**Supplementary Table 1:** Safety profile of previous LNP-mRNA products

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Interventiontype | TreatmentTarget | 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](https://clinicaltrials.gov/show/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 B glycoprotein | Moderna | mRNA-1647  | Phase 1:NCT03382405 (2017-2021)Phase 2: NCT04232280 (2020-2022\*) |  | No data available |  |
|  | 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, lymphophenia, hypertension | [11] |
|  | Triple-negative breast cancer | Personalized neoantigens | BioNTech | TNBC-MERIT | Phase I: NCT02316457 (2016-2023\*) |  |  |  |
|  | 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-36γ | 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, IFNα and GM-CSF | BioNTech | SAR441000/BNT131 | 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 growth factor A | Moderna/AstraZeneca | AZD8601 | Phase II: NCT03370887 (2018-2021) |  |  | [19,20] |
|  | Type II diabetes |  |  | AZD8601 | Phase I: NCT02935712 (2017-2018) |  | Injection site reactions | [21] |

1 Suhr OB, Coelho T, Buades J, *et al.* Efficacy and safety of patisiran for familial amyloidotic polyneuropathy: a phase II multi-dose study. *Orphanet J Rare Dis* 2015;**10**:109. doi:10.1186/s13023-015-0326-6

2 Balwani M, Sardh E, Ventura P, *et al.* Phase 3 Trial of RNAi Therapeutic Givosiran for Acute Intermittent Porphyria. *N Engl J Med* 2020;**382**:2289–301. doi:10.1056/NEJMoa1913147

3 Alberer M, Gnad-Vogt U, Hong HS, *et al.* Safety and immunogenicity of a mRNA rabies vaccine in healthy adults: an open-label, non-randomised, prospective, first-in-human phase 1 clinical trial. *Lancet* 2017;**390**:1511–20. doi:10.1016/S0140-6736(17)31665-3

4 Aldrich C, Leroux-Roels I, Huang KB, *et al.* Proof-of-concept of a low-dose unmodified mRNA-based rabies vaccine formulated with lipid nanoparticles in human volunteers: A phase 1 trial. *Vaccine* 2021;**39**:1310–8. doi:10.1016/j.vaccine.2020.12.070

5 Feldman RA, Fuhr R, Smolenov I, *et al.* mRNA vaccines against H10N8 and H7N9 influenza viruses of pandemic potential are immunogenic and well tolerated in healthy adults in phase 1 randomized clinical trials. *Vaccine* 2019;**37**:3326–34. doi:10.1016/j.vaccine.2019.04.074

6 Bahl K, Senn JJ, Yuzhakov O, *et al.* Preclinical and Clinical Demonstration of Immunogenicity by mRNA Vaccines against H10N8 and H7N9 Influenza Viruses. *Molecular Therapy* 2017;**25**:1316–27. doi:10.1016/j.ymthe.2017.03.035

7 Jacobson JM, Routy J-P, Welles S, *et al.* Dendritic Cell Immunotherapy for HIV-1 Infection Using Autologous HIV-1 RNA: A Randomized, Double-Blind, Placebo-Controlled Clinical Trial. *JAIDS Journal of Acquired Immune Deficiency Syndromes* 2016;**72**:31–8. doi:10.1097/QAI.0000000000000926

8 de Jong W, Aerts J, Allard S, *et al.* iHIVARNA phase IIa, a randomized, placebo-controlled, double-blinded trial to evaluate the safety and immunogenicity of iHIVARNA-01 in chronically HIV-infected patients under stable combined antiretroviral therapy. *Trials* 2019;**20**:361. doi:10.1186/s13063-019-3409-1

9 Leal L, Guardo AC, Morón-López S, *et al.* Phase I clinical trial of an intranodally administered mRNA-based therapeutic vaccine against HIV-1 infection. *AIDS* 2018;**32**:2533–45. doi:10.1097/QAD.0000000000002026

