1338; placebo: 1343) were randomised. Average time to first cardiac event was 620 days for WS® 1442 and 606 days for placebo (event rates: 27.9% and 28.9%, hazard ratio (HR): 0.95, 95% CI [0.82;1.10]; p=0.476). The trend for cardiac mortality reduction with WS® 1442 (9.7% at month 24; HR: 0.89 [0.73;1.09]) was not statistically significant (p=0.269). In the subgroup with LVEF ≥ 25%, WS® 1442 reduced sudden cardiac death by 39.7% (HR 0.59 [0.37;0.94] at month 24; p=0.025). Adverse events were comparable in both groups.

Conclusions: In this study, WS® 1442 had no significant effect on the primary endpoint. WS® 1442 was safe to use in patients receiving optimal medication for heart failure. In addition, the data may indicate that WS® 1442 can potentially reduce the incidence of sudden cardiac death, at least in patients with less compromised left ventricular function.

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Keywords: Crataegus extract WS® 1442; Congestive heart failure; Survival; Efficacy; Safety; Controlled randomised trial

1. Introduction

Hawthorn extracts are used world-wide as a herbal remedy for the treatment of cardiovascular diseases and in particular heart failure. One such product is WS® 1442, a

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dry extract from hawthorn leaves with flowers (4–6.6:1), extraction solvent: ethanol 45% (v/w), adjusted to a content of 17.3-20.1% of oligomeric procyanidins. In a number of European countries, this drug has been registered as a phytopharmaceutical medicinal product for the treatment of early stages of congestive heart failure corresponding to stage II of the New York Heart Association (NYHA) classification. This is in contrast to several other hawthorn products of different quality and composition, which are mainly available as nutraceuticals.

Besides oligomeric procyanidins, WS® 1442 contains mainly flavonoids (flavones, flavonols), including hyperoside, vitexin-rhamnoside, rutin, and vitexin as well as triterpenoids and phenol carboxylic acids [1]. As may be expected by the complex mixture of constituents, WS® 1442 has been observed to interact with multiple pharmacological targets. In vitro experiments with human cardiac tissues have demonstrated a concentration-dependent increase of myocardial contractility which was accompanied by a transient raise in intracellular calcium. This positive inotopic effect is possibly mediated by a cAMP-independent inhibition of Na+/K+-ATPase and goes along with an improved energy turnover of myocytes [2–5]. In contrast to cardiac glycosides, Crataegus extract has been found to prolong both the action potential and the refractory period and thereby possess pronounced anti-arrhythmic properties [2,4,6]. Recently, it has been described that WS® 1442 causes vasorelaxation by an endothelium-dependent and NO-mediated mechanism via eNOS-phosphorylation at serine 1177 [7]. In animal models of ischaemia and reperfusion, a significant reduction of ventricular fibrillation, tachycardia, area of infarction and rate of mortality has been observed. An increased coronary blood flow as well as reduced endothelial dysfunction, inhibition of lipid oxidation and anti-inflammatory properties may contribute to these cardioprotective effects of WS® 1442 [8,9].

In clinical trials, the intake of WS® 1442 was associated with an improved exercise capacity and decreased heart failure symptoms [10–13]. The combination of a positive inotropic effect and mild vasodilation may explain the increase in ejection fraction observed in heart failure patients following treatment with Crataegus extract [14,15].

Previous clinical studies investigating the efficacy of WS® 1442 in patients with congestive heart failure in NYHA class II [10,11,13,16] or III [12] confirmed the efficacy of the herbal extract in chronic heart failure during short-term and long-term administration [17]. However, these studies used left ventricular ejection fraction (LVEF), double product (heart rate × systolic blood pressure × 10⁻²), or exercise tolerance as the primary outcome measure for efficacy, and their protocols restricted concomitant cardiac medication. Typically, patients with more severe forms of congestive heart failure, who suffer from a marked impairment of left ventricular function, are stabilized on an individually titrated combination of several drugs, the most important of which are β-blockers, angiotensin-converting enzyme inhibitors, angiotensin-II-receptor-antagonists, diuretics, and digitalis. Other compounds that increase intracellular cyclic AMP levels tend to improve symptoms of congestive heart failure, but may increase mortality rate [18–21]. Up to now, WS® 1442 has not been studied in this clinical environment.

