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Technology forecast: advanced therapies in late clinical research, EMA approval or clinical application via hospital exemption

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ABSTRACT

Background: The umbrella term ATMPs (Advanced Therapy Medicinal Products) comprises cell therapies, gene therapeutics and tissue engineered products. After implementation of the Regulation 1394/2007, only a couple of products have obtained a centralized European marketing authorisation.

Objectives: The aim of the presented study is to give an overview on ATMPs available within the European Union either via centralized marketing authorisation or via national Hospital exemption. Additionally, a forecast on innovative ATMPs in the process of EMA approval as well as in phase III and IV clinical trial is provided.

Methods: Systematic literature search including 'grey literature' and database reviews as well as manual search following pre-defined search terms.

Results: 8 ATMPs are currently available via centralized marketing authorisation. 6 new product launches are expected before 2020. At least 32 additional ATMPs are available in individual European Union member states via Hospital exemption. Another 31 potential ATMP candidates could be identified in industry-driven phase III research projects.

Conclusion: Advanced therapeutic medicinal therapies are still in their early days, but constantly evolving. By 2020, innovative therapies targeting retinal dystrophy, ß-thalassemia, scleroderma, sickle-cell anaemia, adrenoleukodystrophy and leukaemia shall be available on the market.

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KEYWORDS
ATMP; Advanced Therapeutic Medicinal Product; Hospital exemption; phase III clinical trial; marketing authorisation

Introduction

Recent advancements in biological therapies have initiated a shift from the traditional 'one-size fits all' approach towards personalized medicinal strategies. Advanced Therapy Medicinal Products (ATMPs) are at the forefront of this new tendency. ATMP is the umbrella term for three drug product classes: Somatic cell therapies, gene therapeutics and tissue engineered products as well as a combination of these technologies with a medicinal product. All ATMP classes contain either living cells or viral vectors and are therefore characterized by a high degree of complexity. Cells are usually derived from a patient or an allogeneic donor, processed in the laboratory (e.g. expanded *in vitro* or genetically engineered) and (re-) administered to the patient in a hospital. Gene therapy is designed to introduce genetic material into living cells to compensate for abnormal genes or express a beneficial protein.

On 30 December 2008, the Regulation 1394/2007 amending Directive 2001/83/EC on Advanced Therapy Medicinal Products entered into force and the first European Union wide regulatory framework for ATMPs was established [1]. This framework changed the code of regulatory practices, as a central marketing authorisation issued by the European Medicinal Agency (EMA) was required from now on. Previously, registration was not required for autologous products and pivotal clinical trials were not mandatory [2]. Not all ATMPs target high prevalence indications. In case of orphan diseases with a prevalence not more than 5 in 10.000, the ATMP regulation poses complex challenges to the design of clinical trials [2,3].

In recognition of the small scale and developmental nature of some intra-hospital ATMP applications, the regulation 2001/83/EC includes a 'Hospital exemption' for products not intended to be marketed. ATMPs applied via Hospital exemption must be prepared on a non-routine basis in a non-industrial manner and used as a custom made product for an individual patient [4]. However, the meanings of 'non-routine basis', 'industrial manner' and 'custom made' are not specified by the regulation and interpretations differ among different European countries [5]. ATMPs without a centralized European marketing authorisation can therefore still be approved in individual member states.

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The aim of the presented study is to give an overview on ATMPs currently available within the European Union either via a centralized marketing authorisation or via national approval in an individual member state. ATMPs withdrawn from the market will be identified and the reasons for withdrawal analysed. Additionally, a forecast on innovative ATMPs in the process of EMA approval as well as products in phase III and IV clinical trial will be presented.

Methods

Search strategy

A systematic database review was conducted to identify published studies from Ovid MEDLINE, Ovid EMBASE, the Cochrane Library and clinicaltrials.gov. Details on clinical trials were also collected from clinicaltrialsregister.eu. Additional information was gathered from the homepage of the European Medicines Agency (www.ema.europa.eu) as well as from the webpages of the national competent authorities. A manual search for grey literature was performed following pre-defined search terms. Additionally, the national competent authorities were contacted to obtain information on ATMPs licensed via Hospital exemption.

Key words

ATMP, advanced therapeutic medicinal product, cell therapy, stem cell, stem cell transplantation, umbilical cord, cord blood, bone marrow, bone marrow transplantation, cancer vaccine, tissue engineering, mesenchymal stem cell, somatic cell, allogeneic cell, viable cell, tissue engineering, gene therapy, recombinant nucleic acid, recombinant DNA, nucleic acid therapy, gene transfer, virus delivery, cancer immunotherapy, RNA therapy, tumor vaccine, plasmid DNA, oligonucleotide, transgenic microorganism, genetically modified microorganism, transformed cell line, genetically modified cell line, gene vector, vector

Eligibility criteria

Publications targeting an ATMP approved by the EMA or in the process of an EMA approval as well as manuscripts targeting phase III and IV ATMP clinical trials were included in this review. Additionally, publications on ATMPs administered to patients via Hospital exemption were included. Products were excluded from evaluation if their ATMP status could not be clearly assessed, e.g. in case of cancer immunotherapeutics which had neither been submitted to the EMAs Committee for Advanced Therapies (CAT) for classification nor declared as ATMP in the reference literature. Further inclusion and exclusion criteria are detailed in Table 1.

Table 1. Inclusion and exclusion criteria.

