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CLINICAL TRIALS FOR CELLULAR THERAPY PRODUCTS: CONCLUSIONS REACHED BY FOREIGN REGULATORY BODIES

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Currently, the problem of adopting viable human cell-based drugs – biomedical cell products (BCPs) – in medical practice in the Russian Federation includes, among others, lack of experience in clinical trials for such drugs and insufficient expert assessment under the national state registration procedure. In global practice, by the beginning of 2020, there were over 30 cellular therapy products (human cellular- and tissue-based products) known to have undergone clinical trials for sales licenses from regulatory bodies in the United States, European Union, Japan, and South Korea. Most cellular therapy products are intended for treatment of severe orphan diseases and life-threatening conditions that currently cannot be treated by traditional drugs or methods. The aim of this study is to analyze the global experience in clinical trials for cellular therapy products and also to examine conclusions reached by regulatory authorities with regards to issuance of sales licenses for the products. Particular attention was paid to clinical trials that subsequently led to granting of sales license (state registration). In reviewing such trials, we also focused on the types and number of clinical trials, the number of patients involved in the clinical trials, conclusions made by expert regulatory agencies on the efficacy, safety and risk/benefit ratio. Most of the products were approved for use based on uncontrolled phase II clinical trials. In the clinical trial, apart from the historical group and the placebo-controlled group, there was also a control group that received nothing. The number of patients in most clinical trials was limited, especially for drugs intended for treatment of rare genetic diseases, as well as drugs approved for use in Japan.

Keywords: biomedical cell product, human cellular- and tissue-based products, cell therapy, clinical trials, regulatory findings.

INTRODUCTION

In compliance with the Russia Federal Law No. 180-ФЗ of June 23, 2016 On Biomedical Cell Products, at the biomedical expertise as part of the state registration, the BCPs registration dossier should include a report on the results of clinical trials (CT) the portion of which has been conducted in the Russian Federation in medical institutions accredited to conduct BCP CTs. The list of medical organizations accredited to conduct BCP CTs already contains over 30 institutions [1]. To date, there are no BCP CTs for with permits were issued by the Ministry of Health of Russia in accordance with the Rules of Good Clinical Practice for Work with BCPs approved by the Order of the Ministry of Health of Russia No. 669н of September 22, 2017.

The international practices present, along with the experience of conducting CTs of drugs based on human cells and tissues (BCP analogues), the review of their results assessed by regulatory agencies. In total, there are over 30 drugs of the kind approved for use in medical practice around the world. These can be conditionally divided into the following groups:

1) for treatment of oncology diseases (*Immuncell-LC, CreaVax-RCC* – South Korea; *KYMRIAH, Yescarta* – European Union/EU, US);
2) for treatment of genetic diseases (*Strimvelis, Zynteglo* – EU);
3) for GVHD (graft versus host disease) treatment (*Prochymal,* Canada; *Zalmoxis,* EU; *Temcell,* Japan);
4) for regenerative medicine: treatment of the knee joint cartilage injuries *(MACI,* US; *Spherox,* EU; *JACC,* Japan; *Chondron, Cartistem* – South Korea; *Cartogen,* Australia, Singapore); burns, wounds, scars, diabetic ulcers, etc. (*JACE,* Japan; *Holoderm, KeraHeal, Cure-skin, Kaloderm, KeraHeal-Allo* – South Korea; *Gintuit,* US; *Holoclar,* EU); heart diseases (*HeartSheet,* Japan; *Hearticellfram-AMI,* South Korea); fistulae in Crohn's disease (*Cupistem,* South Korea; *Alofisel,* EU); for elimination of nasolabial creases in cosmetology (*Laviv,* US); for bone reconstruction (*RMS ossron,* South Korea).

The purpose of the present study is to review global experience on CTs of the cell therapy drugs and assessment of their results by regulatory agencies to obtain marketing authorization.

To analyze the global experience in conducting CTs of the drugs based on human cells and tissues (BCP

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analogues), a database of privately and publicly funded clinical studies conducted around the world (ClinicalTrials.gov) was mainly used; there, CTs were searched by the drugs commercial names and their international non-proprietary names (INNs) as well as regulatory permission documents for medical use drugs on the official websites of regulatory bodies of the US, EU, and Japan. It should be noted that open source information is not available for all drugs, in particular, data is limited on the drugs registered in South Korea, currently the leader in the field of cell therapy drugs approved for medical use. Particular attention was paid to CTs resulting in the drug marketing authorization (state registration), CT types and numbers, the number of patients included in the CT, the conclusions made by experts of the regulatory agencies on the efficacy, safety and the expected risk/benefit ratio. The CTs were analyzed for 14 BCP analogues.

