Risk Minimisation Measures of Advanced Therapy Medicinal Products Authorised in the EU between 2009 and 2023; a Cross-Sectional Study

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1.1. Supplementary tables

Table S1. Summary of aRMMs at time of MA for the individual ATMPs authorised in the EU until December 31, 2023 (n=23), including the safety concerns addressed.

ATMP	Indication area	Educational material for HCPs	Educational material for patients/ caregivers	Controlled access or controlled distribution programme*	Safety concerns addressed with aRMMs per ATMP, n/n (%)±	Safety concerns addressed with aRMMs (broad terms)¥	Safety concerns addressed with aRMMs (narrow terms)¥
***Ex vivo* GTMPs**							
Strimvelis®≠ (Fondazione Telethon ETS, Italy)	Severe combined immunodeficiency due to adenosine deaminase deficiency	Yes	Yes	Yes	3/14 (21.4)	General disorders and administration site conditions; Immune system disorders; Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Autoimmune disorders NEC; Neoplasms malignant site unspecified NEC; Therapeutic and nontherapeutic responses
Zalmoxis®≠ (MolMed SpA, Italy)	Adjunctive treatment in haploidentical haematopoietic stem cell transplantation of patients with high-risk haematological malignancies	Yes	No	No	3/22 (13.6)	Immune system disorders; Injury, poisoning and procedural complications	Immune and associated conditions NEC; Product monitoring errors and issues
Kymriah®∞ (Novartis Europharm Limited, Ireland)	Relapsed or refractory B-cell acute lymphoblastic leukaemia; relapsed or refractory diffuse large B-cell lymphoma	Yes	Yes, including patient card	Yes	3/19 (15.8)	Immune system disorders; Injury, poisoning and procedural complications; Nervous system disorders	Immune and associated conditions NEC; Nervous system disorders NEC; Product storage errors and issues in the product use system
Yescarta®∞ (Kite Pharma EU B.V., the Netherlands)	Relapsed/refractory diffuse large B-cell lymphoma; primary mediastinal B-cell lymphoma	Yes	Yes, including patient card	Yes	2/16 (12.5)	Immune system disorders; Nervous system disorders	Immune and associated conditions NEC; Nervous system disorders NEC
Zynteglo® (bluebird bio (Netherlands) B.V., the Netherlands)	Transfusion-dependent β-thalassaemia (TDT) in patients who do not have a β0/β0 genotype	Yes	Yes, including patient card	Yes	6/7 (85.7)	General disorders and administration site conditions; Injury, poisoning and procedural complications; Long term effects; Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Abdominal and gastrointestinal injuries NEC; Long term safety and/or efficacy; Neoplasms unspecified malignancy and site unspecified NEC; Therapeutic and nontherapeutic responses; Transplantation complications

