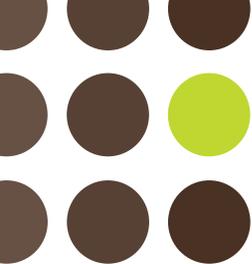


# RARE DISEASES IN CHINA

Rising to meet the challenge





**03** ABSTRACT

**04** INTRODUCTION

**05** LEGISLATION RELATING TO RARE DISEASES

**07** SOCIAL SUPPORT AND ADVOCACY TO INCREASE  
RARE DISEASE AWARENESS

**08** RESEARCH SUPPORT IN RARE DISEASES

**10** ECONOMIC INCENTIVES FOR ORPHAN DRUG ACCESS

**11** PILOT PROJECT TO IMPROVE HEALTHCARE IN RARE DISEASES

**12** CHALLENGES OF RARE DISEASES AND THEIR TREATMENT

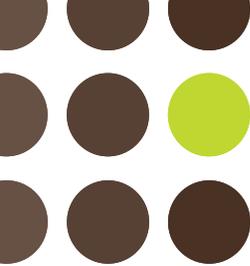
**13** SUMMARY AND FUTURE CONSIDERATIONS

**14** REFERENCES

## Abstract

The diagnosis of rare diseases and the availability of drugs to treat them remain significant challenges to the healthcare system in China. Although several strategies have been employed to promote the identification and treatment of rare diseases, they remain under-recognized in this region. Patient advocacy groups, other non-profit organizations, academic institutions and pharmaceutical companies have recently made significant efforts towards increasing the awareness and understanding of rare diseases. Nevertheless, China is still in the early stages of enacting policies related to rare diseases and regulation of much-needed orphan drugs. Unlike in the US, EU, Japan and Taiwan, there is currently no specific nationwide legislation for orphan drugs in China. Furthermore, Chinese public health insurance does not cover the medical requirements of most rare disease patients.

The recent launch of the first pilot project designed to improve the level of healthcare for rare disease patients in China is an important development. The Chinese Organization for Rare Disorders (CORD) believes it is critical that increased awareness and improved knowledge of rare diseases in China is accompanied by the establishment of appropriate patient registries/networks and reimbursement policies for their treatment. Other key steps would include the implementation of policies relating to fast-track approval, exemptions from large-scale clinical trials, and special approval of orphan drugs in China. Progress on these important issues would place China in a strong position to address the healthcare and societal burdens associated with rare diseases.



## Introduction



According to the World Health Organization, rare diseases affect 6.5–10 individuals in every 10,000 of the general population.<sup>1,2</sup> The European Organisation for Rare Diseases (EURORDIS) estimates that approximately 80% of rare diseases have identified genetic origins, 75% affect children, and that 30% of patients with rare diseases die before the age of 5 years.<sup>3</sup> There are approximately 5,000–7,000 known rare diseases, with 250 new diseases being identified annually.<sup>4</sup> The total rare disease patient population in the United States (US) and the European Union (EU)<sup>4</sup> is estimated to be more than 55 million. It is projected that the rare disease patient population in China is around 10 million people (based on a population of at least 1.3 billion).<sup>5</sup> Any definition for rare diseases adopted in China necessarily encompasses relatively large populations and a higher disease burden compared with less populous countries. Recently, Cui & Han<sup>2</sup> proposed that 300,000–500,000 patients should be used as a reference threshold to define rare diseases in China.

With its enormous population, disparate geography and socioeconomic inequalities, China faces considerable obstacles in improving the standard of care for patients who are affected by rare diseases. Although several strategies relating to rare diseases have been implemented (such as newborn screening and medical expenses reimbursement for children with congenital heart disease and leukemia<sup>6,7</sup>), rare diseases remain under-recognized in China.

Rare diseases, therefore, pose a significant challenge for the Chinese healthcare system.

In this paper we discuss the legislative environment, the progress in social support, advocacy and research, and the key issues and unmet medical needs in China. We also provide some suggestions for how improvements in the diagnosis and treatment of rare diseases could be achieved in the world's most populous country.