PRODUCTS BASED ON CHIMERIC ANTIGEN RECEPTOR TECHNOLOGY (US AND EU)

Some of the latest cell therapy drugs authorized for the US (2017) and EU countries (2018) markets are KYMRIAH (Novartis) and Yescarta (Kite Pharma, Gilead), the products for adoptive immunotherapy based on chimeric antigen receptors (CAR). In the United States, both drugs were assigned the orphan diseases treatment status and the Breakthrough Therapy designation based on the FDA conclusions about the potential significant advantage of CAR therapy over existing therapies [2, 3]. In the European Union, KYMRIAH and Yescarta were the first drugs approved under the Priority Medicines scheme (PRIME) which implies an accelerated procedure for evaluating the CT applications and marketing authorization [4, 5].

As of the second half of 2019, the majority of CTs of KYMRIAH (Novartis) and Yescarta (Kite Pharma, Gilead) in the international CT database ClinicalTrials.gov have the status of "active" or "recruiting" (Table 1).

KYMRIAH was approved for market by the US regulatory agency for the treatment of recurrent/ refractory (r/r) acute lymphoblastic leukemia (ALL) and diffuse large B-cell lymphoma (DLBCL) on the results of two CTs, "ELIANA" (r/r ALL) and "JULIET" (DLBCL) (Table 1), aimed at assessing therapeutic *KYMRIAH* efficacy upon reaching the general remission rate, including complete and partial remission, within 3 months after administration, as well as the response duration [2, 6]. Marketing approval for *Yescarta* in the US and EU was obtained on the basis of one CT, "ZUMA-1" (Table 1).

When considering *KYMRIAH* registration in the EU, the regulatory agency used the comparative data of the "ELIANA" and "JULIET" CTs on the use of the drug manufactured in the EU and in the US [4].

Besides, data of the "JULIET" and "ZUMA-1" CTs on the efficacy as indicated for DLBCL were compared with the results of CTs of maintenance drugs (SCHOLAR-1, PIX301, and CORAL) [4, 7–10].

In general, when evaluating CTs of the products based on chimeric antigen receptors, the following points should be noted:

- *KYMRIAH* and *Yescarta* got marketing authorization based on uncontrolled Phase II CTs without providing long-term observations followed by annual update (trimming) of data;
- CTs assessing different drug doses were absent, the doses were selected on the basis of preclinical studies and literature data (*KYMRIAH*: 0.2–5 × 10^6 CAR-T positive T cells/kg body weight with a weight under 50 kg, 0.1–2.5 × 10^8 CAR-T positive T cells -cells/kg body weight over 50 kg; *Yescarta*: from 2 × 10^6 to 2 × 10^8 CAR-T positive T cells/kg body weight);
- the main risk factors for the drugs are cytokine release syndrome (CRS) and neurotoxicity, besides, there is a high rate of adverse events of class 3 and higher;
- patients were included by phases; in the CT of *Yescarta*, the patients were divided into cohorts depending on the type of non-Hodgkin lymphoma;
- not all patients included in the CT received therapy, the main causes being technical reasons, death of patients, physician's decisions, and others.

F.L. Locke et al. [9] present a comparative analysis of some aspects of CTs of the drugs based on chimeric antigen receptors including *lisocabtagene maraleucel* not yet licensed for sale (Table 2).

The US and EU regulatory agencies concluded that the efficacy of *KYMRIAH* (r/r ALL) and *Yescarta* (DLBCL) in comparison with existing therapies has been proven; serious adverse events (SAEs), in particular CRS and neurotoxicity, were considered manageable, and the risk valuation and identification strategy ensured higher benefits than risks associated with these SAEs [2–6]; long-term CT was a prerequisite for the drugs to be brought to market. For example, the requirements for post-marketing trials of *Yescarta* contain the following: a multicenter prospective CT of safety should be performed, including 1,500 subjects, with an observation interval of 3 months after drug administration for 5 years, and the total duration of observation of 15 years [6].

