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Safety and immunogenicity of a *Klebsiella pneumoniae* tetravalent bioconjugate vaccine (Kleb4V) administered to healthy adults: A first time in human phase I/II randomised and controlled study

C. Alaimo[1,1], N. Karaky[2], R. Lawrence[2], E. Bownes[2], S. Haffner[3], M. Kowarik[1], D. Goldblatt[2], P. Martin[1]

[1]LimmaTech Biologics AG, Grabenstrasse 3, 8952 Schlieren, Switzerland; [2]Great Ormond Street Institute of Child Health, University College London, London, UK; [3]Nuvisan GmbH, Wegenerstraße 13, 89231 Neu-Ulm, Germany

Background: Safe and effective vaccines are urgently needed to prevent infections caused by *Klebsiella pneumoniae* (*K. pneumoniae*), one of the most common antibiotic-resistant pathogens. We aimed to assess the safety and immunogenicity of a tetravalent bioconjugate vaccine Kleb4V, containing O antigen-polysaccharides of the most predominant *K. pneumoniae* serotypes (O1v1, O2a, O2afg and O3b).

Methods: In this observer-blind, randomised, placebo-controlled, phase I/II trial [ClinicalTrials.gov (number NCT04959344)], 166 healthy adults (18-40y n=16, 55-70y n=150) were enrolled and randomised to receive two intramuscular injections of Kleb4V (16µg or 64µg of total O-antigen +/- adjuvant AS03) or placebo on days 1 and 57. While the primary outcome was safety, the secondary outcomes included vaccine antigen immunogenicity.

Results: Kleb4V was well tolerated, with most solicited and unsolicited AEs of mild to moderate intensity. Kleb4V was immunogenic for all four vaccine-serotypes at both antigen doses. O1v1,

Corresponding Author: Professor David Goldblatt, Great Ormond Street Institute of Child Health, University College London 30 Guilford Street, London, WC1N 1EH, United Kingdom, Email d.goldblatt@ucl.ac.uk
Alternate Corresponding Author: Cristina Alaimo Cristina.Alaimo@lmtbio.com

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O2a and O2afg specific IgG increased two weeks after the 1st vaccination and the immune response persisted at six months after the second vaccination. For three of the four vaccine-serotypes, the AS03-adjuvanted formulations showed a superior immune response. O3b responses were reduced compared to the other vaccine antigens.

Discussion: Kleb4V is the first *K. pneumoniae* conjugate vaccine candidate to reach clinical assessment. The Kleb4V bioconjugate was immunogenic, well tolerated and with an acceptable safety profile in the target population of adults aged 55-70 years for all 4 vaccine-serotypes.

Keywords: *Klebsiella pneumoniae*, O-antigen, immunogenicity, vaccine, first time human trial, opsonophagocytic assay, binding assay, safety.

INTRODUCTION

Klebsiella pneumoniae (*K. pneumoniae*) is a major cause of infections in humans[1]. In high-income countries, the burden of *K. pneumoniae* is driven primarily by healthcare-associated infections (HAIs), accounting to 6-17% of HAIs, among vulnerable patients with comorbidities or invasive devices e.g. catheters or mechanical ventilation[2]. The burden of disease due to *K. pneumoniae* is higher in low- and middle-income countries (LMICs) where limited healthcare infrastructure contributes to an increased incidence of both hospital-acquired and community-acquired infections[2]. *K. pneumoniae* is a substantial contributor to death of infants and neonates in the first two years of life in LMICs[3]. In 2019, it was the second leading pathogen in deaths attributed to antimicrobial resistant (AMR) bacteria particularly in South Asia, Sub-Saharan Africa, and parts of Eastern Europe[4,5].

In recent decades, the increase in the acquisition of resistance to a wide range of antibiotics among *K. pneumoniae* strains has severely limited treatment options. This growing public threat has prompted the World Health Organization (WHO) to classify it as a priority 1 pathogen, prioritising the development of treatment strategies and vaccinest[6].

There have been numerous efforts to develop vaccines against *K. pneumoniae* [7] including the use of attenuated bacteria, inactivated whole cells, polysaccharide and lipopolysaccharides, proteins and ribosomal vaccines[8-14] but no licensed vaccines are currently available. The success of glycoconjugate vaccine for other encapsulated bacteria has increased interest in a similar approach for Klebsiella vaccine development.

K. pneumoniae produces two key surface polysaccharides that play an essential role in its virulence. Capsular polysaccharide (CPS) designated as the K antigen, consist of a repeating sugar matrix structure covering the outer bacterial layer while a key structural element of the outer component of the Gram-negative outer membrane is lipopolysaccharide (LPS) which is a conserved lipid A region and an external O-antigen polysaccharide[15]. Eleven unique serotypes have been identified for the O-antigen compared to more than 100 different K structures. A

vaccine targeting the O antigen has been proposed as a rational approach considering the limited number of O structures[15-17].

Epidemiological studies showed that O1, O2, O3, O4 and O5 are the top prominent O types responsible for more than 80% of infections in Africa and South Asia, regions that bear the greatest burden of *K. pneumoniae antibiotic resistance*[18,19].

In view of this, LimmaTech Biologics (LMTB) has developed a tetravalent bioconjugate vaccine (Kleb4V) comprising the O1v1, O2a, O2agf and O3b serotypes linked to the detoxified recombinant exoprotein A of *Pseudomonas aeruginosa* (EPA). The use of EPA aims to induce immunologic memory and enhance immunogenicity to the polysaccharide. According to this data and assuming a cross protection between the O1 serotypes (O1v1 and O1v2), Kleb4V is projected to provide coverage for approximately 70% of *K. pneumoniae* strains causing human infection worldwide although this may vary by region. Here we describe a first in man phase I trial designed to assess the safety and immunogenicity of this vaccine.

