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Special considerations to make cell and gene therapies a success in China

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Executive Summary

Cell and gene therapies are designed to halt a disease in its tracks or reverse its progress rather than simply manage symptoms. They are often one-time treatments that may alleviate the underlying cause of a disease and they have the potential to cure certain conditions. Due to their potentially curative nature, cell and gene therapies can save significant costs for the healthcare system and restore productivity of the patient with economic benefits for the society overall. In contrast, many conventional medicines must be taken continually for weeks, months, or even for life.

The great potential of cell and gene therapies has triggered development of policies that establish dedicated regulatory frameworks to tackle challenges and specific needs around these advanced therapies. In particular in China, lots of movement in this area can be observed with many clinical studies in the field of cell and gene therapies, an increasing number of encouraging policies and special business zones that allow for collaboration between multiple stakeholders that contribute with complementary ideas and skills.

To further progress in this field and to make the country a major power for promising novel treatments, Novartis suggests to the Chinese government to continue on their way to open up for engagement in the area of advanced therapies.

This document continues the discussion about suggestions for an upgraded policy environment related to cell and gene therapies that Novartis started with its paper for the 2019 China Development Forum. This time's focus lays on three areas, (1) Promoting R&D, (2) Optimizing Medical Infrastructure and (3) Enabling Patient Access.

Promoting R&D: Novartis welcomes and supports the intensive efforts of the various government administrations to regulate and promote R&D in rare diseases and particularly in advanced therapies. We recommend to pay additional attention to aligning regulatory and industrial policies and to upgrade the Foreign Investment Legislation in line with technological progress. In addition, fully implemented and enforced Regulatory Data Protection will support and incentivize the continued research and development of new medicines, in particular in the field of cell and gene therapy.

Optimizing Medical Infrastructure: High quality and safe patient treatment with advanced therapies requires an appropriate infrastructure to administer and investment in ongoing supportive care and patient monitoring. Building a world-class infrastructure could position China as a hub in the region, possibly not only serving Chinese patients, but also from other countries. Therefore, Novartis is working in a joint project with the China Medical Biotech Association in Beijing to draft a certification guidance that is in line with international standards and that is mandatory for all medical institutions carrying out cell and gene therapy.

Enabling Patient Access: The significant advances in the development of cell and gene therapy offer transformative benefits to patients, but also present a challenge to constrained healthcare systems. Therefore, mechanisms are needed to supplement the existing funding system by expanding the fiscal space of the healthcare system by a combination of additional components and increasing efficiency in using existing resources. Novartis suggests to the Chinese government to consider the establishment of specialized healthcare funds, promotion of supplemental commercial insurances, and expansion of upgrading the Basic Medical Insurance. Options for applicable pricing and payment models include outcomes-based payments and over-time payments.

Novartis is happy to share its experiences gained in many places of the world and to constructively work together with the Chinese government to make cell and gene therapies a success for patients and the medical society and the country's economy.

Introduction

Medicines have changed the lives of humanity and nobody can imagine a life without them. Thanks to medical progress, the therapeutic benefits of drugs have resulted in increased longevity, the eradication of certain infectious diseases, less side effects compared to older drugs, and others. For example: Using the 1940 U.S. population as reference, the age-adjusted annual heart disease mortality per 100,000 fell by 56% from 307.4 in 1950 to 134.6 in 1996, while age-adjusted annual stroke rates per 100,000 fell by 70% during this same period from 88.8 to 26.5[1]. The death rate for cancer in children ages 0-14 years declined by two-thirds from 1970 (6.3 per 100,000) to 2016 (2.2 per 100,000). This is largely a result of prevention and heathier lifestyles, as well as of improvements in treatment and high rates of participation in clinical trials[2].

The ongoing curiosity and motivation of researchers worldwide, both in research institutions and healthcare companies, is helping tackle health challenges and drive scientific progress that continuously deliver innovative biomedical treatments to prolong survival and improve the quality of life of patients. In the past decade, a number of breakthrough medicines in the field of cell and gene therapies have received marketing approval. For instance, in 2012, Glybera (Alipogene tiparvovec) was approved in Europe as the first gene therapy treatment designed to reverse lipoprotein lipase deficiency (LPLD), a rare inherited disorder, which can cause severe pancreatitis. In 2017, Kymriah (Tisagenlecleucel) was approved in the U.S as the first CAR-T[3] drug to treat B-cell acute lymphoblastic leukemia (ALL) and relapsed or refractory (r/r) diffuse large B-cell lymphoma (DLBCL). More cell and gene therapies are in development to address serious and debilitating diseases; many of them are rare diseases in children. The great potential of such therapies, i.e. better understanding of diseases biology, biomarkers as well as advanced analytics, contributes to the acceleration of drug development and upsurge of innovation, and has gradually triggered the development of industrial clusters globally.

