Sponsor: Novartis Vaccines and Diagnostics GmbH & Co. KG

Investigational Product: Helicobacter pylori vaccine (HP)

Indication: Prevention of Helicobacter pylori infection

Protocol Number: V99P2

Protocol Title: Phase I/II, Randomized, Observer-blind, Placebo-controlled, Single- Center Study of the Tolerability, Immunogenicity, and Efficacy (following *Helicobacter pylori* infectious challenge) of Novartis' Investigational *H. pylori* Vaccine in *H. pylori*-Negative Adults

Phase of Development: Phase I/II

Study Period:

Date of first enrolment: 14 OCT 2008

Date of last visit: 08 MAR 2010

Methodology:

Overview: This is a phase I/II, randomized, observer-blind, placebo-controlled, single-center study in healthy HP-uninfected adults. Novartis' HP vaccine was administered intramuscularly (IM) according to a 0, 1, 2-month vaccination schedule. Placebo vaccine (aluminum hydroxide adjuvant alone) was administered IM at 0, 1, 2 months as a control. Initially 56 healthy HP-uninfected adults 18 through 40 years of age were randomized in a 4:3 ratio to HP vaccine and placebo groups, respectively, as follows:
Group 1 – HP Vaccine administered at 0, 1, and 2 months (32 healthy adults, total)
Group 2 – Placebo administered at 0, 1, and 2 months (24 healthy adults, total)
The study had four phases: screening phase, vaccination phase, HP challenge phase (sub divided into stage 1A, stage 1B and stage 2) and an eradication phase. There were 11 scheduled study visits in total with 4 follow-up phone calls throughout the course of the study. All subjects underwent upper gastrointestinal endoscopy (UGE) at screening and only HP-uninfected subjects were enrolled. One month after the last HP vaccination, 7 subjects (2 placebo and 5 HP vaccine) who comprised stage 1A of the study, were given the oral HP infectious challenge (25 microgram dosage level). A Data Monitoring Committee (DMC) monitored the safety and tolerability of the infectious challenge based on AEs collected up to 2 weeks after the challenge. At 12 weeks post HP challenge the stage 1A subjects received a second UGE in addition to the non-invasive HP tests. The DMC reviewed in unblinded fashion the infection rates of the stage 1A subjects at 12 weeks post HP challenge. The rate of HP infection was 0/2 subjects in the placebo group and 1/5 subjects in the HP vaccine group. With these safety data and infection rates

the DMC considered the HP challenge to be safe and reasonably tolerated, but suggested altering the challenge regimen to enhance the likelihood of 'take' or infection with the HP infectious challenge. The HP challenge regimen was altered per DMC guidance to: (1) increase the HP challenge inoculum 10- fold to 25 microgram dosage level; (2) increase the dose of pre-challenge famotidine; and (3) omit the pre-challenge urea breath test (UBT) (which can alter gastric pH).
Following the change in HP infectious challenge regimen, an additional 7 individuals (3 placebo and 4 HP vaccine recipients) was enrolled into the study: this replacement would allow analysis of a total of 28 subjects undergoing the same HP infectious challenge regimen, as specified in the protocol. This stage 1B of the HP infectious challenge phase yielded 27 subjects (13 placebo and 14 HP vaccine) receiving the revised HP challenge regimen described above.

During a scheduled interim analysis the DMC reviewed unblinded infection rates among the stage 1B subjects (n=27) at 12-weeks post HP infectious challenge. The data yielded three conclusions: (1) The observed rates of HP infection among the HP vaccine recipients (5 of 14, or 36%) and the placebo recipients (6 of 13, 46%) were considered comparable between the two groups; (2) The lack of observed difference in infection rates between the two groups did not support protective efficacy of the HP vaccine; (3) the HP infection rate among placebo recipients was lower than expected (46%, lower than the 50% considered in the study protocol to constitute futility) and the DMC concluded it would be futile to administer the HP challenge to the remaining enrolled study subjects (stage 2 subjects; n=28). Following the recommendation of the DMC, the HP infectious challenge phase was terminated and study subjects completed only follow-up assessments for approximately one month after the last HP vaccination.
UGE was performed on all enrolled subjects during screening, while the stage 1A and 1B subjects (34 subjects who underwent the HP infectious challenge phase) received a second UGE at study visit 10 (12 weeks post HP challenge). Subjects confirmed to be HP-infected at this visit (visit 10) were subjected to HP eradication therapy as specified in the protocol, and a repeat UGE was conducted after the eradication therapy (Visit 11) to confirm HP eradication.