Libmeldy®≠ (Orchard Therapeutics (Netherlands) BV, the Netherlands)	Metachromatic leukodystrophy characterised by biallelic mutations in the arysulfatase A (ARSA) gene	Yes	Yes, including patient card	Yes	6/6 (100)	Injury, poisoning and procedural complications; Investigations; Long term effects; Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Long term safety and/or efficacy; Neoplasms malignant site unspecified NEC; Off label uses; Therapeutic drug monitoring analyses; Transplantation complications
Tecartus®∞ (Kite Pharma EU B.V., the Netherlands)	Relapsed or refractory mantle cell lymphoma	Yes	Yes, including patient card	Yes	2/12 (16.7)	Immune system disorders; Nervous system disorders	Immune and associated conditions NEC; Nervous system disorders NEC
Abecma®∞ (Bristol-Myers Squibb Pharma EEIG, Ireland)	Relapsed and refractory multiple myeloma	Yes	Yes, including patient card	Yes	3/13 (23.1)	Immune system disorders; Infections and infestations; Nervous system disorders	Immune and associated conditions NEC; Infections NEC; Nervous system disorders NEC
Skysona® (bluebird bio (Netherlands) B.V., the Netherlands)	Early cerebral adrenoleukodystrophy in patients with an ABCD1 genetic mutation	Yes	Yes, including patient card	No	5/6 (83.3)	Blood and lymphatic system disorders; General disorders and administration site conditions; Injury, poisoning and procedural complications; Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Marrow depression and hypoplastic anaemias; Neoplasms malignant site unspecified NEC; Therapeutic and nontherapeutic responses; Transplantation complications
Breyanzi®∞ (Bristol-Myers Squibb Pharma EEIG, Ireland)	Relapsed or refractory diffuse large B-cell lymphoma; primary mediastinal large B-cell lymphoma, follicular lymphoma grade 3B	Yes	Yes, including patient card	Yes	3/19 (15.8)	Immune system disorders; Injury, poisoning and procedural complications; Nervous system disorders	Immune and associated conditions NEC; Nervous system disorders NEC; Product preparation errors and issues
Carvykti®∞ (Janssen-Cilag International NV, Belgium)	Relapsed or refractory multiple myeloma	Yes	Yes, including patient card	Yes	3/16 (18.8)	Immune system disorders; Injury, poisoning and procedural complications; Nervous system disorders	Immune and associated conditions NEC; Nervous system disorders NEC; Product preparation errors and issues
***In vivo* GTMPs**							
Glybera®≠ (uniQure biopharma B.V., the Netherlands)	Familial lipoprotein lipase deficiency and with severe or multiple pancreatitis episodes despite dietary fat restrictions	Yes	Yes, including patient card	Yes	16/17 (94.1)	Congenital, familial and genetic disorders; General disorders and administration site conditions; Injury, poisoning and procedural complications; Investigations; Long term effects; Not classifiable; Use in special populations; Vascular disorders	Accidental exposures to product; Anaesthetic and allied procedural complications; Febrile disorders; Gene mutations and other alterations NEC; Haemorrhages NEC; Long term safety and/or efficacy; Muscle, tendon and ligament injuries; Non-site specific embolism and thrombosis; Not

							classifiable; Off label uses; Product administration errors and issues; Therapeutic and nontherapeutic responses; Therapeutic drug monitoring analyses; Use in paediatrics; Use in pregnancy and/or breastfeeding
Imlygic® (Amgen Europe B.V., the Netherlands)	Unresectable melanoma that is regionally or distantly metastatic (Stage IIIB, IIIC and IVM1a) with no bone, brain, lung or other visceral disease	Yes	Yes, including patient card	Yes	9/33 (27.3)	Infections and infestations; Injury, poisoning and procedural complications; Use in special populations	Accidental exposures to product; Herpes viral infections; Product monitoring errors and issues; Use in pregnancy and/or breastfeeding; Use in special populations NEC
Luxturna® (Novartis Europharm Limited, Ireland)	Vision loss due to inherited retinal dystrophy caused by confirmed biallelic RPE65 mutations and who have sufficient viable retinal cells.	Yes	Yes, including patient card	Yes	7/13 (53.8)	Eye disorders; Injury, poisoning and procedural complications; Investigations	Accidental exposures to product; Cataract conditions; Ocular infections, inflammations and associated manifestations; Ophthalmic function diagnostic procedures; Retinal structural change, deposit and degeneration
Roctavian® (BioMarin International Limited, Ireland)	Severe haemophilia A (congenital factor VIII deficiency)	Yes	Yes, including patient card	No	7/10 (70.0)	Congenital, familial and genetic disorders; Hepatobiliary disorders; Injury, poisoning and procedural complications; Investigations; Long term effects; Neoplasms benign, malignant and unspecified (incl cysts and polyps); Vascular disorders	Accidental exposures to product; Gene mutations and other alterations NEC; Hepatocellular damage and hepatitis NEC; Long term safety and/or efficacy; Neoplasms malignant site unspecified NEC; Non-site specific embolism and thrombosis; Therapeutic drug monitoring analyses
Upstaza®≠ (PTC Therapeutics International Limited, Ireland)	Aromatic L-amino acid decarboxylase deficiency with a severe phenotype	Yes	Yes, including patient card	Yes	3/7 (42.9)	Injury, poisoning and procedural complications; Nervous system disorders	Accidental exposures to product; Dyskinesias and movement disorders NEC; Neurological and psychiatric procedural complications
Hemgenix® (CSL Behring GmbH, Germany)	Severe and moderately severe haemophilia B (congenital factor IX deficiency)	Yes	Yes, including patient card	No	7/11 (63.6)	Congenital, familial and genetic disorders; Hepatobiliary disorders; Injury, poisoning and procedural complications; Investigations; Long term effects; Neoplasms benign, malignant and unspecified (incl cysts and polyps); Vascular disorders	Accidental exposures to product; Gene mutations and other alterations NEC; Hepatocellular damage and hepatitis NEC; Long term safety and/or efficacy; Neoplasms malignant site unspecified NEC; Non-site specific embolism and thrombosis; Therapeutic drug monitoring analyses

