Company: Theravance, Inc. (THRX)
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I reviewed eight year-old Theravance (THRX) as a possible long investment since 1) it is conducting two Ph 3 trials for a novel antibiotic, Telavancin, with data expected in mid-'06, 2) it is, with partner GlaxoSmithkline, in Ph 2 trials with a β-agonist bronchodilator for asthma and 3) 50 percent of Theravance stock has downside protection at $9.69 (up to $525 million) by virtue of a put option by shareholders to Glaxo expiring August 2007.

On August 17, THRX closed at $20.64 with 44.2 million shares outstanding at Q2/June end and $202 million of cash and equivalents ($4.57/share). Also, Glaxo owns 9.4 million Class A common (17.6 percent) which afford Board designation rights (as yet, unexercised). Thus, total share count is 53.4 million. The market capitalization is ≈ $910 million or $1.1 billion including Glaxo. Finally, Glaxo is under an open-market standstill until September 2008. Note that almost 70% ($14.26) of the stock's price is currently covered by cash-on-hand plus the put option.

Conclusion: With roughly $340 million in technology value, Theravance is not expensive; however, much of its destiny for the next two years is in Glaxo's hands. Also, the single in-house project, terminal antibiotic candidate Telavancin, is in two equivocal Ph 3 trials. That is, at least one trial is likely to hit the minimum requirement to support an NDA filing, but that approval would not yield a market competitive product. Other projects are much earlier in their development and therefore less relevant over the next 12 months. A long position is warranted based on reduced downside risk and modest potential for substantial appreciation within 12-18 months.

Telavancin

Located in South San Francisco, Theravance is a pure drug discovery company (medicinal chemistry) with no plans to manufacture or market its novel compounds. The Company plans to partner all projects and has done so (exclusively with Glaxo) except for its antibiotic program, including Telavancin, which Glaxo declined.

The Company touts its approach to creating new drugs by incorporating multivalency, i.e., one molecule with more then one target. For example, Theravance claims that Telavancin was *designed* with multiple mechanisms of action to 1) inhibit bacterial cell wall formation (as vancomycin does) and 2) disrupt bacterial cell membrane integrity. A dual-function molecule might be expected to have broader antibiotic activity and be less prone to generating resistant organisms. To this end, Theravance had submitted a patent application in which two molecules (vancomycin and N-decylaminoethylvancomycin) were coupled to each other with a chemical linker arm. This did not result in a useful drug. Further, multivalency was never mentioned in the Company's 2004 publication (J. Antibiotics (Tokyo), 57:326-336) describing the synthesis and discovery of Telavancin. The effort was focused simply on improving the ADME characteristics of a previously described hydrophobic derivative of vancomycin (the N-decylaminoethylvancomycin noted above, which retained VRE and MRSA activity), as quoted below:

> "Specifically, we hoped to reduce liver and kidney accumulation and increase urinary excretion while maintaining potent *in vitro* antibacterial activity and bactericidal properties."

Thus, Theravance appears to be pitching a story (thesis) that is somewhat inconsistent with the actual molecule that is currently being tested for two indications in Ph 3 trials. As always, more important than the real or pitched mechanism of action is the in vivo activity of the drug. Theravance initiated three Ph 2 studies of Telavancin and reported on two of them. The data reported were selective and incomplete, calling into question the wisdom of entering Ph 3 trials.

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Clinical Status

Telavancin, a derivative of vancomycin, is active against VRE (vancomycin-resistant enterococci) and MRSA (methicillin-resistant Staphylococcus aureus, an especially serious infection). In vitro testing (bacterial cultures) and pre-clinical studies (animals) generally support Telavancin's potential utility to treat severe infections, analogous to Cubist's Cubicin, Pfizer's Zyvox and generic vancomycin. Virtually all pivotal clinical trials for these drugs are designed as double blind versus active control drug with *non-inferiority* to the SOC as the PCE. Market adoption often results from non-clinical benefits. For example, Cubicin is dosed q.d., often on an out-patient basis, compared with (inexpensive) vancomycin which is dosed b.i.d. Similarly, patients on (expensive) Zyvox can be started on IV drug, then discharged from the hospital, remaining on the oral version. Oral Vancomycin is not systemically absorbed. The Ph 2 and Ph 3 programs for Telavancin (aka '6424) are summarized below:

Phase 2

1/04: Ph 2 "data" ("FAST 1") for *'6424* in cSST; vs SOC; DB-AC in 169 Pt.s as Telavancin (N=84; *7.5mg/kg*, q.d, ≈ 0.5g) vs vancomycin (N=83, 1g, b.i.d.); Hit PCE of *non-inferior*;
Ph 2 (*2nd*, "FAST 2") in progress for *'6424* in cSST, N=225 Pt.s, Telavancin at *10mg/Kg*;
Ph 2 (*3rd*) in progress for *'6424* in S. aureus bacteremia (uncomplicated), Telavancin at *10mg/Kg* vs SOC;