We report the results of the SPICE (Survival and Prognosis: Investigation of Crataegus Extract WS® 1442 in congestive heart failure) study, which was conducted as a morbidity and mortality trial in patients with chronic heart failure in NYHA functional class II or III and at least moderately impaired left ventricular function despite optimal treatment with an individually titrated regimen of any combination of medically appropriate drugs. The study thus investigated the efficacy of adjunctive WS® 1442 in reducing mortality and morbidity beyond the effect of the treatment considered optimal for the individual patient by the investigator.

2. Methods

2.1. Protocol and design, objectives

A detailed description of the design, objectives and experimental procedures has been published elsewhere [22]. SPICE was performed as a double-blind, randomised, placebo-controlled, multicenter trial performed in 13 European countries. The primary objective of the trial was to assess the efficacy and safety of Crataegus Extract WS® 1442 administered in addition to standard medication in patients suffering from symptoms of NYHA class II-III congestive heart failure despite appropriate, individually titrated treatment. Following a 4-week, single-blind placebo run-in phase, eligible patients were randomised and received the investigational treatment or matching placebo for a period of up to 24 months with follow-up visits scheduled every 3 months.

The study protocol was reviewed and approved by the appropriate independent ethics committees. All participants provided written informed consent. The principles of Good Clinical Practice and the Declaration of Helsinki were adhered to.

2.2. Participants

Male and female out-patients were recruited. Participants had to be at least 18 years old and had to present with clinical signs and symptoms of chronic heart failure, NYHA class II or III, due to ischaemic heart disease, idiopathic dilated cardiomyopathy, or hypertensive heart disease with left ventricular dilatation. A wall motion index ≤1.2 (corresponding to a LVEF ≤35%) determined by transthoracic 2D-echocardiography in a certified central laboratory was required for randomization. Furthermore, eligible patients had to have an exercise time between 2 and 12 min in symptom limited bicycle exercise tests (starting at 25 W workload, with a workload increase of 25 W every 2 min) at
both screening and baseline, with the difference between both visits not exceeding 1 min. There were no restrictions regarding ethnic groups.

Patients suffering from chronic heart failure attributable to haemodynamically significant valvular disease, with a history of cardiac arrest or symptomatic sustained ventricular tachycardia not adequately controlled by drugs or implantation of a defibrillator, were excluded. Other conditions that led to exclusion were sick-sinus-syndrome, 2nd or 3rd degree AV block not controlled by a pacemaker, congenital heart disease, hypertrophic or restrictive cardiomyopathy, left ventricular hypertrophy without dilatation, myocardial infarction, unstable angina, or cardiac surgery within 3 months before study inclusion, peripheral arterial disease symptomatic at rest, as well as chronic obstructive pulmonary disease. Patients with planned surgical or non-surgical cardiac intervention during the treatment period as well as those with diseases that might interfere with the study procedures (e.g., with the bicycle exercise test), or with inadequately controlled insulin dependent diabetes mellitus or arterial hypertension were not eligible for participation.

2.3. Interventions, blinding

WS® 1442 is a dry extract from hawthorn leaves with flowers (4-6.6:1), extraction solvent: ethanol 45% (w/w). The extract is adjusted to 17.3–20.1% oligomeric procyanidins. Film-coated tablets containing 450 mg of the extract were used. Film coated placebo tablets were identically matched. During the double-blind, randomised treatment period the patients had to take 2 film-coated tablets per day corresponding to 900 mg/day of dry extract in case of WS® 1442. β-Blockers, angiotensin converting enzyme (ACE) inhibitors, diuretics, and digoxin or digitoxin were permitted as concomitant medication in any clinically appropriate combination or dose. However, concomitant intake of other Crataegus extract preparations, calcium channel blockers, angiotensin-II-receptor antagonists (except in patients with intolerance to ACE inhibitors), or class-I-antiarrhythmics was not allowed.

