Innovative Medicines

Our Innovative Medicines Division is a world leader in offering patent-protected medicines to patients and physicians. The Innovative Medicines Division researches, develops, manufactures, distributes and sells patented pharmaceuticals.

Global Business Units

The Innovative Medicines Division is composed of two global business units:

- Novartis Oncology
- Novartis Pharmaceuticals

The Novartis Oncology business unit is responsible for the commercialization of products in the areas of cancer and hematologic disorders. The Novartis Pharmaceuticals business unit is organized into the following global business franchises responsible for the commercialization of various products in their respective therapeutic areas: Ophthalmology; Neuroscience; Immunology, Hepatology and Dermatology; Respiratory; Cardiovascular, Renal and Metabolism; and Established Medicines.

Financial Figures

The Innovative Medicines Division is the larger of our two divisions in terms of consolidated net sales. It reported consolidated net sales of USD 37.7 billion in 2019, which represented 79% of the Group’s net sales. The product portfolio of the Innovative Medicines Division includes a significant number of key marketed products, many of which are among the leaders in their respective therapeutic areas.

Key Marketed Products

Novartis Oncology

Tasigna (nilotinib)
is an oral signal transduction inhibitor of the BCR-ABL tyrosine kinase. *Tasigna* is approved in the US, the EU, Japan and other countries for the treatment of:

- Adults and children with Philadelphia chromosome-positive chronic myeloid leukemia (Ph+ CML) in the chronic and/or accelerated phase who are resistant or intolerant to existing treatment
- Newly diagnosed adults and children with Ph+ CML in the chronic phase

Sandostatin SC (octreotide acetate for injection) and Sandostatin LAR (octreotide acetate for injectable suspension) are somatostatin analogs approved in the US, the EU, Japan and other countries for the treatment of:

- Adults with acromegaly, a chronic disease caused by the oversecretion of growth hormone, whose condition is not adequately controlled by surgery or radiotherapy
- Patients with certain symptoms associated with carcinoid tumors and other types of functional gastrointestinal and pancreatic neuroendocrine tumors

Sandostatin LAR is also approved in:

- The EU and other countries for the treatment of patients with advanced neuroendocrine tumors of the midgut or of unknown primary tumor origin
- Japan for the treatment of patients with neuroendocrine tumors of the gastrointestinal tract

*Afinitor/Votubia* (everolimus) is an oral inhibitor of the mTOR pathway. *Afinitor* is approved in the US, the EU, Japan and other countries for oncology indications that vary by country. It is approved for the treatment of:

- Postmenopausal women with advanced hormone receptor-positive (HR+)/human epidermal growth factor receptor 2-negative (HER2-) breast cancer, in combination with the medicine exemestane, when certain other medicines have not worked
- Adults with renal cell carcinoma (advanced kidney cancer) when certain other medicines have not worked
- Adults with a type of cancer known as neuroendocrine tumor (NET) of the pancreas, and non-symptomatic NET of the stomach, intestine (gastrointestinal) or lung that has progressed and cannot be treated with surgery (*Afinitor* is not indicated for use in people with carcinoid tumors that actively produce hormones)

Everolimus is approved for additional indications as *Afinitor/Afinitor Disperz* in the US, Japan and other countries, and as *Votubia* (tablets and dispersible tablets) in the EU. The following indications vary by country:

- Adults with a kidney tumor called angiomyolipoma, which occurs with a genetic condition
called tuberous sclerosis complex (TSC), when the tumor does not require immediate surgery (tablet formulation only)
- Adults and children who have TSC and a brain tumor called subependymal giant cell astrocytoma (SEGA) when the tumor cannot be removed completely by surgery
- Adults and children aged 2 years and older who have TSC and certain types of seizures (epilepsy), as an added treatment to other antiepileptic medicines (dispersible tablet formulation only)

Everolimus is available under the trade names Zortress/Certican for use in transplantation. It is exclusively licensed to Abbott Laboratories and sublicensed to Boston Scientific for use in drug-eluting stents.

Promacta/Revolade (eltrombopag)
is a once-daily oral thrombopoietin receptor agonist that works by stimulating bone marrow cells to produce platelets. It is approved in the US, the EU, Japan and other countries for the treatment of:
- A bleeding disorder called chronic immune (idiopathic) thrombocytopenia in patients who have had an inadequate response or are intolerant to other treatments
- Thrombocytopenia in patients with chronic hepatitis C to allow them to initiate and maintain interferon-based therapy

Promacta/Revolade is also approved in:
- The US and other countries as first-line therapy for adults and children aged 2 years and older with severe aplastic anemia (SAA)
- Japan as first-line therapy for adults with SAA
- The EU and other countries for adults with SAA who are resistant to other treatments

Promacta/Revolade is marketed under a research, development and license agreement between Novartis and RPI Finance Trust (dba Royalty Pharma), as assignee of Ligand Pharmaceuticals.

