CNS Clinical Trials in Russia

PEER REVIEWED

Neurological and psychiatric diseases are becoming the second most health-threatening burden after cardiovascular disorders, and are among the most popular research and development areas worldwide. In Russia, more than 10 % of annual sales refer to neurology and psychiatry medications – ranking in second or third place after GI and endocrinology, cardiovascular drugs and taking the lead in natural volume. More than 40 % of these drugs are analgesic. More than three-quarters of drugs are imported and produced by foreign biopharmaceutical companies.[1] 15 % of medicines from the List of Vitally Needed Important Drugs refer to neurology and psychiatry - reflecting the governmental policy on provision of the population with the most essential and affordable drugs.

According to the current legislation, to market a drug in Russia, it must have been previously clinically researched at Russian sites as well. This could be, for example, an international Phase II or Phase III programme involving Russian investigators. First-in-man studies of foreign drugs in healthy volunteers are forbidden. To initiate first-in-man clinical trials in psychiatry patients in Russia, the sponsor should provide either a very impressive preclinical package, or some Phase I clinical study results from outside of Russia; however, in general it is recommended to place all Phase I research of foreign investigative products abroad.

Nowadays, the population of Russia is around 143.37m. As per current statistics, approximately 40 %[2] of the population suffer from various types of mental illnesses, and more than 20m need psychological help[3]. More than 900,000 people have schizophrenia, and 250-300,000 have manic state[4]. Alcohol addiction affects more than 20m Russian citizens - 60 % of which are 24-30 years old[5] - causing one-third of deaths among men. In accordance with the Federal Law 61-FZ of 12-Apr-2010 On Medicines, clinical research of psychiatry therapies in psychiatry patients declared legally incapable is allowed only on provision of a written informed consent from legal representatives. The Council on Ethics at the Ministry of Healthcare is very cautious of psychiatry studies, and as per the recent ACTO report[6], only half of the protocols in this therapeutic area are approved by the body.

Annually, more than 480,000 Russians suffer from strokes[7], which is one of the key causes of disability and death among the population. In Russia, to approve a clinical study requiring emergency measures, a developer is recommended to include special terms of patients' enrolment into the study protocol. These terms should allow an investigator to escape obtaining a written informed consent from a subject and his/her legal representatives prior to urgent medical interventions, due to the critical condition of a patient. Such protocols are carefully reviewed by the national and local ethics committees.

The Russian market is still looking for new effective medications and state-of-the-art diagnostics in the Alzheimer's disease (AD) and multiple sclerosis (MS) areas. Currently 1.8m Russians have dementia[8] and 150,000 have MS[9]. A number of leading Russian biopharmaceutical companies and life science institutional investors are engaged in development of new disease-modifying therapies in these areas and are actively looking for regional in-licensing and partnering opportunities with foreign drug developers - especially in biologics. Taking into consideration that in Russia most care-givers are relatives, the economic burden of such diseases is substantial.

AD and MS are the most difficult CNS areas for patient enrolment; however, this does not really concern Russia. A number of late-stage projects sponsored by Abbott, Roche, Eli Lilly, Servier, TauRx, Biogen, Teva, Novartis, GSK, Mitsubishi Tanabe and others (as well as Russian companies) are being conducted in the country now. Clinical research of disease-modifying agents requires huge sample sizes of patients to recruit into AD studies, as well as longer treatment periods. Symptom treatment trials are considerably smaller and shorter; however, monotherapy placebo-controlled studies require the recruiting of treatment-naïve patient populations, which is still possible in Russia.

The incidence of epilepsy is 3.4 per 1000 in Russia[10]. Ineffective and untimely therapy is the key reason for aggravation and low curability. Substantial prevalence of generics and lack of certain

drug formulations in the Russian AED market complicate the treatment of patients. Taking into account that epilepsy is one of the four most frequent infant diseases (7 cases per 1000 children) as well as diabetes, bronchial asthma and autism (1 case per 1000 children)[11] , clinical development and launch of novel anti-epileptic drugs becomes a crucial task for the Russian government and biopharmaceutical sector.

As per infant diseases, the problem of child psychoneurology is a burning issue. 83 % of children in Russia have neurological symptoms and signs. In the country, 7-28 % of children suffer from attention deficit hyperactivity disorder (ADHD)[12]. ADHD leads to serious negative social impact if not treated in a timely manner. However, only one international multicentre clinical study and one local clinical trial in this therapeutic area have been conducted in Russia during the last few years. In accordance with the Russian legislation, paediatric clinical trials are permitted only if an investigative product has been previously researched in adults, unless a drug is solely prescribed for infants. A written informed consent form signed by parents and adopters is sine qua non to conduct paediatric clinical research in Russia. Placebo-controlled paediatric studies are limited and account for less than 10 % of paediatric studies in the country. Nevertheless, for instance, in pain therapy a placebo effect is variable; hence, the placebo-controlled design is applicable.

Today there is an urgent unmet need for marketing more effective treatments of pain in Russia, especially non-invasive drugs for oncology palliative care. For the moment, only four non-invasive opioid analgesics are registered in the country in comparison with many registered in the EU. Aside from general legislation covering clinical research such as the Federal Law On Medicines and others, there are special regulations for psychotropic and narcotic medications in Russia stipulating very strict conditions of circulation (including clinical development) of such drugs (Federal Law 3-FZ of 08-Jan-1998; etc.).

According to the recent report of the Association of Oncologists of Russia, the CNS tumour rate is 4.08 per 100,000[13]; incidence of brain tumours in the country is 3.7 per 100,000 .[14] CNS tumours in children rank second place in malignant neoplasms after leukosis, and account for 18 %[15] of all infant oncological diseases. Clinical research in CNS tumours is important in Russia as the required amount of financial resources to treat a patient is enormous for the average man, but the current governmental support is not sufficient to cover the existing need: more than 50-60 % of oncology drugs are paid for by patients and their relatives, despite the fact that these medicines are to be reimbursed by the state[16].

The quality of clinical research data coming from Russia is comparatively high. One-third of FDA/EMA approved drugs studied within international clinical trials have been placed, in part, in Russia, and that percentage is increasing (29 % in 2010, 33 % in 2011, and 37 % in 2012[17]). Most CNS clinical studies - amounting to several hundred - in Russia have been conducted in MS, epilepsy, AD, stroke, depression and schizophrenia; however, the potential of the region in terms of a pool of treatment-naive patients and a number of sites to contribute to international clinical research is huge. A few trials took place in rather challenging indications such as alcohol addiction, where for the moment, most sponsors are presented by the Russian biopharmaceutical companies.

As per SynGR Orange Papers[18], 6-11 % of the total number of clinical studies approved annually in the country are in neurology and psychiatry. However, we expect this share will increase, and more and more new safe and effective disease-modifying therapies will be suggested to Russian patients.

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