Pricing Pfizer’s Tofacitinib to Treat Rheumatoid Arthritis:
Opportunity to Change Company and Industry Image

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This report is dedicated to the memory of Dr. John Vernon, a friend and ex-colleague at Pfizer, who helped teach me health economics. John had agreed to work on this report, and then didn’t have the chance.
**Larry Gorkin**, president of Gorkin & Cheddar Consulting, provides thought-provoking rhetoric through his myriad of written reports. Larry has agreed to present new and upgraded versions on this website. Larry specializes in the critical review of competitive landscapes for developmental drugs and launched products to treat 27 chronic and diverse disease states, including non-small cell lung cancer, acute coronary syndrome, type 2 diabetes, rheumatoid arthritis, and Alzheimer’s disease. He has also analyzed decision-making by the United Kingdom's National Institute for Health and Clinical Excellence (NICE) regarding cost effectiveness of agents to treat these and other disorders. He also wrote content for economic models of cost effectiveness for critical decision-making (e.g., shift from Phase II to Phase III, licensing opportunities). Prior to starting his own firm, Larry, a clinical psychologist by training, spent over 13 years developing his analytic skills at Pfizer, from 1996 to 2009.

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Rheumatoid Arthritis:

Tofacitinib represents a paradigm shift in the treatment of Rheumatoid Arthritis (RA).

While treatment of RA is currently dominated by second-line use of the injected TNF-α blockers, after methotrexate, tofacitinib is the first oral treatment of moderate-to-severe RA.

Pfizer leads in development of an oral treatment for RA, a market in which there appears to be significant “price elasticity.”

Executive Summary

Pfizer leads in development of an oral treatment of moderate-to-severe rheumatoid arthritis (RA) to compete with the tumor necrosis factor – alpha (TNF-α) biologic agents. Tofacitinib has been filed and an advisory committee to the Food & Drug Administration has recommended approval, although a decision was delayed until November 2012. Tofacitinib represents a paradigm shift in the treatment of RA, as the injected TNF-α blockers dominate second-line treatment, after methotrexate.

The price of tofacitinib, if approved, has not been released, but there are rumors that Pfizer will price at a premium due to the greater convenience of an oral treatment.

The “big three” biologic agents consist of Enbrel, Remicade, and Humira, which when combined are expected to generate more than $24 billion in 2012 global sales. The efficacy is quite strong for these drugs, relative to first-line methotrexate. Although these biologic agents have attained commercial approvals in multiple autoimmune disease indications, the bulk of the revenue, an estimated $13 billion, is derived from patients with RA. These biologic agents cost about $18,000 in the U.S., and only about 20% less in other key markets. Arguably based on price, the market share of the TNF-α drugs in developed countries is only about 30%.

There appears to be significant “elasticity” in the RA market, based on this moderate market share currently for the relatively expensive TNF-α blocking agents in the U.S. and key international sites. Given that tofacitinib has demonstrated nearly comparable efficacy to the anti-TNF-α inhibitors (45% versus 40% on the American College of Rheumatology, ACR, change score of 50% from baseline, ACR-50), and appears likely to expand to other indications, the rare opportunity exists for Pfizer, to “do the right thing”, and offer tofacitinib at a significant discount to the TNF-α blocking agents. This “elasticity” would allow Pfizer to generate comparable peak sales across a wide pricing range, as increased volume will compensate for lower pricing. Moreover, the lower price would likely increase the early uptake of tofacitinib, and generate a cost effectiveness argument, in terms of the efficacy criterion of ACR-50, based on setting the cost of tofacitinib at a 50% price reduction or greater versus the mean $18,000 annual base for the TNF-α blocking agents.
Background

Pfizer’s novel oral JAK inhibitor, tofacitinib, treats moderate-to-severe rheumatoid arthritis (RA) patients who have had an inadequate response to one or more disease-modifying anti-rheumatic drugs (DMARDs). An advisory group to the Food & Drug Administration voted 8-2, recommending approval of tofacitinib in the second-quarter of 2012 (4Q12). The FDA, though, has delayed the anticipated Prescription Drug User Fee Act (PDUFA) action date for the new drug application (NDA), for three months, from August until November 2012.

Overview of Rheumatoid Arthritis Outcome Measures

Tofacitinib is designed to compete against “the big three” tumor necrosis factor-alpha inhibitors (TNF-α) blocking agents, Enbrel (etanercept), Remicade (infliximab), and Humira (adalimumab). The goal of a developmental drug treatment program, such as with tofacitinib, is to document the clinical benefit to patients with RA in terms of both symptom improvement and reducing structural damage progression.

The TNF-α inhibitors have altered the treatment paradigm in RA and other autoimmune conditions. In terms of RA symptom relief, the efficacy criterion, particularly in the U.S., has shifted from a 20 percent improvement in the American College of Rheumatology (ACR-20) criteria, prior to the launch of the TNF-α drugs, to a more stringent endpoint of 50 percent improvement (ACR-50), based on the performance of these biologic agents. In this Cochrane review, the TNF-α inhibitors (usually in combination with methotrexate) demonstrated efficacy risk ratios between 2.16 and 3.05, in comparison with the methotrexate-only control arm. Approximately 25 percent of patients treated with the biologic agents, as second-line therapy, achieve the ACR-50 change criteria.

