Innovative Medicines

Our Innovative Medicines Division is a world leader in offering innovation-driven, patent-protected medicines to patients and physicians. The Innovative Medicines Division researches, develops, manufactures, distributes and sells patented pharmaceuticals, and is comprised of two business units:

- **Novartis Oncology**
- **Novartis Pharmaceuticals**
  - Cardio-Metabolic
  - Immunology and Dermatology
  - Ophthalmology
  - Respiratory
  - Neuroscience
  - Established Medicines

On March 2, 2015, we completed the acquisition of the oncology products of GSK, together with certain related assets. In addition, we acquired a right of first negotiation over the co-development or commercialization of GSK’s current and future oncology R&D pipeline, excluding oncology vaccines. The right of first negotiation is for a period of twelve and one half years from the acquisition closing date.

Following an internal reorganization announced on January 27, 2016, nineteen mature products were transferred from our Innovative Medicines Division to the Retail Generics franchise of our Sandoz Division, and Alcon’s Ophthalmic Pharmaceuticals products were transferred to our Innovative Medicines Division.

The Innovative Medicines Division is the largest contributor among the divisions of Novartis and reported consolidated net sales of USD 16 billion in the first half of 2017.

The product portfolio of the Innovative Medicines Division includes more than 60 key marketed products, many of which are leaders in their respective therapeutic areas.
Key Marketed Products

Novartis Oncology

Afinitor/Votubia (everolimus) is an oral inhibitor of the mTOR pathway. Afinitor is approved in more than 120 countries, including the US, EU member states and Japan for patients with advanced renal cell carcinoma following progression or after vascular endothelial growth factor-targeted therapy (in the US, after failure of treatment with sunitinib or sorafenib). Afinitor is also approved in more than 110 countries, including the US, EU member states and Japan for the treatment of progressive, metastatic or unresectable moderately or well-differentiated neuroendocrine tumors (NET) of pancreatic origin. Afinitor was approved in the US in February 2016 and the EU in June 2016 for the treatment of patients with progressive, unresectable or metastatic well-differentiated, nonfunctional NET of gastrointestinal or lung origin, and is now approved for this indication in more than 45 countries worldwide. In addition, Afinitor is approved in combination with exemestane in more than 110 countries for the treatment of postmenopausal women with hormone receptor-positive human epidermal growth factor receptor-2 negative (HR+/HER2-) advanced breast cancer after recurrence or progression following a non-steroidal aromatase inhibitor (in the US, specifically after failure of treatment with letrozole or anastrozole). Everolimus, under the trade name Afinitor in the US and Votubia in the EU, is also approved in more than 100 countries to treat patients with with tuberous sclerosis complex (TSC) who have subependymal giant cell astrocytoma (SEGA) not requiring immediate surgery, and in more than 95 countries to treat patients with TSC who have renal angiomyolipoma not requiring immediate surgery. Most recently, the drug was approved in more than 30 countries as adjunctive treatment for patients aged 2 years and older whose refractory partial-onset seizures, with or without secondary generalization, are associated with TSC. A dispersible tablet for oral suspension formulation is approved for patients with TSC who have SEGA in more than 40 countries including the US (under the trade name Afinitor Disperz), EU member states (under the trade name Votubia) and Japan (under the trade name Afinitor). Everolimus, the active ingredient in Afinitor/Votubia, is also available under the trade names Zortress/Certican for use in transplantation in the US and EU, respectively, and is exclusively licensed to Abbott and sublicensed to Boston Scientific for use in drug-eluting stents.

Exjade and Jadenu (deferasirox) is an oral iron chelator approved for the treatment of chronic iron overload due to blood transfusions in patients two years of age and older, as well as chronic iron overload in patients with non-transfusion-dependent thalassemia in patients 10 years of age and older. Patients with chronic anemia from diseases such as thalassemia, sickle cell disease and myelodysplastic syndromes may require repeated transfusions, which puts them at risk of iron overload. Exjade, a dispersible tablet for oral suspension, was first approved in 2005 and is now approved in more than 100 countries, including the US, EU member states and Japan. An oral film-coated tablet (FCT) formulation that can be swallowed or crushed is approved in several countries including the US, Switzerland and Canada under the tradename Jadenu. It was approved by EMA in 2016 under the tradename of Exjade. Regulatory applications are under review in several countries worldwide. The film-coated tablet formulation has also been developed as granules for patients who cannot swallow tablets, using the same composition. In May 2017, the FDA approved the granules as Jadenu Sprinkle (deferasirox) granules, and Jadenu granules were approved in Japan on July 3, 2017. A regulatory application for the granules has been submitted in the EU under the name Exjade.

Gleevec/Glivec (imatinib mesylate/imatinib) is a kinase inhibitor approved as a targeted therapy for Philadelphia chromosome-positive (Ph+) chronic myeloid leukemia (CML) and to treat patients with metastatic and/or unresectable KIT (CD117) positive (KIT+) gastrointestinal stromal tumors (GIST), and as an adjuvant treatment for certain adult patients following resection of KIT+ GIST. First launched in 2001, Gleevec/Glivec is approved in more than 125 countries. Gleevec/Glivec is also approved in the US, EU and Japan to treat Ph+ acute
lymphoblastic leukemia, a rapidly progressive form of leukemia. In addition, Gleevec/Glivec is approved in the US and EU to treat dermatofibrosarcoma protuberans, a rare solid tumor; hypereosinophilic syndrome; myelodysplastic/myeloproliferative diseases and other rare blood disorders. In the US, Gleevec is also approved for aggressive systemic mastocytosis. Gleevec/Glivec has received approvals in more than 80 countries as a post-surgery (adjuvant setting) therapy for certain adult patients with KIT+ GIST. Following FDA approval in 2013, the EMA approved Gleevec/Glivec in July 2013 for pediatric patients with newly diagnosed Ph+ acute lymphoblastic leukemia in combination with chemotherapy.

**Jakavi** (ruxolitinib) is an oral inhibitor of the JAK1 and JAK2 tyrosine kinases. It is the first JAK inhibitor indicated for the treatment of adult patients with myelofibrosis, including primary myelofibrosis, post-polycythemia vera myelofibrosis or post-essential thrombocytopenia myelofibrosis. Jakavi is currently approved in 104 countries for the myelofibrosis indication including EU countries and Japan. More than 75 countries have also approved Jakavi for the treatment of adult patients with polycythemia vera who are resistant to or intolerant of hydroxyurea, including EU countries and Japan, and regulatory applications have been submitted in other countries. Novartis licensed ruxolitinib from Incyte Corporation for development and commercialization in the indications of oncology, hematology and graft-versus-host disease outside the US. Ruxolitinib, marketed in the US as Jakafi® by Incyte Corporation, is approved by the FDA for the treatment of patients with polycythemia vera who have had an inadequate response to or are intolerant of hydroxyurea. Jakafi® is also approved by the FDA for treatment of patients with intermediate or high-risk myelofibrosis, including primary myelofibrosis, post-polycythemia vera myelofibrosis and post-essential thrombocytopenia myelofibrosis.

**Kisqali** (ribociclib) is a cyclin-dependent kinase inhibitor, a class of drugs that help slow the progression of cancer by inhibiting two proteins called cyclin-dependent kinase 4 and 6 (CDK4/6). These proteins, when over-activated, can enable cancer cells to grow and divide too quickly. Targeting CDK4/6 with enhanced precision may play a role in ensuring that cancer cells do not continue to replicate uncontrollably. In March 2017, Kisqali was approved in the US in combination with an aromatase inhibitor as initial endocrine-based therapy for treatment of postmenopausal women with HR+/HER2- advanced or metastatic breast cancer. The FDA also approved the Kisqali Femara Co-Pack (ribociclib tablets; letrozole tablets). In June 2017, the Committee for Medicinal Products for Human Use (CHMP) of the European Medicines Agency adopted a positive opinion recommending approval of Kisqali in combination with an aromatase inhibitor for treatment of postmenopausal women with HR+/HER2- locally advanced or metastatic breast cancer as initial endocrine-based therapy.