METHODS

Study design and participants

This was a First Time in Human (FTIH) phase I/II, observer-blind, randomised, placebo-controlled study to evaluate the safety and immunogenicity of two doses of a candidate *K. pneumoniae* bioconjugate vaccine (Kleb4V), intramuscular administered twice, 2 months apart, with or without AS03 (a proprietary adjuvant system of GSK). The study was conducted in two steps (Figure S1 – supplementary material): Step 1 (safety cohort), where 16 healthy adults 18-40 years old were enrolled in a staggered fashion in two groups (group 1 and 2, 8 subjects/group) and sequentially administered the Kleb4V target dose (64 ug), non-adjuvanted and thereafter adjuvanted with AS03, or placebo (PBS buffer). Following this, 32 healthy adults 55-70 years old were enrolled via a staggered dose escalating (16µg and 64µg) approach (group 3 to 6, 8 subjects/group) with enrolment of the group receiving the non-adjuvanted dose preceding enrolment of the adjuvanted one; Step 2 (target cohort), where 118 healthy adults 55-70 years old were concomitantly randomised toward any Kleb4V dose with or without AS03, or placebo. Approval was obtained from the Ethics Committee (EC) of the Bavarian State Chamber of Physicians, Muehlbauerstrasse 16, 81677 Munich and all participants provided written informed consent. A list of eligibility criteria, demographic data and other baseline characteristics of the participants are included in Tables S1 and S2 – Supplementary material.

Study Vaccine

Kleb4V contained O antigen-polysaccharides (PS) of *K. pneumoniae* serotypes O1v1, O2a, O2afg and O3b each conjugated to the EPA,. The target dose contained 16µg glycan/serotype,

for a total of 64µg PS, and the low dose 4µg glycan/serotype, for a total of 16µg PS. The trial was conducted in two clinical sites in Germany (Nuvisan sites in Neu Ulm and Gauting).

Randomisation and masking

The study was observer blind. Healthy volunteers, sites personnel, DSRC, sponsor and CRO study teams were blinded, except designated representatives (including the pharmacist, the assigned unblinded biostatistician and monitor). The randomisation list was generated by the CRO and kept in a safe location with restricted access. Blinding was maintained throughout the the study. In the first 2 groups of Step 1 two sentinels were randomized 1:1;and six further subjects per each group 5:1. Randomization in groups 3 to 6 of step 1 was 3:1. Subjects in Step 2 were randomized to receive Kleb4V low (16ug) or target (64ug) dose, both with or without AS03 (N=24 each) or Placebo (N=22).

Procedures

Subjects had 8 onsite visits in Step 1, and 9 in Step 2, including screening, two vaccination visits, follow-up visits 7 days after each injection, 14 days after 1st injection (Step 2 only), 1 month post 1st- and post 2nd injection, and finally 6 months after last injection (Figure S2 – supplementary material).

At each vaccination a diary card was provided for the participant to collect solicited and unsolicited AEs in the 7 days following each vaccination. Unsolicited AEs were collected for 28 days following each injection. Any serious adverse events (SAEs), AEs of special interest (AESIs) i.e. potential immune-mediated diseases (pIMDs) and any AEs leading to vaccine/study withdrawal, were collected for the entire study duration. At screening, vaccination visits and at the visit 7 days following each vaccination, blood was drawn to test safety parameters. In addition, blood was drawn to test immune response against Kleb4V antigens, at the day of each vaccination, 14 days after the 1st injection (in Step 2 only), 1 month post each vaccination and at the final follow up visit.

Outcomes

The primary objective was to obtain first-in-human safety and immunogenicity data following administration of Kleb4V to 55-70 years old adults and identify the preferred formulation of Kleb4V. The safety assessment focussed on the occurrence, severity and relationship of solicited and unsolicited adverse events (AEs) during 7 and 28 days, respectively, following each vaccination, as well as occurrence of SAEs and other medically relevant AEs during the entire study duration. Geometric mean titres (GMTs) of serum IgG against the O-serotypes included in Kleb4V, at baseline and at 28 days post 2nd vaccination were evaluated for the primary immunogenicity assessments.

Antibody measurements

Sera from vaccinees taken at day 15, 29, 85 and 225 were assessed. IgG titres against the 4 vaccine-serotypes were measured using a qualified multiplexed bead assay developed in the University College London (UCL) laboratory[20]. Functional immunity to O1v1, and O1v2 (assessing cross reactive immunity with O1v1) was measured by means of a functional opsonophagocytic killing assay (OPA) , optimized and qualified at the UCL, while functional immunity to O2afg was measured by a Serum bactericidal assay[20]. No functional assay for O2a or O3b existed at the time the samples were available for analysis.

Statistical analysis

The sample size for the target population (55-70 y) was driven by the primary immunogenicity analyses (GMT 28 days after 2nd vaccination) and for each of the 5 treatment arms was estimated to be 30 subjects, assuming that: IgG responses follow a log-normal distribution; a ≥ 2.5-fold difference in IgG (geometric mean ratio = 2.5) in each comparison; Alpha=0.0125 (two-sided); Beta=0.1 (i.e., power = 90%); an overall drop-out rate of 14% (Steps 1 and 2). The sample size of 150 subjects was obtained by combining 32 subjects from Step 1 and 118 subjects from Step 2: for each treatment group except placebo, 6 subjects came from Step 1 and 24 from Step 2; for the placebo group, 8 subjects came from Step 1 and 22 from Step 2.

