COVID-19 – the Next Wave of Vaccines and Therapeutics

IQVIA Pipeline Intelligence

Population immunity gained from both vaccinations and infections has resulted in a steady decline in worldwide COVID-19 diagnoses and hospitalizations since the end of January 2022. However, COVID-19 remains highly transmissible and the emergence of new SARS-CoV-2 variants, including the Delta (B.1.617.2), Omicron (BA.1 and BA.2) variants and a Delta-Omicron recombinant virus (derived from the GK/AY.4 and GRA/BA.1 lineages), poses a challenge to the effectiveness of current vaccines.

According to the World Health Organization, the number of new weekly cases globally reported during the week of 7 to 13 March 2022 increased by 8% (over 11 million new cases) compared with the previous week (over 10 million cases), highlighting the importance of the continued development of next-generation vaccines and therapeutics.[1,2] This article will outline the latest key selected developments for COVID-19 treatments with data sourced from IQVIA Pipeline Intelligence, a proprietary drug pipeline database.

Key selected second-generation COVID-19 vaccines

Following the pharmaceutical industry's successes with the first-generation vaccines that were granted Emergency Use Authorizations/conditional approvals/full approvals for use in the prevention of COVID-19, focus has switched to developing second-generation vaccines to improve the immune response to emerging COVID-19 variants.

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Table 1: Key selected second-generation vaccines in development for COVID-19

INNOVATOR COMPANY	PRODUCT	PLATFORM	DESCRIPTION/TYPE	HIGHEST PHASE	STORAGE °C*
Novavax	NUVAXOVID (NVX CoV2373)	Protein subunit	VLP recombinant protein nanoparticle vaccine + Matrix-M adjuvant	Registered (EU and Canada)	2 to 8
Medicago	COVIFENZ (CoVLP)	Virus-like particles (VLP)	Plant-derived VLP adjuvant vaccine	Registered (Canada)	2 to 8
Valneva	VLA 2001	Inactivated whole virus	Inactivated whole virus adjuvant vaccine	Pre-registration (EU)	2 to 8
Gritstone bio	GRT R910	Self-amplifying mRNA	Self-amplifying mRNA vaccine	Phase I	2 to 8
Walter Reed Army Institute of Research (USA)	SpFN	Spike ferritin nanoparticle	Spike ferritin nanoparticle pan-coronavirus vaccine	Phase I	N/A
CureVac; GlaxoSmithKline	CV2CoV	mRNA	Optimized non-modified mRNA vaccine	Preclinical	5

*Storage details were obtained from the developer's official sources
Source: IQVIA Pipeline Intelligence

Despite the effectiveness of the first-generation vaccines, including BioNTech/Pfizer's COMIRNATY (LNP-encapsulated mRNA vaccine), Moderna's SPIKEVAX (LNP-encapsulated mRNA vaccine), Janssen Pharmaceuticals' JNJ 78436735 (non-replicating adenovirus vector vaccine) and the University of Oxford (UK)/AstraZeneca's VAXZEVRIA (non-replicating simian adenovirus vector vaccine), vaccine resistance due to variants in particular with the emergence of the BA.1 and BA.2 Omicron variants poses a major global health risk.[3]

NUVAXOVID – FIRST AUTHORIZATION FOR PROTEIN BASED COVID-19 VACCINE

Novavax's NUVAXOVID (NVX CoV2373), a Matrix-M protein subunit vaccine utilizing its proprietary recombinant nanoparticle technology platform, was granted conditional marketing authorization in the EU on 2 December 2021 and was later approved in Canada on 17 February 2022 for active immunization to prevent COVID-19 in individuals aged 18 years and older. Emergency Use Authorization has been granted in the USA and India, and the vaccine is pending approval in various countries for this indication. NUVAXOVID comprises antigens derived from the spike S protein of SARS-CoV-2. Data from the PREVENT-19 phase III trial showed that NUVAXOVID achieved an overall vaccine efficacy of 90.4% and 100% protection against moderate-to-severe COVID-19. The vaccine also had an 82.0% vaccine efficacy against the Delta variant and is being tested against the Omicron variant.[4,5,6]

