### 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 composed of two business units:

- **Novartis Oncology**
- **Novartis Pharmaceuticals**
  - Cardio-Metabolic
  - Immunology, Hepatology 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.

In addition, we transferred our over-the-counter ophthalmic products and certain surgical diagnostic products (2017 sales of USD 0.8 billion) from the Innovative Medicines Division to the Alcon Division effective January 1, 2018. Our prescription Ophthalmic medicines business remains with the Innovative Medicines Division. In compliance with IFRS, beginning with our first quarter 2018 results, Novartis has updated its segment financial information to reflect this transfer, both for the current and prior years, to aid comparability of year-on-year results.

The Innovative Medicines Division is the largest contributor among the divisions of Novartis and reported consolidated net sales of USD 17.3 billion in the first half of 2018.

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

The descriptions of individual product indications are not always country-specific, and may contain information that is outside the approved indications in any one country.

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 certain patients with advanced renal cell carcinoma whose disease has progressed on or after certain other treatments. Afinitor has been approved in more than 110 countries, including the US, EU member states and Japan, for the treatment of certain neuroendocrine tumors (NET) of pancreatic origin. It was approved in more than 45 countries, including the US and EU member states, for the treatment of certain patients with nonfunctional NET of gastrointestinal or lung origin. Afinitor, in combination with exemestane, is approved in 117 countries to treat certain postmenopausal women with advanced hormone receptor-positive, HER2-negative breast cancer that has progressed on non-steroidal aromatase inhibitors. All oncology indications are approved under the trade name Afinitor in the tablet formulation. Everolimus, under the trade names Afinitor in the US and Votubia in the EU, is approved in more than 95 countries to treat certain patients with TSC who have renal angiomyolipoma, as well as certain patients with tuberous sclerosis complex (TSC) who have subependymal giant cell astrocytoma (SEGA). The dispersible tablets for oral suspension formulation (Afinitor, Afinitor Disperz, Votubia) is approved for patients with TSC who have SEGAs in more than 40 countries including the US, EU member states and Japan. Dispersible tablets also are approved in more than 30 countries, including the US and EU member states, as adjunctive treatment for TSC-associated partial-onset seizures in patients as young as age two. 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 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 formulation that can be swallowed whole or crushed is approved in more than 60 countries, including the US and EU member countries, under the tradename Jadenu or Exjade. Regulatory reviews are still ongoing in several countries. In addition to the film-coated tablet formulation, an additional formulation has also been developed as granules, as an alternative for patients who cannot swallow tablets, using the same composition as the film-coated tablet formulation. The granules have been approved in the US, Japan and EU, under the names Jadenu Sprinkle, Jadenu and Exjade, respectively.

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 JAK 1/2 inhibitor indicated for the treatment of disease-related splenomegaly or symptoms in patients with primary myelofibrosis (MF), and patients with polycythemia vera (PV) who are resistant to or intolerant of hydroxyurea. Jakavi is currently approved in more than 105 countries for patients with MF and in more than 75 countries for patients with PV, including EU member states and Japan. A five-year follow-up of the two pivotal trials, COMFORT-I and COMFORT-II, suggests a reduced risk of death for patients with MF randomized to Jakavi compared to placebo or best available therapy, respectively. 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 PV and MF with a similar label as outside the US.

Kisqali (ribociclib) is a cyclin-dependent kinase inhibitor, a class of drugs that help slow the growth of tumors by inhibiting two proteins called cyclin-dependent kinase 4 and 6 (CDK4/6) approved for the treatment of postmenopausal women with hormone receptor positive, human epidermal growth factor receptor-2 negative locally advanced or metastatic breast cancer as initial endocrine-based therapy in combination with an aromatase inhibitor. Kisqali has been approved in approximately 60 countries, including in the US in March 2017 and in the EU member states in August 2017. In May 2017, the FDA also approved the Kisqali Femara Co-Pack (ribociclib tablets; letrozole tablets). Kisqali was developed by the Novartis Institutes for Biomedical Research (NIBR) under a research collaboration with Astex Pharmaceuticals.

Kymriah (lisagenlecleucel) suspension for intravenous infusion is a CD19-directed genetically modified autologous chimeric antigen receptor T (CAR-T) cell therapy. Kymriah is approved in the US for the treatment of patients up to 25 years of age with B-cell precursor acute lymphoblastic leukemia that is refractory or in second or later relapse, and of adult patients with relapsed or refractory large B-cell lymphoma after two or more lines of systemic therapy, including diffuse large B-cell lymphoma (DLBCL) not otherwise specified, high grade B-cell lymphoma and DLBCL arising from follicular lymphoma. Kymriah is not indicated for the treatment of patients with primary central nervous system lymphoma. In the EU, the CHMP issued a positive opinion recommending the approval of Kymriah in relapsed/refractory DLBCL after two or more lines of systemic therapy after and in pediatric and young adult patients up to 25 years of age with relapsed/refractory B-cell ALL that is refractory, in relapse post-transplant or in second or later relapse. The European Commission usually follows CHMP recommendation. Additional regulatory filings are under review for Kymriah in Canada, Switzerland, Australia and Japan.

