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Cell and gene therapy approvals in Japan and the need for international harmonization

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1 Supplemental Table 1: Clinical trials of cell-based medical products approved in Japan (with study code and efficacy results).

Brand name	Non-proprietary name/Generic Name	Indications	Study code/Study design	Result* (efficacy endpoint)	Approval status Japan
Cell products potential to compensate organ function					
JACE	human (autologous) epidermal cell sheet	severe burns	**J-TEC003** A multi-centre, open-label, single-arm study	Epithelialization (%) (n = 2) one patient: Very effective (100%) the other patient: Effective (50%)	2007
		giant congenital melanocytic nevi	**GCMN001** A multi-centre, open-label, single-arm study	≥ 95% epithelialization: 8/8 (100%)	2016
		epidermolysis bullosa	**J-TEC-EB (Phase II)** An open-label, single-arm study	Epithelialization (%) (n = 2) Planned estimation using a linear mixed-effects model was not possible.	2018
			J-TEC-01-01 (Phase III) An open-label, single-arm, investigator-initiated study	Epithelialization (%) (n = 3) Subject H-01: 57.01% Subject H-02: 100.00% Subject H-03: 87.70%	
JACC	human autologous tissue for transplantation (autologous cultured cartilage)	traumatic cartilage defect or osteochondritis dissecans of the knee	**J-TEC002** A multi-centre, open-label, single-arm study	Grading criteria for knee function improvement and the arthroscopic assessment system Very effective: 25/30 (83.3%) Effective: 3/30 (10.0%) Neither effective nor ineffective: 2/30 (6.7%)	2012
Nepic	human (autologous) corneal limbus-derived corneal epithelial cell sheet	limbal stem cell deficiency	**EME-01M (Phase III)** An open-label, single-arm study	Success rate of corneal epithelial reconstruction: 6/10 (60.0%)	2020
Ocural	human (autologous) oral mucosa-derived epithelial cell sheet	limbal stem cell deficiency	**COMET01 (Phase III)** An open-label, single-arm study	Success rate of corneal epithelial reconstruction: 6/6 (100.0%)	2021
Sakracy	human (autologous) oral mucosa-derived epithelial cell sheet using human amniotic membrane substrate	adhesions accompanying limbal stem cell deficiency	**170901 (Phase III)** An open-label, single-arm study	Change in the adhesion score (n = 7): −2.6	2022

Cell products expecting paracrine effects					
HeartSheet	human (autologous) skeletal myoblast-derived cell sheet	severe heart failure	**M-51073-21** A multi-centre, open-label, single-arm study	Change in LVEF: Unchanged: 5/7 (71.4%) Worsened: 2/7 (28.6%)	2015 Conditional/Time-limited Approval (5 years) 2020 Extended 3 years
Temcell	human (allogeneic) bone marrow-derived mesenchymal stem cells	acute graft versus host disease	**JR-031-201 (Japanese Phase I/II)** An open-label, single-arm study	OR: 13/14 (92.9%) CR: 10/14 (71.4%) survival: 11/14 (78.6%)	2015
			JR-031-301 (Japanese Phase II/III) An open-label, single-arm study	CR: 12/25 (48.0%)	
Stemirac	human (autologous) bone marrow-derived mesenchymal stem cells	spinal cord injury	**STR01-03 (Phase II)** An open-label, single-arm study	≥1 grade improvement in AIS: 12/13 (92.3%)	2018 Conditional/Time-limited Approval (7 years)
Alofisel	Davadstrocel (human (allogeneic) expanded adipose stem cells)	complex perianal fistulas with Crohn's disease	**Cx601-0101 (Foreign Phase I/IIa)** An open-label, single-arm study	Reduction in the number of draining fistulas: 0: 7/19 (36.8%) 1: 10/19 (52.6%) 2: 2 /19 (10.5%)	2021 (EU approved in 2018)
			Cx601-0302 (Foreign Phase III) A placebo-controlled, randomised, double-blind study	Combined remission; Alofisel: 53/107 (49.5%) Placebo: 36/105 (34.3%)	
			Darvadstrocel-3002 (Japanese Phase III) An open-label, single-arm study	Combined remission: 13/22 (59.1%)	

Abbreviation: AIS, American spinal injury association impairment scale; CR, Complete response; LVEF, Left ventricular ejection fraction; OR, Overall response.

Refer to review reports provided by the Pharmaceuticals and Medical Devices Agency, Japan, retrieved from https://www.pmda.go.jp/english/review-services/reviews/approved-information/0004.html

* Results show the clinical data reviewed for Japanese approval.

Note: Five cell-free artificial skin products approved in Japan as medical devices are not listed in Table 1. Jacemin, melanocyte-containing human (autologous) epidermis-derived cell sheet, and Vyznova, neltependocel, were approved in March 2023.