Inclusion criteria	Exclusion criteria
• Application human medicine	• Publications on basic research or animal experiments without direct clinical application
• Interventional product classified as ATMP	• Articles targeting rules and regulations were used as background information only
• Interventional product is either a licensed ATMP, an ATMP with a marketing license application or applied via hospital exemption or in phase III or IV clinical trial	• Articles on phase I and II clinical trials if no subsequent phase III trial was reported
• Intervention taken place within an EU member state	• Other than European countries
• Language of publication German or English	• Articles in languages other than English or German • Articles not publicly available

Data extraction

The following clinical trial data were extracted using MS Excel 2011: ATMP, registration number, manufacturer, indication, clinical trial status and eventual marketing authorisation status. Duplicates with the same registration number were removed as well as all pre-clinical, phase I and II studies, observational studies, studies performed outside the European Union and studies with an unclear phase assignment. Clinical trials not targeting an ATMP as well as generic conference abstracts not containing concrete clinical data were also excluded.

Results

Search results

The literature search yielded 2.613 publications. After removal of duplicates, pre-clinical, phase I and II studies, observational studies and studies with an unclear phase assignment 502 full text records were considered for evaluation. 91 did not meet the inclusion criteria (mostly studies performed outside of the European Union). Finally, we identified 412 studies for investigation.

The clinical trials database search yielded 1.946 entries in European Union member states. In 1.516 trials, the interventional drug was not an ATMP. 430 clinical trials were included in the evaluation. After manual removal of duplicates resulting from multi-centre international clinical trials, 160 phase III and IV studies were reviewed. 20 did not meet the inclusion criteria (either erroneously reported as phase III in the database or not

targeting an ATMP). Finally, 141 clinical trials were included in the evaluation. A flow chart of clinical trial identification and inclusion is presented in Figure 1.

ATMPs with a valid central European marketing authorisation

Since approval of the first ATMP in 2009, 12 products have obtained a central European marketing authorisation by the European Medicines Agency. An overview on these products is presented in Table 2. By the end of August 2018, 4 licensed ATMPs had retired from the market. Currently 8 ATMPS are available within the European Union: The gene therapies **Imlygic®, Strimvelis®**, and **Zalmoxis®** and the cell based therapies **Holoclar®, Spherox®** and **Alofisel®**. In August 2018, the European Medicines Agency recommended the first two marketing authorisations for chimeric antigen receptor (CAR) T-cells medicines, **Kymriah®** (tisagenlecleucel) and **Yescarta®** (axicabtagene ciloleucel). Both substances belong to a new generation of individualized cancer immunotherapies based on the modification of the patients' immune cells for cancer treatment [6]. Details on ATMPs with a valid central European marketing authorisation are summarized in Table 3.

ATMPs withdrawn from the market

Provenge®, MACI, Glybera® and ChondroCelect® have been withdrawn from the market. **Provenge®** (Sipuleucel-T) was a cellular immunotherapy for treat-

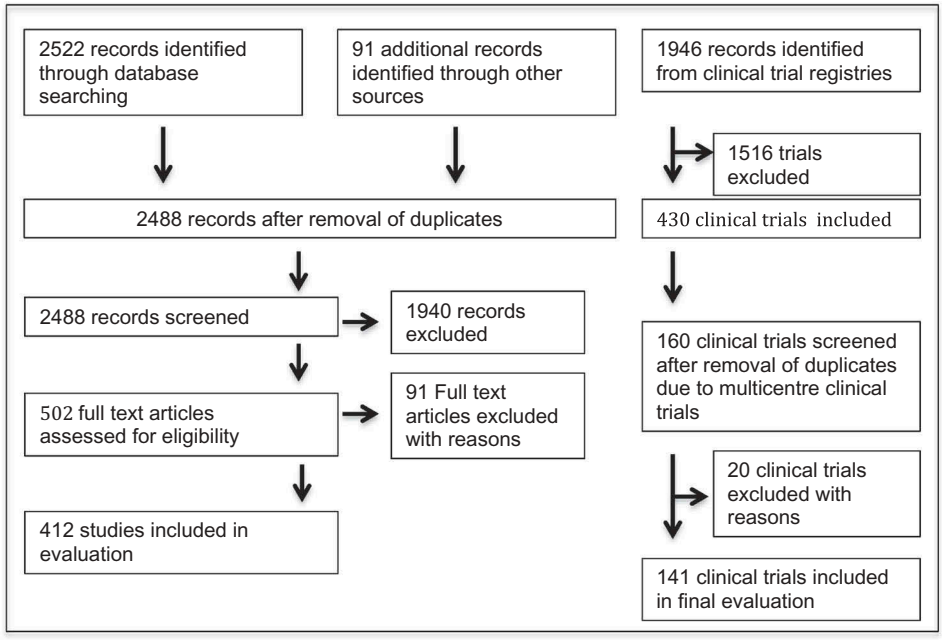

Figure 1. Flow chart of clinical trial identification and inclusion.

Table 2. Overview on ATMPs with past/present marketing authorisation.

Name	Authorisation holder	Indication	Authorisation number	Approval date	Status
Yescarta®	Kite Pharma	B-cell lymphoma	EMEA/H/C/004480	08/2018	APPROVED
Kymriah®	Novartis	ALL, DLBCL	EMEA/H/C/004090	08/2018	APPROVED
Alofisel®	TiGenix	Perianal fistulas in Crohn´s disease	EMEA/H/C/004258	03/2018	APPROVED
Spherox®	CO.DON	Cartilage defects in the knee joint	EU/1/17/1181	05/2017	APPROVED
Zalmoxis®	MolMed	Stem cell transplantation in high-risk blood cancer	EMEA/H/C/002801	06/2016	APPROVED
Strimvelis®	GSK	ADA-SCID	EU/1/16/1097	04/2015	APPROVED
Imlygic®	Amgen	Melanoma	EU/1/15/1064	09/2015	APPROVED
Holoclar®	Chiesi	Severe limbal stem cell deficiency in the eye	EU/1/14/987	03/2015	APPROVED
Provenge®	Dendreon	Metastatic prostate cancer	EMEA/H/C/002513	10/2013	withdrawn in 2015
MACI	Vericel	Cartilage defects in the knee joint	EU/1/13/847	07/2013	withdrawn in 2014
Glybera®	Uniqure	Lipoprotein Lipase Deficiency	EU/1/12/791/001	11/2012	withdrawn in 2017
Chondro Celect®	TiGenix	Cartilage defects	EMEA/H/C/000878	11/2009	withdrawn in 2016

ALL … Acute Lymphoblastic Leukaemia
DLBCL … Diffuse Large B Cell Lymphoma
ADA-SCID … Adenosine Deaminase Severe Combined Immunodeficiency

Table 3. ATMPs with a valid central European marketing authorisation by August 2018.