Adverse events (AEs) (solicited and unsolicited) were collected during the first 7 days following each injection, and during the 4 weeks following HP infectious challenge. AEs occurring after the 7 days following each injection, or after 4 weeks following HP challenge, were recorded if they required medical advice or were of concern to the subject.

There were a total of 4 scheduled blood draws during the study period, with a minimal total blood volume of 363 milliliters (mL), approximately three quarters of a pint of blood, over the 6 month study period.

The major immunogenicity evaluation of humoral and cellular immunity includes HP vaccine-specific antibody studies and peripheral blood mononuclear cell (PBMC) responses to HP vaccine antigens. Briefly, sera (from 10 mL of whole blood drawn

without anticoagulant) were obtained for VacA, CagA, and NAP enzyme-linked immunosorbent assay (ELISAs) during scheduled study visits as follows:

- Pre-vaccination to pre-challenge study visits (visits 1-4, vaccination phase)
- each week for the first four weeks after the HP challenge (visits 5-8, HP challenge phase)
- 12 weeks after the HP challenge (visit 10, HP challenge phase)

Number of Subjects (planned and analyzed):

A total of 63 healthy adult subjects were planned and actually enrolled in this study.

Study Centers:

One study center in Germany

Publication (reference) and/or ClinicalTrials.gov National Clinical Trial (NCT) Number:

NCT00736476

Objectives:

The primary endpoint of the study is prevention of H. pylori infection.

Efficacy and Immunogenicity Objectives:

Primary Objective (Endpoint):

- To assess the efficacy (defined as prevention of infection) of the HP vaccine based on the HP infection rates in the HP vaccine vs. placebo groups at 12 weeks following HP infectious challenge.

Secondary Objectives:

- To determine the time course of HP infection following HP challenge in HP vaccine and placebo groups, as assessed by UGE (upper gastrointestinal endoscopy) and non-invasive HP tests (urea breath test [UBT])and fecal antigen test (FAT)
- To define the humoral and cellular immune responses after HP vaccination and following subsequent infectious challenge with HP
- To identify potential immune markers to distinguish HP vaccination from natural HP infection.
- To correlate mucosal and systemic cellular immune responses as assessed by sampling of gastric mucosa and peripheral blood cells, respectively.
- To define potential immune correlates of protection (prophylactic efficacy).

Safety Objectives:

Primary Objective:

- To assess the tolerability of Novartis' HP vaccine vs. placebo. Measures to evaluate safety will include monitoring of local and systemic adverse events and clinical laboratory tests.

Secondary Objective:

- To assess gastrointestinal symptoms following HP challenge in HP vaccine and placebo groups using the Gastrointestinal Symptom Rating Scale (GSRS)

Test Product, Dose, Mode of Administration, Lot Number:

The investigational HP vaccine is a sterile preparation of three purified antigens, adjuvanted with aluminum hydroxide, in an isotonic buffer solution for intramuscular injection. Lot number provided is Y81D22N1 (expiry date on 26th February 2008).

Duration of Study:

Expected duration of each individual subject's participation for the total study was about 34 weeks. The total duration of the study was about 17 months.

Reference Therapy, Dose, Mode of Administration, Lot Number:

No reference therapy was used in this study.

Statistical Methods:

The statistical evaluation of the results was performed by B&SR as predefined in the Statistical Analysis Plan (SAP). Statistical analyses and the statistical tables and graphs were generated using SAS® version 9.1 or higher (SAS Institute, Cary, NC).

