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The PHH-1V HIPRA vaccine: a new tool in the vaccination strategy against COVID-19

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ABSTRACT

Objectives. Vaccination against SARS-CoV-2 is essential to mitigate the personal, social and global impact of the coronavirus disease (COVID-19) as we move from a pandemic to an endemic phase. Vaccines are now required that offer broad, long-lasting immunological protection from infection in addition to protection from severe illness and hospitalisation. Here we present a review of the evidence base for a new COVID-19 vaccine, PHH-1V (Bimervax®; HIPRA HUMAN HEALTH S.L.U), and the results of an expert consensus.

Materials and methods. The expert committee consisted of Spanish experts in medicine, family medicine, paediatrics, immunology, microbiology, nursing, and veterinary medicine. Consensus was achieved using a 4-phase process consisting of a face-to-face meeting during which the scientific evidence base was reviewed, an online questionnaire to elicit opinions on the value of PHH-1V, a second face-to-face update meeting to discuss the evolution of the epidemiological situation, vaccine programmes and the scientific evidence for PHH-1V and a final face-to-face meeting at which consensus was achieved.

Results. The experts agreed that PHH-1V constitutes a valuable novel vaccine for the development of vaccination programmes aimed towards protecting the population from SARS-CoV-2 infection and disease. Consensus was based on evidence of broad-spectrum efficacy against established and emerging SARS-CoV-2 variants, a potent immunological response, and a good safety profile. The physicochemical properties of the PHH-1V formulation facilitate handling and storage appropriate for global uptake.

Conclusions- The physicochemical properties, formulation, immunogenicity and low reactogenic profile of PHH-1V confirm the appropriateness of this new COVID-19 vaccine.

Keywords: COVID-19, immunogenicity; recombinant protein vaccine

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La vacuna PHH-1V de HIPRA: una nueva herramienta en la estrategia contra la COVID-19

Objetivos. La vacunación frente al SARS-CoV-2 es fundamental para mitigar el impacto personal, social y global de la enfermedad por coronavirus (COVID-19) a medida que pasamos de una fase pandémica a una endémica. Actualmente se requieren vacunas que ofrezcan una protección inmunológica amplia y duradera contra la infección, además de proteger de la enfermedad grave y la hospitalización. En este artículo se presenta una revisión de la evidencia científica para una nueva vacuna COVID-19, PHH-1V (Bimervax®; HIPRA HUMAN HEALTH S.L.U) y los resultados de un consenso de expertos.

Material y métodos. El comité de expertos incluyó expertos españoles en medicina, medicina de familia, pediatría, inmunología, microbiología, enfermería y veterinaria. El consenso se logró mediante un proceso de 4 fases que constó de una reunión presencial durante la cual se revisó la evidencia científica, un cuestionario en remoto para obtener opiniones

sobre el valor de PHH-1V, una segunda reunión presencial de actualización y discusión sobre la evolución de la situación epidemiológica, los programas de vacunas y la evidencia científica para PHH-1V y una última reunión presencial en la que se obtuvo el consenso.

Resultados. Los expertos coincidieron en que PHH-1V constituye una vacuna novedosa y valiosa para el desarrollo de programas de vacunación destinados a proteger a la población de la infección y enfermedad por SARS-CoV-2. El consenso se basó en la evidencia del amplio espectro de eficacia contra las variantes establecidas y emergentes del SARS-CoV-2, una respuesta inmunológica potente y un buen perfil de seguridad. Las propiedades fisicoquímicas de la formulación de PHH-1V facilitan la manipulación y el almacenamiento apropiados para la absorción global.

Conclusiones. Las propiedades fisicoquímicas, formulación, inmunogenicidad y bajo perfil reactogénico de PHH-1V confirman la idoneidad de esta nueva vacuna COVID-19.