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9 Supplemental Table 2: Clinical trials of gene therapy products approved in Japan

Bland name	Category	Transgene	Indications	Study code/Study design (Phase 1 excluded)	Result* (efficacy endpoint)	Approval status		
						US	EU	JP
ex vivo gene therapy products								
Kymriah	CAR T cell (autologous)	CD19 CAFR	B-ALL DLBCL	**B2202 (Phase II)** (B-ALL) A single-arm, multicenter trial	ORR: 61/75 (81.3%)	2017	2018	2019
				C2201 (phase II) (DLBCL) An open-label, multi-centre, single-arm study	Response rate: 43/81 (53.1%)			
				B2205J (Phase II) (B-ALL) An open-label, single-arm study	ORR: 20/29 (69.0%)			
			FL	**E2202 (phase II)** An open-label, multi-centre, single-arm study	CRR: 34/52 (65.4%)	2022	2022	2022
Yescarta	CAR T cell (autologous)	CD19 CAR	LBCL (3rd line)	**ZUMA-1 (Phase I/II)** A single-arm, open-label, multi-centre trial	ORR: 75/92 (81.5%)	2017	2018	2021
				J202 (Phase II) A single-arm, open-label, multicentre trial	ORR: 9/10 (90.0%)			
			LBCL (2nd line)	**ZUMA-7 (Phase III)** A randomised, open-label, multi-centre trial	EFS; Yescarta (n=180): 8.3 months Standard Therapy (n=179): 2 months	2022	2022	2022
Breyanzi	CAR T cell (autologous)	CD19 CAR	LBCL (3rd line) FL (3rd line)	**BMC-001 (Phase II)** A single-arm, open-label, multi-centre trial	ORR: 20/34 (58.8%)	2021	2022	2021
			LBCL (2nd line) FL (2nd line)	**BMC-003 (Phase III)** A randomised, open-label, multi-centre trial	EFS; Bretanzi (n=92): 10.1 months Standard Therapy (n=92): 2.3 months	2022	—	2022
				BMC-001 Cohort 2 (Phase II) A single-arm, open-label, multi-centre trial	ORR: 17/27 (63.0%)			

				017006 (Phase II) A single-arm, open-label, multi-centre trial	ORR: 49/61 (80.3%)			
Abecma	CAR T cell (autologous)	BCMA CAR	multiple myeloma	**MM-001 (Phase II)** A single-arm, open-label, multicenter trial	ORR: 94/128 (73.4%)	2021	2021	2022
Carvykti	CAR T cell (autologous)	BCMA CAR	multiple myeloma	**MMY2001 (Phase Ib/II)** A single-arm, open-label, multi-centre trial	ORR: 94/97 (96.9%)	2022	2022	2022
in vivo gene therapy products								
	plasmid	HGF	chronic arterial obstruction	**ASO Phase III** (ASO) A placebo-controlled, randomised, double-blind study	Rest pain (VAS) or ulcer size HGF: 19/27 (70.4%), Placebo: 4/13 (30.8%)			2019 Conditional/Time-limited approval (5 years)
				TAO (Buerger's disease) An open-label, single-arm study	Largest ulcer size 6/9 (66.7%)			
				Global Phase III (ASO) A global, placebo-controlled, randomised, double-blind study	Major amputation or all-cause death; HGF: 5/23 (21.7%), placebo: 8/23 (34.8%) Time to major amputation or all-cause death; HGF: 505 days, placebo: 381 days			
				US Phase II (ASO) A placebo-controlled, randomised, double-blind study	$TcPO_2$; Placebo (n = 24): 6.1, 0.4 mg × 3 (n = 25): 8.7, 4 mg×2 (n = 21): 5.8, 4 mg × 3 (n = 23): 5.7 Total ulcer size; Placebo: 0.2, 0.4 mg × 3: -1.0, 4 mg × 2: 10.2, 4 mg × 3: 0.3 Rest pain; Placebo: -1.78, 0.4 mg × 3: -1.56, 4 mg × 2: -1.00, 4 mg × 3: -1.79			
				US second Phase II (ASO) A placebo-controlled, randomised, double-blind study	Largest ulcer size; HGF (n = 18): 0.456, Placebo (n = 6): −0.875 Total ulcer size; HGF: 9.956, Placebo: −0.458 Rest pain; HGF: −0.85, Placebo: −0.38 ABPI; HGF: −0.008, Placebo: 0.010 TBPI; HGF: 0.035, Placebo: −0.114			

				US pilot Phase IIb (ASO) An open-label, single-arm study	Number of subjects with improvement of the largest ulcer or rest pain The ulcer size reduced by ≥ 20%: 1/4 VAS reduced by ≥ 20 mm: 1/8			
Zolgensma	AAV9	SMN	spinal muscular atrophy	**CL101 (Phase III)** An open-label, single-arm study	Sitting for ≥ 30 seconds: 10/21 (47%) Survival at 14 months of age: 13/21 (67%)	2019	2020	2020
Delytact	Oncolytic HSV1	LacZ	malignant glioma	**DG01 (Phase II)** An open-label, single-arm study	One-year survival rate: 12/13 (92.3%)			2021 Conditional/Time-limited approval (7 years)

Abbreviations: AAV, Adeno-associated virus; ABPI, ankle-brachial pressure index; ASO, Arteriosclerosis obliterans; B-ALL, Acute B cell lymphoblastic leukaemia; CAR-T, Chimeric antigen receptor T-cells; DLBCL, Diffuse large B-cell lymphoma; EFS, Event-free survival; FL, Follicular lymphoma; ORR, Overall response rate; PMBCL, Primary mediastinal large B-cell lymphoma; SMN, Survival motor neuron; TAO, thromboangiitis obliterans; TBPI, TATA-binding protein I; VAS, Visual analogue scale

Refer to review reports provided by the Pharmaceuticals and Medical Devices Agency, Japan, retrieved from https://www.pmda.go.jp/english/review-services/reviews/approved-information/0004.html

* Results show the clinical data reviewed for Japanese approval.

Note: Luxtana, voretigene neparvovec, was approved in June 2023.