# INNOVATION

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PHOTO ESSAY

## Priming the body's own defenses against cancer

Novartis is working with the University of Pennsylvania in the US to develop a new personalized cancer treatment called chimeric antigen receptor T-cell therapy, or CART for short. Much work will be needed to develop this experimental technology, but if researchers are successful, it has the potential to alter the course of cancer care.

Researchers take patients' T-cells, which are white blood cells that help fight infections, and genetically modify them in super-clean laboratories to recognize a protein expressed by cancer cells. Researchers then reinfuse these T-cells into the patients' blood where they aim to hunt down and eradicate tumor cells.

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# INNOVATION OVERVIEW

*During the past year, we continued to sharpen our research and development strategy and execution. We are prioritizing our most promising new drug candidates and focusing on disease areas where there is patient need and where scientific advances present new opportunities for breakthroughs. Our researchers continue to push the boundaries of science, working to broaden our understanding of diseases, and developing novel medicines and products to address high unmet medical need.*

We believe innovation that produces breakthrough medicines, devices and solutions will be critical in the healthcare industry in the coming years as demographic trends increase pressure on health systems to produce the best results at the lowest overall cost.

To drive innovation at Novartis, in 2015 we invested USD 8.9 billion in research and development for new drugs and medical devices, or 18% of net sales. More than 200 research and development projects are underway, 137 of them in the Pharmaceuticals Division.

Our research and development strategy sets clear priorities. We concentrate on therapeutic areas where there is patient need and where scientific advances present new opportunities, including oncology, cardiovascular, eye care, biosimilars and neuroscience.

We are also exploring new scientific frontiers in areas with great potential for innovation, including immuno-oncology, aging and regenerative medicine, and infectious diseases.

## DRUG DISCOVERY

The Novartis Institutes for BioMedical Research (NIBR) is the innovation engine of Novartis. More than 6 000 NIBR scientists and physicians worldwide work to discover potentially groundbreaking therapies, using molecular signaling pathways – the communication highways inside cells – as a guide for drug discovery. When new molecular entities have been qualified for testing in humans, small-scale proof-of-concept studies are conducted to get an early read on a drug's safety and effectiveness.

More than 80% of compounds in development at Novartis were discovered internally. Likewise, two of the most significant Novartis medicines to receive approval from the US Food and Drug Administration in 2015, *Cosentyx* for psoriasis, and *Entresto* for chronic heart failure, were in-house discoveries.

Novartis maintains alliances with other research organizations to augment in-house capabilities, including more than 300 with academic institutions and more than 100 with biotechnology and pharmaceutical organizations. Novartis added 41 new alliances in 2015.

One example was in gene editing. Novartis formed collaborations with Intellia Therapeutics and Caribou Biosciences to develop expertise in CRISPR, a technology likened to a molecular scalpel for genomes. It enables researchers to alter the genome of a living cell in a specific and reproducible fashion, offering unique opportunities for drug discovery.

## DRUG DEVELOPMENT

After a successful proof-of-concept study, new medicines move into clinical development. Development processes at Novartis vary by division because of the different types of products involved. In the Pharmaceuticals Division, in Ophthalmic Pharmaceuticals at Alcon and at Sandoz for biosimilars, Novartis scientists build development plans with practicing physicians and health authorities.

Clinical trials can involve large numbers of patients and can last from two to five years, depending on the indication and patient population. For other products, such as medical devices or generic drugs, the process can be much shorter. At Alcon, researchers develop new devices and surgical instruments with eye surgeons and research institutes. Development at Sandoz for generics typically involves small clinical studies to show the generic version is equivalent to the original branded medicine.

Even when a proof-of-concept study yields a positive result, rigorous prioritization means a therapy may not be developed at Novartis. In such cases, we may license the compound to another company. For example, in 2015 we sold three mid-stage experimental therapies to Mereo BioPharma Group in exchange for a

**8.9 bn**

Group research and development spending in 2015, amounting to 18% of net sales (USD)

**200 +**

Research and development projects underway at Novartis

*More than 80% of compounds in development at Novartis were discovered internally*

**25**

Biological pathways associated with cancer progression under study at Novartis

**14 m**

New cases of cancer worldwide every year, a figure the WHO believes will rise 70% by 2035

19.5% equity investment in Mereo – BPS804 for brittle bones, BCT197 for respiratory ailments, and BGS649 for low testosterone levels in obese men.

## ONCOLOGY

Cancer remains a serious public health challenge, with 14 million new cases a year and 8.2 million cancer-related deaths annually, according to the World Health Organization (WHO). The number of new cancer cases is expected to rise about 70% within the next two decades – with more than 60% of these in Africa, Asia and Latin America.

It is a critical time in cancer research and development, with groundbreaking advancements happening at a rapid pace. We take a holistic approach to oncology research, growing our presence in targeted treatments and investing significantly in immuno-oncology.

Our focus is on five common types of cancer – melanoma, hematology, lung, breast and renal – with a continued interest in other types where we see significant unmet medical need. We actively pursue the development of novel treatments across our targeted therapy and immuno-oncology portfolios, along with revolutionary cell therapy treatments such as chimeric antigen receptor T-cell (CART) technology.

### Melanoma

Data show that combinations of multiple therapies can lead to better outcomes for patients, short-circuiting cancer's ability to use an alternative disease pathway and continue growing. In melanoma, we have seen the important role the mitogen-activated protein kinase (MAPK) signaling pathway, also known as the RAS-RAF-MEK-ERK pathway, plays in cell proliferation.

Mutations in this pathway have the potential to make normal cells become cancerous, and mutations of the RAF protein, BRAF, are found in about half of all melanomas. The combination of *Tafinlar* (dabrafenib), targeting BRAF, and *Mekinist* (trametinib), targeting MEK – another key protein in this pathway – has demonstrated a significant overall survival benefit in two Phase III studies for patients with BRAF V600E/K mutation-positive metastatic melanoma.

This combination was approved in both the EU and the US in 2015. We are also focusing on the study of a triple combination approach with *Tafinlar* + *Mekinist* and immuno-oncology therapy.

### Hematology

We continue to develop treatments for blood cancers. We expanded our portfolio this year with a new indication for *Jakavi* in polycythemia vera, a disorder of the bone marrow; the approval of *Farydak* for multiple myeloma; and the addition of *Promacta*, an oral medicine that increases the number of platelets in the blood.