The DAS (Disease Activity Score)-28 is a measure of RA disease activity in 28 joints, utilized primarily in Europe. A DAS28 of greater than 5.1 implies active disease, less than 3.2 implies a well-controlled disease, and less than 2.6 equals remission. Scores range from 0 to 9.4, and higher scores indicate more disease activity.

The Van der Heijde modified Sharp radiographic scoring method grades the presence of erosions in the joints of the hands and feet, as well as the presence of joint space narrowing in the hands, wrist, and feet. The maximum erosion score is 160 for hands and wrists and 120 for feet. The maximum joint space narrowing score is 120 for hands and wrists and 48 for feet. Therefore, the total van der Heijde radiographic score ranges from 0 to 448 (Van der Heijde, 1999). Although the relationship is complex, an increasing relation between disability and structural damage with increasing disease duration has emerged. Thus, documentation of a benefit of treatment on structural damage progression has been an important goal of clinical development programs for new products proposed for RA, particularly if the product has a novel target.
The HAQ-DI, composed of 20 items, assesses the extent of the RA patient’s functional ability over the past week (Fries, et al., 1980). There are eight categories, each of which has at least two component questions: (1) Dressing and Grooming, (2) Arising, (3) Eating, (4) Walking, (5) Hygiene, (6) Reach, (7) Grip, and (8) Common Daily Activities. Good psychometric data support the reliability and validity of the HAQ-DI measure, particularly change scores from baseline in clinical trials (e.g., Smolen & Alehata, 2009).

**Epidemiology**

RA is a chronic, inflammatory autoimmune disease, affecting approximately 1% of adults worldwide, approximately 75% of whom are women. The combined number of RA patients in just the U.S., France, Germany, Italy, Spain, UK and Japan in 2010 was estimated to exceed 4.6 million individuals. The majority of patients have persistent, progressive disease, which results in increasing disability, if left untreated.

**Cost of TNF-α Blocking Agents**

The initial cost of Enbrel and the other TNF-α blockers are priced annually in the range of $18,000 to $21,000 per year. Moreover, clinical patients tend to increase their dose, and accompanying cost, of TNF-α blocking agents, particularly JNJ’s Remicade. More than half of subjects experience “dose creep” as compared to about 17% with Enbrel. In the United Kingdom, the cost per year of these agents was estimated ranging from £8,846 to £10,771. Based on 1.6 conversion of U.K. pounds to U.S. dollars, this converts to a range if $14,154 to $17,234, about 20% lower than the corresponding range of these biologic agents in the U.S.

**Increasing Patient Co-Pays for Specialty Drugs by Managed Care in the United states (U.S.)**

An analysis of U.S. patient co-pays was conducted on specialty drugs, with a focus on the TNF-α blocking agents to treat rheumatoid arthritis. In one of the studies, the abandonment rate for TNF-alpha blockers increased most significantly, to 26.4%, at co-pays exceeding $500. In contrast, co-pays under $100 were associated with a discontinuation rate of 4.7%. Co-pays between $101 and $500 had comparable rates between 10.5% and 16.3%.

In market access research conducted prior to the potential launch of tofacitinib, rheumatologists were predicting that, akin to a mini-version of the Viagra launch, patients will request the new oral med, as soon as it becomes available. The question is if there is an increase in their co-pay relative to the injected drugs, “...will the patients be willing to potentially pay several hundred dollars more per month for this medication?”

**Shared Success:**

During 2012 Humira is predicted to replace Lipitor as the world’s top selling drug, with over $9.3B in global sales. But remarkably, at a time when me-too drugs do not perform well commercially Remicade and Enbrel are projected to be second and third, in terms of global revenue in 2012.

And indeed sales are not limited to America. During 1Q12, 54.7% of global TNF-α inhibitor revenue was generated outside the US.
Revenue Generation by TNF-α Blocking Agents

With the patent loss of Pfizer’s statin, Lipitor, in the U.S. in 4Q11, the TNF-α inhibitors have become the most successful commercial, branded drug class. A recent analysis projected the most recently approved of the three biologic agents, Abbott’s Humira, to replace Lipitor as the drug generating the most global revenue, in 2012, with $9.3 billion.

Remarkably, at a time when “me-too” drugs do not perform well commercially, Remicade and Enbrel are projected to be second and third, in terms of global revenue in 2012. The latter two biologics will register approximately $8 billion in global sales. Table 1 provides empiric evidence for these claims, in terms of actual U.S. and international revenue for the “big three” TNF-α blockers for 2Q12. The $6.49 billion in 2Q12 worldwide revenue, suggest that the “big three” anti-TNF-α biologics will combine for more than $25 billion in 2012.

Two other approved anti-TNF-α drugs have been approved, JNJ/Merck’s Simponi (golimumab), with $125 million in 2Q12 international sales, and UCB’s Cimzia (certolizumab pegol), with $272 million in the initial six months of global sales in 2012. Merck did not release separate revenue for Simponi and Remicade in 2Q12, suggesting minimal sales for Simponi, as Merck relinquishes rights to the two drugs to J&J in Canada, Central and South America, the Middle East, Africa and Asia Pacific. These results suggest that Simponi and Cimzia will add slightly more than $1 billion, or about 5%, to the $25 billion total estimate for 2012. Thus, these drugs are marginalized in terms of this report.