As for the use of *KYMRIAH* indicated for DLBCL, despite "modest" efficacy compared to conservative treatment, the response duration was found to be clinically significant. However, in June 2018, the opinion of 12 experts from the European Medical Agency (EMA) from different countries (Norway, Sweden, Netherlands, Italy, Greece, Romania, and Spain) was published, who did not agree with the marketing authorization of the drug according to DLBCL indication: "Due to the high degree of uncertainty in the obtained efficacy results for the DLBCL indication, the potential benefit cannot be determined for this population. Thus, the benefit/risk cannot be established and is thus not positive. As a con-

Table 1

Clinical trials of *KYMRIAH* and *Yescarta*, ClinicalTrials.gov Search Results 09/15/2019

Nos.	CT ID, particulars	Indications	Status	Start Date – End Date	Number of patients (age, years)	Number of countries / medical centers
KYMRIAH (tisagenlecleucel)						
1	NCT02445222, long-term	r/r ALL, DLBCL	Enrollment	11.2015 – 05.2035	620 (3 and older)	11/45
2	NCT02435849, B2202 **(ELIANA);** phase II, uncontrolled	r/r ALL	Active	04.2015 – 11.2022	81 (3–30)	11/ 25
3	NCT02445248, CCTL019C2201 **(JULIET)**; phase II, uncontrolled	DLBCL	Active	07.2015 – 02.2023	116 (18 and older)	10/28
4	NCT02228096, CCTL019-B2205J; phase II, uncontrolled	r/r ALL	Active	08.2014 – 12.2022	64 (3–21)	1 (US)/12
5	NCT02030834; phase IIA, parallel control	NHL	Active	02.2014 – 01.2020	63 (18 and older)	1 (US)/1
Yescarta (*Axicabtagene Ciloleucel, KTE-C19)*						
1	NCT02625480 (ZUMA-4); phase I/II	r/r ALL	Enrollment	02.2016 – (07.2021) 01.2036	100 (2–21)	4/ 21
2	NCT02926833 (ZUMA-6); phase I/II (combined with Atezolizumab)	DLBCL	Active	09.2016 – (02.2019) 08.2033	37 (18 and older)	1 (US)/4
3	NCT02348216, KTE-C19-101 **(ZUMA-1)**; phase I/II	r/r NHL*	Enrollment	01.2015 – (05.2020) 10.2034	250 (18 and older)	6/36
4	NCT03391466, KTE-C19-107 (ZUMA-7); phase III (compared to standard treatment)	r/r DLBCL	Enrollment	12.2017 – (01.2022) 01.2035	350 (18 and older)	9/49
5	NCT03704298, KTE-C19-111 (ZUMA-11); phase I/II (combined with Utomilumab)	r/r DLBCL	Enrollment	11.2018 – (01.2021) 06.2035	48 (18 and older)	1 (US)/3
6	NCT03761056, KTE-C19-112 (ZUMA-12); phase II (first-line therapy)	DLBCL	Enrollment	12.2018 – (07.2020) 12.2034	40 (18 and older)	1 (US)/1
7	NCT03105336, KTE-C19-105 (ZUMA-5); phase II (treatment, expected response 70%)	r/r NHL	Enrollment	06.2017 – (03.2020) 03.2034	80 (18 and older)	2/19
8	NCT02601313, KTE-C19-102 (ZUMA-2); phase II	MCL	Enrollment	11.2015 – (06.2019) 03.2034	130 (18 and older)	3/32
9	NCT02614066, KTE-C19-103 (ZUMA-3); phase I/II	r/r ALL	Enrollment	03.2016 – (01.2020) 03.2034	100 (18 and older)	5/32

Note. r/r – refractory/recurrent form; ALL – acute lymphoblastic leukemia; DLBCL – diffuse large B-cell lymphoma; MCL – mantle cell lymphoma; * Non-Hodgkin types of B-cell lymphomas (NHL – non-Hodgkin lymphoma): Refractory Diffuse Large B Cell Lymphoma (DLBCL), Relapsed Diffuse Large B-Cell Lymphoma, Transformed Follicular Lymphoma (TFL), Primary Mediastinal B-cell Lymphoma (PMBCL), High Grade B-cell Lymphoma (HGBCL).

sequence of the above considerations, and the regulatory environment where both indications were submitted under the same application, the below mentioned delegates disagree with the granting of the marketing authorization including both indications on the ground that the potential benefit is considered not to be sufficiently demonstrated for the DLBCL indication" [4].