In chronic myelogenous leukemia we are studying ABL001, a small molecule designed to inhibit BCR-ABL – an abnormal gene found in most patients with the disease. Researchers studying drug resistance found cancer cells can sometimes reactivate BCR-ABL after treatment, enabling them to resume their destructive activity. Because ABL001 has a novel mechanism of action, it may prevent the cancer cells from doing this and becoming resistant to existing drugs. Numerous combination approaches of ABL001 with other therapies, including immuno-oncology, are being explored for future study.

# INNOVATION OVERVIEW
continued

**Lung**
*Zykadia* (ceritinib) gained EU approval in May for certain patients with anaplastic lymphoma kinase-positive (ALK+) forms of non-small cell lung cancer. This is a new option for patients whose disease has progressed or who are intolerant to an existing therapy, and it specifically targets the genetic makeup of their cancer. We are studying additional mutational targets using our *Tafinlar* + *Mekinist* combination therapy and INC280, our c-MET inhibitor. A recent Phase II study of *Tafinlar* + *Mekinist* showed the combination approach was effective in shrinking tumors in patients with non-small cell lung cancer.

We are researching a potential combination therapy that involves a targeted treatment and an immuno-oncology treatment. We have three combinations with Opdivo®, a PD-1 checkpoint inhibitor, including *Zykadia*, INC280 and EGF816, as part of a collaboration with Bristol-Myers Squibb Co. Clinical trials began early in 2015 to evaluate their efficacy in treating non-small cell lung cancer.

**Advanced breast cancer**
We are exploring molecules that target the PI3K/mTOR pathway, including BKM120 and BYL719, to treat advanced breast cancer. We are also identifying other pathways, such as through LEE011, a small-molecule inhibitor of cyclin-dependent kinase 4 and 6 (CDK4/6).

CDK4 and CDK6 are both components of a switch that controls the cell cycle. Early data suggest LEE011 could benefit patients with advanced breast cancer in combination with standard endocrine therapy.

We are also exploring the possibility of inhibiting multiple pathways simultaneously along with endocrine therapy.

**Renal cell carcinoma**
We are examining the role immuno-oncology can play in the treatment of renal cell carcinoma. Currently, we have an early study of *Votrient* in combination with Keytruda® (MK3475, a PD-1 checkpoint inhibitor) from Merck & Co., and we are exploring the potential of immuno-oncology and immuno-oncology combinations.

**Immuno-oncology**
Our entry into immuno-oncology is focused on understanding the mechanisms involved in a protective immune response. We have six programs in clinical trials and five more expected to enter the clinic by the end of 2016. Our portfolio includes programs based on checkpoint inhibitors for three particular proteins – PD1, TIM3 and LAG3 – acquired from CoStim Pharmaceuticals in 2014.

Also in early development is a novel form of small-molecule therapies called cyclic dinucleotides (CDNs). These next-generation cancer immunotherapies target a cell-signaling pathway known as stimulator of interferon genes (STING). While checkpoint inhibitors are potent in specific tumor types, preclinical studies with Aduro Biotech indicate CDNs may help the body recognize and fight several cancers. We are also collaborating with partners to develop immuno-oncology and targeted therapy combinations.

In October, we added IL-15, adenosine receptor and TGF-beta inhibition programs through the acquisition of Admune Therapeutics as well as licensing agreements with XOMA and Palobiofarma. All three will be explored as monotherapies and in combination with CART technology, novel checkpoint inhibitors, STING agonists and our portfolio of targeted therapies.

**Cell and gene therapy**
Novartis is exploring novel therapies to prime the immune system against tumors or malignancies, including CART technology, being developed with the University of Pennsylvania in the US.

This novel therapy takes patients' white blood cells and re-engineers them to identify and destroy specific cancer cells. CTL019 is in Phase II development for the treatment of relapsed/refractory pediatric acute lymphoblastic leukemia (ALL) and diffuse large B-cell lymphoma (DLBCL).

We continue to work on this revolutionary approach to tackling cancer and we are expanding our trials beyond the US to Europe. We boosted our T-cell processing capacity in 2015, opening a new manufacturing facility in Morris Plains, New Jersey in the US.

6

Immuno-oncology programs in clinical trials with five more expected to enter the clinic by the end of 2016

21%

Reduction in heart failure hospitalizations among patients using *Entresto* in a clinical trial, a clear benefit over existing treatments

26 m+

People worldwide living with heart failure

## CARDIOVASCULAR

Heart failure, which affects more than 26 million people worldwide, is a difficult-to-treat chronic condition in which the heart cannot pump enough blood around the body. It is the leading cause of hospitalization among adults over age 65 in the Western world. About 25% of patients with the disease die within a year of diagnosis and 50% are dead within five years.

Approval in 2015 in the US and EU of *Entresto*, formerly LCZ696, marked a significant advance for patients with chronic heart failure with reduced ejection fraction – when the heart muscle does not contract effectively.

A major study showed *Entresto* reduced the risk of death from cardiovascular causes as well as hospitalizations due to heart failure by 20% and 21%, respectively. LCZ696 is also being assessed in patients who have heart failure with preserved ejection fraction, another form of the disease.

Furthermore, a clinical trial studying RLX030 (serelaxin) in acute heart failure is expected to report in 2017. The study may show whether serelaxin can reduce death and hospitalization rates for patients who have already experienced an episode of acute heart failure.

Coronary artery disease is another area of high unmet medical need. Despite advances in secondary prevention, many patients remain at high risk of stroke, recurrence of heart attacks, and cardiovascular death due to vascular inflammation. ACZ885 is a selective interleukin-1 beta inhibitor currently marketed for the treatment of auto-inflammatory diseases. A trial in more than 10 000 patients who previously had a heart attack is underway. It will determine whether blocking systemic inflammation in these patients can reduce the risk of further cardiac problems. If positive, it will provide a novel cytokine-based therapy for the secondary prevention of cardiovascular disease.

Novartis is also developing new digital technologies to help heart failure patients adhere to their treatment and monitor vital signs. In November, we launched Heart Partner, a heart failure smartphone application for patients and caregivers to help manage treatment. This highlights our commitment to go beyond the pill and ensure the best possible outcomes for patients.