The one major market not included in these estimates is Japan, given that specific additional sales of Remicade and Enbrel are difficult to determine. In Japan, Takeda is a partner in the sales of Enbrel, Mitsubishi-Tanabe is a partner in the sales of Remicade, and Eisai is a partner of Abbott in terms of Humira. It appears that the revenue in Japan, though, is less than 1% of global sales. For example, Eisai reported yen24.0 billion in sales for Humira in fiscal year 2011 (4/11 to 3/12), in Asia, primarily Japan. The conversion for dollar to yen is 79.7 as an average for 2011, which was utilized to determine that the annualized sales of Humira in Asia were $301 million U.S. Even with 50% growth versus the prior year, the revenue during 2Q12 would be less than $100 million. Assuming comparable sales for the other two TNF-α drugs would combine for approximately $300 million U.S. for sales in Japan/Asia in 2Q12.
Table 1: 1Q12 Revenue for (millions $USD) for Key TNF-α Inhibitors

<table>
<thead>
<tr>
<th>Drug</th>
<th>Worldwide Revenue</th>
<th>United States Revenue</th>
<th>International (Ex-US) Revenue</th>
<th>Company</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enbrel</td>
<td>988</td>
<td>0</td>
<td>988</td>
<td>Pfizer (1)</td>
</tr>
<tr>
<td></td>
<td>1,058</td>
<td>991</td>
<td>67</td>
<td>Amgen (2)</td>
</tr>
<tr>
<td>Remicade</td>
<td>594</td>
<td>0</td>
<td>594</td>
<td>Merck (3)</td>
</tr>
<tr>
<td></td>
<td>1,523</td>
<td>890</td>
<td>633</td>
<td>J&amp;J (4)</td>
</tr>
<tr>
<td>Humira</td>
<td>2,326</td>
<td>1,056</td>
<td>1,270</td>
<td>Abbott (5)</td>
</tr>
<tr>
<td>Total</td>
<td>6,489</td>
<td>2,937</td>
<td>3,552</td>
<td></td>
</tr>
<tr>
<td>% of Total</td>
<td></td>
<td>45.3%</td>
<td>54.7%</td>
<td></td>
</tr>
</tbody>
</table>

Source:

(1) http://www.pfizer.com/investors/financial_reports/financial_reports.jsp, 7/31/12 *
(2) http://www.amgen.com/media/media_pr_detail.jsp?releaseID=1719169, 7/26/12
(3) http://www.merck.com/newsroom/news-release-archive/financial/2012_0727.html *

Table 1 also demonstrates that this is not simply a U.S.-based story, given that the slightly more of the global revenue is generated internationally (54.7%). This percentage, though, seems significantly lower than the 66.0% found for the overall rate of international sales of prescription drugs in 2011. The bulk of prescription pharmaceutical sales are composed predominantly of less expensive, oral medications.

The TNF-α blockers have been called a “pipeline in a product”, a claim predicated on the number of other autoimmune indications, beyond rheumatoid arthritis, for which the TNF-α inhibitors have been approved commercially. Humira, for example, has been approved to treat: moderately to severely active rheumatoid arthritis, active polyarticular juvenile idiopathic arthritis, moderate to severe chronic plaque psoriasis, severely active Crohn's disease, when conventional treatment has failed, and moderately to severely active ulcerative colitis in Europe. In 3Q12, an FDA advisory group recommended that Humira be approved for a supplemental indication to treat ulcerative colitis.

Enbrel, by itself, achieved $1.3 billion in global revenue from psoriasis in 2010. Decision Resources estimated the Crohn’s disease market at $3.2 billion, with ¾ of the revenue, $2.4 billion, allocated to the TNF-α blockers, in 2009. The primary recipients are Humira and Remicade.
As implied by Table 1, the TNF-α inhibiting agents will likely generate approximately $25 billion in 2012. While there are a number of disease indications treated by the TNF-α inhibitors, the bulk of the revenue, though, is tied to RA. This class of biologics generates approximately $13 billion in revenue currently in the treatment of moderate-to-severe RA.\(^{30}\) In 2010, sales of the TNF-α inhibitors accounted for 75 percent of major-market RA sales.\(^{31}\)

These findings imply that tofacitinib can potentially target more than half of the annual revenue of the class, based solely on the RA indication, if approved.

**Market Share of TNF-alpha Inhibitors in Key Countries**

Although TNF-α blockers dominate revenue in the pharmacologic treatment of RA, the corresponding results for market share are much less dominant. In a recent report on RA market share in Western countries in 2010, the TNF-αs had a combined market share of 29%.\(^{32}\) Among these, about 20% to 40% of patients treated with a TNF-α inhibitor fail to respond adequately to treatment.\(^{33}\) Other patients lose clinical responsiveness over time (secondary failure or acquired therapeutic resistance), or experience adverse events following treatment with a TNF inhibitor, leading to withdrawal.

This sets the stage for the premise of this article, that a drug with nearly comparable efficacy to the TNF-α blockers, priced sharply lower could offer a unique opportunity to take market share away from these blockbuster biologic agents.

**Introduction to Tafocitinib**

Pfizer’s first-in-class small-molecule, Janus kinase (JAK) inhibitor is tofacitinib, to treat moderate-to-severe RA. The targeted activity in JAK involves intracellular signaling pathways responsible for the activation of pathogenic immune cells.\(^{34}\) T-cells rely on JAK kinases for JAK/STAT cytokine signaling. Accordingly, companies are targeting JAKs to treat rheumatoid arthritis and other autoimmune diseases.