COVIFENZ – FIRST APPROVED PLANT-DERIVED VACCINE AGAINST COVID-19

Medicago's COVIFENZ (CoVLP), a plant-derived vaccine composed of spike glycoprotein expressed as virus-like particles (VLP), was approved on 24 February 2022 in Canada for active immunization to prevent COVID-19 in individuals aged 18 to 64 years. The VLP vaccine is co-administered with GlaxoSmithKline's AS03 adjuvant as a two-dose vaccination regimen given intramuscularly 21 days apart. In a phase II/III trial (CP-PRO-CoVLP-021), COVIFENZ achieved an overall vaccine efficacy rate of 71.0% against all variants of SARS-CoV-2 in this trial, including a 75.3% efficacy against COVID-19 caused by the Delta variant. Medicago stated that COVIFENZ can be adapted to combat the Omicron BA.1 and BA.2 subvariants, and preliminary/exploratory data showed that the vaccine produced neutralizing antibodies against the Omicron variant.[7,8,9]

VLA 2001 – NOVEL INACTIVATED, ADJUVANTED WHOLE VIRUS VACCINE AGAINST COVID-19

Valneva's VLA 2001, an inactivated vaccine comprising whole virus particles of SARS-CoV-2 with high S-protein density in combination with two adjuvants alum and CpG 1018, is currently under rolling regulatory review

in the EU for primary immunization in adults aged 18 to 55 years against COVID-19. VLA 2001 is produced utilizing the company's proprietary Vero-cell platform and designed to target the whole virus instead of just the spike protein to elicit a broad immune response. VLA 2001 demonstrated superior immunogenicity against VAXZEVRIA based on geometric mean titer (GMT) for neutralization antibodies (GMT ratio = 1.39 versus 576.6; p less than 0.0001) in the CoV-Compare phase III trial. VLA 2001 could potentially be available in European countries in second quarter 2022, according to the company.[10,11,12]

GRT R910 – NOVEL SELF-AMPLIFYING mRNA VACCINE AGAINST COVID-19

Gritstone bio is developing a T cell enhance self-amplifying second-generation mRNA vaccine formulated with lipid nanoparticles, GRT R910, as a booster and immunogenicity enhancer of first-generation COVID-19 vaccines. GRT R910 is designed to optimize antigen expression at lower doses relative to conventional mRNA vaccines. It targets antigens from the spike protein and highly conserved non-spike proteins (viral proteins containing T cell epitopes) on the SARS-CoV-2 virus. The ability of self-amplifying mRNA to extend the duration and magnitude of antigen production potentially eliminates the need for repeat administrations and drives elicit broad immune responses across SARS-CoV-2 variants. A phase I trial (CORAL-BOOST) is ongoing evaluating the safety and immunogenicity of GRT R910 in healthy adults aged 60 years and older, including those who were previously vaccinated with VAXZEVRIA. Data from the first cohort (10 mcg GRT R910) of the CORAL-BOOST trial were reported in January 2022, which showed that a single dose of 10 mcg GRT R910 induced neutralizing antibody titers and elicited broad CD8+ T cell responses against conserved non-spike SARS-CoV-2 epitopes and boosted pre-existing spike-specific T cells in 10 individuals who had received two prior doses of VAXZEVRIA.[13,14]

