

PIPELINE TRENDS is produced by the University of Massachusetts Medical School's Clinical Pharmacy Services division and distributed to our clients twice yearly.

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expected June 28, 2012

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Promising New Agents

Phase III

Drug Name: Buprenorphine

Manufacturer: Titan Pharmaceuticals

Indication: Opioid addiction

Formulation: SC implant

Probuphine[™] is a subcutaneous (SC) implant of buprenorphine being studied for the treatment of opioid addiction. Designed to slowly release constant levels of buprenorphine over six months, it has a rate of release similar to intravenous (IV) infusion.

A Phase III (N=163), randomized, double-blind trial compared the buprenorphine SC implant to placebo for the treatment of opioid addiction. The primary endpoint was the proportion of urine samples per patient that were negative for illicit opioids during the first 16 weeks of therapy. Treatment with the buprenorphine SC implant resulted in a greater proportion of negative urine samples over placebo (40.4 versus 28.3 percent, P=0.04). A second Phase III (N=287), randomized trial supported the superiority of buprenorphine SC implant over placebo (P<0.0001). This trial also demonstrated the non-inferiority of buprenorphine SC implant to Suboxone[®] (buprenorphine/naloxone) tablets as measured by the proportion of opioid-negative urine samples over six months (31 versus 33 percent, 95 percent CI of the mean difference -10.8 to 5.9).

By delivering constant levels of buprenorphine, this SC implant may result in less variability in buprenorphine levels when compared to the plasma peaks and troughs associated with sublingual tablets. As a result, buprenorphine SC implants may increase patient compliance and reduce cravings that occur as a result of fluctuations in buprenorphine levels. A new drug application (NDA) for the buprenorphine SC implant is expected to be submitted to the FDA in the third quarter of 2012.

Phase III

Drug Name: Cariprazine

Manufacturer: Forest & Gedeon Richter

Indication: Schizophrenia

Formulation: Oral capsule

Cariprazine, a potent dopamine D3/D2 receptor partial agonist with a preference for D3, is an antipsychotic being studied for the treatment of acute exacerbations of schizophrenia.

In a Phase III (N=617), double-blind, multicenter, fixed-dose, six-week trial, cariprazine was compared to placebo in patients with an acute exacerbation of schizophrenia. Treatment with cariprazine resulted in a greater improvement in the Positive and Negative Syndrome Scale (PANSS) total score, from baseline to week six, relative to placebo (3 mg per day: -6.0, P=0.0044, 6 mg per day: -8.8, P<0.0001). In a similarly designed Phase III (N=446), six-week, fixed-flexible dose study, treatment with cariprazine resulted in a greater improvement in the PANSS total score relative to placebo (3 mg to 6 mg per day: -6.8, P=0.0029, 6 mg to 9 mg per day: -9.9, P<0.0001). Cariprazine has also shown efficacy in patients with acute mania associated with bipolar 1 disorder in Phase III trials and is being investigated in bipolar depression and as adjunctive treatment for Major Depressive Disorder.

Similar to other atypical antipsychotics, cariprazine may have a safer side effect profile due to decreased affinity for serotonergic, histaminergic, muscarinic, and adrenergic receptors. Cariprazine has exhibited increased antagonism at the D3 receptor, which may be associated with enhanced cognition known to improve psychosocial functioning in patients with schizophrenia – offering a potential advantage over Abilify[®] (aripiprazole). An NDA submission for schizophrenia and bipolar mania is planned for 2012.

Promising New Agents

Phase III

Drug Name: Daclatasvir

Manufacturer: Bristol-Myers Squibb
 Indication: Chronic hepatitis C
 Formulation: Oral tablet

Daclatasvir is being studied for the treatment of chronic hepatitis C virus (HCV). This agent is a highly selective HCV NS5A replication complex inhibitor that interferes with viral replication and assembly.