**Promacta/Revolade** (eltrombopag) is a once-daily oral thrombopoietin (TPO) receptor agonist that interacts with the transmembrane domain of the human TPO receptor and initiates signaling cascades similar but not identical to that of endogenous TPO. This induces proliferation and differentiation of human bone marrow progenitor cells, thereby resulting in increased platelet production. It is the only approved once-daily oral thrombopoietin receptor agonist, and is marketed under the brand name Promacta in the US and Revolade in most countries outside the US. It is approved in more than 100 countries for use in the treatment of thrombocytopenia in adult patients with chronic immune (idiopathic) thrombocytopenia (ITP) who are refractory to other treatments. In the US and EU, Promacta/Revolade is approved for patients one year and older with chronic ITP who are refractory to other treatments. Promacta/Revolade is also approved in over 45 countries worldwide for the treatment of patients with severe aplastic anemia (SAA) who are refractory to other treatments. In addition, Promacta/Revolade is approved in more than 50 countries for the treatment of thrombocytopenia in patients with chronic hepatitis C to allow them to initiate and maintain interferon-based therapy. Promacta/Revolade is marketed under a collaboration agreement between Ligand Pharmaceuticals, Inc., and Novartis. Promacta/Revolade was acquired from GSK.
**Rydapt** (midostaurin) is an oral, multi-targeted inhibitor of multiple kinases, which help regulate many essential cell processes, interrupting cancer cells’ ability to grow and multiply. In April 2017, the FDA approved **Rydapt** for use in combination with standard cytarabine and daunorubicin induction and cytarabine consolidation chemotherapy for the treatment of adults with newly diagnosed acute myeloid leukemia (AML), a rare and aggressive blood cancer, who are FLT3 mutation-positive (FLT3+) as detected by an FDA-approved test. **Rydapt** is not indicated as a single-agent induction therapy for the treatment of patients with AML. **Rydapt** was also approved in the US for the treatment of adult patients with aggressive systemic mastocytosis (ASM), systemic mastocytosis with associated hematological neoplasm (SM-AHN) or mast cell leukemia, collectively known as advanced systemic mastocytosis (SM), a group of very rare, life-threatening conditions. **Rydapt** also received approval in Switzerland for use in combination with standard induction and consolidation chemotherapy followed by maintenance monotherapy for treatment of newly diagnosed adult AML patients who have an FLT3 mutation, as well as for the treatment of adult patients with advanced SM. **Rydapt** is the first major treatment advance for people with AML in more than 25 years and the first targeted therapy, addressing a specific mutation in AML – FLT3. Full results from the Phase III RATIFY AML trial were published in *The New England Journal of Medicine* in June 2017.

**Sandostatin SC** and **Sandostatin LAR** (octreotide acetate/octreotide acetate for injectable suspension) are somatostatin analogues indicated for the treatment of patients with acromegaly. **Sandostatin** is also indicated for the treatment of patients with certain symptoms associated with carcinoid tumors and other types of gastrointestinal and pancreatic neuroendocrine tumors. Additionally, **Sandostatin LAR** is approved in more than 60 countries for treatment of patients with advanced neuroendocrine tumors of the midgut or unknown primary tumor location. **Sandostatin** was first launched in 1988 and is is approved in more than 100 countries.

**Tafinlar + Mekinist** (dabrafenib + trametinib) is the first combination of its kind for the treatment of patients with BRAF V600 mutation positive unresectable or metastatic melanoma, as detected by a validated test, in the US, EU and several other markets. **Tafinlar** targets the serine/threonine kinase BRAF in the RAS/RAF/MEK/ERK pathway and Mekinist targets the threonine/tyrosine kinases MEK1 and MEK2 in the MAP kinase pathway, resulting in dual blockade of this pathway. This is the first combination of a BRAF and a MEK inhibitor to demonstrate an overall survival benefit over BRAF inhibitor monotherapy after three years in two Phase III studies in BRAF V600 mutation positive unresectable or metastatic melanoma patients. A five year survival benefit was shown in a landmark study of **Tafinlar+Mekinist**, presented at ASCO 2017 in June, the longest follow up to date of a BRAF and MEK inhibitor combination therapy in patients with BRAF V600-mutant metastatic melanoma. **Tafinlar** and **Mekinist** are each also approved as single agents for the treatment of patients with unresectable or metastatic melanoma in more than 60 and 40 countries worldwide, respectively. **Tafinlar** and **Mekinist** were each acquired from GSK. In April 2017, the European Commission approved **Tafinlar + Mekinist** for the treatment of patients with BRAF V600-positive advanced or metastatic non-small cell lung cancer (NSCLC). The FDA approved the targeted combination therapy for BRAF V600E mutant metastatic NSCLC in June 2017. BRAF V600E mutation positive tumors have been shown to be more aggressive and may lead to a poorer prognosis. BRAF mutations appear in 1-3% of patients with NSCLC. As part of our purchase of oncology products from GSK, we obtained the worldwide exclusive rights granted by Japan Tobacco Inc. to develop, manufacture, and commercialize trametinib.

**Tasigna** (nilotinib) is a signal transduction inhibitor of the BCR-ABL tyrosine kinase. Since its launch in 2007, it has been approved in more than 125 countries to treat patients with Ph+ CML in the chronic and/or accelerated phase who are resistant or intolerant to existing treatment, including **Gleevec/Glivec**. It is also approved in more than 120 markets, including the US, EU, Switzerland and Japan, to treat newly diagnosed patients in the chronic phase. **Tasigna** received EU approval for inclusion of Treatment-free Remission (TFR) data in the product label. **TFR** is the ability to maintain molecular response (MR) after stopping tyrosine kinase inhibitors.
kinase inhibitor (TKI) therapy in Ph+ CML patients in chronic phase (CP) who meet strict eligibility criteria. The approval was based on efficacy and safety findings from the 48-week analysis of two open label trials, ENESTfreedom and ENESTop.

**Votrient** (pazopanib) is a small molecule tyrosine kinase inhibitor that targets a number of intracellular proteins to limit tumor growth and cell survival. It is approved in the US for the treatment of patients with advanced renal cell carcinoma (aRCC), and in the EU for first-line treatment of adult patients with aRCC and for patients who have received prior cytokine therapy for advanced disease. RCC is the most common type of kidney cancer in adults, and nearly one-fifth of patients have advanced RCC at the time of diagnosis. **Votrient** is also indicated for the treatment of patients with advanced soft tissue sarcoma (STS) who have received prior chemotherapy (efficacy in adipocytic STS or gastrointestinal stromal tumors has not been demonstrated). STS is a type of cancer which can arise from a wide variety of soft tissues including muscle, fat, blood vessel and nerves. **Votrient** is approved in more than 100 countries worldwide for aRCC and in more than 90 countries for advanced STS. **Votrient** was acquired from GSK.

