OMTM, Volume *18*

Supplemental Information

Mitigating Deficiencies in Evidence during Regulatory Assessments of Advanced Therapies: A Comparative Study with Other Biologicals

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Table 1 List of ATMP submissions

Commercial name	INN	Type	Cell source	Vector type	Indication	ICD 10 disease classification	Developer	SME	Initial evaluation	Type of MA	OD	OD date	Submission date	CHMP opinion date	Withdrawal date	E.C. decision date
Chondro-Celect [1]	Characterized viable autologous cartilage cells expanded *ex vivo* expressing specific marker proteins	TEP	Autologous	NA	Cartilage defects	Diseases of the musculoskeletal system and connective tissue	TiGenix N.V.	yes	Authorized	Full	no	NA	01.06.2007	25.06.2009	NA	05.10.2009
MACI[2]	Matrix-applied characterized autologous cultured chondrocytes	TEP	Autologous	NA	Cartilage defects	Diseases of the musculoskeletal system and connective tissue	Genzyme Europe	no	Authorized	Full	no	NA	01.09.2011	24.04.2013	NA	27.06.2013
Provenge [3]	Autologous peripheral blood mononuclear cells activated with prostatic acid phosphatase granulocyte-macrophage colony-stimulating factor (sipuleucel-T)	CTMP	Autologous	NA	Prostatic neoplasms	Malignant neoplasms except for lymphoid, hematopoietic and related tissue	Dendreon UK LTD	yes	Authorized	Full	no	NA	30.12.2011	27.06.2013	NA	06.09.2013
Spherox[4]	Spheroids of human autologous matrix-associated chondrocytes	TEP	Autologous	NA	Cartilage defects	Diseases of the musculoskeletal system and connective tissue	CO.DON AG	yes	Authorized	Full	no	NA	03.12.2012	15.05.2017	NA	10.07.2017
Imlygic [5]	Talimogene laherparepvec	GTMP	NA	herpes simplex virus type-1 (HSV-1)	Melanoma	Malignant neoplasms except for lymphoid, hematopoietic and related tissue	Amgen	no	Authorized	Full	no	NA	28.08.2014	22.10.2015	NA	16.12.2015
Strimvelis [6]	Autologous CD34+ enriched cell fraction that contains CD34+ cells transduced with retroviral vector that encodes for the human ADA cDNA sequence	GTMP	Autologous	Retroviral vector	ADA-SCID	Diseases of the blood and blood-forming organs	Glaxo SmithKline	No	Authorized	Full	yes	26.08.2005	01.05.2015	01.04.2016	NA	26.05.2016
Alofisel [7]	Darvadstrocel	CTMP	Allogeneic	NA	Anal fistula	Diseases of the digestive system	TiGenix N.V.	yes	Authorized	Full	yes	08.10.2009	02.03.2016	14.12.2017	NA	23.03.2018
Kymriah [8]	Tisagenlecleucel	GTMP	Autologous	Lentivirus	ALL DLBCL	Malignant neoplasms primary of lymphoid, hematopoietic and related tissue	Novartis	no	Authorized	Full	yes	26.04.2014	02.11.2017	28.06.2018	NA	22.08.2018
Yescarta [9]	Axicabtagene ciloleucel	GTMP	Autologous	Retrovirus	DLBCL	Malignant neoplasms of lymphoid hematopoietic and related tissue	Kite Pharma	yes	Authorized	Full	yes	16.11.2014	29.07.2017	28.06.2018	NA	23.08.2018

Commercial name	INN	Type	Cell source	Vector type	Indication	ICD 10 disease classification	Developer	SME	Initial evaluation	Type of MA	OD	OD date	Submission date	CHMP opinion date	Withdrawal date	E.C. decision date
Luxturna [10]	Voretigene neparvovec	GTMP	NA	Adeno-associated viral type 2 (AAV2)	retinal dystrophy	Diseases of the eye and adnexa	Spark Therapeutics	yes	Authorized	Full	yes	02.04.2012	29.07.2017	20.09.2018	NA	22.11.2018
Holoclar[11]	Ex vivo expanded autologous human corneal epithelial cells containing stem cells	TEP	Autologous	NA	Limbal stem-cell deficiency	Diseases of the eye and adnexa	Chiesi Farmaceutici	no	Authorized	Conditional	yes	07.11.2008	06.03.2013	18.12.2014	NA	17.02.2015
Zalmoxis[12]	Allogeneic T cells genetically modified with a retroviral vector encoding for a truncated form of the human low-affinity nerve growth factor receptor (ΔLNGFR) and the herpes simplex I virus thymidine kinase (HSV-TK Mut2)	CTMP	Allogeneic	Retrovirus	HSCT, blood cancer	Malignant neoplasms primary of lymphoid, hematopoietic and related tissue	MolMed SpA	yes	Authorized	Conditional	yes	20.10.2003	05.03.2014	23.06.2016	NA	18.08.2016
Zynteglo[13]	Autologous CD34+ cells encoding βA-T87Q-globin gene	GTMP	Autologous	Lentivirus	beta-thalassemia	Diseases of the blood and blood-forming organs	bluebird bio	yes	Authorized	Conditional	yes	24.01.2013	21.08.2018	28.03.2019	NA	29.05.2019
Glybera [14]	Alipogene tiparvovec	GTMP	NA	Adeno-associated virus type 1 (AAV1)	LPL deficiency	Endocrine nutritional and metabolic diseases	Amsterdam Molecular Therapeutics	yes	Authorized	Exceptional circumstances	yes	08.03.2004	23.12.2009	19.07.2012	NA	25.10.2012
Cerepro (2007) [15]	sitimagene ceradenovec	GTMP	NA	adenovirus serotype 5 (Ad 5)	high-grade glioma	Malignant neoplasms except lymphoid, hematopoietic and related tissue	Ark therapeutics	yes	Withdrawn	NA	yes	06.02.2002	04.10.2005	26.04.2007	13.07.2007	NA
Advexin [16]	contusugene ladenovec	GTMP	NA	adenovirus serotype 5 (Ad 5)	Li-Fraumeni cancer	Malignant neoplasms, except lymphoid hematopoietic and related tissue	Gendux Molecular Limited	yes	Withdrawn	NA	yes	23.10.2006	06.09.2007	NA	17.12.2008	NA
Contusugene Ladenovec Gendux (CLG) [17]	contusugene ladenovec	GTMP	NA	adenovirus serotype 5 (Ad 5)	squamous cell carcinoma	Malignant neoplasms except for lymphoid, hematopoietic and related tissue	Gendux Molecular Limited	yes	Withdrawn	NA	no	NA	02.07.2008	NA	12.06.2009	NA
Cerepro (2010) [18]	sitimagene ceradenovec	GTMP	NA	adenovirus serotype 5 (Ad 5)	high-grade glioma	Malignant neoplasms except for lymphoid, hematopoietic and related tissue	Ark therapeutics	yes	Withdrawn	NA	yes	06.02.2002	28.11.2008	17.12.2009	08.03.2010	NA