The Immunogenicity endpoints were evaluated in the per-protocol population of participants who completed the two-dose vaccination schedule. Immunogenicity objectives included evaluating the geometric mean ratio (GMR), IgG responses, expressed as the ratio between the baseline and the post vaccine timepoint of interest. The GMR was analysed using analysis of covariance (ANCOVA), with treatment as a fixed factor and baseline titre as a covariate. Dunnett's procedure compared the four active treatment groups to placebo, accounting for multiplicity, with a study-wide alpha level of 0.05. For these primary comparisons, treatment ratios, adjusted p-values and two-sided confidence intervals with adjusted coverage were computed following the back-transformation of the results to the original scale. The number and percentage of vaccinees presenting at least a 4-fold increase in their IgG titres against the four serotypes, referred as responders, were also calculated. The corresponding exploratory 95% confidence intervals were calculated using the Clopper-Pearson method.

A summary of the descriptive statistics for antibody functionality included the minimum, maximum, and median titres for opsonophagocytic assay (OPA)/serum bactericidal assay (SBA) titre for each serotype across the treatment groups, along with the GMT and GMR from baseline, are all presented with 95% confidence intervals. The safety endpoints were evaluated descriptively in the safety population, which comprised participants who received at least one dose of the vaccine.

Role of the funding source

The funders were involved in the study design, study operations, data collection, analysis, interpretation, and writing of the manuscript and report. The funders had final responsibility for the decision to submit for publication.

RESULTS

Between 29 June 2021 and 26 Sep 2022, 289 individuals were screened, 166 subjects were included and randomly assigned while 161 completed the study and were eligible for immunogenic assessment (Figure 1). Five participants (four vaccinees, one placebo) dropped out due to reasons unrelated to vaccination or safety events (four subjects after the 1st vaccination and one subject after the 2nd vaccination). The mean age of participants in the target group who received the different formulations were 60.7 ± 4.13 yr for the low dose, 61.1 ± 4.36 yr for the low adjuvanted dose, 60.2 ± 4.96 yr for the target dose, 61.5 ± 4.96 yr for the target adjuvanted dose and 60.4 ± 4.00 yr for the placebo.

No potential immune-mediated diseases (pIMDs) were reported in this study, and most AEs were of mild to moderate intensity (Table S3 – supplementary material). All participants (n=12) aged 18-44 years, who received either the 64 µg Kleb4V or 64 µg Kleb4V adjuvanted with AS03, reported solicited AEs related to vaccination, primarily localized reactions at the injection site, and two reported unsolicited AEs. Among the four participants aged 18-44 years administered with placebo, two participants reported solicited and unsolicited AEs, which were considered related to the investigational product. As well in the target age group (55-70 years), the incidence of solicited AEs deemed related to vaccination, was higher in the vaccinated groups vs. placebo, namely 60% (n=18) and 90.0% (n=27) in the 16 µg group without and with AS03, respectively; 80 (n=24) and 96.7% (n=29) in the 64 µg group without and with AS03, respectively; vs. 36.7% (n=11) of the participants who received placebo . For both age groups, there was no difference in the number of subjects reporting solicited AEs after the 1st and 2nd dose, however, the severity of AEs increased after the second vaccination. Among the 18-40 yr. participants, AEs of severe intensity only occurred in two participants after 2nd vaccination with Kleb4V (receiving adjuvanted and not adjuvanted formulation). In the older age group, the number of subjects with severe solicited AEs was similar after the 1st and 2nd vaccination except for the 16 µg Kleb4V + AS03 group, where more subjects reported severe solicited AEs after the 2nd vaccination. Severe local reactions were reported among vaccinees following 1st (4 subjects) and 2nd vaccination (4 subjects), mostly in the adjuvanted 64 µg Kleb4V group. All cases were transient and resolved with no sequelae.

A higher incidence of unsolicited AEs related to the investigational product was reported after administration of 64 µg compared to 16 µg Kleb4V (i.e. 16.7% after 16 µg Kleb4V with/ without AS03, vs. 36.7% after 64 µg Kleb4V and 46.7% after 64 µg Kleb4V adjuvanted with AS03)

(Table S3 – supplementary material). Overall, five subjects experienced six SAEs: one subject after administration of 64 µg Kleb4V, one subject after administration of 64 µg Kleb4V adjuvanted with AS03 and three subjects after placebo administration. All SAE were considered not related to the investigational product.

The geometric mean serotype-specific IgG titers (GMT), 28 days after the second vaccination (D85) in the target group (55-70 yr old), showed a statistically significant increase for each of the four serotypes in all vaccine groups compared to placebo (p<0.0008) (Figure 2).

IgG responses, expressed as the ratio between the baseline and D85 timepoint, are shown in Table 1. In general, the GMR was highest for O1v1 and lowest for O3b (Table 1). The reduced immunogenicity of O3b may be attributable to its distinctive glycan structure, which is rich in mannan, similar to that described for the *Escherichia coli* O8 serotype commonly found in humans and therefore more likely to be tolerated[21]. The Kleb4V 64µg formulation was in general the most immunogenic and when adjuvanted with AS03, resulted in improved responses to O2a, O2afg and O3b (Table 1 and Figure 2). IgG responses on D15 and D29 following receipt of the first dose can also be seen in Figure 2. While not part of the formal analysis, it is clear that in general responses to the 4 O antigens in the vaccine developed rapidly over the first 4 weeks following receipt of vaccine, with little increase following the second vaccination.