**Zykadia** (ceritinib) is an oral, selective inhibitor of anaplastic lymphoma kinase (ALK), a gene that can fuse with others to form an abnormal “fusion protein” that promotes the development and growth of certain tumors in cancers including non-small cell lung cancer (NSCLC). **Zykadia** is approved in over 70 countries worldwide and indicated for the treatment of adult patients with ALK positive advanced NSCLC previously treated with crizotinib. In May 2017, the FDA approved the expanded use of **Zykadia** in first-line ALK-positive metastatic NSCLC, providing a new treatment option for previously untreated patients. The European Commission approved the first line treatment of patients with advanced NSCLC whose tumors are ALK-positive in June 2017. Approximately 3-7% of all patients with NSCLC have an ALK gene rearrangement.

**Novartis Pharmaceuticals**

**Cardio-Metabolic**

**Entresto** (sacubitril/valsartan) is now approved in 86 countries and launched in more than 40 countries as of July 2017, and has been prescribed to more than 290,000 patients with heart failure with reduced ejection fraction worldwide since July 2015. **Entresto**, an angiotensin receptor nepriylsin inhibitor (ARNI), demonstrated significant superiority in the reduction of risk of cardiovascular mortality or heart failure hospitalization (20%) over and above enalapril in the PARADIGM-HF trial, representing the first major advance in heart failure in over two decades.

**Galvus** (vildagliptin) and **Eucreas** (vildagliptin and metformin single-pill combination) are indicated for the treatment of type 2 diabetes. **Galvus** and **Eucreas** were first approved in 2007. **Galvus** is currently approved in more than 130 countries, including the EU, Japan (as **Equa**), Latin America and Asia-Pacific. **Eucreas** was the first single pill combination of a DPP-4 inhibitor and metformin approved in Europe. It is also currently approved in more than 125 countries and marketed under the trade name **GalvusMet**, **Galvumet**, **EquMet**, **Sobrea**, **Zomarist Met**, **Jaira M** and **Glucemix Met**. In 2012, **Galvus** received approval in the EU for expanded use as a second-line monotherapy for type 2 diabetes patients who cannot take metformin. In 2012, the European Commission approved the use of **Galvus** and **Eucreas** in combination with other diabetes treatments. The first new approval was for the use of vildagliptin in combination with insulin, with or without metformin, for patients with type 2 diabetes when diet, exercise and a stable dose of insulin do not result in glycemic control. The second approval was for the use of vildagliptin in triple combination with metformin and a sulphonylurea for the treatment of type 2 diabetes when diet and exercise plus dual therapy with these two agents do not provide adequate glycemic control. **Galvus** monotherapy indication was approved in China in April 2015. **Eucreas** was approved in Japan in September
2015 under the name *Equmet* as the first single-pill metformin/DPP-4 inhibitor combination approved in that country.

**Immunology and Dermatology**

**Cosentyx** (secukinumab) is a fully human monoclonal antibody that selectively neutralizes circulating interleukin-17A (IL-17A). Cosentyx was launched in February 2015 and more than 90,000 patients have been treated with Cosentyx to date. Cosentyx is the only fully human monoclonal antibody that selectively neutralizes interleukin-17A (IL-17A) and is approved to treat psoriasis (PsO), ankylosing spondylitis (AS) and psoriatic arthritis (PsA). In clinical trials, Cosentyx has shown superiority over Enbrel® and Stelara®, providing rapid and sustainable efficacy for patients with PsO. In January 2015, Cosentyx became the first IL-17A inhibitor and biologic approved in the EU as a first-line systemic treatment of moderate-to-severe plaque PsO in adult patients, and in the US as a treatment for moderate-to-severe plaque PsO in adult patients who are candidates for systemic therapy or phototherapy. Cosentyx is approved for the treatment of moderate-to-severe plaque PsO in 77 countries, including the US, EU, Switzerland, Canada and Australia. Cosentyx is also approved in around 70 countries for the treatment of adults with AS and PsA, including the US, EU, Canada, and Australia. In Japan, Cosentyx is approved for the treatment of moderate-to-severe plaque PsO, pustular PsO, and PsA.

**Ilaris** (canakinumab) is a human monoclonal antibody that selectively binds and neutralizes interleukin-1β (IL-1β), a pro-inflammatory cytokine. Since 2009, Ilaris has been approved in more than 70 countries for the treatment of children and adults suffering from cryopyrin-associated periodic syndromes, a group of rare disorders characterized by chronic recurrent fever, urticaria, occasional arthritis, deafness, and potentially life-threatening amyloidosis. In 2013, Ilaris was approved in the EU for the treatment of acute gouty arthritis in patients who cannot be managed with standard of care, and in the US, EU and other countries for the treatment of systemic juvenile idiopathic arthritis. In 2016, the FDA granted three simultaneous approvals for the expanded use of Ilaris to treat three rare and distinct types of periodic fever syndromes: tumor necrosis factor-receptor associated periodic syndrome, hyperimmunoglobulin D syndrome/mevalonate kinase deficiency and familial Mediterranean fever. Ilaris is the first and only FDA approved biologic treatment for these rare autoinflammatory diseases, which are also referred to as Hereditary Periodic Fevers. The European Commission approved Ilaris for the same three Periodic Fever Syndromes in February 2017. In 2016, the European Commission also approved a license extension for Ilaris to treat patients with Adult-Onset Still’s Disease.

**Myfortic** (enteric-coated formulation of mycophenolate sodium) is approved in more than 90 countries for the prevention of acute rejection of kidney allografts, and is indicated in combination with cyclosporine and corticosteroids. Myfortic was first approved in the US in 2004 and in the EU in 2003.

**Neoral** (cyclosporine, USP Modified) is an immunosuppressant to prevent organ rejection following a kidney, liver, or heart transplant. Neoral is also approved for use in lung transplant in many countries outside of the US. This micro-emulsion formulation of cyclosporine is also indicated for the treatment of selected autoimmune disorders such as endogenous uveitis, nephrotic syndrome, psoriasis, rheumatoid arthritis and atopic dermatitis. First launched in 1995, Neoral is marketed in approximately 100 countries.

**Xolair** (omalizumab) is a recombinant, DNA-derived, humanized IgG1K monoclonal antibody. Xolair is designed to block IgE, which limits the release of mediators in the early and late phases of the allergic inflammatory cascade. Xolair is approved in 85 countries, including the US, Canada, Australia, the EU countries, Switzerland and, since March 2017, in Japan as a treatment for chronic spontaneous urticaria (CSU), also known as chronic idiopathic urticaria (CIU). Xolair has been launched for CSU/CIU in 50 countries, including the US, Switzerland, Canada and most EU countries. Xolair is also a treatment for moderate-to-severe or severe
persistent allergic asthma (SAA), which is addressed below in the Respiratory section. All Xolair sales are booked in the Respiratory franchise. Novartis co-promotes Xolair with Genentech in the US and share a portion of operating income, but does not record any US sales. Novartis records all sales of Xolair outside the US.

Zortress/Certican (everolimus) is an oral inhibitor of the mTOR pathway, indicated to prevent organ rejection following solid organ transplantation. Zortress/Certican, is approved in more than 100 countries to prevent organ rejection in adult heart and kidney transplant patients, continued to show growth. It is also approved for liver transplant patients in over 70 countries, including EU countries and the US. Everolimus, the active ingredient in Zortress/Certican, is marketed for other indications under the trade names Afinitor/Votubia. Everolimus is also exclusively licensed to Abbott and sublicensed to Boston Scientific for use in drug eluting stents.