Holoclar®	Holoclar® was the first stem cell based ATMP approved by the European Union. The product is based on *ex vivo* expanded autologous human corneal epithelial cells [10]. The cells are isolated from a limbus tissue biopsy, expanded *in vitro* and cryopreserved for alignment with the patient´s medical care. After thawing, the cells are seeded onto a fibrin matrix for transplantation [11].
Imlygic®	Imlygic®was the first oncologic gene therapy reaching EMA approval. The product is based on a genetically modified oncolytic virus replicating within the tumoral tissue to produce granulocyte-macrophage colony stimulating factor (GM-CSF). Intratumoral application leads to tumor cell lysis and the release of tumor-derived antigens, which – in combination with GM-CFS – amplify the body´s anti-tumoral immune response [12].
Strimvelis®	Strimvelis® is designed to treat severe combined immunodeficiency (SCID) due to Adenosin desaminase deficiency (ADA-SCID) in patients who cannot be treated with a bone marrow transplant due to lack of a suitable donor [13]. The product is based on autologous CD 34+ cells transduced with a retroviral vector encoding for the human ADA cDNA sequence [10].
Zalmoxis®	Zalmoxis® is a patient specific immunogenic therapy serving as adjunctive treatment in haplo-identical haematopoietic stem cell transplantation in patients with leukaemia and high-risk haematological malignancies [14]. Data from 45 patients treated with Zalmoxis showed a survival rate of 49% after one year. Survival in the control group was 37% [15].
Spherox®	Spherox® are spheroids of human autologous matrix-associated chondrocytes for treatment of cartilage defects in the knee joint [16]. Data of 30 patients after an average follow-up of 3 years demonstrate a significant increase in quality of life, pain reduction and an improvement of joint function [17].
Alofisel®	Alofisel® consists of adipose tissue derived allogeneic mesenchymal stem cells for injection into the perianal fistula tract in Cohn's disease [18]. Local application of Alofisel® in conjunction with surgical preparation of the fistula tract has been shown to induce and maintain fistula closure, but a high placebo effect due to background therapies was noted in the phase III clinical trial [19].
Kymriah®	Kymriah® (**CTL019/tisagenlecleucel**) is intended for children and young adults with relapsed or refractory B-cell acute lymphoblastic leukaemia and for adult patients with diffuse large B-cell lymphoma who are ineligible for stem cell transplantation. In paediatric patients, an overall remission rate of 81% was achieved in the ELIANA trial [20]. Adult patients with diffuse large B-cell lymphoma achieved an overall response rate of 52% [21]. Treatment related adverse events occurred in 95% of the patients, mostly as cytokine release syndrome.
Yescarta®	Yescarta® (**axicabtagene ciloleucel**) is a chimeric antigen receptor T-cell therapy to treat aggressive non-Hodgkin´s lymphomas. In patients with large B-cell lymphoma, primary mediastinal B-cell lymphoma and transformed follicular lymphoma, the overall response rate was 71%. Complete remission was achieved in 57% (5/7) of the patients [22]. Adverse events include anaemia, neutropenia and decreased white blood cell count. Grade III or higher cytokine release syndrome is observed in 13% and neurologic events in 28% of the patients [23]. 71% of the patients treated for relapsed or refractory B-precursor acute lymphoblastic leukaemia (ALL) responded to the treatment either as complete response or complete response with incomplete hematologic recovery [24]. However, one patient experienced a fatal cytokine release syndrome [25].

ment of metastatic castration resistant prostate cancer. The substance was able to prolong median patient survival by 4,1 months. After a 3 years follow up, the proportion of patients alive in the vaccine group was 50% higher than in the control group [7]. Provenge® was approved by the EMA in 2012 and priced $93.000 per treatment [8]. Supply chain conditions were highly complex: Within a cooled, insulated container, shelf live was only 18 hours [9]. Due to the high price, a highly complex way of administration and reimbursement issues the product failed on the market and the manufacturer filed bankruptcy in 2015 [8].

MACI was on the market since 1998 in individual EU countries according to national procedures [10]. In 2013, the product was granted a central marketing authorisation for repair of cartilage defects in the knee joint. Due to commercial reasons, the company closed the European manufacturing site in 2014. Consequently, the marketing authorisation was suspended and expired during the suspension period [11].

Glybera® was an adenoassociated viral vector for treatment of lipoprotein lipase deficiency (LLD), a ultra-rare disease affecting only 1 in a million people [12]. The product was authorised under exceptional circumstances based on data received from 3 phase III trials enrolling a total of 27 patients [13]. Despite the clinical success, the product was a commercial failure. Four and a half years after making history for obtaining EMA approval as the first gene therapy in a regulated market, the manufacturer did not renew marketing approval and Glybera® was withdrawn in October 2017. In fact, only one patient had been treated with the commercial form of the LLD therapy, which was priced at 1,1 Million € [14].