Diagnosis and Main Criteria for Inclusion and Exclusion:

Inclusion Criteria

Individuals eligible to be enrolled into this study were those:

- who were 18 to 40 years of age and in good health as determined by the outcome of a medical history, physical examination and clinical judgment of the investigator
- able to comprehend and follow all required study procedures
- willing and able to sign an informed consent form
- who were determined not to be HP-infected based on the results of non-invasive testing (i.e. HP serological test, UBT, FAT) and UGE
- who had a negative urine pregnancy test and use of hormonal or barrier method of birth control (females of childbearing age) throughout the 12-month duration of the study

Exclusion Criteria

Individuals not eligible to be enrolled into this study are those who:

- had daily contact with children age 2 or younger
- had remote or current HP infection (as determined by HP serology, non-invasive

HP testing, or by UGE)

- had major gastrointestinal surgery (e.g., other than appendectomy), documented peptic ulcer disease, gastrointestinal hemorrhage, gall bladder disease, inflammatory bowel disease, frequent diarrhea, or irritable bowel syndrome
- had significant esophageal, gastric or duodenal pathology (gastric atrophy, dysplasia, or intestinal metaplasia ulcer or other abnormalities of the upper gastrointestinal tract) as determined by medical evaluation or UGE
- had drug or alcohol dependence based on investigator clinical judgment
- had significant acute or chronic medical or psychiatric illness
- had any serious chronic or progressive disease (e.g., any history of neoplasm, diabetes, cardiac disease, autoimmune disease, HIV infection or AIDS, or blood dyscrasias, signs of cardiac or renal failure or severe malnutrition)
- had a known or suspected disease of the immune system, or were receiving immunosuppressive therapy, including use of systemic corticosteroids or chronic use of inhaled high-potency corticosteroids within the previous 60 days regular use of salicylates, nonsteroidal anti-inflammatory drugs, anticoagulants, or gold salts
- had allergy or intolerance to aspirin, other salicylates, lidocaine**,** lansoprazole, omeprazole, H_2-receptor antagonists, bismuth, metronidazole, tetracycline, penicillin, amoxicillin, or macrolide antibiotics or use of any of these agents within 4 weeks prior to study entry
- had taken antibiotics within 7 days prior to enrollment or medical condition requiring the use of antibiotics during the course of the study
- had a known bleeding diathesis, or any condition that was associated with a prolonged bleeding time
- use of medications that interacted with bismuth, lansoprazole, omeprazole, amoxicillin, metronidazole, tetracycline, or macrolide antibiotics
- had received another investigational agent within 90 days or before completion of the safety follow-up period in another study, whichever was longer, prior to enrollment and unwilling to refuse participation in another investigational trial through the end of the study
- were pregnant or nursing mothers

- had any other serious chronic disease including progressive neurological disease or seizure disorder
- had received blood, blood products or a parenteral immunoglobulin preparation within the previous 60 days
- had a history of severe allergic reactions after previous vaccinations, such as anaphylactic shock, asthma, urticaria, or other serious allergic reaction or hypersensitivity to any vaccine component requiring medical intervention
- had either received, or for whom there was intent to immunize with any other vaccine(s) within 30 days prior, through 30 days following, study injection; exception: licensed flu-vaccine should not be administered within 14 days prior to enrollment but may be administered while on study if medically appropriate
- had any condition which in the opinion of the investigator and/or the medical monitor interfered with the evaluation of the study objectives
- work for or under the direct and full-time supervision of the Principal Investigators

Criteria for Evaluation:

Measures of Efficacy and Immunogenicity:

Efficacy Parameters:

Primary: HP infection assessed by UGE (histopathology, HP culture and rapid urease test [RUT]) and non-invasive tests (UBT and FAT) at 12 weeks after HP challenge (visit 10).

Secondary: Time course of HP infection after HP challenge assessed by non-invasive tests (UBT and FAT) and UGE (histopathology, HP culture and RUT) (visits 5-10).

Criteria For Assessing Efficacy Objectives:

Helicobacter pylori infection rates were to be compared in HP-vaccine and placebo recipients at 12 weeks after HP challenge (visit 10, primary efficacy analysis).

Helicobacter pylori infection rates over 3 months following HP challenge were to be compared in HP-vaccine recipients and placebo subjects (visits 5-10, secondary efficacy analysis).

The low rate of infections in the placebo group precluded any conclusive findings regarding the HP vaccine efficacy.

