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Novartis highlights innovative approach to drug discovery with dynamic advance in exploratory pipeline

- *Novartis Institutes for BioMedical Research focused on discovery projects based on powerful fundamental scientific mechanisms and greatest medical needs*
- *Exploratory pipeline advances with 40% increase in size of portfolio of New Molecular Entities from 2005, and a 60% improvement in the transition of compounds from Proof-of-Concept to confirmatory clinical trials*
- *Robust pipeline of biological drugs emerging from sustained internal investments, now represent 25% of exploratory pipeline*
- *139 projects now in clinical development*

Cambridge, Massachusetts, November 19, 2008 — Novartis highlighted at an investor event today the success of its pharmaceuticals research strategy in delivering novel compounds to the clinic, reflecting the benefits of sustained investments in Research and Development.

A total of 88 New Molecular Entities (NMEs) are in the exploratory pipeline, a 40% increase since 2005. Highlighting improved productivity, 80% of compounds that were successful in Proof-of-Concept clinical trials in 2006-2007 have been transitioned to confirmatory Phase II/III trials. This is a 60% improvement from trials during 2003-2005.

The priority of drug discovery efforts are in diseases where there is greatest patient need coupled with strong molecular understanding of the disease. Homogeneous populations, defined either as a genetic disease or by biomarkers, provide the pathway to the clinic. This approach has improved the success rate from exploratory to confirmatory clinical development.

“Our strategy is working to deliver more effective medicines to patients rapidly,” said Mark Fishman, MD, President of the Novartis Institutes for BioMedical Research. “In a relatively short time we have dramatically increased the size and power of our pipeline and believe many of these compounds have the potential to change the practice of medicine.”

Building an industry leadership position in biologics

Novartis has been building its position in biological therapeutics, especially monoclonal antibodies. They now constitute 25% of the pre-clinical research portfolio. Clinical development is expedited by the new Biologics Unit, which has brought together talents and expanded infrastructure dedicated specifically to protein therapeutics. A 2007 survey shows Novartis has 14 biological projects in clinical development, ranking among the top competitors in the pharmaceutical industry.

Innovative science delivering valuable therapies

Novartis has been consistently ranked as having one of the industry's strongest and most novel pipelines, with 139 projects in clinical development (Phase I trials to registration).

"We are working to transition pharmaceuticals development into highly integrated teams that consistently deliver innovative medicines to patients with biotech-like intensity, focus and flexibility," said Trevor Mundel, MD, Head of Global Development Functions and designated to become Global Head of Development as of December 1. "We are taking advantage of empowered teams and powerful new technologies to move more quickly and flexibly with a broad portfolio."

Novartis is utilizing model-based drug development, an important new technology. The FDA has encouraged the industry to shift to quantitative evaluation from empirical analysis in early-stage research. A drug-disease model translates quantifiable knowledge and beliefs about disease processes and drug action into predictions of measurable markers and responses of interest to drug development scientists, payors and regulators. It is particularly useful in accelerating clinical trials, especially drug dosing. The Novartis Modeling & Simulation group, which involves about 50 associates, is considered one of the most experienced in the industry.

One example of this approach was the development of **BAF312**, a selective sphingosine 1-phosphate (S-1-P) receptor agonist that is planned to enter confirmatory studies in 2009 for use in patients with multiple sclerosis. Applying lessons from FTY720, which is now in Phase III trials for MS, the Modeling & Simulation team was able to accelerate the dose selection decision, provide a narrower range of doses for Phase III and reduce by over 50% the number of patients in the Phase II group.

Recent plans to acquire Nektar's pulmonary business unit, set to be completed by the end of 2008, have also accelerated the competitive position of Novartis in respiratory drug development, providing advanced device platforms as well as expertise in formulation and packaging technologies.

Among projects highlighted at the event:

- **ACZ885** (canakinumab) is a new treatment for a group of rare, but potentially life-threatening, auto-inflammatory diseases called Cryopyrin-Associated Periodic Syndromes (CAPS), which includes Muckle-Wells Syndrome. The first submissions were previously planned for 2009, but are being moved forward to the end of 2008 after data from two clinical studies showed adults and children achieved rapid and long-lasting clinical remission of these diseases. Orphan drug status has already been granted to ACZ885 in the European Union and US for treating CAPS, and also in the US and EU for Systemic Juvenile Idiopathic Arthritis (SJIA), the most severe form of arthritis in children. Phase III trials in SJIA are set to begin in 2009. Studies are also either underway or are planned to start in patients with gout (Phase II started in 2008), adult rheumatoid arthritis (Phase III start in 2010) and type 2 diabetes (Phase II start in 2009).
- **QAB149** (indacaterol) will be submitted for first regulatory approvals in late 2008 as a 24-hour bronchodilator for Chronic Obstructive Pulmonary Disease (COPD), an incurable and common condition in which the lungs have been damaged, usually from smoking. Initial results from the Phase III program involving over 6,000 patients in 30 countries showed strong efficacy and an acceptable safety profile. In the pivotal studies, QAB149 dosed once daily met its objective after 52 weeks of treatment of showing a statistically significant improvement in FEV1 levels (a common lung function test) 24 hours after patients were given either the 150 µg or the 300 µg doses of QAB149 compared to a placebo.

