

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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Investigational Indications

Ranibizumab
for the treatment of diabetic macular edema

Rilonacept
for prevention of gout flares

FDA Updates

Boceprevir and telaprevir
receive FDA approval

Cladribine and naltrexone SR/ bupropion SR
both receive complete response letter

Promising New Agents

Phase III

Drug Name: Aclidinium bromide

Manufacturer: Almirall, Forest

Indication: COPD

Formulation: Dry powder inhaler

Aclidinium bromide, a long-acting, inhaled anticholinergic bronchodilator, is an antagonist at the M2 and M3 muscarinic receptors. It is being studied for the treatment of chronic obstructive pulmonary disease (COPD).

Three Phase III, randomized, double-blind trials compared acclidinium bromide 200 µg and 400 µg twice daily to placebo in patients with moderate to severe COPD. In each study, the primary endpoint was the change in morning trough forced expiratory volume in one second (FEV1), from baseline to week 12. In the ATTAIN study (N=828), acclidinium bromide at doses of 200 µg and 400 µg produced statistically significant increases in trough FEV1 at week 12 versus placebo (77 and 105 mL, respectively, P≤0.0001). In the ACCORD COPD I study (N=561), similar increases in trough FEV1 over placebo were seen with 200 µg and 400 µg of acclidinium bromide (86 and 124 mL, respectively, P<0.0001). However, in the ACCORD COPD II study (N=544), the increase in trough FEV1 versus placebo (72 mL, P=0.001), for the anticipated therapeutic dose of 400 µg, was less than that of the other two Phase III trials. The most common adverse effects were COPD exacerbation, dyspnea, headache, and nasopharyngitis.

Due to its favorable effects on trough FEV1 and low incidence of anticholinergic side effects, acclidinium bromide may compete with Spiriva[®] (tiotropium bromide). However, once-daily tiotropium bromide maintains an advantage in dosing frequency. A New Drug Application (NDA) submission is planned for mid-2011.

BLA

Drug Name: Aflibercept

Manufacturer: Regeneron, Bayer

Indication: Wet AMD

Formulation: Intravitreal injection

Aflibercept is under FDA review for the treatment of the neovascular form of age-related macular degeneration (wet AMD). By inhibiting vascular endothelial and placental growth factors, aflibercept may reduce the abnormal growth of blood vessels that damage the retina through blood and fluid leaks.

In two double-blind, non-inferiority, Phase III studies, VIEW 1 (N=1,217) and VIEW 2 (N=1,240), patients with wet AMD were randomized to intravitreal aflibercept 0.5 mg monthly, 2 mg monthly, or 2 mg every two months following three monthly loading doses, or intravitreal Lucentis[®] (ranibizumab) 0.5 mg monthly for 12 months. The primary endpoint in both studies was the proportion of patients who maintained vision at 12 months, defined as the loss of fewer than 15 letters on the Early Treatment Diabetic Retinopathy Study eye chart. In VIEW 1, aflibercept 0.5 mg monthly, 2 mg monthly, and 2 mg every two months showed non-inferiority to ranibizumab in the proportion of patients maintaining vision (95.9, 95.1, and 95.1 versus 94.4 percent, respectively, P value not reported). Similar results were also seen in VIEW 2 between the aflibercept and ranibizumab groups (96.3, 95.6, and 95.6 versus 94.4 percent, respectively, P value not reported). The incidence of side effects was similar among all treatment groups.

An FDA decision on the Biologics License Application (BLA) for the indication of wet AMD is expected on Aug. 20, 2011. If approved, aflibercept may offer less frequent dosing without compromising efficacy compared to ranibizumab for this indication.

● Non-Specialty ● Specialty

Promising New Agents

Phase III

Drug Name: Dimethyl fumarate
Manufacturer: Biogen Idec
Indication: RRMS
Formulation: Oral capsule

Dimethyl fumarate is an oral agent being studied for the treatment of relapsing-remitting multiple sclerosis (RRMS). It produces anti-inflammatory effects by suppressing nuclear factor κ B-dependent transcription, while also reducing oxidative neuronal death and maintaining myelin integrity.