The percentage of participants with ≥ 4-fold IgG responses on Day 85 compared to baseline were high for the adjuvanted 64 µg formulation, and in a similar range for serotypes O1v1, O2a and O2afg (range 89-93%, Table 1). Percentages were lower for O3b, although increased for the recipients of the two adjuvanted formulations (~50%).

At the final visit six months after the second vaccination (D225), most of the target population, administered with the adjuvanted 64 µg formulation, still showed GMTs at least fourfold higher than at baseline for O1v1 (96%), O2a and O2afg (89%) (Table S4), and about half of them (48%) for serotype O3b.

Functionality of the antibody response generated following vaccination, was evaluated for the vaccine serotypes O1v1 and O2afg by OPA and SBA, respectively. These were the only two assays available and qualified at the time the study was undertaken. There was a significant increase over and above baseline in functional antibody for all vaccine groups when assessed on D85 (Figure 3 and Table 2) although functionality did not appear to correlate with the amount of antigen or the presence of adjuvant. For O1v1, fold increases above baseline measured on D29 were slightly higher than at D85 with no clear impact of AS03. For O2afg, fold increases rose between D29 and D85 with the greatest increases in the group who received the unadjuvanted 64 µg formulation (44.8 increased to 58.6%). Cross-reactivity toward serotype O1v2, not included in the vaccine, was also measured by OPA. The overall pattern of functional antibody post vaccination mirrored that of O1v1 (Figure 3c) although fold increases over baseline were significantly lower than those seen for O1v1 (Table 2) on both D29 and D85. There was a clear

correlation between antibody titres and functional activity; O1v1 (r=0.77, p<0.0001) and O2afg (r=0.55, p<0.0001) (Figure S3- Supplementary material).

DISCUSSION

This is the first in human study of a novel Klebsiella bioconjugate vaccine. All Kleb4V formulations were generally well tolerated; 8 participants experienced severe local reactions (6% of all Kleb4V-administered subjects), with 6 of them in the groups receiving the AS03-adjuvanted vaccine formulations. Adverse events were limited and resolved without any lasting effects. The majority of both solicited and unsolicited adverse events were of mild to moderate severity. The Kleb4V bioconjugate was shown to be immunogenic with high percentage of subjects exhibiting at least a 4-fold increase of IgG compared to baseline against O1v1, O2a and O2afg at all visits. In general, the 64 µg formulation was superior to the 16 µg formulations, and the adjuvanted formulations triggered a better immune response than the non-adjuvanted ones. Such an effect was less evident for serotype O1v1, probably because of its generally higher immunogenicity compared with the other vaccine serotypes.

Multiple vaccine modalities have been explored for *K. pneumoniae* over the past five decades. Early whole-cell or lysate preparations demonstrated immunogenicity in small studies but raised safety and standardization concerns[10,12,22,23].Subsequent efforts focused on vaccine development based on CPS. A notable historical effort was a 24-valent CPS vaccine (including K2, K3, K5, K9, K10, K15–18, K21, K22, K25, K28, K30, K35, K43, K52, K53, K55, and K60–64) that entered a Phase 1 clinical trial and was immunogenic and well tolerated when co-administered with a *Pseudomonas* O-antigen conjugate[9,24,25]. However, CPS formulations face inherent challenges with more than 100 K serotypes, substantial geographic variability and the poor immunogenicity of unconjugated polysaccharide in young children[26].

Therefore, efforts have included a focus on O-antigen–based conjugate strategies with at least 11 O serotypes being recognized compared to more than 100 capsular K antigens[18,27]. In particular, serotypes O1, O2, O3, O4 and O5 typically account for ~80–90% of clinical isolates, supporting the rationale for multivalent O-antigen vaccines. Encouraging preclinical data have been provided by Hegerle *et al.* in 2018 who reported a quadrivalent O-antigen conjugate (O1, O2, O3, O5) linked to *Pseudomonas* flagellin that elicited functional antibodies to the four O-antigen polysaccharides types and protection in mice and rabbit models[28].

Similarly a heptavalent O-antigen bioconjugate vaccine (O1v1, O1v2, O2a, O2afg, O3, O3b and O5) developed by Omniose and collaborators, recently reported their preclinical evaluation, showing immunogenicity in animals against each of the seven bioconjugates, with limited cross-reactivity among subtypes and variable complement-mediated killing across strains[11]. Similar to our findings in humans, O1v1 IgG rabbit antisera recognized both O1v1 and O1v2 bacterial serotypes[11].

These immunogenicity results underscore the promise of O antigen targeting and suggest that epitope accessibility is possible with an O antigen vaccine. This is a relevant as several studies have suggested that the capsule may sterically mask underlying O-antigens, reducing the accessibility of anti-O antibodies and potentially limiting functional efficacy[29,30]. Therefore, in designing Kleb4V, we focused on the O1v1, O2a, O2afg and O3b antigens because they are more conserved across clinically relevant isolates, are accessible to antibodies on the bacterial surface, and have demonstrated functional bactericidal activity in preclinical models.