**Review of Phase III Efficacy with Tofacitinib**

All five pivotal phase III, ORAL trials met their primary endpoints, in terms of tofacitinib 5-mg or 10-mg dosing.\(^{35}\) Differences from placebo in ACR-20 response rates in these studies ranged from 17% to 33% for the 5-mg dose and from 23% to 39% for the 10-mg dose. On another efficacy endpoint, the Disease Activity Score in 28 joints, results were inconsistent depending on the type of statistical analysis done.
In a double-blind, placebo-controlled, six-month study of moderate-to-severe RA, 611 patients were randomized, to 5-mg tofacitinib twice daily, 10-mg tofacitinib twice daily, or placebo for 3 months. A second Phase III study combined tofacitinib versus placebo among 717 RA patients with background therapy of stable methotrexate. Along with the 5- and 10-mg of tofacitinib twice daily, this study included Humira (plus methotrexate), 40-mg once every other week, dosed as in labeling, along with a placebo control group. The primary end points, assessed at month three, for these two Phase III studies were:

- Percentage with at least a 20% improvement in the ACR 20
- Change from baseline in Health Assessment Questionnaire–Disability Index (HAQ-DI) scores (which range from 0 to 3, with higher scores indicating greater disability)
- Percentage of patients with a Disease Activity Score for 28-joint counts based on the erythrocyte sedimentation rate (DAS28-4[ESR]) of < 2.6 (with scores ranging from 0 to 9.4 and higher scores indicating more disease activity)

In the first study (footnote 32), 59.8% of the 5-mg tofacitinib group and 65.7% of the 10-mg tofacitinib group versus 26.7% of the combined placebo groups achieved ACR-20 responses (p<0.001 for both comparisons vs. placebo. Similarly, the reductions from baseline in HAQ-DI scores were greater in the 5-mg and 10-mg tofacitinib groups than in the placebo groups (−0.50 and −0.57 points, respectively, vs. −0.19 points; p<0.001). In contrast, the percentage of patients with a DAS28-4[ESR] < 2.6 was not significantly higher with tofacitinib than with placebo. That is, 5.6% with 5-mg and 8.7% with 10-mg tofacitinib, as compared to 4.4% with placebo; p = 0.62 and p = 0.10 for the two respective comparisons.

In the second study (footnote 33), the three active treatments plus methotrexate did not differ from each other (51.5% and 52.6%, respectively, for 5- and 10-mg tofacitinib, and 47.2% for 40-mg Humira), but were all significantly higher (p<0.001) in terms of ACR-20 response rates versus placebo (28.3%). Greater reductions in the HAQ-DI score at month three and higher percentages of patients with a DAS28-4[ESR] below 2.6 at month six in the active-treatment groups than in the placebo group were observed.

The choice of Humira, as the comparative agent has been challenged. That is, Humira is not considered the RA standard-of-care by physicians. In a recent survey of rheumatologists, the leading drug to treat RA specifically was the TNF-α blocker, Enbrel, with 40% of the vote versus 30% for Humira. In contrast, the Pfizer Phase III study did follow the recommendation of rheumatologists that the TNF-α inhibitors should not be tested as monotherapy as active comparative agents. Following failure with methotrexate, the TNF-α are recommended in combination with methotrexate (or other DMARDs), since combination therapy has “greater efficacy” than the biologic agents as monotherapy. It is estimated, however, that 30% of patients on biologic drugs for rheumatoid arthritis in the U.S. and Western Europe are prescribed as monotherapy, according to the EUropean League Against Rheumatism (EULAR) President Maxime Dougados, MD, of Rene Descartes University in Paris.
In a Phase III study with RA patients who responded inadequately to non-biologic DMARDs, most often methotrexate (N = 792), ACR-20, a DAS28-4(ESR) response and HAQ-DI at three months follow-up were evaluated. In the 5-mg, 10-mg, and placebo groups, respectively, ACR 20 responses at 6 months were 52.7%, 58.3%, and 31.2%; DAS28-4(ESR) responses of less than 2.6 at 6 months were 11.0%, 14.8% and 2.7%, respectively. Decreases in HAQ-DI in the 5-mg and 10-mg tofacitinib groups were 0.46 and 0.56, respectively, compared with 0.21 in the placebo group (p<0.0001), with a minimum clinically important difference of 0.22.42

The impact of tofacitinib on structural damage, documented by radiography, was reported in the Oral Start, a Phase III study, among 958 patients with moderate-to-severe RA, in 3Q12.43 Patients were randomized to tofacitinib, dosed at 5-mg and 10-mg twice daily or methotrexate, each as monotherapy. Structural damage was significantly less likely to occur with tofacitinib than methotrexate, based on a one-year planned comparison. These results are important, because prior to the advisory meeting, FDA reviewers were unable to draw definite conclusions about tofacitinib’s ability to prevent progression of structural damage in RA, among 10,532 patients analyzed.44

**Review of Phase III Safety with Tofacitinib**

Four deaths occurred in the ORAL Sync Phase III study, although only one death was deemed related to the tofacitinib treatment, according to a Pfizer press release.45 In one of the studies published recently in the New England Journal of Medicine,46 six patients experienced serious infections while prescribed tofacitinib. In the other study,47 adverse events occurred more frequently with tofacitinib than with placebo, including pulmonary tuberculosis, which developed in two patients in the 10-mg tofacitinib group.

