

Vertex: More than Incivek

Pipeline Agents for RA, CF, and HCV Impact Hot Targets

Vertex Pharmaceuticals

Symbol: VRTX

Market Cap: \$5.75 billion

Lead Drug: **Incivek** (telaprevir)

Indication: **Hepatitis C Infection**

Developmental Stage: **Marketed**

2012 Projected Worldwide

Revenue: **\$1.8 billion**

Peak Projected Worldwide

Revenue: **\$2.9 billion in 2015**

Pipeline:

Hepatitis C (HCV):

- **VX-222** (phase II), 55%(B) IAI, worldwide sales of \$1.0 billion in 2018
- **VX-759** (phase I)
- **VX-985** (phase I)

Rheumatoid Arthritis (RA)

- **VX-509** (phase II), 63%(A) IAI, worldwide sales of \$480 million in 2019

Cystic Fibrosis (CF)

- **Ivacaftor / VX-770** (submitted for FDA approval), 85%(B) IAI, worldwide sales of \$313 million in 2018
- **Lumacaftor / VX-809** (phase II), 40%(C) IAI, worldwide sales of \$323 million in 2018
- **VX-661** (phase I)

Epilepsy:

- **VX-765** (phase II), 25%(C) IAI

Influenza A virus:

- **VX-787** (phase I)

- Only six months after the approval of Incivek, **Vertex (VRTX)** is a profitable biotech company managing the strongest drug launch in history.
- However, concern about competition has tempered long-term expectations for Incivek as several companies race to develop the first all-oral regimen for hepatitis C (HCV) viral infection.
- Even after the recent acquisitions of Anadys (ANDS) and Pharmasset (VRUS), *inThought* continues to expect consolidation among HCV drug developers.
- **Vertex offers a rare combination of current revenue and long-term promise from its drug pipeline.** In this report, we review the most promising agents in Vertex's pipeline, presenting our revenue forecasts and probability of approval analyses of those compounds.
- In addition to Incivek, **Vertex has the most advanced gene-targeted cystic fibrosis (CF) drug in development.**
- **Vertex's phase II rheumatoid arthritis (RA) drug impacts a hot target, the JAK kinase.** Promising phase II data were presented this month at the American College of Rheumatology meeting.
- **VX-222 could complement Incivek as part of an all-oral HCV regimen.**

Vertex's transition from research biotech to commercial pharmaceutical company has been impressive. Incivek's launch is on-track to become the fastest to \$1 billion, a feat all the more impressive considering the concurrent launch of Merck's competing HCV drug Victrelis (boceprevir). Investors are now questioning the sustainability of Incivek's momentum, with Vertex's stock price decreasing over 50% since Incivek was approved. Potential acquirers may have a different view of Vertex's value, noting not only the near-term revenue potential of Incivek but also the value of several pipeline agents that impact unique and hot targets.

We therefore present models of the most promising drugs in Vertex's pipeline. Next to market will likely be ivacaftor (VX-770, proposed brand name Kalydeco) for cystic fibrosis (CF). Vertex also has a JAK inhibitor for RA that could compete with Pfizer's similar agent tofacitinib. In HCV, VX-222 could compliment Incivek, providing the coveted all-oral combination so many companies are striving to create. Earlier in development, Vertex has compounds for epilepsy, influenza A with a focus on the H1N1 and H5N1 subtypes, and additional HCV and CF compounds.

Adding ribavirin to Incivek plus VX-222 may yield results similar to Abbott and Bristol Myers Squibb's all-oral trials.