Lutathera (USAN: lutetium Lu 177 dotatate/INN: lutetium (177Lu) oxodotreotide) is an intravenously administered, radiolabelled somatostatin analogue. Lutathera belongs to a class of treatments called RadioLigand Therapy (RLT). Lutathera is approved in the US for the treatment of somatostatin receptor positive gastroenteropancreatic neuroendocrine tumors (GEP-NETs), including foregut, midgut, and hindgut neuroendocrine tumors in adults. Lutathera is approved in Europe for the treatment of unresectable or metastatic, progressive, well differentiated (G1 and G2), somatostatin receptor positive GEP-NETs in adults. Lutathera has received orphan drug designation from the FDA and the EMA. Lutathera is an Advanced Accelerator Applications product.

Promacta/Revolade (eltrombopag) is a once-daily oral thrombopoietin receptor agonist that works by stimulating bone marrow cells to produce platelets. It 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 the treatment of thrombocytopenia in adult patients with chronic immune (idiopathic) thrombocytopenia (ITP) who have had an inadequate response or are intolerant to other treatments. In the US and EU, Promacta/Revolade is approved for patients
one year and older with chronic ITP who have had an insufficient response to other treatments. **Promacta/Revolade** is approved in Japan for aplastic anemia as first-line therapy and for patients who are refractory to other treatments. It is also approved in 45 countries for the treatment of patients with severe aplastic anemia (SAA) who are refractory to other treatments (in the US for the treatment of patients with SAA who have had an insufficient response to immunosuppressive therapy and in the EU for the treatment of adults with acquired SAA who were either refractory to prior immunosuppressive therapy or heavily pretreated and are unsuitable for hematopoietic stem cell transplant). In May 2018, the FDA granted a Priority Review to **Promacta** for the first-line treatment of severe aplastic anemia. **Promacta/Revolade** is also 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. In addition, **Promacta** was granted Breakthrough Therapy designation by the FDA to reduce bleeding risk and increase survival by increasing platelet counts in patients acutely exposed to myelosuppressive doses of radiation. **Promacta/Revolade** is marketed under a collaboration agreement between Ligand Pharmaceuticals, Inc. and Novartis. **Promacta/Revolade** was acquired from GSK.

**Rydapt** (midostaurin) is the first targeted treatment for newly diagnosed FLT3-mutated acute myeloid leukemia (AML) and the first approved treatment for aggressive systemic mastocytosis (ASM), systemic mastocytosis with associated hematological neoplasm (SM-AHN), and mast cell leukemia (MCL), are collectively referred to as advanced systemic mastocytosis (ASM). **Rydapt** is an oral targeted therapy that inhibits FLT3, a driver of AML, and KITD816V, which is associated with advanced SM. **Rydapt** was approved in the US and EU and has since been approved in 14 countries worldwide. **Rydapt** is approved for use in sequential combination with standard daunorubicin and cytarabine in the induction phase; in sequential combination with high-dose cytarabine in the consolidation phase; and in certain countries outside the US as a single agent in the maintenance phase for adults in complete response. **Rydapt** is also approved for use as monotherapy for the treatment of adults with advanced SM. Indications vary by country and not all indications are available in every country. In the US, in addition to the advanced SM indication, **Rydapt** is approved in combination with standard cytarabine and daunorubicin induction and cytarabine consolidation chemotherapy, for the treatment of adult patients with newly diagnosed AML who are FLT3 mutation-positive as detected by an FDA-approved test. **Rydapt** is not indicated as a single-agent induction therapy for the treatment of patients with AML.

**Sandostatin SC** (octreotide acetate for injection) and **Sandostatin LAR** (octreotide acetate for injectable suspension) are somatostatin analogues indicated for the treatment of patients with acromegaly, a chronic disease caused by over-secretion of growth hormone in adults. **Sandostatin SC and Sandostatin LAR** are also indicated for the treatment of patients with certain symptoms associated with carcinoid tumors and other types of gastrointestinal and pancreatic neuroendocrine tumors. **Sandostatin LAR** is approved for treatment of patients with advanced neuroendocrine tumors of the midgut or unknown primary tumor location.

**Signifor LAR** (pasireotide), a somatostatin analogue, was approved in the US on June 30 as a long-acting release formulation for patients with Cushing’s disease. It was approved for this indication in Japan in March 2018 and in the EU in 2017. It is also approved in the EU, US and Japan for patients with acromegaly.