From the Phase III RA program (N = 3,030), a pooled analysis of the safety data from these studies revealed that the all-cause mortality incidence rate for all doses of tofacitinib was 0.572 per 100 patient-years (12 deaths per 2,098 patient-years) in the Phase III trials, which is consistent with the reported rates from individual clinical trials with biologic DMARDs in RA patients (0 to 7.41 per 100 patient-years).48

The incidence of malignancy during the blinded studies was 0.6 per 100-patient-years among patients receiving 5-mg tofacitinib and among patients in one study who received Humira as a comparator. In contrast, the incidence in the 10-mg tofacitinib group was 0.9 per 100-patient-years, and the rates increased further during long-term extension phases of the trials. While higher, base rates remain at low absolute levels. Seven cases of lymphoma among treated patients, with several atypical cases, were noted by 5/12, versus none among patients receiving placebo.
The treatment-emergent infections, with rates greater than five percent in any treatment group in the observational safety studies, were nasopharyngitis, upper respiratory tract infection, urinary tract infection, bronchitis, herpes zoster and influenza. In regard to serious infections, the pooled safety data show that the incidence rate for all doses of tofacitinib was 2.91 per 100 patient-years in the Phase III trials and 3.00 per 100 patient-years in the observational safety studies, which is consistent with rates described in observational databases for TNF-α inhibiting therapies (2.6 to 10.5 per 100 patient-years). Given these results from the Phase III program, it remains unknown whether the risks associated with tofacitinib such as increased cholesterol and liver enzyme levels, are easily remedied or indicators that patients on the drug face future cardiac disease and serious organ damage.

There is little surprise the briefing documents state the data suggests treatment with tofacitinib is associated with an increased risk of serious infections, including opportunistic infections, like tuberculosis. The TNF-α inhibitor suppress the immune system and carry similar warnings in their labels as a result. The FDA has issued “black-box warnings” on Enbrel, Remicade and Humira, including warnings about serious infections, involving various organ systems and sites due to bacterial, mycobacterial (e.g., tuberculosis), fungal (e.g., histoplasmosis, aspergillosis, candidiasis, coccidioidomycosis, blastomycosis, pneumocystosis), viral (e.g., hepatitis B), and other opportunistic pathogens (organisms that usually do not cause disease in healthy people, but can cause serious illness when a person’s immune system has weakened). More recently, serious infection with Legionella and Listeria bacteria have been added to the labeling of the TNF-α inhibiting agents. The FDA also has a black box warning for cancer associated with the use of the anti-TNF-α agents among children and adolescents.

Adverse events that occurred significantly more frequently among those randomized to tofacitinib included headache and upper respiratory tract infection. Tofacitinib was associated reductions in neutrophil counts and with elevations in LDL-c levels in all studies. In response, Pfizer has determined that concomitant treatment with Lipitor (atorvastatin), versus placebo, lessens the dyslipidemia observed with tofacitinib, in a Phase II study of 111 RA patients on background tofacitinib. Following an open-label lead-in period, Scottish patients randomized to tofacitinib plus Lipitor had a 35% reduction in mean low-density lipoprotein cholesterol (LDL-C), as compared with a 5.8% increase observed in tofacitinib-treated patients randomized to concomitant placebo.

The point of this section is to demonstrate that the target biologics for tofacitinib, the anti-TNF-α agents, have a significant and salient record for serious adverse events. Despite these concerns, these drugs have been extraordinarily successful. In contrast, the true safety profile will never be known unless tofacitinib is approved and sufficient prescribing occurs to build an incident database for serious, low frequency clinical events. This analysis, though, provides empiric evidence that the safety profile of the TNF-α blockers allows tofacitinib to experience a wide-range of safety concerns and still remain on the market.
Tofacitinib in the Treatment of Ulcerative Colitis

Ulcerative colitis is one of the two major types of inflammatory bowel disease (IBD, along with Crohn’s disease). Unlike Crohn’s disease, which can affect any part of the gastrointestinal tract, ulcerative colitis characteristically involves the large bowel. According to a 2012 Decision Resources report, in the U.S., the prevalence of Crohn’s in 2011 was 498,000 patients and UC was 582,000 patients.56

Three TNF-α blocking agents are approved to treat Crohn’s disease and ulcerative colitis, including Remicade, Humira and Cimzia. In a Cochrane analysis of these biologic agents, plus one other (i.e., Elan/Biogen-IDEC’s cell adhesion molecule, Tysabri (natalizumab), 27 clinical studies were included (Ford, et al., 2011). Anti-TNFα antibodies were superior to placebo in preventing relapse of luminal Crohn’s disease (relative risk, RR, of relapse=0.71). Infliximab was superior to placebo in inducing remission of moderate to severely active UC (RR=0.72). Sales of maintenance therapies for Crohn’s disease greatly exceeded sales of acute therapies, in a 2010 analysis.57

In a Phase II study of 194 patients with ulcerative colitis, four doses of tofacitinib were investigated, 0.5-mg/day, 3-mg/day, 10-mg/day or 15-mg/day, along with a placebo-control group.58 Efficacy was defined in terms of a clinical change in the Mayo scoring system for ulcerative colitis, including a 30% reduction in rectal bleeding. In the study, 32, 48, 61, and 78 percent responded clinically, respectively, consistent with a dose-dependent response.

