

Supplementary Table S1: Safety profile of previous LNP-mRNA products

Intervention type	Treatment Target	Payload (Protein/RNA expressed)	Manufacturer	Product	Trials	(AE rate) [SAE rate]	Severe Adverse reactions	Reference
LNP delivery of non-expressed RNA	Polyneuropathies	siRNA to silence transthyretin	Sanofi Genzyme	Onpattro/patisiran	Phase I: NCT01559077 (2012) NCT02053454 (2014) Phase 2: NCT01617967(2012) NCT01961921 (2013) Phase 3: NCT01960348 (2013-2017) NCT02510261 (2015) NCT03759379 (2019) NCT03862807 (2019) NCT03997383 (2019)	(3/29, 10%) [2/29, 6%]	urinary tract infection, sepsis, nausea, vomiting, extravasation-related cellulitis	[1]
				Givosiran		[6/40, 15%]		[2]
LNP delivery of RNA expressing foreign antigen	Rabies	rabies virus glycoprotein	CureVac AG	CV7201	NCT02241135 (2013-2018)	(79/101, 78%) [10/101, 10%]	Bell's Palsy (1/101, 1%)	[3]
	Rabies	rabies virus glycoprotein	CureVac AG	CV7202	Phase 1: NCT03713086 (2018-2021)	(9/10, 90%) [5/10, 50%]	Lack of appetite (3/10) Night sweats (2/10) Dizziness (1/10) Tachycardia (1/10)	[4]
	Chikungunya virus	Chikungunya virus antigens	Moderna	VAL-181388 / mRNA-1388	Phase 1: NCT03325075 (2017-2020)		No data available	
	Cytomegalovirus	Pentameric complex and	Moderna	mRNA-1647	Phase 1:		No data available	

		B glycoprotein			NCT03382405 (2017-2021) Phase 2: NCT04232280 (2020-2022*)			
	Metapneumovirus and parainfluenza virus type 3 (MPV/PIV3)	MPV and PIV3 F glycoproteins	Moderna	mRNA-1653	Phase I: NCT03392389 (2017-2019)		No data available	
	Respiratory Syncytial Virus (RSV)	F glycoprotein	Moderna	mRNA-1345	Phase 1: NCT04528719(2020-2023*)		Recruiting	
	Zika Virus (ZIKV)	Pre-membrane and envelope glycoproteins	Moderna	mRNA-1893	Phase I: NCT04064905 (2019-2021)		No data available	
	Influenza H7N9	Haemagglutinin	Moderna	mRNA-1851	Phase 1: NCT03345043 (2016-2018)	(53.3-73.3%) 30/90, 20-30%]		[5,6]
	Influenza H10N8	Haemagglutinin	Moderna	mRNA-1440	Phase 1: NCT03345043 (2016-2018)	(>80%) [5/84, 6%]		[5,6]
	HIV-1		Argos Therapeutics	AGS 004	Phase II: NCT00672191 (2008-2011)	(25/35, 72%) lower than placebo arm [0/35, 0%] No difference in viral load between arms.	Local site reactions,	[7]

					Phase I: NCT02042248 (2014-2016)	Data not available		
					Phase II: NCT01069809 (2010-2015)	Data not available		
					Phase II: NCT02888756 (2017-2018)	(16/26, 100%) [2/16, 12.5%] same as placebo arm	Gastrointestinal disorders	[8]
					Phase I: NCT02413645 (2015-2016)	[1/21, 5%]		[9]
					Phase I/II: NCT00833781 (2009-2013)	[0/10, 0%]		[10]
					Phase I/II: NCT00381212	(7/10, 70%) [2/10, 20%]		
Cancer vaccine	Non-small-cell lung cancer, colorectal cancer, pancreatic adenocarcinoma	KRAS antigens	National Cancer Institute	(NCI)-4650	Phase II: NCT03480152 (2018-2020)	(4/4, 100%) [0/4, 0%]		
	Melanoma	Personalized neoantigens	Moderna	mRNA-4157	Phase II: NCT03897881 (2019-2024*)			
	Gastrointestinal cancer	Personalized neoantigens	Moderna	mRNA-4650	Phase I/II: NCT03480152 (2018-2019)	(4/4, 100%) [0/4, 0%]		
	Melanoma	NY-ESO-1, tyrosinase, MAGE-A3, TPTE	BioNTech	FixVac	Phase I: NCT02410733 (2015-2023*)	[23/92, 25%]	Lymphocyte count decreased, lymphopenia, hypertension	[11]
	Triple-negative	Personalized neoantigens	BioNTech	TNBC-MERIT	Phase I: NCT02316457 (2016-2023*)			