Palabras clave: COVID-19, inmunogenicidad; vacuna proteína recombinante

INTRODUCTION

Coronavirus disease (COVID-19) is a highly transmissible infectious disease caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) [1]. The virus was first detected as a human pathogen in China in late 2019 [2]. On 30th January 2020 the World Health Organization (WHO) defined that the outbreak of the novel coronavirus constituted a Public Health Emergency of International Concern and declared it as a pandemic on 11th March 2020. On 14th March 2020, the Spanish Government approved Royal Decree 463/2020 declaring a State of Alarm, with drastic measures to protect the health of citizens, contain the spread of SARS-CoV-2 and reinforce the National Health System. Among these measures were the limitation of mobility and free movement of people, home confinement and the closure of various economic activities.

As of March 2023, over 13.7 million confirmed SARS-CoV-2 cases have been reported in Spain. The burden of this pandemic has fallen disproportionately on older and vulnerable adults [3]. Of the 13.5 million confirmed cases in Spain by November 2022, 2.9 million (21%) were among people aged >60 years. Moreover, the risk for severe illness following SARS-CoV-2 infection increases with age and the presence of underlying medical conditions. Currently, the incidence of severe cases of COVID-19 and the number of hospitalisations due to this disease have fallen or stabilised in most countries. This is due, in large part, to active immunisation campaigns using existing vaccines which have proven to be highly effective in reducing hospitalizations due to severe COVID-19-related illness and COVID-19-related deaths. However, the precise case fatality rate remains obscured as it is calculated based on confirmed cases and is therefore influenced by the ability of the system to detect and quantify deaths due to COVID-19 illness and by the ability to confirm and detect all cases of the disease, including asymptomatic cases [4].

Vaccination against SARS-CoV-2 is essential to mitigate the personal, social and global impact of this disease as we move from a pandemic to an endemic phase [1,5,6]. The aim of the national, European and global vaccination strategy has been to reduce the incidence of severe COVID-19-related illness and the associated hospitalisations and deaths, thereby reducing the health and socio-economic impact of this disease. Many national vaccination strategies have prioritised members of the population with the greatest risk for severe illness and death – those of older age and with underlying health conditions. However, the emergence and circulation of different SARS-CoV-2 variants with different mutations affecting the transmissibility of the virus, has impacted the efficacy of currently available vaccines. Additionally, there is evidence of a poor immune response among individuals who are already immunocompromised [7]. Although primary vaccination offers high protection against severe disease, national and international studies using mRNA COVID-19 vaccines show a reduction in effectiveness in adults from 3–6 months post-vaccination, especially in terms of infection rates [8]. Consequently, most national vaccine strategies include additional booster doses with either the same vaccine class (homologous booster) or a different vaccine class (heterologous booster) as both approaches have proven to provide appropriate immunogenicity [9,10]. The benefit of a booster dose against severe disease is most evident among people aged ≥60 years and those younger with underlying diseases, while among those aged <60 years the benefit is most apparent in terms of the rate of symptomatic infection [11].

To date, the most widely used vaccine technology for primary and booster vaccination programmes against SARS-CoV-2 has been mRNA-based, particularly in Europe, with adenoviral vector-based vaccines also used in some countries [4]. These technologies offered a rapid route to vaccine development and manufacture to address the urgent need for immunological protection against the severe illness and death caused by a pandemic virus. The focus is now beginning to move beyond these immediate needs to the development of vaccines that also offer broad and long-lasting immunological protection from infection using established vaccine development technologies. One such established technology is adjuvanted recombinant protein vaccines, a technology used safely and effectively for vaccination against hepatitis B, human papilloma virus and influenza [12].

The SARS-CoV-2 pandemic also highlighted the importance of National-level vaccine development to complement international efforts and ensure country-level preparedness for future health crises. The vaccination strategy against COVID-19 in Spain has been modified as vaccines have been authorised and become available for use, in accordance with advances in scientific knowledge and epidemiological changes as the pandemic has evolved. On 30th March 2023, the European Medicines Agency (EMA) recommended approval of Bimervax® (PHH-1V) from HIPRA HUMAN HEALTH S.L.U as a COVID-19 booster vaccine [13,14]. PHH-1V is an adjuvanted recombinant protein vaccine based on the receptor binding domain (RBD) sequences of the Beta and Alpha variants of SARS-CoV-2 [13].