The market for anti-TNF-α agents to treat ulcerative colitis was approximately $1.5 billion in 2009.59 Given 8.8% compounded growth expected in major markets from 2007 to 2012 in the IBD market,60 and based on the epidemiology, one might suspect that combined sales for IBD is conservatively $2.5 billion in 2012. The finding that tofacitinib has potential efficacy in ulcerative colitis, one of many indications served by the TNF-α inhibitors, does suggest that Pfizer’s oral agent may eventually gain regulatory approval in a number of disease indications, further increasing the revenue generated annually by this agent. According to the Pfizer webpage, as of August 9, 2012, tofacitinib was being developed for psoriasis, psoriatic arthritis, ankylosing spondylitis, Crohn’s disease, and transplantation rejection, along with RA and ulcerative colitis.61

Poor Image of the Pharmaceutical Industry

In 1Q12, only 42% believed that the pharmaceutical companies have a “good corporate reputation”, and significantly even less, 31%, believe that pharmaceutical companies “act with integrity”.62 There are several reasons that account for this poor reputation of the industry, including, safety recalls of high profile branded products, high prices of recent launches, attempts to prevent generic completion to branded pharmaceuticals, and the off-label promotion of branded drugs. These occurrences undermine the credibility of the industry. With this salient, I once suggested rhetorically to the head of U.S. Marketing at Pfizer that the slogan of the company should be changed to the following: “We’ll help keep you alive,..., so you can hate us longer.”
Safety Recalls
When drugs approved by the FDA are recalled due to safety concerns this damages both the reputation of the FDA and the industry. For example, approximately 13 years passed since the withdrawal of Wyeth’s Fen-Phen to treat obesity/weight loss due to heart-valve problems, although two treatments have been approved commercially in 3Q12, Arena’s Belviq and Vivus’ Qsymia.63

Nissen’s meta-analysis of GSK’s Avandia, in 2007, claimed that the anti-diabetic drug led to marked relative increases in the rates of mortality and myocardial infarction.64 Consequently, Avandia was removed from the European market and marginalized in the U.S. market. Accordingly, Avandia generated $3.2 billion in global revenue in 2006,65 but has been shunned by patients and reduced to negligible sales. In 2011, Avandia global revenue was the equivalent of $579 million, down 47% versus global sales in 2010.66

Few drugs were withdrawn from the market before 1980, but then high single digits of launched drugs were withdrawn in the 1980’s, over ten drugs were withdrawn in the 1990’s, and nearly twenty approved drugs were withdrawn between 2000 and 2009.67 This trend has been disturbing to the public, and led to a greater focus on drug safety by regulators. This has led to increased costs in drug development, particularly in the Phase III trials for regulatory approval.68

High Prices for Newly Launched Pharmaceuticals
For the past few years, it seems that when a company has a successful, innovative product, senior management at the drug manufacturer does not appear to be using pricing models to determine reasoned pricing, but simply charge markedly more than what is available currently in that disease indication. This approach includes several cancer drugs brought to market at a cost of $90,000+ annually since 2010

1. Pfizer’s Xalkori, an ALK inhibitor to treat a subset of non-small cell lung cancer;69
2. Roche’s Zelboraf to treat the subset of advanced melanoma with a BRAF600 genetic mutation;70
3. Dendreon’s Provenge for the treatment of castration-resistant prostate cancer;71
4. Seattle Genetics’ Adcetris (brentuximab vedotin) in Hodgkin lymphoma (HL) and analplastic large cell lymphoma (ALCL);72
5. Bristol-Myers’ Yervoy, a CTLA4 inhibitor to treat advanced melanoma;73
6. Pfizer’s Inlyta (axitinib) to treat second-line advanced kidney cancer.74
7. Roche’s Erivedge (vismodegib) was approved today by the U.S. FDA for the treatment of basal cell carcinoma (BCC), the most common form of skin cancer.75
8. AstraZeneca’s Camprelsa (vandetanib) to treat medullary thyroid cancer.76
Consumers don’t care that research and development costs have been rising precipitously, and that companies only have a limited time to recoup those costs before a drug loses patent protection. The patients focus on the increased hit to their pocketbook with new drugs, either out-of-pocket or in terms of co-pays. The sharply rising cost of prescription drugs, relative to the level of innovation, contributes to the lowered image of the industry.

**Off-Label Promotion of pharmaceuticals**

In 3Q12, the U.S. Department of Justice announced that GlaxoSmithKline (GSK) had agreed to pay $3 billion in criminal and civil fines for illegally marketing Paxil and another antidepressant, Wellbutrin; for withholding information on the cardiovascular risks of Avandia, a diabetes drug that has been linked to increased mortality; and for promoting Advair, an inhaled drug to treat chronic obstructive pulmonary disease (COPD) and severe asthma, to patients with mild asthma, even though it wasn’t approved or appropriate for them. Payment of billions of dollars for fraudulent, off-label marketing of branded drugs seems normative. Other examples include: (1) Abbott paying $1.5 billion for off-label promotion of anti-seizure medication, Depokate; J&J will pay $1.2 billion for off-label promotion of the anti-psychotic agent, Risperdal; Lilly agreed to pay $1.4 billion to settle charges relating to the fraudulent promotion of the anti-psychotic agent, Zyprexa; and Pfizer’s fraud settlement with the U.S. Department of Justice of $2.3 billion to resolve criminal and civil allegations that the company illegally promoted drug use off-label. The four drugs included the painkiller Bextra, the atypical antipsychotic Geodon, the antibiotic Zyvox, and the anti-epileptic Lyrica.