ChondroCelect® (characterized, viable autologous cartilage cells expanded *ex vivo* expressing specific marker proteins) was approved in October 2009. The pivotal clinical trial demonstrated a superior structural cartilage repair when compared to standard Microfracture treatment [15]. Despite positive results, the product was withdrawn from the market in 2016 due to a lack of reimbursement in key European countries [9].

ATMPs in the process of EMA approval (planned launch before 2020)

Until 2020, 6 new ATMPs shall be launched on the European market. Developing companies, indications and clinical/regulatory status are summarized in Table 4. The Committee for Medicinal products for Human Use (CHMP) has already recommended the granting of a marketing authorisation for **Luxturna™**, a gene therapy for treatment of inherited retinal dystrophy [16]. **LentiGlobin™** is a potential gene therapy for correction of transfusion dependant thalassemia and sickle cell disease. Published

Table 4. ATMPs in the process of marketing authorisation or with a planned marketing launch.

Product	Developer	Indication	Regulatory/ Clinical status
Luxturna™	Novartis	Biallelic RPE65-mediated retinal dystrophy	MAA submitted EMA: CHMP pos. opinion 09/2018 Phase III NCT00999609 Open-label, randomized controlled trial At least 24 patients planned Estimated study completion date 2029
LentiGlobin™	BlueBird Bio	Transfusion dependant ß-thalassemia, sickle cell disease	MAA submitted EMA: accelerated approval granted Phase III NCT02906202 Single arm, multi site, single dose study Approx. 23 patients planned Estimated study completion date 2020
Habeo™	Cytori Therapeutics	Hand dysfunction due to scleroderma	EMA: Orphan drug designation granted Phase n.a. NCT02396238 prospective, randomized, multi-center device trial 88 patients enrolled Study completion date 2018
Lenti-D™	BlueBird Bio	Cerebral adrenoleukodystrophy	Phase II/III NCT01896102 Single arm open label 30 patients planned Estimated study completion date 2021
Neocart®	Histogenics corporation	Cartilage repair	Phase III NCT01066702 245 participants enrolled Randomized, open label Estimated study completion date 2020
ATIR101	Kiadis Pharma	AML, ALL or myelodysplastic syndrome	MAA submitted response to EMA submitted 03/2018 Phase III NCT02999854 Randomized controlled multicenter open-label study 250 participants planned Estimated study completion date 2021
JCAR 017	Celgene	DLBCL	EMA: PRIME Phase III NCT03575351 Randomized open label study 182 participants planned Estimated study completion date 2023
bb2121	Celgene	Multiple myeloma	EMA: PRIME eligibility 11/2017 Phase III NCT03651128 Multicenter randomized open label 381 participants planned Estimated study completion date 2025
Tab-cel™	Atara Biotherapeutics	EBV associated post-transplant lymphoproliferative disorder	Phase III NCT03392142 Multi-center, single arm, open label 33 participants planned Estimated study completion date 2020
Lenadogene nolparvovec	GenSight Biologics SA	Vision loss from Leber hereditary optic neuropathy	Phase III NCT02652767 Randomized, double-masked, sham-controlled clinical trial 36 participants planned Estimated study completion date 2019
REX-001	Rexgenero	Critical limb ischemia	EMA: Certificate for manufacturing and non-clinical data 01/2018 Phase III NCT03174522 Randomized, double-blind, controlled clinical trial 78 participants planned Estimated study completion date 2021

(*Continued*)

Table 4. (Continued).

Product	Developer	Indication	Regulatory/ Clinical status
Multistem	Athersys	Ischemic stroke	Phase III NCT03545607 Randomized, quadruple-masked clinical trial 300 participants planned Estimated study completion date 2021
PLX-PAD	Pluristem therapeutics	Critical limb ischemia	Phase III NCT03006770 Multicenter randomized controlled clinical trials 246 participants planned Estimated study completion date 2020

EMA … European Medicines Agency
MAA … Marketing Authorisation Application
CHMP … Committee for Medicinal products for Human Use
AML … Acute Myeloid Leukaemia
ALL … Acute Lymphoblastic Leukaemia
DLBCL … Diffuse Large B Cell Lymphoma
EBV …. Epstein Barr Virus
PRIME …PRIority MEdicines scheme

data from the phase I/II study report that 4 out of 7 patients remained transfusion free for more than 90 days [17]. **Lenti-D™** is another gene therapy for treatment of childhood cerebral adrenoleukodystrophy, a genetic disease causing progressive damage to the brain [18]. The cell therapeutic product **Habeo™** is an injection of adipose-derived regenerative cells to treat hand involvement in systemic sclerosis [19]. Despite not reaching significance in the phase III trial, clinically meaningful improvements in hand function were achieved in a subgroup of patients with diffuse cutaneous scleroderma [20]. A managed access programme is currently being established to provide access for patients in advance of the full marketing authorisation [21]. **Neocart®** is an autologous chondrocyte-based tissue implant. In contrast to the promising phase I and II results, the primary efficacy endpoints were not met in the subsequent phase III clinical trials [22]. As the data are still being analysed, eventual consequences for the European market launch are currently unclear. **ATIR101** is a cell based immunotherapeutic product containing T-lymphocyte enriched leukocytes. The product is intended to restore lymphocyte levels in patients undergoing stem cell transplantation from a partially matched (haploidentical) family donor. Conditional approval is expected for Q1 2019.

ATMPs with a planned launch in or after 2020

Two further CAR T-cell therapies currently in phase III clinical trial are planned for a centralized European market approval: **JCAR017** (lisocabtagene maraleucel, liso-cel) is a treatment for aggressive B-cell non-Hodgkin´s lymphoma. Data from the phase I study demonstrated an overall response rate of 66% with 50% of the patients achieving complete response at three months [23]. **bb2121** is intended to treat multiple myeloma. Published efficacy data from the phase I trial report an overall treatment response of 95,5% [24]. Filing of a marketing authorisation application is anticipated for 2019 [25].