These new technologies and treatment options come with specific needs and challenges, as the development takes a long time and requires significant investment. The Chinese government has acknowledged those needs and indicated support for new biomedical technologies, via pilots in specific economic zones and favourable policies. Novartis welcomes the favourable policies developed by the central and provincial governments in China over the past years, in particular in the field of cell and gene therapies, and is pleased to have the opportunity to provide our recommendations for further consideration in this area at the 2020 China Development Forum.

In our paper that we presented at the 2019 China Development Forum, we focused on cell and gene therapies and, amongst other things: (1) asked for one registration pathway for clinical trials and products via the National Medical Product Administration for all stakeholders engaged in this field; (2) stressed the need for clear and transparent mechanisms to enable fast and reliable import and export of ingredients, human material, and other types of material, which would be not only vital for the therapies produced outside of China, but also for export of locally produced products; and (3) asked the Chinese health authorities for establishing additional policies and standards consistent with the international standards on cell and gene therapies, including waivers for local drug quality testing and GMP requirements. We are especially pleased to see the Consultation Paper GMP Annex for Cell Therapy Products that has been issued for public consultation in the end of 2019. We look forward to and welcome government's further actions and improvements on the issues mentioned above.

The present document will continue discussing policy aspects related to cell and gene therapies to advocate a better environment for these advanced therapies in China, and will focus on the following three areas: (1) Promoting R&D, (2) Optimizing Medical Infrastructure, and (3) Enabling Patient Access.

Novartis believes that further policy development and piloting in these areas as well as their subsequent implementation and enforcement will bring other important advantages in addition to the therapeutic benefits. These include a potential cure from the disease, quality of life by easing the burden for patients and caregivers, as well as socio-economic development, through direct cost savings for the healthcare system in the long-run and the economy as a whole. Important will be that these policy developments are applied by all stakeholders that are engaged in the field of cell and gene therapy to create a playing level field amongst all stakeholders and achieve in the best possible care for patients. Moreover, the availability

[1] Centers for Disease Control and Prevention. Achievements in Public Health, 1900–1999: Decline in Deaths from Heart Disease and Stroke -- United States, 1900–1999. MMWR Morb Mortal Wkly Rep. 1999;48(30):649–656.
[2] American Cancer Society, Cancer Facts & Figures 2019, https://www.cancer.org/content/dam/cancer-org/research/cancer-facts-and-statistics/annual-cancer-facts-and-figures/2019/cancer-facts-and-figures-2019.pdf
3 CAR-T: Chimeric antigen receptor T cells are T cells that have been genetically engineered to produce an artificial T-cell receptor for use in immunotherapy.

of an adequate policy framework that is in line with international standards will benefit Chinese biotech companies, as such a framework enables them to be competitive also outside of China.

Situational Analysis and Recommendations

1. Promoting R&D

1.1. Further opening up on advanced therapies

Situational analysis in China

Measures to foster innovation

The *13th Five-year Plan for the Development of The Biological Industry* and the *13th Five-year Plan for Health Science and Technology Innovation* emphasize the development and application of cell and gene therapies to improve the treatment options for patients. Until 2019, China had set up 18 free trade zones covering all major regions of China; some of them have given the development of cell and gene therapies a high priority, including Hebei, Hainan, Chongqing and Tianjin. In addition, local governments have built special cell therapy industrial parks to promote development and established in the recent three years pilot programs, including in the Zhangjiang Cell Industrial Park in Shanghai, the China Cell Valley in Nanjing and the Tianjin Binhai New Area. Each local government expects to achieve tens of billions RMB of market size in the field of advanced therapies, which may lead to a boom in the domestic market.

Many enterprises have set up R&D centers in China due to their recognition of China's improving business environment. Thousands of enterprises, medical institutions, universities and scientific research institutes have carried out basic research and clinical research in cell and gene therapy. As a result, taking R&D in advanced therapies, including significant developments in cell and gene therapy, as an example, lots of progress can be observed. Today, more than 900 clinical studies with stem cells are being carried out in mainland China (of about 6,700 in total world-wide), second only to the United States and the European Union[4]. In terms of gene therapy, according to a recent report from Boston Consulting Company, 75 clinical trials of gene therapy have been initiated worldwide in 2018, which is almost double the trials started in 2016, and this momentum is likely to continue in the coming years[5].