PRODUCTS BASED ON HUMAN CELLS AND TISSUES PERMITTED FOR USE IN THE EU

In the EU today, two drugs (*Holoclar* and *Zalmoxis*) have conditional registrations based on limited data with the provision to annually update the efficacy and safety reports [11–13].

Holoclar (*Holostem Terapie Avanzate S.R.L.*), a limbal stem cell-based drug for the treatment of eye burns,

Table 2

Comparative characteristics of some aspects of clinical trials of drugs based on chimeric antigen receptors

Clinical study	JULIET	TRANSCEND	ZUMA-1
Drug	*KYMRIAH*	*lisocabtagene maraleucel*	*Yescarta*
Number of patients included	165	134	119
Number of patients receiving therapy	111 (67%)	114 (85%)	108 (91%)
Chemotherapy before use	Yes	Yes	No
Cytokine release syndrome 3/4	22% of 111 patients	1%	11% (12 of 108)
Neurological events	12%	11 (15%) of 73 patients	32% (35)

including chemical burns, received conditional registration from the EMA on the benefit/risk assessment based on the results of two retrospective uncontrolled studies (on the retrospective medical records, HLSTM01 and HLSTM02), with 200 patients since 1998. In addition, the developer must provide additional data from the prospective HLSTM03 study by December 2020 [11, 14–16].

In the CT HLSTM01, *Holoclar* efficacy was evaluated on 104 patients aged 13 to 79 years who received treatment in the presence of moderate and severe limbal stem cell deficiency 12 months after the drug administration. At the time of the drug administration, the average condition duration from the moment of injury was 18 years (median 10 years). A total of 75 cases (72.1%) of effective drug use are reported. These results were confirmed by an independent peer review of pre- and post-*Holoclar* implantation images of patients' eyes based on the assessment of superficial neovascularization [12].

The most serious adverse responses to *Holoclar* are corneal perforation and ulcerative keratitis, which may occur within 3 months of the drug implantation. As the side effects of Holoclar treatment are generally controllable, EMA experts concluded that the benefits outweigh the risks and recommended that it be approved for use in the EU. *Holoclar* has been given the so-called "conditional approval" [11, 12].

Zalmoxis (*MolMed SpA*) based on genetically modified cells (allogeneic T cells genetically modified with a replication-defective γ-retroviral vector encoding a truncated nerve growth factor receptor ΔLNGFR and herpes simplex virus thymidine kinase HSV-TK Mut2) to restore bone immunity after bone marrow transplantation in cancer patients was classified as an unsecured medical need and registered on the basis of two CTs (NCT00423124, NCT00914628) compared to retrospective (historical) control. The control (retrospective comparison) group included patients who underwent haploidentical transplantation and underwent graft versus host disease (GVHD) prevention by two most widely used methods, depletion of T cells in the graft and cyclophosphamide and immunosuppressants after transplant. In total, the effect of drug treatment in 37 patients (23 in NCT00423124 and 14 in NCT00914628) was comparable to the data of 140 patients from retrospective groups who received treatment in 2005–2013. Differences were observed in mortality from recurrences within 1 year: 22% in the drug group and 43% in the control group [13].

The EMA experts' conclusions regarding the benefit-risk of using *Zalmoxis*, given the limited treatment options and poor prognosis for cancer patients and hematopoietic stem cell transplant recipients, included the following aspects:

1. Annual update of the status of included patients and participation of new health institutions. It is important to prove that the sampling size appears to be sufficient for statistically significant differences in overall survival between retrospective comparison and the control groups [13, 17].
2. *Zalmoxis* efficacy has been proven in terms of one-year overall survival growth and reduced mortality from recurrences as compared with the control group.
3. *Zalmoxis* safety profile is considered acceptable. The main risk is GVHD which can be successfully treated with ganciclovir that affects the drug's genetically modified T cells [13, 17].