SPFN – NOVEL PAN-CORONAVIRUS VACCINE

Researchers at the Walter Reed Army Institute of Research (USA) are developing SpFN, a spike ferritin nanoparticle pan-coronavirus vaccine against COVID-19 and all its variants. The vaccine is designed to recognize multiple spike proteins at once by utilizing ferritin, which has a structure with 24 sides, all of which can attach to a different viral protein. By using ferritin in a pan coronavirus vaccine, the nanoparticle can produce various coronavirus antigens not just from SARS-CoV-2 variants but other coronavirus species. In preclinical studies, SpFN demonstrated immune responses against several variants of SARS-CoV-2 in primates immunized with SpFN and the original SARS virus from 2002. A phase I trial was completed in December 2021.[15]

Despite the effectiveness of the first-generation vaccines, vaccine resistance due to variants in particular with the emergence of the BA.1 and BA.2 Omicron variants poses a major global health risk.[3]

CV2COV – NON-CHEMICALLY MODIFIED, ENHANCED mRNA VACCINE AGAINST COVID-19

CureVac and GlaxoSmithKline's CV2CoV, a second-generation mRNA vaccine, is currently in preclinical development. CV2CoV contains non-modified nucleosides but with optimized non-coding regions and is engineered to improve RNA stability to enhance antigen expression of SARS-CoV-2. In November 2021, preclinical data were reported, which demonstrated that macaques immunized with 12 mcg CV2CoV achieved better activation of innate and adaptive immune responses, which resulted in earlier response onset, higher antibody titers and stronger memory B and T cell activation compared with immunization with 12 mcg CVnCoV (the companies' first-generation mRNA vaccine). Higher antibody neutralizing capacity was observed with CV2CoV across a range of relevant variants, including the Delta variant. In addition, the immunogenicity of CV2CoV (12 mcg) was comparable to COMIRNATY (30 mcg). CV2CoV is expected to enter clinical testing with a phase I trial in seropositive adults planned to commence in March 2022.[16,17]

Key selected antivirals and monoclonal antibodies for COVID-19

As the effects of COVID-19 continue to grow, researchers have also focused on developing other drug types to treat COVID-19, including antivirals to inhibit replication of SARSCoV-2, neutralizing monoclonal antibodies due to their high specificity to the receptor-binding domain of the SARS-CoV-2 spike protein and other novel therapeutics.

LAGEVRIO – FIRST ORAL ANTIVIRAL FOR COVID-19

Merck & Co and Ridgeback Biotherapeutics' LAGEVRIO (molnupiravir), an orally bioavailable form of a ribonucleoside analog, was approved in the UK on 4 November 2021 to treat mild-to-moderate COVID-19, becoming the first oral antiviral medicine authorized for this disease. LAGEVRIO is designed to inhibit the replication of multiple RNA viruses including SARS-CoV-2 and is an important addition to the armamentarium against COVID-19 as it can be administered outside the hospital setting. LAGEVRIO has subsequently been approved in Japan (December 2021) and Australia (January 2022), granted Emergency Use Authorization in the USA (December 2021) and Mexico (January 2022), and is under rolling regulatory review in the EU since October 2021 for this indication.[18]

EVUSHELD – FIRST MONOCLONAL ANTIBODY TREATMENT FOR PREVENTION OF COVID-19

AstraZeneca's EVUSHELD, a long-acting monoclonal antibody combination of tixagevimab and cilgavimab, was granted approval in the UK as the first antibody treatment for pre-exposure prophylaxis against COVID-19 in adults and adolescents aged 12 years and older. Tixagevimab and cilgavimab are derived from B-cells donated by convalescent COVID-19 patients. The approval was based on data from the PROVENT phase III trial, which showed that EVUSHELD achieved an 83.0% relative risk reduction in the incidence of symptomatic COVID-19 after a median follow-up of 6.5 months. The monoclonal antibody combination has been recommended for approval in the EU and was granted Emergency Use Authorization in the USA for this indication.[19,20]