A number of important government administrations are working hard to further develop China's regulatory regime that will benefit R&D of advanced therapies. The National Medical Products Administration (NMPA, former China Food and Drug Administration), the Ministry of Science and Technology and the National Health Commission have started to draft or have issued relevant rules and regulations.

Many diseases that are addressed by cell and gene therapy are rare diseases. It is positive that China’s government has been also paying increasing attention to rare diseases in order to provide cutting-edge treatments for underserved patients and drafted a number of policies and guidelines in the recent past. Rare diseases have been included in the major health planning and strategy, including the five-year plan on public healthcare (2016-2020) and the *Healthy China 2030 Plan*. In 2018, an official ‘Rare Disease List’ has been published that includes 121 rare diseases and a series of specific policies has been released.

2019 Foreign Investment Negative List

The recently issued Chinese Foreign Investment Law (FIL) has come into effect on January 1, 2020, aiming at improving the business environment for foreign investors and ensuring that foreign invested enterprises participate in market competition on an equal basis. As R&D in the field of advanced therapies requires a solid and open-minded policy environment to encourage innovation, Novartis is pleased to notice that the 2019 version of Chinese Foreign Investment Legislation lists "new drug production using bioengineering technology" in the catalogue for encouraging foreign investment. However, we also saw that the FIL is accompanied by an Investment Negative List that contains an element that appear to be in conflict with the above-mentioned positive industry policies, which is Item 28 “Investment in the development and application of human stem cells, genetic diagnosis and treatment technology is prohibited”. This item could be interpreted as a prohibition of engagement in the field of stem cell and

[4] registered on clinical trials.gov and on the World Health Organization clinical trial registration platform (ICTRP) world-wide: https://clinicaltrials.gov/ct2/results?term=stem+cell&recrs=abdefgm (as of January 15, 2020)
[5] https://www.fiercepharma.com/pharma/gene-and-cell-therapy-r-d-will-kick-into-high-gear-2020-despite-hurdles-experts-say

gene therapies. Clarification and alignment between different types of policies and legislation will be helpful to ensure that Novartis can appropriately support patient needs in this area going forward.

Novartis suggestions

Measures to foster innovation

Novartis welcomes and supports the intensive efforts of the various government administrations to regulate and promote R&D in rare diseases and particularly in advanced therapies.

One important area that could benefit from further attention is the existing rare disease list. Given that about 7,000 rare diseases are known in the medical society to date, there is a need for China's regulators to provide a mechanism to increase the number of diseases on the list, for instance via establishing an official definition of a rare disease. The US FDA defines a rare disease as a condition that affects fewer than 200,000 people. In Europe, it must be a life-threatening or chronically debilitating disease with a prevalence of the condition of not more than 5 in 10,000. Novartis is happy to provide additional information about practices adopted by other countries in defining a rare disease if requested.

2019 Foreign Investment Negative List

The new Foreign Investment Law lays great emphasis on equal national treatment of foreign investment and giving foreign investors equal protections. However, Novartis has the view that industrial regulations that promote advanced therapies and foreign investment regulations should be closer aligned. In order to keep up to date with scientific and technological progress and to promote the development of relevant industries in the field of advanced therapies even more, we suggest to progressively relax the restrictions of foreign investment in the field of manufacturing and R&D of advanced therapies, taking into considerations that this type of engagement is centered on treatment in a limited patient population. This would allow investments from abroad that bring knowhow and jobs into the country, and can also help Chinese industry standards come more in line with globally recognized ones. Especially the established free trade zones that focus on cell and gene therapy will benefit from further opening up from a foreign investment perspective and will facilitate meaningful exchange between local and international institutions in these areas.

2.2 Improving the implementation of regulatory data protection (RDP)

Situational analysis in China

In 2002, in the context of becoming a WTO member, China introduced Regulatory Data Protection (RDP) in the *Regulations for Implementation of the Drug Administration Law (DAL)* and in 2007 in the *Drug Registration Regulation (DRR)*. Consequently, both legislations provide that, once NMPA grants a marketing authorization for a medicine with a new active product ingredient (API), no authorization shall be granted to a subsequent marketing application of a medicine containing the same API and referring to the registration documents of the first authorization of this API for a set period. In the mentioned legislations the set period is six years, the same as detailed in the China-Switzerland Free Trade Agreement of 2013. This Free Trade Agreement further clarifies that the subsequent marketing application shall not rely on or refer to the registration data of the first authorization during this period, and that RDP shall be established for chemical entities, biologics, and agricultural chemical products.