## Legislation relating to rare diseases

In many countries orphan drug legislation has been introduced to stimulate the discovery of novel treatments for rare diseases. The legislation often includes commercial and tax incentives for pharmaceutical companies developing the drugs. The key incentives for orphan drug developers in the US and EU include market exclusivity (7 and 10 years for the US and EU, respectively), protocol assistance and follow-up, reduced or waived regulatory fees, and tax credits for clinical trials.<sup>8</sup> This legislation is widely judged to have been successful in encouraging research and development. According to the Food and Drug Administration (FDA), orphan drug approvals in the US reached an all-time high in 2014.<sup>9</sup> Further incentives will be introduced in the US with new legislation due to be enacted in 2015.<sup>9</sup>

Currently, there is no specific nationwide legislation for orphan drugs in China. Furthermore, the Chinese public health insurance system does not cover the healthcare needs of most rare disease patients, and it offers very limited reimbursement for rare disease treatments and orphan drugs. The number of rare diseases covered is currently about 10–15 and the coverage varies tremendously across different provinces.<sup>1</sup>

**Table 1** provides comparisons of rare disease legislation in China and other parts of the world. Recognition of the term ‘rare disease’ in China dates back to 1999. According to the 1999 edition of ‘Regulation for the Approval of New Drugs’, medicines indicated for intractable diseases (such as acquired immune deficiency syndrome [AIDS], cancers and rare diseases) were given priority for fast-track approval. In 2002, the China Food and Drug Administration (CFDA) issued a ‘Request for Importation and Registration of Drugs’ regulation, which exempted orphan and anti-HIV drugs (approved by the FDA/European Medicines Agency [EMA]) from registration studies. The ‘Drug Registration Regulations’ in 2007 further stated that special approvals would be given to drugs with proven clinical benefits for the treatment of AIDS, malignant tumours and rare diseases. Despite efforts to improve orphan drug legislation, the CFDA has yet to implement measures for fast-track approval, exemption from large-scale clinical trials and special approvals for orphan drugs that are currently unavailable in China but approved for use in other countries.

## Laws and regulations relating to rare diseases worldwide\*

	USA	EU	JAPAN	TAIWAN	CHINA
<b>Disease prevalence</b>	0.75‰	0.5‰	0.4‰	0.1‰	N/A
<b>Estimated affected population</b>	>20 million	25–30 million	<50,000	>2000	10 million
<b>Government officials involved</b>	FDA/OOPD	EMA/COMP	MHLW	DOH	CFDA
<b>Legal framework</b>	Orphan Drug Act (1983) Rare Diseases Act of 2002 (2002)	Regulation (EC) No. 141/2000 (1999)	Revised orphan drug regulation (1993)	Rare Disease Control and Orphan Drug Act (2000)	N/A
<b>Drug fast-track approval</b>	Yes	Yes (centralized application)	Yes	Yes	Yes
<b>Protocol assistance in clinical trial</b>	Yes	Yes	Yes	Yes	N/A
<b>Tax benefits</b>	Up to 50% for clinical expenses	Managed by member countries	15% tax credits Up to 14% corporate tax reduction	N/A	N/A
<b>Market exclusivity</b>	7 years	10 years	10 years	10 years	N/A

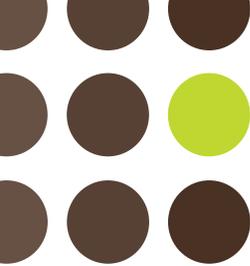
\*Adapted from Song *et al* (2012)<sup>4</sup>, Hall & Carlson (2014)<sup>8</sup>, Liu *et al* (2010)<sup>10</sup> and Montoya (2011)<sup>11</sup>  
CFDA: China Food and Drug Administration, COMP: Committee of Orphan Medicinal Products, DOH: Department of Health, EMA: European Medicines Agency, FDA: Food and Drug Administration, MHLW: Ministry of Health, Labour and Welfare, N/A: not available, OOPD: Office of Orphan Products and Development

**Table 1**

## Social support and advocacy to increase rare disease awareness

Home Babies of the Moon-the China Albinism Association, Haemophilia Home of China, Neuromuscular Disease Association of China, China Organization of Lymphangiomyomatosis and China-Dolls Centre for Rare Disorders are some of the social support groups actively working to increase rare disease awareness in China.<sup>1</sup> The Chinese Organization for Rare Disorders (CORD) is a non-profit organization established in 2013 to support the initiation and development of various rare disease organizations. CORD has started a China Rare Disease Organizations Network which currently includes 23 member organizations. China-Dolls Centre for Rare Disorders and CORD have also initiated nationwide advocacy and communication campaigns to increase awareness of rare diseases and the difficulties faced by patients and their families. In the last 5 years, approximately 100 million people have been educated about rare diseases through various outreach campaigns. CORD has also set up a website ([www.hanjianbing.org](http://www.hanjianbing.org)) which provides information about rare diseases, disease registries and the locations of treatment centres.