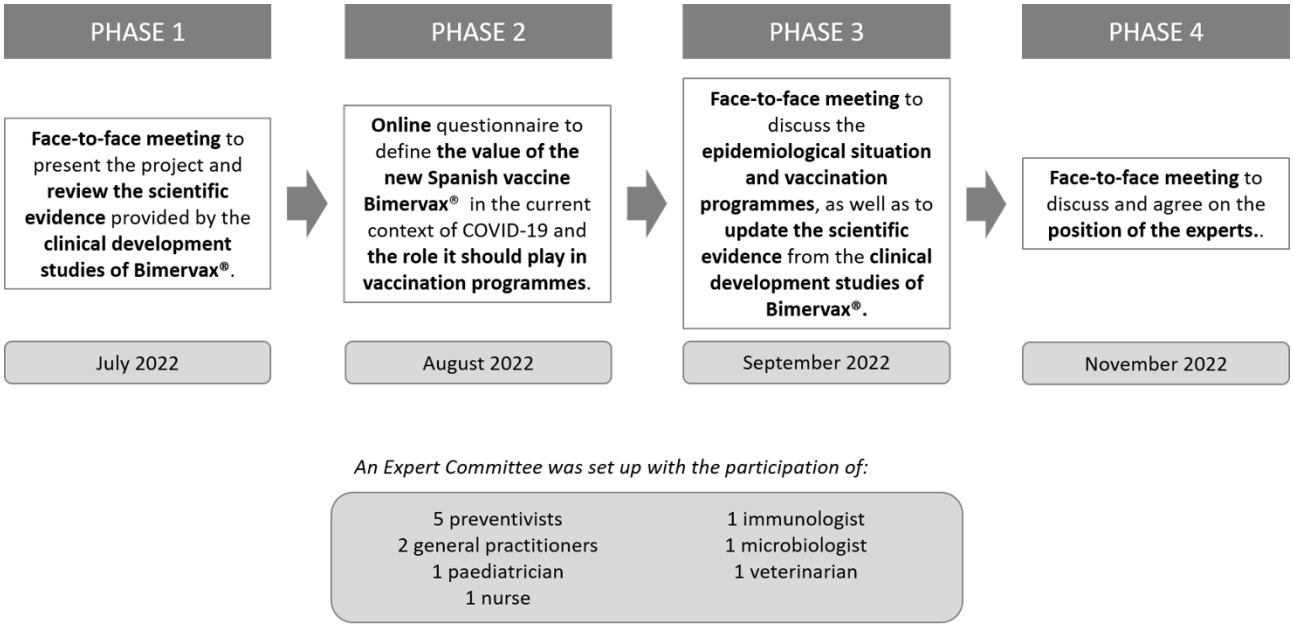

Figure 1 | **Four-phase process for review of the scientific evidence and consensus development**

The aim of this work was to present a review of the evidence base for PHH-1V and the consensus among vaccine experts on the utility of the new vaccine PHH-1V in the current context of COVID-19 illness prevention, and the role that this new vaccine should play in the implementation of booster vaccination programmes.

MATERIAL AND METHODS

An expert committee was convened consisting of Spanish experts in preventive medicine (n=5), family medicine (n=2), paediatrics (n=1), immunology (n=1), microbiology (n=1), nursing (n=1) and veterinary medicine (n=1). Consensus was achieved using a 4-phase process (Figure 1). Phase 1 consisted of a face-to-face meeting during which the scientific evidence base, consisting of the clinical development studies of PHH-1V, was reviewed. Phase 2 consisted of an online questionnaire to elicit opinions on the value of PHH-1V in the current context of the COVID-19 pandemic from the perspective of vaccine formulation, efficacy, safety and storage characteristics, and the role it should play in vaccination programmes. Phase 3 was a face-to-face update meeting to discuss the evolution of the epidemiological situation, vaccine programmes and the scientific evidence for PHH-1V. Consensus was achieved during a final face-to-face meeting.