The less prevalent, though regionally significant, serotype O5 was not included in Kleb4V. Similar to serotype O3, O5 consists of a linear polymannose chain. However, despite the comparable mannose linkages, studies report limited cross-reactivity between these serotypes, likely due to the β-linked Manp unique to the O5 repeat unit, which may alter the overall O-antigen conformation and immunogenicity[27]. Inclusion of the O5 serotype in future generation of multivalent Klebsiella vaccines could therefore be considered. While anti-CPS immunity is likely to be important for protective immunity, O-antigen–targeted strategies, if successful, will provide broader strain coverage with fewer vaccine antigens.

There are two recent efforts in Klebsiella conjugate vaccine that are under early development, with no publicly available data to our knowledge. A conjugate vaccine is being designed at the University of Maryland, to be given to pregnant women from low- and middle-income countries, to pass protection to their babies via maternal antibodies[31]. Another vaccine candidate (CladeVax) is a nasal spray vaccine being developed at Tulane University against MDR *K. pneumoniae*. CladeVax is designed to protect the immunocompromised and the.

In conclusion, Kleb4V has an acceptable safety profile and was immunogenic in healthy adults aged between 55 and 70 years. This target age group was chosen for this phase I/II in order to reflect the population most commonly exposed to Klebsiella infections, especially in nosocomial environments.

The absence of an immuno-correlate or surrogate of protection currently represents a limitation and means that an efficacy trial of a Klebsiella vaccine with a clinical endpoint would be required. However, the extensive sample size required for such an efficacy trial remains a concern, despite recent efforts to identify populations at elevated risk of Klebsiella infection in order to de-risk a clinical proof-of-concept efficacy study[32]. Should an immune correlation become available (for example from epidemiological studies with mothers and newborns), the data available from Kleb4V could be potentially useful for predicting clinical efficacy. To date, to our knowledge, Kleb4V is the only Klebsiella bioconjugate vaccine tested in phase I/II trials in humans, and its positive safety and immunogenicity outcomes pave the way to continue further its clinical development, expanding on formulation studies and efficacy clinical proof of concept trials.

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Figure 1. Trial profile. Selection and screening and randomization of patients at the Neu-Ulm site and the Gauting site in Germany, where 124 and 42 subjects were included, respectively. The 166 subjects included were randomised and treated and 161 subjects completed the study as planned. All subjects were treated with two doses of the same formulation and were included in the safety set. Subjects who did not receive the 2nd vaccination and/or had no immunogenicity evaluation available for the visit 1 month post 2nd vaccination (Visit 8) were excluded from the immunogenicity analysis set (IAS). Kleb4V target dose=64 µg, Kleb4V low dose=16 µg, AS03 (adjuvant; PBS) and placebo (PBS).