sCTMPs							
Provenge® (Dendreon UK Ltd, United Kingdom)	Symptomatic or minimally symptomatic metastatic (non-visceral) castrate resistant prostate cancer	Yes	Yes, including patient card	No	2/17 (11.8)	Infections and infestations; Injury, poisoning and procedural complications	Infections NEC; Product selection errors and issues
Alofisel®≠ (Takeda Pharma A/S, Denmark)	Complex perianal fistulas in adult patients with non-active/mildly active luminal Crohn's disease	Yes	No	No	2/11 (18.2)	Infections and infestations; Injury, poisoning and procedural complications	Infectious transmissions; Medication errors, product use errors and issues NEC
TEPs							
Chondro-Celect®≠ (TiGenix N.V., Belgium)	Single symptomatic cartilaginous defects of the femoral condyles of the knee (ICRS grade III or IV)	Yes	No	Yes	7/8 (87.5)	General disorders and administration site conditions; Injury, poisoning and procedural complications; Musculoskeletal and connective tissue disorders	Cartilage disorders; Joint related disorders NEC; Joint related signs and symptoms; Therapeutic and nontherapeutic responses; Transplantation complications
MACI®≈ (Vericel Denmark ApS, Denmark)	Symptomatic, full-thickness cartilage defects of the knee (grade III and IV of the Modified Outerbridge Scale)	Yes	No	Yes	10/16 (62.5)	General disorders and administration site conditions; Infections and infestations; Injury, poisoning and procedural complications; Musculoskeletal and connective tissue disorders; Vascular disorders	Application and installation site reactions; Arthropathies NEC; Infections NEC; Joint related disorders NEC; Medication errors, product use errors and issues NEC; Non-site specific embolism and thrombosis; Transplantation complications
Holoclar®≠ (Holostem s.r.l., Italy)	Moderate to severe limbal stem cell deficiency, unilateral or bilateral, due to physical or chemical ocular burns	Yes	Yes	No	7/13 (53.8)	Eye disorders; General disorders and administration site conditions; Infections and infestations; Injury, poisoning and procedural complications	Glaucomas (excl congenital); Infections NEC; Lid, lash and lacrimal infections, irritations and inflammations; Medication errors, product use errors and issues NEC; Off label uses; Product monitoring errors and issues; Therapeutic and nontherapeutic responses
Spherox®≠ (CO.DON Gmbh, Germany)	Articular cartilage defects of the femoral condyle and the patella of the knee	Yes	No	Yes	11/11 (100)	General disorders and administration site conditions; Infections and infestations; Injury, poisoning and procedural complications; Long term effects; Not classifiable	Infections NEC; Infectious transmissions; Long term safety and/or efficacy; Medication errors, product use errors and issues NEC; Musculoskeletal procedural complications; Not classifiable; Product monitoring errors and issues; Therapeutic and nontherapeutic responses; Transplantation complications

* An overview of the content of controlled access and controlled distribution programmes for the individual ATMPs is provided in Table 3.
± This proportion was calculated with the number of safety concerns that were in place at time of MA for the specific ATMP as the denominator. The numerator was the number of safety concerns that were in place at time of MA and addressed by aRMMs for the specific ATMP.
¥ Safety concerns are provided using their corresponding broad and narrow terms as described in the study methods. One broad or narrow term can cover multiple specific safety concerns.
∞ These ATMPs are classified as chimeric antigen receptor T (CAR T) cells.
≠ ATMP has not been approved in the US at our DLP (January 31, 2024). Note: Libmeldy® (Orchard Therapeutics (Netherlands) BV, the Netherlands) is referred to as Lenmeldy® in the US, which was authorised after our DLP.
≈ ATMP is classified as TEP, cATMP.
Note: no aRMMs were in place at MA for Zolgensma® (Novartis Europharm Limited, Ireland) and Ebvallo® (Pierre Fabre Medicament, France).
aRMM, additional risk minimisation measure; ATMP, advanced therapy medicinal product; DLP, data lock point; EU, European Union; GTMP, gene therapy medicinal product; HCP, healthcare professional; MA, marketing authorisation; NEC, not elsewhere classified; sCTMP, somatic-cell therapy medicinal products; TEP, tissue-engineered medicinal product; US, United States.