Tafinlar + Mekinist (dabrafenib + trametinib)
is an oral combination therapy. Tafinlar and Mekinist are kinase inhibitors of the BRAF and MEK1/2 proteins, respectively, approved in combination in the US, the EU, Japan and other countries for the treatment of:
- Adults with unresectable (not removable through surgery) or metastatic melanoma with a BRAF V600 mutation
- Adults with stage III melanoma with a BRAF V600 mutation as an adjuvant treatment
- Adults with advanced non-small cell lung cancer with a BRAF V600 mutation

Additionally, the combination is approved in the US and other countries for the treatment of:
Adults with locally advanced or metastatic anaplastic thyroid cancer with a BRAF V600 mutation

Tafinlar and Mekinist are also indicated as single agents to treat patients with unresectable or metastatic melanoma with a BRAF V600 mutation. Novartis has worldwide exclusive rights to develop, manufacture and commercialize trametinib granted by Japan Tobacco Inc.

Gleevec/Glivec (imatinib mesylate/imatinib)
is an oral kinase inhibitor. Gleevec is approved in the US for the treatment of:

- Newly diagnosed adults and children with Ph+ CML in the chronic phase
- Adults in the chronic, accelerated or blast crisis phase of Ph+ CML after failure of interferon-alpha therapy
- Adults with relapsed or refractory Philadelphia chromosome-positive acute lymphoblastic leukemia (Ph+ALL)
- Newly diagnosed children with Ph+ ALL, in combination with chemotherapy
- Adults with KIT (CD117)-positive gastrointestinal stromal tumors (GISTs) that cannot be surgically removed and/or have spread to other parts of the body
- Adults who have had their KIT (CD117)-positive GIST completely surgically removed
- Adults with advanced hypereosinophilic syndrome (HES) and/or chronic eosinophilic leukemia (CEL) who have a rearrangement of two genes called FIP1L1 and PDGFR-alpha

Glivec is approved in the EU, Japan and other countries for the treatment of:

- Newly diagnosed adults and children with Ph+ CML for whom bone marrow transplantation is not considered as the first line of treatment
- Adults and children in the chronic phase of Ph+ CML after failure of interferon-alpha therapy, or in the accelerated or blast crisis phase of Ph+ CML
- Adults with relapsed or refractory Ph+ ALL, as monotherapy
- Newly diagnosed adults and children with Ph+ ALL, in combination with chemotherapy
- Adults with KIT (CD117)-positive GISTs that cannot be surgically removed and/or have spread to other parts of the body
- Adults with advanced HES and/or chronic CEL with the FIP1L1-PDGFR-alpha rearrangement
- Adults who have had their KIT (CD117)-positive GIST completely surgically removed and who are at significant risk of relapse

Gleevec/Glivec is also approved in other rare cancers, including:

- In the US and the EU for the treatment of adults with myelodysplastic/myeloproliferative diseases, a group of diseases of the blood and bone marrow
- In the US for the treatment of adults with aggressive systemic mastocytosis (a form of mast cell disease), and adults with dermatofibrosarcoma protuberans (a rare skin cancer) when surgery is not possible or the disease has spread
Jakavi (ruxolitinib)
is an oral inhibitor of the JAK1 and JAK2 tyrosine kinases that is the first therapy approved in the EU, Japan and other countries to treat two kinds of myeloproliferative neoplasms, a group of related and rare blood cancers characterized by the overproduction of blood cells in the bone marrow. It is approved for the treatment of:

- Adults with myelofibrosis, including primary myelofibrosis, post-polycythemia vera myelofibrosis and post-essential thrombocythemia myelofibrosis
- Adults with polycythemia vera who are resistant or intolerant to a medication called hydroxyurea

Novartis licensed ruxolitinib from Incyte Corporation for development and commercialization in the indications of oncology, hematology and graft-versus-host disease outside the US. Incyte Corporation markets ruxolitinib as JakafiR in the US.

Exjade and Jadenu (deferasirox)
are oral iron chelators approved in the US, the EU, Japan and other countries for the treatment of:

- Adults and children aged 2 years and older who have chronic iron overload due to blood transfusions
- Adults and children aged 10 years and older who have chronic iron overload with non-transfusion-dependent thalassemia (a group of blood disorders that do not require regular blood transfusions)

Votrient (pazopanib)
is an oral tyrosine kinase inhibitor that targets a number of growth factors to limit new blood vessel and tumor growth. *Votrient* is approved in the US and Japan for the treatment of:

- Adults with advanced renal cell carcinoma (RCC)
- Adults with advanced soft tissue sarcoma (STS) who have received chemotherapy (it is not known if *Votrient* is effective in treating adipocytic STS or certain gastrointestinal tumors)

*Votrient* is also approved in the EU for the treatment of:

- Adults with advanced RCC as first-line therapy, and adults with advanced RCC who have received cytokine therapy for advanced disease
- Adults with certain subtypes of advanced STS who have received chemotherapy for metastatic disease or whose cancer has progressed within 12 months after neoadjuvant therapy

Kisqali (ribociclib)
is an oral cyclin-dependent kinase inhibitor. It is approved in the US, the EU and other countries for the treatment of:

- Pre-, peri- and postmenopausal women with HR+/HER2- advanced or metastatic breast cancer, in combination with an aromatase inhibitor as initial endocrine-based therapy
- Postmenopausal women with HR+/HER2- locally advanced or metastatic breast cancer, in combination with fulvestrant as initial endocrine based-therapy or following disease progression on endocrine therapy

*Kisqali* was developed by the Novartis Institutes for BioMedical Research under a research collaboration with Astex Pharmaceuticals.