Non-profit organizations and academic institutions are also actively involved in the development and dissemination of information associated with rare disease awareness in China.<sup>1</sup> In April 2010, the Chinese Charity Foundation, the China Health Education Centre and Tsinghua University sponsored the “Symposium on Rare Disease” to discuss China’s status on research policy, and the healthcare and insurance systems related to rare diseases and their treatment. In October 2010, China’s first rare disease control association was established in the Shandong Academy of Medical Sciences as a platform for rare diseases diagnosis and treatment.<sup>12</sup> This was followed by the formation of China’s first rare disease specialist association in February 2011. In early 2013, the Shandong Academy of Medical Sciences announced the launch of the China Rare Diseases Prevention and Treatment Alliance on Rare Diseases Day in Jinan, China. The Alliance includes 17 medical institutions from 13 provinces in China representing a population of approximately 0.7 billion. The Alliance aims to set up treatment centres and provide research and education on rare diseases across the country. In September 2014, CORD organized the Third China Rare Disease Summit in Beijing. The summit, attended by government workers, medical experts, law professors, pharmaceutical companies, rare diseases organizations and media representatives, discussed healthcare, policy, and social and work issues related to rare diseases in China.<sup>13</sup>



## Research support in rare diseases



Research funding for rare diseases is mainly provided by the National Natural Science Foundation of China (NSFC). From 1999 to 2007, the NSFC funded 366 projects, of which 32 were rare disease related.<sup>14</sup> During this period, NSFC provided a total funding of approximately RMB 89 million (USD ~14 million), equating to approximately RMB 10 million (USD ~1.6 million) annually.<sup>14</sup> Academic institutions have played an active role in supporting research programmes for rare diseases. The Huazhong University of Science and Technology and the Hong Kong University launched the Chinese Rare Disease Research Consortium (CRDRC) in September 2013 to establish the national registry for rare diseases. With more than 20 universities and 50 specialists as members, the CRDRC aims to team up with several other researchers and organizations to invest in rare disease research in China. The CRDRC also plans to identify 5–30 rare disease genes/year, implement molecular diagnosis and translational research based on these genes, and to facilitate the development of therapeutic strategies for rare diseases.<sup>15</sup>

China's large population means that the absolute number of patients suffering from many rare diseases is likely to be very high compared to most developed markets. If it were possible to ensure the accurate identification of these patients and to maintain their details in effective registries this could present a major opportunity for researchers and others involved in the study of rare diseases and the development of effective treatments. For example, although no national population-based epidemiological studies of myasthenia gravis (MG) have yet been conducted in China,<sup>16</sup> the MG support group, Aili Myasthenia Gravis Care Centre, estimates that there are currently 650,000 patients with MG in China.<sup>17</sup> Any such research initiative would, of course, need to take into account the potential differences between the presentation of rare diseases due to racial and other genetic or geographic differences. Some of the features of MG in China are presented in **Figure 1**.

## Focus on Myasthenia Gravis (MG) in China

MG is a rare acquired autoimmune disease mediated mainly by auto-antibodies against acetylcholine receptors located on the synapses of the skeletal muscles leading to impaired neuromuscular transmission.

According to its clinical presentation, MG is classified as ocular or generalized MG; secondary generalization is common in many populations. Generalized MG is often associated with a poor prognosis; thus, understanding the factors that may affect this process is of great clinical importance.

It has been demonstrated that all races are susceptible to MG; differences in relation to clinical phenotypes have been reported between Caucasian and Asian patients.

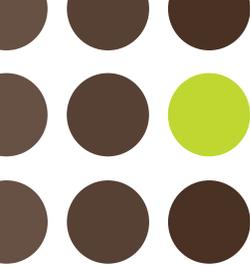
Childhood MG (onset <15 years) is uncommon in North America and Europe,<sup>18</sup> but is believed to account for up to 50% of Chinese patients, mostly comprising pure ocular presentation.<sup>19,20</sup>

A number of classification systems for MG have been adopted, the most common being the Myasthenia Gravis Foundation of America (MGFA) Clinical Classification.<sup>21</sup> An alternative clinical absolute and relative scoring system for MG in Chinese patients was proposed in 1997.<sup>22</sup> This system is officially recommended by the Consensus of Chinese Experts in the Diagnosis and Treatment of Myasthenia Gravis.<sup>23</sup>

Differences between the progression of MG in Asian and Caucasian patients have been reported. Studies have indicated a relatively lower rate of generalization of ocular MG in Chinese patients.<sup>24</sup> It has been suggested that differences in the rate of secondary generalization might be attributed to differences in race, severity of disease, or the impact of early treatment with immunosuppressive drugs such as corticosteroids.<sup>25,26</sup>

Larger, prospective clinical studies on MG will improve understanding of the factors which influence the incidence, presentation and progression of MG in patients in China and other countries. Such a development should be expected to improve the diagnosis and management of MG patients worldwide and support the development of new treatments for this rare disease.