In DEFINE, a two-year, double-blind,

randomized, Phase III study, dimethyl fumarate 240 mg two or three times daily was compared to placebo in over 1,200 patients with RRMS. Compared to placebo, treatment with either dose of dimethyl fumarate significantly reduced the proportion of patients who relapsed at two years ($P < 0.0001$), the primary endpoint. In the twice-daily group, the reductions in the primary endpoint, the annualized relapse rate (ARR), and the progression of disability were 49, 53, and 38 percent, respectively, compared to placebo (P values not reported). Similar

reductions were seen in the three-times-daily group. According to preliminary data from DEFINE, dimethyl fumarate has demonstrated a favorable safety and tolerability profile.

The increased dosing frequency with dimethyl fumarate may be a disadvantage compared to once-daily oral Gilenya[®] (fingolimod). Additionally, fingolimod may produce greater reduction in ARR (54 to 60 percent versus placebo) than what has been shown thus far with dimethyl fumarate. An NDA submission is planned by the end of 2011.

Phase III

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

Elvitegravir is an oral integrase inhibitor being studied for the treatment of human immunodeficiency virus type 1 (HIV-1) infection. It interferes with HIV replication by blocking the integration of the virus into the human genome.

A Phase III, randomized, double-blind, non-inferiority trial compared elvitegravir 150 mg daily (N=351) to

Isentress[®] (raltegravir) 400 mg twice daily (N=351), both added to a ritonavir-boosted protease inhibitor and a second antiviral agent, in treatment-experienced adults with an HIV viral load of at least 1,000 copies/mL. The proportion of patients achieving and maintaining a viral load of less than 50 copies/mL through week 48, the primary endpoint, was similar between the elvitegravir and raltegravir treatment groups (59 versus 57.8 percent, 95 percent CI for the difference: -6 to 8.2 percent), meeting pre-defined criterion for non-inferiority. The frequency of severe and

life-threatening adverse events was similar in the two groups.

The once-daily dosing of elvitegravir may be an advantage over twice-daily raltegravir, the only FDA-approved integrase inhibitor. Elvitegravir, combined with Truvada[®] (emtricitabine/tenofovir) and cobicistat, an investigational boosting agent with no anti-HIV activity, is in Phase III trials. This new tablet formulation, called Quad, may become the second complete once-daily regimen available. NDA submissions for Quad and elvitegravir are planned for the first half of 2012.

Phase III

Name: Laquinimod
Manufacturer: Teva
Indication: RRMS
Formulation: Oral capsule

Laquinimod is a novel, once-daily oral immunomodulator being studied for the treatment of RRMS. Although the exact mechanism of action is unknown, laquinimod is thought to reduce the infiltration of immune cells into the central nervous system and to change the cytokine balance in favor of an anti-inflammatory T helper-2 lymphocyte profile. These effects may reduce myelin

destruction and axonal damage, which are associated with disability in RRMS.

Laquinimod 0.6 mg once daily was compared to placebo in ALLEGRO, a two-year, randomized, double-blind, Phase III study (N=1,106) of patients with RRMS. Compared to placebo, patients treated with laquinimod experienced a 23 percent reduction in ARR ($P = 0.0024$), the primary endpoint in the study. Compared to placebo, treatment with laquinimod was also associated with a 36 percent reduction in the risk of confirmed disability progression, as measured by the Expanded Disability Status Scale

($P = 0.0122$), as well as a 33 percent reduction in the progression of brain atrophy ($P < 0.0001$). The most common adverse effects included headache, nasopharyngitis, and back pain. Although liver enzyme elevations occurred more frequently with laquinimod than placebo, they were asymptomatic and reversible.

While the reduction in ARR versus placebo seen with laquinimod (23 percent) may be lower than that seen with fingolimod (54 to 60 percent), this agent may become another once-daily treatment option for RRMS. An NDA submission is planned by the end of 2011.

Promising New Agents

Phase III

Name: Lixisenatide

Manufacturer: Zealand, Sanofi-Aventis
 Indication: Type 2 diabetes mellitus
 Formulation: Subcutaneous injection

Lyxumia® (lixisenatide), a once-daily glucagon-like peptide-1 (GLP-1) agonist, is being studied for the treatment of type 2 diabetes mellitus.