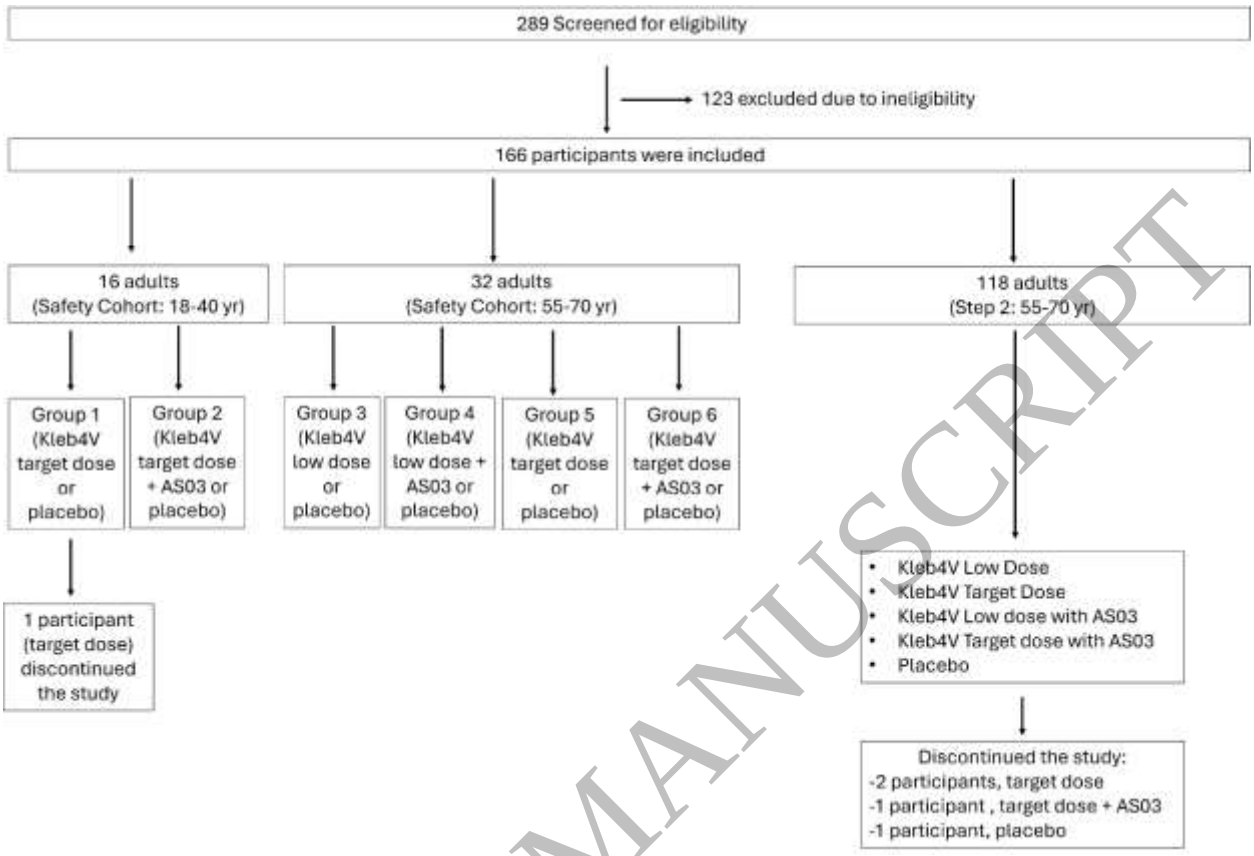
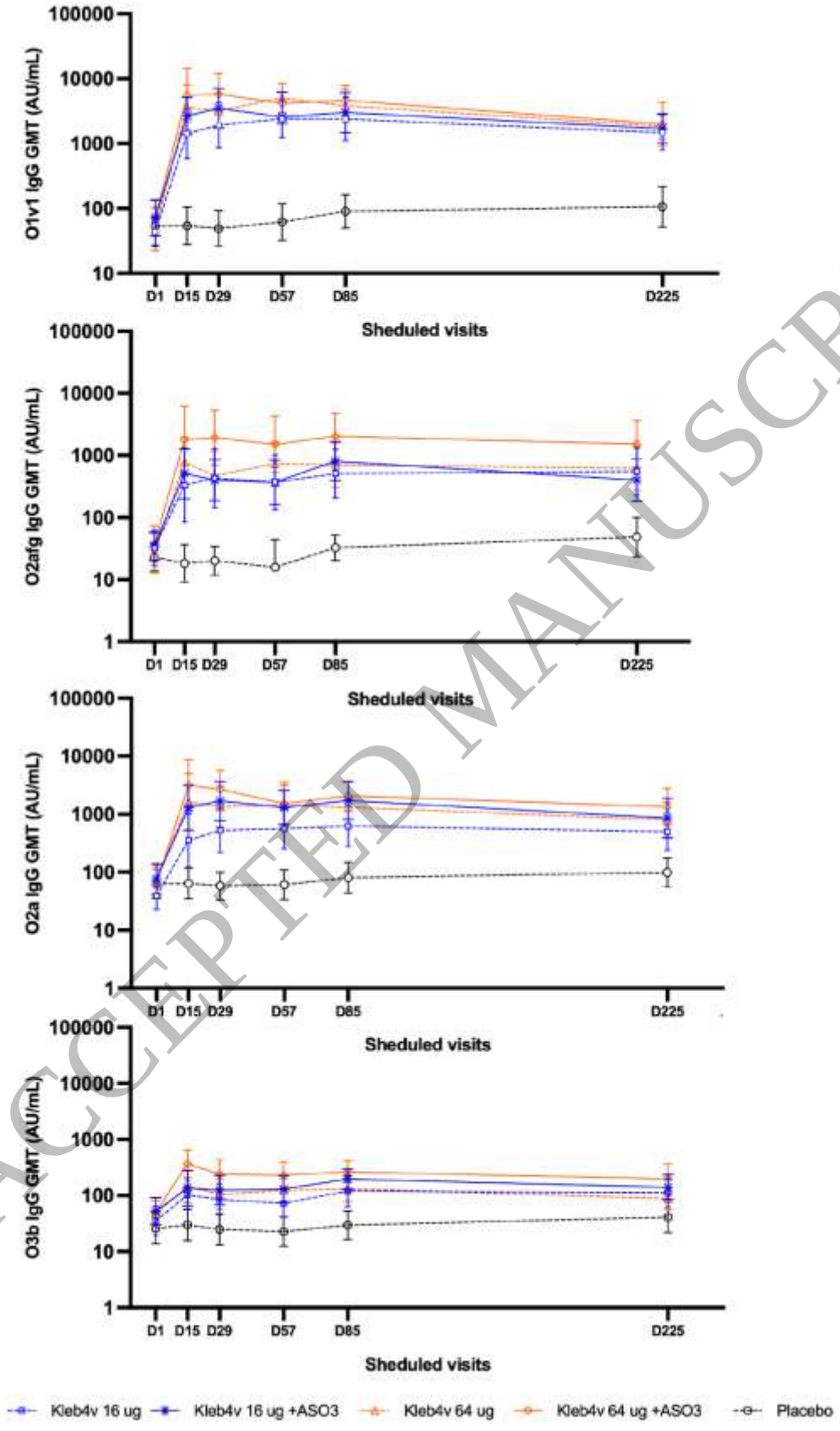


Figure 2. Antibody specific IgG in sera of vaccinees (55-70 years (IAS), as measured by a multiplex Luminex, to O antigens (a) O1v1, (b) O2a, (c) O2afg and (d) O3b which were included in the vaccine. Data is expressed as GMTs of antibody titres and 95% confidence interval. Vaccine was administered on Day1 and Day 57 and antibody titres were measured at each of the 6 visits on the days indicated.



DOI: 10.1093/infdis/jiaf600

Figure 3. Functional activity of antibody specific IgG in sera of vaccinees (55-70 years (IAS) specific to O antigens (a) O1v1, (b) O2afg and (c) O1v2. O1v1 and O2afg antigens were included in the vaccine, and O1v2 was tested for cross reactivity. Functional activity was measured at each visit by opsonophagocytic (O1v1 and O1v2) or a bactericidal (O2afg) assay and expressed in GMTs of opsonic indices (OI) and 95% confidence interval. Vaccine was administered on Day 1 and Day 57 and antibody titres were measured 28 days after the first and second vaccination.