QAB149, also had a fast onset of action similar to the short-acting bronchodilator albuterol. QAB149 further showed a satisfactory safety profile even when studied for one year at the 600 µg dose. This compound is expected to form the foundation of the Novartis respiratory franchise, led by the potential combinations QMF149 (indacaterol with the corticosteroid mometasone) and QVA149 (indacaterol with the anti-muscarinic NVA237) in COPD and QMF as well in asthma.

- *Afinitor* (everolimus, RAD001), an oral inhibitor of the mTOR pathway, is expected to receive a regulatory decision from the FDA within the first quarter of 2009 for patients with advanced kidney cancer. The FDA has requested some data clarification and reformatting related to previously submitted oncology studies as well as additional data from the ongoing trial in pancreatic neuroendocrine tumors (pNET). As a result, the action date has been extended by three months, but the FDA has not asked for additional studies. *Afinitor* was accepted for priority review in mid-2008 based on results of the RECORD-1 trials that showed it more than doubled the time without tumor growth in patients with advanced kidney cancer after failure of standard treatment. Regulatory submissions have also been made in the EU and Switzerland, with more filings planned in 2009. Clinical trials are continuing as planned in other cancers.
- FTY720 (fingolimod) has the potential to be the first sphingosine-1-phosphate receptor (S-1-P) modulator, a new class of therapeutics that act on inflammation and may have a direct beneficial effect on the central nervous system. First results from the Phase III TRANSFORMS trial comparing this once-daily oral compound against the once-weekly interferon beta-1a injection in relapsing remitting MS patients are expected by early 2009. Regulatory submissions are on track for the end of 2009 that will include completed data from the TRANSFORMS and FREEDOMS I trials as well as a subset of data from the FREEDOMS II trial. A new Phase III trial called INFORMS was started in the third quarter of 2008 in patients with primary progressive MS, a form of this disease for which there is no available treatment.
- LCZ696 is a novel dual-acting molecule that blocks the angiotensin receptor blocker (ARB) and neutral endopeptidase inhibition (NEP). The compound is set to enter Phase III trials in 2009 as a potential option to replace ACE inhibitors as the standard of care for heart failure. Phase II studies involving 1,300 patients showed LCZ696 provided superior blood pressure reductions compared with valsartan alone, and was well-tolerated with no reported cases of angioedema (swelling).
- *Tekturma/Rasilez* (aliskiren), the first new type of high blood pressure medicine in more than a decade, forms the foundation for single-pill combination therapies that provide new options to treat cardiovascular disease and sustain the Group's leading hypertension franchise. These include a combination with *Diovan* (valsartan) set for submission in the US by the end of 2008 and in the European Union in 2009, a single-pill combination with the calcium channel blocker amlodipine, and a triple-combination therapy with *Tekturma/Rasilez*, amlodipine and a diuretic. All of these therapies are expected to be approved before the loss of market exclusivity for the flagship high blood pressure medicine *Diovan* in the US in September 2012.
- *Lucentis*, the leading approved therapy for the "wet" form of age-related macular degeneration showed successful results in the Phase II RESOLVE study with statistically significant vision improvement compared to placebo in patients with diabetic macular edema (DME), an eye condition linked with high blood sugar that causes blindness. The Phase III RESTORE study was started in May 2008 in DME, with submission in Europe planned for 2010. Genentech holds the US rights.

- **AFQ056**, a metabotropic glutamate receptor 5 (mGluR5) antagonist, has the potential to become the first approved treatment for Parkinson's Disease levodopa-induced dyskinesia (PD-LID). No therapy has been approved for this disease, which is a complication after dopamine-replacement therapy in Parkinson's patients and characterized by a variety of hyperkinetic movements. AFQ056 recently showed positive results in a Proof-of-Concept trial in PD-LID and is proceeding in development with planned submissions after 2011. AFQ056 shows potential in other diseases, and a Proof-of-Concept study is underway for symptomatic treatment of adults with Fragile X syndrome.

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