10 Gandhi RT, Kwon DS, Macklin EA, *et al.* Immunization of HIV-1-Infected Persons With Autologous Dendritic Cells Transfected With mRNA Encoding HIV-1 Gag and Nef: Results of a Randomized, Placebo-Controlled Clinical Trial. *JAIDS Journal of Acquired Immune Deficiency Syndromes* 2016;**71**:246–53. doi:10.1097/QAI.0000000000000852

11 Sahin U, Oehm P, Derhovanessian E, *et al.* An RNA vaccine drives immunity in checkpoint-inhibitor-treated melanoma. *Nature* 2020;**585**:107–12. doi:10.1038/s41586-020-2537-9

12 Papachristofilou A, Hipp MM, Klinkhardt U, *et al.* Phase Ib evaluation of a self-adjuvanted protamine formulated mRNA-based active cancer immunotherapy, BI1361849 (CV9202), combined with local radiation treatment in patients with stage IV non-small cell lung cancer. *J Immunother Cancer* 2019;**7**:38. doi:10.1186/s40425-019-0520-5

13 Eigentler T, Bauernfeind FG, Becker JC, *et al.* A phase I dose-escalation and expansion study of intratumoral CV8102 as single-agent or in combination with anti-PD-1 antibodies in patients with advanced solid tumors. *JCO* 2020;**38**:3096–3096. doi:10.1200/JCO.2020.38.15\_suppl.3096

14 Doener F, Hong HS, Meyer I, *et al.* RNA-based adjuvant CV8102 enhances the immunogenicity of a licensed rabies vaccine in a first-in-human trial. *Vaccine* 2019;**37**:1819–26. doi:10.1016/j.vaccine.2019.02.024

15 Translate Bio Announces Results from Second Interim Data Analysis from Ongoing Phase 1/2 Clinical Trial of MRT5005 in Patients with Cystic Fibrosis (CF). BioSpace. https://www.biospace.com/article/translate-bio-announces-results-from-second-interim-data-analysis-from-ongoing-phase-1-2-clinical-trial-of-mrt5005-in-patients-with-cystic-fibrosis-cf-/ (accessed 13 Oct 2022).

16 Burris HA, Patel MR, Cho DC, *et al.* A phase I multicenter study to assess the safety, tolerability, and immunogenicity of mRNA-4157 alone in patients with resected solid tumors and in combination with pembrolizumab in patients with unresectable solid tumors. *JCO* 2019;**37**:2523–2523. doi:10.1200/JCO.2019.37.15\_suppl.2523

17 Costello CL, Gregory TK, Ali SA, *et al.* Phase 2 Study of the Response and Safety of P-Bcma-101 CAR-T Cells in Patients with Relapsed/Refractory (r/r) Multiple Myeloma (MM) (PRIME). *Blood* 2019;**134**:3184–3184. doi:10.1182/blood-2019-129562

18 Gregory T, Cohen AD, Costello CL, *et al.* Efficacy and Safety of P-Bcma-101 CAR-T Cells in Patients with Relapsed/Refractory (r/r) Multiple Myeloma (MM). *Blood* 2018;**132**:1012. doi:10.1182/blood-2018-99-111419

19 Anttila V, Saraste A, Knuuti J, *et al.* Synthetic mRNA Encoding VEGF-A in Patients Undergoing Coronary Artery Bypass Grafting: Design of a Phase 2a Clinical Trial. *Mol Ther Methods Clin Dev* 2020;**18**:464–72. doi:10.1016/j.omtm.2020.05.030

20 Late-Breaking Science Abstracts and Featured Science Abstracts From the American Heart Association’s Scientific Sessions 2021 and Late-Breaking Abstracts in Resuscitation Science From the Resuscitation Science Symposium 2021. *Circulation* 2021;**144**:e564–93. doi:10.1161/CIR.0000000000001041

21 Gan L-M, Lagerström-Fermér M, Carlsson LG, *et al.* Intradermal delivery of modified mRNA encoding VEGF-A in patients with type 2 diabetes. *Nat Commun* 2019;**10**:1–9. doi:10.1038/s41467-019-08852-4