The draft Circular 55 of May 2017, published by the China Food and Drug Administration (today NMPA), attempted to improve the RDP system and proposed policies with more detail and procedures for different levels of protection for different types of drugs. In Nov 2017, Circular 42, jointly published by the General Office of the Central Committee of the Communist Party of China and the General Offices of the State Council, also called for improving and implementing RDP for a variety of drugs. In April 2018, new draft RDP rules were published. They suggested to grant six years protection for small molecule drugs and 12 years for biologics, similar to the US system. Unfortunately, those rules have not been implemented to date. Furthermore, under the draft rules, full RDP term has been suggested to be granted only under certain conditions, i.e. depending on the availability of clinical trials data in Chinese patients and timing of the filing of marketing authorization applications in China versus other countries.

Despite the existing legal basis, the implementation and enforcement of the RDP rules remain unclear. In view of the extensive activities in the field of cell and gene therapy, Novartis believes that RDP rules should get special attention, in China, but also in other parts of the world. This is because those non-traditional therapies may not always be in a position to benefit from traditional forms of patent protection. This is, for instance, because they may not involve new molecules as such, standard "compound" patent

protection may not be applicable, and many jurisdictions do not recognize patents for other aspects of therapies that may be applicable.

Novartis suggestions

RDP is a critical form of intellectual property protection that helps to incentivize both the development of new drugs and the rigorous study of their safety, efficacy and quality. RDP establishes a fixed period of time after a new medicine is approved during which third parties cannot rely on the originator's proprietary regulatory data to obtain approval for the same or similar medicine. It is independent from patent protection and plays a critical role in incentivizing and rewarding drug innovation particularly in circumstances where patents are unavailable or insufficient to effectively protect a new medicine. Due to the unique nature of advanced therapies, the patent protection in many new areas of cell and gene therapies differs from traditional patent protection. And in some countries and circumstances patent protection may not be as strong as it typically is for new chemical active ingredients. In these cases, the effective implementation of RDP is particularly important for the protection of intellectual achievements of such advanced therapies.

Novartis supports the implementation of RDP systems in all countries world-wide, because RDP strikes a proper balance between incentivizing the continued development of new medicines and serving a variety of public interests. For example, RDP helps to improve patient safety when new medicines enter the market, by providing a window during which safety can be further studied in real-world conditions and suitable adjustments made before generic versions enter the market. RDP also helps to accelerate and increase access to new medicines: Given the substantial investment required to introduce a new medicine into a given market, where other factors are equal, innovators are more likely to prioritize those markets with RDP systems in place that prevent a new medicine from being immediately copied, resulting in the introduction of a new medicine in those markets sooner.

Therefore, we ask the Chinese government to implement RDP rules in line with international standards as quickly as possible. We also suggest to not connecting the grant of the full RDP term with conditions. Instead, we suggest China to refer to the international experiences and recognize all medicines approved for the first time in China as innovative drugs, and enable them to benefit from the full data protection period equally. We also propose to establish a data protection period for new indications of registered medicines to continuously promote drug innovation. For innovative drugs that have been approved before the implementation of the measures, a six-year data protection period shall be given according to the existing laws and regulations.

2. Optimizing Medical Infrastructure

Situational analysis in China

At the China Development Forum in Beijing in March 2019, Novartis suggested in its policy paper that medical institutions that are engaged with cell and gene therapy should be certified in order to ensure high-quality therapy with maximum patient safety. The presentation of the policy paper helped us to connect with and to become a member of the China Medicinal Biotech Association (CMBA), a non-profit social organization mainly composed of entities that are engaged in the R&D, education, production and application of pharmaceutical biotechnology, willing to optimize the advanced therapy industry environment in China.

Cell and gene therapy is often a one-time treatment that targets the underlying cause of disease and has the potential to cure patients. The indications are usually serious diseases, and every step in production and use impacts a patient's chance of survival. Taking CAR-T therapies as an example of a living personalized medicine, the patient's autologous cells are genetically modified *in vitro* and then infused back to the same patient. This innovative treatment model requires a fundamental change of the hospital's role, from a diagnosis and treatment provider to a complex mix of a manufacturing site doing apheresis[6], i.e. cell collection, separation, processing, storage and preparation for shipment, and a treatment site.