Ophthalmology

Lucentis (ranibizumab) is a recombinant humanized high affinity antibody fragment that binds to vascular endothelial growth factor A (VEGF-A), a key mediator of intraocular neovascularization. Lucentis is an anti-VEGF therapy specifically designed for the eye, minimizing systemic exposure. Lucentis is approved for six indications: neovascular age-related macular degeneration (nAMD), visual impairment due to diabetic macular edema (DME), visual impairment due to macular edema secondary to branch retinal vein occlusion (BRVO), visual impairment due to macular edema secondary to central retinal vein occlusion (CRVO), visual impairment due to choroidal neovascularization secondary to pathologic myopia (myopic CNV) and visual impairment due to choroidal neovascularization (CNV) secondary to other pathologies. In 2016, the EC approved Lucentis to treat patients with visual impairment due to rare conditions causing choroidal neovascularization (CNV). This new indication is now approved in 51 countries in addition to the EU. Further submissions have been filed in 27 countries, including Switzerland. The Lucentis pre-filled syringe has now launched in 32 countries. Lucentis is licensed from Genentech, and Novartis holds the rights to commercialize the product ex-US. Genentech holds the rights to commercialize Lucentis in the US.

Travoprost Group, comprising Travatan (travoprost), TravatanZ (travoprost) and Duotrov (travoprost and timolol), are indicated for the reduction of elevated intraocular pressure (IOP) in patients with open-angle glaucoma or who have ocular hypertension. Single agent travoprost products (Travatan, TravatanZ, Travatan BAK-Free and Izba) are prescribed as first-line agents. DuoTrav is a fixed-dose combination solution of the prostaglandin analogue travoprost with the beta-blocker timolol, approved as a second-line treatment, marketed in more than 140 countries, including countries of the EU, Canada and China.

Systane Group is a portfolio of ocular health products, most of which are indicated for the temporary relief of burning and irritation due to dryness of the eye. The Systane portfolio includes Systane Ultra (polyethylene glycol 400 and propylene glycol), Systane Balance (propylene glycol) and Systane Hydration (polyethylene glycol 400, propylene glycol and hyaluronic acid). They are treatments for daily and nighttime symptomatic relief, as well as products for everyday lid hygiene, and for discomfort associated with contact lens wear. They are also indicated for the temporary relief of burning and irritation due to dryness of the eye. Systane Ultra is sold in more than 80 countries, including the US, Canada, EU countries, Latin America and Asia. Systane Balance is sold in more than 60 countries. Systane Hydration was launched in March 2015 and is now sold in more than 35 countries across Europe, Canada and Australia.

Topical Olopatadine Group, including Patanol (olopatadine), Pataday (olopatadine) and Pazeo (olopatadine) are olopatadine hydrochloride ophthalmic solutions of different concentrations that are approved to treat the signs and symptoms of allergic conjunctivitis (Patanol), as well as ocular itching associated with allergic conjunctivitis (Pataday and
Pazo). Olopatadine products are marketed in more than 100 countries, including the US, countries of the EU, Canada and China.

**Respiratory**

**Ultibro Breezhaler** (indacaterol/glycopyrronium bromide)/**Utibron Neohaler** (indacaterol/glycopyrrolate) is a fixed-dose combination of the long-acting beta₂-adrenergic agonist (LABA) indacaterol and the long-acting muscarinic antagonist (LAMA) glycopyrronium bromide. *Ultibro Breezhaler* was approved in the EU in 2013 as a once-daily maintenance bronchodilator treatment to relieve symptoms in adult patients with chronic obstructive pulmonary disease (COPD), and, in Japan, the MHLW approved *Ultibro Inhalation Capsules* delivered through the low resistance *Breezhaler* inhalation device, for relief of various symptoms due to airway obstruction in COPD (chronic bronchitis, emphysema). In October 2015, the combination was approved in the US under the name *Utibron Neohaler* as a twice-daily dual bronchodilator treatment for the long-term maintenance treatment of airflow obstruction in patients with COPD, including chronic bronchitis and/or emphysema. The combination is approved in more than 90 countries and launched in more than 50 countries. The LAMA glycopyrronium bromide is approved individually as once-daily *Seebrir Breezhaler* in the EU, *Seebrir (glycopyrronium) Inhalation Capsules* 50 mcg administered through the *Breezhaler* device in Japan, and twice-daily *Seebrir Neohaler* in the US, where the active ingredient is known as glycopyrrolate. It is now approved in more than 90 countries. Glycopyrronium bromide and certain use and formulation intellectual property were exclusively licensed to Novartis in April 2005 by Sosei and Vectura. The LABA indacaterol is approved individually as once-daily *Onbrez Breezhaler* in the EU, *Onbrez Inhalation Capsules* delivered through the *Breezhaler* inhalation device in Japan, and *Arcapta Neohaler* in the US. It is now approved in more than 100 countries worldwide. In December 2016, Sunovion Pharmaceuticals Inc. acquired the US commercialization rights for *Utibron Neohaler, Arcapta Neohaler* and *Seebrir Neohaler*. Novartis will continue to market *Ultibro Breezhaler, Onbrez Breezhaler and Seebrir Breezhaler* outside of the US.

**Xolair** (omalizumab) is approved for the treatment of moderate-to-severe, or severe, persistent allergic asthma in more than 90 countries, including the US since 2003, the EU since 2005, and Japan since 2009. *Xolair* is provided as lyophilized powder for solution for injection, and in addition as liquid formulation in a pre-filled syringe in most European countries. We co-promote *Xolair* with Genentech in the US and share a portion of operating income, but we do not record any US sales. Novartis records all sales of *Xolair* outside the US.

**Neuroscience**

**Gilenya** (fingolimod) is the first oral therapy approved to treat relapsing forms of multiple sclerosis (RMS). In the EU, *Gilenya* is indicated for adult patients with high disease activity despite treatment with at least one disease modifying agent, or rapidly evolving severe relapsing-remitting MS. *Gilenya* impacts four key measures of disease activity: relapses, MRI lesions, brain shrinkage (brain volume loss) and disability progression. Its effectiveness on all of these measures has been consistently shown in multiple controlled clinical studies and in the real-world setting. As of November 2016, more than 180,000 patients have been treated in clinical trials and in a post-marketing setting with more than 395,000 total patient years of exposure. *Gilenya* is currently approved in more than 80 countries around the world. *Gilenya* is licensed from Mitsubishi Tanabe Pharma Corporation.

**Established Medicines**

**Diovan** (valsartan), together with **Diovan HCT/Co-Diovan** (valsartan and hydrochlorothiazide), is an angiotensin II receptor blocker (ARB). *Diovan* is the only agent in its class approved to treat all of the following: high blood pressure (including children six to 18 years), high-risk heart attack survivors and patients with heart failure. First launched in 1996,
Diovan is available in more than 120 countries for treating high blood pressure, in more than 90 countries for heart failure, and in more than 70 countries for heart attack survivors. First launched in 1997, Diovan HCT/Co-Diovan is approved in over 100 countries worldwide.

Exelon (rivastigmine tartrate) and Exelon Patch (rivastigmine transdermal system) are cholinesterase inhibitors indicated for the treatment of Alzheimer's disease (AD) dementia and Parkinson's disease (PD) dementia. They are the oral and transdermal formulations, respectively, of the cholinesterase inhibitor rivastigmine. Exelon capsules have been available since 1997 to treat mild to moderate AD dementia and are approved in more than 85 countries. In 2006, Exelon became the only cholinesterase inhibitor to be approved for mild to moderate PD dementia in addition to AD in both the US and EU. Exelon Patch was approved in 2007 in the US and EU and has been approved for the treatment of mild-to-moderate AD in more than 85 countries, including more than 20 countries where it is also approved for Parkinson's disease dementia. The once-daily Exelon Patch has shown comparable efficacy and superior tolerability to the highest recommended doses of Exelon capsules, with significant improvement in cognition and overall functioning compared to placebo. In 2013, the FDA expanded the approved indication for Exelon Patch to also include the treatment of patients with severe Alzheimer’s disease. In 2013, European Marketing Authorization was obtained for the higher dose in mild-to-moderate AD. The higher dose has been approved in more than 50 countries. The severe indication has now been approved in more than 10 countries.