In three randomized, double-blind, placebo-controlled, Phase III trials in the GetGoal program, lixisenatide reduced HbA1c when used as monotherapy in the 12-week -MONO (N=361) trial, as an add-

on to a sulfonylurea (SU) (with or without metformin) in the 24-week -S (N=859) trial, and as an add-on to basal insulin (with or without a SU) in the 24-week -L-ASIA (N=311) trial (P<0.0001 versus placebo for all). In the GetGoal-S study, treatment with lixisenatide was also associated with weight loss compared to placebo (P<0.0001).

When added to metformin in the 24-week, Phase III GetGoal-X trial (N=639), lixisenatide met the primary endpoint of non-inferiority in HbA1c reduction from baseline compared to twice-daily

exenatide, with fewer patients reporting symptomatic hypoglycemia (2.5 versus 7.9 percent, P<0.05).

In an indirect comparison, once-daily Victoza® (liraglutide) was shown to produce greater reductions in HbA1c compared to lixisenatide when used as monotherapy (0.84 to 1.14 percent versus 0.73 to 0.85 percent). Without direct comparisons, it is unclear if the differences in pharmacokinetic profiles among the various GLP-1 agonists will lead to any clinical advantages. An NDA submission is planned for 2012.

Phase III

Name: Mipomersen

Manufacturer: Genzyme, Isis
 Indication: Hypercholesterolemia
 Formulation: Subcutaneous injection

Mipomersen is being studied for the treatment of hypercholesterolemia. It inhibits the synthesis of apolipoprotein B, the structural core of all atherogenic lipids, thereby decreasing the formation of low-density lipoprotein (LDL).

In a 26-week trial, 158 patients with high risk of coronary heart disease (CHD), who were receiving a maximally tolerated

dose of a statin with or without other lipid-lowering therapy, and who had an LDL of at least 100 mg/dL and triglycerides less than 200 mg/dL, were randomized to add-on mipomersen 200 mg weekly or placebo. The primary endpoint, change from baseline in LDL levels at two weeks after the last dose, was greater with mipomersen than placebo (37 versus 5 percent reduction, P<0.001). A second 26-week trial included 58 patients with severe hypercholesterolemia who were on a maximally tolerated statin and at least one other lipid-lowering therapy, with LDL of

at least 300 mg/dL or 200 mg/dL with CHD. Add-on mipomersen produced 36 percent reduction in LDL versus 13 percent increase seen with placebo (P<0.001). Common adverse events included elevated alanine aminotransferase levels, flu-like symptoms, and injection site reactions.

The results of these Phase III trials are planned to be submitted in the initial NDA, expected in the second half of 2011, for the indication of homozygous familial hypercholesterolemia. Mipomersen may be used as an add-on to lipid-lowering agents in patients who are difficult to get to goal.

Phase III

Drug Name: Tofacitinib

Manufacturer: Pfizer
 Indication: Rheumatoid arthritis
 Formulation: Oral tablet

Tofacitinib is an oral Janus kinase (JAK) inhibitor being studied for the treatment of rheumatoid arthritis (RA). Unlike current RA therapies, which target extracellular cytokines, tofacitinib modulates the intracellular JAK pathway to improve inflammatory immune response in patients with RA.

In ORAL Sync, a 12-month Phase III study (N=792), patients with moderately

to severely active RA were randomized to tofacitinib 5 mg or 10 mg twice daily or placebo, both as an adjunct to existing non-biologic disease-modifying antirheumatic drug (DMARD) therapy. A greater proportion of patients receiving tofacitinib 5 mg or 10 mg achieved a 20 percent improvement in the American College of Rheumatology criteria at six months compared to placebo (52.7 and 58.3 versus 31.2 percent, respectively, P<0.0001 for both). Moreover, 11 and 14.8 percent of patients treated with tofacitinib 5 mg and 10 mg, respectively, were considered to be in remission at

six months (Disease Activity Score 28-4 [DAS28-4] of less than 2.6), compared to 2.7 percent of patients in the placebo group (P<0.001 and P<0.0001, respectively). Infection was the most commonly reported adverse event. Four deaths occurred in the tofacitinib groups; one was due to respiratory failure found to be related to tofacitinib.