Alofisel (Darvadstrocel) for the treatment of complex pararectal fistulas in patients with Crohn's disease (adipose tissue stem cells) was approved by the EMA based on placebo-controlled ADMIRE-CD CT (NCT01541579) Phase III: a total of 212 patients were randomized, 205 received local injections of the drug or placebo into the lesion. The patients did not respond to standard treatments such as antibiotics, immunosuppressants, or therapy with tumor necrosis factor (anti-TNF) inhibitors. During the CT, the patients received adjuvant treatment with immunosuppressants (18%), anti-TNF drugs (33%), or with both (28%) [18].

The drug received marketing authorization in the presence of limited data on safety and a small effect compared to control (remission of the disease after 24 weeks in the experimental group occurred 15% more often than in the placebo group, and 17% after 52 weeks), given that the benefits of its use (mainly efficacy) for the treatment of complex anal fistulas that did not respond to standard treatments outweigh the risks. The data on *Alofisel* safety are limited, though there is sufficient information on the nature of side effects. Given the "modest" efficacy compared to standard treatments and the presence of only one large-scale CT (NCT01541579), the benefit/risk data on the drug use will be obtained in the ongoing

multicenter, placebo-controlled phase III CT Cx601-303 (NCT03279081) [19, 20].

Spherox (Co.don AG), a chondrocyte-based drug for the treatment of osteochondral lesions of the knee joint, was approved for use on the basis of the prospective, uncontrolled, phase II CT (with 4-year follow-up) with 75 patients 4–10 cm^2 grade III/IV focal defects of the knee cartilage using three doses of the drug. In all 3 dose groups, there was a significant improvement ($\alpha < 0.05$) on the Knee Injury and Osteoarthritis Outcome Score (KOOS) after 12, 24, 36 and 48 months compared to the state before the drug [21].

Besides, a multicenter, prospective, randomized, controlled phase III CT is ongoing to compare the efficacy and safety of treatment with *Spherox* of cartilage defects (1 to less than 4 cm^2) in the knee condylus and 5-year micro fracturing treatment. The micro fracturing treatment is not recommended for the restoration of large defects (no more than two defects in cartilage of 1 to 1.5 cm^2). The main efficacy data in this CT are based on interim analyzes in 12 and 24 months after treatment. The final report on this CT should be submitted by March 1, 2021 [22].

The EMA has found *Spherox* safety profile acceptable and most of the expected side effects related to surgery (way of the drug administration); the CT should be continued for long-term effects for 5 years [22, 23].

Further, we should dwell turn our attention to the CTs recognized by the EMA regulatory agency during the state registration of a drug for the treatment of such genetic disease as the severe combined immunodeficiency associated with the adenosine deaminase (ADA) gene defect. The drug, *Strimvelis (GSK)*, is based on genetically modified cells and is classified by the disease as an unmet medical need. All CTs of *Strimvelis* were non-randomized, single-group, open; intra-subject comparison was performed before and after treatment; the survival endpoint was compared with the retrospective (historical) control [24, 25]. Given the rarity of the disease (less than 50 children per year in the US and the EU in total), this was accepted as acceptable by the experts of the EU regulatory agency. A total of one main CT (AD 1115611), several pilot CTs (AD 1117056, AD 1117054, AD 1117064) have finished and one CT (AD 1115611, long-term) is ongoing (CTs have been launched since 2000). Given the rarity of the disease, in the marketing application, the applicant provided data on *Strimvelis* efficacy for 12 patients from the main CT and for 6 patients from the pilot CTs [25, 26].

The primary efficacy endpoint in the main study (AD1115611) was survival: 100% survival was observed for all patients with the mean follow-up of 6.9 years, which is higher than the most recent published historical comparative index of 67% overall survival seen in 15 marrow bone transplant patients with the mean follow-up of 6.5 years [24]. The survival rate also exceeds 86 and 83% for HLA-compatible transplant recipients (n = 42) and related donors (n = 12), respectively.

The EMA experts concluded that the evidence on *Strimvelis* efficacy is beyond doubt, but the problem is the use of the drug in centers other than the one where the CT of the drug was performed, due to the short shelf life of the product (6 hours).