BEBTELOVIMAB – MONOCLONAL ANTIBODY THAT RETAINS ACTIVITY AGAINST OMICRON

Lilly's bebtelovimab, a neutralizing IgG1 monoclonal antibody targeting the spike protein of SARS-CoV-2, is being developed for the treatment of mild-to-moderate COVID-19 as a monotherapy and in combination with other monoclonal antibodies. The monoclonal antibody was granted Emergency Use Authorization on 11 February 2022 in the USA for non-hospitalized adult and pediatric patients (aged 12 years and older) with mild-to-moderate COVID-19. Data from

Table 2: Key selected therapies in development for COVID-19

INNOVATOR COMPANY	DRUG NAME	MODE OF ACTION/ROUTE OF ADMINISTRATION	PRODUCT TYPE	HIGHEST PHASE
Merck & Co; Ridgeback Biotherapeutics	LAGEVRIO (Molnupiravir)	RNA polymerase inhibitor; oral administration	Ribonucleoside analog	Registered (UK, Japan and Australia)
AstraZeneca	EVUSHELD (tixagevimab + cilgavimab)	Neutralizing antibodies; intramuscular injection	Dual monoclonal antibody combination	Registered (UK)
Lilly	Bebtelovimab	Neutralizing IgG1 antibody to SARS-CoV-2 spike protein; IV administration	Monoclonal antibody	Emergency Use Authorization (USA)
Memo Therapeutics	COVAB 36	Inhaled SARS-CoV-2-neutralizing antibody	Monoclonal antibody	Preclinical
Cocrystal Pharma	CDI 988; CDI 873	3CL protease inhibitors; oral administration	Small molecules	Preclinical

Source: IQVIA Pipeline Intelligence

the BLAZE-4 phase II trial showed that bebtelovimab maintained binding and neutralizing activity across currently known and reported variants of SARS-CoV-2, including Omicron BA.2.[21]

COVAB 36 – NOVEL INHALED MONOCLONAL ANTIBODY FOR COVID-19

Memo Therapeutics is developing COVAB 36, an inhaled humanized monoclonal antibody for the treatment of COVID-19. COVAB 36 was identified using a microfluidic single-cell molecular cloning and screening system and was found to neutralize all variants of SARS-CoV-2 prior to Omicron in preclinical studies; tests against Omicron are currently being conducted by the company. According to Memo Therapeutics, its antibody discovery platform allows for rapid antibody repertoire mining and the fast development of a combination antibody to partner COVAB 36 targeted against emerging variants. Phase I evaluation is expected to commence in first quarter 2022.[22]

CDI 988 AND CDI 873 – NOVEL BROAD SPECTRUM ANTIVIRAL DRUGS FOR COVID-19

Cocrystal Pharma's CDI 988 and CDI 873, oral antiviral therapies targeting a conserved region in the active site of SARS-CoV-2 main (3CL) protease required for viral RNA replication, are under preclinical evaluation for the treatment of COVID-19. In preclinical studies, both CDI 988 and CDI 873 demonstrated in vitro potency against SARS-CoV-2 with activity maintained against current variants of SARS-CoV-2 including Omicron. Cocrystal plans to initiate a first-in-human trial with one selected candidate later in 2022.[23]

Future directions

Two years into the COVID-19 pandemic, the emergence of potent variants has highlighted the need for newer and different vaccines that improve benefit. Researchers have made advances with the development of recombinant VLP vaccines which have repetitive surface patterns enabling the triggering of strong immune responses, plant-based vaccines that can be rapidly produced and stored for a longer period of time and self-amplifying RNA vaccines that have enhanced antigen expression at lower doses compared with conventional mRNA. However, further innovations are urgently required to develop more effective vaccines and ultimately a pan-coronavirus vaccine that can protect against all SARS-CoV-2 variants and multiple types of coronaviruses. In conjunction with vaccines, the development of therapies could also form an additional strategy to combat COVID-19 and treat individuals who are infected.[24,25]

Further innovations are urgently required to develop more effective vaccines and ultimately a pan-coronavirus vaccine that can protect against all SARS-CoV-2 variants and multiple types of coronaviruses.

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