11/2/04: PR; Ph 2 data ("FAST 1") for *'6424* in cSST; *167* Pt.s as Telavancin (*7.5mg/kg*; for MRSA subset (N=22), *82% cure*) vs vancomycin (MRSA subset (N=26), *69% cure*) *but*, no p-value for MRSA subset; Similar AE, dropout rates;
Hit PCE of *non-inferior*;

12/7/04: Ph 2 data (*2nd*, "FAST 2") for *'6424* in cSST; N=201 (or 210) Pt.s at 18 sites US, S.Africa; Like Fast 1, but Telavancin at *10mg/Kg*; Telavancin (*96.1% "cure"*) vs SOC (*93.5%*), non-inferior; For MRSA subset (no Ns), Telavancin (*92.3% "eradication"*) vs SOC (*68.4%*), p=0.043 (close); Similar AE;

Phase 3

12/04: Ph 3 begins (*1st*), 2 trials in 750 pt.s each (30% MRSA) in cSST (less MRSA occurrences) and HAP (soon; more frequent MRSA); In both, PCE is *non-inferiority* overall and *superiority* to vancomycin in MRSA;

1/26/05: Ph 3 begins ("ATTAIN"), 2 trials in 750 pt.s each in HAP; DB-AC vs vancomycin in pneumonia due to S. aureus, Streptococcus pneumoniae; ATTAIN is Assessment of Telavancin for Treatment of MRSA Pneumonia (huh?);

3/28/05: *Fast track* for Telavancin;

First, note that Telavancin has never been tested in hospital-acquired pneumonia (*HAP*). It was entered into Ph 3 testing based on pre-clinical demonstrations of reaching adequate pulmonary concentrations. This is a high-risk trial by any criteria and success is essentially unpredictable. For complicated skin and soft-tissue (*cSST*) infections, the story is slightly more, um, complicated. Both FAST 1 and FAST 2 (7.5mg/kg vs 10.0mg/Kg) demonstrated non-inferiority to vancomycin and should perform similarly in the Ph 3 trial (10.0mg/Kg). However, in FAST 1, a subset analysis of MRSA patients suggested superiority, but no p-value was provided. In Fast 2, the number of patients in the MRSA subsets were omitted, but the p-value (p=0.043) was reported. Assuming similar MRSA incidence rates in both trials, the conclusion of superiority is tenuous at best. Further, Fast 1 reported *cure rates* for the MRSA subset (based on clinical evaluation) while Fast 2 reported *eradication rates* (microbiological testing). The PCE for both Ph 3 trials is non-inferiority to vancomycin for cure rates. And, a second PCE (not required for NDA submission) is superiority in cure rate (not bacterial eradication) for MRSA patients. Thus, prior clinical data do not support the likelihood of Telavancin successfully hitting both PCEs in either Ph 3 trial.

To summarize, the Ph 3 trial of Telavancin in HAP lacks clinical precedent, and is therefore unpredictable and risky. The Ph 3 trial in cSST is likely to hit the first, and sufficient, PCE of non-inferiority to vancomycin. The data do not predict that Telavancin will prove superior to vancomycin in MRSA. Theravance will release more complete results from the FAST 2 trial at ICAAC, beginning September 21.

Risk Assessment

- *Downside risks:* Data from the cSST trial are expected well ahead of the HAP trial results. Success in cSST is likely (but see below) while the HAP indication remains at very high risk. Extant data are equivocal (small number of patients, incomplete data set) on the potential for MRSA superiority. At worst, Theravance will have a me-too antibiotic on the market by mid-'07, competing against generic vancomycin, Cubist's Cubicin, Pfizer's Zyvox and, via Pfizer's Vicuron acquisition, possibly dalbavancin (PDUFA date extended to September 21). The Company's second most advanced project, under GSK control, is '797 for COPD and asthma. The drug has only completed Ph 2a testing, in a single, ascending dose regimen. Based on '797's mechanism of action (long-acting, β_2 agonist), a black box label is virtually certain, assuming clinical success and FDA approval.

- *Upside opportunity:* Clearly positive, FAST 2 data in September should provide a boost to Theravance, leading to increased optimism for Telavancin to hit the critical, MRSA superiority endpoint in cSST. If the data are less than robust or negative, the stock may sink a bit further, but not much. A corporate partnership for Telavancin would also add significant value for two reasons. First, the right new partner would lend increased validity to Theravance's antibiotic program. Second, Glaxo's perceived dominance at the Theravance table would be mitigated, although GSK still retains FROR for most projects in the pipeline. The likelihood of Telavancin receiving an NDA approval by mid-'07 is high. The quality of the package insert ("clinical superiority against MRSA") is unpredictable.

With the information in hand, the upside opportunity has an edge over the downside risks.