As for the safety, there is a risk of insertional mutagenesis due to the use of a retroviral vector in the product manufacture; nevertheless, to date, no cases of leukemia, myelodysplastic syndrome or malignant neoplasm have been noted. The possible occurrence of an autoimmune disease is an issue that can be addressed with adjuvant standard therapy. Accordingly, from a clinical point of view, the benefit/risk ratio of *Strimvelis* is considered positive. However, the registration conditions were to conduct post-marketing CT analysis for the emergence of replication-competent retroviruses, assessment of genotoxicity and immunogenicity, and forming a register of patients treated with *Strimvelis* [25–27].

Zynteglo (bluebird bio) based on genetically modified hematopoietic stem cells transduced with a lentiviral vector encoding the βA-T87Q-globin gene, has received the EMA conditional approval for marketing under PRIME, as it is aimed at treating a serious, recognized orphan disease for which there is an unmet medical need. The stated *Zynteglo* indication is the treatment of patients over 12 years of age with transfusion β-thalassemia (TDT), without β0/β0 genotype, for whom HSC transplantation is required without related donors.

The drug received conditional marketing authorization based on a clinical program comprising 5 CTs: two phase I/II CTs (HGB-205 and HGB-204), three phase II CTs (HGB-207, HGB-212, and a long-term CT LTF-303). As of December 13, 2018, a total of 32 patients, excluding the β0/β0 genotype have been treated (11 adolescents and 21 adults). Age ranged from 12 to 35 years old. At the end of 2018, the follow-up after drug administration continued for about 60 months. Continuing long-term CT LTF-303 includes all patients from previous CTs for 15-year follow-up. The EMA recognized the benefit of the drug treatment in the study population despite the limited number of patients participating in the CT and the lack of long-term safety data. The safety profile includes adverse events (AEs) associated with mobilization, apheresis, and conditioning. As for the use of a lentiviral vector for genetic modification of cells, there is a theoretical risk of insertional mutagenesis. Additional data on *Zynteglo* efficacy and safety will come from ongoing CTs (HGB-207 and HGB-212) as well as long-term patient monitoring in the CT (LTF-303 and REG-501) [28]

CELL THERAPY PRODUCTS AUTHORIZED FOR USE IN THE US

In the US, *Laviv (Fibrocell)*, a drug based on fibroblasts has been approved for use in cosmetology to eliminate nasolabial creases. The registration application for *Laviv* was first filed in 2009 and contained the results of two Phase III CTs (NCT00655356, NCT00649428) conducted between 2006–2009. In total, the drug was used in 210 patients with 211 as control (saline administration). In 2009, the marketing application was rejected because the drug was not intended for a life-threatening condition and safety standards had to be set at a high level. The US regulatory agency required a histological examination of tissue in the area of the drug injection, which was subsequently performed. Based on the CT results, the regulatory agency concluded that the drug had a favorable risk-benefit ratio. However, post-marketing CTs have been recommended by regulators to assess the risks of skin cancer in the injection site and the risk of autoimmune reactions. Fibrocell conducted post-marketing research (NCT02120781) [29]. It should be noted that since September 2016, this technique has no longer been present in the US market, the manufacturer retained its patent rights but reduced the production of the drug due to low demand [30].

CELL THERAPY PRODUCTS AUTHORIZED FOR USE IN JAPAN

In Japan, since November 2013, the clinical use of gene and cell therapy products has been allowed for 7 years, subject to availability of data indicating their efficacy and safety in phase I CT [31].

In Japan, a distinctive feature of CTs of drugs approved for medical use is the small number of patients.

HeartSheet (Terumo Corporation) based on myoblasts for the treatment of severe heart failure in patients who do not respond to standard therapies, was conditionally released on the basis of the CT M-51073-21 with retrospective control with 7 patients; active control was not used due to the complexity of the drug implementation (heart surgery). The primary endpoint of efficacy was the change in left ventricular ejection fraction (LVEF) from baseline to week 26 after transplantation: in 5 patients this parameter did not change, decreasing in 2 patients [32, 33]. However, due to the improvement in exercise tolerance (walking), the effectiveness of this therapy was recognized in 5 out of 7 patients.