## RESPIRATORY

Some respiratory diseases are so severe patients have to fight for breath while carrying out simple tasks. Novartis is developing treatments for several respiratory illnesses, including chronic obstructive pulmonary disease (COPD), a life-threatening yet preventable and treatable lung disease affecting 210 million people worldwide and caused mainly by smoking and air pollution.

In October, we received US approval for QVA149 in patients with moderate-to-severe COPD. QVA149 combines two active substances, glycopyrronium bromide and indacaterol. Two pivotal studies showed this combination improved lung function compared to the individual components. Outside the US, QVA149 has been marketed as *Ultibro Breezhaler*, and a large study comparing it with the widely used medicine Seretide® showed *Ultibro* reduced the risk of COPD exacerbations. In early 2016, Novartis announced a collaboration with Qualcomm to provide patients with real-time access to data on their use of the inhaler used in several Novartis COPD treatments, including *Ultibro Breezhaler*. Patients will access the data transmitted wirelessly by the Qualcomm digital monitor via a smartphone and Novartis COPD mobile application.

Asthma remains the most common respiratory disease worldwide and Novartis aims to expand its portfolio beyond *Xolair*. A pivotal trial of QVM149 started in 2015, studying a once-daily combination of drugs called long-acting beta agonists and long-acting muscarinic agents with an inhaled corticosteroid in a single device.

A Phase III study for QAW039, a potential first-in-class oral anti-inflammatory treatment for asthma, is also underway. This has the potential to reduce asthma exacerbations and has a safety profile that may be suitable for children, for whom asthma is the most common chronic disease.

# INNOVATION OVERVIEW
continued

Another potential therapy, QGE031 (ligelizumab) is in Phase II trials. It could become the first of a new generation of anti-IgE antibody treatments for severe asthma, chronic urticaria (hives) and other indications. IgE (immunoglobulin E) has been implicated in mediating many chronic inflammatory and allergic diseases. Data show QGE031 achieved better suppression of IgE than *Xolair* and that deeper IgE suppression translates to superior efficacy in blocking allergic responses in patients' skin and lungs.

## IMMUNOLOGY AND DERMATOLOGY

Immune system disorders affect hundreds of millions worldwide and can severely impact quality of life and even life expectancy.

In early 2015, we received approval in the US and EU for *Cosentyx*, a monoclonal human antibody targeting a protein called interleukin-17A (IL-17A) for the treatment of moderate-to-severe plaque psoriasis in adults. As IL-17A stimulates inflammation, we are also pursuing *Cosentyx* for use in immune-related disorders such as psoriatic arthritis (PsA) and ankylosing spondylitis (AS), a debilitating chronic condition that leads to excessive formation of new bone, resulting in spinal damage. A recent Phase III study in AS showed significant improvement in patient symptoms after one year of treatment. *Cosentyx* was approved for both AS and PsA in Europe in 2015, and in the US in January 2016.

Work is also underway with QAW039 for atopic dermatitis, the most common form of eczema, following a positive proof-of-concept trial in adults with a moderate-to-severe form of the disease.

## NEUROSCIENCE

In neuroscience we are studying conditions such as multiple sclerosis (MS), neuropathic pain, sporadic inclusion body myositis (sIBM), migraine and Alzheimer's disease. Disorders of the brain, including forms of dementia and mental illness, affect hundreds of millions worldwide.

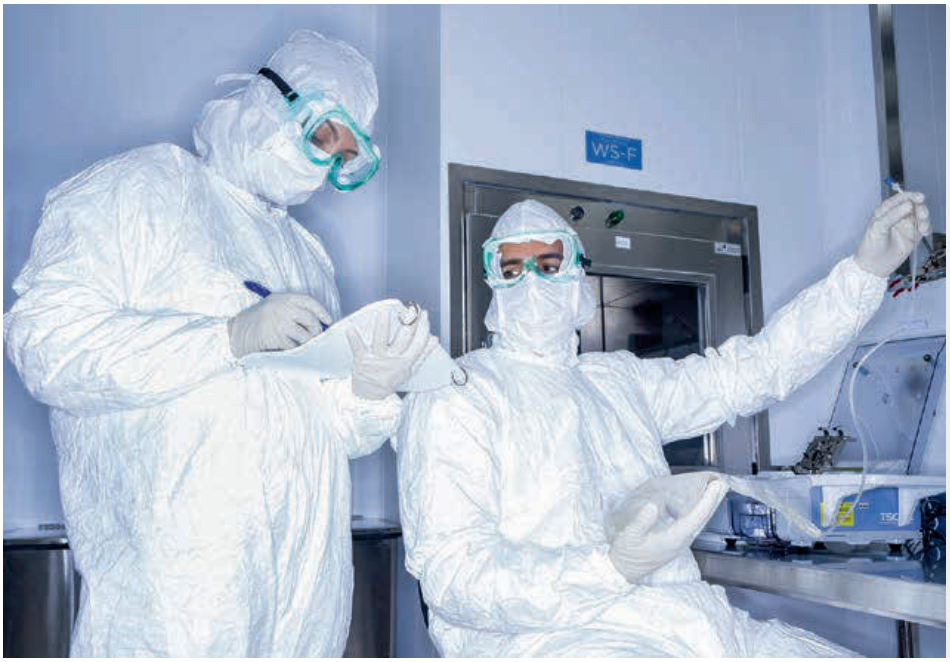
### Multiple sclerosis

Novartis is studying ways of treating progressive forms of MS, which are the most significant source of disability and for which there are no approved therapies.

We are studying BAF312, or siponimod, a second-generation selective S1P1/5 receptor modulator, in the largest Phase III trial in secondary progressive MS.

*Cosentyx was shown to be effective for three indications: psoriasis, psoriatic arthritis and ankylosing spondylitis*

*We are studying BAF312, or siponimod, in the largest Phase III trial in secondary progressive MS*




Research scientists wear multiple layers of protective clothing as part of a strict anti-contamination protocol at the Novartis cell processing facility in Morris Plains, New Jersey in the US.

44m

People globally have Alzheimer's disease or a related dementia

We are also working to broaden our portfolio of MS treatments. In 2015, we acquired the remaining rights to ofatumumab, which we currently market for oncology indications as *Arzerra,* from GlaxoSmithKline. Ofatumumab is a human monoclonal antibody targeting the CD20 protein and being developed for relapsing-remitting MS. Phase II results show a significant reduction in the cumulative number of new brain lesions in patients with MS, and Phase III trials will start in 2016. We see ofatumumab as offering a significant potential benefit for patients.