Three groups were included in a Phase II (N=43), open-label trial: patients with chronic HCV genotype 1b with a prior

null response to peginterferon alfa (alfa plus ribavirin (RBV), patients considered ineligible for alfa plus RBV, or those with prior intolerance to alfa plus RBV. All were treated with daclatasvir 60 mg once daily and asunaprevir, an investigational NS3 protease inhibitor (PI), 200 mg twice daily for 24 weeks. Sustained virologic response (SVR) 12 weeks post-treatment was achieved in 77 percent of patients (P-value not reported). At 24 weeks post-treatment, 100 percent of patients who achieved SVR at 12 weeks maintained undetectable viral loads (P-value not reported). Common

treatment-related adverse events included headache, nasopharyngitis, elevated liver enzymes, diarrhea, and fever. Currently, daclatasvir is in Phase III studies in treatment-naïve patients as well as in a head-to-head comparison with telaprevir.

Daclatasvir may be an oral option that has a unique mechanism of action for the treatment of HCV. When used in combination with a PI, it may represent an alternative for difficult-to-treat patients with HCV genotype 1, the most prevalent genotype, including null responders and those intolerant to standard therapy.

NDA

Drug Name: Hydrocodone

Manufacturer: Zogenix
 Indication: Chronic pain
 Formulation: ER oral capsule

Zohydro™ is an oral, extended-release (ER) formulation of hydrocodone being developed for the treatment of moderate to severe chronic pain in patients requiring around-the-clock opioid therapy.

In a Phase III, double-blind trial, over 300 opioid-experienced adult patients with moderate to severe chronic low

back pain not adequately relieved by their existing therapy were randomized to receive hydrocodone ER 20 mg to 100 mg or placebo every 12 hours. Treatment with hydrocodone ER resulted in improved pain relief from baseline to week 12 as measured by the average 24-hour pain intensity ratings, the study's primary endpoint, when compared to placebo (P=0.008). A greater proportion of patients who received hydrocodone ER experienced at least a 30 percent or at least a 50 percent improvement in pain intensity compared to placebo (68 versus 31 percent

and 48 versus 23 percent, respectively, P<0.001 for both). Common adverse events occurring in more than 5 percent of patients treated with hydrocodone ER included constipation, nausea, and urinary tract infections.

If approved, hydrocodone ER may become the first hydrocodone product without acetaminophen, reducing the risk of liver toxicity. Hydrocodone ER may also provide consistent pain relief compared to currently available immediate release opioids. An NDA was submitted to the FDA on May 2, 2012.

NDA

Drug Name: Quad

Manufacturer: Gilead Sciences
 Indication: HIV-1 infection
 Formulation: Oral tablet

Quad is under FDA review for the treatment of human immunodeficiency virus type 1 (HIV-1) infection. It is a once-daily formulation of the investigational integrase inhibitor elvitegravir (EVG), combined with emtricitabine (FTC), tenofovir (TDF), and cobicistat (COBI), a boosting agent with no anti-HIV activity.

In a Phase III (N=700), double-blind, trial, treatment-naïve adults with HIV-

1 were randomized to EVG/COBI/FTC/TDF or Atripla® (efavirenz [EFV]/FTC/TDF). Results showed a similar proportion of patients achieved a viral load of less than 50 copies/mL at week 48 in both the EVG/COBI/FTC/TDF and the EFV/FTC/TDF groups (88 versus 84 percent, 95 percent CI for the difference -1.6 to 8.8), meeting the pre-defined criterion for non-inferiority. In a similarly designed Phase III (N=708), double-blind trial, a similar proportion of patients achieved a viral load of less than 50 copies/mL at week 48 who received EVG/COBI/FTC/TDF or Reyataz® (atazanavir [AZT]) 300 mg boosted by

Norvir® (ritonavir) plus Truvada® (FTC/TDF) (90 versus 87 percent, 95 percent CI for the difference -1.9 to 7.8) again, meeting the pre-defined criterion for non-inferiority. Nausea was more common, while CNS side effects and rash were reduced with EVG/COBI/FTC/TDF versus EFV/FTC/TDF.

If approved, EVG/COBI/FTC/TDF may offer the advantage of once-daily dosing, and fewer CNS side effects and rash compared with EFV/FTC/TDF, the only single tablet once-daily regimen currently available. An FDA decision is expected on Aug. 27, 2012.

Promising New Agents

Phase III

Drug Name: Tedizolid

Manufacturer: Trius Therapeutics
 Indication: Gram positive infections
 Formulation: IV/oral tablet

Tedizolid, a second generation oxazolidinone, is in development as an IV and oral treatment for serious gram positive infections, including those caused by methicillin-resistant *Staphylococcus aureus* (MRSA). By binding to the 50S ribosome, tedizolid inhibits bacterial protein synthesis.