Tofacitinib, with its new mechanism of action, may be combined with traditional DMARDs to offer RA patients another treatment option before starting injectable biologic DMARDs. An NDA submission is planned by the end of 2011.

Projected Generic Entry*

- **Nasacort® AQ (triamcinolone)**
6/2011
- **Levaquin® (levofloxacin)**
6/2011
- **Uroxatral® (alfuzosin ER)**
7/2011
- **Anzemet® (dolasetron)**
7/2011
- **Zyprexa® and Zyprexa®
Zydis® (olanzapine)**
10/2011
- **Symbyax® (olanzapine/fluoxetine)**
10/2011
- **Malarone® (atovaquone/proguanil)**
10/2011
- **Lipitor® (atorvastatin)**
11/2011
- **Caduet® (amlodipine/atorvastatin)**
11/2011
- **Solodyn® (minocycline ER)†**
11/2011
- **Tazorac® (tazarotene)**
12/2011
- **Combivir® (lamivudine/
zidovudine)**
12/2011
- **Entocort® EC (budesonide)**
2/2012
- **Lexapro® (escitalopram)**
3/2012
- **Seroquel® (quetiapine)**
3/2012
- **Gabitril® (tiagabine)**
3/2012
- **Avandia® (rosiglitazone),
Avandamet® (rosiglitazone/
metformin), Avandaryl®
(rosiglitazone/glimepiride)**
3/2012

*Dates are estimates, current as of 6/15/11, and are subject to change due to any patent litigation or additional patents.
†45, 90 and 135 mg extended-release tablets.

Investigational Indications

Lucentis® (ranibizumab)

Two Phase III trials compared ranibizumab to placebo in patients with diabetic macular edema (DME). The primary endpoint was the proportion of patients who were able to read at least 15 more letters on an eye chart at 24 months versus baseline. In the RIDE study (N=382), 33.6 and 45.7 percent of patients treated with monthly injections of ranibizumab 0.3 mg and 0.5 mg, respectively, achieved the primary endpoint, versus 12.3 percent with placebo. The RISE study also met the same endpoint. Ranibizumab, approved for the treatment of wet AMD and macular edema following retinal vein occlusion, would be the first FDA-approved medication for DME.

Information available at www.gene.com.

Arcalyst® (rilonacept)

Three Phase III trials studied rilonacept for reducing flares in gout patients currently taking or newly starting uric acid-lowering therapy. In the PRE-SURGE 2 study (N=248), rilonacept was self-administered subcutaneously with a loading dose of 160 mg followed by 80 mg weekly, or 320 mg followed by 160 mg weekly. At 16 weeks, both doses of rilonacept reduced the mean number of gout flares by 72 percent versus placebo (P<0.0001). A supplemental BLA for this indication is planned for mid-2011.

Information available at www.regeneron.com.

FDA Updates

Boceprevir (Victrelis™) and telaprevir (Incivek™)

In May 2011, two oral hepatitis C virus (HCV) NS3/4A protease inhibitors, boceprevir and telaprevir, received FDA approval for the treatment of HCV genotype 1 infection in combination with peginterferon alfa and ribavirin. The agents have shown increased rates of sustained virological response compared to the current standard of care and may shorten duration of HCV therapy from 48 to 24 or 28 weeks for some patients. Both were approved for three-times-daily administration in treatment-naïve and treatment-experienced patients.

Cladribine (Movectro®)

On March 2, 2011, Merck Serono announced it had received a complete response letter (CRL) from the FDA regarding the NDA for cladribine for the treatment of RRMS. While the CRL indicated that the evidence from the CLARITY trial supported the effectiveness of cladribine in RRMS, it included a request for further information on the safety, risks, and overall benefit-risk profile. Merck Serono plans to request a meeting with the FDA to determine if data from ongoing studies, CLARITY EXTENSION, ORACLE MS, and ONWARD, expected in 2011 and 2012, or safety information from already completed studies, can address FDA concerns.