We also continue to explore the IL-17 pathway, associated with clinical disease activity in patients with MS, with CJM112.

**Neuropathic pain**

Nerve damage caused by physical injury or diseases such as diabetes, MS and shingles can result in a complex chronic pain state called neuropathic pain. This condition affects up to 7–8% of the adult population, and 40% of patients do not respond to existing treatments. We are investigating EMA401, a novel angiotensin II type 2 receptor (AT2R) antagonist, following our acquisition of Spinifex Pharmaceuticals. EMA401 works in the spinal cord outside the blood brain barrier and may avoid side effects such as dizziness or confusion.

**Muscle wasting**

We are developing BYM338 (bimagrumab) for patients with sIBM, a rare muscle wasting disorder. Currently in Phase III clinical trials for sIBM, we are also studying its potential for patients with age-related sarcopenia. This degenerative condition, usually characterized by a significant decrease in muscle mass and increased frailty, affects 30% of those aged 60–70 and more than 50% of people over 80.

**Migraine**

Migraine is a severe headache condition affecting more than 10% of the population worldwide. Novartis is collaborating with Amgen on potential treatments for this leading cause of disability. They include AMG 334, a fully human monoclonal antibody; AMG 301; and potentially another Amgen investigational compound. AMG 334 is in Phase III trials and AMG 301 is in Phase I trials.

**Alzheimer's disease**

About 44 million people globally have Alzheimer's disease or a related dementia. Current treatments manage symptoms but cannot alter the course of the disease. Once the disease is detected, neurological damage to the patient is irreversible and slow decline in memory, thinking and reasoning skills results.

We are investigating potential new therapies and studying patients with a genetic risk of developing Alzheimer's, for example in partnership with Amgen to develop a BACE inhibitor program in Alzheimer's. This includes the oral therapy CNP520 (which is also part of a major collaborative study with the Banner Alzheimer's Institute in people with a genetic risk of developing this disease). BACE inhibitors block an enzyme called beta-secretase that is involved in the production of amyloid beta, a protein that creates brain plaques, considered to be a major cause of Alzheimer's. This research will assess the efficacy of CNP520 and of CAD106 in limiting the build-up of protein aggregates linked to the emergence of Alzheimer's. CAD106 is an anti-amyloid active immunotherapy that has completed Phase IIa trials and is not included in the collaboration with Amgen.

# INNOVATION OVERVIEW
continued

## EYE CARE

Alcon, the eye care division of Novartis, is developing innovative products that enhance quality of life by helping people see better. According to the WHO, more than 80% of all visual impairment can be prevented, treated or cured. We offer a broad portfolio of products, including surgical devices and platforms to treat cataracts, refractive errors and retinal conditions; medicines for chronic diseases such as glaucoma and dry eye; compounds in development for the potential treatment of age-related macular degeneration (AMD); as well as contact lenses and lens care solutions.

### Surgical

Alcon develops ophthalmic surgical equipment, intraocular lenses (IOLs) and disposable surgical equipment to treat cataracts, a clouding of the natural lens of the eye that is the leading cause of preventable blindness worldwide. In addition, Alcon offers equipment to assist surgeons performing corneal refractive and vitreoretinal surgical procedures.

Alcon's most recent innovations in cataract treatment are *PanOptix*, a new advanced-technology IOL that addresses near, intermediate and distance vision, as well as the *UltraSert* pre-loaded IOL device that enables surgeons to insert IOLs with more precision and control during surgery, further enhancing patient outcomes. We are also in late-stage development of our new next-generation IOL polymer material, *Clareon*, which maintains the benefits of our *AcrySof* platform, including refractive and rotational stability, unfolding characteristics, improved visual outcomes, and a reduction in glistenings and surface haze.

### Ophthalmic pharmaceuticals

In ophthalmic pharmaceuticals, we address chronic and progressive eye diseases such as glaucoma, dry eye and ocular infections. A Phase III clinical trial program is underway for RTH258, a novel anti-vascular endothelial growth factor (anti-VEGF) agent to treat patients with wet AMD. Patients with wet AMD suffer vision loss when blood vessels grow into the eye and damage the retina. We are also researching early-stage compounds in glaucoma and dry eye, as well as gene therapies for rare and orphan eye diseases.

We continue to study OAP030, also known as Fovista®, and E10030, an anti-platelet-derived growth factor (anti-PDGF) agent from Ophthotech, as a combination treatment with an anti-VEGF agent for wet AMD. A Phase III program to evaluate this combination is underway and initial data is expected in 2016.

### Vision care

Alcon is working with Verily, formerly Google Life Sciences, on innovations using its "smart lens" technology to address certain ocular conditions. This "smart lens" technology involves sensors, microchips and other miniaturized electronics embedded within lenses.

The first is a lens to help compensate for the decrease in accommodation of the eye's natural lens in patients with presbyopia who cannot read without glasses. Patient trials are expected to begin in 2016. The "smart lens" has the potential to help restore the eye's natural autofocus on near objects, either in the form of an accommodative contact lens or an IOL as part of refractive cataract treatment.

The second area of focus is on a glucose-sensing lens to help diabetic patients monitor glucose levels via tear fluid in the eye. This work is at pre-proof-of-concept stage.

*We are researching early-stage compounds in glaucoma and dry eye, as well as gene therapies for rare and orphan eye diseases*

6

Additional biosimilar filings planned by Novartis within the next two years

584 000

People die every year from malaria, a disease for which Novartis is developing new compounds

## BIOSIMILARS

Our generics division, Sandoz, is developing biosimilars – protein drugs with essentially the same active ingredient as existing biological drugs that have lost patent protection. Biosimilars represent an innovative and lower-cost way of extending patient access to high-quality medicines for some serious diseases.

Novartis is a leader with three products on the market, including *Zarxio*, which launched in the US during 2015. It is called *Zarzio* outside the US. We also have a strong pipeline with five biosimilars in oncology and immunology in Phase III development or nearing registration. Filings were accepted in the US and EU in November for etanercept, a biosimilar to Enbrel® for several autoimmune diseases, and in the US for pegfilgrastim (Peg G-CSF) for treating neutropenia associated with chemotherapy. Other biosimilars include rituximab for rheumatoid arthritis and follicular lymphoma, a biosimilar to Humira® (adalimumab) for psoriasis, and epoetin alfa for anemia associated with chronic kidney disease. Novartis plans an additional six biosimilar filings within the next two years.