The Japanese Pharmaceuticals and Medical Devices Agency made the following conclusions:

1. The CTs of the drug were initially planned as research-purposed; however, the drug has potential therapeutic efficacy for patients who do not respond to standard treatments.
2. A retrospective comparison with patients who receiving other treatments between 2007 and 2014 and have been included in the University of Tokyo Hospital database did not reveal significant differences in condition between the 2 patient groups (*HeartSheet* drug group and other treatment group) within two years after using the drug.
3. As of October 30, 2014, 6 out of 7 patients survived for more than 1 year after using the drug. In two clinical studies (MP0604 and HM0801), 19 more patients were treated with the drug, 2 died in 2.5 years after transplantation, but a causal relationship between deaths and the drug was ruled out. As of September 2015, 14 out of 17 patients were alive for more than 2 years after transplantation, the longest life expectancy was 7 years.
4. Long-term safety of the drug: the pre-clinical trial of the drug efficacy in mini-pigs, drug cells are not detected 13 weeks after transplantation. In the unregistered CTs (MP0604 and HM0801) in humans, cells were not detected on biopsy within several months after transplantation. These results indicate that the drug does not remain in the body for a long time and therefore is unlikely to create safety problems for a long period after transplantation. Due to one case of colon cancer, it is necessary to evaluate the effect of the drug for malignant tumors [32].

JACE (Japan Tissue Engineering Co., Ltd., J-TEC) based on keratinocytes was approved for seven years in 2007 for the treatment of severe burns (over 30% of total body surface) according to the results of the CT J-TEC003 (2004) which includes 2 patients [34]. By 2013, the drug preparation was reported taking place in 4.5 years (since January 2009, drug treatment has been covered by the national health insurance) for 370 burn patients; 35% of the products were ultimately not used due to patients' death or for other reasons; During this time, *JACE* was used in over 240 patients aged from 1 to 80 years [35]. In November 2015, wound treatment after removal of the Giant congenital melanocytic nevi (GCMN) was added to the indications based on the CT 3SI-GCMN001 with 8 patients. According to experts from the Japanese regulatory agency, despite the small number of patients participating in this CT, the presented results are acceptable for the drug registration as a new treatment option for wounds after GCMN removal, since *JACE* efficacy was shown in 95% of cases [36].

The conclusions of the safety experts included the following:

1. At GCMN, the onset of malignant melanoma is possible; however, the disease develops for several years. The long-term follow-up of 52 weeks of the patients after using *JACE* is too short to detect a tumor caused by the drug; however, given that the drug does not include genetically modified cells, the manifestation of tumorigenic potential of cells is unlikely. Besides, the development of tumors was not detected when using the drug for the treatment of burns. Therefore, a

follow-up of 52 weeks to assess the safety of the drug for GCMN treatment was taken as acceptable. Safety data collection will continue after the completion of the CT.

2. Due to the risks associated with xenotransplantation of 3T3-J2 cells obtained from the mouse embryos which are used in the manufacture of the drug as feeder cells, the applicant must ensure the 30-year preservation of the final product and the protocol of use [34].

In January 2016, *JACE* was approved with a re-registration period of 10 years for two indications for use [34, 36].

The registration application was submitted in Japan for *Temcell* (JCR Pharmaceuticals Co., Ltd, previously registered in Canada as *Prochymal*®, Osiris Therapeutics Inc., US) based on mesenchymal stem cells (MSC) of bone marrow (BM). The filed evaluation of the efficacy and safety of the drug included the results from Japan's uncontrolled phase I/II CT (JR-031-201) and its continuation in the CT (JR-031-202) as well as the phase II/III CT (JR-031-301) with acute GVHD patients refractory to corticosteroids; 39 patients were enrolled in three CTs. The reference data presented were complemented by the results of the comparative CT of *Prochymal* conducted by Osiris Therapeutics Inc. (US) with 163 patients (81 controls) [37, 38].

The conclusions of the Japanese regulatory agency experts included the following:

1. Based on the benefits and risks of *Temcell* that were demonstrated in the submitted CTs, *Temcell* can be considered a second-line acute GVHD therapy for patients who do not respond to corticosteroids as a first-line therapy.
2. Since the data on *Temcell* safety is limited, for all patients treated with *Temcell*, the following information should be provided: on deaths, underlying disease recurrences, risks of malignant tumors with the exception of the underlying disease, risks of tumorigenic and carcinogenic properties, risks associated with intravenous infusion of allogeneic cells (events possibly associated with circulatory disorders due to cell embolism and thrombus formation; events possibly associated with intravascular hemolysis; events possibly associated with an immune response); on gastrointestinal bleeding and others [37].