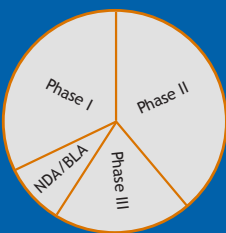
Naltrexone SR/bupropion SR (Contrave®)

Orexigen and Takeda received a CRL from the FDA on Jan. 31, 2011, regarding the NDA for a sustained-release (SR) formulation of naltrexone and bupropion for the treatment of obesity. The CRL requested a randomized, double-blind, placebo-controlled trial of sufficient size and duration to show that the risk of cardiovascular events does not adversely impact the drug's benefit-risk profile. The trial subsequently proposed by Orexigen was rejected by the Division of Metabolic and Endocrinologic Products as inadequate. In response, Orexigen plans to hold clinical development for its U.S. obesity programs and to appeal this rejection.



Industry Trends

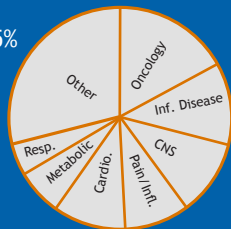
Agents in Clinical Development



Phase I - 32%
Phase II - 38%
Phase III - 21%
NDA/BLA - 9%

Pipeline Research

Oncology - 16%
Infectious Disease - 15%
CNS - 13%
Pain and Inflammation - 9%
Cardiology - 8%
Metabolic - 6%
Respiratory - 5%
Other - 28%



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Additional Promising New Agents

Drug Name	Manufacturer	Indication	Product Timeline
Oxycodone IR abuse-resistant tablet	Acura, King	Treatment of moderate to severe pain	PDUFA date 6/17/2011
Oxycodone ER abuse-resistant capsule (Remoxy®)	Pain Therapeutics, Pfizer	Treatment of moderate to severe pain	PDUFA date 6/23/2011
Zolpidem sublingual tablet (Intermezzo®)	Transcept, Purdue	Middle of the night awakenings	PDUFA date 7/14/2011
Ticagrelor (Brilinta™)	AstraZeneca	Treatment of ACS	PDUFA date 7/20/2011
Indacaterol (Arcapta™ Neohaler™)	Novartis	COPD	FDA response expected in 7/2011
Sumatriptan transdermal patch (Zelrix™)	NuPathe	Treatment of migraine	PDUFA date 8/29/2011
Clobazam (Onfi™)	Lundbeck	Lennox-Gastaut syndrome	FDA response expected in 10/2011
Dapagliflozin	AstraZeneca, Bristol-Myers Squibb	Type 2 diabetes	PDUFA date 10/28/2011
Tafluprost ophthalmic solution (Safutan®)	Merck, Santen	Reduction of elevated IOP	NDA accepted 3/2011
Rivaroxaban (Xarelto®)	Johnson & Johnson, Bayer	AF, prevention of VTE	NDA for use in AF and response to CRL for VTE prevention submitted in 1/2011
Dihydroergotamine inhalation (Levadex®)	MAP Pharmaceuticals	Acute treatment of migraine	NDA submitted 5/2011
Peginesatide* (SC, IV)	Affymax, Takeda	Anemia in chronic renal failure	NDA submitted 5/2011
Perampanel	Eisai	Adjunct treatment of refractory partial onset seizures	NDA submission planned for second quarter of 2011
Apixaban (Eliquis®)	Bristol-Myers Squibb, Pfizer	AF	NDA submission planned for second half of 2011
Mirabegron	Astellas	Treatment of overactive bladder	NDA submission planned for second half of 2011
Oral calcitonin	Tarsa	Treatment of postmenopausal osteoporosis	NDA submission planned for fourth quarter of 2011

Table Abbreviations: ACS = acute coronary syndrome, AF = atrial fibrillation, COPD = chronic obstructive pulmonary disease, CRL = complete response letter, ER = extended release, IOP = intraocular pressure, IR = immediate release, IV = intravenous, NDA = new drug application, PDUFA = Prescription Drug User Fee Act, SC = subcutaneous, VTE = venous thromboembolism

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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