[6] Apheresis is a medical technology in which the blood of a person is passed through an apparatus that separates out one particular constituent and returns the remainder to the circulation.

Therefore, cell therapy institutes are certified through FACT[7] in the US and JACIE[8] in many EU mem ber states. China has not yet established qualification standards on medical institutions for cell and gene therapy.

This situation triggered the start of a collaboration of CMBA, Novartis engaged in cell and gene therapy to work on a "Study on regulations for medical institutes for advanced therapy in China". This project aims to develop a guideline on the qualification of hospitals that engage in advanced therapies, such as cell therapies and gene therapies, with a special focus on CAR-T therapies. Project steps include collecting information on international standards and practice for hospital certification, interviews with experts, and consultation workshops with relevant stakeholders. After the kick-off of the project, an early draft guideline had been discussed in two consultation workshops with hospital experts that confirmed the high interest and need for such a guideline. As soon as an advanced version of the guideline is available, it will be shared with the National Health Commission and other relevant authorities.

Novartis suggestions

Administering cell and gene therapy can involve complex, multi-step processes and need healthcare professionals with specific skills and experience. High quality and safe patient treatment with advanced therapies requires an appropriate infrastructure to administer and investment in ongoing supportive care and patient monitoring. Therefore, Novartis recommends to formulate a practicable certification guidance that is in line with international standards and that is mandatory for all medical institutions carrying out cell and gene therapy. Furthermore, the guidance should not only be applied to upcoming therapies, but also to those that are already used and tested. The qualification of hospitals need to consider several dimensions, one on an operational level covering infrastructure, personnel and governance and two on the time-dimension looking at appropriate procedures before, during and after treatment.

The qualification process should include regulation on:

Qualification area	Covered elements (not exhaustive list)
Facilities and equipment	Availability of cell lab and apheresis collection centre, intensive care unit, which are appropriate, clean and of high quality, and a pharmacy, to provide drugs for key adverse events
Hospital personnel	Covering different and specific expertise and experience, set up in multidisciplinary cooperation teams that are able to apply ongoing supportive care and safety monitoring as well as long-term follow up
Governance procedures	Conduct of comprehensive and specific training; good communication mechanisms; clear decision making processes; clear definition of roles and responsibilities within the hospital and related players, like manufacturing sites and qualified transportation courier; environmental assessment; risk assessment & risk management plans, etc.

Some special considerations should be also made on how to best apply the biohazard standards suggested by WHO[9] when it comes to handling gene therapy products and disposal of waste that contains potentially infectious agents or material.

In addition, as the nature of gene therapy is to alter genes or their function in the human body, long-term follow-up of patients that went through gene therapies is needed to ensure that patients are safe and do not experience unwanted effects. Hospitals should submit periodic evaluation reports with uniform data formats. The US FDA asks, therefore, for 15 years follow-up of treated patients, the European Medicines Agency for a minimum of ten years. In China, systematic patient registries are still not established to date. For the establishment of such registries, it is important to build a data infrastructure in the hospitals that is managed by personnel that is skilled and trained to handle patient data.

Novartis welcomes very much the joint project with CMBA. We are pleased to share the experience we gained with our CAR-T and gene therapies world-wide and to support the discussion and drafting of this

[7] The FACT Standards promote improvement and progress in cellular therapy and regenerative medicine. Meeting these requirements demonstrates a commitment to controlling every aspect that impacts the quality of products and therapeutic care. http://www.factwebsite.org/Standards/

[8] JACIE Standards are evidence-based requirements set by international teams of world-renowned experts vested in the improvement and progress of cellular therapy. https://www.ebmt.org/about-jacie-standards

[9] https://www.who.int/csr/resources/publications/biosafety/en/Biosafety7.pdf

important document. We hope that this guideline can be a valuable reference for decision making for relevant ministries to ensure that existing and upcoming therapies follow high standards for the benefit of the patients. This guideline could, for instance, be a basis for policies encouraging building up cell and gene therapy centers that foster partnerships between manufacturers and medical institutions. This will help establish high quality industrial standards for the benefit of patients.

3. Enabling Patient Access

Situational analysis in China

Today, approximately 96% of the Chinese population is covered by the three major public medical insurances, i.e. universal healthcare coverage has been achieved. However, challenges still exist due to the low financing level, the low risk-pooling capacity and specific gaps, as well as the financial pressure due to the increasing demands.

