

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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## Promising New Agents

Phase III

### Drug Name: Alemtuzumab

Manufacturer: Sanofi  
Indication: RRMS  
Formulation: Intravenous infusion

Lemtrada™ (alemtuzumab), a humanized monoclonal antibody, is being studied for the treatment of relapsing-remitting multiple sclerosis (RRMS). By targeting CD52 on lymphocytes and monocytes, this agent depletes the T- and B-cells that may be responsible for cellular damage in RRMS.

In CARE-MS I (N=581), a two-year, randomized, Phase III study, two annual cycles of intravenous (IV) alemtuzumab, 12 mg daily for five days at month 0 and for three days at month 12, were compared to subcutaneous (SC) Rebif® (interferon beta-1a), 44 mcg three times weekly for two years, in patients with RRMS who were naive to all suppressive therapy except steroids. After two years, 78 percent of patients who received alemtuzumab remained relapse-free versus 59 percent with interferon beta-1a (P<0.0001). Common adverse events with alemtuzumab included infusion reactions and an increased risk of infections. In the CARE-MS II study (N=840), two annual cycles of IV alemtuzumab, 12 mg daily for five days at month 0 and for three days at month 12, were compared to SC interferon beta-1a, 44 mcg three times weekly over two years, in patients who had a relapse while on prior therapy. Treatment with alemtuzumab resulted in a 49 percent reduction in relapse rate versus interferon beta-1a (P<0.0001).

Alemtuzumab may offer a more effective alternative to interferon beta-1a, one of the current standards of care, for both treatment-experienced and treatment-naive patients. A new drug application (NDA) is planned for early 2012.

NDA

### Drug Name: AMR101

Manufacturer: Amarin Corporation  
Indication: Hypertriglyceridemia  
Formulation: Oral capsule

AMR101 (icosapent ethyl) is an omega-3 fatty acid agent that contains at least 96 percent eicosapentaenoic acid (EPA) ethyl ester. AMR101 does not contain docosahexaenoic acid (DHA), an omega-3 acid shown to decrease triglycerides (TG) and to increase low-density lipoprotein (LDL). AMR101 is under FDA review for the treatment of very high TG.

The MARINE trial, a multi-center, randomized, double-blind, Phase III study (N=229), compared two doses of AMR101 (1 g twice daily and 2 g twice daily) to placebo in patients with very high TG (baseline TG between 500 mg/dL and 2,000 mg/dL). After 12 weeks, treatment with either AMR101 1 g or 2 g twice daily resulted in a reduction in placebo-corrected median TG levels when compared to baseline, the study's primary endpoint (-19.7 [P=0.0051] and -33.1 percent [P<0.0001], respectively). Greater reductions were seen in patients with baseline TG above 750 mg/dL and in those treated with a statin. Neither dose of AMR101 resulted in a significant increase in placebo-corrected median LDL. The most commonly reported adverse effects were diarrhea, nausea, and eructations. Results from the Phase III ANCHOR trial showed that treatment with AMR101 benefits patients with very high TG who were also on statin therapy.

If approved, AMR101 may compete with Lovaza® (a mixed-ester omega-3 agent comprised of EPA and DHA) and fibrates, both of which lower TG but may raise LDL. AMR101 may represent a treatment option for patients with high TG who also have elevated LDL. An FDA decision is expected July 26, 2012.

# Promising New Agents

NDA

**Drug Name: Carfilzomib**

Manufacturer: Onyx Pharmaceuticals  
 Indication: RRMM  
 Formulation: Intravenous infusion

Carfilzomib, a second-generation proteasome inhibitor (PI), is currently under FDA review for the treatment of relapsed and refractory multiple myeloma (RRMM). This agent demonstrates greater selectivity for the chymotrypsin-like (CT-L) subunit on hematological tumor cells than Velcade® (bortezomib), a first-generation PI. Such selectivity is thought

to produce a targeted effect with less generalized cytotoxicity.