## INFECTIOUS DISEASES

There is a pressing need for new drugs to tackle tropical diseases that can be devastating in developing countries, such as malaria; Chagas disease, a tropical disease that can lead to heart failure; and human African trypanosomiasis (HAT), also known as African sleeping sickness, a potentially fatal and difficult-to-treat disease endemic in many sub-Saharan African countries.

Novartis is developing new compounds for malaria, which kills about 584 000 people worldwide every year. We have two potential therapies in Phase II clinical trials, KAE609 (cipargamin) and KAF156. Both act against the two parasites responsible for the majority of malaria deaths, Plasmodium vivax and the more virulent Plasmodium falciparum. Current antimalarials, including *Coartem*, are not effective against Plasmodium vivax. KAE609 and KAF156 are new classes of compounds that treat malaria in different ways from current therapies, and could help combat growing resistance to existing artemisinin-based therapies.

Another challenge to public health is the growing resistance of bacteria to antibiotics. Novartis is working on new antibiotics to treat bacteria that are showing resistance to older antibiotics derived from penicillin as well as to carbapenems, a potent antibiotic class typically used when everything else has failed.

We are also exploring new treatments for viral infections, including respiratory viruses such as influenza and respiratory syncytial virus (RSV), and viruses that threaten patients with undeveloped or compromised immune systems, such as those with HIV/AIDS and those receiving chemotherapy or organ transplants.

# PIPELINE

*Novartis is consistently rated as having one of the industry's most respected development pipelines, with more than 200 projects in clinical development, as of December 31, 2015.*

Many of these projects, which include new molecular entities as well as additional indications and different formulations for marketed products, are for potentially best-in-class or first-in-class medicines that could significantly advance treatment standards for patients worldwide. This table provides an overview of selected projects in confirmatory development.

We use the traditional pipeline model as a platform (e.g., Phase I-III). However, we have tailored the process to be simpler, more flexible and more efficient.

## GLOSSARY

**Project/product** Project refers to the Novartis reference code (combination of three letters and three numbers) used for projects in development. Product refers to the brand name for a marketed product.

**Common name** Official international non-proprietary name or generic name for an individual molecular entity as designated by the World Health Organization

***Glossary continued on page 54***

## MAJOR DEVELOPMENT PROJECTS

| Project/product | Division | Common name | Mechanism of action |
|---|---|---|---|
| **ONCOLOGY** | | | |
| ABL001 | Pharmaceuticals | – | BCR-ABL inhibitor |
| ASB183 | Pharmaceuticals | afuresertib | AKT inhibitor |
| LJM716 | Pharmaceuticals | elgemtumab | HER3 mAb[3] |
| PIM447 | Pharmaceuticals | – | Pan-PIM inhibitor |
| EGF816 | Pharmaceuticals | – | Epidermal growth factor receptor inhibitor |
| BGJ398 | Pharmaceuticals | infigratinib | Pan-FGF receptor kinase inhibitor |
| *Tafinlar + Mekinist* | Pharmaceuticals | dabrafenib + trametinib | BRAF inhibitor + MEK[4] inhibitor |
| INC280 | Pharmaceuticals | capmatinib | c-MET inhibitor |
| BKM120 | Pharmaceuticals | buparlisib | PI3K[5] inhibitor |
| BYL719 | Pharmaceuticals | alpelisib | PI3Kα[6] inhibitor |
| *Tasigna* | Pharmaceuticals | nilotinib | BCR-ABL inhibitor |
| LCI699 | Pharmaceuticals | osilodrostat | Aldosterone synthase inhibitor |
| LEE011 | Pharmaceuticals | ribociclib | CDK4/6[7] inhibitor |
| PKC412 | Pharmaceuticals | midostaurin | Signal transduction inhibitor |
| *Signifor* LAR (SOM230) | Pharmaceuticals | pasireotide | Somatostatin analogue |
| *Zykadia* (LDK378) | Pharmaceuticals | ceritinib | ALK[9] inhibitor |
| *Votrient* | Pharmaceuticals | pazopanib | Angiogenesis inhibitor |
| *Arzerra* | Pharmaceuticals | ofatumumab | Anti-CD20 mAb[3] |
| *Afinitor/Votubia* (RAD001) | Pharmaceuticals | everolimus | mTOR[10] inhibitor |
| *Promacta/Revolade* | Pharmaceuticals | eltrombopag | Thrombopoietin receptor agonist |
| *Jadenu* *Exjade* film-coated tablet (FCT) | Pharmaceuticals | deferasirox | Iron chelator |
| **CARDIOVASCULAR AND METABOLISM** | | | |
| ACZ885 | Pharmaceuticals | canakinumab | Anti-interleukin-1ß monoclonal antibody |
| RLX030 | Pharmaceuticals | serelaxin | Recombinant form of human relaxin-2 hormone |
| *Entresto* (LCZ696) | Pharmaceuticals | valsartan, sacubitril (as sodium salt complex) | Angiotensin receptor, neprilysin inhibitor |

[1] Filings that have received approval in either the US or EU but are awaiting approval in the other market
[2] Phase and planned filing dates refer to lead indication in development.
[3] Monoclonal antibody
[4] Combination of mitogen-activated protein kinase and extracellular signal-regulated kinase
[5] Phosphoinositide 3-kinase inhibitor
[6] Phosphoinositide 3-kinase alpha inhibitor
[7] Cyclin-dependent kinase 4/6
[8] Non-steroidal aromatase inhibitor
[9] Anaplastic lymphoma kinase
[10] Mammalian target of rapamycin
[11] Diffuse large B-cell lymphoma

