Fact Sheet: Clinical evidence supporting the Watchman™ Left Atrial Appendage (LAA) Closure Device

Data from several clinical trials have demonstrated the safety and the efficacy of the Watchman Left Atrial Appendage (LAA) Closure Device as a proven device alternative to warfarin for reducing risk of stroke in patients with atrial fibrillation (AF). In fact, Watchman is the most studied LAA closure device in the world with over 2,400 patients enrolled in prospective studies and nearly 6,000 patient years of follow-up. In addition, it is also the only LAA closure device with long-term clinical data, whose efficacy has been demonstrated under two large multi-centre, prospective, randomised clinical trials.

- **The PROTECT AF Trial**
  The Watchman LAA Closure Device for Embolic PROTECTion in Patients with Atrial Fibrillation (PROTECT AF) trial was designed to demonstrate the safety and effectiveness of the device in patients with non-valvular AF who are eligible for warfarin therapy and have a CHADS<sub>2</sub> stroke risk score of ≥ 1. A total of 707 patients were randomised 2:1 to the Watchman device or warfarin control. The PROTECT AF long-term follow-up data showed that the Watchman device was statistically superior to warfarin and demonstrated a 40 percent relative risk reduction for the combined endpoint of all-cause stroke, cardiovascular or unexplained death and systemic embolism compared to long-term warfarin therapy. In addition, the study also showed a relative risk reduction and non-inferiority to warfarin in all-stroke (32 percent); and superiority to control for all-cause mortality (34 percent), cardiovascular mortality (60 percent), hemorrhagic stroke (85 percent) and disabling stroke (63 percent).¹

- **The PREVAIL Trial**
  A second randomised prospective clinical trial was designed to confirm the results of the PROTECT AF study as well as validate the safety of the Watchman implant procedure when performed by new implanting physicians. The Prospective Randomised EVAluation of the Watchman LAA Closure Device In Patients with Atrial Fibrillation Versus Long Term warfarin Therapy (PREVAIL) trial enrolled 407 patients at 41 US sites and has compared the Watchman device to warfarin in high-risk patients with AF, who are eligible for long-term warfarin therapy. The PREVAIL trial results showed low complication rates with both new and experienced implanters and significantly lower complications than during the early stage of the PROTECT AF trial. The device and procedural data in PREVAIL are consistent with prior Watchman trials and continue to support the utility of the Watchman device as an alternative to warfarin for the prevention of embolic stroke in high-risk patients with non-valvular AF.

- **CAP registry**
  Following the pivotal PROTECT AF trial, the Watchman device was studied in a non-randomised registry of patients undergoing Watchman implantation, the Continued Access Protocol (CAP) Registry. This registry demonstrated ongoing improvement in the device’s safety procedure and occurrence of adverse events due to more training and the growing experience of the implanting physicians.
  The study design:
  - In the CAP registry, an additional 460 patients were implanted with the device at 26 centres, which had previously participated in the PROTECT AF trial.
- Although non-randomised, this registry had the same inclusion and exclusion criteria, procedure/treatment protocol, and clinical endpoints as PROTECT AF.
- Average age of patients was 74 years and average CHADS² score equalled 2.4 overall.
- Implanted patients received oral anticoagulation therapy with warfarin after the procedure.

The results:
- 95 percent of all 460 patients taking part in the study were implanted successfully.
- The trial demonstrated a 32 percent decrease of pericardial effusions, the most common adverse event in the Watchman device group, as clinicians gained more experience with the procedure.
- Rates of pericardial effusion declined at all centres involved as the experience of the implanting clinicians with the procedure increased.
- The number of procedure-related strokes was reduced to 0 (in contrast to 1.7 in the PROTECT AF trial).
- 95 percent of implanted patients were able to discontinue oral anticoagulation therapy with warfarin at 45 days.