Criteria For Assessing Immunogenicity Objectives:

The immunogenicity response of HP vaccine group was compared to the placebo.

The primary measures of humoral immunogenicity for each HP antigen are:

- Post-vaccination ELISA concentration for each of the three antigens: CagA, NAP and VacA

The primary measure of HP vaccine-induced T cell immune responses is:

- Frequencies of antigen-specific cytokine-secreting T cells

Safety Endpoints:

The tolerability of the HP vaccine was compared to the placebo during the vaccination phase. Measures included adverse events and clinical laboratory tests were collected.. During the HP challenge phase, tolerability of the challenge was monitored using the GSRS.

To ensure eradication of HP infection in HP-infected subjects, follow-up UBT and UGE with biopsy was performed approximately 4-6 weeks after the completion of eradication treatment (visit 11). A few subjects without confirmed HP infection (negative by UGE, UBT and FAT) yet persistent mucosal inflammation at the scheduled second UGE performed at visit 10 were followed up at the discretion of the investigator to confirm resolution of mucosal inflammation.

Results:

Table 1: Overview of Subject Populations

	Placebo (N=27)	HP Vaccine (N=36)	Total (N=63)
Population:			
Enrolled	27 (100%)	36 (100%)	63 (100%)
Safety	27 (100%)	36 (100%)	63 (100%)
Modified Intention-to-treat	27 (100%)	35 (97%)	62 (98%)
Per Protocol	27 (100%)	35 (97%)	62 (98%)

Abbreviation: HP = *Helicobacter pylori*

Table 2: Summary of Study Terminations- All Enrolled Set

	Number of Subjects (% of Total)		
	Placebo	**HP Vaccine**	**Total**
Total number of subjects enrolled	27	36	63
Completed	27 (100%)	35 (97%)	62 (98%)
Completed protocol	27 (100%)	35 (97%)	62 (98%)
Premature withdrawal	0	1 (3%)	1 (2%)
Death	0	0	0
Adverse event	0	1 (3%)	1 (2%)

Abbreviation: HP = *Helicobacter pylori*

Table 3: Demography and Other Baseline Characteristics-Enrolled Population

	Placebo	HP Vaccine	Total
	N=27	N=36	N=63
Age (Years):	24.0±3.3	27.6±5.7	26.1±5.1
Sex:			
Male	10 (37%)	20 (56%)	30 (48%)
Female	17 (63%)	16 (44%)	33 (52%)
Race:			
Caucasian	27 (100%)	36 (100%)	63 (100%)
Weight (kg):	67.48±16.36	74.18±14.34	71.31±15.48
Height (cm):	173.9±9.3	175.4±9.7	174.8±9.5
Meet study criteria:			
Yes	27 (100%)	36 (100%)	63 (100%)

Categorical parameters: N (%); Non-categorical parameters: Mean±Standard Deviation.
Abbreviation: HP = *Helicobacter pylori*.

Table 4: Summary of test results for infection at 12 weeks after HP challenge (Stage 1B group)

	Placebo N=13	**HP Vaccine N=14**
Results no invasive test		
UBT positive	0	0
FAT positive	1 (8%)	3 (21%)
Results endoscopies tests		
HP culture positive	6 (46%)	5 (36%)
Rapid urease test positive	0	1 (7%)
Histopathology positive	0	1 (7%)
Positive HP infection	6 (46%)	5 (36%)

Abbreviation: FAT = fecal antigen test; HP = *Helicobacter pylori*; UBT = urea breath test
Categorical parameters: N (%)

Table 5: Percentage of subjects with PositiveSummary of Non-Invasive Tests, by Visit (Stage 1B group)

Visits	Placebo		HP Vaccine	
	(N=13)	(N=13)	(N=14)	(N=14)
	UBT positive	FAT positive	UBT positive	FAT positive
Baseline	0	0	0	0
HP Challenge (visit 4)	0	0	0	0
1 WPC (visit 5)	1 (8%)	9 (69%)	4 (29%)	9 (64%)
2 WPC (visit 6)	0	9 (69%)	1 (7%)	8 (57%)
3 WPC (visit 7)	1 (8%)	5 (38%)	0	2 (14%)
4 WPC (visit 8)	0	4 (31%)	0	3 (21%)
8 WPC (visit 9)	0	4 (31%)	0	3 (21%)
12 WPC (visit 10)	0	1 (8%)	0	3 (21%)
Post Eradication (visit 11)	0 (N=7)	0 (N=7)	0 (N=7)	0 (N=7)

Abbreviation: FAT = fecal antigen test; HP = *Helicobacter pylori*; UBT = urea breath test; WPC = weeks post challenge.