RESULTS

Vaccine formulation. PHH-1V is formulated as an emulsion for intramuscular injection [15]. The active substance is a fusion heterodimer based on the SARS-CoV-2 RBD, which includes the B.1.351 (Beta) and B.1.1.7 (Alpha) variants fused into a single peptide via recombinant DNA technology (Figure 2a) [13]. The peptide is expressed in a Chinese Hamster Ovary (CHO) cell line. Each individual dose consists of 0.5 mL of vaccine containing 40 µg of the active substance in phosphate buffered saline supplemented with a squalene (SQBA) adjuvant consisting of an inner oil phase of squalene and an outer aqueous phase of sodium citrate-citric acid buffer.

Expert consensus: The PHH-1V dimer includes key mutations (K417N, E484K and N501Y) which were present in the latest Variants Of Concern (VOC) [16–19] and may play a role in cross-neutralization (Figure 2b). The adjuvant has the role to enhance and induce an earlier, more robust and long-lasting immune response against the recombinant RBD. The ready-to-use formulation without the need for reconstitution prior to use will be of benefit for vaccination programmes.

Clinical evaluation of PHH-1V. The safety and immunogenicity of PHH-1V has been evaluated in a double-blind, Phase 2b randomised, controlled, non-inferiority clinical trial (NCT05142553) as a heterologous booster to subjects who had previously received the complete course of the mRNA-based COVID-19 monovalent vaccine BNT162b2 (Cominarty®; Pfizer-BioNTech) at least 182 days prior to the booster dose [20]. The control arm of the study consisted of a homologous booster dose. The study was conducted at multiple centres in Spain and included 782 healthy adults (≥18 years of age) who were randomised either to receive PHH-1V or the mRNA vaccine. The primary outcome measures were immunogenicity against