2.4. Outcomes

The primary outcome measure for treatment efficacy was the number of days between baseline and the first cardiac event, defined as a composite of cardiac death (sudden cardiac death, death due to progressive heart failure, fatal myocardial infarction), non-fatal myocardial infarction, or hospitalization due to progressive heart failure. Sudden cardiac death was defined as death without warning or within 1 h of symptoms. This composite endpoint was chosen under consideration of the many potential mechanisms of action of Crataegus extract. Secondary efficacy outcome measures included each individual endpoint contributing to a cardiac event, workload during exercise testing, echocardiographic measures, as well as quality of life and pharmacoeconomic assessments. The assessments of safety and tolerability were based on spontaneous reports of adverse events (AEs) and routine laboratory measurements. Adverse events were closely monitored by an independent Data Safety and Monitoring Committee (DSMC); an independent Critical Event and Endpoint Committee assessed all serious adverse events for fulfilment of the criteria for a cardiac endpoint and, if applicable, assigned it to one of the pre-defined endpoint categories. All echocardiography recordings were evaluated by two certified core laboratories [22].

2.5. Random sequence generation, allocation concealment, implementation

Patients meeting the selection criteria at baseline were randomised at a ratio of 1:1 to WS® 1442 or placebo. The randomization was performed in blocks stratified by trial centre. The block size was withheld from the investigators. A biometrician otherwise not involved in the trial, generated the code using a validated computer program. The study drugs were dispensed to the centres in numbered containers. Upon inclusion into randomised treatment the local investigator allocated each patient the lowest available number. Breaking the code was restricted to those emergency cases which absolutely required knowledge of patients’ treatment for medical management. In case of opening an emergency envelope, time, date, name of the person opening and the reason for opening were documented on the envelope and in the corresponding CRF. All emergency envelopes had to be returned to the biometric division to be checked up for completeness and closure when the trial was completed.

2.6. Statistical methods, sample size

The main objective of the trial was to demonstrate superiority of WS® 1442 over placebo in the prevention or postponement of cardiac events. Time until first cardiac event was evaluated by Kaplan-Meier survival analysis. The treatment groups were compared using a log-rank test stratified for countries. As prespecified in the protocol, this test was performed on the intention-to-treat (ITT) analysis set which included all randomised patients to confirm the primary hypothesis. All secondary efficacy and safety measures were exploratory, i.e. all p-values have to be considered as descriptive.

The trial was performed according to a group sequential design with two interim analyses that were performed by the DSMC after occurrence of about 1/3 and 2/3 of the expected total number of cardiac events, respectively. The members of the DSMC were two cardiologists and a statistician who were otherwise not involved in the trial. The global type I error level was α=0.05 (two-sided). According to the group sequential boundaries of the Peto-Haybittle design [23,24] local type I error levels of α1=α2=0.001 were applied to each interim analysis in order to reserve a level of α3=0.0494 for the final analysis.

According to data from the literature [25,26] a 24-month rate of cardiac events of approximately 30% was expected in
the placebo group. WS® 1442 was assumed to improve the event rate by 20%, i.e., a rate of cardiac events of about 24% was anticipated in patients treated with the herbal extract. Following these assumptions, 1155 evaluable patients per group were required in order to obtain a power of 90%. Before the first interim analysis a blinded sample size review [27] was performed to re-assess the assumed overall rate of cardiac events. As a result of the blinded sample size re-calculation the initially planned sample size was increased by 230 patients to assure the desired power of 90%.

3. Results

3.1. Recruitment, participant flow

In 145 clinical centres in 13 European countries, 3601 patients were recruited and 2681 (WS® 1442: 1338; placebo: 1343) were randomised and treated. All randomised patients were included into the ITT analysis of efficacy as well as into the safety analysis. About 50% of the patients were recruited in Poland, the Czech Republic and in Germany. On average each centre recruited about 18 patients (interquartile range: 2×1270=2540 patients to assure the desired power of 90%).