**Tafinlar + Mekinist** (dabrafenib + trametinib) combination is approved in more than 70 countries, including the US, EU member states and Japan, for certain patients with BRAF V600 mutation-positive unresectable or metastatic melanoma, as detected by a validated test. Additional approved indications include patients with BRAF V600 mutation-positive advanced non-small-cell lung cancer, as detected by a validated test; for the adjuvant treatment of patients with BRAF V600E or V600K mutations; involvement of lymph node(s) following complete resection, as detected by an FDA-approved test; and in anaplastic thyroid cancer that cannot be removed by surgery or has spread to other parts of the body (metastatic), and has a type of abnormal BRAF V600E gene. **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. Tafinlar and Mekinist were each acquired from GSK. 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 oncogenic BCR-ABL tyrosine kinase (TKI). Since its launch in 2007, it has been approved in more than 130 countries, including the US, EU member states, Switzerland and Japan, to treat patients with Philadelphia chromosome-positive chronic myeloid leukemia (Ph+ CML) in the chronic and/or accelerated phase who are resistant to or intolerant of existing treatment, including Gleevec/Glivec. Tasigna is also approved to treat newly diagnosed Ph+ CML patients in the chronic phase. Tasigna is the only second-generation TKI that contains treatment-free remission data in its prescribing information. Treatment-free remission is the ability of eligible adult patients with Ph+ CML in chronic phase to maintain deep molecular response after stopping TKI therapy. These patients no longer take daily oral therapy, but continue to be actively managed through frequently scheduled monitoring to identify possible loss of molecular response. More than 50 countries, including the US, EU member states and Switzerland, include TFR information in Tasigna’s prescribing information. Two long-term TFR studies, ENESTfreedom (1st line) and ENESTop (second line after imatinib), showed that about half of all CML patients treated with Tasigna who were eligible to stop Tasigna therapy remained in remission almost three years after stopping therapy. Both TFR studies also confirmed the durability and safety of attempting TFR with Tasigna in eligible patients, as nearly all eligible CML patients who lost major molecular response (MMR) in the TFR phase of the studies regained MMR after restarting Tasigna therapy.

Votrient (pazopanib) is a small molecule tyrosine kinase inhibitor that targets a number of growth factors to limit new blood vessel and tumor growth and cell survival. Votrient is approved in the US for the treatment of patients with advanced renal cell carcinoma (RCC), and in the EU for first-line treatment of adult patients with advanced RCC 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), and in the EU for the treatment of adult patients with selective subtypes of advanced STS who have received prior chemotherapy for metastatic disease or who have progressed within 12 months after (neo)adjuvant therapy. 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 advanced RCC and in more than 90 countries for advanced STS. Votrient was acquired from GSK.

Novartis Pharmaceuticals

Cardio-Metabolic

Entresto (sacubitril/valsartan) is a first-in-class angiotensin receptor/neprilysin inhibitor indicated for the treatment of symptomatic chronic heart failure with reduced ejection fraction (HFrEF). It acts to enhance the protective neurohormonal systems of the heart (neprilysin system) while simultaneously suppressing the harmful system (the renin-angiotensin-aldosterone system, or RAAS). Entresto was approved in the US and in the EU in 2015. Entresto is now approved in more than 100 countries, and launched in more than 70 countries. Both the European Society of Cardiology heart failure guidelines and the US heart failure guidelines have given a class I recommendation, the strongest class of recommendation, for the use of sacubitril/valsartan in patients with HFrEF.
**Immunology, Hepatology and Dermatology**

**Cosentyx** (secukinumab) is a fully human monoclonal antibody that selectively neutralizes interleukin-17A (IL-17A). IL-17A is a cornerstone cytokine involved in the pathogenesis of psoriasis, ankylosing spondylitis and psoriatic arthritis. **Cosentyx** is marketed in 73 countries, including the US, Japan and the EU. Key indications include the treatment of moderate-to-severe plaque psoriasis, ankylosing spondylitis and psoriatic arthritis. Phase III five-year data showed high and long-lasting skin clearance in patients with moderate-to-severe plaque psoriasis with a sustained favorable safety profile. **Cosentyx** in ankylosing spondylitis and psoriatic arthritis showed sustained improvements in signs and symptoms in up to 80% of patients, as well as rapid and sustained pain relief. With **Cosentyx**, almost 80% of ankylosing spondylitis patients have no radiographic progression of the spine at four years. New data presented in 2018 showed that two thirds of patients with moderate to severe plaque psoriasis treated with **Cosentyx** reported no impact of the skin disease on their quality of life.

**Ilaris** (canakinumab) is a selective, high-affinity fully human monoclonal antibody that inhibits interleukin-1β (IL-1β), a key cytokine in the inflammatory pathway, by blocking the action of IL-1β for a sustained period of time. **Ilaris** is approved in more than 70 countries as a treatment for various inflammatory conditions, especially for adults and children with cryopyrin-associated periodic syndrome, systemic juvenile idiopathic arthritis, and the symptomatic treatment of refractory acute gouty arthritis. **Ilaris** is also approved for patients with adult-onset Still’s disease in Europe, and for three rare and distinct types of Periodic Fever Syndromes, also known as Hereditary Periodic Fevers, in the US, Japan and the EU.

**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 the EU, Switzerland and more than 80 countries as a treatment for chronic spontaneous urticaria (CSU), also known as chronic idiopathic urticaria (CIU). CSU is a skin condition that appears spontaneously and causes persistent hives and/or painful deeper swelling of the skin for six weeks or more. The approval for CSU in the EU includes use as add-on therapy for the treatment of CSU in adult and adolescent (12 years and above) patients with inadequate response to H1 antihistamine treatment, and, in the US, for the treatment of adults and adolescents (12 years of age and above) with CIU who remain symptomatic despite H1 antihistamine treatment. In addition, data demonstrated retreatment efficacy with **Xolair** in CSU patients after a treatment pause. 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.