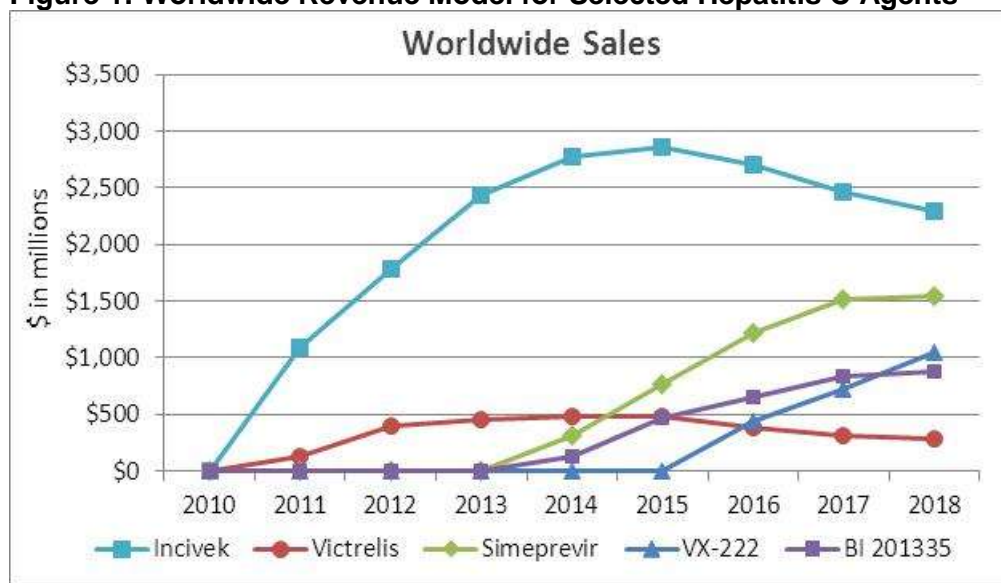
Hepatitis C

This summer, the FDA approved two protease inhibitors to be used in combination with pegylated interferon and ribavirin for the treatment of adult patients with chronic genotype 1 hepatitis C virus infection. The compounds Incivek (telaprevir) by Vertex and Victrelis (boceprevir) by Merck launched within weeks of each other. Both agents are dosed three times a day.

Incivek has a relatively straight-forward 12-week dosing regimen, and the majority of patients qualify for shortened 24-week therapy with interferon and ribavirin. Victrelis uses an interferon and ribavirin lead-in treatment, and dosing time depends on patient viral response. Also, fewer patients qualify for a shortened 28-week therapy with interferons, meaning that 48 weeks are the potential treatment time for many.

At least to date, physicians and patients have strongly preferred Incivek to Victrelis, with prescriptions at a 3:1 ratio in the U.S. Incivek is on track to reach over \$1 billion in sales in the first nine months on the market. We project 2012 sales of \$1.8 billion worldwide and peak sales of \$2.9 billion in 2015.

Figure 1: Worldwide Revenue Model for Selected Hepatitis C Agents



Source: Company data and inThought estimates

Incivek

Incivek (telaprevir) is an NS3/4A protease inhibitor that has been shown to significantly reduce viral load quickly when combined with current standard of care (SOC), increasing sustained viral response (SVR) from an average of 45% of patients to as high as 79% in treatment naïve patients. Treatment is typically 24 weeks vs. 48 with the SOC. Weighted Average Cost (WAC) is \$49,200 for a full 12 week course in the U.S.

Incivek's direct competition is Merck's NS3 protease inhibitor, Victrelis, which increases viral response rates slightly less than does Incivek. Merck has a co-promotion agreement with Roche, which markets Pegasys. Victrelis's WAC is \$1,100 per week.

VX-222 and VX-759

VX-222 is a non-nucleoside inhibitor of the NS5B polymerase, an enzyme required for HCV replication. VX-759 is considered to be a back-up compound to VX-222, and Vertex has noted that development of VX-759 could be halted if VX-222 results are strong.

In a phase II study evaluating the combination of VX-222, Incivek, pegylated interferon and ribavirin in a 12-week course, 93% of treatment-naïve, genotype 1 patients achieved SVR. Vertex is now beginning to study VX-222, Incivek, and ribavirin in a 12-week, all-oral regimen that excludes the injected interferons. An all-oral combination had been tried previously, but the exclusion of the ribavirin booster allowed viral breakthrough in a small number of patients. *inThought* expects this new arm will provide results similar to Abbott and Bristol Myers Squibb's all-oral trials that included ribavirin, which have shown impressive efficacy and limited resistance. A phase III trial of VX-222 is planned in the first half of 2012.

In preclinical trials, VX-759 was able to block the replication of HCV in the cellular replicon model against genotype 1a and 1b infections. Phase Ib results of VX-759 indicated that the drug should be used as part of a combination treatment to maintain viral suppression and prevent the development of resistant organisms.

As with tofacitinib, serious infections, cholesterol increases, and mortality will be issues for VX-509.