A Phase III (N=667), randomized,

double-blind trial, evaluated the safety and efficacy of oral tedizolid, 200 mg once daily for six days followed by four days of placebo, versus oral Zyvox® (linezolid), 600 mg twice daily for 10 days, in patients with acute bacterial skin and skin structure infections. Cessation of infection spread and absence of fever at 48 to 72 hours was achieved by 79.5 and 79.4 percent of patients in the tedizolid and linezolid groups, respectively, meeting the study's non-inferiority criteria (P-value not reported). Treatment-related adverse events were greater in patients treated

with linezolid compared to tedizolid (31 versus 24.2 percent, respectively, P-value not reported). Gastrointestinal (GI) events, the most commonly reported adverse event, occurred in fewer patients in the tedizolid group than in the linezolid group (16.3 versus 25.4 percent, P=0.004).

Tedizolid offers a shorter treatment duration, fewer GI side effects, and once-daily dosing compared to twice-daily linezolid. Tedizolid may represent a new option for difficult-to-treat infections as it has also demonstrated activity against linezolid-resistant organisms.

NDA

Drug Name: Teduglutide

Manufacturer: NPS Pharmaceuticals
 Indication: Short bowel syndrome
 Formulation: SC injection

Gattex® (teduglutide), a recombinant analog of human glucagon-like peptide 2 (GLP-2), is currently under FDA review for the treatment of short bowel syndrome (SBS). Repeated administration of GLP-2 promotes expansion and growth of the intestinal mucosa and reduces enterocyte apoptosis.

In STEPS, a Phase III (N=86), double-

blind trial, the percentage of patients who achieved at least a 20 percent reduction in weekly parenteral nutrition (PN) volume compared to baseline at week 20 and maintained that response at week 24 was higher with SC teduglutide 0.05 mg/kg daily compared to placebo in adults with SBS (63 versus 30 percent, respectively, P=0.002). In STEPS 2 (N=88), an open-label, extension of STEPS, 91 percent of patients treated with teduglutide maintained reductions in PN and IV fluid volume, defined as a 20 to 100 percent reduction from baseline, after 12 months.

Additionally, after 12 months of treatment with teduglutide, 24 percent of patients needed at least three fewer days of PN or IV fluids per week, and seven patients no longer required PN or IV fluid (P-value not reported). The most commonly reported adverse events were GI-related.

Through intestinal rehabilitation, teduglutide may improve the integrity and function of the existing intestine, and may also reduce or eliminate the need for PN or IV fluids, which is often associated with complications. An FDA decision is expected Sept. 30, 2012.

Phase III

Drug Name: Tivozanib

Manufacturer: AVEO Pharmaceuticals
 Indication: Renal cell carcinoma
 Formulation: Oral capsule

Tivozanib, a tyrosine kinase inhibitor selective for vascular endothelial growth factor (VEGF) receptors -1, -2, and -3, is being studied for the treatment of advanced renal cell carcinoma (RCC). Inhibition of VEGF receptors may prevent cancer cell survival and angiogenesis.

In a Phase III (N=517), randomized, open-label, multicenter trial, four-week cycles of oral tivozanib 1.5 mg daily for

three weeks, followed by one week off, was compared to continuous four-week cycles of oral Nexavar® (sorafenib) 400 mg twice daily in patients with a history of no more than one prior systemic therapy for advanced RCC. After 24 months, there was greater improvement in median progression-free survival in patients who received tivozanib compared to sorafenib in the overall study population (11.9 versus 9.1 months, P-value not reported) and the treatment-naïve subgroup, representing 70 percent of all patients (12.7 versus 9.1 months, P-value not reported). Common adverse

events included reversible hypertension and dysphonia, while off-target toxicities, such as mucositis, fatigue, and hand-foot syndrome, which are commonly associated with other targeted VEGF therapies, were low in patients treated with tivozanib.

Given its selectivity for VEGF receptors, tivozanib may offer a safer alternative compared to first-line VEGF inhibitors such as Sutent® (sunitinib) and Votrient™ (pazopanib). This may allow tivozanib to be combined with standard chemotherapy, increasing its use in other forms of cancer. An NDA submission is planned for the third quarter of 2012.