The NDA submission was based on an open-label, Phase IIB trial (N=266) evaluating carfilzomib in patients with progressive RRMM who had received prior therapy with bortezomib and either Thalomid® (thalidomide) or Revlimid® (lenalidomide). Patients received IV carfilzomib 20 mg/m<sup>2</sup> twice weekly for three weeks followed by 12 days of rest for the first 28-day cycle and increased to 27 mg/m<sup>2</sup> for up to 12 cycles. Carfilzomib achieved an overall response rate,

defined as at least a partial response, of 24 percent with a median duration of response of 7.8 months (P-value not reported). The ongoing Phase III ASPIRE trial is evaluating carfilzomib in combination with lenalidomide and low-dose dexamethasone in patients with relapsed multiple myeloma who had received one to three prior therapies.

As a result of the selectivity for the CT-L subunit, carfilzomib may offer an improved safety profile compared to bortezomib. An FDA decision on this NDA is expected July 27, 2012.

NDA

**Drug Name: Insulin degludec**

Manufacturer: Novo Nordisk  
 Indication: Diabetes  
 Formulation: Subcutaneous injection

Degludec (insulin degludec), an ultra-long-acting insulin, is in development as a potential treatment for type 1 and type 2 diabetes mellitus (DM). Upon SC injection, it forms soluble multihexamers that gradually dissociate, allowing once-daily dosing with the potential to extend the dosing interval to three times weekly.

Two randomized, open-label, Phase

III trials compared insulin degludec to Lantus® (insulin glargine), both taken once daily with mealtime NovoLog® (insulin aspart) for 52 weeks. Patients with type 1 DM in both groups of the BEGIN™: BB T1 LONG study (N=629) experienced a 0.4 percent A1C reduction (estimated treatment difference [ETD]: 0.01 percent, 95 percent CI -0.14 to 0.11). In the BEGIN™: BB study (N=992), patients with type 2 DM on insulin degludec or insulin glargine, with or without metformin (Glucophage®) or Actos® (pioglitazone), experienced an A1C reduction of 1.2 and

1.3 percent, respectively (ETD: 0.08 percent, 95 percent CI -0.05 to 0.21). Rates of nocturnal hypoglycemia with insulin degludec were 25 percent lower in both type 1 and type 2 DM, 4.4 versus 5.9 (P=0.021) and 1.4 versus 1.8 (P=0.0399) episodes per patient-year, respectively.

On Sept. 29, 2011, two NDAs were submitted, one for insulin degludec and one for DegludecPlus (70 percent insulin degludec and 30 percent insulin aspart). If approved, insulin degludec may reduce dosing frequency and offer a lower risk of hypoglycemia over insulin glargine.

NDA

**Drug Name: Linaclotide**

Manufacturer: Ironwood, Forest  
 Indication: CC, IBS-C  
 Formulation: Oral capsule

Linaclotide is an agonist of guanylate cyclase type-C currently under FDA review for the treatment of chronic constipation (CC) and irritable bowel syndrome with constipation (IBS-C). By binding to and activating the guanylate cyclase C receptor on the luminal surface of the intestinal epithelium, linaclotide increases fluid secretion, accelerates intestinal transit, and may decrease visceral pain.

In two randomized, parallel-group, double-blind, Phase III studies (N=1,276), patients with CC were randomized to receive once-daily linaclotide 145 mcg or 290 mcg or to receive placebo for 12 weeks. The primary endpoint for both trials was three or more complete spontaneous bowel movements (CSBM) per week and an increase of one or more CSBM per week from baseline during at least 9 of 12 weeks. In these two trials, the primary endpoint was reached by 21.2 and 16 percent of patients in the linaclotide 145 mcg groups and 19.4 and 21.3 percent of patients in the linaclotide 290 mcg groups

compared to 3.3 and 6 percent of patients in the placebo groups (P<0.01 for all versus placebo). Additionally, in patients with IBS-C, treatment with linaclotide 290 mcg has been shown to result in improvements in quality of life (P<0.001) and in abdominal pain and discomfort (P-value not reported) over placebo.

If approved, linaclotide may provide multisymptom relief, improving the pain and discomfort associated with constipation, along with the convenience of once-daily dosing over twice-daily Amitiza® (lubiprostone). An FDA decision on this NDA is expected in June 2012.