Our 55%(B) *inThought* Approvability Index (IAI) score for VX-222 is based on the clinical results and molecule type of this compound. Protease inhibition has unequivocal, peer-reviewed support. We believe that polymerase inhibition will gain similar support. VX-222 has been well tolerated, with no serious adverse events observed. In studies, the compound has been efficacious enough to allow most patients to stop therapy by week 12, which is half the time of the current shortened therapy. This month, Vertex released quadruple therapy results showing 93% SVR in a 12-week regimen, providing confidence in the efficacy of the compound.

In our model, we assume that VX-222 will be used as an add-on polymerase inhibitor to Incivek. Our peak worldwide sales estimate for VX-222 in 2018 is \$1,047 million in annual sales.

Rheumatoid Arthritis

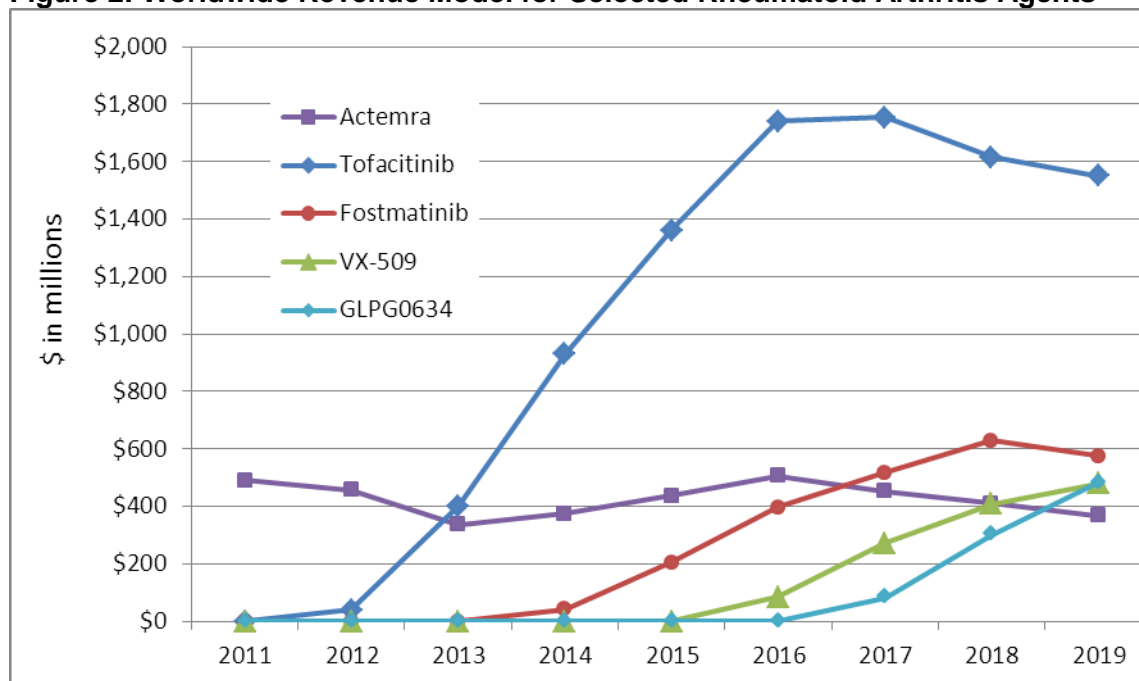
At the American College of Rheumatology (ACR) meeting earlier this month in Chicago, Vertex presented phase II data from 200 rheumatoid arthritis (RA) patients treated with VX-509, its JAK3 inhibitor, or placebo. Efficacy was impressive. Safety, although not perfect, was sufficient to move the program forward to phase III.

Oral kinase inhibitors are a new class of oral therapies being developed by several pharmaceutical and biotech companies for the treatment of RA. The hope is to replace TNF inhibitors and other biologics with an oral pill that matches TNF inhibitors' efficacy and safety.

The most advanced oral kinase inhibitor is Pfizer's JAK inhibitor tofacitinib. An impressive phase III program has shown consistently impressive efficacy and acceptable safety in over 3000 patients. Tofacitinib was the hot topic at ACR this year, with most of the phase III trials now completed. Pfizer will file for approval in the U.S. this year, and has already done so in Europe. *inThought* models an 85%(A) IAI with peak revenue of \$1.8 billion in 2017.