Commercial name	INN	Type	Cell source	Vector type	Indication	ICD 10 disease classification	Developer	SME	Initial evaluation	Type of MA	OD	OD date	Submission date	CHMP opinion date	Withdrawal date	E.C. decision date
Oranera [19]	multilayered cell-sheet of autologous oral mucosal epithelial cells	TEP	Autologous	NA	Limbal stem-cell deficiency	Diseases of the eye and adnexa	CellSeed Europe Ltd	yes	Withdrawn	NA	no	NA	01.06.2011	NA	14.03.2013	NA
Raligize	axalimogene filolisbac	GTMP	NA	NA	cervical cancer	Malignant neoplasms except for lymphoid, hematopoietic and related tissue	Advaxis Inc	no	Withdrawn	NA	no	NA	13.02.2018	NA	10.07.2018	NA
Hyalograft C autograft [20]	characterized viable autologous chondrocytes expanded in vitro, seeded and cultured on a hyaluronan-based scaffold	TEP	Autologous	NA	Cartilage defects	Diseases of the musculoskeletal system and connective tissue	Anika Therapeutics	yes	Withdrawn	NA	no	NA	28.02.2012	NA	14.01.2013	NA
Heparesc[21]	Human heterologous liver cells	CTMP	Allogeneic	NA	urea cycle disorders	Endocrine, nutritional and metabolic diseases	cytonet	yes	Rejected	NA	yes	14.09.2007	05.12.2013	22.10.2015	NA	21.12.2015

SME: small and medium-sized enterprise; O.D.: orphan designation; MA: marketing authorization; CHMP: Committee for Medicinal Products for Human Use; E.C.: European Commission; GTMP: gene therapy medicinal product; TEP: tissue-engineered product; CTMP: cell therapy medicinal product; LPL: lipoprotein lipase, HSCT: hematopoietic stem cell transplantation, ALL: acute lymphoblastic leukemia; DLBCL: diffuse large B-cell lymphoma; ADA-SCID: adenosine deaminase deficiency - severe combined immune deficiency.

