

# ACUSPHERE

## ACUSPHERE INC. ISSUES LETTER TO SHAREHOLDERS

LEXINGTON, MASS., March 10, 2011 -- Acusphere, Inc. (ACUS.PK) today issued the following letter to shareholders:

Dear Fellow Shareholders:

As I have done in the past, I want to provide you with an annual update on the Company's progress and our plans. Since our pivotal announcement that we secured \$10 million in financing from Burrill & Company's venture capital group in June 2010, we have been working diligently to support continued development of our lead product candidate, Imagify™ (Perflubutane Polymer Microspheres) for Injectable Suspension, and I am very pleased with our accomplishments.

Imagify is under development as a cardiovascular drug intended for the detection of coronary artery disease (CAD), the leading cause of death in the U.S.. It remains the leader in myocardial perfusion assessment with ultrasound, an important investigational area. It continues to show promise in addressing a potential \$2 billion market in the U.S. alone, as a radiation-free test for perfusion assessment offering compelling cost and convenience advantages over the current standard of care, nuclear stress testing. We continue to believe strongly in Imagify's potential for the indication proposed, and we remain committed to realizing that opportunity for the benefit of Acusphere and its shareholders.

When we announced the June 2010 financing, we shared more details on our strategic approach to securing regulatory approval of Imagify, which utilizes a two-track focus:

1. fulfilling the necessary requirements for filing a Marketing Authorisation Application (MAA) to the European Medicines Agency (EMA) for Imagify in the European Union (EU) in mid-2011, and
2. reaching agreement with the United States Food and Drug Administration (FDA) under the Special Protocol Assessment (SPA) process on the design of a Phase 3 study demonstrating that stress ultrasound with Imagify has benefits relative to stress ultrasound without Imagify.

The financing agreement with Burrill was structured to provide Acusphere with additional financing options as the company met key milestones on the road to achieving those goals. We are delighted that we have in fact met with substantial initial success, and we're so pleased to have the strong support of excellent advisors and financial partners through Burrill.

### **The European Opportunity**

This fall, we participated in promising pre-submission meetings with the European rapporteurs, the regulators who lead the review process of the company's MAA filing. This is a critical step in the process, as it enabled the company to secure initial perspectives and potential questions or challenges that can then be effectively addressed in the MAA filing. Most importantly, from these meetings, we gained confidence that the European Union review of Imagify may result in a different outcome than the FDA review of our New Drug Application (NDA).

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Why? Through this process, we learned important distinctions in how European regulators view products like Imagify. For instance, European regulators are more concerned than regulators in the U.S. about radiation safety. Laws have been in place in the EU for more than 10 years precluding doctors from using radioactive medical procedures when non-radioactive alternatives exist. This concern about radiation safety is supported by continuing evidence raised over the last few years in the most prestigious medical journals in the world. For that reason, the radiation safety benefit that Imagify can provide may weigh more heavily in our favor in the EU's risk-benefit assessment, which is an important part of the final approval decision. In the U.S., FDA does not yet appear to regard radiation safety as a significant problem in cardiac imaging.

Secondly, European guidelines discourage placebo trials, like the ones that FDA is now requiring us to design, and encourage instead comparator trials, which was the design we employed in our clinical trials to support our NDA filing. Therefore an EU review would ascribe little value to the placebo trial that we are working with FDA currently to finalize, so there is no point in delaying MAA submission while we wait for results from a U.S. trial.

Therefore, we are moving speedily to accomplish the next steps involved in readying the MAA for filing by the middle of the year, recognizing that doing so makes Acusphere more attractive as a potential partner to a European or global company. Regulatory review of the MAA typically takes one year from filing. We believe our Imagify Phase 3 clinical program demonstrates that the efficacy of Imagify with ultrasound is non-inferior, or equivalent, to nuclear stress. Imagify was evaluated in more than 1,000 patients and as a result, we believe that it is well tolerated, with a safety profile similar to other drugs used in this patient population. There is a 3 million procedure/\$600 million addressable market for Imagify in Europe, based simply upon existing procedures. We believe this market could grow significantly since the population is similar to the U.S. and the prevalence of heart disease is similar as well (the U.S. addressable market is approximately \$2 billion.) Imagify is a radiation-free alternative to nuclear stress testing and each episode of nuclear stress testing delivers a radiation dose equivalent to between 140-800 chest x-rays depending upon the radiopharmaceutical used.

## **U.S. Plans**

We are continuing active discussions with FDA about a SPA, a process that creates a written agreement between the FDA and a sponsor on the clinical trial design, including clinical endpoints and size of clinical trial. The process is intended to provide assurance that if the agreed-upon clinical trial protocol is followed, the clinical trial endpoints are achieved and there is a favorable risk benefit profile, the data should then likely support approval of a NDA. As noted, FDA has requested a placebo-controlled Phase 3 trial for Imagify, one that demonstrates that ultrasound with Imagify has benefits over ultrasound without Imagify, to supplement the comparator trials that we have completed in years past, where we compared Imagify's efficacy against the 'standard of care,' nuclear stress testing.

A few words of background: It is widely accepted that ultrasound alone is not capable of assessing myocardial perfusion (e.g. blood flow in the heart muscle). The ability to evaluate perfusion in the heart muscle allows for early detection of CAD. We believe that Imagify, if approved, has the potential to improve the ability of heart stress ultrasound tests (stress ultrasound) to compete more effectively with the nuclear stress test, an inconvenient and expensive standard for assessing perfusion today that has inherent radiation safety risks. More than 10 million nuclear stress tests and stress ultrasounds are performed each year in the U.S., providing Imagify with an addressable market of more than \$2 billion per year in the U.S. alone.