Lutathera (USAN: lutetium Lu 177 dotatate/INN: lutetium (177Lu) oxodotreotide) is an intravenous radioligand therapy approved in the US for the treatment of:

- Adults with somatostatin receptor-positive gastroenteropancreatic neuroendocrine tumors (GEP-NETs), including foregut, midgut and hindgut neuroendocrine tumors

*Lutathera* is also approved in the EU and other countries for the treatment of:

- Adults with unresectable or metastatic, progressive, well-differentiated (G1 and G2), somatostatin receptor-positive GEP-NETs

Kymriah (tisagenlecleucel) suspension for intravenous infusion is a CD19-directed genetically modified autologous chimeric antigen receptor T-cell (CAR-T) therapy.

*Kymriah* is approved in the US, the EU, Japan and other countries for the treatment of:

- Patients up to 25 years old with B-cell acute lymphoblastic leukemia that is refractory or in second or later relapse
- Adults with relapsed or refractory diffuse large B-cell lymphoma after two or more lines of systemic therapy

Piqray (alpelisib) is an oral kinase inhibitor. It is approved in the US and other countries for the treatment of:

- Postmenopausal women, and men, with HR+/HER2-advanced or metastatic breast cancer with a PIK3CA mutation, in combination with fulvestrant following disease progression on or after an endocrine-based regimen

*Piqray* received US approval in May 2019.

Adakveo (crizanlizumab)
is a humanized monoclonal antibody that binds to P-selectin, a cell adhesion protein that plays a central role in the multicellular interactions that can lead to vaso-occlusion in sickle cell disease. Delivered as an intravenous infusion, Adakveo is approved in the US to:

- Reduce the frequency of vaso-occlusive crises (VOCs), or pain crises, in patients aged 16 years and older with sickle cell disease

Adakveo received US approval in November 2019.

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**Novartis Pharmaceuticals Business Unit**

**Ophthalmology**

Lucentis (ranibizumab)

is a recombinant, humanized, high-affinity antibody fragment that binds to vascular endothelial growth factor A (VEGF-A), a protein that causes the growth of blood vessels in the eye, which can lead to vision loss. Lucentis is an injectable anti-VEGF therapy specifically designed for the eye, minimizing systemic exposure. It is approved in the EU, Japan and other countries. Approvals and indications vary by country:

- Adults with neovascular (wet) age-related macular degeneration (AMD)
- Adults with visual impairment due to choroidal neovascularization (CNV)
- Adults with CNV secondary to pathologic myopia
- Adults with visual impairment due to diabetic macular edema
- Adults with visual impairment due to macular edema secondary to retinal vein occlusion (branch and central retinal vein occlusion)
- Adults with moderately severe to severe non-proliferative diabetic retinopathy and proliferative diabetic retinopathy
- Preterm infants with retinopathy of prematurity (ROP) in zone I (stage 1+, 2+, 3 or 3+) or zone II (stage 3+), or aggressive posterior ROP

Lucentis is licensed from Genentech, and Novartis holds the rights to commercialize the product outside the US. Genentech holds the rights to commercialize Lucentis in the US.

Xiidra (lifitegrast ophthalmic solution)

is a prescription eye drop designed to block the interaction between LFA-1 and ICAM-1, inhibiting the formation of the immunological synapse and reducing inflammation. Xiidra is approved in the US and other countries for the treatment of:

- The signs and symptoms of dry eye disease in patients over 17 years old
Novartis acquired Xiidra from Takeda Pharmaceutical Company Limited and began recording sales as of July 1, 2019. Xiidra is marketed in the US. It is not currently marketed in the EU or Japan.

Beovu (brolucizumab)

is an injectable, humanized single-chain antibody fragment that acts as an anti-VEGF agent. It is approved in the US for the treatment of:

- Patients with neovascular (wet) age-related macular degeneration

*Beovu* received US approval in October 2019.

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**Immunology, Hepatology and Dermatology**

Cosentyx (secukinumab)

is an injectable fully human monoclonal antibody that specifically inhibits interleukin-17A (IL-17A), a cytokine involved in the pathogenesis of psoriasis, ankylosing spondylitis and psoriatic arthritis. It is approved in the US, the EU, Japan and other countries for the treatment of:

- Adults with moderate-to-severe plaque psoriasis
- Adults with active ankylosing spondylitis
- Adults with active psoriatic arthritis

*Cosentyx* is also approved in Japan for the treatment of:

- Adults with pustular psoriasis

Ilaris (canakinumab)

is an injectable, selective, high-affinity, fully human monoclonal antibody that inhibits interleukin-1 beta (IL-1 beta), a key cytokine (a type of protein) in the inflammatory pathway. *Ilaris* is approved in the US, the EU, Japan and other countries for the treatment of:

- Adults and children with cryopyrin-associated periodic syndromes
- Adults and children with tumor necrosis factor receptor-associated periodic syndrome
- Adults and children with hyperimmunoglobulin D syndrome/mevalonate kinase deficiency
- Adults and children with familial Mediterranean fever
- Adults and children with systemic juvenile idiopathic arthritis