Novel treatments as a result of substantial scientific advances, particularly the increasing personalization of treatment strategies, offer significant benefits to patients, but also pose new challenges that current pricing and reimbursement models struggle to address. These include uncertainty around the magnitude and duration of clinical benefit for cell and gene therapies, different clinical benefit of medicines used across indications and combinations, one-off cost to the system and affordability in general. More comprehensive reimbursement insurance is less common, accounting for only 30% of premium payments in 2015, according to the *Opportunities Open Up in Chinese Private Health Insurance* report from 2016 by Boston Consulting Group/Munich[10].

With aging population, constant increase of residents' health demands, innovation of medical technology and faster access of innovative drugs, the pressure on the healthcare system is increasing in China. The total health expenses in 2018 grew by 10.2%, more than the GDP growth of 6.6%. In 2018, the national medical insurance fund expenditure grew beyond 23.6% while the revenue growth was 19.3%[11].

In a situation of relatively low reimbursement rates of the Basic Medical Insurance (BMI) for treatments that target cancer or rare diseases, patients have to bear high out of pocket payments. To meet these clinical needs, the National Health Security Administration (NHSA) has already set up dual reimbursement mechanism that consists of regular updating the National Reimbursement Drug List (NRDL) and the national negotiation process. Both are effectively increasing the accessibility of innovative drugs to patients and reducing the disease burden.

On regional level, we observe some initiatives that try to address these challenges with special programs. For instance, in Zhejiang, Qingdao City, Shanghai, and Guangdong, payments for specific medicines, including those for rare diseases, are done via the Critical Disease Insurance. However, the Critical Disease Insurance is funded by the BMI fund, i.e. there is no separate funding approach, which may limit the chances to fully cover all needed treatments. Another option is supplementing public healthcare funding by private health insurances. And although the market for private health insurance is growing rapidly, coverage is still quite low. 2018 data show a participation rate of residents' commercial health insurance of only 6.1% and of households of 10.2%[12].

Establishing and optimizing the financing and payment system of these advanced treatments is an important issue that the government and the industry need to solve in collaboration as soon as possible.

Novartis suggestions

The last decade has been marked by significant advances in the development of cell and gene therapy that offer transformative benefits to patients, but present a challenge to constrained healthcare systems that struggle to cope with demographic change and complex incentive and payment systems. These challenges are not unique to cell and gene therapy, but they appear to be more pronounced in those advanced therapies. In particular one-off treatments, as are the case for many cell and gene therapies, increase the financial risk of payers. Therefore, financial arrangements or risk sharing need to be agreed based on a comprehensive evaluation of the value and benefits of the new treatments and to address uncertainties around the long-term clinical benefit. This value evaluation should consider via health technology assessment, for instance, the long-term benefit of such one-off therapies for patients, the

[10] https://www.bcg.com/publications/2016/insurance-health-care-payers-providers-opportunities-open-up-in-chinese-private-health-insurance.aspx

[11] NHSA website, http://www.nhsa.gov.cn/art/2019/6/30/art_7_1477.html

[12] 2018 China household urban wealth health report

healthcare system as well as for the whole society. Novartis' CAR-T cell and gene therapies Kymriah and Luxturna are examples of treatments that have gone through value-based assessment by a number of HTA agencies and are being reimbursed in several countries in Europe.

Principally, payers need to tackle two types of questions: (1) how to fund the treatment, and (2) what payment model to use. This means, the Chinese government needs to consider the creation of a bigger fiscal space for health by combining new sources of revenues and reducing inefficiencies and waste in the system, as well as changing the provider payment models.

(1) Potential funding models

As mentioned before, basic healthcare coverage in China is managed by the BMI. Special treatments, e.g. for cancer or rare diseases, are often not reimbursed or to a very limited extend. Therefore, mechanisms are needed to supplement the existing system by additional components. Novartis suggests to the Chinese government to consider the following options: establishment of a specialized rare disease fund, promotion of supplementary commercial insurances, or upgrading the BMI.

Specialized disease fund: One option is to establish specialized disease funds, like rare disease funds, to cover high-cost therapies. Establishment of a rare disease fund with higher reimbursement rates and caps to reduce out-of-pocket cost will ease access to these important medicines and take significant financial burden from Chinese patients.