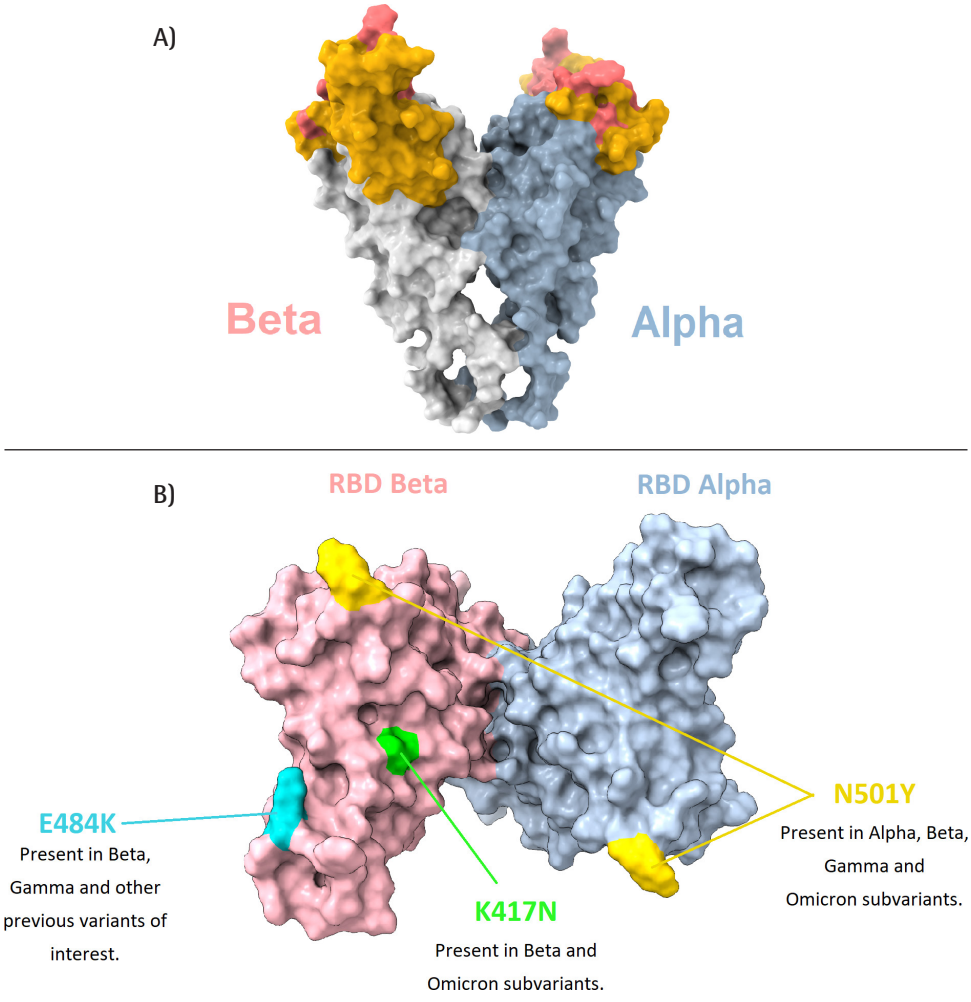

Figure 2 | **a) PHH-1V antigen: recombinant protein based on the receptor binding domain (RBD) sequences of the Beta and Alpha variants of SARS-CoV-2. b) Top view of the PHH-1V antigen and locations of key mutation that are present in most relevant VOC at present. Adapted from iScience [13]**

the Wuhan-Hu-1 strain of SARS-CoV-2 (neutralisation titre measured as the individual inhibitor concentration [IC_{50}] and geometric mean titre [GMT] from baseline to Day 14) and tolerability. Secondary endpoints included immunogenicity against additional SARS-CoV-2 variants of concern (Beta, Delta and Omicron BA.1) and the T-cell response towards the spike glycoprotein of SARS-CoV-2. The study has been recently completed and interim data are available for 782 subjects, 522 of whom received PHH-1V and 260 who received BNT162b2, with follow-up to Day 182 (6 months) [15]. The safety evaluation consisted of adverse event monitoring (safety population n=765 [PHH-1V n=513, BNT162b2 n=252]). The majority of subjects in both vaccine groups reported at least one adverse event (PHH-1V 89.3% of subjects, BNT162b2 94.4% of subjects). The most frequently reported adverse events to Day 28 in both vaccine groups were injection site pain (79.7% and 89.3%, respectively), fatigue (27.5% and 42.1%, respectively) and headache (31.2% and 40.1%, respectively). The overall frequency of adverse events was statistically significantly lower among subjects who received PHH-1V than among those who received BNT162b2 (Table 1) [20]. The majority of adverse events in both groups were mild. A non-inferior neutralising antibody response against the original Wuhan-Hu-1 strain was achieved for PHH-1V compared with BNT162b2 at Day 98 and superiority at Day 182 after immunisation [15,20]. PHH-1V achieved statistically significantly superior neutralising antibody responses at Days 14, 28, 98 and 182 against the Beta and Omicron BA.1 variants and at Days 98 and 182 against the Delta variant compared to BNT162b2 [15,20]. A robust T cell response was observed on Day 14 with a significant increase in interferon-gamma (IFN-γ) expression by CD4+ and CD8+ T cells [20]. A Phase 3 study is also ongoing (NCT05246137) in which 2,646 subjects aged ≥16 years received

Table 1 Frequency of Adverse Events by Treatment Group among the safety population