Tofacitinib has specificity for the JAK1 and JAK2 isoforms over JAK3. Vertex hopes that its JAK3 specific inhibitor VX-509 can match the efficacy of tofacitinib but avoid some of the safety issues, such as serious infections and increased lipid levels.

Figure 2: Worldwide Revenue Model for Selected Rheumatoid Arthritis Agents



Source: Company data and inThought estimates.

The phase II data suggest that VX-509 will succeed on one of those points but not the other. Efficacy appears to be as good as tofacitinib, but not superior. As with tofacitinib, serious infections and mortality will be an issue for VX-509. In the phase II trial, serious adversities occurred in 5% of VX-509 recipients vs. 2% with placebo, cholesterol and other lipids increased with VX-509, and two deaths occurred in the 100mg dose arm.

We model a 63%(A) IAI for VX-509, with an estimated U.S. approval date of March 2016. If approved, we model worldwide revenue of \$480 million by 2019. Phase III trials should begin shortly, but based on the huge phase III program Pfizer conducted for tofacitinib, Vertex will need a partner to fund the phase III trials.

If successful, VX-509 will face competition not only from tofacitinib but from other oral kinase inhibitors. Rigel and AstraZeneca's syk inhibitor is in phase III trials. Galapagos last week reported promising phase II results of its JAK2 inhibitor GLPG0634, which so far does not appear to raise cholesterol in the same way as tofacitinib and VX-509. Figure 2 shows our revenue projections for these oral kinase inhibitors compared to the marketed IL6 inhibitor Actemra (Roche).

Cystic Fibrosis

Ivacaftor (VX-770, proposed brand name Kalydeco) is an orally available, small molecule agent thought to directly increase the gating ability of defective ion channels at the cell surface of cystic fibrosis (CF) patients, thereby restoring the function of the aberrant CFTR protein, the defective cell membrane protein responsible for initiation and progression of the disease. It was developed through a collaboration between Vertex and Cystic Fibrosis Foundation Therapeutics. Phase III development of ivacaftor for use in patients aged ≥6 years with cystic fibrosis (G551D mutation in CFTR gene) has been completed in the U.S., Canada, and the EU. Regulatory submissions have been made in the U.S. and EU.

Based on impressive phase III STRIVE study data presented at the recent North American Cystic Fibrosis Conference and published in *The New England Journal of Medicine* (Nov. 3, 2011; 365:1663-72), ivacaftor is highly likely to be approved in a timely manner. The drug's experimental benefit to risk ratio in the phase III program supports our elevating its IAI score to 85%(B) from 50%(C).

While it is highly likely to be used in the 4%-5% of CF patients with the G551D mutation, ivacaftor's commercial promise has always been tempered by the uncertainty of its appropriateness for the majority of CF patients. We are maintaining ivacaftor's worldwide revenue forecast of \$313 million in 2018. Upside to this projection will depend upon whether the agent displays therapeutic activity beyond those with the G551D mutation. All of the impressive ivacaftor results to date have been in this CF subpopulation.

Relevant molecular and clinical results that suggest ivacaftor would also benefit CF patients with a ΔF508 mutation would help Vertex realize its potential in 70-90% of U.S. and EU patients with CF. *In vitro*, ivacaftor stimulates activity in ΔF508, but to a significantly lesser extent than it does G551D. Whether this degree of activity will suffice to lead to clinical benefit in ongoing phase III programs in Australia and Canada (as well as phase II programs in the US, Belgium, Germany, Australia, and New Zealand) remains to be seen, and the predictive value of prior investigation is severely limited. Only the DISCOVER trail, to date, has tested monotherapeutic ivacaftor in this subpopulation.