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## **Operational Plans**

As we move forward on both fronts, we remain active in discussions with potential partners, especially now that we have achieved some critical milestones and secured necessary funding. To that end, we retained Torrey Partners, an advisory firm, to assist us with partnering activities. The principal advisor at Torrey is Pete Garrambone, who brings impressive expertise in partnering in our arena. He formerly led Strategic Development at Pfizer and was responsible for M&A, closing some \$200 billion in transactions during his tenure. He then became Senior Vice President of Business Development at Reliant Pharmaceuticals, a cardiovascular drug company acquired by Glaxo Smith Kline for \$1.65 billion.

The June 2010 financing provided \$10 million in debt financing through the sale of a senior secured note and warrant. The initial tranche was for \$5 million and the resulting senior secured note has a five year term and an interest rate of 10%, compounded annually and accrued on the principal amount of the note payable in cash on the maturity date. Accompanying the note is a warrant to purchase 83,333,333 common shares at an exercise price of \$0.12 per share. The warrant was exercisable immediately and has a term of 5 years. Acusphere also has the option to draw on two additional \$2.5 million tranches upon filing the MAA and upon reaching agreement with (FDA) under the SPA process on the design of an FDA-required Phase 3 study. These tranches will be on similar terms as the initial tranche with the exception of the warrant coverage, which, for each tranche, will be a warrant to purchase 27,777,778 common shares at an exercise price of \$0.10-0.12 per share.

Thanks to this financing – both the initial tranche and our access to one of the additional tranches that was accelerated based upon the company's progress - Acusphere had approximately \$5 million in cash at year end 2010. Acusphere expects to draw another \$2.5 million from Burrill upon filing the MAA, which will then enable us to continue operations through year end 2011. In our continued effort to manage our costs, we recently relocated to office space in Lexington, Massachusetts. This new location meets our needs and our budget, and affords us proximity to many critical contacts in the Greater Boston area.

Before I close, I want to express my deepest regrets about the recent passing of one of Acusphere's directors, and an important professional mentor to many of us, Frank Baldino, Founder, President and CEO of Cephalon Inc. Frank was one of the most encouraging supporters of Acusphere, and as a director, his advice was insightful, focused and reliable. We will miss him.

In summary, then, we believe Acusphere is poised for new success in 2011. We are focusing on a handful of critical steps that will pave the way for the long-term success of our lead product candidate, Imagify. These include:

- 1) filing the MAA in Europe,
- 2) reaching agreement on a SPA with FDA, and
- 3) exploring potential partnerships.

We appreciate your continued support as we strive to move Imagify forward, and help position it and Acusphere to achieve their potential in the future.

Sincerely,  
Sherri C. Oberg

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President and CEO

## **About Acusphere, Inc.**

Acusphere (ACUS.PK) is a specialty pharmaceutical company focused on the development and regulatory review for approval of our lead product candidate, Imagify™ (Perflubutane Polymer Microspheres) for Injectable Suspension. Imagify is a cardiovascular drug for the detection of coronary artery disease, the leading cause of death in the United States, for which a New Drug Application (NDA) was submitted to the U.S. Food & Drug Administration (FDA) in April 2008 and filed in June 2008. Imagify and the Company's other product candidates were created using proprietary technology that enables Acusphere to control the porosity and size of nanoparticles and microspheres in a versatile manner that allows them to be customized to address the delivery needs of a variety of drugs. For more information about Acusphere visit the Company's web site ([www.acusphere.com](http://www.acusphere.com)).

## **Forward-looking Statements**

*The above press release contains forward-looking statements, including statements regarding, the MAA submission for Imagify and likelihood of regulatory approval and the commercial opportunity for Imagify. There can be no assurance that Imagify will be approved for the indication the Company is seeking, or at all. The Company's actual results may differ materially from those anticipated in these forward-looking statements based upon a number of factors, including uncertainties associated with research, development, testing and related regulatory approvals, including uncertainties regarding regulatory evaluation of the Company's proposed Special Protocol Assessment with FDA and proposed Pediatric Investigational Plan with EMA which must be agreed upon before filing the MAA, and uncertainties regarding the potential effects of not achieving clinical endpoints, capital needs and uncertainty of additional financing, uncertainties regarding the cost, timing and ultimate success of the qualification of the Company's commercial manufacturing facility in accordance with applicable regulatory requirements, complex manufacturing, high quality requirements, lack of commercial manufacturing experience, dependence on third-party manufacturers, suppliers and collaborators, uncertainties associated with intellectual property, competition, loss of key personnel, uncertainties associated with market acceptance and adequacy of reimbursement, technological change and government regulation. The Company notes that effective as of March 3, 2009, pursuant to a Form 15 filing made with the SEC, it is not currently required to file periodic reports with the SEC, including annual reports on Form 10-K, quarterly reports on Form 10-Q and current reports on Form 8-K. Readers are cautioned not to place undue reliance on any forward-looking statements, which speak only as of the date of this press release. The Company undertakes no obligation to publicly release the results of any revisions to these forward-looking statements that may be made to reflect events or circumstances that occur after the date of this press release or to reflect the occurrence of unanticipated events.*

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