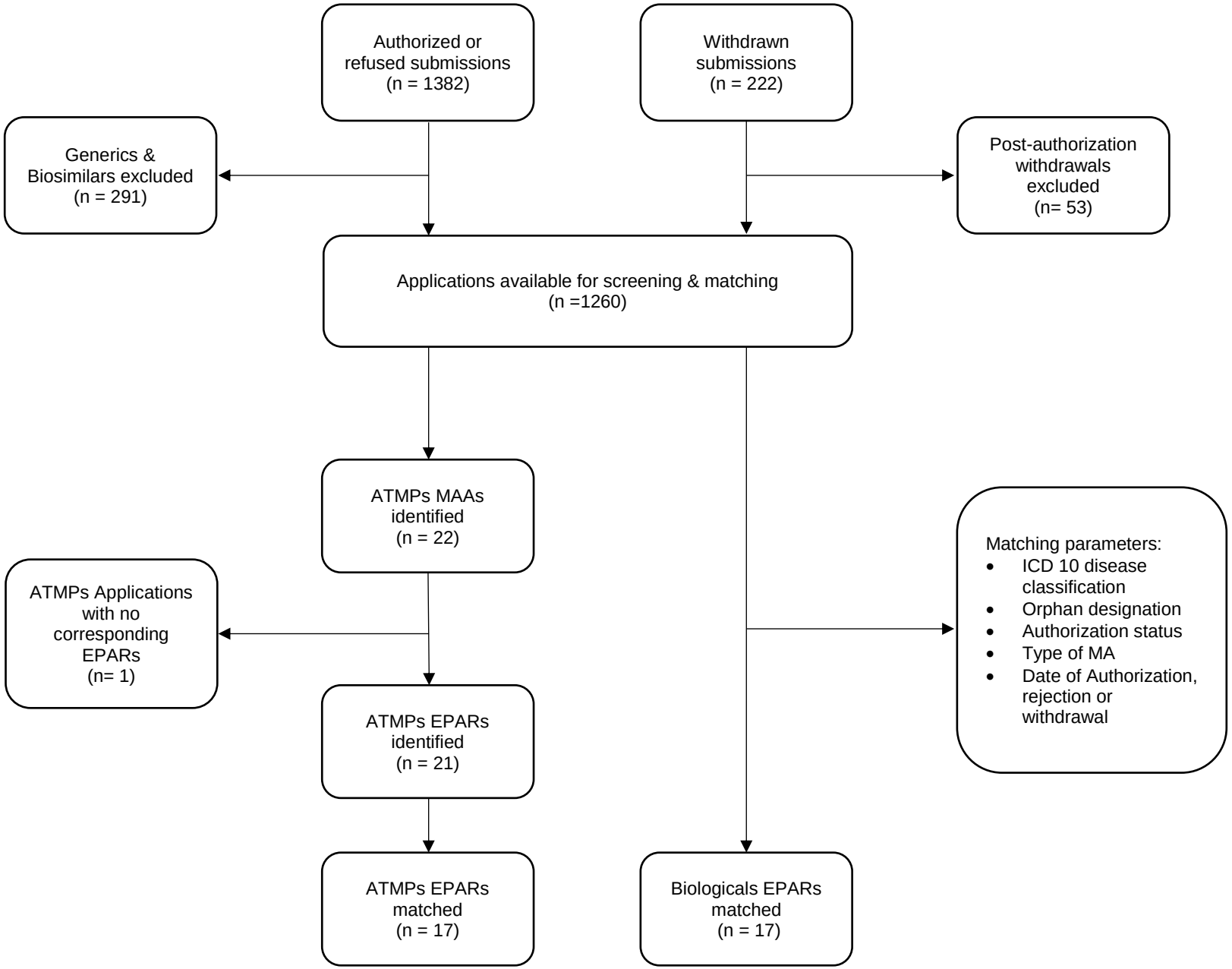

Figure 1 flow chart of the screening of the EMA database, data retrival and products matching.

ATMPs: advanced therapy medicinal products, MAA: marketing authorization application, MA: marketing authorization, EPAR: European public assessment report, ICD: International Classification of Diseases.

Table 2 list of the matched Biological Medicinal Products

Commercial name	INN	Type	Indication	Developer	SME	ICD 10 disease classification Indication	Initial MA status	Type of MA	OD	OD date	Submission date	CHMP opinion date	Withdrawal date	E.C. decision date	ATMP Match
Simponi [22]	Golimumab	monoclonal antibody	Rheumatoid arthritis, Psoriatic arthritis Axial, spondyloarthritis	Centocor B.V. currently (Janssen Biologics B.V.)	No	Diseases of the musculoskeletal system and connective tissue	Authorized	Full	No	NA	03.03 .2008	25.07 .2009	NA	01.10 .2009	Chondrocelect
Krystexxa [23]	Pegloticase	Recombinant Enzyme	Gouty arthritis	Savient Pharma	No	Diseases of the musculoskeletal system and connective tissue	Authorized	Full	No	NA	03.05 .2011	18.10 .2012	NA	08.01 .2013	MACI
Kadcyla [24]	Trastuzumab emtansine	monoclonal antibody (antibody-drug conjugate)	Advanced or metastatic breast cancer	Roche	No	Malignant neoplasms except for lymphoid, hematopoietic and related tissue	Authorized	Full	No	NA	30.08 .2012	19.09 .2013	NA	15.11 .2013	Provenge
Kevzara [25]	Sarilumab	monoclonal antibody	Chronic idiopathic arthritis	Sanofi-aventis group	No	Diseases of the musculoskeletal system and connective tissue	Authorized	Full	No	NA	24.06 .2016	21.04 .2017	NA	23.06 .2017	Spherox
Portrazza[26]	Necitumumab	monoclonal antibody	Squamous non-small cell lung cancer	Eli Lilly Netherlands	No	Malignant neoplasms except for lymphoid, hematopoietic and related tissue	Authorized	Full	No	NA	01.12 .2014	17.12 .2015	NA	15.02 .2016	Imlygic
Alprolix [27]	Eftrenonacog alfa	Recombinant coagulation factor (fusion protein)	Hemophilia B	Biogen Idec Ltd	No	Diseases of the blood and blood-forming organs	Authorized	Full	Yes	08.06 .2007	04.06 .2015	25.02 .2016	NA	12.05 .2016	Strimvelis
Revestive[28]	Teduglutide	Recombinant Hormone	Short bowel syndrome	Nycomed Denmark	No	Diseases of the digestive system	Authorized	Full	Yes	11.12 .2001	03.03 .2011	14.12 .2017	NA	03.08 .2012	Alofisel
Besponsa [29]	Inotuzumab ozogamicin	monoclonal antibody (antibody-drug conjugate)	Precursor Cell Lymphoblastic Leukemia-Lymphoma	Pfizer Limited	No	Malignant neoplasms of lymphoid, hematopoietic and related tissue	Authorized	Full	Yes	07.06 .2013	14.04 .2016	21.04 .2017	NA	28.06 .2017	Kymriah
Mylotarg [30]	Gemtuzumab ozogamicin	monoclonal antibody (antibody-drug conjugate)	Acute myeloid leukemia	Pfizer Limited	No	Malignant neoplasms of lymphoid, hematopoietic and related tissue	Authorized	Full	Yes	18.10 .2000	01.12 .2016	22.02 .2018	NA	19.04 .2018	Yescarta
Oxervate [31]	Cenegermin	Recombinant growth factor	Neurotrophic keratitis	Dompé farmaceutici	No	Diseases of the eye and adnexa	Authorized	Full	yes	NA	03.11 .2016	18.05 .2017	NA	06.07 .2017	Luxturna
Adcetris [32]	Brentuximab vedotin	monoclonal antibody (antibody-drug conjugate)	Hodgkin's lymphoma	Takeda Global Research	No	Malignant neoplasms of lymphoid, hematopoietic and related tissue	Authorized	Conditional approval	Yes	15.01 .2009	31.05 .2011	19.07 .2012	NA	25.10 .2012	Zalmoxis
Strensiq [33]	Asfotase alfa	Recombinant Enzyme (Fusion protein)	Hypophosphatasia	Alexion Europe	No	Endocrine, nutritional and metabolic diseases	Authorized	Exceptional circumstances	Yes	03.12 .2008	01.07 .2014	25.06 .2015	NA	28.08 .2015	Glybera
Theraloc [34]	Nimotuzumab	monoclonal antibody	High-grade glioma.	Oncoscience AG	Yes	Malignant neoplasms except for lymphoid, hematopoietic and related tissue	Withdrawn	NA	Yes	02.09 .2004	04.10 .2007	NA	01.12 .2008		Cerepro (2007)