3.2. Baseline data

Baseline demographic and clinical parameters were comparable in both groups (Table 1). More than 80% of the randomised patients were male, and about half of the participants were 60 years of age or older. In total, 42% (WS® 1442) and 45% (placebo) of the participants had NYHA class III congestive heart failure. All but 6 patients received concomitant cardioactive medication, and about 90% took at least 3 concomitant cardioactive drugs. In each treatment group, about 85% of the patients took diuretics (about 39% spironolactone), 83% received ACE-inhibitors, 64% were treated with β-blockers (almost one half with carvedilol and almost one third with metoprolol), and 56% with digitalis and nitrates. Concomitant antiarrhythmics (mostly amiodarone) were used by about 22% of the study participants. One subject (0.07%) in the WS® 1442 group and 5 subjects (0.37%) in the placebo group had NYHA stage II at the screening visit. These patients had NYHA stage II at the screening visit.

Table 1

| Demographic and clinical characteristics at baseline (intention-to-treat; numbers are means±SD and medians unless stated otherwise; p-values are two-sided) |
|-----------------|---------------|---------------|
| WS® 1442 (n=1338) | Placebo (n=1343) | p |
| **Sex (n (%))** | | | |
| female | 222 (16.6%) | 213 (15.9%) | 0.61* |
| male | 1116 (83.4%) | 1130 (84.1%) | 0.51 |
| **Age [years]** | | | |
| 59.8±10.6 | 60.0±10.7 | 0.15 $$ |
| **Body Mass Index [kg/m²]** | | | |
| 27.0±3.9 | 26.6±3.7 | 0.24 $$ |
| **Smoking (n (%))** | | | |
| Non-smoker | 611 (45.7%) | 621 (46.2%) | 0.95 $$ |
| Smoker | 144 (10.8%) | 145 (10.8%) | 0.84 $$ |
| Ex-smoker | 583 (43.6%) | 577 (43.0%) | 0.84 $$ |
| **NYHA class (n (%))** | | | |
| I* | 3 (0.2%) | 6 (0.5%) | 0.18 $$ |
| II | 769 (57.5%) | 731 (54.4%) | 0.18 $$ |
| III | 566 (42.3%) | 606 (45.1%) | 0.18 $$ |
| **Left ventricular ejection fraction at screening** | | | |
| 23.8±6.8 | 23.9±6.6 | 0.78 $$ |
| **Bicycle exercise duration (s)** | | | |
| 320.0±135.8 | 300.0±135.2 | 0.24 $$ |
| **Number of concomitant cardioactive drugs (n (%))** | | | |
| none | 2 (0.2%) | 4 (0.3%) | 0.55 $$ |
| 1 or 2 | 150 (11.2%) | 144 (10.7%) | 0.61 $$ |
| 3 | 331 (24.7%) | 359 (26.7%) | 0.61 $$ |
| more than 3 | 855 (63.9%) | 836 (62.3%) | 0.61 $$ |

*χ²-test; **t-test.

*These patients had NYHA stage II at the screening visit.

3.3. Investigational treatment

Across the follow-up period the interquartile range for treatment compliance (assessed by medication counting) was 96.2%–102.3% for WS® 1442 and 96.3%–101.5% for placebo. Disposition of patients is shown in Fig. 1.

3.4. Efficacy

Fig. 2 shows the Kaplan-Meier cumulative hazard curves for the composite primary endpoint. The 24-month event rates were 27.9% (373 of 1338) and 28.9% (388 of 1343) in the WS® 1442 and placebo groups respectively. The average time to first cardiac event was 620 (95% confidence interval: 608; 632) and 606 (593; 619) days. The difference between the two groups did not reach statistical significance (p=0.51, log rank test stratified by country).

Among the events contributing to the composite endpoint, patients treated with WS® 1442 showed a tendency towards lower 24-month event rates than the placebo group for death of any cause, death of cardiac cause, sudden cardiac death, death due to progressive heart failure and non-fatal myocardial infarction, but none of the differences reached the level of statistical significance (Table 2).