# Promising New Agents

NDA

**Drug Name: Morphine/oxycodone**

Manufacturer: QRxPharma

Indication: Moderate-severe acute pain

Formulation: Oral capsule

MoxDuo® immediate release (IR) (morphine/oxycodone), formulated in a three-to-two ratio, is being reviewed by the FDA for its potential as a treatment for moderate-to-severe acute pain.

In a double-blind, multi-center, Phase III trial (N=197), patients with moderate-to-severe postoperative bunionectomy pain were randomized to one of the following:

morphine/oxycodone 12 mg/8 mg or 6 mg/4 mg, morphine 6 mg or 12 mg, or oxycodone 4 mg or 8 mg, all administered every six hours. This study evaluated the sum of pain intensity differences from 0 to 24 hours following the first dose (SPID24). Morphine/oxycodone 12 mg/8 mg reduced SPID24 by 54.3 percent versus 28.5, 35.7, and 30 percent in patients receiving morphine 12 mg (P=0.009), oxycodone 8 mg (P=0.037), and morphine/oxycodone 6 mg/4 mg (P=0.01), respectively. Morphine/oxycodone 6 mg/4 mg demonstrated comparable analgesia to morphine 12

mg and oxycodone 8 mg with a 50 to 75 percent reduction in opioid side effects such as nausea, vomiting, and dizziness (P-values not reported). Additionally, a safety study demonstrated a greater risk of oxygen desaturations in patients receiving morphine or oxycodone alone compared to morphine/oxycodone (P<0.009 and P<0.002, respectively).

If approved, morphine/oxycodone IR may represent an alternative analgesic for patients who may have tolerability issues with opioids. An FDA decision on this NDA is expected June 25, 2012.

NDA

**Drug Name: Ridaforolimus**

Manufacturer: Merck, Ariad

Indication: Metastatic sarcoma

Formulation: Oral tablet

Ridaforolimus, an inhibitor of the mammalian target of rapamycin (mTOR), is an orphan drug currently under FDA review for the treatment of metastatic soft-tissue or bone sarcomas. Inhibition of mTOR interferes with cellular protein synthesis, cell cycle progression, cellular proliferation, and survival in cancer cells.

In the double-blind, randomized,

Phase III, SUCCEED trial (N=711), ridaforolimus, 40 mg daily for five consecutive days each week, was compared to placebo in patients with metastatic soft-tissue or bone sarcomas who previously demonstrated a favorable response to chemotherapy. Treatment with ridaforolimus reduced the risk of progression or death by 28 percent versus placebo (HR 0.72, P=0.0001). Median progression-free survival (PFS) was increased in the ridaforolimus group compared to placebo (17.7 versus 14.6 weeks, P-value not reported). Treatment

with ridaforolimus also led to a reduction in average target tumor lesion size of 1.3 percent versus a 10.3 percent increase seen with placebo (P<0.0001). Additionally, the proportion of patients alive and free from disease progression after three months was greater in the ridaforolimus group compared to the placebo group (70 versus 54 percent, P-value not reported).

Ridaforolimus may provide a sustained therapeutic benefit for patients who previously responded to chemotherapy for metastatic sarcoma. On Oct. 5, 2011, the FDA accepted the NDA for review.

NDA

**Drug Name: Teriflunomide**

Manufacturer: Sanofi

Indication: RRMS

Formulation: Oral tablet

Aubagio™ (teriflunomide) is an oral immunomodulator in development for the treatment of relapsing forms of multiple sclerosis (MS). Teriflunomide exerts its effect by reversibly inhibiting dihydroorotate dehydrogenase, thereby blocking the proliferation and action of activated T- and B-cells.

In TEMSO, a randomized, double-blind, Phase III trial (N=1,088), patients

ages 18 to 55 with relapsing forms of MS were randomized to once-daily teriflunomide, 7 mg or 14 mg, or placebo. After 108 weeks, treatment with both 7 mg and 14 mg of teriflunomide resulted in a reduction in the annualized relapse rate relative to placebo (-31.2 and -31.5 percent, respectively; P-values not reported). During this period, 53.7 and 56.5 percent of patients in the teriflunomide 7 mg and 14 mg groups, respectively, remained relapse-free compared to 45.6 percent in the placebo group (P=0.01 and P=0.003, respectively). Adverse events experienced by more

than 10 percent of patients and seen with greater frequency in the teriflunomide group included diarrhea, nausea, hair thinning or decreased hair density, and elevated alanine aminotransferase levels.