Exforge (valsartan and amlodipine besylate) is a single-pill combination of the ARB Diovan and the calcium channel blocker amlodipine besylate. First approved for the treatment of high blood pressure in Switzerland in 2006, and in the US and EU in 2007, it is now available in more than 100 countries. Exforge HCT (valsartan, amlodipine besylate and hydrochlorothiazide) is a single pill combining three widely prescribed high blood pressure treatments: an ARB, a calcium channel blocker and a diuretic (hydrochlorothiazide). Exforge HCT was approved in the EU and the US in 2009, and is now available in more than 75 countries.

Ritalin, Ritalin LA, Focalin and Focalin XR (methylphenidate HCl, methylphenidate HCl extended release, dexmethylphenidate HCl and dexmethylphenidate HCl extended release) are indicated for the treatment of attention deficit hyperactivity disorder (ADHD) in children. Ritalin LA and Focalin XR are additionally indicated for ADHD in adults. Ritalin is also indicated for narcolepsy. Ritalin was first marketed during the 1950s and is available in more than 70 countries. Ritalin LA is available in more than 30 countries. Focalin comprises the active d-isomer of methylphenidate and therefore requires half the dose of Ritalin. Focalin and Focalin XR are available in the US.

Voltaren/Cataflam (diclofenac sodium/potassium/resinate/free acid) is a leading non-steroidal anti-inflammatory drug (NSAID) for the relief of symptoms in rheumatic diseases such as rheumatoid arthritis and osteoarthritis, and for various other inflammatory and pain conditions. Voltaren/Cataflam was first registered in 1973 and is available in more than 140 countries. This product is marketed by the Innovative Medicines Division in a wide variety of dosage forms, including tablets, drops, suppositories, ampoules and topical therapy. Our Sandoz Division also markets generic versions of the product. In addition, we have licensed the Voltaren trademarks to our consumer healthcare joint venture with GSK to be used in the marketing of low-dose oral forms and the topical form of Voltaren as over-the-counter products.
Key Development Projects

**ACZ885** (canakinumab) was first approved in 2009 for cryopyrin-associated periodic syndromes (CAPS) as *Ilaris*. Novartis announced positive topline results from the global Phase III CANTOS study investigating the efficacy, safety and tolerability of ACZ885 in combination with standard of care in people with a prior heart attack and inflammatory atherosclerosis. CANTOS met the primary endpoint, demonstrating that when used in combination with standard of care, ACZ885 reduces the risk of major adverse cardiovascular events (MACE) in patients with a prior heart attack and inflammatory atherosclerosis. MACE is a composite of cardiovascular death, non-fatal myocardial infarction and non-fatal stroke. ACZ885 has been shown to reduce cardiovascular risk in people with a prior heart attack by selectively targeting inflammation.

**Afinitor/Votubia** and **Afinitor Disperz** (everolimus) are oral inhibitors of the mTOR pathway. The Phase III EXIST-3 clinical trial in patients with tuberous sclerosis complex (TSC) who have refractory partial-onset seizures (uncontrollable seizures localized to a specific area of the brain) found that adjunctive therapy with everolimus significantly reduced refractory seizures associated with TSC compared to placebo in patients receiving a stable regimen of 1-3 anti-epileptic drugs. This data was published in *The Lancet* in September 2016. In December 2016, *Votubia* was recommended by the CHMP for approval as an adjunctive treatment for patients aged two years and older whose refractory partial-onset seizures, with or without secondary generalization, are associated with TSC.

**AMG 334** (erenumab) is an anti-CGRP receptor monoclonal antibody designed for migraine prevention. It is the only anti-CGRP receptor monoclonal antibody that is fully human and binds selectively to the calcitonin gene-related peptide (CGRP) receptor, believed to play a critical role in mediating the incapacitating pain of migraine. In 2016, we announced positive data from four Phase II and III clinical studies involving more than 2,600 patients experiencing four or more migraine days per month. Across the comprehensive clinical program, AMG 334 demonstrated clinically meaningful, statistically significant and sustained efficacy in reducing the number of migraine days per month versus placebo. AMG 334 also showed significant improvements on the impact migraine had on patients’ disability and quality of life (emotional well-being and everyday life, such as missed work days or time spent away from friends and family), compared to placebo. In all studies, the safety profile of AMG 334 was comparable to placebo. In May 2017, Novartis and Amgen submitted regulatory filing to both the FDA and EMA for review. Novartis and Amgen will co-commercialize erenumab in the US. Amgen has exclusive commercialization rights in Japan and Novartis has exclusive commercialization rights in the rest of world. Both companies will continue co-development.

**Arzerra** (ofatumumab) is a human monoclonal antibody that is designed to target the CD20 molecule found on the surface of chronic lymphocytic leukemia (CLL) cells and normal B-lymphocytes. Results from the Phase III PROLONG study evaluating ofatumumab maintenance therapy versus no further treatment (observation) in patients with relapsed CLL who responded to induction treatment at relapse formed the basis for submissions made in 2015 to the EMA and FDA for this indication. In September 2015, the FDA granted Priority Review for ofatumumab as maintenance therapy in relapsed CLL, and in January 2016 the FDA approved *Arzerra* for extended treatment of patients who are in complete or partial response after at least two lines of therapy for recurrent or progressive CLL. In the EU, the CHMP did not recommend approval for *Arzerra* as maintenance treatment for patients with relapsed CLL. Results from the Phase III COMPLEMENT 2 study in 2015 showed that treatment with ofatumumab plus fludarabine and cyclophosphamide significantly improved median progression-free survival by 54% compared to treatment with fludarabine and cyclophosphamide alone in patients with relapsed CLL. Results of this study were submitted to the EMA and FDA in 2016. In May 2016, the FDA granted Priority Review for ofatumumab in combination with fludarabine and cyclophosphamide in relapsed CLL and approved this indication in August 2016. In November 2016, the CHMP issued a positive opinion for ofatumumab in combination with fludarabine and cyclophosphamide in relapsed CLL, which...
was followed in December 2016 by European Commission approval of the product for use in this indication. A Phase III trial of Arzerra is also underway to investigate ofatumumab in refractory non-Hodgkin’s lymphoma. Arzerra is marketed under a license agreement between Novartis and Genmab A/S. Novartis is also investigating ofatumumab (disclosed as OMB157) in two Phase III studies for relapsing multiple sclerosis.

BAF312 (siponimod) is an oral, second-generation sphingosine 1-phosphate (S1P) receptor modulator in Phase III development for multiple sclerosis. BAF312 binds selectively to the S1P receptors 1 and 5, and readily penetrates into the central nervous system. Positive results from the EXPAND Phase III study, evaluating the efficacy and safety of BAF312 in 1,651 patients with secondary progressive multiple sclerosis, were presented in September 2016. Data showed BAF312 had meaningful and significant effects on disability progression, relapses and MRI disease activity in people with secondary progressive MS. Following recent discussions with the FDA, Novartis intends to submit an application for the approval of oral once-daily BAF312 in relapsing multiple sclerosis. The submission will be supported by data from the Phase II BOLD study in relapsing remitting MS and the larger Phase III EXPAND study in secondary progressive MS and label is expected to reflect the unique characteristics of the advanced patient population studied in EXPAND. Novartis anticipates submitting BAF312 datasets for FDA review in early 2018, following a pre-New Drug Application (NDA) meeting in the third quarter of 2017.