Many countries in the world have set up various mechanisms to support patients with rare diseases with social and medical help as well as with funding for their treatments. The UK Cancer Drug Fund, for instance, funds cancer drugs in England and supported over 95,000 patients since its inception in 2011. It receives its budget from the National Health Service (NHS) and conducts drug funding only after special approval by the National Institute for Health and Care Excellence (NICE). In Singapore, a Rare Disease Fund has been jointly established by the Ministry of Health and the SingHealth Fund. It combines community donations and government-matched contributions to financially support Singapore citizens with specific rare diseases.

In China, the governments of Qingdao City and Zhejiang have set up special funds for rare diseases by means of financial allocation. These funds reimburse the treatment expenses of rare diseases independently of the medical insurance. For example, the Qingdao municipal finance department contributed 300 million RMB (approx. 44 mil USD) to set up a special fund for medical assistance for serious diseases since 2012. This fund covers diseases like multiple sclerosis, hyperphenylalanine fever and kosei disease, and reimburses 70% of the part, which exceeds 50,000 RMB (approx. 7,300 USD) per year, with a cap of 200,000 RMB (approx. 29,000 USD)/year/patient. Zhejiang released a policy to establish a multiple security system for patients with rare disease, including a rare disease fund. The fund will initially be financed by the Critical Disease Insurance with two RMB/year/citizen. Patients will benefit from an 80-100% reimbursement depending of the treatment cost. The out-of-pocket part will continue to apply for the local medical assistance. Government public finance via BMI, Critical Disease Insurance, medical assistance, charity assistance and out-of-pocket payment work together to enable the treatment access of patients with rare diseases in these regions.

Learning from the successful experiences in Qingdao City, Zhejiang and other regions, we suggest to the Ministry of Finance, Ministry of Civil Affairs, NHSA and other relevant departments to work together to accelerate the establishment of a multiple security mechanism for patients with rare diseases.

Commercial insurances: The current public medical insurance is insufficient to meet China's growing health insurance demand, creating significant growth opportunities for commercial health insurance to supplement the social-medical security system. Demand for increasing health insurance is being driven by a number of factors, such as increasing personal health expenditure, an aging population, accelerating urbanization, a burgeoning middle-class and the growing incidence of chronic disease. To reduce pressure on the social health care system, it would be prudent for the government to accelerate the development of commercial health insurance while it further strengthens the effective management of its medical insurance funds. The market's main health insurance products currently are the BMI and a private Critical Disease Insurance. They have the advantage of being similar to life insurance products, which are well understood by companies and consumers alike. In addition, policy makers could explore the inclusion of a mandatory component into the Critical Disease Insurance that covers curative medicines for severely burdening rare diseases to build a firmer safety net for patients.

Further promotion of commercial insurances via favourable policies and collaboration between public and private entities that supplement the basic medical coverage of BMI could be an additional option work for the high-priced drugs. Another option could be to explore mandatory insurance for rare diseases

Upgrade of BMI: Novartis suggests to the Chinese government to include drugs that treat rare diseases, of which an increasing number will be cell and gene therapies, in the BMI. This will bring China's universal health coverage to a more advanced level as it will deepen coverage of special medical needs. At present, a variety of cell or gene therapies have been included in the national health care system in many countries. For instance, the Japanese authorities announced in May 2019 that patients receiving the CAR-T therapy Kymriah, will be covered by the public medical insurance. The out-of-pocket payment by the patients is 10-30% of the total treatment fee depending on their income including an upper limit of the monthly individual payment[13].

Premier Li Keqiang stated at the press conference for the first session of the 13th National People's Congress in 2018 that "More efforts will be adopted in this respect and this year, the central government subsidies for basic public health care scheme will be raised. Half of the increase will be spent for serious illness medical insurance program, enabling more serious illnesses to be covered, benefiting more than 20 million people." And indeed, we have observed that NHSA has already opened a window for negotiation for NRDL inclusion for a part of rare disease drugs, assuming that the administration will continue this trend. In addition, reform efforts by NHSA related to the BMI include the gradual cancelling of individual accounts and increasing premiums of pooling accounts. Other measures focus on the establishment of global budgets, national centralized procurement, payment reforms with a focus on Disease Related Groups (DRG), funds supervision, and other means.