Table S2. Description of safety concerns at time of MA, including presence of aRMMs, among ATMPs authorised in the EU up to December 31, 2023.

	Safety concerns n=338, n (%)	Safety concerns addressed with aRMMs n=127, n (%)	All ATMPs n=25, n (%)	ATMPs addressed with aRMMs n=23, n (%)	ATMPs addressed with aRMMs per safety concern, %*
Safety concerns related to risks					
Injury, poisoning and procedural complications	59 (17.5)	41 (32.3)	22 (88.0)	19 (82.6)	86.4
Transplantation complications	13 (3.8)	11 (8.7)	7 (28.0)	6 (26.1)	85.7
Poisoning and toxicity	7 (2.1)	0 (0.0)	6 (24.0)	0 (0.0)	0.0
Accidental exposures to product	7 (2.1)	7 (5.5)	6 (24.0)	6 (26.1)	100
Medication errors, product use errors and issues NEC	4 (1.2)	4 (3.1)	4 (16.0)	4 (17.4)	100
Product monitoring errors and issues	5 (1.5)	5 (3.9)	4 (16.0)	4 (17.4)	100
Product preparation errors and issues	4 (1.2)	2 (1.6)	4 (16.0)	2 (8.7)	50.0
Non-site specific procedural complications	4 (1.2)	0 (0.0)	4 (16.0)	0 (0.0)	0.0
Off label uses	3 (0.9)	3 (2.4)	3 (12.0)	3 (13.0)	100
Product administration errors and issues	2 (0.6)	1 (0.8)	2 (8.0)	1 (4.3)	50.0
Abdominal and gastrointestinal injuries	1 (0.3)	1 (0.8)	1 (4.0)	1 (4.3)	100
Anaesthetic and allied procedural complications	1 (0.3)	1 (0.8)	1 (4.0)	1 (4.3)	100
Cardiac and vascular procedural complications	1 (0.3)	0 (0.0)	1 (4.0)	0 (0.0)	0.0
Muscle, tendon and ligament injuries	1 (0.3)	1 (0.8)	1 (4.0)	1 (4.3)	100
Musculoskeletal procedural complications	2 (0.6)	2 (1.6)	1 (4.0)	1 (4.3)	100
Neurological and psychiatric procedural complications	1 (0.3)	1 (0.8)	1 (4.0)	1 (4.3)	100
Product selection errors and issues	1 (0.3)	1 (0.8)	1 (4.0)	1 (4.3)	100
Product storage errors and issues in the product use system	1 (0.3)	1 (0.8)	1 (4.0)	1 (4.3)	100
Site specific procedural complications NEC	1 (0.3)	0 (0.0)	1 (4.0)	0 (0.0)	0.0
Investigations	24 (7.1)	5 (3.9)	18 (72.0)	5 (21.7)	27.8
Therapeutic drug monitoring analyses	15 (4.4)	4 (3.1)	15 (60.0)	4 (17.4)	26.7
Virus identification and serology	8 (2.4)	0 (0.0)	8 (32.0)	0 (0.0)	0.0
Ophthalmic function diagnostic procedures	1 (0.3)	1 (0.8)	1 (4.0)	1 (4.3)	100
Infections and infestations	25 (7.4)	12 (9.4)	15 (60.0)	7 (30.4)	46.7
Infections NEC	13 (3.8)	6 (4.7)	12 (48.0)	5 (21.7)	41.7
Infectious transmissions	6 (1.8)	2 (1.6)	6 (24.0)	2 (8.7)	33.3
Herpes viral infections	5 (1.5)	4 (3.1)	2 (8.0)	1 (4.3)	50.0
Bacterial infections	1 (0.3)	0 (0.0)	1 (4.0)	0 (0.0)	0.0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	15 (4.4)	6 (4.7)	15 (60.0)	6 (26.1)	40.0
Neoplasms malignant site unspecified NEC	12 (3.6)	5 (3.9)	12 (48.0)	5 (21.7)	41.7
Neoplasms unspecified malignancy and site unspecified NEC	1 (0.3)	1 (0.8)	1 (4.0)	1 (4.3)	100
Oncologic complications and emergencies	1 (0.3)	0 (0.0)	1 (4.0)	0 (0.0)	0.0
Plasma cell myelomas	1 (0.3)	0 (0.0)	1 (4.0)	0 (0.0)	0.0
Immune system disorders	36 (10.7)	8 (6.3)	13 (52.0)	8 (34.8)	61.5
Immune and associated conditions NEC	18 (5.3)	7 (5.5)	10 (40.0)	7 (30.4)	70.0
Autoimmune disorders NEC	6 (1.8)	1 (0.8)	6 (24.0)	1 (4.3)	16.7