BYL719 (alpelisib) is an orally bioavailable, alpha isoform-specific PI3K inhibitor. In breast cancer cell lines harboring PIK3CA mutations, BYL719 has been shown to potentially inhibit the PI3K/AKT/mTOR pathway and have antiproliferative effects. In addition, cancer cell lines with PIK3CA mutations were more sensitive to alpelisib than those without the mutation across a broad range of different cancers. BYL719 is being studied in the Phase III SOLAR-1 trial in combination with fulvestrant in men and postmenopausal women with hormone receptor-positive advanced breast cancer who received prior treatment with aromatase inhibitor and a Phase II trial to determine the maximum tolerated dose in combination with fulvestrant in PIK3CA mutated estrogen receptor-positive breast cancer patients.

CNP520 is a BACE inhibitor, designed to prevent the production of different forms of the amyloid protein which accumulates in the brains of individuals with Alzheimer’s Disease (AD). CNP520 is being co-developed with Amgen. It is an oral medication currently in Phase II/III trials. The studies are conducted in collaboration with Banner Alzheimer’s Institute as part of the Alzheimer’s Prevention Initiative (API). The API Generation Program will focus on cognitively healthy, high-risk older adults to determine whether treatment can prevent or delay the emergence of symptoms of the disease. Generation Study 1 was initiated in 2015, while Generation Study 2 is starting in July 2017. CNP520 received Fast Track designation from the FDA in December 2016.

Cosentyx (secukinumab) is a fully human monoclonal antibody that selectively neutralizes circulating IL-17A. In January 2016, Cosentyx was approved by the FDA for the treatment of adults with ankylosing spondylitis (AS) and adults with psoriatic arthritis (PsA). In October 2016, the Swiss health authority Swissmedic also approved Cosentyx for the treatment of AS and PsA. New results for Cosentyx published in the Journal of the American Academy of Dermatology from the head-to-head CLEAR study showed that Cosentyx remains superior to Stelara® in sustaining skin clearance (PASI 90 to PASI 100) at 52 weeks for adults with moderate-to-severe psoriasis. In addition, long-term data from the Phase III SCULPTURE study presented at a European medical meeting in October 2016 showed that Cosentyx delivers high and long-lasting skin clearance in patients with moderate-to-severe plaque psoriasis out to four years of treatment. Secukinumab is also in Phase III development for non-radiographic axial spondyloarthritis, and new head-to-head clinical trials are planned in AS and PsA to compare Cosentyx versus adalimumab.

CTL019 (lisadenleucel) is an investigational therapy that uses chimeric antigen receptors (CARs) to direct the patient’s own immune system to fight certain types of cancer. CARs are
engineered proteins that enable patient’s own T cells to specifically seek out target proteins present on a patient’s cancerous tumor. When these CAR-T cells are re-introduced into the patient’s blood, they demonstrate the potential to bind to the cancer cells and destroy them. CTL019 targets a protein called CD19 that is expressed with a number of B-cell malignancies. Data presented in June 2017 from the pivotal global Phase II ELIANA trial of CTL019 in relapsed/refractory (r/r) pediatric and young adult patients with B-cell acute lymphoblastic leukemia showed that 83% of patients achieved complete remission or complete remission with incomplete blood count recovery within three months post CTL019 infusion. No minimal residual disease was detected among responding patients. In addition, the estimated relapse-free rate was 75% at six months and 64% at 12 months among responders. Earlier in the year a Biologics License Application (BLA) was submitted for CTL019 in pediatric and young adult patients with r/r B-cell acute lymphoblastic leukemia (ALL), and the FDA granted Priority Review for this filing. In April 2017, the FDA granted Breakthrough Therapy Designation to CTL019 for the treatment of adult patients with r/r diffuse large B-cell lymphoma (DLBCL). In June 2017, interim results from the global, pivotal CTL019 trial JULIET in adult patients with r/r DLBCL were presented and the primary endpoint of best overall response rate (ORR) was met. In July 2017, the FDA held an Oncologic Drugs Advisory Committee meeting to discuss the Biologics License Application (BLA) of CTL019 for the treatment of r/r pediatric and young adult patients with B-cell ALL. The committee unanimously (10-0) recommended approval of CTL019 on July 12, 2017. The FDA will consider the vote as it reviews the BLA, although it is not obligated to follow the recommendation.

**CTL119** is a humanized CD19-directed CAR-T cell therapy in initial clinical development for multiple B-cell malignancies. Findings from a pilot study with CTL119 in combination with ibrutinib in patients with r/r chronic lymphocytic leukemia (CLL) were presented at the Annual Meeting of the American Society of Clinical Oncology (ASCO) in 2017. The pilot study demonstrated that eight of nine evaluable patients had no signs of CLL in their bone marrow at three months as tested by flow cytometry and/or analysis for minimal residual disease. One of those patients had a partial response.

**EMA401** is a novel angiotensin II Type 2 receptor (AT₂R) antagonist in Phase II development. Targeting AT₂R is an emerging approach to neuropathic pain treatment. AT₂R antagonists block the pain signaling pathways in the peripheral nervous system. Positive results from a Phase II clinical trial of EMA401 in post-herpetic neuralgia, a painful condition that develops in some people following herpes zoster (shingles), were published in a major medical journal in February 2014. In addition, thus far, EMA401 has not been associated with central nervous system side effects such as dizziness or confusion, which are typically associated with existing therapies. Novartis has recently initiated a Phase Ib, dose-ranging study with EMA401 in post-herpetic neuralgia.

**Entresto** (sacubitril/valsartan) is a first-in-class angiotensin receptor/neprilysin inhibitor approved and marketed for the treatment of chronic heart failure with reduced ejection fraction (HFrEF). In addition, Novartis is conducting multiple studies of Entresto as part of the FortiHFy clinical program. This includes two large outcome studies. The first, PARAGON-HF, a Phase III trial of Entresto in patients with chronic heart failure with preserved ejection fraction, has completed enrollment with results expected in 2019. Novartis has commenced recruitment in PARADISE-MI, a Phase IIIb trial for patients at high risk for heart failure after an acute myocardial infarction, with results expected in 2020.

**FTY720** (fingolimod) is a sphingosine 1-phosphate receptor modulator approved for the treatment of relapsing forms of multiple sclerosis as Gilenya. A Phase III study of fingolimod in pediatric multiple sclerosis was initiated in 2013. Results from the study are anticipated in 2017.

**Jakavi** (ruxolitinib) is an oral inhibitor of the JAK 1 and JAK 2 tyrosine kinases. The Phase III study ReTHINK was initiated in the first quarter of 2016 to evaluate the efficacy and safety of
Jakavi in early myelofibrosis patients. Novartis licensed ruxolitinib from Incyte Corporation for development and commercialization in the indications of oncology and hematology outside the US. In the second quarter of 2016 the license was amended to also include rights to research, develop and commercialize ruxolitinib in graft-versus-host disease outside the US. Ruxolitinib is marketed in the US as Jakafi® by Incyte Corporation.