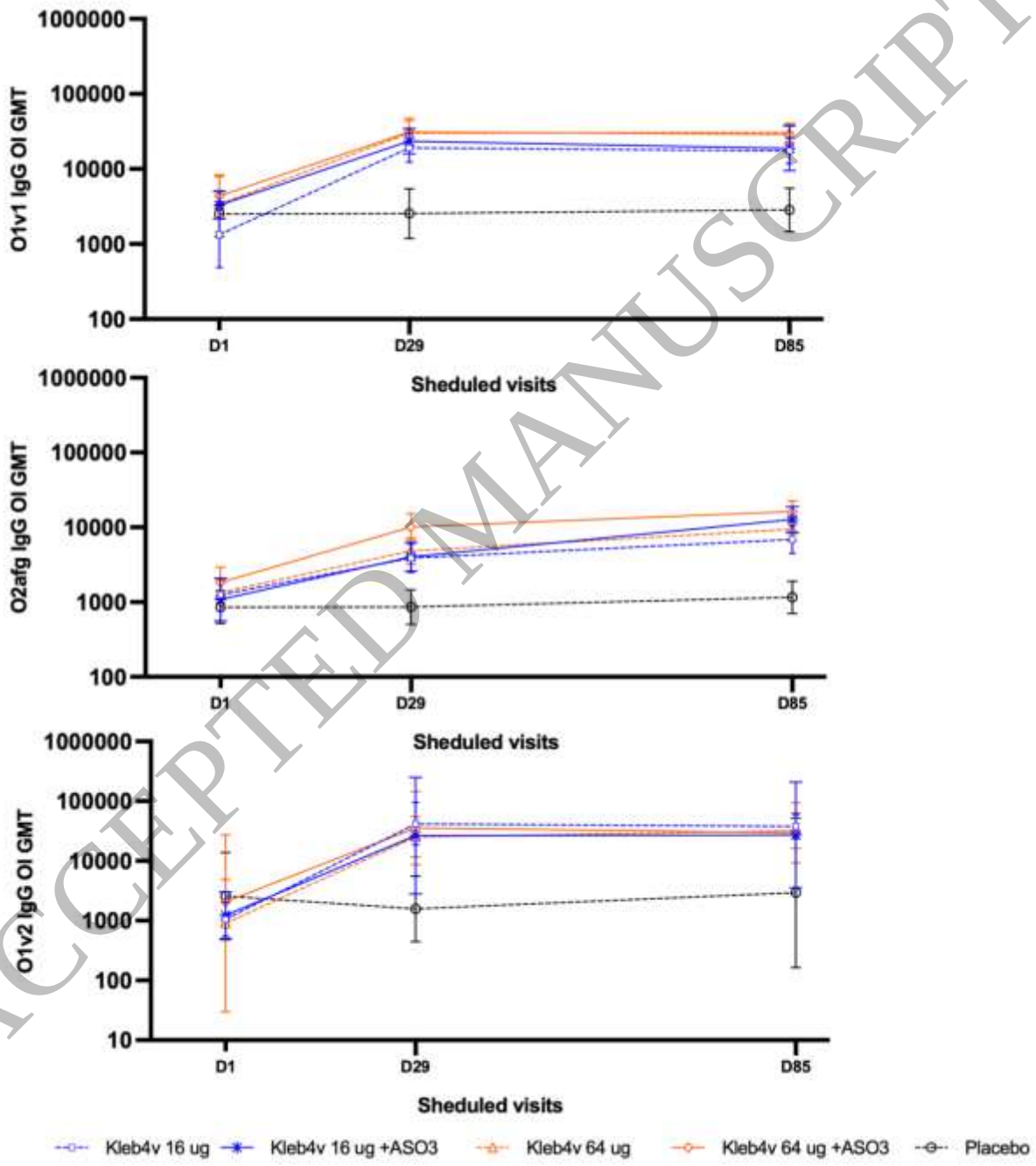


Table1. Comparison of serum IgG titres specific to O1v1, O2a, O2afg and O3b between baseline and Day 85 (visit 8) in the target population (55-70 years).

		Serotype O1v1				Serotype O2a				Serotype O2afg				Serotype O3b			
Vaccine Group	**n**	**Geometric Mean (95%CI)**	**GMR***	***p*-value****	**Fold Increase ≥4 n (%, 95%CI)**	**Geometric Mean* (95% CI)**	**GMR**	***p*-value**	**Fold Increase ≥4 n (%, 95%CI)**	**Geometric Mean* (95% CI)**	**GMR**	***p*-value**	**Fold Increase ≥4 n (%, 95%CI)**	**Geometric Mean* (95% CI)**	**GMR**	***p*-value**	**Fold Increase ≥4 n (%, 95%CI)**
Kleb4V 16µg	**29**	2709.3 (1582.2; 4639.4)	29.4	<.0001	27 (93.1%, 77.2;99.2)	853.3 (483.2;1507.1)	10.8	<.0001	24 (82.8%, 64.2-94.2)	487 (273.2;868.0)	12.1	<.0001	21 (72.4%, 52.8-87.3)	126.9 (81.5;197.7)	3.5	0.0004	12 (41.4%, 23.5-61.1)
Kleb4V 16µg + AS03	**30**	2520.4 (1472.3; 4314.7)	27.3	<.0001	25 (83.3%, 65.3;94.4)	1398.1 (794.9;2458.8)	17.8	<.0001	22 (73.3%, 54.1-87.7)	690.4 (387.4;1230.7)	17.2	<.0001	26 (86.7%, 69.3-96.2)	168.8 (108.4;263.0)	4.7	<.0001	16 (53.3%, 34.3-71.7)
Kleb4V 64µg	**29**	4115.5 (2405.0; 7042.6)	44.6	<.0001	28 (98.6%, 82.2-99.9)	1161.6 (660.4;2043.2)	14.8	<.0001	24 (82.8%, 64.2-94.2)	757.1 (424.7;1349.6)	18.9	<.0001	25 (86.2%, 68.3-96.1)	121.6 (78.1;189.5)	3.4	0.00008	10 (34.5%, 17.9-54.3)
Kleb4V 64µg + AS03	**29**	4107.5 (2398.8; 7033.4)	44.5	<.0001	27 (93.1%, 77.2-99.2)	1984.6 (1129.1;3488.4)	25.2	<.0001	26 (89.7%, 72.6-97.8)	1692.6 (948.5;3020.5)	42.2	<.0001	27 (93.1%, 77.2-99.2)	238.6 (153.1;371.9)	6.6	<.0001	15 (51.7%, 32.5-70.6)
Placebo	**29**	92.3 (54.0;157.9)			4 (13.8%, 3.9-31.7)	78.7 (44.7; 138.2)			1 (3.4%, 72.6-97.8)	40.1 (22.5;71.6)			5 (17.2%, 5.8-35.8)	35.9 (23.0;56.2)			5 (17.2%, 5.8-35.8)