	PHH-1V (N=513)	BNT162b2 (N=252)	OR (95% CI)	p value*
Total Adverse Events	1581; 458 (89.3)	1061; 238 (94.4)	0.49 [0.26, 0.91]	**0.0219**
Injection site pain	748; 409 (79.7)	466; 225 (89.3)	0.47 [0·30, 0.75]	**0.0010**
Headache	193; 160 (31.2)	122; 101 (40.1)	0.68 [0.49, 0.94]	**0.0190**
Fatigue	166; 141 (27.5)	115; 106 (42.1)	0.52 [0.38, 0.72]	**0.0001**
Myalgia	107; 100 (19.5)	93; 86 (34.1)	0.47 [0.33, 0.66]	**0.0001**
Injection site induration	45; 44 (8.6)	44; 43 (17.1)	0.46 [0.29, 0.72]	**0.001**
Injection site erythema	33; 33 (6.4)	37; 36 (14.3)	0.41 [0.25, 0.70]	**0.0007**
Intensity				
Mild	1382; 342 (66)	885; 146 (57.9)	1.45 [1.06, 1.98]	**0.02**
Moderate	187;108 (21)	165; 85 (33.7)	0.52 [0.37, 0.74]	**0.0002**
Severe	12; 8 (1)	11; 7 (2.8)	0.55 [0.20, 1.74]	0.27
Serious Adverse Events (SAEs)	1; 1 (0)	0; 0 (0.0)	∞ [0.03, ∞]	1
Treatment-related Adverse Events	1384; 434 (84)	975; 231 (91.7)	0.5 [0.29, 0.83]	**0.0061**
COVID-19 cases ≥ 14 days post-booster	52; 52 (10)	31; 30 (11.9)	0.83 [0.51, 1.36]	0.45

Data are shown as the "total number of events; total number of subjects (percentage)". For the total adverse events, only those events with a frequency ≥ 10% of treated patients are shown. OR=Odds ratio and p-value of Fisher's exact test are shown to compare between groups. In bold, statistically significant differences. Adapted from Lancet Regional Health- Europe [20]

PHH-1V as a booster vaccination following primary immunisation with either an mRNA or an adenovirus-based vaccine. In the preliminary results of that Phase 3 study, PHH-1V induced a strong humoral response at Day 14 after immunization independently of the previous vaccination (BNT162b2, ChAdOx1-S [Vaxzevria®, AstraZeneca, UK], mRNA 1273 [SPIKEVAX®, Moderna Biotech, Spain], Ad26.COV2-S [Jcovden®, Jannsen-Cilag International NV]), with no differences in safety profile [15,21]. Serum samples from individuals vaccinated with PHH-1V are being further evaluated for neutralising antibody responses against the Omicron BA.4 and BA.5 sub-variants. Those preliminary results indicate potent immunogenic responses against these sub-variants 14 days after the booster vaccination [22].

Expert consensus: The data from the Phase 2b study indicate a potent humoral response of PHH-1V from Day 14 up to 6 months after immunisation when administered as a booster vaccine in individuals previously vaccinated with BNT162b2 [15,20]. The safety data from the Phase 2b trial support an acceptable safety profile for PHH-1V with statistically fewer adverse events reported by subjects compared with BNT162b2 [20]. Together, the clinical trial results available to date indicate a robust humoral response against all variants studied (Wuhan-Hu-1, Beta, Delta and Omicron BA.1) at 6 months and against Omicron BA.4 and BA.5 variants at Day 14 [15,20]. The robust T cells responses observed following booster vaccination with PHH-1V are encouraging as such responses are critical to confer protection against severe COVID-19 disease as cell-mediated immunity specifically destroys virus-infected cells [23].

Storage characteristics. PHH-1V must be stored at 2ºC to 8ºC with a shelf-life of 12 months [15].

Expert consensus: PHH-1V does not require freezing or deep-freezing during distribution or onsite storage. The one-year shelf-life at temperatures of 2ºC to 8ºC facilitates storage and distribution within different logistical and healthcare situations and reduces costs compared with vaccines requiring freezing/deep freezing during storage and distribution. The logistical advantages are particularly important for any vaccination programme and specially for developing countries and geographic areas that are difficult to access.