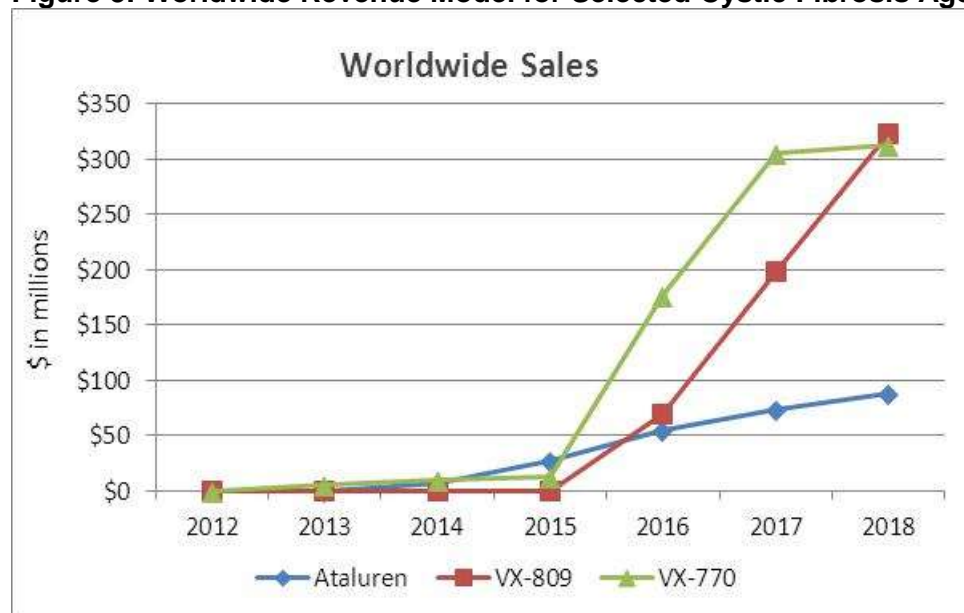
While sweat chloride advantages were seen, these did not translate to significant clinical benefit over 16 weeks.

Recent Results

The recent phase III results demonstrate that ivacaftor promotes lung function improvements beginning at 2 weeks that are sustained through 48 weeks of administration. Statistically and clinically significant improvements were observed at the levels of pulmonary exacerbation risk, patient-reported respiratory symptoms, weight, and sweat chloride concentration.

The investigation was a 167-subject (at least 12 years of age, each with at least one G551D-CFTR mutation), randomized, double-blind, placebo-controlled trial in which enrollees were randomized to receive either ivacaftor 150mg every 12 hours or placebo for 48 weeks. The primary endpoint was estimated mean change from baseline, through week 24, in the percent of predicted forced expiratory volume in 1 second (FEV1), a classic pulmonary function test.

Figure 3: Worldwide Revenue Model for Selected Cystic Fibrosis Agents



Source: Company data and *inThought* estimates.

Ivacaftor outperformed placebo at this primary endpoint by 10.6 percentage points ($p < 0.001$). Moreover, ivacaftor recipients were 55% less likely to experience a pulmonary exacerbation than those receiving placebo, through week 48 ($p < 0.001$). Robust statistical and clinical ivacaftor advantages were also seen at respiratory symptomology, quality of life, weight gain, and sweat chloride endpoints. Importantly, the proportion of enrollees experiencing serious adverse events with ivacaftor was 24% compared with 42% for placebo. Adverse event rates were comparable.

Phase III Efficacy

Interim 12-week results from the phase III PERSIST extension trial showed that absolute and relative changes in lung function were sustained through week 12 for a total of 60 weeks of treatment. In patients treated with placebo during the STRIVE study who switched to ivacaftor in the PERSIST study, improvements in lung function through week 12 were similar to those observed among those treated with ivacaftor in the first 12 weeks of the STRIVE study.

The placebo-controlled ENVISION trial of 52 children 6-11 years with the G551D mutation also met a primary endpoint of mean absolute change from baseline in percentage predicted FEV1 through 24 weeks, 17.4% to 12.5%. At week 48, ivacaftor was also associated with favorable weight gain (5.9 vs 3.1kg from baseline) and reduced levels of sweat chloride (56 mmol/L vs 3 mmol/L), compared with placebo. A trend towards improvement in respiratory symptoms was observed at 48 weeks with ivacaftor.

Phase II Efficacy

Ivacaftor did not significantly improve lung function, compared with placebo, over 16 weeks in the 140-patient DISCOVER trial. However, there was

a significant reduction in sweat chloride levels in ivacaftor recipients, compared with placebo recipients (-2.9 mmol/L; $p < 0.04$). Notably, enrollees here had two copies of the $\Delta F508$ mutation.