### Figure 1



## Economic incentives for orphan drug access



Pharmaceutical companies have been collaborating with charitable foundations to relieve the financial burden of patients with rare diseases.<sup>1</sup> In 2003, the China Charity Federation and Novartis Pharmaceuticals in China launched a disease relief programme and Glivec® (imatinib mesylate) was given to chronic myelogenous leukaemia and gastrointestinal stromal tumour patients whose incomes were below the local poverty line.

In 2009, the China Charity Foundation and Genzyme Corporation initiated a charitable endowment and Cerezyme® (imiglucerase), valued at RMB 200 million (USD ~32 million), was donated to Chinese patients with Gaucher's disease. The China Charity Foundation also started an assistance foundation for rare diseases in 2009, followed in 2010 by the  $\beta$ -thalassaemia assistant project for patients receiving Exjade® (deferasirox). In 2011, the Qingdao Municipal Charity Foundation and Bayer launched a charity fund to support children with haemophilia who required Kogenate® FS (recombinant coagulation factor VIII).

Although these initiatives have provided access to treatment for some rare disease patients, offering commercial and tax incentives might further encourage pharmaceutical companies to invest in orphan drug discovery.

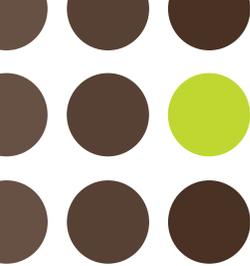
## Pilot project to improve healthcare in rare diseases

In 2013, China launched its first pilot project to support the improvement of rare disease treatment and management.<sup>6</sup> It was initiated by the China Rare Diseases Prevention and Treatment Alliance as a national network that incorporates approximately 100 provincial and municipal medical centres covering 13 provinces with a population of 0.7 billion. This pilot project focuses on 20 representative rare diseases: arrhythmogenic right ventricular cardiomyopathy, congenital myotonia, congenital pyriform sinus fistula, Duchenne and Becker muscular dystrophy, epidermolysis bullosa, Fahr's syndrome, familial aortic aneurysm, hereditary spastic paraplegia, left ventricular non-compaction, Marfan syndrome, myotonic dystrophy, neurofibromatosis, osteogenesis imperfecta, primary tethered spinal cord syndrome, primary cardiac sarcomas, pseudoxanthoma elasticum, Sturge–Weber syndrome, thoracic aortic aneurysm and dissection, tuberous sclerosis complex, and Wilson's disease.

### The pilot project aims to:

- i. develop and test medical guidelines and clinical pathways for the abovementioned diseases;
- ii. establish a patient registry and data repository through the national rare disease network; and
- iii. establish a supporting molecular genetic testing centre for rare diseases.

The main challenge in implementing this pilot project is bridging the gap between primary care clinicians and the 13-province network involved in the project.<sup>6</sup> There are plans to address this issue through a national educational campaign to increase knowledge and awareness of rare diseases among primary care doctors working in resource-constrained circumstances.<sup>6</sup>



## Challenges of rare diseases and their treatment



Compared with the US and EU, there are very few orphan drugs available in China and there is a pressing need to consider how access to treatments already approved for use in other markets can be facilitated. Those available orphan drugs are approved in China for treating common diseases only, despite being licensed for the treatment of rare diseases outside of China.<sup>27</sup> According to the Medical Insurance Directory, China currently has 119 orphan drugs that are at various stages of licensing and registration. Of these, 49 (41%) are covered by national medical insurance. Some of these drugs are fully reimbursed, while most of them are partially reimbursed. Limited reimbursement assistance is available to patients enabling them to purchase the drugs at a reduced price.