Immunodeficiency disorders NEC	6 (1.8)	0 (0.0)	6 (24.0)	0 (0.0)	0.0
Allergic conditions NEC	2 (0.6)	0 (0.0)	2 (8.0)	0 (0.0)	0.0
Allergies to food, food additives, drugs and other chemicals	2 (0.6)	0 (0.0)	2 (8.0)	0 (0.0)	0.0
Transplant rejections	2 (0.6)	0 (0.0)	1 (4.0)	0 (0.0)	0.0
General disorders and administration site conditions	15 (4.4)	9 (7.1)	11 (44.0)	8 (34.8)	72.7
Therapeutic and nontherapeutic responses	11 (3.3)	7 (5.5)	10 (40.0)	7 (30.4)	70.0
Applications and instillation site reactions	1 (0.3)	1 (0.8)	1 (4.0)	1 (4.3)	100
Febrile disorders	1 (0.3)	1 (0.8)	1 (4.0)	1 (4.3)	100
Healing abnormal NEC	1 (0.3)	0 (0.0)	1 (4.0)	0 (0.0)	0
Trophic disorders	1 (0.3)	0 (0.0)	1 (4.0)	0 (0.0)	0
Nervous system disorders	11 (3.3)	7 (5.5)	9 (36.0)	7 (30.4)	77.8
Nervous system disorders NEC	6 (1.8)	6 (4.7)	6 (24.0)	6 (26.1)	100
Increased intracranial pressure disorders	2 (0.6)	0 (0.0)	2 (8.0)	0 (0.0)	0.0
Central nervous system haemorrhages and cerebrovascular accidents	1 (0.3)	0 (0.0)	1 (4.0)	0 (0.0)	0.0
Dyskinesias and movement disorders NEC	1 (0.3)	1 (0.8)	1 (4.0)	1 (4.3)	100
Encephalopathies toxic and metabolic	1 (0.3)	0 (0.0)	1 (4.0)	0 (0.0)	0.0
Blood and lymphatic system disorders	10 (3.0)	1 (0.8)	9 (36.0)	1 (4.3)	11.1
Marrow depression and hypoplastic anaemias	7 (2.1)	1 (0.8)	7 (28.0)	1 (4.3)	14.3
Haematological disorders	1 (0.3)	0 (0.0)	1 (4.0)	0 (0.0)	0.0
Neutropenias	1 (0.3)	0 (0.0)	1 (4.0)	0 (0.0)	0.0
Thrombocytopenias	1 (0.3)	0 (0.0)	1 (4.0)	0 (0.0)	0.0
Not classifiable	11 (3.3)	3 (2.4)	8 (32.0)	2 (8.7)	25.0
Not classifiable	11 (3.3)	3 (2.4)	8 (32.0)	2 (8.7)	25.0
Vascular disorders	8 (2.4)	5 (3.9)	6 (24.0)	4 (17.4)	66.7
Non-site specific embolism and thrombosis	5 (1.5)	4 (3.1)	5 (20.0)	4 (17.4)	80.0
Haemorrhages NEC	2 (0.6)	1 (0.8)	2 (8.0)	1 (4.3)	50.0
Peripheral embolism and thrombosis	1 (0.3)	0 (0.0)	1 (4.0)	0 (0.0)	0.0
Metabolism and nutrition disorders	6 (1.8)	0 (0.0)	6 (24.0)	0 (0.0)	0.0
Electrolyte imbalance NEC	6 (1.8)	0 (0.0)	6 (24.0)	0 (0.0)	0.0
Hepatobiliary disorders	4 (1.2)	2 (1.6)	4 (16.0)	2 (8.7)	50.0
Hepatocellular damage and hepatitis NEC	3 (0.9)	2 (1.6)	3 (12.0)	2 (8.7)	66.7
Hepatic failure and associated disorders	1 (0.3)	0 (0.0)	1 (4.0)	0 (0.0)	0.0
Congenital, familial and genetic disorders	3 (0.9)	3 (2.4)	3 (12.0)	3 (13.0)	100
Gene mutations and other alterations NEC	3 (0.9)	3 (2.4)	3 (12.0)	3 (13.0)	100
Cardiac disorders	2 (0.6)	0 (0.0)	2 (8.0)	0 (0.0)	0.0
Cardiac disorders NEC	1 (0.3)	0 (0.0)	1 (4.0)	0 (0.0)	0.0
Ischaemic coronary artery disorders	1 (0.3)	0 (0.0)	1 (4.0)	0 (0.0)	0.0
Eye disorders	7 (2.1)	7 (5.5)	2 (8.0)	2 (8.7)	100
Cataract conditions	1 (0.3)	1 (0.8)	1 (4.0)	1 (4.3)	100
Glaucomas (excl congenital)	1 (0.3)	1 (0.8)	1 (4.0)	1 (4.3)	100
Lid, lash, and lacrimal infections, irritations and inflammations	1 (0.3)	1 (0.8)	1 (4.0)	1 (4.3)	100
Ocular infections, inflammations and associated manifestations	1 (0.3)	1 (0.8)	1 (4.0)	1 (4.3)	100