**Delay of Generic Drug Competition**

In 3Q12, the Third Circuit U.S. Court of Appeals ruled that pay-for-delay settlements between brand-name and generic drugmakers, to prevent the introduction of equivalent generic agents, are a violation of antitrust law, unless the parties can prove otherwise. Critics of the deals, including the Federal Trade Commission, indicate that they violate fair trade and restrict consumer access to low-cost, drug alternatives. In contrast, decisions by other appellate courts in recent years had upheld such deals as legitimate.

Merck has taken up the challenge by pushing the pay-for-delay controversy to the U.S. Supreme Court. Merck is asking the court to, once and for all, determine whether the reverse settlements violate federal antitrust laws. As the U.S. faces budget shortfalls for social programs and expanding costs for Medicare and Medicaid coverage, extending monopolies for brand name drug companies would be an extremely unpopular move. The Congressional Budget Office estimates that if the legislation is passed, it could reduce total sending on drugs by about $11 billion over a decade by allowing earlier entry of lower-priced generic drugs.
Arguably, a similar attempt at manipulation of the market has been unveiled through the efforts of Senator Grassley (R-Iowa). Between the years 2006 and 2008, the most powerful patient advocacy group for schizophrenia, the National Alliance of Mental Illness (NAMI), garnered 3/4 of its income of $23 million from pharmaceutical companies. Not surprisingly, NAMI was being used as a shill to push access to atypical antipsychotic agents, which cost about $8 per day versus twenty-five cents per day for typical antipsychotic agents. These drugs do not appear to differ in efficacy, but only in adverse event profiles.

**Opportunity for Pfizer via Elasticity of Demand for Tofacitinib**
Pfizer is under pressure from the patent loss of Lipitor in 4Q12. Ironically, Pfizer cut prices on Lipitor, albeit after the most successful drug in history had lost patent protection in the U.S. Following patent loss, however, U.S. sales in 1Q12 were reduced by 71%. Clearly, Pfizer is relying on tofacitinib as a multi-billion dollar opportunity for Pfizer, although the company has not spoken about how many billions may be generated at peak sales.

The question is if tofacitinib is approved, at least initially, when will the oral agent be used? Will it be relegated to third-line use by patients who demonstrate an inadequate response to both methotrexate and then add-on TNF-α inhibition? As noted previously, this subgroup constitutes approximately 30% of those administered these biologic agents. In contrast, it is possible that tofacitinib will experience wider use, as an option following failure with methotrexate monotherapy. This is likely to occur if, as hypothesized, the price offered by Pfizer is markedly lower, relative to the approximate $18,000 per year TNF-α biologic. In markets outside the U.S., where the TNF-α blocking drugs sell for a discount, then Pfizer would be expected to sell at a lower price than the local pricing as well.

Pfizer and its biotech partner, Protalix, announced this year that the “orphan drug” to treat Gaucher’s disease, Elelyso, will be available to U.S. patients priced at a discount of 25% below the cost of market leader, Sanofi/Genzyme’s Cerezyme (imiglucerase). In this case, the Pfizer price is $150,000 annually versus the $200,000 annually for the market leader. I explore this anomalous pricing strategy in a prior report, and ask rhetorically if this pricing strategy applies only to drugs that cost “six figures”?

Tofacitinib, as an oral drug, is, a priori, less expensive to manufacture than the TNF-α inhibiting drugs. This does not necessarily translate into lower pricing, however. When Pfizer launched the oral tyrosine kinase inhibitor, Sutent, to treat advanced renal cell carcinoma, the price of $54,000 annually in 2006, was comparable to the leading monoclonal antibody, Roche’s Avastin, to treat advanced colorectal cancer. The latter was launched at $4,400 per month in 2004, for an annual cost of $52,800.
Pfizer also has a potential “conflict of interest” with tofacitinib, in terms of pricing, given that Pfizer receives the international revenue from Enbrel, via the Wyeth acquisition in 3Q09. As presented in Table 1, Pfizer generated nearly $1 billion in 2Q12. Given that in the absence of a true head-to-head trial, Enbrel is perceived as having the most efficacy of the anti-TNF-α agents in the treatment of RA, Enbrel would potentially be most exposed by a marked reduction in pricing of tofacitinib, relative to the biologics. Therein lies the rub for Pfizer.

Decision Resources conducted a survey of U.S. physicians and payers regarding the potential impact of tofacitinib on the RA market. If tofacitinib were priced at a 16 percent or greater discount to Humira, at least 45 percent of surveyed managed care organization (MCO) pharmacy directors would place the drug on a preferred brand formulary tier during its first year on the market. MCOs were informed of the approximate annual cost of Humira therapy and were asked to assume that tofacitinib demonstrates efficacy similar to that of the TNF-alpha inhibitors and has an acceptable safety profile.

In contrast, if presented with a less reduced price for tofacitinib (a discount of 1 percent to 15 percent to Humira), only 20 percent of surveyed pharmacy directors said their MCO would reimburse for tofacitinib on a preferred brand tier in their largest commercial plan. A second survey by Reimbursement Intelligence, without reference to pricing, with 30 payers, indicated that 71 percent of payers would require prior authorization, and 42 percent would require patients to fail on methotrexate.

While the TNF-α biologic agents are markedly more expensive, in general, than oral drugs, the former drugs are actually low in cost relative to other specialty biologic agents, such as to treat cancer (see section on High Prices for Newly Launched Pharmaceuticals).