Results from the six-year extension of TEMSO demonstrated a safety profile similar to the first 108 weeks, indicating teriflunomide is well tolerated. As a result, this agent may offer an advantage over Gilenya™ (fingolimod), which is associated with serious adverse events including lymphocytopenia, bradyarrhythmia, and atrioventricular block. On Oct. 20, 2011, the FDA accepted the NDA.

# Projected Generic Entry\*

- **Tazorac® (tazarotene)**  
12/2011
- **Clarinet® (desloratadine), Clarinet-D® (desloratadine/pseudoephedrine)**  
1/2012
- **Avalide® (irbesartan/hydrochlorothiazide)**  
3/2012
- **Avandia® (rosiglitazone), Avandamet® (rosiglitazone/metformin), Avandaryl® (rosiglitazone/glimepiride)**  
3/2012
- **Avapro® (irbesartan)**  
3/2012
- **Geodon® (ziprasidone)**  
3/2012
- **Lexapro® (escitalopram)**  
3/2012
- **Seroquel® (quetiapine)**  
3/2012
- **Provigil® (modafinil)**  
4/2012
- **Plavix® (clopidogrel)**  
5/2012
- **Viramune® (nevirapine)**  
5/2012
- **Lescol® and Lescol® XL (fluvastatin)**  
6/2012
- **TriCor® (fenofibrate)**  
7/2012
- **Actos® (pioglitazone)**  
8/2012
- **Singulair® (montelukast)**  
8/2012
- **Xopenex® (levalbuterol)†**  
8/2012

\*Dates are estimates, current as of 12/15/11, and are subject to change due to any patent litigation or additional patents.

†Levalbuterol inhalation solution, not HFA.

## Investigational Indications

### Afinitor® (everolimus)

The BOLERO-2 study (N=724) evaluated everolimus in postmenopausal women with estrogen receptor positive and human epidermal growth factor type-2 receptor negative advanced breast cancer with recurrence or progression despite prior treatment with Arimidex® (anastrozole) or Femara® (letrozole). Treatment with oral everolimus 10 mg daily plus oral Aromasin® (exemestane) 25 mg daily increased PFS compared to exemestane 25 mg alone (6.9 versus 2.8 months, P<0.001). A supplemental NDA submission for this indication is planned for the end of 2011.

Information available at [www.novartis.com](http://www.novartis.com)

### Xarelto® (rivaroxaban)

In the Phase III ATLAS ACS 2-TIMI 51 (N=15,526) study, patients with recent acute coronary syndrome were randomized to receive either twice-daily rivaroxaban 2.5 mg or 5 mg or placebo added to standard therapy. Pooled results from both doses of rivaroxaban demonstrated a lower rate of occurrence of the primary endpoint, a composite of death from cardiovascular causes, myocardial infarction, or stroke, compared to placebo (8.9 and 10.7 percent; P<0.008). Major bleeding occurred in 2.1 percent of patients treated with rivaroxaban versus 0.6 percent treated with placebo (P<0.001). A supplemental NDA for this indication has not yet been submitted.

Information available at [www.xarelto.com](http://www.xarelto.com)

## FDA Updates

### Cladribine (Movectro®)

On June 22, 2011, Merck announced its decision to end the development of cladribine for the treatment of RRMS, following discussions with the FDA. From these discussions, Merck concluded that data from the ongoing clinical trials would unlikely address the FDA requirements for cladribine approval and that a new clinical trial program would take several years to complete. Merck intends to complete the core 96-week treatment period of the CLARITY extension, ORACLE MS, and ONWARD clinical trials, while also continuing to follow participants of the cladribine studies through the PREMIERE registry.