Kisqali (ribociclib) is a cyclin dependent kinase inhibitor, a class of drugs that help slow the progression of cancer by inhibiting two proteins called cyclin dependent kinase 4 and 6 (CDK4/6). Following a Breakthrough Therapy designation in March 2017, Kisqali was approved by the US FDA in combination with an aromatase inhibitor as initial endocrine-based therapy for treatment of postmenopausal women with hormone receptor positive, human epidermal growth factor receptor-2 negative (HR+/HER2-) advanced or metastatic breast cancer. In June 2017, the Committee for Medicinal Products for Human Use (CHMP) of the European Medicines Agency adopted a positive opinion recommending approval of Kisqali in combination with an aromatase inhibitor for treatment of postmenopausal women with HR+/HER2- locally advanced or metastatic breast cancer as initial endocrine-based therapy. Novartis is continuing to assess Kisqali through the MONALEESA clinical trial program, which includes two additional Phase III trials, MONALEESA-3 and MONALEESA-7. These trials are evaluating Kisqali in combination with multiple endocrine therapy partners across a broad range of patients, including premenopausal women. MONALEESA-3 is evaluating Kisqali in combination with fulvestrant compared to fulvestrant alone in postmenopausal women with HR+/HER2- advanced breast cancer who have received no or a maximum of one prior endocrine therapy. MONALEESA-7 is investigating Kisqali in combination with endocrine therapy and goserelin compared to endocrine therapy and goserelin alone in premenopausal women with HR+/HER2- advanced breast cancer who have not previously received endocrine therapy. These trials are fully enrolled. Kisqali was developed by Novartis as part of a drug discovery collaboration with Astex Pharmaceuticals.

LIK066 is an inhibitor of the sodium-glucose co-transporter-1 (SGLT1) and sodium-glucose co-transporter-2 (SGLT2). The dual mechanism (renal and intestinal) acts to improve multiple metabolic end points including glycemic control, weight, blood pressure and lipid bio markers. We expect to initiate Phase II dose ranging studies for obesity in the first half of 2017.

LJN452 is a potent, non-bile acid, Farnesoid X receptor (FXR) agonist, which is being developed for the treatment of nonalcoholic steatohepatitis (NASH). LJN452 has been shown to reduce steatosis, inflammation, and fibrosis in animal models, alongside a favorable safety profile in first-in-human studies. This oral treatment is designed to break the cycle of fatty build-up in the liver and harness the body’s built-in mechanisms for coping with excess bile acid. Recruitment is underway for the first LJN452 clinical study in NASH patients.

OMB157 (ofatumumab) is a fully human monoclonal antibody administered by subcutaneous injection in development for multiple sclerosis (MS). OMB157 works by binding to the CD20 molecule on the B cell surface and inducing B cell depletion. Positive Phase Ib results in MS patients were presented in 2014 and showed a 98% reduction in the number of new brain lesions in the first 24 weeks after ofatumumab administration. The unique characteristics, dose and dosing regimen of OMB157 allow faster B cell recovery following treatment suspension, enabling more controlled management of complex patients. Novartis initiated a Phase III program for OMB157 in relapsing MS in August 2016. We expect to complete the Phase III program in MS in 2019. Ofatumumab is marketed by Novartis for oncology indications as an intravenous infusion under the brand name Arzerra.

Pegpleranib is an oligo-nucleotide aptamer that inhibits the action of platelet-derived growth factor (PDGF). The pegpleranib Phase III program originally consisted of three clinical trials to evaluate the safety and efficacy of pegpleranib in combination with anti-VEGF drugs for the treatment of neovascular age related macular degeneration (nAMD). In December 2016, Novartis announced initial topline results from two pivotal Phase III clinical studies evaluating the safety and efficacy of pegpleranib in combination with Lucentis (ranibizumab) for the
treatment of nAMD. These studies, OPH1002 and OPH1003, sponsored by Ophthotech Corporation, did not meet the primary endpoint of superiority for the pegpleranib and ranibizumab combination therapy, measured as best corrected visual acuity in terms of additional letter gains over ranibizumab monotherapy. In November 2015, Genentech entered into an agreement with Novartis to participate in certain rights related to the Novartis licensing and commercialization agreement with Ophthotech Corporation for pegpleranib. We continue to hold the license for the rights to develop and exclusively market pegpleranib outside the US.

QAW039 (fevipirant) is an oral prostaglandin D2 inhibitor that is being developed to reduce the frequency and severity of asthma exacerbations, particularly in patients with moderate to severe asthma. This compound is designed to block the activity of T-helper type-2 (Th2) cells, which are thought to contribute to the disease by releasing signals that maintain eosinophilic airway inflammation. In a Phase II study completed in August 2015, QAW039 reduced sputum eosinophils, drivers of airway inflammation, in patients with persistent moderate-to-severe asthma. Pivotal Phase III trials are underway in severe asthma.

QVM149 (indacaterol, glycopyrronium, mometasone furoate) is a once daily fixed-dose triple combination therapy being investigated in moderate-to-severe asthma patients who are uncontrolled on a long-acting beta-agonist (LABA) combined with an inhaled corticosteroid (ICS) or who are already taking a triple combination LABA, long-acting muscarinic antagonist (LAMA) and ICS. QVM149 consists of indacaterol (a LABA), glycopyrronium (a LAMA) and mometasone furoate (an ICS) delivered via the Breezhaler device. QVM149 is currently in Phase III clinical trials. This Phase III program is also designed to deliver data to support regulatory filings by Novartis for QMF149, a once daily combination of indacaterol and mometasone furoate. This Phase III program is to support registration of QVM149 and QMF149 outside the US only.

RTH258 (brolucizumab) is a novel anti-vascular endothelial growth factor (anti-VEGF) agent that is currently being tested in neovascular age-related macular degeneration (nAMD) patients. RTH258 is a single chain antibody fragment that may be longer-acting than currently approved treatments for AMD, potentially enabling patients to extend the time between treatments. The Phase III HAWK and HARRIER trials in nAMD each met their primary and key secondary endpoints. We expect the results of these trials to be presented later in 2017.

Rydatp (PKC412; midostaurin) is an oral, multi-targeted, kinase inhibitor for treatment of patients with FLT3-mutated acute myeloid leukemia (AML) and advanced systemic mastocytosis (SM). In the RATIFY study, patients who received PKC412 plus standard induction and consolidation chemotherapy and as monotherapy up to one year for maintenance experienced a 23% improvement in overall survival compared to those treated with standard induction/consolidation chemotherapy and placebo. The median overall survival for patients in the PKC412 treatment group was 74.7 months, versus 26.0 months for patients in the placebo group. PKC412 is the first compound to illustrate an overall survival benefit targeting FLT3 in AML. In an advanced SM pivotal Phase II study, PKC412 demonstrated an overall response rate, defined as a major or partial response, of 60% in patients. The median duration of response was 24.1 months. These data are the basis for the worldwide regulatory filings for PKC412 for newly diagnosed FLT3-mutated AML and advanced SM. The full analysis of the Rydatp phase III RATIFY (CALGB 10603) trial data were published in the New England Journal of Medicine in June 2017.

SEG101 (crizanlizumab, formerly SelG1) is a humanized anti-P-selectin monoclonal antibody that is being investigated in the reduction of vaso-occlusive pain crises (VOC) in patients with sickle cell disease (SCD), a hereditary blood disorder characterized by sickle-shaped red blood cells. VOC is a hallmark of SCD. Results from the SUSTAIN study, which met its primary endpoint showed that crizanlizumab reduced the median annual rate of sickle cell-related pain crises compared to placebo by 45.3% in SCD patients with or without hydroxyurea therapy who were given the 5mg/kg dose every 4 weeks. Health authority
submissions are planned for the fourth quarter of 2018 in the US and in January 2019 in the EU.

**Signifor** (pasireotide) is a somatostatin analogue in development as a long-acting release formulation for patients with Cushing’s disease. An application has been submitted to the EMA for this indication.

