

## Clinical Affairs Update Q4, 2009

The following is a document summarizing Volcano's clinical study activities on a global basis. Our clinical study activity falls in three primary categories:

- 1) Percutaneous Coronary Intervention
- 2) Pharmaceutical plaque progression and regression studies
- 3) Understanding the disease process

### Understanding the Disease Process

**PROSPECT** (Providing Regional Observations to Study Predictors of Events in the Coronary Tree) sponsored by Abbott Vascular and Volcano, is a first of its kind multi-center natural history study of plaque. The purpose of this imaging study of patients with unstable atherosclerotic lesions, was to identify imaging modalities or blood markers of inflammation that indicate which non-flow limiting lesions are at higher risk for future acute coronary events. Approximately 700 ACS patients in the United States and Europe with single or double vessel CAD have been enrolled and will be followed for up to five years. In addition to angiography, IVUS grayscale, VH® IVUS tissue characterization, IVUS palpography and biomarkers were utilized to explore the relationship between observations of these modalities and subsequent cardiac events. To establish a baseline, IVUS imaging was performed on all three major coronary arteries and biochemical features that can be used to measure the progress of disease or the effects of treatment, or biomarkers, were assessed. PROSPECT baseline data was presented at TCT 2008 and concluded that 3-vessel imaging is feasible in most patients. It was also noted that at least one non-culprit lesion with an IVUS MLA <4.0mm<sup>2</sup> was identified in 43% of the patients. VH-TCFAs were identified in the coronary tree in 52% of patients and were more widespread than previously described.

Additional follow up data presented at TCT 2009 in San Francisco demonstrates that the measurements made using grayscale and VH IVUS did have a statistically significant impact in determining the likelihood of a particular lesion type to cause an event. The highest risk PROSPECT plaque type being VH Thin Cap Fibroatheromas with a minimum lumen area of less than or equal to 4mm<sup>2</sup> and a plaque burden greater than or equal to 70%. All three of these important parameters (each an independent predictor) when combined

showed that the particular lesion imaged at baseline had a 17.2% chance of causing an event within three years. It is important to note that current practice of using angiography alone cannot measure plaque burden or the presence of VH-TCFAs, which were the two most significant predictors of lesion risk in the study. These measures can only be collected using Volcano's proprietary Eagle Eye® Gold IVUS catheter which not only visualizes and measures plaque burden but also collects signals for VH imaging allowing display of four plaque components.

<http://ir.volcanocorp.com/releasedetail.cfm?ReleaseID=411467>

**SPECIAL** (Study of Prospective Events in Coronary Intermediate Atherosclerotic Lesions), is a natural history study of vulnerable plaque. The purpose of the study is to identify imaging modalities and/or blood markers of inflammation which may aid in the identification of vulnerable plaque which increases risk of future acute coronary events. 257 patients were enrolled including ACS with single or double vessel CAD at 28 centers in Japan, with half randomized into a VH IVUS arm and half into a non-VH IVUS arm. Patients in the VH IVUS arm were imaged with angiography and these images were supplemented by VH IVUS tissue characterization and biomarkers. Patients in the non VH IVUS arm were imaged with angiography alone. In the event of a MACE, and at 12-month follow-up, patients were re-imaged with either VH IVUS or angiography alone. The two primary endpoints of the study are the MACE associated with progression of plaque during a 12-month period and the progression of plaque as measured by angiography and our VH IVUS functionality 12 months after intervention. SPECIAL is designed to validate the clinical significance of vulnerable plaque and provide additional information on silent plaque progression which can lead to clinical events. The 12-month follow-up was completed in August of 2009.

**Volcano VH Registry** is a registry that enrolled over 2500 patients in 40 sites in the US, Europe and Japan. The primary objective was to correlate plaque characteristics with patient demographics, clinical presentations and cardiac risk factors. Volcano's grayscale and VH IVUS technology was used in all cases. The resulting data has generated over 65 publications of the data including clinical papers, book chapters, reviews, and abstracts. For a complete listing of the publications as well as summary slides and detailed information regarding VH IVUS, go to [www.vhivus.com](http://www.vhivus.com).

### **Percutaneous Coronary Intervention**

#### **BLAST (Bifurcation Lesion Analysis and Stenting)**

Volcano is sponsoring the BLAST trial where we expect to demonstrate that IVUS with VH guidance leads to better post procedural outcomes when compared to angiography alone.

220 patients in approximately 15 sites in the US and Europe will be enrolled and randomized to using angiography alone or angiography with grayscale IVUS and VH to best determine the treatment of the lesion. Enrollment has started and is almost at the halfway point.