Retinal structural change, deposit and degeneration	3 (0.9)	3 (2.4)	1 (4.0)	1 (4.3)	100
Musculoskeletal and connective tissue disorders	8 (2.4)	8 (6.3)	2 (8.0)	2 (8.7)	100
Joint related disorders NEC	3 (0.9)	3 (2.4)	2 (8.0)	2 (8.7)	100
Cartilage disorders	1 (0.3)	1 (0.8)	1 (4.0)	1 (4.3)	100
Arthropathies NEC	1 (0.3)	1 (0.8)	1 (4.0)	1 (4.3)	100
Joint related signs and symptoms	3 (0.9)	3 (2.4)	1 (4.0)	1 (4.3)	100
Respiratory, thoracic and mediastinal disorders	1 (0.3)	0 (0.0)	1 (4.0)	0 (0.0)	0.0
Bronchospasm and obstruction	1 (0.3)	0 (0.0)	1 (4.0)	0 (0.0)	0.0
Surgical and medical procedures	1 (0.3)	0 (0.0)	1 (4.0)	0 (0.0)	0.0
Therapeutic procedures NEC	1 (0.3)	0 (0.0)	1 (4.0)	0 (0.0)	0.0
Safety concerns related to context of use					
Long term effects	25 (7.4)	6 (4.7)	23 (92.0)	6 (26.1)	26.1
Long term safety and/or efficacy	25 (7.4)	6 (4.7)	23 (92.0)	6 (26.1)	26.1
Use in special populations	67 (19.8)	4 (3.1)	20 (80.0)	2 (8.7)	10.0
Use in pregnancy and/or breastfeeding	15 (4.4)	2 (1.6)	14 (56.0)	2 (8.7)	14.3
Use in special populations NEC	34 (10.1)	1 (0.8)	12 (48.0)	1 (4.3)	8.3
Use in paediatric**s**	11 (3.3)	1 (0.8)	10 (40.0)	1 (4.3)	10.0
Use in elderly	7 (2.1)	0 (0.0)	7 (28.0)	0 (0.0)	0.0

*This proportion was calculated with the number of ATMPs that had safety concerns within the broad or narrow terms as the denominator (column 'All ATMPs'). The numerator was the number of ATMPs that had aRMMs for the safety concerns within the broad and narrow terms (column 'ATMPs addressed with aRMMs'). This proportion reflects the need for aRMMs within the different categories.

aRMM, additional risk minimization measure; ATMP, advanced therapy medicinal product; EU, European Union; MA, marketing authorisation; NEC, not elsewhere classified.