Fig. 3A and B shows the cumulative hazard curves in cardiac mortality and sudden cardiac death. Sudden cardiac death accounted for 58.7% of all cases of cardiac mortality. With WS® 1442 there was a non-significant relative reduction in cardiac mortality by 9.7% (HR 0.89, 95% CI [0.73;1.09]); p=0.269 and sudden cardiac deaths by 15.4% (HR 0.84, 95% CI [0.64;1.09]; p=0.184). Among the 2681 patients randomised to treatment, 1139 (42.5%) had an initial left ventricular ejection fraction between 25% and 35% (upper limit for inclusion). In this pre-specified subgroup, cardiac mortality in the WS® 1442 group as compared to placebo was
reduced by 20% (HR 0.78, 95% CI [0.56;1.10]; \( p = 0.158 \)), with a significant reduction in sudden cardiac deaths by 39.7% (HR 0.59, 95% CI [0.37;0.94]; \( p = 0.025 \)) (Fig. 3C and D). These represent an exploratory analysis, and therefore should be treated with caution. \( p \)-values at different time-points are shown in Fig. 4.

3.5. Safety/tolerability

During treatment, 897 patients randomised to WS® 1442 (67.0%) reported 2196 adverse events (AEs) and 917 patients treated with placebo (68.3%) experienced 2279 AEs. This corresponded to one AE in 388 days of exposure for WS® 1442 and to one AE in 370 days for placebo.

Serious AEs were observed in 524 patients (39.2%) in the WS® 1442 group (873 events, one in 976 days of exposure) and in 552 patients (41.1%) in the placebo group (923 events, one in 914 days). In both study groups the most frequently reported AEs were cardiac disorders (WS® 1442 group 30.3%, placebo group 30.7%), followed by metabolic and nutritional disorders (16.5% and 17.2%, e. g., hypercholesterolaemia, hyperlipidaemia), infections (13.0% and 16.2%, e. g., influenza, bronchitis), and by general disorders (10.2% and 11.9%, e. g., chest pain, pyrexia).

4. Discussion

Congestive heart failure is among the leading causes of death in the Western world. While ACE inhibitors, \( \beta \)-blockers, and aldosterone receptor blockers have been shown to reduce over-all mortality [28,29], treatment with cyclic adenosine monophosphate increasing agents may result in a deterioration of outcome [19,20,21]. Digoxin, on the other hand, which is to date the only positive inotropic drug shown to be devoid of harmful effects on mortality during long-term treatment [5], improved exercise tolerance and quality of life.
and reduced the need for hospitalization in heart failure patients, but had no beneficial effect on over-all mortality [25,30]. However, in a post-hoc analysis it was found that lower serum digoxin concentrations are associated with improved survival [31]. A clinically relevant reduction of the risk of sudden cardiac death could be demonstrated for β-blockers alone [32–34]. The efficacy of Crataegus extract WS® 1442 in improving exercise capacity and subjective symptoms was previously demonstrated in patients with milder forms of heart failure, with limited concomitant medication, and with short follow-up periods between 4 and 16 weeks [10–13,16].

In the light of these facts, the SPICE study was planned and designed to assess the effectiveness and safety of the Crataegus extract WS® 1442 when given to patients with more advanced heart failure, who were receiving optimal standard pharmacological therapy. Due to the potential mechanisms of action of Crataegus extract, we have chosen a primary end-point composed of three components: Firstly, the inotropic effect of WS® 1442 demonstrated in vitro was expected to reduce hospitalization and death rate due to progression of heart failure. Secondly, the anti-ischaemic properties of Crataegus as demonstrated in a number of animal models might lead to a reduction of fatal and non-fatal myocardial infarction. And thirdly, the anti-arrhythmic and anti-fibrillatory effects of Crataegus might have an influence on sudden cardiac death.

In the SPICE study, special care was taken to include a very homogeneous and well defined population of patients in order to reach the expected 24-month rate of cardiac events of approximately 30%, and to investigate patients who receive optimal medical treatment. This aim was reached by introducing left ventricular ejection fraction equal to or lower than 35% as an inclusion criterion, as assessed by a certified central laboratory before randomization. The fact that the patients were on optimal pharmacological treatment can be seen from Table 1; more than 60% of the patients in both groups had four or more, and almost 90% had at least three concomitant cardioactive drugs at baseline.