**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 (wet) 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 83 countries, including the EU and Switzerland. Further submissions have been filed in 19 countries. The **Lucentis** pre-filled syringe has now been launched in 33 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. The information published on January 2018 stated that 86 countries had approved **Lucentis’** newest indication. The correct data was 68 countries.
**Travatan** (travoprost), **Travatan Z** (travoprost) and **Duotrov** (travoprost/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**, **Travatan Z**, **Travatan** BAK-Free and **Izba**) are prescribed as first-line agents and are marketed in more than 110 countries, including the US, EU, Canada and China. **DuoTrav** is a fixed-dose combination solution of the prostaglandin analogue travoprost with the beta-blocker timolol and is approved as a second-line treatment in adults for the reduction of IOP in patients with open-angle glaucoma or ocular hypertension who are insufficiently responsive to topical beta-blockers or prostaglandin analogs. **Duotrav** is currently marketed in more than 110 countries, including the EU, Canada and China. The information published on January 2018 stated that travoprost products were marketed in 140 countries. This number included countries in which these products were filed and/or registered but not marketed.

**Respiratory**

**Xolair** (omalizumab) is a recombinant, DNA-derived, humanized IgG1K monoclonal antibody which selectively block IgE, and thereby the early and late phases of the allergic inflammatory cascade. **Xolair** is approved for the treatment for moderate-to-severe, or severe persistent allergic asthma for children (ages six and older) and adults in more than 90 countries, including the US since 2003, the EU since 2005, Japan since 2009 and China since 2018. **Xolair** is provided either as lyophilized powder for resolution or as liquid formulation in a pre-filled syringe in a growing number of markets. Novartis co-promotes **Xolair** with Genentech in the US under a profit sharing agreement, but does not book US sales. Novartis records all sales of **Xolair** outside the US.

**Neuroscience**

**Aimovig** (erenumab) is the first anti-CGRP treatment for migraine prevention to be approved in Australia, Switzerland and the United States. In May 2018, **Aimovig** received a positive opinion from the Committee for Medicinal Products for Human Use (CHMP) of the European Medicines Agency (EMA) and EU approval is anticipated in the coming months. More than 3,000 patients have participated in the **Aimovig** clinical trial program across four placebo-controlled Phase II and Phase III trials in episodic and chronic migraine, their open-label extensions as well as in LIBERTY, a Phase IIIb dedicated study in a difficult-to-treat treatment failure population. Safety and tolerability data at three years showed **Aimovig** had a safety profile consistent with the spectrum and rate of adverse events (AEs) seen in shorter-term placebo-controlled studies with low rates of injection reactions and high tolerability. Novartis and Amgen co-commercialize **Aimovig** in the US. Amgen has exclusive commercialization rights in Japan and Novartis has exclusive commercialization rights in the rest of the world. The companies plan to continue global co-development.

**Gilenya** (fingolimod) is an oral disease-modifying therapy approved to treat relapsing forms of multiple sclerosis (RMS). Since its initial approval for adults with RMS, **Gilenya** has been used to treat more than 255,000 patients worldwide. In May 2018, **Gilenya** received FDA approval for the treatment of children and adolescents 10 to less than 18 years of age with relapsing forms. **Gilenya** has a reversible lymphocyte redistribution effect targeting both focal and diffuse central nervous system damage caused by multiple sclerosis (MS) and impacts four key measures of disease activity: relapses, MRI lesions, brain shrinkage (brain volume loss) and disability progression. **Gilenya** is currently approved in more than 89 countries around the world. **Gilenya** is licensed from Mitsubishi Tanabe Pharma Corporation.

**Established Medicines**

**Galvus** (vildagliptin), an oral Dipeptidyl peptidase-4 (DPP-4) inhibitor, and **Eucreas**, a single-pill combination of vildagliptin and metformin, are indicated for the treatment of type 2 diabetes. The products 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 (also under the trade name *Galvus Met*), and is currently approved in more than 120 countries. 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 EU approved the use of *Galvus* 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 use of vildagliptin in triple combination with metformin and a sulfonylurea is also approved in the EU for the treatment of type 2 diabetes when diet and exercise plus dual therapy with vildagliptin and metformin do not provide adequate glycemic control. *Eucreras* was approved in Japan in 2015 under the name *Equmet* as the first single-pill combination metformin/DPP-4 inhibitor approved in that country.

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 130 countries for treating high blood pressure, in more than 80 countries for heart failure and heart attack survivors. First launched in 1997, Diovan HCT/Co-Diovan is approved in over 120 countries worldwide.

Exelon capsules/oral solution (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. Exelon capsules have been available since 1997 to treat mild to moderate AD dementia and are approved in more than 80 countries. In 2006, Exelon capsules 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 90 countries, including more than 20 countries where it is also approved for Parkinson’s disease dementia. The once-daily formulation 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 (15cm²) to also include the treatment of patients with severe Alzheimer’s disease. In 2013, European Marketing Authorization was also obtained for the higher dose in mild-to-moderate AD. The severe indication has now been approved in more than 10 countries. Exelon Patch was approved in China in 2017.

Exforge (valsartan and amlodipine besylate) is a single-pill combination of the angiotensin II receptor blocker (ARB) valsartan and the calcium channel blocker (CCB) amlodipine. 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 130 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 100 countries.