Commercial name	INN	Type	Indication	Developer	SME	ICD 10 disease classification Indication	Initial MA status	Type of MA	OD	OD date	Submission date	CHMP opinion date	Withdrawal date	E.C. decision date	ATMP Match
Oncophage [35]	vitespen	Autologous Tumor-Derived Protein-Peptide Complex	Renal cell carcinoma	Antigenics Therapeutics Limited	No	Malignant neoplasms except for lymphoid, hematopoietic and related tissue	Withdrawn	NA	Yes	11.04.2005	29.09.2008	NA	23.11.2009		Advexin
Zafiride [36]	Ngr-human tumor necrosis factor-alpha	Recombinant cytokine (Fusion protein)	Advanced malignant pleural mesothelioma	Molmed	Yes	Malignant neoplasms except for lymphoid, hematopoietic and related tissue	Withdrawn	NA	Yes	03.06.2008	03.12.2016	NA	01.06.2017		Cerepro (2010)
Plivensia [37]	Sirukumab	monoclonal antibody	Rheumatoid arthritis	Janssen-Cilag	No	Diseases of the musculoskeletal system and connective tissue	Withdrawn	NA	No	NA	12.09.2016	NA	26.10.2017		Hyalograft C autograft
Elelyso [38]	Taliglucerase alfa	Recombinant Enzyme	Type 1 Gaucher disease	Pfizer Ltd	No	Endocrine, nutritional and metabolic diseases	Rejected	NA	Yes	23.03.2010	25.11.2010	03.07.2012	NA	25.10.2012	Heparesc

SME: small and medium-sized Enterprise, OD: orphan designation, MA: marketing authorization, CHMP: Committee for Medicinal Products for Human Use, EC: European Commission

