**Supplementary Table 1:** 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](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] |

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