Anacor’s Drug Tavaborole Should Receive FDA Approval

On May 29, 2013, Anacor Pharmaceuticals (ANAC) announced successful completion of pre-NDA (New Drug Approval) communication with the U.S. Food and Drug Administration (FDA) related to tavaborole, Anacor’s lead drug candidate for the treatment of onychomycosis. More recently, on July 26, 2013, Anacor indicated that it had submitted its NDA to the FDA. The FDA has sixty days to decide whether to accept this NDA for review. Based on scientific literature and clinical data analysis of drug efficacy and safety, we believe the NDA for tavaborole will be accepted for review and then approved by mid-2014.

Background

Anacor is a biopharmaceutical company with eight drug candidates in its pipeline. Its lead product candidates include two topically administered dermatologic compounds, tavaborole (formerly AN2690) and AN2728. Tavaborole is an antifungal for the treatment of onychomycosis. AN2728 is a topical anti-inflammatory for the treatment of atopic dermatitis and psoriasis.

Onychomycosis, commonly known as nail fungal infection, is the most common disease of the nails and constitutes about a half of all nail abnormalities. The disease affects about 14% of people in North America. A fungus named dermatophyte causes distal subungal onychomycosis, the most common type of onychomycosis. Dermatophyte can infect the nail bed as well as the underside of the nail plate. Symptoms include discoloration, nail thickness, and nail brittleness. If left untreated, the skin underneath the nail plate can become inflamed and painful. Due to the resulting physical appearance, negative psychological effects often accompany these infections.

Tavaborole is a novel topical treatment for onychomycosis, which penetrates through the nail and kills the fungus by blocking protein synthesis. The fungus uses an enzyme called leucyl-tRNA synthetases (LeuRS) to catalyze the attachment of the amino acid leucine to the tRNA-Leu during translation of the genetic code. Tavaborole forms a stable adduct with tRNA-Leu and inhibits the LeuRS enzyme, in turn blocking protein synthesis and leading to the death of the fungus. The formation of the tavaborole-tRNA adduct requires the chemical element boron. Notably, boron chemistry is the unique feature of Anacor’s technology platform.

Tavaborole demonstrates solid efficacy and safety in Phase III trials

In January 2013, Anacor announced positive results from two phase III clinical studies of tavaborole (ref1, ref2). Each study enrolled approximately 600 patients with a clinical diagnosis of distal subungal onychomycosis involving 20 to 60% of the total area of the target great toenail. Patients were randomly assigned 2:1 to treatment (5% tavaborole solution) or vehicle and received the appropriate topical compound for 48 weeks. At the end of week 52, primary and secondary endpoints were assessed.

Notably, tavaborole met all primary and secondary endpoints with statistical significance in both trials. The primary endpoint was “complete cure” as determined by the presence of both a
completely clear nail and a mycologic cure. In the trial known as Study 301, 6.5% of patients treated with tavaborole achieved a complete cure, while only 0.5% of patients in the vehicletreated arm achieved a complete cure. In another trial, Study 302, the complete cure rate was 9.1% in the tavaborole-treated arm versus 1.5% in the vehicle-treated arm. The secondary endpoints included having (i) a completely clear or almost clear nail only, (ii) a mycologic cure only, and (iii) a completely clear or almost clear nail with mycological cure. In Study 301, the percentages of patients who met these endpoints in the tavaborole-treated arm and the vehicle-treated arm were, respectively: (i) 26.1% vs. 9.3%, (ii) 31.1% vs. 7.2%, (iii) 15.3% vs. 1.5%. The results for secondary endpoints in Study 302 were similar to those in Study 301, and all comparisons were statistically significant.

Tavaborole was also demonstrated to be very safe. There were no adverse effects associated with its use. Furthermore, there was essentially no detectable amount of the drug in the blood or urine. The rates of discontinuation as a result of adverse events were quite low as well – they were slightly higher than those for the vehicle-treated arm (2.8% vs. 1.6% in Study 301, and 0.8% vs. 0.5% in Study 302).

**Tavaborole is advantageous to existing therapies**

Primary treatment options for onychomycosis include debridement and pharmacologic therapies. Debridement entails the cutting, clipping, and scraping of the nail. This is only a temporary solution, as it does not treat the underlying fungal infection. Currently, there are two types of available pharmacologic therapies, Lamisil and Penlac, both of which have generic versions on the market. Lamisil is an oral treatment. It represents 80% of total prescriptions for this condition and demonstrates an efficacy of 38% over a 12-week period. However, Lamisil has been linked to rare but severe liver toxicity that can result in death or the need for a liver transplant. Given tavaborole’s favorable safety profile, tavaborole may be readily adopted in place of Lamisil and Lamisil’s generic counterparts.

In contrast to Lamisil, Penlac is a topical treatment. Penlac is effective for 5.5 to 8.5% of patients over a 48-week period, with no adverse side effects. However, Penlac must be combined with debridement to be effective. As a result, Tavaborole is significantly more convenient than Penlac and its generic alternatives.