*Geometric Mean Ratio, Active vs Placebo

**Dunnett p-value

Table 2. Summary data of GMT for OPA (O1v1, O1v2) and SBA (O2afg) to the different O serotypes: fold increase ≥4 from baseline population 55-70 years.

			Treatment				
Serotype	**Visit**		**Kleb4V 16µg (N=29)**	**Kleb4V 16µg + AS03 (N=30)**	**Kleb4V 64µg (N=29)**	**Kleb4V 64µg + AS03 (N=29)**	**Placebo (N=29)**
O1v1 (OPA)	V5 (D29)	n	16	15	18	15	0
		Percentage	55.2	50.0	62.1	51.7	0.0
		95% CI in %	(35.7;73.6)	(31.3;68.7)	(42.3;79.3)	(32.5;70.6)	-
	V8 (D85)	n	17	14	17	12	1
		Percentage	58.6	46.7	58.6	41.4	3.4
		95% CI in %	(38.9;76.5)	(28.3;65.7)	(38.9;76.5)	(23.5;61.1)	(0.1;17.8)
O1v2 (OPA)	V5 (D29)	n	6	3	3	5	0
		Percentage	20.7	10.0	10.3	17.2	0.0
		95% CI in %	(54.1;100)	(11.8;88.2)	(11.8;88.2)	(35.9;99.6)	-
	V8 (D85)	n	6	4	4	6	0
		Percentage	20.7	13.3	13.8	20.7	0.0
		95% CI in %	(54.1;100)	(22.3;95.7)	(22.3;95.7)	(54.1;100)	-
O2afg (SBA)	V5 (D29)	n	10	7	14	13	0
		Percentage	34.5	23.3	48.3	44.8	0.0
		95% CI in %	(17.9;54.3)	(9.9;42.3)	(29.4;67.5)	(26.4;64.3)	-
	V8 (D85)	n	15	19	21	17	3
		Percentage	51.7	63.3	72.4	58.6	10.3
		95% CI in %	(32.5;70.6)	(43.9;80.1)	(52.8;87.3)	(38.9;76.5)	(2.2;27.4)

* In associazione con altri antiretrovirali, per i pazienti adulti con infezione da HIV-1 resistente a molti farmaci, per i quali non è altrimenti possibile stabilire un regime antivirale soppressivo[1]

HIV-1 MDR: Virus HIV-1 multiresistente; PLHIV: Persone che vivono con l'HIV.

Classe di rimborsabilità: H
Prezzo al pubblico: (IVA inclusa) al netto degli sconti obbligatori di legge: € 4.951,24
600 mg - compressa a rilascio prolungato - uso orale - flacone (HDPE)
A.I.C. n. 049362015/E (in base 10) (confezione da 60 compresse)
Regime di dispensazione: medicinale soggetto a prescrizione medica limitativa, da rinnovare volta per volta, vendibile al pubblico su prescrizione di centri ospedalieri o di specialisti - infettivologo (RNRL).

La segnalazione delle reazioni avverse sospette che si verificano dopo l'autorizzazione del medicinale è importante, in quanto permette un monitoraggio continuo del rapporto beneficio/rischio del medicinale.

Agli operatori sanitari è richiesto di segnalare qualsiasi reazione avversa sospetta tramite il sito web dell'Agenzia Italiana del Farmaco: https://www.aifa.gov.it/content/segnalazioni-reazioni-avverse

▼Medicinale sottoposto a monitoraggio addizionale. Ciò permetterà la rapida identificazione di nuove informazioni sulla sicurezza. Agli operatori sanitari è richiesto di segnalare qualsiasi reazione avversa sospetta.

1. Rukobia Riassunto delle Caratteristiche del Prodotto
RCP RUKOBIA

ViiV Healthcare

Codice deposito aziendale: PM-IT-FST-JRNA-250001.
Materiale promozionale rivolto esclusivamente ai medici
Depositato in AIFA il: 15/07/2025.
VIETATA LA DISTRIBUZIONE AL PUBBLICO.

Consulta il Riassunto delle Caratteristiche del Prodotto attraverso il QRcode