| Potential indication/disease area | Route of administration | Planned filing dates [1,2] | PHASE I | PHASE II | PHASE III | SUBMISSION |
|---|---|---|---|---|---|---|
| Chronic myeloid leukemia | Oral | ≥2020 | PHASE I | | | |
| Solid and hematologic tumors | Oral | ≥2020 | PHASE I | | | |
| Solid tumors | Intravenous infusion | ≥2020 | PHASE I | | | |
| Hematologic tumors | Oral | ≥2020 | PHASE I | | | |
| Solid tumors | Oral | 2018 | | PHASE II | | |
| Solid tumors | Oral | ≥2020 | | PHASE II | | |
| BRAF V600+ NSCLC,[2] BRAF V600+ melanoma (adjuvant), BRAF V600+ colorectal cancer | Oral | 2016 | | PHASE II | | |
| Non-small cell lung cancer | Oral | 2018 | | PHASE II | | |
| Metastatic breast cancer, hormone receptor-positive, aromatase inhibitor resistant/mTOR naïve, 2nd line (+ fulvestrant) [lead indication]; metastatic breast cancer, hormone receptor-positive, aromatase inhibitor and mTOR inhibitor resistant, 3rd line (+ fulvestrant); solid tumors | Oral | 2016 | | | PHASE III | |
| Hormone receptor-positive, HER2-negative advanced breast cancer (postmenopausal women), 2nd line (+ fulvestrant) [lead indication]; solid tumors | Oral | 2019 | | | PHASE III | |
| Chronic myeloid leukemia treatment-free remission | Oral | 2016 | | | PHASE III | |
| Cushing's disease | Oral | 2017 | | | PHASE III | |
| Hormone receptor-positive, HER2-negative advanced breast cancer (postmenopausal women), 1st line (+ letrozole) [lead indication]; hormone receptor-positive, HER2-negative advanced breast cancer (premenopausal women), 1st line (+ tamoxifen + goserelin or NSAI[8] + goserelin); hormone receptor-positive, HER2-negative advanced breast cancer (postmenopausal women), 1st/2nd line (+ fulvestrant); solid tumors | Oral | 2016 | | | PHASE III | |
| Acute myeloid leukemia [lead indication], aggressive systemic mastocytosis | Oral | 2016 | | | PHASE III | |
| Cushing's disease | Long-acting release, intramuscular injection | 2016 | | | PHASE III | |
| ALK[9]+ advanced non-small cell lung cancer (1st line, treatment naïve),[2] ALK[9]+ advanced non-small cell lung cancer (brain metastases) | Oral | 2017 | | | PHASE III | |
| Renal cell carcinoma (adjuvant) | Oral | 2016 | | | PHASE III | |
| Chronic lymphocytic leukemia (extended treatment),[2] chronic lymphocytic leukemia (relapse), non-Hodgkin's lymphoma (refractory) | Intravenous infusion | US registration<br>EU registration | | | | SUBMISSION |
| Non-functioning GI and lung neuroendocrine tumors,[2] tuberous sclerosis complex seizures, DLBCL[11] | Oral | US registration<br>EU registration | | | | SUBMISSION |
| Pediatric immune thrombocytopenia | Oral/oral suspension | US approved<br>EU registration | | | | SUBMISSION |
| Iron overload | Oral FCT | US approved<br>EU registration | | | | SUBMISSION |
| Secondary prevention of cardiovascular events | Subcutaneous injection | 2017 | | | PHASE III | |
| Acute heart failure | Intravenous infusion | 2017 | | | PHASE III | |
| Chronic heart failure with preserved ejection fraction,[2] post-acute myocardial infarction | Oral | 2019 | | | PHASE III | |

# PIPELINE
continued

**Mechanism of action** Specific biochemical interaction with a molecular target such as a receptor or enzyme, through which a drug substance produces its pharmacological effect

**Potential indication/indications** Disease or condition for which a compound or marketed product is in development and is being studied as a potential therapy

**Route of administration** Path by which a medicinal preparation is administered into the body, such as oral, subcutaneous or intravenous

**Phase I** First clinical trials of a new compound, generally performed in a small number of healthy human volunteers, to assess the clinical safety and tolerability, as well as metabolic and pharmacologic properties of the compound

**Phase II** Clinical studies with patients who have the target disease, with the aim of continuing the Phase I safety assessment in a larger group, assessing the efficacy of the drug in the patient population, and determining the appropriate doses for further evaluation

**Phase III** Large-scale clinical studies with several hundred to several thousand patients, which are conducted to establish the safety and efficacy of the drug-specific indications for regulatory approval. Phase III trials also may be used to compare a new drug against a current standard of care to evaluate the overall benefit-risk relationship of the new medicine.

***Glossary continued on page 56***

## MAJOR DEVELOPMENT PROJECTS

| Project/product | Division | Common name | Mechanism of action |
|---|---|---|---|
| **RESPIRATORY** | | | |
| QAX576 | Pharmaceuticals | – | Anti-interleukin-13 monoclonal antibody |
| QMF149 | Pharmaceuticals | indacaterol, mometasone furoate (in fixed-dose combination) | Long-acting beta2-agonist and inhaled corticosteroid |
| QAW039 | Pharmaceuticals | fevipiprant | CRTH2 antagonist |
| QVM149 | Pharmaceuticals | indacaterol, mometasone furoate, glycopyrronium bromide (in fixed-dose combination) | Long-acting beta2-agonist, long-acting muscarinic antagonist and inhaled corticosteroid |
| **IMMUNOLOGY AND DERMATOLOGY** | | | |
| CJM112 | Pharmaceuticals | – | Anti-interleukin-17 monoclonal antibody |
| QAW039 | Pharmaceuticals | fevipiprant | CRTH2 antagonist |
| LJN452 | Pharmaceuticals | – | FXR agonist |
| VAY736 | Pharmaceuticals | – | Anti-BAFF (B-cell-activating factor) antibody |
| QGE031 | Pharmaceuticals | ligelizumab | High-affinity anti-IgE monoclonal antibody |
| *Ilaris* (ACZ885) | Pharmaceuticals | canakinumab | Anti-interleukin-1ß monoclonal antibody |
| *Cosentyx* (AIN457) | Pharmaceuticals | secukinumab | Anti-interleukin-17 monoclonal antibody |
| **NEUROSCIENCE** | | | |
| CAD106 | Pharmaceuticals | – | Beta-amyloid-protein therapy |
| CNP520 | Pharmaceuticals | – | BACE inhibitor |
| EMA401 | Pharmaceuticals | – | Angiotensin II receptor antagonist |
| OMB157 | Pharmaceuticals | ofatumumab | Anti-CD-20 monoclonal antibody |
| BAF312 | Pharmaceuticals | siponimod | Sphingosine-1-phosphate receptor modulator |
| *Gilenya* | Pharmaceuticals | fingolimod | Sphingosine-1-phosphate receptor modulator |
| AMG 334 | Pharmaceuticals | – | Selective CGRP receptor antagonist |
| BYM338 | Pharmaceuticals | bimagrumab | Inhibitor of activin type II receptor |
| **CELL AND GENE THERAPY** | | | |
| CTL019 | Pharmaceuticals | tisagenlecleucel-T | CD19-targeted chimeric antigen receptor T-cell immunotherapy |
| FCR001 | Pharmaceuticals | – | Inducing stable donor chimerism and immunological tolerance |
| HSC835 | Pharmaceuticals | – | Stem cell regeneration |
| **INFECTIOUS DISEASES** | | | |
| KAF156 | Pharmaceuticals | – | Imidazolopiperazines derivative |
| KAE609 | Pharmaceuticals | cipargamin | PfATP4 inhibitor |
| EXE844b | Alcon | finafloxacin | Anti-infective |