Ivacaftor significantly improved CFTR function at day 14 in a phase IIa trial in adults with CF who had at least one G551D mutation. Furthermore, FEV1 values improved significantly with all doses of ivacaftor (75, 150 and 250mg), compared with placebo, at day 14, and the difference in lung function improvement remained significant at day 28. Sweat chloride values improved by at least 20 mmol/L in 93% of ivacaftor recipients but not in any placebo recipients.

Safety

Tolerability in STRIVE was reassuring. Adverse events reported in at least 5% more ivacaftor recipients than placebo recipients were respiratory tract infections, nasal congestion, headache, dizziness, rash, and bacteria in the sputum. Events leading to withdrawal were less frequent in the ivacaftor group than the placebo group (1% vs 5%). Adverse events reported in interim 12-week results from the PERSIST extension trial included pulmonary exacerbations, cough, productive cough, upper respiratory tract infection, hemoptysis, headache, and abdominal pain.

In ENVISION, no patients discontinued treatment due to adverse events in either group. The most common adverse events were of respiratory nature, which included cough, congestion, wheezing, and other respiratory symptoms. Other common adverse events included headache, throat pain, vomiting, and cystic fibrosis pulmonary exacerbations.

Adverse events reported more frequently in ivacaftor recipients than placebo recipients in

Ataluren is the Only Other Gene-targeted CF Drug in Late-Stage Clinical Development

IAI: 49%(C) :: 2018 Revenue Forecast: \$88 million

PTC Therapeutics' ataluren is a fascinating small molecule that promotes so-called "read-through of premature truncation codons" so as to promote the molecular manufacture of viable proteins such as the CFTR. Approximately 10% of CF worldwide, and 50% in Israel, is due to nonsense-mediated, truncated CFTR (*Lancet* vol. 372, iss. 9640; pp 719-727; 30 August 2008). Having navigated phases I and II CF trials successfully, enrollment is complete in an initial 238-patient, phase III trial (NCT00803205) in adult and pediatric patients with nonsense mutation-mediated CF. An extension program is also underway.

DISCOVER included nausea, cough, rash, and contact dermatitis. None of these events was serious and none resulted in treatment withdrawal. The most common adverse events observed in other phase II investigation were fever, cough, nausea, pain and runny nose.

Lumacaftor (VX-809)

Lumacaftor is an orally available, small molecule thought to enhance the number of channels of the CFTR protein at the cell surface. It was discovered as part of research collaboration with Cystic Fibrosis Foundation Therapeutics. Lumacaftor is undergoing phase II development in North America, the EU, Australia, and New Zealand.

Initial lumacaftor data support cautious optimism for its advancement to phase III investigation in a timely manner. New insight discussed at NACF regarding its mechanism of action plus the reassurance of the ivacaftor program supports our elevating its IAI score to 40%(C) from 33%(C).

We are maintaining lumacaftor's worldwide revenue forecast of \$323 million in 2018. Significant upside to this projection is possible given the likelihood of increased pursuit of the $\Delta F508$ mutation population. However, it remains to be seen just how much is dependent upon combination administration with ivacaftor in the more prevalent subpopulation.

Monotherapeutic Results

In its phase IIa trial, lumacaftor once daily at both the 100mg and 200mg doses for 28 days significantly decreased sweat chloride levels compared with baseline and placebo in 89 CF patients homozygous for the $\Delta F508$ mutation. Preliminary data from this randomized, double-blind, placebo-controlled program also showed that a dose-response for change in sweat chloride was observed across all four dose groups (25, 50, 100 and 200mg).

Preliminary phase IIa data showed that lumacaftor was well tolerated. One patient in each of the lumacaftor treatment arms discontinued treatment due to adverse events. The most frequently occurring adverse events were referable to the respiratory system.

Combination Efficacy Results

In the first part of a phase II trial, lumacaftor (day 0-14) and lumacaftor plus ivacaftor in combination (day 15-21) significantly decreased sweat chloride levels in CF patients compared with baseline levels and a placebo cohort. This was in subjects (n=62) with two copies of the $\Delta F508$ mutation. A decrease in sweat chloride of 4.21 mmol/L was observed from baseline to day 14 in patients receiving lumacaftor 200mg (p=0.008), along with a significant decrease of 9.10 mmol/L from day 14 to day 21 in patients receiving lumacaftor 200mg plus ivacaftor 250mg (p<0.001), a total decrease of 13.17 mmol/L. A decrease was also observed in the final seven days in patients receiving lumacaftor 200mg plus ivacaftor 150mg but the change was not significant. A decrease of >15.0 mmol/L was observed in 8/17 patients and a decrease of >20 mmol/L in 4/17.