For the composite primary endpoint that included cardiac death, non-fatal myocardial infarction and hospitalization due to progressive heart failure, confirmatory proof of efficacy of WS® 1442 was not achieved. Crataegus extract did not reduce the need for hospitalization due to progression of heart failure, the most frequently reported event contributing to the composite endpoint. The same was true for death due to progression of heart failure. However, WS® 1442 tended to lower sudden cardiac death rate, which was particularly pronounced in patients with an LVEF between 25% (approximate median of all randomised patients) and 35% (upper limit for inclusion). These findings illustrate potential anti-arrhythmic and/or anti-ischaemic properties of Crataegus extract WS® 1442. In this context it is noteworthy that the prevalence of implantable cardioverter defibrillator (ICD) therapy was very low. Although the lack of effect on pump failure related endpoints was unexpected, the anti-arrhythmic action of WS® 1442 confirms the findings from animal experiments, in which it was shown to effectively prevent reperfusion arrhythmias.

Both digoxin and WS® 1442 are known to increase exercise capacity. However, WS® 1442, with its tendency to reduce sudden cardiac death rate, may have a more favourable safety profile than digoxin.

In the SPICE trial, administration of WS® 1442 was associated with an excellent safety and tolerability profile. The adverse events observed during treatment with WS® 1442 were of the same types and occurred at comparable rates as those in the placebo group. Of note, despite the positive inotropic effect of Crataegus extract preparations [2,35] observed in vitro, WS® 1442 did not lead to an increase in mortality rate. In contrast, a tendency for reduction of cardiac mortality was observed.

In a recent systematic review based on data from 24 controlled clinical studies with Crataegus preparations and

<table>
<thead>
<tr>
<th>Event</th>
<th>WS® 1442 (n=1338)</th>
<th>Placebo (n=1343)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death (any cause)</td>
<td>219 (16.4)</td>
<td>240 (17.9)</td>
<td>0.29</td>
</tr>
<tr>
<td>Death of cardiac disease</td>
<td>180 (13.5)</td>
<td>200 (14.9)</td>
<td>0.27</td>
</tr>
<tr>
<td>Sudden cardiac death</td>
<td>102 (7.6)</td>
<td>121 (9.0)</td>
<td>0.18</td>
</tr>
<tr>
<td>Death due to progressive heart failure</td>
<td>64 (4.8)</td>
<td>69 (5.1)</td>
<td>0.63</td>
</tr>
<tr>
<td>Fatal myocardial infarction</td>
<td>14 (1.0)</td>
<td>10 (0.7)</td>
<td>0.43</td>
</tr>
<tr>
<td>Non-fatal myocardial infarction</td>
<td>13 (1.0)</td>
<td>21 (1.6)</td>
<td>0.15</td>
</tr>
<tr>
<td>Hospitalization due to progression of heart failure</td>
<td>253 (18.9)</td>
<td>245 (18.2)</td>
<td>0.78</td>
</tr>
<tr>
<td>Total no. of patients with cardiac event</td>
<td>373 (27.9%)</td>
<td>388 (28.9%)</td>
<td>0.51</td>
</tr>
</tbody>
</table>

Numbers of individual events do not sum up to total as some patients had multiple events.
Fig. 3. Cumulative hazard curves for cardiac mortality (A, C) and sudden cardiac death (B, D) — all patients (A, B) or patients with LVEF $\geq 25\%$ (C, D).

Fig. 4. Cardiac mortality and sudden cardiac death in total population and subgroup LVEF $\geq 25\%$. Plot shows hazard ratios and 95% confidence intervals. All $p$-values are explorative. They are computed by two-sided log rank tests.
more than 5500 patients analyzed, Daniele and colleagues [36] emphasized a good tolerability of the herbal extract and the absence of drug interactions (that is particularly important in patients receiving multiple drugs). The results of the SPICE trial are in line with this meta-analysis.

In conclusion, add-on treatment with WS® 1442 to a conventional heart failure regimen did not show a significant difference in the composite endpoint including cardiac death, non-fatal myocardial infarction and hospitalization due to progressive heart failure. Analysis of the secondary outcomes may suggest that WS® 1442 can reduce sudden cardiac death in patients with LVEF between 25 and 35%. Because WS® 1442 was well tolerated and had an excellent safety profile, the results of this study suggest that further exploration of WS® 1442 in patients with heart failure at high risk for sudden cardiac death may be warranted.

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Appendix

Trial organization — SPICE Trial Study Group

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