CELL THERAPY PRODUCTS AUTHORIZED FOR USE IN SOUTH KOREA

ClinicalTrials.gov database contains data on 4 CTs of *Immuncell-LC (Green Cross Cell)* based on activated T-lymphocytes for the treatment of hepatocellular carcinoma, but only for one the results are published: CT Phase II/III (NCT00699816) of the indications for use of the drug. 114 patients received the drug, the control group included 112 people that did not receive therapy. The conclusions of the regulatory agency were based on the prolongation of disease-free and overall survival at the drug use for treatment of hepatocellular carcinoma with mild and moderate AEs (Table 3) [39].

Table 3

Data on *Immuncell-LC* (NCT00699816) efficacy

Group	*Immuncell-LC*	Control
Number of patients		
Started CT	115	115
Ended CT	114	112
Not ended CT	1	3
Dropped out due to protocol violence	1	3
Recurrence-free survival in ... months, percentage		
12	79.9	65.1
24	72.5	53.8
36	60.9	44.3
48	49.6	39.6
Total survival in ... months, percentage		
1	2	3
12	100.0	98.0
24	100.0	91.8
36	97.5	88.1
48	95.9	84.8
Median overall survival	n/a	

Adverse events were mild or moderate. Overall, AEs occurred more frequently in the immunotherapy group (62%) than in the control group (41%).

Hearticellgram-AMI (Pharmicell) is approved for the treatment of patients with acute myocardial infarction (MI) through improving the left ventricle function after intracoronary administration; autologous to BM MSC. There are the results of one CT phase II/III (NCT01392105) with parallel control: the experimental group (33 patients) and the control group (36 patients). During the observation period, 58 patients have completed the CT (3 patients from the experimental group and 8 from the control group dropped out to the protocol violation by corticosteroids administration). The conclusions of the regulatory agency included the following: intracoronary infusion of human BM MSCs for 1 month is safe with a slight improvement in left ventricular ejection fraction (LVEF) after 6 months [40].

One of the main issues in the use of MSCs in MI is the time limitation of use of the autologous MSCs in the acute phase: it is impossible to use autologous MSCs immediately, since the collection and cultivation of cells takes more than 3 weeks. However, the optimal time for SC therapy has not been precisely determined. The possible interval for achieving maximum efficacy appears to be between acute inflammatory response and scar formation. Several experimental studies and clinical subgroup analyses suggest that stem cell therapy may be effective during the first month after MI, but not in the acute phase

(24 h after IM). Further randomized CT should confirm the optimal treatment time (NCT01652209) [40].

CONCLUSION

Thus, the analysis of the global experience of conducting CTs and the subsequent approval by the regulatory agencies of the safety and efficacy data for drugs based on human cells – BCPS analogues showed that:

– predominantly, the products were approved for use on the basis of uncontrolled CT II phases;
– in some cases, historical control, placebo, or inclusion to the CT of groups without product usage;
– in most CTs, the number of patients did not exceed 100, with the exception of the cosmetics product (*LAVIV*). The CT had a limited number of patients, especially for drugs for rare genetic diseases (*Strimvelis,* 18 patients) and approved for use in Japan (*HeartSheet,* 7 patients, *JACE,* 2 and 8 patients).

An analysis of reviewing CTs by foreign regulatory agencies showed that the products received marketing authorization considering:

– limited data on efficacy and safety given the inclusion in the CT of a limited number of patients and the timing of the studies;
– "modest" efficacy (*Alofisel* – remission in the experimental group by 15% more often than in the control group) or efficacy with "limitations" (*Zalmoxis* – decrease in mortality from recurrences and increase in one-year survival; *Hearticellgram-AMI* – LVEF (primary point) changed insignificantly, with the increase in exercise tolerance).

The decisions on risk/benefit by EU and US regulators are mainly based on the of the classification as an unmet medical need for national health care or the lack of available treatments for patients who do not respond to standard treatments (*Alofisel, Strimvelis, Zalmoxis, KYMRIAH, Yescarta*). Besides, the availability of a conditional drug registration mechanism in the EU makes it possible to use drugs with a limited safety base for quick access to treatment for patients based on risk/benefit conclusions (*Zalmoxis, Holoclar, Zynteglo*). A prerequisite is long-term CT and the creation of drug patient registries.

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