1.2. Supplementary figure

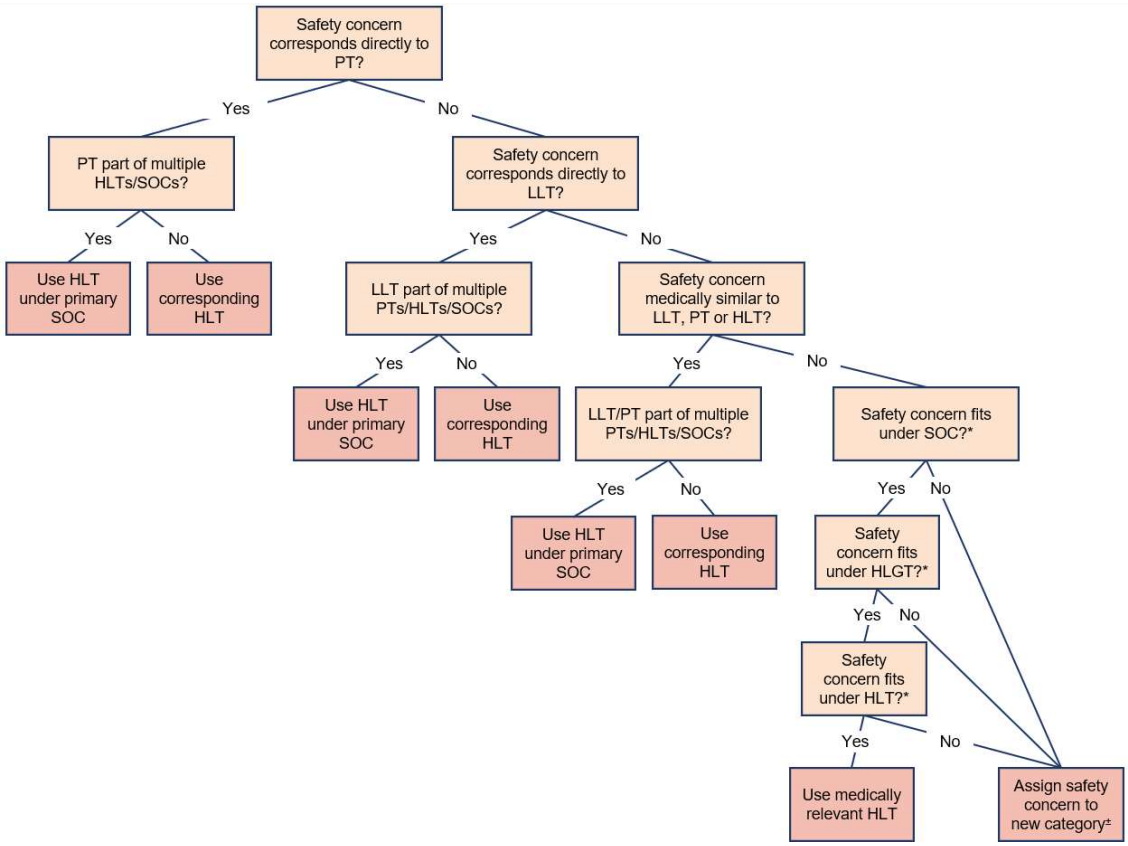

Fig. S1. Decision tree for classification of safety concerns related to risks into narrow terms.
*Fitting means identification of the most medically relevant SOC/HLGT/HLT according to the researchers.
±Translating safety concerns into HLTs was not always possible. Safety concerns that did not fall into any MedDRA® HLT and were related to context of use were classified according to the following predefined narrow terms: 'Use in pregnancy and/or breastfeeding', 'Use in paediatrics (<18 years of age)', 'Use in elderly (≥65 years of age)', 'Use in special populations NEC', and 'Long term safety/efficacy'; and broad terms: 'Use in special populations' and 'Long term effects', in line with previous research. Safety concerns that could not be classified using MedDRA® or our context of use categories were classified in the separate category: 'Not classifiable'.
Note: for safety concerns that represent more than one condition, which could not be classifiable according to the decision tree, the most clinically serious condition according to the researchers was chosen to classify the safety concern based on the decision tree.
HLGT, High Level Group Term; HLT, High Level Term; LLT, Lowest Level Term; MedDRA®, Medical Dictionary for Regulatory Activities; NEC, not elsewhere classified; PT, Preferred Term; SOC, System Organ Class.