**ADAPT-DES (Assessment of Dual AntiPlatelet Therapy with Drug-Eluting Stents)**. Volcano is excited to participate in the ADAPT-DES trial being conducted in approximately 10 sites in both the US and Europe. ADAPT-DES is a prospective registry of at least 11,000 and up to 15,000 patients with coronary artery disease undergoing stent assisted intervention using DES. The objective of the study is to determine the frequency, timing and correlates (clinical and angiographic) of drug eluting stent thrombosis in the study population and the relationship of aspirin and/or clopidogrel response in this population. There is an IVUS sub-study that will include 3,000 patients to determine whether one or more IVUS parameters are independent predictors of stent thrombosis. Enrollment is well underway and over the halfway point.

#### **VICTORY (VH in Carotids Observational Registry)**

Volcano is sponsoring a multicenter, nonrandomized prospective registry in Europe to confirm the feasibility of IVUS and VH during carotid interventions. The registry will enroll 150 patients at approximately 10 sites in Italy, Poland and Scotland. Enrollment has started and more than half of the patients have been enrolled.

**ATHEROREMO** is a European collaborative project on inflammation and vascular wall **Remodeling in Atherosclerosis**. It is a single center trial to enroll 800 patients with CAD including stable and unstable

angina, STEMI and NSTEMI. The primary objective is to correlate coronary artery disease imaging phenotype as determined by IVUS-Virtual Histology with biomarkers. Enrollment has started and remains robust.

### **Pharmaceutical Trials**

**TRUTH / KCPR** is being conducted in Japan and the main objective to enroll 160 patients into 2 arms has been achieved. Patients received either pitavastatin or pravastatin to investigate regression of coronary arteriosclerosis, lipid levels, and inflammatory markers in patients with coronary heart disease. We then evaluated plaque compositional change of the coronary artery with VH-IVUS. The evaluation lesion is defined as the lesion having more than 50% of plaque except 5 mm distal and proximal of the stent. Primary endpoint is quantitative change in each of the four plaque components measured by VH IVUS. The secondary endpoint is quantitative changes in the coronary parameters measured by grayscale IVUS and evaluation of MACE, percent change of serum lipid and other markers. The TRUTH study is closed to enrollment and follow up. Publication of the manuscript describing the results is underway.

**AQUARIUS ( Aliskiren QUantitative Atherosclerosis Regression Intravascular Ultrasound Study)**, is a randomized, double blind study to evaluate the efficacy and safety of aliskiren on the progression of atherosclerosis in patients with coronary artery disease in addition to optimal background therapy. The study is sponsored by Novartis. It will be conducted in approximately 10 countries and will enroll approximately 600 patients. The primary objective is to measure the change in the progression of coronary atherosclerosis (defined as change from baseline in percent atheroma volume) as assessed by IVUS. Approximately 50 of the sites will be using Volcano s5 IVUS systems to obtain the images. Enrollment has started and expects to be complete early next year. The trial will conclude in 2012.

#### **IBIS2 (in cooperation with GSK)**

Integrated Biomarker and Imaging Study 2 European multi-center, randomized, placebo-controlled one year treatment study in 330 ACS and non-ACS subjects with angiographically documented CAD. The objective of this study was to estimate the effect of GSK's Lp-PLA(2) inhibitor on circulatory biomarkers, endothelial dysfunction, coronary plaque volume and composition using grayscale IVUS, VH-IVUS and palpography. The results of this exciting trial were released at the ESC in Munich on September 1, 2008. The study showed that necrotic core continues to expand

despite treatment with standard of care among patients receiving placebo. The publication can be found in *Circulation*.

(*Circulation*. 2008;118:1172-1182.

### **In Summary**

Volcano IVUS technologies (grayscale and VH IVUS) have been used successfully and will continue to be used in global interventional trials. A review of the current bibliography of published data may be provided to you by your local sales or clinical representatives, or by going to the Volcano website at [www.volcanocorp.com/clinical/clinical-papers-references.asp](http://www.volcanocorp.com/clinical/clinical-papers-references.asp) or to [clinicaltrials.gov](http://clinicaltrials.gov).

### **Volcano Corporation**

3661 Valley Centre Drive, Suite 200  
San Diego, CA 92130  
Phone: 916-638-8008  
Phone: 800-228-4728  
E-mail: [info@volcanocorp.com](mailto:info@volcanocorp.com)

### **Volcano Clinical Affairs**

7100 Euclid Ave #125  
Cleveland, Ohio 44103  
Phone: 216-426-6104

### **Volcano Europe**

Excelsiorlaan 41  
B - 1930 Zaventem  
Belgium  
Phone: + 32 2 679 10 76  
Fax: + 32 2 679 10 72

### **Volcano Japan**

Hamamatsucho Square 6F  
1-30-5, Hamamatsucho, Minato-ku, Tokyo  
105-0013 Japan  
Phone : +81-3-6430-9400