Categorical parameters: N (%)

Table 6: Summary of test results for infection at 12 weeks after HP challenge (Stage 1A group)

	Placebo N=2	**HP Vaccine N=5**
Results no invasive test		
UBT positive	0	0
FAT positive	1 (50%)	0
Results endoscopies tests		
HP culture positive	0	1 (20%)
Rapid urease test positive	0	0
Histopathology positive	0	0
Positive HP infection	0	1 (20%)

Abbreviation: FAT = fecal antigen test; HP = *Helicobacter pylori*; UBT = urea breath test
Categorical parameters: N (%)

Table 7: Percentage of subjects with Positive Non-Invasive HP Tests, by Visit (Stage 1A group)

Visits	Placebo		HP Vaccine	
	(N=2)	(N=2)	(N=5)	(N=5)
	UBT positive	FAT positive	UBT positive	FAT positive
Baseline (visit 0)	0	0	0	0
HP Challenge (visit 4)	0	0	0	0
1 WPC (visit 5)	1 (50%)	0	0	2 (40%)
2 WPC (visit 6)	2 (100%)	1 (50%)	1 (20%)	4 (80%)
3 WPC (visit 7)	0	0	0	1 (20%)
4 WPC (visit 8)	0	0	0	2 (40%)
8 WPC (visit 9)	0	0	0	0
12 WPC (visit 10)	0	1 (50%)	0	0
Post Eradication (visit 11)	0 (N=1)	0 (N=1)	0 (N=1)	0 (N=1)

Abbreviation: FAT = fecal antigen test; HP = *Helicobacter pylori*; UBT = urea breath test; WPC = weeks post challenge.

Categorical parameters: N (%)

Table 8: Summary of Geometric Mean Concentrations (95% CI) - PP population

Visits	Placebo (N=27)			HP Vaccine (N=35)		
	CagA	NAP	VacA	CagA	NAP	VacA
Baseline (visit 0)	2.95 (2.09-4.18)	5.84 (4.92-6.93)	21 (15-29)	2.42 (1.78-3.29)	4.59 (3.95-5.33)	18 (14-25)
1 month after the first vaccination (visit 2)	2.55 (1.55-4.19)	5.47 (3.68-8.13)	23 (15-33)	2.89 (1.87-4.48)	35 (25-50)	214 (154-298)
2 month after the first vaccination (visit 3)	2.56 (1.5-4.39)	5.15 (3.66-7.24)	23 (16-33)	7.74 (4.83-12)	236 (175-319)	2468 (1818-3350)
3 month after the first vaccination [HP Challenge (visit 4)]	2.54 (1.5-4.29)	5.1 (3.68-7.07)	19 (13-28)	23 (15-37)	148 (111-197)	502 (355-709)

Abbreviation: GMC = Geometric Mean Concentration; HP = *Helicobacter pylori*; Inj = injection
Categorical parameters: GMC (95% Confidence Interval)

Table 9: Summary of Geometric Mean Concentration (95% CI)-PP Population (Stage 1B group)