Tab-cel™ is an allogeneic T-cell immunotherapy to treat Epstein Barr Virus (EBV) associated post-transplant lymphoproliferative disorder and other EBV associated tumors [26]. The product was accepted into the EMA Priority Medicines regulatory pathway and is available to eligible patients through a multicentre expanded access protocol [27]. Evaluation of the expanded access programme demonstrates a response rate of 80% after hematopoietic stem cell transplantation and 83% after solid organ transplantation at a medium follow up of 3,3, months. Overall survival at 1 year among all patients treated was 90,3% [28].

Lenadogene nolparvovec (GS-010) is a gene therapy for treatment of Leber's hereditary optic neuropathy (LHON), a genetic disorder leading to a rapid loss of bilateral central vision [29]. **REX-001 (Rexmylocel)** are autologous bone marrow mononuclear cells administered through an intra-arterial catheter to treat critical limb ischemia [30,31]. **Multistem®** is an off the shelf cell therapy product applicable for treatment of multiple distinct diseases. Multistem cells are currently in phase III clinical trials for treatment of ischaemic stroke and phase II for ulcerative colitis [32,33]. Phase I studies for acute myocardial infarction and Graft vs. Host Disease have been completed [34,35].

PLX-PAD PLacental e**X**panded cells are mesenchymal-like stromal cells applicable without tissue or genetic matching. The cell-released cytokines, chemokines and growth factors are supposed to facilitate tissue regeneration [36]. PLX-PAD was granted FDA fast track approval and was accepted into the EMA Adaptive Regulatory Pathway [36] . Data of all ATMPs with a planned launch in or after 2020 are summarized in Table 4.

ATMPS available in individual European member states via hospital exemption

A survey performed by the Pharmaceutical Committee of the European Commission in 2012 reported that 37% of the responding European member states had ATMPs legally on the market and 22% had issued Hospital exemptions for ATMP products [37]. In 2018, 47% of the responding countries reported to have issued Hospital exemptions. Data are summarized in Table 5.

The national competent authorities of Germany, Czech Republic, Ireland, Lithuania, Norway, Sweden, Italy and the Netherlands stated to have national approvals for ATMPs. No national approvals are currently issued in Austria, Belgium, Estonia, Hungary, Iceland, Latvia, Portugal and the UK. Tumor vaccines and autologous chondrocytes for restoration of cartilage defects are the most commonly used ATMP products under the Hospital exemption. Other cell types applied are oral mucosa cells, skin cells, bone marrow derived and mesenchymal stem cells as well as limbal stem cells (Figure 2).

ATMPS in phase III or IV clinical trial

Apart from ATMPs following the centralized marketing authorisation pathway, 141 phase III and four phase IV clinical trials investigating potential ATMPs were identified. The majority (74%) of these are academic trials without an industrial sponsor. The remaining 26% are industry-driven research projects examining 31 different ATMP candidates. Indications are coronary artery disease, urinary stress incontinence, critical limb ischemia and chronic leg ulcers as well as cartilage restoration, oncological indications, mucopolysaccharidosis and spinal muscular atrophy. Most ATMP candidates in

Table 5. Hospital exemption for ATMPs.

Country	Hospital exemption issued in 2012	Hospital exemption issued in 2018	Cell types applied via Hospital exemption
Austria	no	no	
Belgium	yes	no	
Bulgaria	?	?	
Croatia	no	?	
Cyprus	no	?	
Czech Republic	no	yes	Chondrocytes
Denmark	yes	?	
Estonia	no	no	
Finland	no	?	
France	yes	?	
Germany	yes	yes	Cytokine induced killer cells, dendritic cells, chondrocytes, mesenchymal stroma cells, engineered oral mucosa, bone marrow derived progenitor cells
Greece	no	?	
Hungary	no	no	
Iceland	no	no	
Ireland	no	yes	Limbal stem cells
Italy	no	?	
Latvia	no	no	
Liechtenstein	?	?	
Lithuania	no	yes	Dendritic cells, cytokine activated killer cells, T-cells, stromal vascular fraction cells
Luxembourg	no	?	
Malta	no	?	
Netherlands	yes	yes	Lymphocytes, mesenchymal stem cells, mononuclear cells, T-cells
Norway	?	yes	Chondrocytes, autologous T-cells, autologous dendritic cells, skin cells
Poland	no	?	
Portugal	no	no	
Romania	no	?	
Slovakia	no	?	
Slovenia	no	?	
Spain	yes	?	
Sweden	no	yes	Chondrocytes, mesenchymal stem cells, mesenchymal stromal cells, fetal stem cells, keratinocytes
UK	no	no	

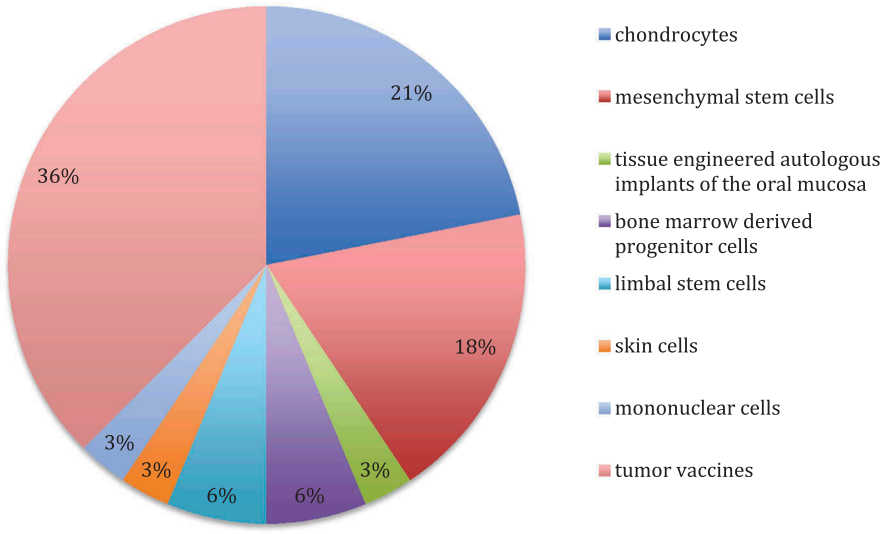

Figure 2. ATMP products applied in individual European member states via Hospital exemption.