*Ilaris* is also approved in the EU for the treatment of:

- Adults with Still’s disease
- Adults with refractory acute gouty arthritis
Neuroscience

Gilenya (fingolimod)

is an oral sphingosine-1-phosphate (S1P) receptor modulator that has a reversible lymphocyte redistribution effect and readily crosses the blood-brain barrier to bind to the S1P receptors based in the central nervous system. It is approved in the US for the treatment of:

- Adults and children aged 10 years and older with relapsing forms of multiple sclerosis, including clinically isolated syndrome, relapsing-remitting multiple sclerosis (RRMS) and active secondary progressive multiple sclerosis (SPMS)

Gilenya is also approved in the EU for the treatment of:

- Adults and children aged 10 years and older who have highly active RRMS despite treatment with at least one disease-modifying agent, or who have rapidly evolving severe RRMS

Gilenya is licensed from Mitsubishi Tanabe Pharma Corporation.

Zolgensma (onasemnogene abeparvovec-xioi, previously known as AVXS-101)

is a gene therapy delivered as a single-dose intravenous infusion. It is designed to provide a functional copy of the human survival motor neuron (SMN) gene to halt disease progression through sustained SMN protein expression. Zolgensma is approved in the US for the treatment of:

- Children less than 2 years old who have spinal muscular atrophy with biallelic mutations in the SMN1 gene

Zolgensma received US approval in May 2019 and is marketed by AveXis, a Novartis company.

Aimovig (erenumab)

is a once-monthly injection that can be self-administered or administered by another trained person. It is specifically designed to block the calcitonin gene-related peptide receptor (CGRP-R), which plays a critical role in migraine. It is approved:

- In the US for the prevention of migraine in adults
- In the EU for the prevention of migraine in adults who have at least four migraine days per month
Aimovig is launched in 38 countries. Novartis and Amgen co-commercialize Aimovig in the US, where Amgen records sales. Novartis has exclusive commercialization rights for all ex-US territories, excluding Japan. The collaboration continues during the previously announced litigation between the companies and will remain in force until and unless a final court decision terminates the agreements.

Mayzent (siponimod)

is an oral, selective S1P receptor modulator. It binds selectively to the S1P receptor subtypes 1 and 5, and penetrates the central nervous system, where it may impact central nervous system inflammation and repair mechanisms. Mayzent is approved:

- In the US for the treatment of adults with relapsing forms of multiple sclerosis, including clinically isolated syndrome, relapsing-remitting multiple sclerosis (RRMS) and active secondary progressive multiple sclerosis (SPMS)
- In the EU for the treatment of adults with SPMS with active disease

Mayzent received US approval in March 2019 and EU approval in January 2020.

Respiratory

Xolair (omalizumab)

is an injectable prescription medicine and the only approved antibody designed to target and block immunoglobulin E (IgE). It is approved in the US, the EU, Japan and other countries for the treatment of:

- Adults and children aged 6 years and older with moderate-to-severe, or severe, persistent allergic asthma
- Adults and children aged 12 years and older with chronic spontaneous urticaria/chronic idiopathic urticaria (hives)

Xolair is also approved in Japan for the treatment of:

- Patients with severe seasonal allergic rhinitis (hay fever)

Xolair is provided as lyophilized powder for reconstitution, and as liquid formulation in a pre-filled syringe.

Novartis co-promotes Xolair with Genentech in the US and shares a portion of operating income, but Novartis does not record any US sales.

Cardiovascular, Renal and Metabolism

Entresto (sacubitril/valsartan)
is an oral, first-in-class angiotensin receptor/neprilysin inhibitor. It enhances the protective neurohormonal systems of the heart (the neprilysin system) while simultaneously suppressing the harmful system (the renin-angiotensin-aldosterone system). \textit{Entresto} is approved in the US, the EU and other countries for the treatment of:

- Adults who have symptomatic chronic heart failure with reduced ejection fraction (HFrEF)

\textit{Entresto} is also approved in the US for the treatment of:

- Children aged 1 year and older who have symptomatic heart failure with systemic left ventricular systolic dysfunction

\textit{Entresto} is approved in 112 countries.

\textbf{Established Medicines}

\textbf{Galvus/Equa (vildagliptin)}

is an oral inhibitor of the DPP-4 enzyme. It is approved in the EU, Japan and other countries for the treatment of:

- Adults with type 2 diabetes when used as monotherapy; in dual combination with metformin, a sulfonylurea or a thiazolidinedione; in triple combination with a sulfonylurea and metformin; and as an add-on to insulin (with or without metformin)

An oral single-pill combination of vildagliptin and metformin, marketed as \textit{Eucreas/EquMet/GalvusMet}, is also approved in the EU, Japan and other countries for the treatment of type 2 diabetes. Sumitomo Dainippon Pharma Co. Ltd. promotes \textit{Equa} and \textit{EquMet} in Japan.