While it is highly likely to be used in the 4%-5% of CF patients with the G551D mutation, ivacaftor's use in the majority of CF patients is uncertain.

Lumacaftor monotherapy as well as lumacaftor plus ivacaftor in combination were well tolerated with similar safety profiles and no serious adverse events in the first part of a phase II trial. The most commonly reported adverse events were respiratory in nature and occurred in approximately half of people across all arms of the study. One study subject receiving lumacaftor in the monotherapy portion of the study discontinued treatment due to an increase in respiratory symptoms during the first 7 days of the investigation.

Epilepsy

VX-765 is a second-generation interleukin-1 β converting enzyme (ICE) inhibitor that has been in development for at least 11 years. ICE (caspase 1) regulates the production of the inflammatory mediators interleukin-1 and interferon- γ . Programs have been discontinued in psoriasis, "inflammatory disorders," and "cardiovascular disorders." The construct continues in phase II investigation for treatment-resistant partial seizures. A phase IIa study has been completed, and Vertex plans to conduct a 400+ patient phase IIb study of VX-765 in the same indication beginning during 2012.

In late 2010, Vertex completed a 75-subject, randomized, double-blind, placebo-controlled, phase IIa, proof-of-concept trial of VX-765 for treated-resistant, partial seizures (VX09-765-401;

NCT01048255). Study subjects received 6 weeks treatment with VX-765 following a 6-week baseline period to monitor seizure frequency. Top-line data, reported in March 2011, revealed that VX-765 reduced the seizure rate compared with placebo (13-19% of patients experienced a reduction in seizure rate vs 0-9% with placebo). The most common adverse events in both the VX-765 and placebo treatment groups were headache, dizziness, fatigue, and gastrointestinal disorders, all mainly of mild to moderate severity. Dizziness was the only adversity of 10% or greater frequency in patients who received VX-765. There was one treatment discontinuation due to adverse events in the VX-765 treatment group.

Relevant preclinical and translational work has matured, especially since the 2006 publication of related rodent work in *Epilepsia* (Vol. 47, Issue 7, pp 1160-1168, July 2006) describing certain VX-765 and predecessors' preclinical experimentation and trials. However, we still believe the program needs more preclinical and clinical work before committing it to our Vertex revenue model. Its IAI score is 25%(C).

Conclusion

Vertex has an enviable and rare combination of strong current revenue and a diverse pipeline. Potential interesting combinations with Vertex include Abbott, Bristol-Myers Squibb, and Johnson & Johnson, all of which have active programs in both RA and hep C.

inThought Approvability Index

The *inThought* Approvability Index (IAI) is a dynamic tool that assesses the progress of a drug candidate through clinical development, evaluating strength of clinical data and trial design, benchmarked against historical parameters and likelihood to maintain forward momentum. Points are assigned for specific line items relating to safety, efficacy, and other factors in each phase of clinical development. Possible points total 100 upon drug approval, and are allocated in each phase according to the historical approval rate of similar drugs, such that the current points of a drug relate to its probability of approval. In addition, a letter grade is assigned and reflects the momentum of a drug candidate in its current phase, with "A" indicating significantly above average/likely to progress, "C" indicating average, and "F" indicating significantly below average/unlikely to progress.

inThought Revenue Forecasts

inThought revenue forecasts employ a proprietary model developed to assess both currently approved and developmental drugs. Models are developed for a given therapeutic area using a "top-down" approach based on the addressable patient population, allowing for detailed assessment of a compound's real or potential competitive landscapes. Epidemiological considerations include estimates of disease incidence, prevalence, growth rates, and death rates. Models are developed separately for the U.S., Europe, and Japan. *inThought* drug revenue models look seven years into the future and three years into the past. For developmental agents, the revenue forecast assumes the drug is approved. Risk adjusted valuations can be developed by multiplying the revenue potential, if approved, by the probability of approval as assessed by the IAI.

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