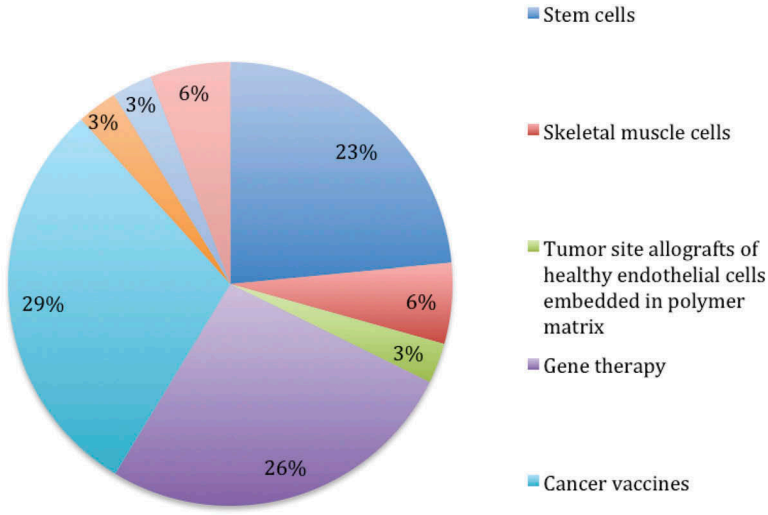

Figure 3. Potential ATMP candidates in industry-driven phase III clinical trials.

the industrial pipeline are cancer vaccines (29%), followed by gene (25%) and stem cell therapies (23%). Details are presented in Figure 3. 13 studies are still active at the time of this report and have no results published. 3 studies with published results failed to demonstrate clinical efficacy in phase III. The marketing authorisation application of Cerepro® (Ark Therapeutics) was withdrawn for this reason [38]. Data on potential ATMPs in the industrial pipeline are summarized in Table 6.

The majority of clinical trials performed in an academic setting target stem cell transplantation for oncological indications (68%). Most of them are not embraced by the ATMP definition, as autologous stem cells for transplantation after chemotherapy are usually neither substantially manipulated nor intended to be used for a different essential function. Other indications are myocardial infarction and heart failure (9%), critical limb ischemia (6%), stroke, burns and infertility. Except for one tumor vaccine, all academic clinical trials investigate cell therapeutic products (Figure 4). Details on ATMP candidates developed in academic settings are presented in Table 7.

Conclusion

Advanced therapeutic medicinal therapies are still in their early days, but constantly evolving. Until 2017, more than 900 ATMPs have been examined in clinical trials worldwide [39]. Despite this impressive number of

Table 6. ATMP candidates in the industrial pipeline in phase III/IV clinical trial.

ATMP candidate	Clinical trial identifier	Sponsor	Indication	Study State
Autologous CD133+ bone marrow stem cells	NCT00950274	Miltenyi Biotec GmbH	Chronic ischemic coronary artery disease	Terminated (slow recruitment)
Skeletal muscle derived cells	2014–001656-34	Innovacell Biotechnologie AG	Stress urinary incontinence	Completed
Tumor site allografts of healthy endothelial cells embedded in polymer matrix	Unknown	Shire (Pervasis)	Treatment/ Prevention of metastatic cancer	Unknown
Bone marrow derived mononuclear cells	NCT01285297	Cardiogenesis	Transmyocardial revascularisation	Completed
C-CURE (bone marrow derived cardiopoietic cells)	NCT01768702	Celyad (formerly named Cardio3 BioSciences)	Ischaemic heart failure	Completed
Generx (FGF-4 gene therapy)	NCT02928094	Angionetics Inc.	Coronary artery disease	Completed
Riferminogene pecaplasmid (Gene therapy)	NCT00566657	Sanofi	Critical limb ischemia	Completed (failure to detect efficacy)
Cerepro (cancer vaccine)	EUDRACT2004-000464–28.	Ark Therapeutics	Operable high-grade glioma	Completed; MAA withdrawn (unable to demonstrate a clinically meaningful benefit)
Autologous chondrocytes	EUDRACT2016-002817–22	TETEC Tissue Engineering Technologies – AG	Cartilage damage	Active
Keratinocytes	EUDRACT2012-003286–18	Smith & Nephew	Chronic leg ulcer	Terminated (failure to detect efficacy)
Autologous dendritic cells	EUDRACT2012-000871–17	Argos Therapeutics, Inc.	Renal cell carcinoma stage IV	Active
Autologous dendritic cells	NCT02111577	Sotio a.s.	Metastatic castration resistant prostate cancer	Active
Cancer vaccine	NCT01383148	Transgene	Non small cell lung cancer	Terminated (reason unclear)
Pexa-Vec (Cancer vaccine)	NCT02562755	SillaJen, Inc.	Hepatocellular Carcinoma	Recruiting
AVXS-101 (Gene Therapy)	NCT03461289	AveXis, Inc.	Spinal Muscle Atrophy	Recruiting
CER-001 (Gene Therapy)	NCT02697136	Cerenis Therapeutics, SA	Primary Hypoalphalipoproteinemia	Recruiting
Autologous fat enhanced with regenerative cells	NCT00616135	Cytori Therapeutics	Cosmetic breast deformities	Completed
AMG0001 (Gene Therapy)	NCT02144610	AnGes USA, Inc.	Critical limb ischemia	Terminated (strategy amendment)
Autologous Muscle Derived Cells	NCT01893138	Cook MyoSite|Cook Group Incorporated	Female Urinary Sphincter Repair	Active, not recruiting
Cancer vaccine	NCT01817738	CureVac AG	Prostate cancer	Terminated
Valoctocogene Roxaparvovec (Gene Therapy)	NCT03392974	BioMarin Pharmaceutical	Hemophilia A	Recruiting
AAVrh10-h.SGSH Gene Therapy	NCT03612869	LYSOGENE	Mucopoly-saccharidosis	Not yet recruiting
Bone marrow stem cells	NCT00462774	Miltenyi Biotec GmbH	Ischaemic heart failure	Completed
Progenitor Cells	NCT00279175	Eli Lilly and Company	Acute Myocardial Infarction	Completed
Cancer vaccine	NCT00676507	NovaRx Corporation	Non-small Cell Lung Cancer	Completed
GSK2696274 (Gene Therapy)	NCT03392987	GlaxoSmithKline	Metachromatic Leukodystrophy	Recruiting
Mesenchymal Stem Cells	NCT00366145	Osiris Therapeutics	Acute Graft Versus Host Disease	Completed
NiCord® cord blood stem cells	NCT02730299	Gamida Cell ltd	Hematologic malignancies	Recruiting
TG4010 (Cancer vaccine)	NCT00415818	Transgene	Non-Small Cell Lung Cancer	Completed
DCVax®-L (Cancer vaccine)	NCT00045968	Northwest Biotherapeutics	Glioblastoma	Unknown status
AAV2-REP1(Gene Therapy)	NCT03496012	Nightstar Therapeutics	Choroideremia	Recruiting