\textbf{Diovan (valsartan)}

is an oral angiotensin II receptor blocker (ARB). It is approved in the US, the EU, Japan and other countries for the treatment of:

- Adults and children with hypertension (high blood pressure)
- Patients with heart failure
- Patients with left ventricular failure and/or left ventricular systolic dysfunction following a myocardial infarction (heart attack)
- Hypertensive patients who have impaired glucose tolerance and are at risk of heart disease

An oral single-pill combination of valsartan and hydrochlorothiazide, marketed as \textit{Diovan HCT/Co-Diovan}, is also approved in the US, the EU, Japan and other countries for the treatment of hypertension.
Exforge (valsartan and amlodipine besylate)
is an oral single-pill combination of the ARB valsartan and the calcium channel blocker amlodipine besylate. It is approved in the US, the EU, Japan and other countries for the treatment of:

- Adults with hypertension

An oral single-pill combination of valsartan, amlodipine besylate and hydrochlorothiazide, marketed as Exforge HCT, is also approved in the US, the EU, Japan and other countries for the treatment of hypertension.

Zortress/Certican (everolimus)
is an oral inhibitor of the mTOR pathway. It is approved in the US, the EU, Japan and other countries for the prophylaxis of:

- Organ rejection in adults at low to moderate immunological risk receiving an allogeneic kidney or liver

Transplant It is also approved in the EU and Japan for the prophylaxis of:

- Organ rejection in adults receiving a heart transplant

Everolimus is available under the trade names Afinitor/Votubia for use in oncology. It is exclusively licensed to Abbott Laboratories and sublicensed to Boston Scientific for use in drug-eluting stents.

Egaten (triclabendazole)
is an oral narrow-spectrum anthelmintic agent that inhibits a parasitic flatworm’s motility and interferes with the worm’s microtubular structure and function. Egaten is approved in the US, France and Egypt for the treatment of:

- Patients aged 6 years and older with fascioliasis, a parasitic infection commonly known as liver fluke Infestation

Egaten received US approval in February 2019. It is the only medicine for fascioliasis recommended by the World Health Organization (WHO) and is on the WHO Model List of Essential Medicines. Novartis has been donating Egaten to the WHO for the treatment of fascioliasis since 2005.

Key Development Projects

ABL001 (asciminib)
is an investigational oral BCR-ABL inhibitor that binds to the allosteric site of its target (BCR-ABL1). A broad clinical development program is investigating ABL001 as a monotherapy and
as a combination therapy for the treatment of chronic myeloid leukemia (CML). This program includes the Phase III ASCEMBL third-line study, and the Phase II ASC-4MORE first-line study of ABL001 plus imatinib in patients with CML in chronic phase without achieving deep molecular response. Novartis is studying ABL001 in patients with and without genetic mutations that make them resistant to many targeted CML therapies.

ACZ885 (canakinumab)

is an injectable human monoclonal antibody designed to bind to human interleukin-1 beta (IL-1 beta). ACZ885 was first approved as Ilaris in 2009 for cryopyrin-associated periodic syndromes, a group of rare auto-inflammatory disorders. At the 2017 European Society of Cardiology Congress, Novartis presented data from CANTOS, a Phase III study evaluating quarterly injections of ACZ885 in people with a prior heart attack and inflammatory atherosclerosis. A blinded, pre-planned analysis of these data revealed a 77% reduction in lung cancer mortality and a 67% reduction in lung cancer cases in patients treated with 300 mg of ACZ885. These findings suggest the potential benefit of inhibiting tumor-promoting inflammation in cancer treatment. Based on these CANTOS findings, Novartis initiated three Phase III studies of ACZ885 in lung cancer: the CANOPY trials. Study outcomes may begin to be reported in 2021. During 2019, Novartis presented Trials in Progress (TiP) updates at the American Society of Clinical Oncology (ASCO) annual meeting, and an overview of the Phase III CANOPY trials at the European Society for Medical Oncology (ESMO) Congress.

AVXS-101 (onasemnogene abeparvovec, approved in the US as Zolgensma)

is a gene therapy designed to address the genetic root cause of spinal muscular atrophy (SMA) by providing a functional copy of the human survival motor neuron (SMN) gene to halt disease progression through sustained SMN protein expression. The US Food and Drug Administration (FDA) approved the intravenous formulation of AVXS-101 as Zolgensma in May 2019 for the treatment of pediatric patients less than 2 years old who have SMA with biallelic mutations in the SMN1 gene. Regulatory reviews are underway in Europe, with a CHMP opinion anticipated in the first quarter of 2020, and in Japan, with a decision anticipated in the first half of 2020. AVXS-101 is in ongoing clinical studies, including the global Phase III STR1VE clinical program (consisting of STR1VE-US, STR1VE-EU and STR1VE-AP) to evaluate the intravenous formulation of AVXS-101 in patients who have SMA type 1, and the multinational Phase III SPR1NT trial in presymptomatic patients who have SMA with two or three copies of the SMN2 gene. Additionally, AVXS-101 intrathecal administration is being studied in a Phase I/II STRONG trial in patients who have SMA type 2 and three copies of the SMN2 gene. The STRONG trial is currently on partial clinical hold based on findings in a small preclinical animal study, and the Company is working with the FDA to determine next steps to resume dosing. New data from trials were presented at 2019 congresses, including the American Academy of Neurology Annual Meeting.