Projected Generic Entry*

- **Lescol® XL (fluvastatin)**
6/2012
- **Clarinet®/Clarinet-D® (desloratadine/desloratadine & pseudoephedrine)**
7/2012
- **TriCor® (fenofibrate)**
7/2012
- **Actos® (pioglitazone)**
8/2012
- **Singulair® (montelukast)**
8/2012
- **Xopenex® (levalbuterol)†**
8/2012
- **Detrol® (tolterodine)**
9/2012
- **Diovan®/Diovan HCT® (valsartan/valsartan & hydrochlorothiazide)**
9/2012
- **Revatio® (sildenafil)**
9/2012
- **Lidoderm® (lidocaine patch)**
11/2012
- **Actoplus Met® (pioglitazone & metformin)**
12/2012
- **Atacand®/Atacand HCT® (candesartan/candesartan & hydrochlorothiazide)**
12/2012
- **Evoxac® (cevimeline)**
12/2012
- **Maxalt®/Maxalt-MLT® (rizatriptan)**
12/2012
- **Opana® ER (oxymorphone)**
1/2013
- **Zometa® (zoledronic acid)**
3/2013

*Dates are estimates, current as of 6/15/12, and are subject to change due to any patent litigation or additional patents.

†Levalbuterol inhalation solution, not hydrofluoroalkane

Investigational Indications

Incivek® (telaprevir)

In a Phase II (N=62) trial, adults coinfecting with HCV genotype 1 and HIV were randomized to receive telaprevir, Pegasys® (peginterferon alfa-2a) and Copegus® (ribavirin), or peginterferon alfa-2a and ribavirin alone. All patients were naïve to HCV treatment and either not receiving antiretroviral therapy (ART) or taking an AZT- or EFV/FTC/TDF-based ART regimen. Interim results showed that sustained virologic response (SVR) 12 weeks after completing treatment was achieved in 74 percent of patients receiving add-on telaprevir versus 45 percent of those receiving ribavirin and peginterferon alfa-2a alone (P-value not reported).

Information available at www.vertex.com

Victralis® (boceprevir)

In a Phase IIb (N=100) trial, adults coinfecting with HCV genotype 1 and stable HIV, who were HCV treatment-naïve and on ART, were randomized to boceprevir 800 mg three times daily with weekly PEG-Intron™ (peginterferon alfa-2b) plus daily ribavirin or peginterferon alfa-2b plus ribavirin alone. Interim results showed that SVR at 12 weeks after ending treatment was achieved in 60.7 percent of patients treated with add-on boceprevir and 26.5 percent of those treated with peginterferon alfa-2b plus ribavirin alone (P-value not reported).

Information available at www.merck.com

FDA Updates

Apixaban (Eliquis®)

On Feb. 29, 2012, Bristol-Myers Squibb and Pfizer announced that the FDA extended the action date by three months for the NDA for apixaban, an oral direct Factor Xa inhibitor in development for the prevention of stroke and systemic embolism in patients with atrial fibrillation. After the initial NDA was filed, the manufacturers of apixaban submitted additional information that was considered a major amendment to the application requiring more time for FDA review. Currently, there are no plans for the FDA advisory committee to review this NDA. An FDA decision is expected on June 28, 2012.

Dapagliflozin

On Jan. 19, 2012, the FDA issued a complete response letter (CRL) to AstraZeneca and Bristol-Myers Squibb regarding the NDA for dapagliflozin for the treatment of adults with type 2 diabetes. Additional clinical data was requested to better assess the benefit-risk profile of dapagliflozin. The CRL came after the Endocrinologic and Metabolic Drugs Advisory Committee previously voted against approval in July 2011 due to safety concerns regarding increased risk of liver toxicity and breast and bladder cancers. The manufacturers have stated they will work closely with the FDA to determine appropriate next steps for the NDA.