projects, the number of ATMPs on the market is still considerably low, and some of them were withdrawn only a couple of years after their market launch. Up to date, there are 8 ATMPs available via a centralized European marketing authorisation. Information on their commercial success is still very limited. GlaxoSmithKline,

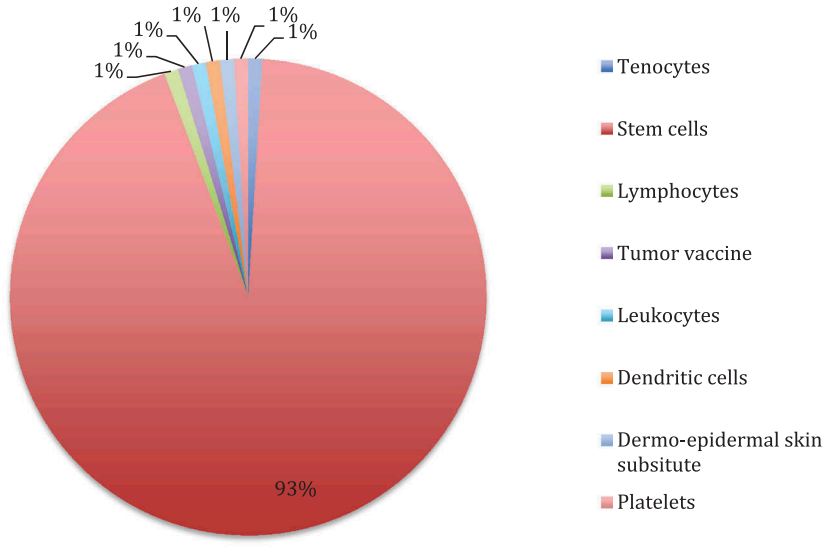

Figure 4. Stem cell therapies and potential ATMP candidates applied in academic phase III and IV clinical trials.

Table 7. Overview on academic phase III/IV ATMP clinical trials (Stem cell transplantation for haematological malignancies not included).

Trial Identifier	Phase	Sponsor	Product/Procedure	Indication
NCT00434616	III	Franziskus-Krankenhaus	Autologous bone marrow cells	Critical limb ischemia
NCT01803347	III	Instituto de Investigación Sanitaria de la Fundación Jiménez Díaz	Autologous expanded adipose-derived stem cells	Anal fistula
NCT01569178	III	Queen Mary University of London	Bone marrow derived mononuclear cells	Acute myocardia infarction
NCT03477500	III	NCT03477500 Haukeland University Hospital	Autologous stem cells	Multiple sclerosis
ISRCTN54371254	III	EBMT Central Office	Autologous hematopoietic stem cells	Diffuse cutaneous systemic sclerosis
EUDRACT2015-000431–32	III	Universidad Autónoma de Madrid (U.A.M.)	Autologous human bone marrow-derived expanded mesenchymal stromal cells	Diaphyseal metaphyseal fracture and non union
n/a	III	Unknown	Renal cell tumor vaccine	Renal carcinoma
NCT00297193	III	European Group for Blood and Marrow Transplantation | The Broad Foundation	Autologous Stem Cells	Cohn's Disease
NCT02437708	III	Universitaire Ziekenhuizen Leuven	Stem cells	Periapical bone healing in infected immature primary teeth
NCT01818310	II|III	University Hospital Ostrava|Ministry of Health, Czech Republic|Regional Council of the Moravian-Silesian region, KU MSK	Autologous Bone Marrow Aspirate Concentrate	No-Option Critical Limb Ischemia
NCT02849613	II|III	University Hospital, Grenoble	Regenerative Stem Cell Therapy	Stroke
NCT00904501	III	CHU de Reims |Etablissement Francais du Sang	Bone Marrow Autograft	Limb Ischemia
NCT03325504	III	Universidad Autonoma de Madrid	Mesenchymal stem cells + Biomaterial	Bone Healing in Non-Union
NCT01489501	III	CellSeed France S.A.R.L.|FGK Clinical Research GmbH	Oral mucosal epithelial cell sheet	Limbal Stem Cell Deficiency
NCT00938847	III	Asklepios proresearch Cordis Corporation	Bone Marrow Derived Mononuclear	Myocardial Regeneration
NCT01983748	III	University Hospital Erlangen	Dendritic Cells Plus Autologous Tumor RNA	Uveal Melanoma
NCT01693042	II|III	Johann Wolfgang Goethe University Hospital	Autologous Bone Marrow-derived Mononuclear Cells	Chronic Post-infarction Heart Failure
NCT01753440	II|III	AHEPA University Hospital	Allogeneic Stem Cells Implantation Combined With Coronary Bypass Grafting	Ischemic Cardiomyopathy
NCT01759212	II|III	AHEPA University Hospital	Left Ventricular Assist Device + Allogeneic Mesenchymal Stem Cells Implantation	End-stage Heart Failure
NCT03112122	IV	Istituto Ortopedico Rizzoli	Bone Marrow Concentrate	Bone Marrow Edema
NCT03110679	IV	Istituto Ortopedico Rizzoli	Autologous Bone Marrow Concentrate	Osteoarthritis