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 treating selected autoimmune disorders such as psoriasis and rheumatoid arthritis. First launched in 1995, Neoral is marketed in approximately 100 countries.
**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 approximately 120 countries. Diclofenac is available as various formulations with different salts, which are: diclofenac sodium/potassium/resinate/free acid/diethylamine. This product is marketed in a wide variety of dosage forms, including tablets, drops, suppositories, ampoules and topical therapy. Novartis transferred its rights for the over-the-counter products of **Voltaren** to GSK.

**Zortress/Certican** (everolimus) is an oral inhibitor of the mammalian target of rapamycin (mTOR) pathway, indicated to prevent organ rejection following solid organ transplantation. Under the trade name **Certican**, it is approved in more than 90 countries to prevent organ rejection for renal and heart transplant patients, and in addition, in more than 70 countries worldwide to prevent organ rejection for liver transplant patients. In the US, under the trade name **Zortress**, the drug is approved for the prophylaxis of organ rejection in adult patients at low-moderate immunologic risk receiving a kidney transplant as well as for the prophylaxis of allograft rejection in adult liver transplant recipients. Everolimus is also available from Novartis in different dosage strengths and for different uses in non-transplant patient populations under the brand names **Afinitor**, **Afinitor Disperz** and **Votubia**. Everolimus is also exclusively licensed to Abbott and sublicensed to Boston Scientific for use in drug-eluting stents.

**Key Development Projects**

**ABL001** (asciminib) is a potent and specific inhibitor of the protein BCR-ABL. It binds to a distinct region of the protein, resulting in a mechanism of action that is different compared to tyrosine kinase inhibitors (TKIs) approved to treat Philadelphia chromosome-positive chronic myelogenous leukemia (Ph+ CML). Because of its unique receptor binding site, the compound may have the potential to be prescribed in combination with TKIs approved to treat Ph+ CML. Clinical trials investigating ABL001 are ongoing. A Phase III clinical study was initiated in October 2017 comparing the efficacy of ABL001 versus bosutinib in patients with CML-CP who are either resistant or intolerant to two prior TKIs.

**ACZ885** (canakinumab) was first approved in 2009 for cryopyrin-associated periodic syndromes as **Ilaris**. In 2017, data from CANTOS, a Phase III study evaluating quarterly injections of ACZ885 in people with a prior heart attack and inflammatory atherosclerosis, was presented at the European Society of Cardiology Congress and published simultaneously in The New England Journal of Medicine and The Lancet. CANTOS met its primary endpoint with a statistically significant 15% reduction of major adverse cardiovascular events (MACE) in patients with a prior heart attack and inflammatory atherosclerosis who were treated with 150mg of ACZ885 in addition to standard of care including lipid-lowering therapy. This effect was driven by 24% relative reduction in risk of heart attack. A non-significant 10% reduction in risk of cardiovascular death was also observed. A sub-group of study participants, in the 150 mg arm, whose inflammation was reduced below the median high-sensitivity C-reactive protein level, measured at three months after one dose of treatment, saw a 27% relative risk reduction on the primary MACE endpoint. Inflammation in the tumor micro-environment, mediated by interleukin-1ß, is hypothesized to play a major role in cancer invasiveness, progression and metastasis. Accordingly, Novartis conducted a sub-analysis of the CANTOS data to assess whether IL-1ß inhibition with canakinumab may reduce the incidence of site-specific cancers and warrant further investigation. A review of a blinded, pre-planned oncology safety analysis revealed, during the median 3.7-year follow-up period, a 77% reduction in lung cancer mortality and 67% reduction in lung cancer incidence in patients treated with 300 mg of ACZ885 vs placebo and without a previous diagnosis of cancer. After consultations with health authorities, Novartis is studying the efficacy and safety of ACZ885 in NSCLC in three pivotal NSCLC studies.
**AVXS-101** is a gene therapy candidate currently in development for the one-time treatment of spinal muscular atrophy (SMA) Types 1, 2 and 3. SMA is caused by a genetic defect in the *SMN1* gene that codes SMN, a protein necessary for survival of motor neurons, that leads to progressive muscle weakness and paralysis and is the leading cause of genetic infant mortality. AVXS-101 is designed to address the monogenic root cause of SMA and prevent further muscle degeneration by addressing the defective and/or loss of the primary SMN gene. AVXS-101 also targets motor neurons, providing rapid onset of effect and crossing the blood brain barrier to allow effective targeting of both central and systemic features. AVXS-101 is currently being studied in a US pivotal trial in patients with SMA Type 1 (STR1VE), Phase 1 US trial in patients with SMA Type 2 (STRONG) and a multi-national trial in pre-symptomatic patients with SMA Types 1, 2 and 3 (SPR1NT). A pivotal trial in the EU (STR1VE EU) is expected to initiate in the first half of 2018, and a Phase 3 trial in pediatric SMA patients with Types 1, 2 and 3 (REACH) is expected to initiate late in the fourth quarter of 2018 or early 2019. A BLA for intravenous delivery of AVXS-101 is expected to be filed with the FDA in the second half of 2018.

**Arzerra** (ofatumumab) is a fully 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. Arzerra is approved as monotherapy for the treatment of patients with CLL who are refractory after prior treatment with fludarabine and alemtuzumab, and is also approved for other indications in CLL in the US and EU. A Phase III trial to investigate ofatumumab in refractory non-Hodgkin’s lymphoma (NHL) did not meet its primary endpoint and an indication in NHL will not be pursued. Novartis is also investigating ofatumumab (disclosed as OMB157) in two Phase III studies for relapsing multiple sclerosis. Arzerra is marketed under a license agreement between Novartis and Genmab A/S.