Recently, the speculation is that Pfizer will charge a premium price for tafocitinib, even higher than the “modestly priced” anti-TNF-α biologics. This claim is predicated on the enhanced convenience of an oral pill versus an injected biologic, holding efficacy : safety somewhat equivalent. This represents a poor decision by Pfizer, not only financially, but because there is a unique opportunity for Pfizer to gain an incredible amount of “good will”, at a time when the industry is demeaned and demonized.

Arguably, there is significant “elasticity” in the RA market, based on the moderate market share, estimated at 29%, for the TNF-α blocking agents have in the U.S. and key international markets. Accordingly, demand for the oral drug, based on impressive and comparable efficacy, would generate similar revenue, across a wide range of pricing options. That is, as the price of tofacitinib decreases, demand and adherence will increase proportionately, so as to compensate for the lower price and yield comparable peak sales, as seen in Table 2.
Table 2. Peak Sales of Tofacitinib

<table>
<thead>
<tr>
<th>Annual Cost (per patient)</th>
<th>Peak Number of Patients</th>
<th>Peak Revenue</th>
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</thead>
<tbody>
<tr>
<td>$4,000</td>
<td>2,000,000</td>
<td>$8 billion</td>
</tr>
<tr>
<td>$8,000</td>
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<tr>
<td>$12,000</td>
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<td>$20,000</td>
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</tr>
<tr>
<td>$24,000</td>
<td>333,333</td>
<td>$8 billion</td>
</tr>
</tbody>
</table>

Moreover, the pricing decision will affect uptake of the launched tofacitinib in year 1, with greater market share occurring at significantly lower drug access costs. This is depicted in Figure 1.

FIGURE 1. Uptake of Tofacitinib
As compared to the TNF-α, a lower price for tofacitinib would also lead to an improved incremental cost effectiveness ratio (ICER) in terms of efficacy in RA (percent achieving ACR-50). The argument for cost effectiveness can be made using the traditional equation of the differences in costs over the differences in efficacy, as explained in Appendix 1.

Based on these analyses, Pfizer has the rare opportunity “to do the right thing”, that is, create great positive press for itself, and generate the same revenue, by competing on price with the TNF-α blockers. A lower price would clearly accelerate uptake, following launch, given the restraint due to the lack of safety info on tofacitinib’s novel anti-JAK mechanism of action. Lower priced oral agents to treat moderate-to-severe RA could generate an hypothesized $8 billion in peak sales in RA, could advance to this level in less time with a discounted price, and be recognized as cost effective relative to the anti-TNF-α blocking agents, if the reduction is at least a dramatic 50% cut in price. At the 1Q12 earnings conference call in May 2012, Pfizer reportedly declined to discuss the pricing of tofacitinib.97
References


Appendix 1

To determine the efficacy of TNF-α inhibitors following an inadequate response to methotrexate, results for the “big three” agents were evaluated and combined. Results from Humira (40-mg every other week) plus methotrexate was based on 1,469 patients who were followed for up to 7 years. 98 ACR-50 results averaged 40%, in a combination of controlled trials and open-label extensions. Among 1,432 patients tested with Remicade (ranging from 3-mg/kg to 10-mg/kg) from two large trials for one year, the average ACR-50 response was approximately 45%. This efficacy average was estimated from an FDA document on Remicade. 99 For Enbrel (25-mg, subcutaneously twice a week), 682 patients on background therapy with methotrexate were evaluated after one year of treatment in a double-blinded study. 100 The average ACR-50 achievement was quite high, approximately 63%. In contrast, when Enbrel was evaluated as monotherapy, the ACR-50 scores have been about lower, ranging from 38% (N = 101) to 48% (N = 223). 101 Based on these results, Enbrel is perceived as having the most efficacy in moderate-to-severe RA, with ACR-50 scores averaging above 50%. Accordingly, the estimated ACR-50 efficacy across the “big three” injected TNF-α blockers was registered as approximately 45%.

To derive a comparative mean efficacy for tofacitinib in RA, one of the Phase III studies randomized 483 patients to either 5- or 10-mg/day, without background methotrexate, for one-year of treatment. 102 Tofacitinib, across the two doses, significantly increased ACR-50 response rates 45% and 35%, for the 10-mg and 5-mg doses respectively. Accordingly, the mean ACR-50 change with tofacitinib was estimated at 40%, versus the 45% for the anti-TNF-α biologics.

To determine an incremental cost-effectiveness ratio (ICER) that would render tofacitinib as cost effective relative to the TNF-α inhibitors, the mean cost of the latter was set at $18,000 U.S. The criterion for cost effectiveness is approximately $45,000 U.S., given the equivalency to the £30,000. 103 Based on the formulaic approach, if Pfizer sets the price of tofacitinib at $9,000 or less annually, this will provide evidence of a cost-effectiveness advantage for the new oral launch, given the marginal efficacy difference between the oral drug and its injected competitors.

Based on these analyses, Pfizer has the rare opportunity “to do the right thing”, that is, create great positive press for itself, and generate the same revenue, by competing on price with the TNF-α blockers. A lower price would clearly accelerate uptake, following launch, given the restraint due to the lack of safety info on tofacitinib’s novel anti-JAK mechanism of action. Lower priced oral agents to treat moderate-to-severe RA could generate an hypothesized $8 billion in peak sales in RA, could advance to this level in less time with a discounted price, and be recognized as cost effective relative to the anti-TNF-α blocking agents, if the reduction is at least a dramatic 50% cut in price. At the 1Q12 earnings conference call in May 2012, Pfizer reportedly declined to discuss the pricing of tofacitinib. 104
EndNotes:


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