Access to good quality information and educational resources on rare diseases is still limited and further work is needed in this area. National patient registries offer a potential resource for researchers and for the patients and families affected by rare diseases. The China-Dolls Centre for Rare Disorders started a voluntary rare disease patient registry in May 2010 and to date it has registered approximately 3,000 patients representing 30 rare diseases. One-third of patients in the registry have osteogenesis imperfecta.<sup>28</sup> Although 80% of rare diseases have known genetic origins,<sup>3</sup> the availability of genetic testing is still limited in China because of insufficient molecular diagnostic resources and the associated high cost of testing. The expansion/development of the genetic testing programme is important because early diagnosis and treatment of inherited rare diseases are central to affected children receiving good treatment and supportive care. Genetic testing can also identify other vulnerable family members and assist family planning.

## Summary and future considerations

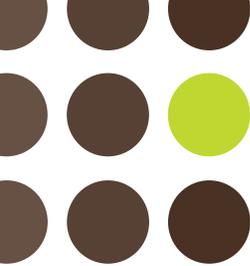
The diagnosis and treatment of rare diseases are an important public health issue and a challenge for medical care in China. The country is still in the early stages of implementing policies related to rare diseases and orphan drug regulations. The recent launch of the nation's first pilot project to improve the levels of rare disease healthcare represents a significant development. We offer the following suggestions to improve the diagnosis and treatment of rare diseases in China.

Firstly, it will be beneficial to create a comprehensive patient registry to facilitate diagnoses which will, in turn, help establish the true prevalence of rare diseases in China. This should further increase public awareness of the issues and encourage the discovery of new orphan drugs. The creation of a transparent network that includes both national and local registration systems to monitor the prevalence of rare diseases would be valuable. This network could also help support pharmaceutical companies accelerate the development and trials of their orphan drugs. In addition, the network could provide assistance with orphan drug designation, registration and marketing applications.

Fast-track approval should be considered for orphan drugs that have been approved in other markets. In addition, post-marketing surveillance could be undertaken where there are insufficient patients available for large-scale clinical trials. This could help the authorities and policy makers to assess the effectiveness of orphan drugs used for the treatment of certain rare diseases. Tax exemptions could also be considered for research and development costs to help stimulate the innovation of novel orphan drugs.

Lastly, adopting 'sales trigger' policy may be useful in introducing foreign drugs into the market.<sup>10</sup> Such a policy would allow the authorities to negotiate with foreign sponsor companies on total sales for each orphan drug. Under this condition, when sales exceed the agreed target, the market exclusivity on the drug will expire and the government can open the market for other foreign competitors to enter the market.

Overall, China has started to employ significant efforts to increase public awareness of rare diseases. Nevertheless, legislation relating to rare diseases remains a 'work in progress'. Although the road ahead could be difficult, we hope that the above suggestions will be considered to help improve rare disease diagnosis and treatment.