BYL719 (alpelisib, approved in the US as Piqray)

is an orally bioavailable, alpha-specific PI3K inhibitor approved in combination with fulvestrant for the treatment of postmenopausal women, and men, with HR+/HER2-, PIK3CA-mutated, advanced or metastatic breast cancer. Piqray received FDA approval based on results of the
Phase III SOLAR-1 trial, which showed that **Piqray** plus fulvestrant nearly doubled median progression-free survival compared to fulvestrant alone. Novartis is conducting a Phase II open-label trial, called BYLieve, to evaluate BYL719 plus fulvestrant or letrozole in patients with HR+/HER2-, PIK3CA-mutated advanced breast cancer who have progressed on prior therapy. Novartis is also planning to evaluate BYL719 in triple negative breast cancer; head and neck squamous cell carcinoma; ovarian cancer; and PIK3CA-related overgrowth spectrum, for which BYL719 received FDA breakthrough therapy designation.

**CFZ533 (iscalimab)**

delivered subcutaneously as an injection, is a fully human, Fc-silenced IgG1 monoclonal antibody that blocks the CD40 receptor. CFZ533 is in clinical development to prevent graft rejection after organ transplantation and to treat several autoimmune diseases, including Sjogren’s syndrome. In the proof-of-concept study, CFZ533 demonstrated the ability to preserve graft function and pristine histology, confirming preclinical in vivo data. Recruitment is underway for two Phase II studies in kidney and liver transplant recipients (CIRRUS I and CONTRAIL I, respectively), and for a Phase II study in patients with Sjogren’s syndrome (TWINSS).

**Cosentyx (secukinumab)**

is an injectable fully human monoclonal antibody that specifically inhibits interleukin-17A (IL-17A). In August and December 2019, Novartis submitted positive data to the EMA and the FDA, respectively, from the Phase III PREVENT trial, which evaluated the efficacy and safety of **Cosentyx** in patients with non-radiographic axial spondyloarthritis. In November 2019, Novartis disclosed first results from the EXCEED head-to-head trial comparing **Cosentyx** to HumiraR (adalimumab) in patients with active psoriatic arthritis (PsA). While narrowly missing statistical significance for superiority in ACR20, the primary endpoint of the EXCEED trial, **Cosentyx** showed numerically higher results versus HumiraR. **Cosentyx** is in a Phase III head-to-head trial versus the Sandoz biosimilar **Hyrimoz** (adalimumab) in ankylosing spondylitis; Phase III trials in pediatric psoriasis, juvenile idiopathic arthritis and hidradenitis suppurativa; and a Phase II trial in giant cell arteritis.

**Entresto (sacubitril/valsartan)**

is an oral, first-in-class angiotensin receptor/neprilysin inhibitor. Novartis is conducting multiple studies of sacubitril/valsartan as part of the FortiHFy clinical program, designed to generate additional data on sacubitril/valsartan and increase understanding of heart failure. The PIONEER-HF and TRANSITION studies both read out in 2018 and confirmed safety and superiority of **Entresto** versus enalapril in patients with chronic heart failure with reduced ejection fraction (HFrEF) who were stabilized following admission to the hospital for an acute decompensated heart failure event. The PROVE and EVALUATE trials read out in 2019. The PROVE-HF trial showed significant improvements in measures of cardiac structure and function at six months and one year in HFrEF patients; EVALUATE-HF results complemented PROVE-HF findings. The FortiHFy program also includes studies to investigate sacubitril/valsartan use in novel indications and expanded patient populations. These include PARAGON-HF and PARALLAX-HF, Phase III trials of sacubitril/valsartan in
patients with chronic heart failure with preserved ejection fraction (HFpEF). Results of PARAGON-HF were published in September 2019, and while the trial narrowly missed its primary endpoint with a 13% treatment effect against an active valsartan comparator, the totality of evidence suggests that treatment with sacubitril/valsartan may result in clinically important benefits in HFpEF. US regulatory submission for HFpEF is on track for early 2020. PARALLAX-HF enrollment is complete and results are expected to be presented in 2020. Other trials include PARADISE-MI, a Phase III trial in patients at high risk of developing heart failure after a heart attack (post-acute myocardial infarction). Enrollment is ongoing and results are expected in 2020. Additionally, PARALLEL-HF is a Phase III trial for HFrEF patients in Japan (Novartis reported results in March 2019, and a marketing authorization submission in Japan is under review), and PANORAMA-HF is a Phase III trial in pediatric patients with heart failure (enrollment is ongoing and results are expected in 2021).

INC280 (capmatinib)

is an investigational oral, potent and selective MET inhibitor. The GEOMETRY trial – a Phase II study in adult patients with advanced nonsmall cell lung cancer (NSCLC) harboring MET exon 14 skipping mutations – is ongoing, as are additional early-stage studies in combination with other compounds. During 2019, Novartis presented primary efficacy results from the GEOMETRY trial at ASCO, and the FDA granted breakthrough therapy designation to INC280 as a first-line treatment for patients with metastatic MET exon 14 skipping-mutated (METex14) NSCLC. Breakthrough therapy designation covers both treatment-naïve patients and patients previously treated with platinum-based chemotherapy. INC280 is licensed by Novartis from Incyte Corporation. Under the Collaboration and License Agreement, Novartis has exclusive worldwide development and commercialization rights to INC280, and Incyte Corporation maintains certain rights to exercise options for both co-development and co-detailing in the US.