[1] Filings that have received approval in either the US or EU but are awaiting approval in the other market
[2] Phase and planned filing dates refer to lead indication in development.

| Potential indication/disease area | Route of administration | Planned filing dates [1,2] | PHASE I | PHASE II | PHASE III | SUBMISSION |
|---|---|---|---|---|---|---|
| Allergic diseases | Subcutaneous injection | ≥2020 | | PHASE II | | |
| Asthma | Inhalation | 2018 | | | PHASE III | |
| Asthma | Oral | 2019 | | | PHASE III | |
| Asthma | Inhalation | 2018 | | | PHASE III | |
| Immune disorders | Subcutaneous injection | ≥2020 | | PHASE II | | |
| Atopic dermatitis | Oral | ≥2020 | | PHASE II | | |
| Non-alcoholic steatohepatitis | Oral | ≥2020 | | PHASE II | | |
| Primary Sjoegren's syndrome | Subcutaneous injection | ≥2020 | | PHASE II | | |
| Chronic spontaneous urticaria/ inducible urticaria | Subcutaneous injection | ≥2020 | | PHASE II | | |
| Hereditary periodic fevers | Subcutaneous injection | 2016 | | | PHASE III | |
| Ankylosing spondylitis,[2] psoriatic arthritis,[2] non-radiographic axial spondyloarthritis | Subcutaneous injection | US registration EU approved | | | | SUBMISSION |
| Alzheimer's disease | Intramuscular injection | ≥2020 | | PHASE II | | |
| Alzheimer's disease | Oral | ≥2020 | | PHASE II | | |
| Neuropathic pain | Oral | ≥2020 | | PHASE II | | |
| Relapsing multiple sclerosis | Subcutaneous injection | 2019 | | PHASE II | | |
| Secondary progressive multiple sclerosis | Oral | 2019 | | | PHASE III | |
| Chronic inflammatory demyelinating polyradiculoneuropathy | Oral | 2017 | | | PHASE III | |
| Migraine | Subcutaneous injection | | | | PHASE III | |
| Sporadic inclusion body myositis [lead indication], hip fracture, sarcopenia | Intravenous infusion | 2016 | | | PHASE III | |
| Pediatric acute lymphoblastic leukemia [lead indication], diffuse large B-cell lymphoma | Intravenous infusion | 2016 | | PHASE II | | |
| Renal transplant | Intravenous infusion | ≥2020 | | PHASE II | | |
| Stem cell transplantation | Intravenous infusion | ≥2020 | | PHASE II | | |
| Malaria | Oral | 2019 | | PHASE II | | |
| Malaria | Oral | ≥2020 | | PHASE II | | |
| Otitis media-tympanostomy tube surgery | Topical | 2016 US | | | PHASE III | |

# PIPELINE
continued

**Advanced development** Medical device project for which a positive proof of concept has been established and studies are being conducted to establish the safety, efficacy or performance to address regulatory requirements for obtaining marketing authorization

**Submission** An application for marketing approval has already been submitted to one or both of the following regulatory agencies: the US Food and Drug Administration (FDA), the European Medicines Agency (EMA). Novartis has not yet received marketing authorization from both regulatory agencies. The application contains comprehensive data and information gathered during human clinical trials and animal studies conducted through the various phases of drug development.

## MAJOR DEVELOPMENT PROJECTS

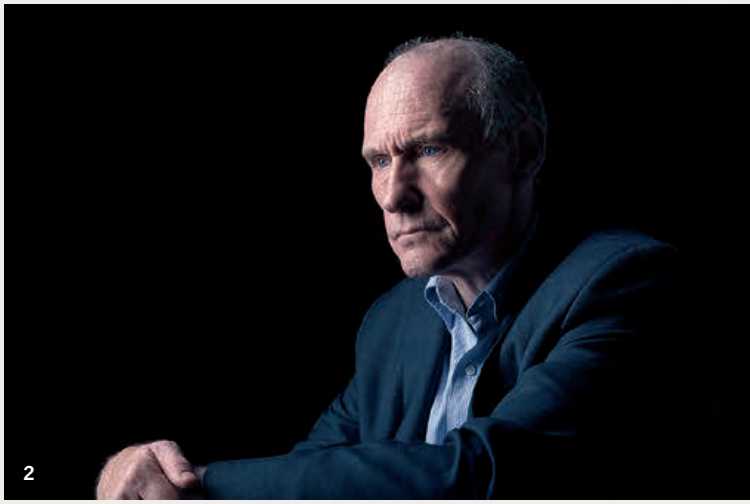
| Project/product | Division | Common name | Mechanism of action |
|---|---|---|---|
| **OPHTHALMOLOGY** | | | |
| *Lucentis* | Pharmaceuticals | ranibizumab | Anti-vascular endothelial growth factor (VEGF) monoclonal antibody fragment |
| OAP030 (Fovista®) | Pharmaceuticals | pegpleranib | Aptamer anti-platelet-derived growth factor |
| *Jetrea* ready-diluted injection | Alcon | ocriplasmin | Alpha-2 antiplasmin reducer |
| RTH258 | Alcon | brolucizumab | Anti-VEGF single-chain antibody fragment |
| *Ilevro* ophthalmic suspension | Alcon | nepafenac (0.3%) | Anti-inflammatory |
| *AcrySof IQ ReSTOR* Toric 2.5 D IOL | Alcon | – | Multifocal, aspheric and cylinder-correcting intraocular lens |
| *AOSept* Plus/ *Clear Care* Plus with *HydraGlyde* | Alcon | – | Disinfection and cleaning |
| *AcrySof* IQ Aspheric IOL with *UltraSert* | Alcon | – | Pre-loaded intraocular lens delivery device |
| *AcrySof IQ ReSTOR* Toric 3.0 D IOL | Alcon | – | Multifocal, aspheric and cylinder-correcting intraocular lens |
| **BIOSIMILARS** | | | |
| GP2013 | Sandoz | rituximab | Anti-CD20 antibody |
| GP2017 | Sandoz | adalimumab | TNF-α inhibitor |
| HX575 | Sandoz | epoetin alfa | Erythropoiesis-stimulating agent |
| HX575 s.c. | Sandoz | epoetin alfa | Erythropoiesis-stimulating agent |
| GP2015 | Sandoz | etanercept | TNF-α inhibitor |
| LA-EP2006 | Sandoz | pegfilgrastim | Pegylated granulocyte colony-stimulating factor |