## References

1. Gong S, Jin S. Current progress in the management of rare diseases and orphan drugs in China. *Intractable Rare Dis Res* 2012;1:45-52.
2. Cui Y, Han J. A proposed definition of rare diseases for China: from the perspective of return on investment in new orphan drugs. *Orphanet J Rare Dis* 2015;10:28.
3. What is a rare disease? 2015. Available at: [www.eurordis.org/sites/default/files/publications/Fact\\_Sheet\\_RD.pdf](http://www.eurordis.org/sites/default/files/publications/Fact_Sheet_RD.pdf). Accessed: 16 March 2015.
4. Song P, Gao J, Inagaki Y et al. Rare diseases, orphan drugs, and their regulation in Asia: Current status and future perspectives. *Intractable Rare Dis Res* 2012;1:3-9.
5. Wang JB, Guo JJ, Yang L et al. Rare diseases and legislation in China. *Lancet* 2010;375:708-709.
6. Cui Y, Zhou X, Han J. China launched a pilot project to improve its rare disease healthcare levels. *Orphanet J Rare Dis* 2014;9:14.
7. Gu X, Wang Z, Ye J et al. Newborn screening in China: phenylketonuria, congenital hypothyroidism and expanded screening. *Ann Acad Med Singapore* 2008;37:107-4.
8. Hall AK, Carlson MR. The current status of orphan drug development in Europe and the US. *Intractable Rare Dis Res* 2014;3:1-7.
9. Young D. Record approvals, new legislation: Big things happening in rare disease. *Script Intell* 2015;No. 3741, 6 March: Available at: [www.scripintelligence.com](http://www.scripintelligence.com).
10. Liu BC, He L, He G et al. A cross-national comparative study of orphan drug policies in the United States, the European Union, and Japan: towards a made-in-China orphan drug policy. *J Public Health Policy* 2010;31:407-420; discussion 420-421.
11. Montoya ID. Rare diseases: Challenges and resources. *J Nurs Educ Pract* 2011;1:1-3.
12. Zhao H, Cui Y, Zhou X et al. Study and analysis of the state of rare disease research in Shandong Province, China. *Intractable Rare Dis Res* 2012;1:161-166.
13. Yao Y. Third China Rare Disease Summit held in Beijing. 2014. Available at: [www.womenofchina.cn/womenofchina/html1/news/china/1409/1071-1.htm](http://www.womenofchina.cn/womenofchina/html1/news/china/1409/1071-1.htm). Accessed: 16 March 2015.
14. Song P, Gao J, Inagaki Y et al. Intractable and rare diseases research in Asia. *Biosci Trends* 2012;6:48-51.
15. China celebrates the founding of the Chinese Rare Disease Research Consortium. 2013. Available at: <http://www.irdirc.org>. Accessed: 24 February 2015.
16. Guo J, Dang D, Li H-Z et al. Current overview of myasthenia gravis and experience in China. *Neuroimmunol Neuroinflamm* 2014;1:127-130.
17. Life times: 650,000 myasthenia gravis patients urgently require assistance. Available at: <http://www.mg-care.org/channel/content.asp?id=644>. Accessed: 1 April 2015.
18. Phillips LH. The epidemiology of myasthenia gravis. *Ann N Y Acad Sci* 2003;998:407-412.
19. Zhang X, Yang M, Xu J et al. Clinical and serological study of myasthenia gravis in HuBei Province, China. *J Neurol Neurosurg Psychiatry* 2007;78:386-390.
20. Liu W, Men L, He X et al. Clinical analysis on 1520 patients with myasthenia gravis in southern China. *Chin J Neuroimmunol Neurol* 2006;13:326-330.
21. Jaretzki A, III, Barohn RJ, Ernstoff RM et al. Myasthenia gravis: recommendations for clinical research standards. Task Force of the Medical Scientific Advisory Board of the Myasthenia Gravis Foundation of America. *Neurology* 2000;55:16-23.
22. Wang S, Xu X, Sun H et al. A clinical absolute and relative score system for myasthenia gravis. *Chin J Neurol* 1997;30:87-90.
23. Li Z, Hu X, Neuroimmunology Branch of the Chinese Society for Immunology Neuroimmunology Branch - Chinese Society of Neurology - Chinese Medical Association. Consensus of Chinese experts in the diagnosis and treatment for myasthenia gravis. *Chin J Neuroimmunol Neurol* 2012;29:484-505.
24. Jing J, Zhang X, Yu L et al. Factors affecting the progression from ocular to generalized myasthenia gravis. *Chin J Neuro* 2014;47:21-25.
25. Leeamornsiri S, Chirapapaisan N, Chuenkongkaew W. Clinical profiles of Thai patients with ocular myasthenia gravis in Siriraj Hospital. *J Med Assoc Thai* 2011;94:1117-1121.
26. Yang ZX, Xiong H, Zhang YH et al. [Clinical characteristics and follow-up management of 135 children with myasthenia gravis]. *Beijing Da Xue Xue Bao* 2011;43:455-459.
27. Shi LW. International Research Center of Medicinal Administration Peking University. Personal communication. *February* 2015.
28. Han J, Cui Y, Zhou X. Rare diseases research in China: Opportunities, challenges, and solutions. *Intractable Rare Dis Res* 2012;1:10-12.



## Acknowledgments

Comradis® would like to thank The Chinese Organization for Rare Disorders (CORD) for its contribution to the development of this paper.

**Comradis® is dedicated to supporting the development of, and access to, effective treatments for rare diseases and uncommon cancers.**



For further information, please contact:

**Comradis Limited**

Boat Race House  
61-67 Mortlake High Street  
London SW14 8HL UK

E-mail: [team@comradis.biz](mailto:team@comradis.biz)  
[www.comradis.biz](http://www.comradis.biz)

Comradis® is part of AMICULUM®, an independent, privately owned cluster of agencies which deliver value-added services and consultancy to pharmaceutical, biotechnology and medical device companies worldwide ([www.amiculum.biz](http://www.amiculum.biz)).

SHANGHAI • SINGAPORE • DUBAI • LONDON • OXFORD • MANCHESTER • PRINCETON • CHICAGO