- **The ASAP Study**
The ASAP (Aspirin And Plavix®) study was a non-randomized feasibility study designed to determine if the Watchman device is a safe and effective treatment for patients with atrial fibrillation who are contraindicated to long-term oral anticoagulation therapy. The prospective, multi-centre study evaluated 150 patients with AF not eligible for warfarin therapy, who were implanted and treated with dual antiplatelet therapy for six months post-procedure. Subjects were followed for a mean average of 14.4 months. Data showed a 77 percent reduction of ischemic stroke risk in high risk patients with AF who are contraindicated to warfarin³.

- **CAP 2 registry**
The Continued Access to PREVAIL (CAP 2) Registry is a multi-centre prospective non-randomized study allowing continued access to the Watchman Device, following the PREVAIL trial, during regulatory review of the pre-market application for the Watchman Device.
The primary objective of the CAP 2 registry was to collect additional safety and effectiveness data on the Watchman Device in subjects with non-valvular atrial fibrillation who are deemed by their physicians to be suitable for warfarin therapy. The results of the CAP 2 Registry were part of the Watchman Patient-Level Meta-Analysis (see below).

- **Watchman Patient-Level Meta-Analysis**
In order to put the totality of data into context and perspective, a patient-level meta-analysis was performed using all randomized trial data to account for differences in follow up and number of patients. To evaluate the benefit-risk profile for the totality of data, the PROTECT AF and PREVAIL datasets were combined with were combined with all registry data and again analyzed as a traditional patient-level meta-analysis. Combining these data sets provides a perspective on device performance as demonstrated in the rigors of a randomized trial, as well as in the registry setting which more closely resembles real world experience.
This is possible because in both randomized trials, patients were randomized to the same treatment strategies (Watchman vs. Warfarin) and primary efficacy endpoint definitions, and all trials had similar inclusion/exclusion criteria. Though registries had no control group, the same criteria around device and primary efficacy definitions applied. Watchman Device performance was consistent over the entire data set.

The Results: The totality of the randomized clinical trial and registry data in the meta-analysis demonstrates that in patients with non-valvular AF:

- Local therapy with Watchman provides similar benefit to warfarin for the composite efficacy endpoint of stroke, systemic embolism or CV death
- Compared with long-term warfarin, patients randomized to Watchman have a significant improvement in survival, particularly freedom from CV death;
- Although all-cause stroke rates are identical between groups, the pathophysiology of stroke was significantly different; more warfarin patients experiencing hemorrhagic strokes and more device patients experiencing ischemic strokes; Once accounting for the procedure-related events isolated to the early experience in PROTECT AF, there was not a statistical difference in the ischemic stroke rates seven days post procedure
- By one year, approximately 95 percent of device patients discontinued warfarin;
- Although all-cause bleeding was similar between groups, when periprocedural bleeding was excluded, bleeding rates were significantly higher in patients treated with chronic warfarin;
- Device performance was consistent over the entire data set – both randomized clinical trials and registries, the latter of which are likely to more closely resemble real world experience.

About Boston Scientific
Boston Scientific transforms lives through innovative medical solutions that improve the health of patients around the world. As a global medical technology leader for more than 35 years, we advance science for life by providing a broad range of high performance solutions that address unmet patient needs and reduce the cost of healthcare. For more information, please visit: www.bostonscientific.eu

Media Contact
Sharron Tansey  Simonetta Balbi
Market Access, Health  Media Relations and Corporate
Economics & Government Affairs  Communications Europe
+44 7770 834 947  +39 338 79 36 422
TanseyS@bsci.com  balbis@bsci.com

References
2 Holmes DR et al. Randomized Trial of LAA Occlusion. JACC. Vol. 64: 1-12 , 2014
5 Data on file Boston Scientific
6 Holmes, DR et al. JACC 2015; In Press

Indications, contraindications, warnings and instructions for use can be found in the product labeling supplied with each device. Information for the use only in countries with applicable health authority product registrations. This document may not be used in France.