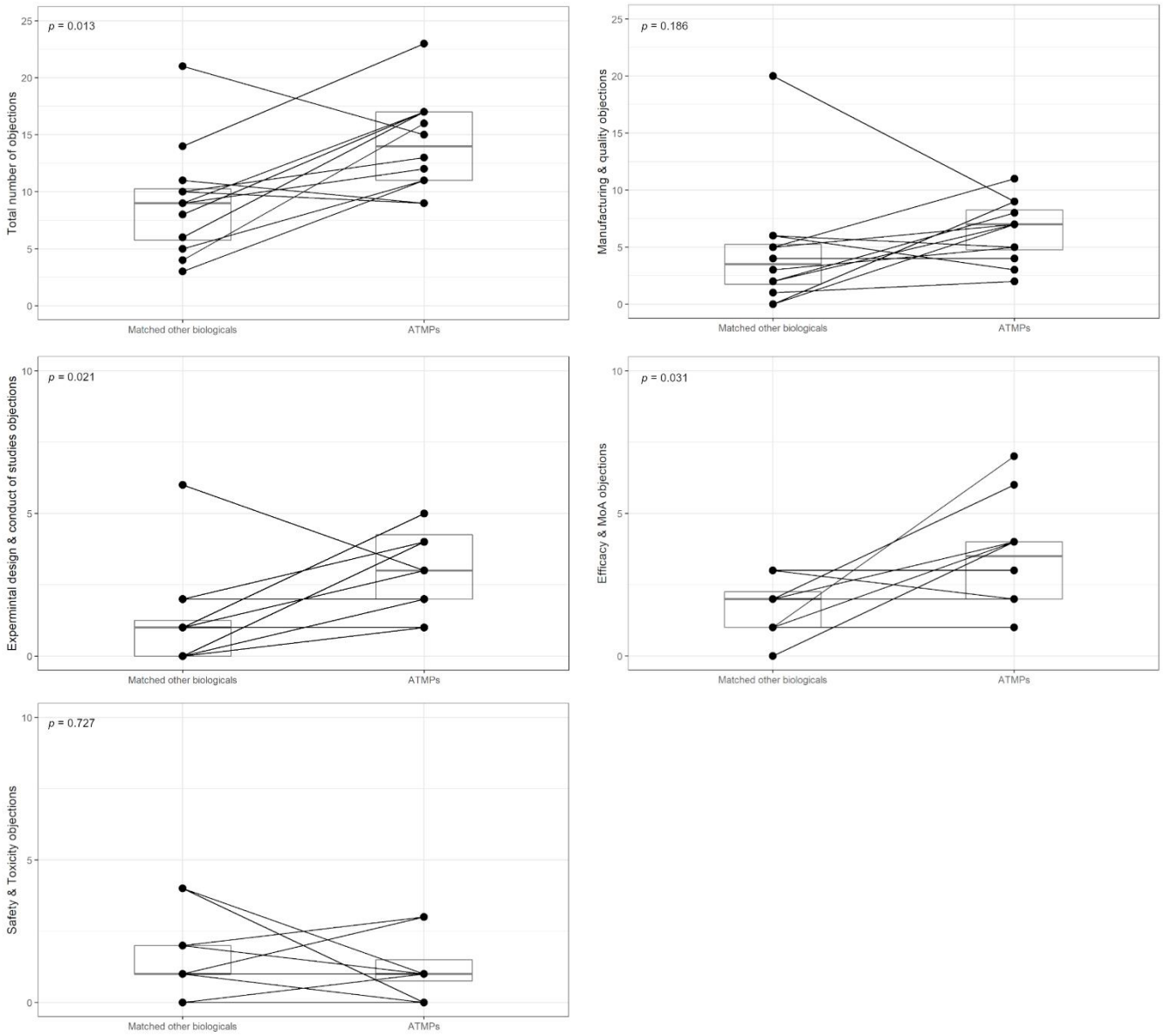

Figure 2 Paired dot plots and boxplots of objections in matched authorized ATMPs and biologicals submissions. ATMPs (authorized and failed) were matched to other biologicals via a matched-pair experimental design to compare the difference in the evaluation process between both. Regulatory objections were scored using quantitative assessment of the European public assessment reports (EPARs) of each product. The groups were compared statistically using two-tailed Wilcoxon signed-rank test. In the authorized cohorts ATMPs showed significantly higher differences in the total number of objections, the experimental design and conduct of the studies, and the efficacy and mode of Action (MoA) as depected in the figure. Statistical test: Wilcoxon signed-rank test.