**The market for tavaborole is unclear due to competition from Valeant’s drug efinaconazole**

The global market for onychomycosis was valued at $2.1 billion in 2010 and has been forecast to reach $3.4 billion by 2017. The overall market for pharmacological treatments is large considering that Lamisil had sales of $1.2 B and Penlac had sales of $125 M prior to facing generic competition. However, the market for tavaborole is unclear due to its potential competitor efinaconazole, another topical treatment developed by Valeant Pharmaceuticals. Clinical trial data indicate that 15.2 to 17.8% of patients achieved complete cure in 52 weeks using efinaconazole (ref3) as compared to 6.5 to 9.1% for tavaborole. Although the clinical trials were conducted with different patient cohorts, the almost 2-fold difference in efficacy has had a significant impact on investor sentiment. On January 2013, Anacor’s stock dropped 20% despite
positive announcements regarding a set of two phase III clinical trials for tavaborole, possibly because these trials did not substantiate superiority over efinaconazole.

Valeant filed its NDA for efinaconazole in July of 2012 and received a complete response letter (CRL) from the FDA on May 2013. The issues raised in the CRL appear to relate exclusively to the Chemistry, Manufacturing, and Control section of the NDA. Valeant believes these concerns are quite addressable and plans to submit a response to the FDA in the near term. It should be noted that Anacor is also in legal proceedings with Valeant for breach of contract relating to services provided to Anacor by Valeant’s subsidiary Dow Pharmaceuticals. Valeant has agreed not to launch efinaconazole until the two parties meet at an arbitration hearing scheduled for September of this year. Nevertheless, efinaconazole could still go to market several months ahead of tavaborole, which is expected to launch no sooner than mid-2014.

**AN2728 is another noteworthy catalyst in Anacor’s pipeline**

Long term, other product candidates in Anacor’s pipeline could serve as strong catalysts. For example, Anacor’s second lead drug candidate, AN2728, is a topical treatment for atopic dermatitis and psoriasis. Anacor has demonstrated the safety and efficacy of AN2728 across numerous phase II clinical trials for both diseases \(^\text{ref3}\). On March 21, 2013, upon release of AN2728’s phase II data, Anacor’s stock price increased 26%. Anacor has also initiated another phase II clinical trial for atopic dermatitis and anticipates initiating a phase III study either later this year or in early 2014.

For investors interested in long-term opportunities, it is worth noting that all of Anacor drug candidates are derived from boron chemistry, a technological platform considered Anacor’s key competitive advantage. Boron based chemistry offers access to biological targets not amenable to intervention by traditional carbon-based compounds. Preclinical activity suggests that boron-containing chemicals have utility across a wide spectrum of disease areas. Historically, the challenge in leveraging this platform has been related to chemical synthesis. However, Anacor has recently made significant advances in the synthesis of boron-based compounds. This could provide long-term growth through a meaningfully broad intellectual property landscape.

**Scientific Summary**

Based on the efficacy and safety data of tavaborole’s two phase III clinical trials, we believe tavaborole will receive NDA acceptance and then FDA approval. However, an early launching of efinaconazole might pose a threat to market adoption of tavaborole.

**Investment Context**

The future of Anacor and tavaborole still remains shaky due to legal and financial constraints. Anacor and Valeant are slated to participate in an arbitration hearing in September of 2013 to determine whether an agreement can be reached on issues stemming from a previous business relationship gone awry. Anacor claims damages of $215 M. Valeant has agreed not to market efinaconazole until after this hearing. Notably, Valeant does not yet have FDA approval to launch efinaconazole. The company is in the process of resubmitting its NDA for efinaconazole.
after receiving a Complete Response Letter (CRL) from the FDA in May of this year. Nevertheless, given that concerns raised in this CRL appear to be focused exclusively on the Chemistry, Manufacturing, and Controls section of the NDA, it seems likely that Valeant would receive approval for efinaconazole upon resubmission. If and when this were to occur, it would likely mean that Valeant could bring efinaconazole to market many months ahead of when Anacor could do the same for tavaborole. Furthermore, efinaconazole is chemically more similar to existing treatments for fungal infections, suggesting that care providers might be more inclined to prescribe efinaconazole until they reach a certain comfort level with tavaborole and other boron-containing drugs. This type of dynamic may be exacerbated by an early launch of efinaconazole.

However, possibly more worrisome for investors is the potential debt overhang Anacor has recently begun to build. On June 7, 2013, Anacor entered into a $45 M loan agreement with Hercules Technology. The associated notes are arranged into three tranches, the first of which, comprising $30 M, was drawn at the agreement’s close and used to retire more than $22 M of existing notes. The new notes accrue interest at a sizeable mark (11.65 to 14.90%, in contrast to the sub-10% rate of the earlier notes) and exist with a $75 M shelf registration established in December of 2012 that appears to remain nearly completely outstanding. Given Anacor’s high cost of debt and the potential for a more-than-10% dilution event resulting from the 2012 shelf registration, investors in both primary and secondary markets may be rightly hesitant about the short-term promise of Anacor common stock.

Furthermore, Anacor has indicated a need for additional financing ahead of expected commercialization efforts for tavaborole. Given that the FDA may reach a decision on tavaborole in mid-2014, such capital raising would likely occur within the next six to nine months. If Anacor were to face a delay in the approval decision before raising additional equity, it would place especially burdensome financial pressure on the company. Anacor would need additional liquidity precisely when its stock would have a low value. This underscores why we predict that the company will soon issue a significant amount of equity under its existing shelf registration. The recent run-up in Anacor’s stock price over the last month makes the current time an especially attractive one for such issuance. However, we also note that an appealing time for the issuance would be just subsequent to the FDA’s decision to accept Anacor’s NDA for review.

Additional disclosure: Beacon VP Investments is a team of analysts. This article was written by Rozy Vig and Yuqi Qin.

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