Indication. PHH-1V has been approved by EMA for its use in people aged >16 years as a booster vaccination against COVID-19 [15]. Future studies will evaluate the potential for PHH-1V as a primary vaccination and in people aged <16 years. Also, additional evidence in pregnant women and immunocompromised individuals will be assessed.

Expert consensus: No further limitations of use are expected from other evaluation bodies.

Finally, Table 2 summarises the main characteristics of the PHH-1V vaccine.

Table 2 Characteristics of the PHH-1V vaccine (Bimervax®; HIPRA Scientific, S.L.U. and Laboratorios HIPRA, S.A., Spain) [15]

Formulation	Emulsion for intramuscular injection Recombinant protein adjuvanted vaccine based on the receptor binding domain (RBD) sequences of the Beta and Alpha variants of SARS-CoV-2
Handling	Ready-to-use preparation, no requirement for reconstitution prior to use
Storage	Must be stored between 2ºC and 8ºC
Shelf-life	12 months when stored between 2ºC and 8ºC
Dosing	Single-dose
Safety	Low reactogenicity
Effectiveness	Long duration of immunity demonstrated in clinical trials. At 6 months, individuals who received a booster dose of PHH-1V had significantly higher neutralising antibody titres than those who received the BNT162b2 mRNA vaccine against all variants tested (Wuhan, Beta, Delta and Omicron BA.1)
Protection against new variants	Broad spectrum protection against all variants studied to date (Wuhan, Beta, Delta. Omicron BA.1 and Omicron BA.4/5)
Authorisation	Initial license is for use as a booster dose in people aged ≥16 years previously vaccinated with a mRNA vaccine

DISCUSSION

Mass vaccination programmes against SARS-CoV-2 have drastically reduced the global mortality and morbidity associated with the pandemic [1]. However, the current epidemiological situation at a global or European level cannot be considered completely under control. Since the beginning of the pandemic more than 1,850 SARS-CoV-2 lineages have been identified worldwide, with 9 variants of the virus and their descendant lineages considered of concern [16]. The ancestral Wuhan strain was followed by the Alpha, Beta, Gamma, and Delta variants, and, more recently, by the Omicron variants. The Omicron variant has given rise to a number of highly transmissible sub-variants able to evade natural or vaccine-induced immunity to varying degrees [24,25]. For this reason, second-generation vaccines are now required that generate neutralising immune responses against a wider range of variants to minimize the potential immune escape capability of potential future variants and with longer duration of humoral immunity. In addition to demonstrating robust immune responses in previously unvaccinated individuals, future vaccine candidates must also demonstrate immunogenicity in individuals previously vaccinated with the same type of vaccine (homologous booster) or a different type (heterologous booster). A previous study demonstrated a highly immunogenic response following real-world heterologous booster vaccination with the mRNA-based BNT162b2 vaccine and the adenoviral vector-based ChAd-BNT (AstraZeneca, UK) vaccine [26]. Indeed, data are emerging to suggest a more robust immune response may be elicited through heterologous booster vaccination [27–29]. But a recent Cochrane report points out the complexity to stablish comparisons between studies with different vaccination schedules, vaccines, and time endpoints, concluding that further studies on heterologous vaccination are needed. A favourable reactogenicity profile and prolonged duration of action are also beneficial to support coverage and compliance with national vaccination programs. Storage and shelf-life characteristics are also important features of future SARS-CoV-2 vaccines to enable distribution within different national and supply chain situations [30].

PHH-1V is based on a fusion heterodimer protein consisting of the RBD of two SARS-CoV-2 variants, Beta and Alpha, that elicits high and long-lasting levels of neutralising antibodies against all studied variants, as well as a strong cellular immunity response, when used as heterologous booster in previously vaccinated individuals with mRNA and vector vaccines [15,20,22]. These features along with a favourable reactogenicity profile, ready- to-use formulation without the need for reconstitution, storage at 2ºC to 8ºC and a prolonged shelf-life mean that PHH-1V is a suitable, next generation vaccine option for either annual, seasonal, or targeted immunisation programmes against SARS-CoV-2 to improve the protection of high-risk groups. The favourable reactogenicity profile for PHH-1V may be of relevance in the context of the slowing of the uptake of SARS-CoV-2 booster vaccinations reported in many countries worldwide [31,32].