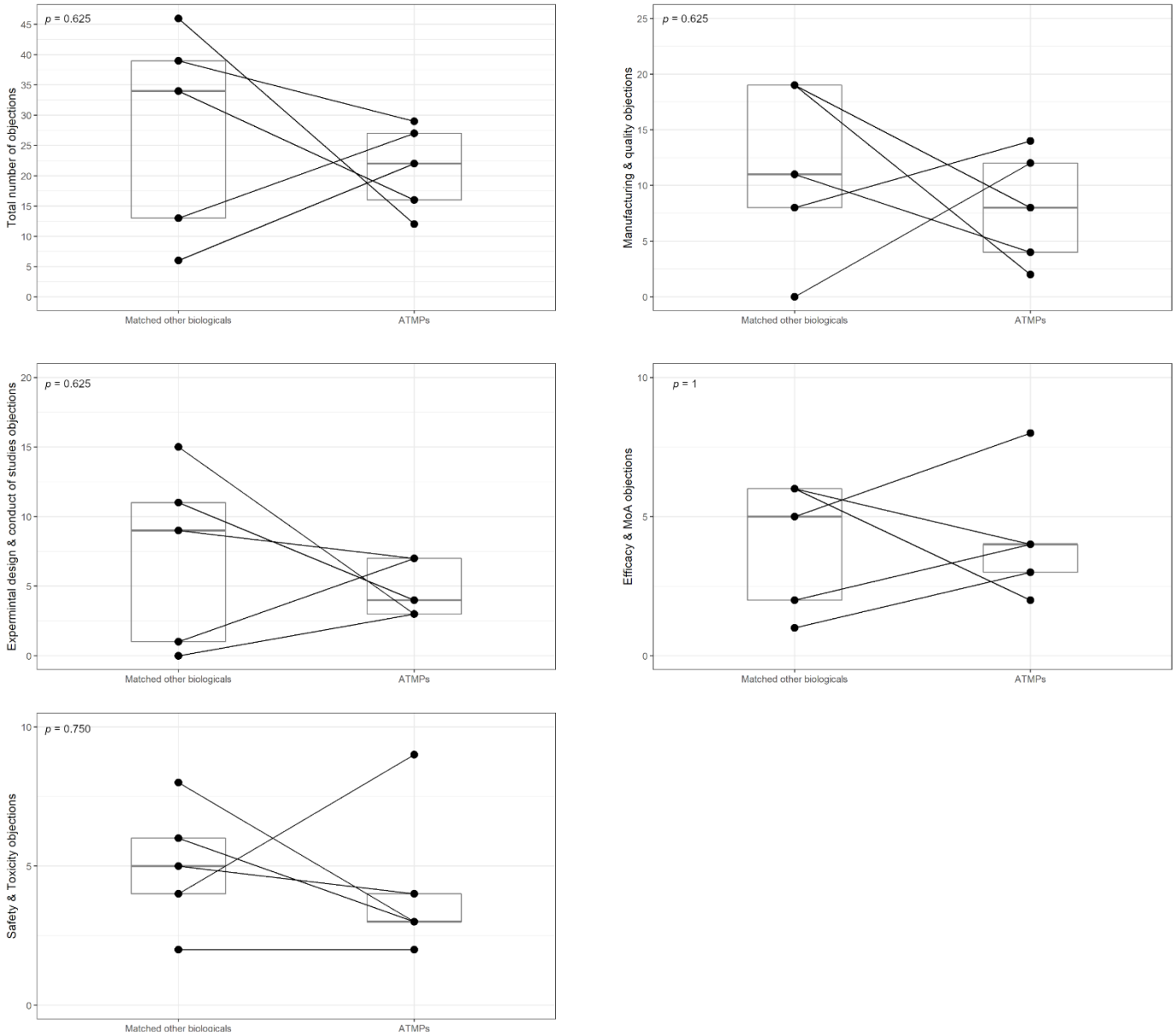

Figure 3 Paired dot plots and boxplots of objections in matched failed ATMPs and biologicals submissions. ATMPs (authorized and failed) were matched to other biologicals via a matched-pair experimental design to compare the difference in the evaluation process between both. Regulatory objections were scored using quantitative assessment of the European puplic assessment reports (EPARs) of each product. The groups were compared statistically using two-tailed Wilcoxon signed-rank test. In the failed cohorts no statistically significant difference were noted in any of the comparisons. Statistical test: Wilcoxon signed-rank test.

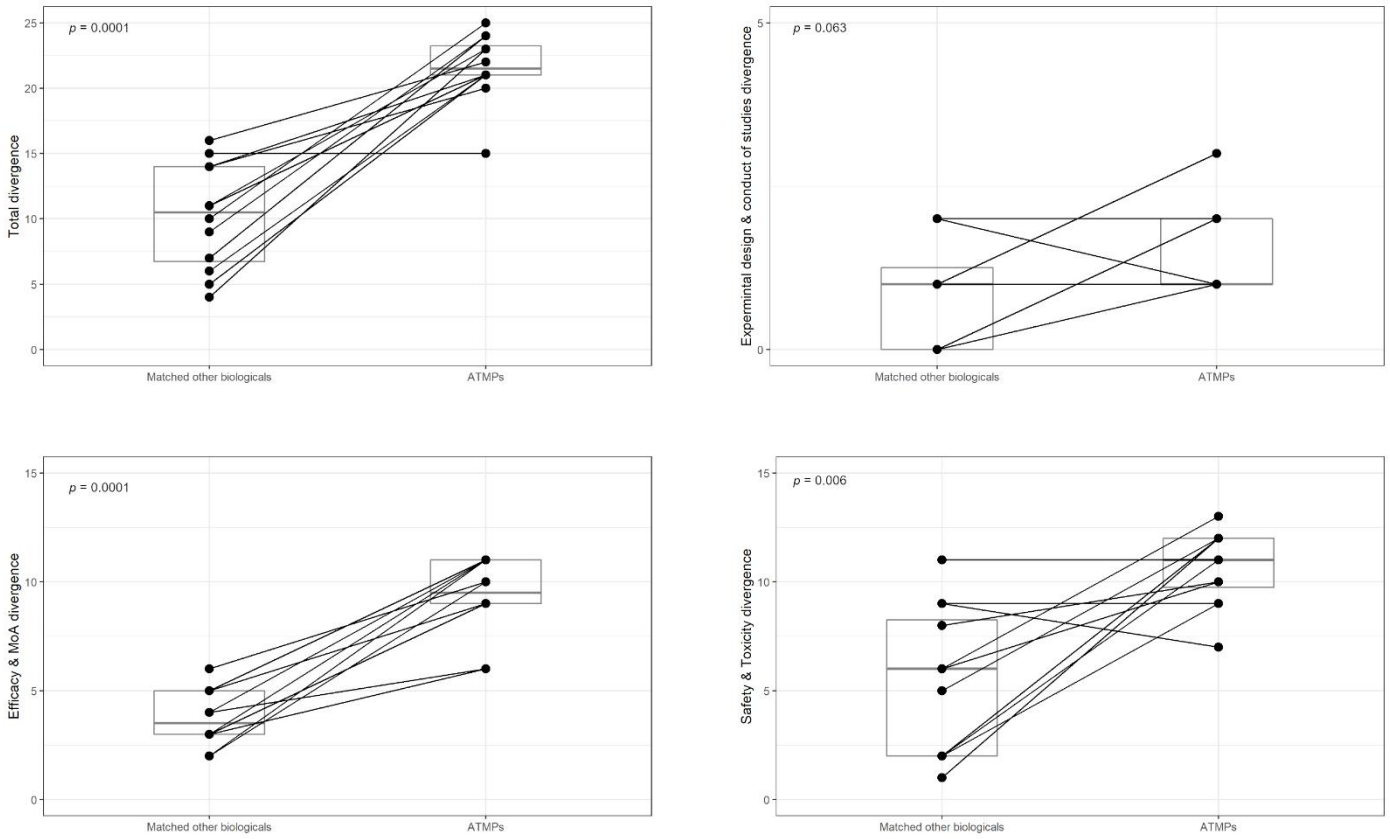

Figure 4 Paired dot plots and boxplots of divergence in matched authorized ATMPs and biologicals submissions. ATMPs (authorized and failed) were matched to other biologicals via a matched-pair experimental design to compare the difference in the evaluation process between both. Divergence from the regulatory requirments laid down in Annex I of Directive 2001/83/EC were measured using quantitative assessment of the omitted studies in the European puplic assessment reports (EPARs) of each product. The groups were compared statistically using two-tailed Wilcoxon signed-rank test. Significantly higher divergence were noted in the total numbers of divergence, the divergence in the efficacy and mode of action studies, as well as the divergence in safety and toxicity studies in the ATMPs cohort compared to the matched other biologicals. Statistical test: Wilcoxon signed-rank test.