**BAF312** (siponimod) is an oral, second-generation sphingosine 1-phosphate (S1P) receptor modulator under development for the treatment of secondary progressive multiple sclerosis (SPMS). BAF312 binds selectively to the sphingosine 1-phosphate receptor subtypes 1 and 5, and distributes effectively to the brain where it may impact central nervous system inflammation and repair mechanisms. Results from the Phase III EXPAND study, evaluating efficacy and safety for SPMS were published in *The Lancet* in March 2018. The findings showed that BAF312 improved outcomes for people living with SPMS and reduced three- and six-month confirmed disability progression against placebo, with a safety profile similar to fingolimod. Additional analyses from EXPAND showed that BAF312 reduced the risk of disability progression largely disassociated from relapses in patients with secondary progressive multiple sclerosis (SPMS) and had meaningful benefit on patients’ cognitive processing speed. Novartis is planning to file BAF312 in the US and EU in 2018 for SPMS. If approved, siponimod would be the first disease-modifying therapy to delay disability progression in typical SPMS patients, including many who had reached a non-relapsing stage and high level of disability.

**BYL719** (alpelisib) is an investigational alpha-specific PI3K inhibitor. In patients living with advanced or metastatic breast cancer (aBC) who harbor a PIK3CA mutation, BYL719 has demonstrated antitumor activity by potentially inhibiting the PI3K pathway. Preclinical data suggest targeting the alpha isoform of PI3K may offer improved specificity and a different adverse event profile compared to pan-PI3K inhibitors that are less selective. Novartis is studying BYL719 in the Phase III registration trial SOLAR-1, in combination with fulvestrant for the treatment of hormone-receptor positive, human epidermal growth factor receptor-2 negative (HR+/HER2-) aBC in adult men and postmenopausal women who received prior treatment with an aromatase inhibitor. Novartis is also studying BYL719 in the Phase II BLYieve trial in combination with fulvestrant or letrozole in adult men and pre- and postmenopausal women with HR+/HER2- aBC with PIK3CA mutation who have progressed on or following prior CDK4/6 inhibitor therapy.

**CTL019** (tisagenlecleucel, approved in the US as Kymriah) is a CD19-directed genetically modified autologous chimeric antigen receptor T (CAR-T) cell therapy that uses the patient’s
own immune system to fight certain types of cancer. CARs are engineered proteins that enable a patient’s own T cells to seek out specific target proteins present on a patient’s cancerous tumor. When these 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 associated with a number of B-cell malignancies. In August 2017, the FDA approved CTL019 as Kymriah for the treatment of patients up to 25 years of age with B-cell precursor acute lymphoblastic leukemia (ALL) that is refractory or in second or later relapse. In May 2018, Kymriah was approved in the US for the treatment of adult patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL) after two or more lines of systemic therapy, including diffuse large B-cell lymphoma (DLBCL) not otherwise specified (the most common type of non-Hodgkin lymphoma); high grade B-cell lymphoma, and DLBCL arising from follicular lymphoma. Kymriah is not indicated for the treatment of patients with primary central nervous system lymphoma. Both indications received priority review by the FDA. In the EU, in June 2018, the CHMP issued a positive opinion on the Marketing Authorization Application for the treatment of adult patients with relapsed/refractory DLBCL after two or more lines of systemic therapy, and for pediatric and young adult patients up to age 25 with relapsed/refractory B-cell ALL that is refractory, in relapse post-transplant, or in second or later relapse. This year, Novartis is starting pivotal clinical studies of CTL019 in relapsed/refractory follicular lymphoma, adult relapsed/refractory ALL, first-line high-risk pediatric ALL, DLBCL after first relapse, and relapsed/refractory chronic lymphocytic leukemia. Novartis and the University of Pennsylvania’s Perelman School of Medicine, which developed this CD19-directed CAR T cell therapy, have a global collaboration to research, develop and commercialize CAR-T therapies for the investigational treatment of cancers.

Cosentyx (secukinumab) is a fully human monoclonal antibody that selectively neutralizes circulating IL-17A. Cosentyx is in Phase III development in non-radiographic axial spondyloarthritis. We expect results from this trial in 2019. Cosentyx is also in a Phase III head-to-head clinical trial in psoriatic arthritis against Humira® (adalimumab) and a Phase III head-to-head clinical trial in ankylosing spondylitis against the proposed biosimilar adalimumab in development by Sandoz. In May 2018, Novartis announced the plan to initiate ARROW, a head-to-head trial assessing the mechanistic superiority of direct IL-17A inhibition over IL-23 inhibition.

EMA401 is a novel angiotensin II Type 2 receptor (AT₂R) antagonist. Targeting AT₂R is an emerging approach to neuropathic pain treatment. AT₂R antagonists block the pain signaling pathways in the peripheral nervous system. The first Phase II study to assess the potential of EMA401 in post herpetic neuralgia was initiated in 2017, with the second Phase II in painful diabetic neuropathy study initiated in the first quarter of 2018.

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.