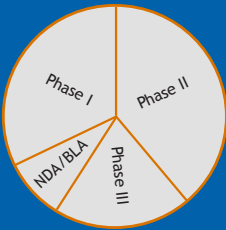
Ridaforolimus (Taltorvic®)

On June 5, 2012, the FDA issued a CRL regarding the NDA for ridaforolimus, an oral inhibitor of mammalian target of rapamycin, seeking approval as maintenance treatment for metastatic soft-tissue or bone sarcoma. The FDA declined approval for this agent, requesting that additional clinical trials be conducted to further evaluate safety and efficacy. The FDA's Oncologic Drugs Advisory Committee previously voted 13 to 1 against approval, citing concern that the increase in progression-free survival was small compared to placebo, given the side effect profile of ridaforolimus, which includes infection, rash, and potential kidney damage.



Industry Trends

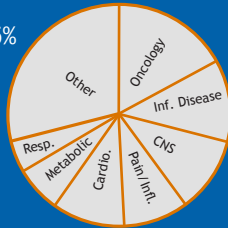
Agents in Clinical Development



Phase I - 33%
Phase II - 37%
Phase III - 21%
NDA/BLA - 9%

Pipeline Research

Oncology - 16%
Infectious Disease - 15%
CNS - 12%
Pain and Inflammation - 9%
Cardiology - 8%
Metabolic - 6%
Respiratory - 5%
Other - 29%



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Additional Promising New Agents

Drug Name	Manufacturer	Indication	Product Timeline
Lorcaserin	Arena Pharmaceuticals, Eisai	Weight management	PDUFA date 6/27/2012
Apixaban (Eliquis®)	Bristol-Myers Squibb, Pfizer	Atrial fibrillation	PDUFA date 6/28/2012
AMR101	Amarin	Very high triglycerides	PDUFA date 7/26/2012
Delayed-release low-dose prednisone (Lodotra®)	Horizon Pharma	Rheumatoid arthritis	PDUFA date 7/26/2012
Carfilzomib (IV)*	Onyx Pharmaceuticals	Relapsed and refractory multiple myeloma	PDUFA date 7/27/2012
Tofacitinib*	Pfizer	Rheumatoid arthritis	FDA decision expected 8/2012
Budesonide (Uceris™)	Santarus	Mild to moderately active UC	PDUFA date 10/16/2012
IPX066	Impax Pharmaceuticals	Idiopathic Parkinson's disease	PDUFA date 10/21/2012
Treprostinil	United Therapeutics	Pulmonary arterial hypertension	PDUFA date 10/27/2012
CRTX 080	Cornerstone Therapeutics	Hyponatremia	PDUFA date 10/29/2012
Lomitapide	Aegerion Pharmaceuticals	HoFH	PDUFA date 12/29/2012
Mipomersen (Kynamro™) (SC)*	Genzyme, Isis Pharmaceuticals	HoFH	PDUFA date 1/29/2013
Ponatinib*	Ariad Pharmaceuticals	CML	NDA submission planned for third quarter of 2012
rhPTH (Natpara™) (SC)	NPS Pharmaceuticals	Hypoparathyroidism	BLA submission planned for second half of 2012
Methotrexate (Vibex™) (SC)	Antares Pharma	Rheumatoid arthritis	NDA submission planned for first half of 2013
BEMA® Buprenorphine/naloxone	BioDelivery Sciences International	Opioid dependence	NDA submission planned for first half of 2013

Table Abbreviations: BLA = biologics license application, CML = chronic myeloid leukemia, HoFH = homozygous familial hypercholesterolemia, IV = intravenous, NDA = new drug application, PDUFA = prescription drug user fee act, rhPTH = recombinant human parathyroid hormone, SC = subcutaneous, UC = ulcerative colitis

Note: All agents are administered orally unless otherwise indicated.
*Designates specialty drug.



Who We Are and What We Do



The University of Massachusetts Medical School's Clinical Pharmacy Services is a comprehensive prescription drug management program developed in 1999 as part of the Medical School's Commonwealth Medicine division, primarily to provide drug utilization review for Massachusetts Medicaid. Today, we bring exceptional depth and experience in the development and implementation of unique, client-customized, managed care-related clinical pharmacy functions including, but not limited to, evidence-based formulary support, pharmacoeconomic modeling, drug utilization review, medication therapy management, clinical call center support, and provider/patient education.

PIPELINE TR_xENDS is an educational resource produced twice yearly to deliver critical information at the highest level of quality to our clients. We hope that you find this resource of value, and we welcome your suggestions for improvement.



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