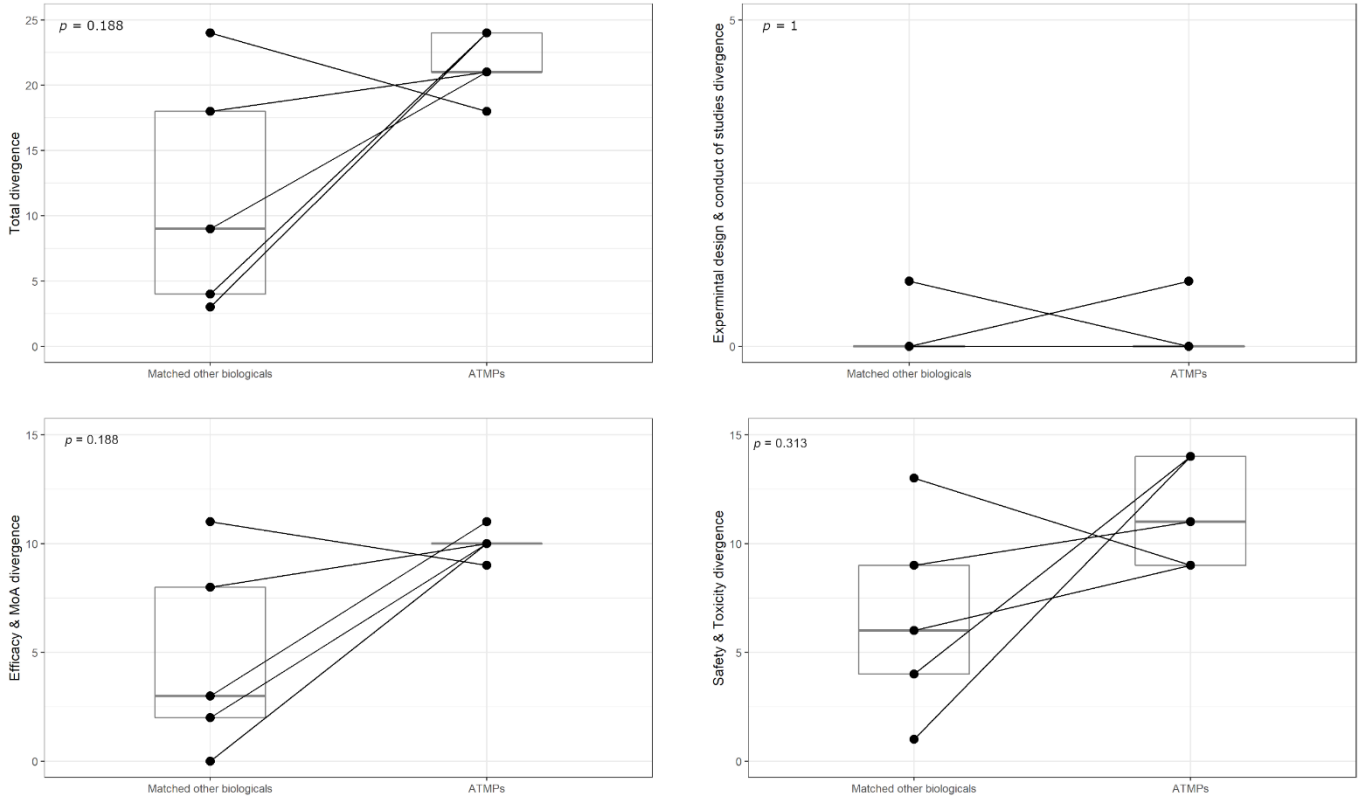

Figure 5 Paired dot plots and boxplots of divergence in matched failed ATMPs and biologicals submissions. ATMPs (authorized and failed) were matched to other biologicals via a matched-pair experimental design to compare the difference in the evaluation process between both. Divergence from the regulatory requirments laid down in Annex I of Directive 2001/83/EC were measured using quantitative assessment of the omitted studies in the European puplic assessment reports (EPARs) of each product. The groups were compared statistically using two-tailed Wilcoxon signed-rank test. No statsticall significant differences were reported in the divergence in the total numbers or the divergence in any of the evidence domains. Statistical test: Wilcoxon signed-rank test.

Table 3 evidence domains, data requirments, and definitions.

Evidence domains	Data requirments	Definition		reference
Quality of manufactured product	**Good manufacturing practice (GMP) compliance**	Compliance to the set of guidelines that ensure that the produced active pharmaceutical ingredients are consistent high quality. The guidelines include rules for quality management, personnel, building and facility, process equibment, documentation, material mangment, production, packaging, and storage.		[39]
	Control of materials (starting, raw, excipients)	Materials used in production of the active pharmaceutical ingredients and the final products. The quality of each material should be confirmed by an appropriate set of test methods and acceptance criteria (specification).		[39]
	Manufacturing process design & control stratgey	Manufacturing process should be clearly defined and controlled. Control strategy is defined as the planned set of controls that are derived from the current product and the understanding of the manufacturing process that assures process performance and product quality.		[39]
	Manufacturing process validation	Evidence that the manufacturing process when operated within defined parameters, can produce an intermediate or active pharmaceutical ingrediet with consistent set of predifiened specifications and quality attributes.		[39]
	Choice of Analytical methods (e.g., assays)	Suitability of the analytical methods used for process control, release testing and stability.		[40]
	Analytical methods validation	A documented program that provides a high degree of assurance that a specific process, method, or system will consistently produce a result meeting pre-determined acceptance criteria		[39,40]
	Comparability	The activities, including study design, conduct of studies, and evaluation of data, that are designed to investigate whether the products are comparable.		[41,42]
	Stability testing	Data on the stability of of the drug substance and drug product under different conditions that confirms the product remins within specifiction when stored or handled as intended.		[43]
	Product characterization, specification & acceptance criteria	Determination of physicochemical properties, biological activity, purity and impurities by appropriate analytical methods. The outcome of such studies are used to identify relevant test methods. Acceptance criteria are established from batch data, process characterisation and other studies.		[44]
Experimental design and conduct of the studies	**Non-clinical studies**	**GLP compliance**	Compliance to the set of rules and criteria laid down in Directive 2004/9/EC and Directive 2004/10/EC. GLP is a quality system concerned with the organisational process and the conditions under which non-clinical health and environmental safety studies are planned, performed, monitored, recorded, reported and archived.	[45]
		Animal models & experiments	*In vivo* and/or *in vitro* studies designed to explore the pharmacology, PK/PD and biodistribution, toxicity and other desirable or undesirable biological effects. Such studies aim to mimic the human disease and intended route of administration, dose and dosing schedule intended for humans.	[46]
	Clinical studies	**GCP & protocol compliance**	Compliance to the princibles of good clinical practice that insure that the design, conduct, recording and repoting of the clinical studies are of high quality. Deviation from such principles should be assessed for its impact on the quality and the integrity of the clinical studies.	[47]