**Tafinlar** (dabrafenib) targets the serine/threonine kinase BRAF in the RAS/RAF/MEK/ERK pathway and **Mekinist** (trimetinib) targets the threonine/tyrosine kinases MEK1 and MEK2 in the MAP kinase pathway, resulting in dual blockade of this pathway, which is the main escape mechanism for resistance. **Tafinlar + Mekinist** is the first combination of BRAF and MEK inhibitors to report three years of follow-up survival data in two Phase III studies in BRAFv600+ unresectable or metastatic patients. A five year survival benefit was shown in a landmark study of Tafinlar+Mekinist, presented at ASCO 2017 in June, the longest follow up to date of a BRAF and MEK inhibitor combination therapy in patients with BRAF V600-mutant metastatic melanoma. A Phase III study is also underway for BRAF V600 mutation positive melanoma patients in the adjuvant setting. The **Tafinlar + Mekinist** combination received EU and US approval for the treatment of BRAF V600-positive advanced non-small cell lung cancer (NSCLC) in April and June 2017, respectively.

**Tasigna** (nilotinib) is a selective tyrosine-kinase inhibitor that inhibits the BCR-ABL protein produced by the Philadelphia chromosome, which is found in most people who have chronic myeloid leukemia (CML). Novartis has an ongoing global clinical trial program to evaluate the potential for Philadelphia chromosome positive (Ph+) CML patients to maintain remission after stopping nilotinib. **ENESTfreedom, ENEStop, ENESTgoal, and ENESTpath** will evaluate the feasibility of stopping treatment, and achieving successful Treatment-free Remission in patients with Ph+ CML in the chronic phase with sustained deep molecular response on nilotinib.

**UNR844** is a potential first-in-class topical treatment in development for presbyopia. Presbyopia is a common age-related loss of near distance vision characterized by a progressive inability to focus on objects nearby, making everyday activities, such as reading, challenging. In a phase I/II masked, placebo-controlled proof-of-concept study, 50 patients were treated daily for 90 days with topical UNR844 and 25 patients with placebo. UNR844 showed a statistically significant difference to placebo in distant corrected near vision at all time points measured (from day eight). At day 90, 82% of participants treated with UNR844 had 20/40 near vision (or 0.30 LogMAR) versus 48% in the placebo group. Near vision of 20/40 allows for the majority of near vision tasks in most people. UNR844 was acquired by Novartis through the acquisition of Encore Vision, Inc., in January 2017.

**VAY736** is a highly specific and potent monoclonal antibody against the B-cell activating factor receptor with enhanced antibody-dependent cell-mediated cytotoxicity against B cells. VAY736 is in Phase II development for the treatment of primary Sjoegren’s syndrome, a systemic autoimmune disorder characterized by progressive lymphocytic destruction of exocrine glands and other organs resulting not only in eye and mouth dryness, but frequently complicated by severe fatigue and extraglandular organ involvement.

**ZPL389** is a once-daily oral H4 receptor antagonist in development for atopic dermatitis, commonly known as eczema. ZPL389 is a potential first-in-class oral treatment for moderate-to-severe eczema. In a proof-of-concept study, ZPL389 showed a clinically and statistically significant reduction of eczema. After eight weeks of treatment, the compound reduced the Eczema Area and Severity Index (EASI) core by 50% in a study of 98 patients. In clinical studies conducted to date, ZPL389 has a favorable safety profile. ZPL389 was acquired by Novartis through the acquisition of Ziarco Group Limited in January 2017.

**Zykadia** (ceritinib) is a potent and highly selective oral anaplastic lymphoma kinase (ALK) inhibitor that is in development for ALK positive (ALK+) cancers. Two Phase III clinical trials
compared to chemotherapy. Results from the Phase III ASCEND-4 study found that patients with ALK+ advanced NSCLC treated with first-line Zykadia had a median progression-free survival (PFS) of 16.6 months, compared to 8.1 months in patients treated with standard first-line chemotherapy with maintenance. The ASCEND-5 study assessed median progression-free survival (PFS) in patients previously treated with crizotinib and one or two prior regimens of cytotoxic chemotherapy (including platinum doublet), who then received Zykadia or standard chemotherapy. There was a statistically significant and clinically meaningful improvement in median PFS for patients taking Zykadia versus chemotherapy as determined by a blinded independent review committee.

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You should not place undue reliance on these statements. Such forward looking statements are based on our current beliefs and expectations regarding future events, and are subject to significant known and unknown risks and uncertainties. Should one or more of these risks or uncertainties materialize, or should underlying assumptions prove incorrect, actual results may vary materially from those set forth in the forward looking statements. There can be no guarantee that any new products will be approved for sale in any market, or that any new indications will be approved for any existing products in any market, or that any approvals which are obtained will be obtained at any particular time, or that any such products will achieve any particular revenue levels. Nor can there be any guarantee that the review of options being undertaken to maximize shareholder value of the Alcon Division will reach any particular results, or at any particular time. Neither can there be any guarantee that Novartis will be able to realize any of the potential strategic benefits, synergies or opportunities as a result of the significant reorganizations of recent years, including the creation of the Pharmaceuticals and Oncology business units to form the Innovative Medicines Division, the creation of the Global Drug Development organization and Novartis Operations (including Novartis Technical Operations and Novartis Business Services), the transfer of the Ophthalmic Pharmaceuticals products of our Alcon Division to the Innovative Medicines Division, the transfer of selected mature, non-promoted pharmaceutical products from the Innovative Medicines Division to the Sandoz Division, and the transactions with GSK, Lilly and CSL. Neither can there be any guarantee that shareholders will achieve any particular level of shareholder returns. Nor can there be any guarantee that the Group, or any of its divisions, will be commercially successful in the future, or achieve any particular credit rating or financial results. In particular, our expectations could be affected by, among other things: regulatory actions or delays or government regulation generally; the potential that the strategic benefits, synergies or opportunities expected from the significant reorganizations of recent years, including the creation of the Pharmaceuticals and Oncology business units to form the Innovative Medicines Division, the creation of the Global Drug Development organization and Novartis Operations (including Novartis Technical Operations and Novartis Business Services), the transfer of the Ophthalmic Pharmaceuticals products of our Alcon Division to the Innovative Medicines Division, the transfer of selected mature, non-promoted pharmaceutical products from the Innovative Medicines Division to the Sandoz Division, and the transactions with GSK, Lilly and CSL may not be realized or may take longer to realize than expected; the inherent uncertainties involved in predicting shareholder returns or credit ratings; the uncertainties inherent in the research and development of new healthcare products, including clinical trial results and additional analysis of existing clinical data; our ability to obtain or maintain proprietary intellectual property protection, including the ultimate extent of the impact on Novartis of the loss of patent protection and exclusivity on key products which commenced in prior years and will continue this year; safety, quality or manufacturing issues; global trends toward health care cost containment, including government, payor and general public pricing and reimbursement pressures; the particular prescribing preferences of physicians and patients; uncertainties regarding actual or potential legal proceedings, including, among others, actual or potential product liability litigation, litigation and investigations regarding sales and marketing practices, intellectual property disputes and government investigations generally; general economic and industry conditions, including uncertainties regarding the effects of the persistently weak economic and financial environment in many countries; uncertainties regarding future global exchange rates; uncertainties regarding future demand for our products; and uncertainties regarding potential significant breaches of data security or data privacy, or disruptions of our information technology systems; and other risks and factors referred to in Novartis AG’s current Form 20-F on file with the US Securities and Exchange Commission. 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