(*Continued*)

Table 7. (Continued).

Trial Identifier	Phase	Sponsor	Product/Procedure	Indication
NCT02454231	II|III	University of Florence|Tuscany Region	Stem Cells	Life Threatening Limbs Arteriopathy
NCT00539266	II|III	Leiden University Medical Centre	Autologous Bone Marrow-derived Mononuclear Cells	Limb Ischemia
NCT03042572	II|III	The Netherlands Organisation for Health Research and Development|UMC Utrecht	Allogeneic Mesenchymal Stromal Cells	No-option Ischemic Limbs
NCT01343836	II|III	Erasmus Medical Center	Autologous Tenocyte Implantation	Chronic Achilles Tendinopathy
NCT03229564	II|III	University of Zurich|ETH Zurich (Switzerland)|Julius Clinical, The Netherlands	Autologous Dermo-epidermal Skin Substitute	Treatment of Burns in Children
NCT02323620	III	American Heart of Poland	Bone marrow derived mononuclear cells	Myocardial infarction
NCT03404063	II|III	John Paul II Hospital, Krakow|KCRI|National Center for Research and Development, Poland	CardioCell (Wharton´s Jelly derived mesenchymal stem cells)	Acute Myocardial Infarction
NCT03423732	II|III	John Paul II Hospital, Krakow|KCRI|National Center for Research and Development, Poland	CardioCell (Wharton´s Jelly derived mesenchymal stem cells)	No-option Critical Limb Ischemia
NCT02248532	II|III	University Medical Centre Ljubljana	CD34+ Cells	Dilated Cardiomyopathy
NCT02144987	IV	Instituto Valenciano de Infertilidad, IVI VALENCIA	Bone Marrow Stem Cells	Asherman's Syndrome and Endometrial Atrophy
NCT03535480	IV	Instituto de Investigacion Sanitaria La Fe	Autologous Bone Marrow Stem Cells	Premature Ovarian Failure
NCT02389010	III	Centro Nazionale Sangue|Italian National Cord Blood Network	Platelet Gel From Cord Blood	Diabetic Foot Ulcers
NCT00747708	II|III	Barts & The London NHS Trust	Bone Marrow Derived Adult Stem	Chronic Heart Failure

for example, has announced the first reimbursement of Strimvelis® for its first patient in March 2017 despite being approved under a full performance-based reimbursement scheme since 2016 [40].

7 European Union member states reported providing additional ATMPs outside of clinical trials via Hospital exemption regulation. Due to a poor return rate, the data of the 2018 survey are of limited significance. However, combining the actual data with the results of the 1012 report published by the European Commission [37], there are still only 8 countries having issued Hospital exemptions. At the 26th Annual EuroMeeting in Vienna, concerns were raised that European member states might consider the Hospital exemption as an opportunity for early clinical development prior to clinical trials [41]. ATMPs that had been legally on the market before 2008 might avoid the complex authorisation procedure by evading under the Hospital exemption regulation. However, considering the actual survey result in combination with the 2012 data, these concerns have not been verified on a large scale.

6 new ATMPs shall be launched until 2020 and offer new treatment modalities for retinal dystrophy, ß-thalassemia, scleroderma, sickle-cell anaemia, adrenoleukodystrophy and leukaemia. **Luxturna™, LentiGlobin™** and **ATIR101** have already submitted a central marketing authorization application. For Luxturna™, the Committee for Medicinal products for Human Use has issued a positive opinion recommending approval [42]. **LentiGlobin™** has been granted accelerated assessment by the EMA and ATIR101 expects conditional approval in 2019 [43,44]. **Habeo™** and **Neocart®** did not reach significance in the primary efficacy endpoints in their respective phase III clinical trials, and eventual consequences for their marketing launch are unclear. For **LentiD™**, a modified paediatric investigation plan was accepted by the EMA in September 2018 [45]. 7 additional ATMPs currently in phase III clinical development are planned for a marketing authorisation application in or after 2020.

131 phase III clinical trials with ATMPs could be identified apart from the centralized marketing authorisation procedure. 31 ATMP candidates are industrial research projects with an assumptive interest in obtaining a marketing authorisation. However, reaching phase III stage does not guarantee a roadmap to successful clinical translation: Out of 19 finalized clinical trials, 26% were terminated prematurely and 23% of the ATMP candidates finally failed to demonstrate efficacy when evaluated against the current standard of care.

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