	breast cancer							
	HPV-positive cancers	HPV oncoproteins E6 and E7	BioNTech	HARE-40/BNT113	Phase I/II: NCT03418480 (2017-2024*)			
	Melanoma	Personalized neoantigens	BioNTech	RO7198457	Phase II: NCT03815058 (2019-2024*)			
	Ovarian cancer	Ovarian cancer antigens	BioNTech	W_ova1	Phase I: NCT04163094 (2019-2023*)			
	Solid tumours	OX40L	Moderna	mRNA 2416	Phase II: NCT03323398 (2017-2021)		Terminated, efficacy endpoints not met	
	Solid tumours	OX40L, IL-23 and IL-36 γ	Moderna	mRNA-2752	Phase I: NCT03739931 (2018-2023*)			
	Solid tumours	IL-12	MedImmune	MEDI1191	Phase I: NCT03946800 (2019-2027*)			
	Solid tumours	IL-12sc, IL-15sushi, IFN α and GM-CSF	BioNTech	SAR441000/BN T131	Phase I: NCT03871348 (2019-2024*)			
	Advanced Melanoma		BioNTech	BNT111	Phase II: NCT04526899(2021-2024*)	[23 grade 3 or above events out of 89 participants]	Pyrexia, chills, lymphocyte count decreased, lymphopenia, hypertension, dizziness	[11]
	Cancer	KRAS	Moderna	mRNA-5671/V941	Phase I: NCT03948763 (2019-2022)	Data not available		
	Non-small cell lung cancer		CureVac	CV9202	Phase Ib: NCT01915524	[4/26, 15.4%]	Dysphagia, fatigue, pyrexia	[12]

	Urea Disorder	Ornithine carboxylase	Arcturus	ARCT-810	Phase I: NCT04416126 (2020-2020) Phase I: NCT04442347 (2020-2022*)	Data not available		
	Solid tumours		CureVac	CV8102	Phase I: NCT03291002 (2017-2023*)	[2/14]		[13]
	Rabies vaccine adjuvant		CureVac	CV8102 (co-administered with Rabipur)	Phase I: NCT02238756 (2014-2016)	[11 events out of 37 participants]	Pain, headache, myalgia/arthralgia, fatigue	[14]
	Solid tumours		BioNTech	BNT122 (RO7198457)	Phase II: NCT04486378 (2021-2027*)			
	Generalized myasthenia gravis		Cartesian	Descartes-08	Phase II: NCT04816526 (2021-2025*)			
	Cystic Fibrosis		Translate Bio	MRT5005	Phase I/II: NCT03375047 (2018-2021)	[1/16, 6%]	Pulmonary exacerbation	[15]
	Methylmalonic aciduria		Moderna	mRNA-3704	Phase I/II: NCT03810690 (2019-2020) Terminated due to a business decision			
	Cancer		Moderna	mRNA-4157	Phase I: NCT03313778 (2017-2025*)	[no drug related SAEs in 33 patients]		[16]
	Multiple myeloma		Poseida	P-BCMA-101	Phase II: NCT03288493	Unknown, though several SAEs in 12 patients	cytopenias and febrile neutropenia	[17,18]
	Ischemic heart disease	vascular endothelial	Moderna/AstraZeneca	AZD8601	Phase II: NCT03370887 (2018-2021)			[19,20]

		growth factor A						
	Type II diabetes			AZD8601	Phase I: NCT02935712 (2017-2018)		Injection site reactions	[21]

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