

Cubist Pharmaceuticals Acquisition of Calixa Therapeutics FAQ's

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Q. What is Calixa's Corporate History?

A. Calixa was founded in 2007 by Drs. Eckard Weber and James Ge. Calixa successfully acquired the global (excluding certain Asia-Pacific and Middle East territories) development and commercialization rights for CXA-101 (formerly FR-264,205) from Astellas Pharma Inc. Calixa assembled a management team and Scientific Advisory Board with extensive recent experience in the clinical development of anti-infectives, especially beta-lactam antibiotics (such as ertapenem, doripenem and ceftaroline), and raised \$30 million in Series A funding from three highly respected venture capital firms: Domain Associates, Canaan Partners and Frazier Healthcare Ventures.

Q. What is the history of this novel cephalosporin's development?

A. Calixa's most advanced product candidate, CXA-101, is an IV formulation of a novel broad-spectrum cephalosporin in-licensed from Astellas, that has demonstrated excellent *in vitro* potency especially against multi-drug resistant *Pseudomonas aeruginosa*, which differentiates it from other cephalosporins.

The IND for CXA-101 was filed in June 2008, and two Phase 1 studies were successfully completed by January 2009. A Phase 2 study in complicated urinary tract infection (cUTI) was initiated in the second quarter of 2009 and we expect to see data from this trial in 2010.

CXA-201 (combination of CXA-101 and tazobactam in a fixed 2:1 ratio) has an enhanced spectrum of *in vitro* activity and therefore high potential clinical utility as first-line therapy for serious Gram-negative infections in hospitalized patients. CXA-201 has completed Phase 1 trials (single ascending dose and multiple ascending dose). Cubist anticipates advancing the program for cUTI and complicated intra-abdominal infections cIAI in the first half of 2010. The next study in the cUTI program will take into consideration the results of the ongoing cUTI trial with CXA-101 and, in addition, a Phase 2 trial of CXA-201 for cIAI is planned for the 1H10. In 2H10, we also expect to begin lung pharmacokinetic studies of CXA-201 to support an indication in nosocomial pneumonia.

In addition to the IV development program (CXA-101 and CXA-201), the same cephalosporin is being evaluated (pre-clinically) for inhaled administration (the CXA-301 program) in cystic fibrosis patients to address multi-drug resistance (including to tobramycin) in *Pseudomonas aeruginosa* infections.

Q. What are the specifics of the deal terms?

A. Cubist paid Calixa stockholders \$100 Million, subject to certain adjustments and escrow provisions. As a result of the acquisition, Calixa became a wholly-owned subsidiary of Cubist. Cubist will also be required to make potential payments to the Calixa stockholders of up to \$310 Million in the event that certain development, regulatory, and commercial milestones related to products which incorporate CXA-101 are achieved.

Q. Will you develop -101 and -201 or just -201?

A. CXA-201 provides broader coverage against a range of Gram-negative bacteria and thus is our planned compound for development. However, the unique profile of CXA-101 remains attractive relative to current therapies and so development at a future date may be a consideration.

Q. What is the purpose of tazobactam in the combination therapy?

A.

- Tazobactam (TAZ) is the most commonly-used IV beta-lactamase inhibitor – used since the early 1990s in combination with piperacillin as Zosyn®.
- With the addition of TAZ, CXA-101 gains broader coverage (*in vitro*) over all common extended spectrum beta-lactamase (ESBL)-producing enterobacteriaceae.
- With the combination of TAZ, we expect the compound will be highly-differentiated from other cephalosporins in terms of coverage over both *P. aeruginosa* and ESBL-producing enterobacteriaceae.

Q. Is the regulatory path forward more challenging for a combination product like CXA-201?

A. If both compounds in the combination were novel this might be more challenging, but there is a well worn path for review of such agents when one is known. In the case of CXA-201 (combination of CXA-101 with tazobactam), CXA 101 is from a known class with which physicians are quite comfortable—and the compound has been separately tested in the clinic. Tazobactam, the companion compound, has been on the market since the early 1990s as part of the combination therapy Zosyn®. Given the history of cephalosporins, as well as this particular beta-lactamase inhibitor, we see a navigable regulatory path forward.

Q. What are your assumptions in getting to the \$1B peak sales opportunity in U.S. and EU figure?

A. We looked at the overall market opportunity for a Gram-negative agent with the spectrum and potency (especially against multi-drug resistant pseudomonas) of CXA-201. We sized the market overall for hospital-acquired Gram-negative infections at more than \$2.5B in the U.S. and Europe in 2013. Since most agents in this market will be generic when we launch, this dollar value understates the market opportunity.

We then made assumptions about the competitive environment and the label we'd target based on our development plan. With these environmental assumptions, we then made reasonable pricing assumptions for an agent with the distinctive characteristics of CXA-201, and our analysis suggested peak sales of >\$500 million in the U.S. alone and approximately \$1 Billion for the US and the EU combined.

Q. What is the intellectual property on CXA-201?

A. We have an exclusive license to patents that include composition of matter protection through 2023 in the EU and at least 2024 in the U.S. for products that incorporate CXA-101.