Two other recombinant protein SARS-CoV-2 vaccines have been also approved for use, NVX-CoV2373 (Novavax) and MV B.1.351 (Sanofi-GSK). Both vaccines have demonstrated robust immunogenicity against common variants, including B.1.1.7, and acceptable safety profiles [33,34]. MV B.1.351 has demonstrated robust immunogenicity when given as a heterologous booster vaccination in individuals previously vaccinated with the mRNA-based BNT162b2 vaccine [34]. Subtle difference in terms of the mechanisms by which the different vaccine classes (mRNA-, adenoviral vector- and recombinant protein-based) elicit immune response have emerged [35]. Studies are now needed to determine whether these sub-

tle differences have implications for the ways in which these vaccines are deployed, for example, whether individuals who are immunocompromised might benefit preferentially from an adjuvanted vaccine. Adjuvanted vaccines induce high levels of protective antibodies, long-lasting immune response of memory cells and a higher degree of cross-immunisation than do non-adjuvanted [36–41]. The improved amplitude of the response achieved with adjuvanted versus non-adjuvanted vaccines may offer an advantage in the face of antigenic drift such as is being observed for the SARS-CoV-2 virus.

In summary, PHH-1V is a bivalent, adjuvanted vaccine based on an established technology, with a broad-spectrum efficacy against established and emerging SARS-CoV-2 variants and elicits a prolonged neutralising antibody response. The physicochemical properties of the PHH-1V formulation facilitate handling and storage appropriate for global uptake. As such, PHH-1V constitutes a valuable novel vaccine for the development of national vaccination programmes aimed towards protecting the population from SARS-CoV-2 infection and disease.

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CONFLICTS OF INTERESTS

- Gloria Mirada Masip: has received honoraria from Pfizer, GSK, MSD, Sanofi and HIPRA for educational activities and advise.
- Ángel Gil de Miguel has received honoraria for conferences and consultancy services from Sanofi, MSD, GSK, Seqirus, Moderna, HIPRA, AstraZeneca and Pfizer.
- María Fernández-Prada has received honoraria from Pfizer, GSK, Seqirus, MSD, HIPRA, Sanofi and Sanofi-Genzyme as member of advisory boards and speaker in educational activities.
- Carmen Cámara Hijón has received honoraria from Pfizer and HIPRA as advisor.
- Fernando Moraga-Llop has received honoraria from Pfizer, GSK, MSD and HIPRA as advisor and speaker in educational activities.
- Jorge Vázquez is full-time employee at VINCES consultancy working for HIPRA as advisor.
- Joan Puig-Barberá has received honoraria from CSL, Novavax, Sanofi and HIPRA as advisor and speaker in educational activities.
- Júlia Vergara-Alert has received institutional grants and/or financial support from Grifols, HIPRA, Rokote laboratories, Dentaid, and PharmaMar.
- Cristina Borralleras and Salomé de Cambra are employees of HIPRA.
- Daniel Ocaña Rodríguez has received honoraria from Pfizer, GSK, Seqirus, MSD, HIPRA, Sanofi and Sanofi-Genzyme as member of advisory boards and speaker in educational activities.
- Pilar Arrazola has received honoraria from HIPRA as advisor.
- Javier Castrodeza Sanz has received honoraria from Pfizer, GSK, AstraZeneca, Seqirus, Sanofi and HIPRA as scientific advisor and speaker in educational activities.
- José Mª Eiros has received honoraria from AstraZeneca, BioMerieux, HIPRA, GSK, Pfizer, Sanofi and, Seqirus as advisor, researcher, and speaker in educational activities.

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