Gilenya (fingolimod) is a sphingosine 1-phosphate receptor modulator approved for the treatment of relapsing forms of multiple sclerosis in adults as Gilenya. Results from the Phase III PARADIGMS study, investigating the safety and efficacy of oral once-daily Gilenya in children and adolescents (ages 10 to 17) with multiple sclerosis showed that oral fingolimod resulted in an 82% reduction in the number of relapses in the patient population over a period of up to two years, compared to interferon beta-1a intramuscular injections. In December 2017, the FDA granted Gilenya Breakthrough Therapy designation for relapsing forms of multiple sclerosis in pediatric patients (ages 10 to 17). Gilenya is not currently approved for pediatric use.
INC280 (capmatinib) is an investigational, highly selective MET inhibitor. In June 2016, Novartis initiated ongoing Phase II studies to prospectively explore the efficacy and safety of capmatinib in patients with MET molecular aberrations (including MET amplification and MET exon 14 mutation) in advanced non-small cell lung cancer. INC280 is licensed by Novartis from Incyte Corporation.

Jakavi (ruxolitinib) is an oral inhibitor JAK 1/2 inhibitor currently in Phase III development in acute graft-versus-host disease and chronic graft-versus-host disease. 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.

KAF156 belongs to a novel class of antimalarial compounds called imidazolopiperazines. It has the potential to clear malaria infection, including resistant strains, as well as 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 $P$. falciparum and $P$. vivax parasites. In August 2017, Novartis began a Phase IIb study to test multiple dosing combinations and dosing schedules of KAF156 and lumeferantrine, including the feasibility of a single dose therapy in adults, adolescents and children.

Kisqali (ribociclib) is a selective cyclin-dependent kinase inhibitor that helps slow the growth of tumors by inhibiting two proteins called cyclin-dependent kinase 4 and 6 (CDK4/6). Novartis is continuing to assess Kisqali through the MONALEESA clinical trial program, which includes MONALEESA 2, MONALEESA 3 and MONALEESA 7. These trials are evaluating Kisqali in multiple endocrine therapy combinations across a broad range of patients, including premenopausal women. MONALEESA-3 showed that Kisqali plus fulvestrant demonstrated superior efficacy, with a median progression-free survival (PFS) of 20.5 months vs. 12.8 months for fulvestrant alone, among overall study population of first- and second-line postmenopausal patients with HR+/HER2- aBC. The most common (≥5%) grade 3/4 adverse events in patients receiving Kisqali plus fulvestrant compared to fulvestrant alone were neutropenia (53.4% vs 0%) and leukopenia (14.1% vs 0%). MONALEESA-7 showed that Kisqali plus an oral endocrine partner demonstrated significant efficacy with sustained benefit of nearly two years (median PFS 23.8 vs 13.0 months for endocrine therapy alone) in premenopausal or perimenopausal women with HR+/HER2- advanced or metastatic breast cancer. The most common (≥5%) grade 3/4 adverse events in patients receiving Kisqali combination therapy compared to endocrine therapy alone were neutropenia (60.6% vs 3.6%) and leukopenia (14.3% vs 1.2%). In addition, Novartis will be collaborating with Translational Research In Oncology (TRIO) on an upcoming phase III clinical trial of ribociclib with endocrine therapy in the adjuvant treatment of HR+/HER2- early breast cancer (EBC). The trial will be called NATALEE (New Adjuvant TriAl with LEE).

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 (tropifexor) 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, inducing B cell depletion. Phase Ib results in MS patients were presented in 2014 showed significant and meaningful reduction in the number of new inflammatory brain lesions in the first 24 weeks of ofatumumab administration. Novartis initiated a Phase III program for OMB157 in relapsing MS in August 2016. The program is on track, and 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.

**PDR001** (spartalizumab) is an investigational PD-1 antagonist that may restore the ability of immune cells to induce cell death and fight cancer. PDR001 is currently being evaluated in a Phase III trial in combination with Tafinlar + Mekinist for metastatic BRAF V600+ melanoma.

**QAW039** (fevipiprant) is being investigated in the reduction of asthma attacks in patients with severe asthma and in the improvement of lung function in patients with moderate asthma. This compound is designed to block the activity of the DP2 receptor, an upstream driver of allergen- and non-allergen dependent inflammation in asthma, resulting in reduction in IL-4, IL-5, and IL-13, inhibition of eosinophil migration, and inhibition of smooth muscle cells growth in the airway. Phase II clinical data shows a positive effect on symptoms (asthma control questionnaire) and lung function, and reduction in sputum eosinophils.

**QMF149** (indacaterol acetate/mometasone furoate) is a once daily fixed-dose combination being investigated in asthmatic patients who are uncontrolled on an inhaled corticosteroid. QMF149 combines indacaterol acetate (an inhaled long-acting beta2-adrenergic agonist with 24-hour duration of action) and mometasone furoate (an inhaled corticosteroid with 24 hour duration of action) delivered via the Breezhaler device, a single dose dry powder inhaler. QMF149 is currently in Phase III clinical trials to support registration outside the US.