### Dapagliflozin

On Oct. 26, 2011, AstraZeneca and Bristol-Myers Squibb announced that the FDA has extended the review for dapagliflozin, a sodium-glucose cotransporter 2 inhibitor seeking approval for type 2 DM. In July 2011, the Endocrinologic and Metabolic Drugs Advisory Committee voted 9-6 against approval. While the committee was encouraged by the potential for weight loss and the lower risk of hypoglycemia with this agent, there was concern about the increased risk of both breast and bladder cancers. Other concerns included an increased risk for genitourinary and urinary tract infections. An FDA response is expected Jan. 28, 2012.

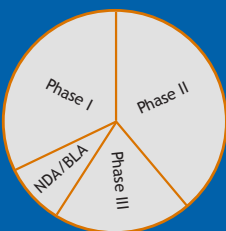
### Phentermine/topiramate (Qnexa®)

On Nov. 3, 2011, VIVUS announced that the FDA has accepted the resubmission of the NDA for phentermine/topiramate controlled-release capsules for the treatment of obesity, including weight loss and maintenance of weight loss. The FDA previously issued a complete response letter on Oct. 28, 2010, regarding the initial NDA for this product, requesting more information on its teratogenic potential and cardiovascular safety. The newly proposed labeling includes a contraindication for women of childbearing potential along with a proposed Risk Evaluation and Mitigation Strategy. An FDA response is expected April 17, 2012.



## Industry Trends

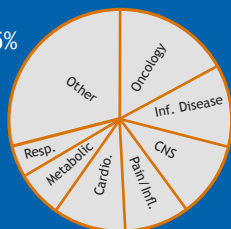
### Agents in Clinical Development



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
Exenatide once weekly (Bydureon™) (SC)	Amylin, Eli Lilly, Alkermes	Type 2 diabetes	PDUFA date 1/28/2012
Staccato loxapine (Adasuve™)	Alexza	Acute agitation in schizophrenia or bipolar disorder	PDUFA date 2/4/2012
Dihydroergotamine inhalation (Levader®)	MAP Pharmaceuticals	Acute treatment of migraine	PDUFA date 3/26/2012
Peginesatide* (SC, IV)	Affymax, Takeda	Anemia in chronic kidney disease	PDUFA date 3/27/2012
Apixaban (Eliquis®)	Bristol-Myers Squibb, Pfizer	Atrial fibrillation	PDUFA date 3/28/2012
Acclidinium bromide (Eklira®)	Almirall, Forest	COPD	FDA decision expected 4/2012
Mirabegron	Astellas Pharma	Treatment of overactive bladder	PDUFA date 6/29/2012
Cobicistat/emtricitabine/elvitegravir/tenofovir	Gilead Sciences	Treatment of HIV	NDA submitted 10/27/2011
Perampanel	Eisai	Adjunct treatment of partial-onset seizures	FDA refused to accept NDA 7/29/2011
Oxycodone ER (Remoxy®) abuse deterrent capsule	Pain Therapeutics, Pfizer	Moderate-to-severe pain	CRL received 6/24/2011
Tafluprost ophthalmic solution (Saflutan®)	Merck & Co.	Reduction of elevated IOP	CRL received 11/7/2011
Mipomersen (Kynamro™)	Genzyme, Isis	Hypercholesterolemia, FH	NDA submission for FH planned for fourth quarter of 2011
Tofacitinib*	Pfizer	Psoriasis, RA	NDA submission for RA planned for end of 2011
Dimethyl fumarate*	Biogen Idec	RRMS	NDA submission planned for first half of 2012
Laquinimod*	Active Biotech, Teva	RRMS	NDA submission planned for early 2012
TC-5214	Targacept, AstraZeneca	Major depressive disorder	NDA submission planned for second half of 2012

**Table Abbreviations:** COPD = chronic obstructive pulmonary disease, CRL = complete response letter, ER = extended release, FH = familial hypercholesterolemia, HIV = human immunodeficiency virus, IOP = intraocular pressure, IV = intravenous, NDA = new drug application, PDUFA = prescription drug user fee act, RA = rheumatoid arthritis, RRMS = relapsing-remitting multiple sclerosis, SC = subcutaneous

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.

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