The best solution for improving the funding of healthcare needs is perhaps a combination of all the three above-mentioned options as well as some efforts to improve efficiencies in the healthcare provision. In the mid- to long-term, Novartis suggests to establish a system in which several relevant stakeholders work hand-in-hand including the BMI/disease funds, charity assistance, medical assistance, commercial health insurance and out of pocket, i.e. a multi-channel funding system for advanced therapies. Although including innovative therapies into the BMI coverage will slightly increase the healthcare budget at the initial stage, in the mid- to long-term we believe that in particular curative treatments will relieve pressure on the healthcare budget as the patient will not return to healthcare facilities regarding this disease. Instead, the cured person may be able to return to work and/or will contribute to other areas of society.

(2) Potential payment models

Novartis elaborates in the following pricing and payment options and suggests to the Chinese government to explore them via pilots for their suitability in the Chinese context. Options for applicable pricing and payment models include outcomes-based payments and over-time payments.

Outcomes-based payment / pay for performance: Payments for medicines are related to the measurable real-world performance of the treatment at pre-defined points in time. This can be a useful access tool that help to resolve uncertainties on clinical benefit and to collect additional evidence of the treatment effect over time. These multilateral agreements usually include patients, manufacturers, and payers, including the government, and insurance companies. They can comprise of a variety of features, such as (1) a 'money-back guarantee' (to refund all or part of the money in the case of treatment failure or relapse), or (2) 'conditional proceeding' of treatment (only continue to treat patients with a positive reaction), or (3) determine the amount of payment in accordance with the proportion of treated patients with a positive reaction to the therapy. The Organization for Economic Co-operation and Development (OECD) and European Member States describe in their working paper of January 15, 2020 how such kind of performance-based managed entry agreements for new medicines work and suggest possible improvements going forward[14].

Novartis runs an outcome-based reimbursement framework for its CAR-T cell therapy, Kymriah, for instance, in Australia, Italy and the US. This framework results in payments at intervals and only if patients are in remission after this one-off treatment. To ensure an appropriate and transparent assessment of the patient's health status, a comprehensive treatment monitoring system, including data collection, regular efficacy evaluation as well as clear definitions of outcomes need to be established. Such a monitoring system would ideally comprise of thorough documentation of the patient's medical history and pre-treatment health status, IT tools and skilled personnel to properly manage patients' data and analyses, as well as regular task-specific training for the entire hospital personnel that is involved in the treatment and outcome evaluation.

Over-time payments / instalment payments: These types of payment allow payers to make payments to manufacturers over fixed periods for each patient that receives therapy. Novartis suggests to the

[13] https://www.japantimes.co.jp/news/2019/05/15/national/science-health/japans-health-insurance-cover-new-cancer-therapy-costs-¥33-million/#.XicCgK1YY_t
[14] https://ec.europa.eu/health/sites/health/files/policies/docs/2019_entryagreements_newmedicines_oecdeu_en.pdf

Chinese government to introduce financial instruments in the area of healthcare to spread the risk, such as instalment payments. Structuring payments this way may help mitigate the high up-front cost that would otherwise be associated with one-off therapies. Spain's central government, for instance, is offering low-interest loans to regional health authorities to pay for expensive hepatitis-C treatment[15]. Another example relates to Spark Therapeutics that offers outcomes-based and instalment plans for their gene therapy Luxturna[16] in the USA.

Conclusion

The curative effect of cell and gene therapy gives hope to patients suffering from critical diseases, such as cancers, rare diseases, and immunodeficiency diseases, as there was often no sufficient therapy available to treat those diseases. After years of investment in R&D, cell and gene therapies are achieving great success globally and are gradually applied in clinical practice. In addition, China is paying increasing attention to advanced therapies and started to release a number of favourable policies for their development. However, there are still areas where additional or modified regulation in line with international standards, is needed.

The suggestions made in this document, i.e. improving the business environment for the cell and gene therapy, establishing high-standard hospital certification and supervision, and exploring innovative payment methods and appropriate funding mechanism, will help promote innovation, ensure quality and safety as well as enable patient access to advanced therapies. Building a communication and coordination mechanism with all relevant stakeholders to shape a regulatory framework for advanced therapies globally would be a long-term goal to align requirements internationally. Novartis, playing a leading role in the field of cell and gene therapies globally, is pleased to support the Chinese government with its experiences from other countries and regions to further develop policies in this field.

Joint collaborative efforts by the government, medical society and industry will make cell and gene therapy a success in China and will help the country to move towards a leading role in the world in the near future.

[15] Gene therapy: evidence, value and affordability in the US health care system

[16] Luxturna has received marketing authorization in the US for the treatment of Leber's congenital amaurosis, an inherited disorder causing progressive blindness.