**QVM149** (indacaterol acetate, glycopyrronium bromide, mometasone furoate) is a fixed-dose combination of indacaterol acetate (an inhaled long-acting beta2-adrenergic agonist with 24-hour duration of action), glycopyrronium bromide (an inhaled long-acting muscarinic antagonist with 24-hour duration of action), and mometasone furoate (an inhaled corticosteroid with 24-hour duration of action) in development for once-daily maintenance treatment of poorly controlled asthmatic patients to be delivered via the Breezhaler device, a single dose dry powder inhaler. All three mono-components have previously been developed as individual drugs for either chronic obstructive pulmonary disease or asthma. QVM149 is currently in Phase III clinical trials to support registration outside the US.

**RLX030** (serelaxin) is a novel recombinant form of the human hormone relaxin 2, and is believed to act through multiple mechanisms to reduce stress on the heart, kidneys and other organs. In 2017, Novartis announced the global Phase III RELAX-AHF-2 study investigating the efficacy, safety and tolerability of RLX030 in patients with acute heart failure (AHF) did not meet its primary endpoints of reduction in cardiovascular death through day 180 or reduced worsening heart failure through day five when added to standard therapy in patients with AHF.

**RTH258** (brolucizumab) is a single-chain antibody fragment that acts as an anti-vascular endothelial growth factor (anti-VEGF) agent. Brolucizumab is currently in development for neovascular (wet) age-related macular degeneration (nAMD) and diabetic macular edema. In nAMD, brolucizumab met its primary efficacy endpoint of non-inferiority to aflibercept in mean change in best-corrected visual acuity in two Phase III studies. Additionally, superiority was shown in three pre-specified secondary endpoints that are considered key markers of nAMD disease, central subfield retinal thickness (CST), retinal fluid (intraretinal fluid and/or subretinal fluid) and disease activity. These results were achieved with more than 50% of patients maintained on a 12-week treatment interval (q12w) immediately following the loading phase to week 48 (secondary endpoint). The findings from a pre-specified secondary analysis showed that patients assessed as appropriate for q12w after loading had more than a 80%
probability of being maintained on q12w through week 48. Target filing of the nAMD indication is Dec 2018, upon completion of activities and documentation to support the commercial scale-up of the product. Phase III studies in diabetic macular edema are scheduled to start in 2018.

SEG101 (crizanlizumab) is a humanized anti-P-selectin monoclonal antibody that is being investigated in the prevention of vaso-occlusive crises (VOC) in patients with sickle cell disease (SCD), a hereditary blood disorder characterized by sickle-shaped red blood cells and which early on progresses into a systemic vascular disease. This progression to chronic vascular disease is the primary driver of recurring vaso-occlusive events, including pain crises. Results from the Phase II SUSTAIN study demonstrated that crizanlizumab reduced the median annual rate of VOCs leading to a healthcare visit, compared to placebo in patients with or without hydroxyurea therapy. Novartis acquired crizanlizumab as part of a corporate acquisition in 2016.

Tafinlar (dabrafenib) targets the serine/threonine kinase BRAF in the RAS/RAF/MEK/ERK pathway and Mekinist (trametinib) 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 being evaluated in a Phase III trial in combination with PDR001 for metastatic BRAF V600+ melanoma, in a Phase II trial for neuroendocrine tumors and in Phase I trials in other tumor types.

UNR844 has the potential to be a first-in-class topical treatment in development for presbyopia. UNR844 is believed to work through reduction of disulfide bonds, softening the crystalline lens. 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 25 patients receiving topical UNR844 and 25 patients receiving a placebo. UNR844 treatment led to an improvement in distance-corrected near vision, compared to the placebo treatment. 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 (BAFF-R) with enhanced antibody-dependent cell-mediated cytotoxicity against BAFF-R positive B cells. VAY736 is in Phase II development for the treatment of primary Sjögren’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. VAY736 is also being tested for patients with autoimmune hepatitis, another chronic autoimmune disorder, characterized by hepatocyte injury and destruction of the liver architecture leading to fibrosis/cirrhosis, and ultimately to end stage liver disease requiring liver transplantation.

VAY785 (emricasan) is an investigational, first-in-class, oral, pan-caspase inhibitor being investigated for the treatment of chronic liver diseases including nonalcoholic steatohepatitis (NASH) with advanced fibrosis (scarring) and cirrhosis. In multiple Phase II clinical trials, VAY785 has demonstrated significant, rapid and sustained reductions in elevated levels of key biomarkers of inflammation and cell death, which play a role in the severity and progression of liver disease. VAY785 is being developed in collaboration with Conatus Pharmaceuticals Inc.

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
tumors are ALK+. In June 2017, the European Commission approved expanding the use of Zykadia for the first-line treatment of patients with metastatic non-small cell lung cancer whose tumors are ALK+, as detected by an FDA-approved test. In June 2017, the European Commission approved expanding the use of Zykadia for the first-line treatment of patients with advanced non-small cell lung cancer whose tumors are ALK+.

Zykadia (ceritinib) is a potent and highly selective oral anaplastic lymphoma kinase (ALK) inhibitor that is in development for ALK positive (ALK+) cancers. In May 2017, the FDA approved the expanded use of Zykadia to include the first-line treatment of patients with metastatic non-small cell lung cancer whose tumors are ALK+. In May 2017, the FDA approved the expanded use of Zykadia to include the first-line treatment of patients with metastatic non-small cell lung cancer whose tumors are ALK+.

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