[1] Filings that have received approval in either the US or EU but are awaiting approval in the other market
[2] Phase and planned filing dates refer to lead indication in development.
[12] Choroidal neovascularization secondary to conditions other than age-related macular degeneration and pathologic myopia

| Potential indication/disease area | Route of administration | Planned filing dates [1,2] | PHASE I | PHASE II | PHASE III | SUBMISSION |
|---|---|---|---|---|---|---|
| Choroidal neovascularization,[12] retinopathy of prematurity | Intravitreal injection | 2016 | | | PHASE III | |
| Neovascular age-related macular degeneration | Intravitreal injection | 2017 | | | PHASE III | |
| Vitreomacular traction | Intravitreal injection | 2017 Japan | | | PHASE III | |
| Wet age-related macular degeneration | Intravitreal injection | ≥2018 | | | PHASE III | |
| Postsurgical macular edema in patients with diabetes | Topical | Submitted EU 2018 US | | | PHASE III | |
| Cataractous lens replacement with or without presbyopia, and with astigmatism | Surgical | 2016 US | ADVANCED DEVELOPMENT | | | |
| Contact lens care | Lens care | 2017 Japan | ADVANCED DEVELOPMENT | | | |
| Cataractous lens replacement | Surgical | Submitted Japan | ADVANCED DEVELOPMENT | | | SUBMISSION |
| Cataractous lens replacement with or without presbyopia, and with astigmatism | Surgical | Submitted US | ADVANCED DEVELOPMENT | | | SUBMISSION |
| Non-Hodgkin's lymphoma, chronic lymphocytic leukemia, rheumatoid arthritis, granulomatosis with polyangiitis (also known as Wegener's granulomatosis), and microscopic polyangiitis and others (same as originator) | Intravenous | | | | PHASE III | |
| Arthritides (rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis), plaque psoriasis and others (same as originator) | Subcutaneous | | | | PHASE III | |
| Anemia in chronic kidney disease, chemotherapy-induced anemia and others (same as originator) | Subcutaneous and intravenous | US | | | PHASE III | |
| Anemia in chronic kidney disease | Subcutaneous | Submitted EU (extension nephrology, appproved as *Binocrit* since 2007) | | | | SUBMISSION |
| Arthritides (rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis), plaque psoriasis and others (same as originator) | Subcutaneous | Submitted US Submitted EU | | | | SUBMISSION |
| Chemotherapy-induced neutropenia and others (same as originator) | Subcutaneous | Submitted US | | | | SUBMISSION |

1

*Although results so far are promising, important questions remain, such as managing a potentially serious side effect called cytokine release syndrome, ensuring the safety of the procedure and understanding why some patients relapse*



2

1 Researchers at the Novartis facility in Morris Plains check on the production process for human T-cells.
2 Dr. Carl June of the University of Pennsylvania developed gene transfer therapy to prime the body's own immune cells to fight cancer.
3 A technician prepares a container with liquid nitrogen to transport human cells from one part of the facility in Morris Plains to another.
4 CART patient Doug Olson enjoys sailing with his grandchildren.

→ CONTINUED FROM PAGE 43

Dr. Carl June, director of translational research at the University of Pennsylvania's Abramson Cancer Center, is a pioneer in developing CART therapy. His research into gene therapy as a possible treatment for cancer began more than 20 years ago when he was a scientist in the US Navy, studying potential HIV therapies. Dr. June encountered patients who appeared to have benefited from treatment with genetically re-engineered T-cells, and he believed the same approach might work in cancer.

In 1999, Dr. June joined the University of Pennsylvania, where he and his team began working to develop the first CART therapy for patients with cancer. It took a further decade of study and work to overcome the challenge of producing sufficient quantities of re-engineered T-cells before the therapy was ready for trial and the first small group of leukemia patients could receive the treatment.

CART is a radical break from existing cancer therapies, as 69-year-old retiree Doug Olson can attest. Diagnosed at 49 with chronic lymphocytic leukemia, Mr. Olson endured four unsuccessful rounds of chemotherapy until 2010 when, after 14 years of treatment, he became an early patient in Dr. June's CART trials at the University of Pennsylvania.

Mr. Olson continues to lead a full life. He is an avid runner and enjoys sailing with his grandchildren.

The first CART treatment being developed by Novartis and the University of Pennsylvania is CTL019, a potential therapy for children with acute lymphoblastic leukemia (ALL) for whom all other treatments ultimately failed. In a Phase II clinical trial of pediatric patients, 93% had no detectable cancer after 28 days. Although results so far are promising, important questions remain for Dr. June and Novartis, such as managing a potentially serious side effect called cytokine release syndrome, ensuring the safety of the treatment and understanding why some patients relapse.

To expand trials of CART therapy to more patients, in 2015 Novartis began operating a facility in the US state of New Jersey to process much larger numbers of patients' T-cells. The process of modifying patients' immune cells is complex, and scaling up the manufacturing of modified T-cells remains a challenge.

Inside the facility, logistics experts track the production process on large computer screens, displaying the many steps required for each patient's T-cells to be re-engineered. First, the T-cells are removed from a cancer patient's blood sample. Technicians then use deactivated viruses to insert genes into the T-cells, enabling them to grow a cancer-hunting receptor. These modified cells are multiplied until there are enough of them for the therapy. Then the cells are prepared for shipment and transported back to the patient's medical center, where clinicians infuse the reprogrammed cells.

Meanwhile, Dr. June and Novartis are also exploring whether CART technology can be effective in treating other, more common cancers.