KAF156 (ganaplacide)

belongs to a novel class of antimalarial compounds called imidazolopiperazines. It has the potential to clear malaria infection, including resistant strains, and to block the transmission of the malaria parasite. As demonstrated in a Phase IIa proof-of-concept trial, the compound is fast-acting and potent across multiple stages of the parasite’s lifecycle, rapidly clearing both Plasmodium falciparum and Plasmodium vivax parasites. A Phase IIb study tested multiple dosing combinations and dosing schedules of KAF156 and lumefantrine in adults and adolescents, and confirmed good safety and efficacy of all doses. The safety and efficacy of the combination will now be evaluated in younger children.

Kisqali (ribociclib)

is an oral, cyclin-dependent kinase inhibitor. Novartis continues to investigate Kisqali in patients with HR+/HER2- breast cancer, and it is the only CDK4/6 inhibitor to achieve statistically significant overall survival in two Phase III trials with two distinct patient populations. Novartis presented overall survival results from MONALEESA-7 at ASCO 2019 and from MONALEESA-3 at ESMO 2019, and continues to assess Kisqali in MONALEESA-2, COMPLEEMENT-1 and the NataLEE adjuvant trial. These trials are evaluating Kisqali in
multiple endocrine therapy combinations across a broad range of patients, including men and premenopausal women. *Kisqali* was developed by the Novartis Institutes for BioMedical Research under a research collaboration with Astex Pharmaceuticals.

KJX839 (inclisiran)

is a long-acting, small-interfering RNA (siRNA) administered twice a year as a subcutaneous injection. It is in development in atherosclerotic cardiovascular disease and primary hyperlipidemia (including familial hypercholesterolemia) for patients who have already had an event like a heart attack or stroke, or who are risk-equivalent. Pivotal Phase III trial results were presented at the European Society of Cardiology Congress and the American Heart Association Scientific Sessions in 2019 by The Medicines Company, prior to its acquisition by Novartis. A cardiovascular outcomes study, ORION-4, is ongoing.

Kymriah (tisagenlecleucel)

is a CD19-directed genetically modified autologous chimeric antigen receptor T-cell (CAR-T) therapy delivered as an intravenous infusion. Since 2018, Novartis has initiated six trials for new or expanded indications for *Kymriah* – diffuse large B-cell lymphoma (DLBCL) in second line, high-risk pediatric acute lymphoblastic leukemia (ALL), relapsed/refractory follicular lymphoma, pediatric non-Hodgkin lymphoma, relapsed/refractory DLBCL in combination with ibrutinib, and relapsed/refractory DLBCL in combination with pembrolizumab – as well as a study of *Kymriah* in adult ALL planned for a 2020 start. Novartis and the University of Pennsylvania’s Perelman School of Medicine developed *Kymriah* under a global collaboration.

LJN452 (tropifexor)

is an oral, highly potent and selective nonsteroidal multimodal farnesoid X receptor (FXR) agonist in development as both a monotherapy and a combination therapy for the treatment of nonalcoholic steatohepatitis (NASH). LJN452 is designed to target the three major facets of NASH (steatosis, inflammation and fibrosis), and has demonstrated the ability to reduce all three in animal models. Recruitment is complete for two Phase II studies: FLIGHT FXR (the monotherapy study) and TANDEM (the combination study with cenicriviroc). Additional collaborative studies are underway to explore the role of LJN452 as a backbone in combination therapies.

LNP023

is an oral, selective factor B inhibitor of the alternative complement pathway. It is in development for the treatment of rare complement-driven renal diseases, including IgA nephropathy, membranous nephropathy and C3 glomerulopathy. LNP023 is also in development for the treatment of paroxysmal nocturnal hemoglobinuria. Phase II studies in all indications are initiated.

177 Lu-PSMA-617
delivered as an intravenous infusion, is an investigational radioligand therapy in development for metastatic castration-resistant prostate cancer (mCRPC). Designed to target the prostate-specific membrane antigen present in most patients with mCRPC, 177Lu-PSMA-617 potentially offers a differentiated targeted treatment option. A Phase III study of 177Lu-PSMA-617 in patients with mCRPC, called VISION, is ongoing.

Lutathera (lutetium Lu 177 dotatate/lutetium (177Lu) oxodotreotide)

is an intravenous radioligand therapy. A randomized Phase III trial called NETTER-1 continues to assess overall survival in patients who received Lutathera and long-acting octreotide to treat inoperable, progressive, well-differentiated (Grade 1 and Grade 2), somatostatin receptor-positive midgut neuroendocrine tumors.