		Clinical Study methodology	All the aspects related to the design of the main clinical study submitted for the marketing authorization. These aspects include the control arm of the trial, randomization, blinding, adequacy of the sample size and statistical methods.	[48]
		Study population	Data that show that the included population in the study is well-defined through clear inclusion and exclusion criteria which is crucial for assessing the target population and the intended indication.	[47]
		Choice of Endpoints	Study endpoints are the response variables that are chosen to assess drug effects that are related to pharmacokinetic parameters, pharmacodynamic measures, efficacy and safety. A primary endpoint(s) should reflect clinically relevant effects and is typically selected based on the principal objective of the study. Secondary endpoints assess other drug effects that may or may not be related to the primary endpoint. Endpoints and the plan for their analysis should be prospectively specified in the protocol.	[48]
Efficacy & mode of action	**Non-clinical evidence**	**Pharmacodynamics studies**	Primary non-clinical PD studies should address the mode of action (MoA) related to intended therapeutic use and provide knowledge on the interaction of the investigational medicinal product with the intended target as well as with related targets.	[49]
		Pharmacokinetics/Biodistribution studies (PK/BD)	Non-clinical part of the PK/BD that focus on the interaction of the investigation medicinal product with the taget action site, hence influencing the efficacy of the product. This either include the traditional Pharmacokinetic studies (absorbtion, distribution) or other BD assessments such as distribution, persistence of the drug product.	
	Clinical evidence	**Primary Pharmacodynamics studies**	Studies on the mode of action and/or effects of a substance in relation to its desired therapeutic target are primary pharmacodynamic studies. Evidence that can provide early estimates of activity and potential efficacy and may guide the dose and dosing regimen in later studies.	[48,50]
		Pharmacokinetics/Biodistribution (PK/BD)	See nonclinical PK/BD	
		Dose finding studies	A dose-finding study is a clinical trial that aims to outline the no-effect dose, the mean effective dose, and the maximal effective dose while taking tolerability into account to define an optimal dose.	[51]
		Clinical efficacy results	The degree to which a medicinal product produces a beneficial effects under ideal and controlled conditions. Usually obtained from the main study submitted in the marketing authorization application.	[52]
		Long-term clinical efficacy	The long-term benefits of the medicinal product	
		Indication	The disease(s) or condition(s) and population(s) that a medicine is intended to treat.	[53]
		Post-hoc analysis and meta-analysis and supportive studies	Any studies or analyses other than that of the main study that are conducted and included in the marketing authorization application to support the claims of the efficacy. These studies include post-hoc analyses, meta-analyses across studies, and other supportive studies.	
Safety & Toxicity	**Non-clinical evidence**	**Non-clinical Toxicity studies**	Non-clinical studies that measure functional indices of potential toxicity in animal studies. This include general toxicity studies, genotoxicity, tumorgenicity, immunotoxicity, and local tolerance.	[50]

		Pharmacokinetics/Bioditribution PK/BD	Non-clinical Part of the PK/BD that focus on the interaction of the drug product with sites other than the taget action site, hence influencing the safety of the product. This either include the traditional Pharmacokinetic studies (metabolism, and excreation) or other BD assessments such as mobilization, clearance, shedding, and off-target distribution of the biologicaly active substance.	
	Clinical evidence	**Adverse events**	Any untoward medical occurrence in a patient or clinical trial subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment.	[48]
		Long term safety data	The long-term studies to identify any undesirable effects of the product	
		Secondary pharmacodynamics studies	Secondary pharmacodynamic studies (previously referred to as general pharmacology) can be defined as studies on the mode of action and/or effects of a substance not related to its desired therapeutic target.	[50]
		Pharmacokinetics/Bioditribution PK/BD	see nonclinical PK/BD	
	Risk-management plan		Risk management plans include: (1) the identification or characterisation of the safety profile of the medicinal product, with emphasis on important identified and important potential risks and missing information, and also on which safety concerns need to be managed proactively or further studied (the ‘safety specification’); 2. the planning of pharmacovigilance activities to characterise and quantify clinically relevant risks, and to identify new adverse reactions (the ‘pharmacovigilance plan’); 3. the planning and implementation of risk minimisation measures, including the evaluation of the effectiveness of these activities (the ‘risk minimisation plan’).	[54]

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