OMB157 (ofatumumab)

administered as a subcutaneous injection, is a fully human monoclonal antibody that works by binding to the CD20 molecule on the B-cell surface and inducing B-cell depletion. OMB157 is in development to treat multiple sclerosis (MS). Novartis announced in August 2019 that the Phase III ASCLEPIOS I and II studies met their primary endpoints in patients with relapsing forms of MS. Compared to AubagioR (teriflunomide), OMB157 showed a statistically significant reduction in the number of confirmed relapses, evaluated as the annualized relapse rate; highly significant suppression of both Gd+ T1 lesions and new or enlarging T2 lesions; and a relative risk reduction in three- and six-month confirmed disability worsening in pre-specified pooled analyses. Novartis is conducting a registration study for OMB157 in Japan, which started in March 2018.

PDR001 (spartalizumab)

delivered as an intravenous infusion, is an investigational PD-1 antagonist that may restore the ability of immune cells to induce cell death and fight cancer. Novartis is evaluating PDR001 in combination with Tafinlar + Mekinist in a Phase III trial (COMBI-i) for unresectable or metastatic BRAF V600 mutation-positive melanoma, and presented results from the safety run-in part and biomarker cohort at ASCO in 2019. Novartis is also evaluating PDR001 as a combination therapy with other Novartis drugs in clinical trials for different tumor types, including metastatic melanoma.

QAW039 (fevipiprant)
is an investigational, novel, once-daily pill that blocks the DP2 pathway, a regulator of the inflammatory cascade. In December 2019, Novartis announced that development of QAW039 in asthma would be discontinued after the Phase III LUSTER-1 and LUSTER-2 core registration trials did not meet the clinically relevant threshold for reduction in asthma attacks (exacerbations) in moderate to severe patients with unresolved asthma despite treatment with inhaled therapies. In addition, as announced in October 2019, results of the Phase III ZEAL-1 and ZEAL-2 studies did not meet the primary efficacy endpoint of lung function (FEV1) improvement in patients with moderate asthma.

**QGE031 (ligelizumab)**

administered subcutaneously as a once-monthly single injection, is a next-generation, high-affinity anti-IgE monoclonal antibody that is highly potent in blocking the IgE/FceR1 pathway. QGE031 is in clinical development for the treatment of chronic spontaneous urticaria/chronic idiopathic urticaria (CSU/CIU). In a CSU/CIU Phase IIb study, a clear dose response was demonstrated and a higher percentage of CSU/CIU patients had complete symptom control with QGE031 72 mg or 240 mg than with omalizumab 300 mg or placebo. QGE031 is being investigated in two ongoing Phase III twin trials, PEARL 1 and PEARL 2, which are recruiting more than 2,000 patients across 48 countries.

**RTH258 (brolucizumab, approved in the US as Beovu)**

is an injectable, humanized, single-chain antibody fragment that acts as an anti-vascular endothelial growth factor (anti-VEGF) agent. The FDA approved RTH258 as Beovu in October 2019 for the treatment of neovascular (wet) age-related macular degeneration, and regulatory filings are under review in the EU, Japan and certain other countries. RTH258 is in clinical development for diabetic macular edema and retinal vein occlusion.

**SEG101 (crizanlizumab, approved in the US as Adakveo)**

is a humanized monoclonal antibody that binds to P-selectin, a cell adhesion protein that plays a central role in the multicellular interactions that can lead to vaso-occlusion in sickle cell disease. It is delivered as an intravenous infusion. The FDA approved SEG101 as Adakveo in November 2019 to reduce the frequency of vaso-occlusive crises (VOCs), or pain crises, in patients aged 16 years and older with sickle cell disease. Novartis continues to study SEG101 in sickle cell disease through the SENTRY clinical trial program, which includes SOLACE-adults, SOLACE-kids, STAND, SPARTAN and STEADFAST. These studies are evaluating SEG101 for the treatment of VOCs in children and adults, as well as priapism and other complications, such as sickle cell nephropathy.

**TQJ230**

is an injectable antisense oligonucleotide designed to target elevated lipoprotein(a) (Lp(a)), which increases the risk of heart disease. The results of a Phase II trial announced in 2018 showed that TQJ230 reduced Lp(a) in patients by as much as 80%. The Lp(a) HORIZON trial, a Phase III trial in patients with established cardiovascular disease and elevated Lp(a), was

UNR844

is a potential first-in-class topical treatment in development for presbyopia, 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) a challenge. UNR844 is believed to work through the reduction of disulfide bonds, softening the crystalline lens. 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 were treated with placebo. UNR844 showed a statistically significant difference to placebo in binocular distance-corrected near vision at all time points measured (from Day Eight). At Day 90, 82% of participants treated with UNR844 had 20/40 binocular 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.

ZPL389 (adriforant)

is a once-daily oral H4 receptor antagonist. It is in Phase II clinical development for the treatment of atopic dermatitis (AD) to evaluate its benefit on key outcomes, such as reduction of the severity of AD lesions and reduction of itch. The Phase II ZEST study is investigating the effect of several doses of ZPL389 versus placebo. ZPL389 has already demonstrated significant clinical and statistical improvements in eczema lesions, leading to a 50% reduction in Eczema Area and Severity Index (EASI) score compared to placebo after eight weeks of treatment, with a favorable safety profile in the proof-of-concept study.

Accordion:

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