Visits	Placebo (N=27)						HP Vaccine (N=35)					
	CagA		NAP		VacA		CagA		NAP		VacA	
	Infected (N=6)	Non-infected (N=7)	Infected (N=6)	Non-infected (N=7)	Infected (N=6)	Non-infected (N=7)	Infected (N=5)	Non-infected (N=9)	Infected (N=5)	Non-infected (N=9)	Infected (N=5)	Non-infected (N=9)
Baseline (visit 0)	4.17 (1.48-12)	3.53 (1.35-9.23)	5.46 (3.56-8.38)	11 (7.35-16)	20 (9.61-42)	41 (21-82)	2.25 (0.72-7.02)	2.64 (1.13-6.16)	4.4 (2.75-7.04)	4.4(3.1-6.24)	21 (9.26-47)	24 (13-44)
1 month after the first vaccination (visit 2)	3.84 (0.83-18)	3.06 (0.74-13)	5.46 (3.11-9.59)	8.48 (5.03-14)	16 (6.89-37)	33 (15-72)	2.24 (0.42-12)	4.54 (1.31-16)	19 (10-36)	62 (39-99)	117 (46-295)	285 (143-569)
2 month after the first vaccination (visit 3)	4.08 (1-17)	2.95 (0.8-11)	5.54 (3.3-9.31)	6.61 (4.09-11)	25 (11-56)	33 (16-70)	2.39 (0.51-11)	14 (4.52-45)	117 (66-206)	235 (154-359)	1219 (501-2966)	2754 (1419-5344)
3 month after the first vaccination [HP Challenge (visit 4)]	3.84 (1.13-13)	2.63 (0.85-8.12)	5.35 (3.3-8.66)	6.59 (4.22-10)	20 (9.35-42)	34 (17-68)	13 (3.29-48)	93 (34-250)	101 (60-172)	251 (170-373)	565 (247-1292)	979 (529-1814)
2 WPC (visit 6)	3.92 (1.22-13)	3.59 (1.21-11)	5.58 (3.49-8.94)	8.3 (5.37-13)	24 (11-53)	45 (22-94)	16 (4.39-57)	134 (51-348)	125 (75-209)	275 (187-404)	606 (252-1453)	912 (475-1751)
4 WPC (visit 8)	4.11 (1.35-13)	3.39 (1.21-9.5)	4.4 (2.7-7.16)	8.32 (5.3-13)	28 (14-57)	46 (24-89)	30 (8.89-102)	261 (105-648)	179 (105-305)	325 (219-484)	2174 (995-4752)	1943 (1085-3479)
12 WPC (visit 10)	7.51 (2.03-28)	4.73 (1.41-16)	4.4 (2.68-7.24)	8.01 (5.05-13)	58 (29-115)	73 (39-138)	149 (35-625)	202 (69-588)	115 (67-199)	208 (139-313)	3467 (1632-7366)	1469 (838-2577)

Abbreviation: GMC = Geometric mean concentration; HP = *Helicobacter pylori*; Inj. = injection; WPC = weeks post challenge;
Categorical parameters: GMT (95% Confidence Interval)

Table 10: Summary of Geometric Mean Concentration (95% CI)-PP Population (Stage 1A group)

Visits	Placebo (N=27)						HP Vaccine (N=35)					
	CagA		NAP		VacA		CagA		NAP		VacA	
	Infected (N=0)	Non-infected (N=2)	Infected (N=0)	Non-infected (N=2)	Infected (N=0)	Non-infected (N=2)	Infected (N=1)	Non-infected (N=4)	Infected (N=1)	Non-infected (N=4)	Infected (N=1)	Non-infected (N=4)
Baseline (visit 0)	0	1.77 (1.77-1.77)	0	4.4 (4.4-4.4)	0	9.22 (1.89-45)	7.02*	1.77 (1.77-1.77)	19*	4.4 (4.4-4.4)	50 (5.35-471)	32 (11-100)
1 month after the first vaccination (visit 2)	0	1.77 (0.073-43)	0	4.4 (1.6-12)	0	9.22 (0.97-88)	7.58 (0.084-687)	4.52 (0.47-43)	334 (80-1392)	56 (28-115)	851 (35-20582)	271 (55-1334)
2 month after the first vaccination (visit 3)	0	1.77 (0.044-71)	0	4.4 (1.19-16)	0	9.22 (1.79-47)	72 (0.39-13262)	5.23 (0.39-71)	2254 (354-14349)	399 (158-1007)	8557 (845-86625)	2009 (631-6391)
3 month after the first vaccination [HP Challenge (visit 4)]	0	1.77 (0.19-17)	0	4.4 (1.66-12)	0	9.22 (2.5-34)	66 (2.81-1568)	20 (4.09-97)	1309 (330-5198)	423 (212-843)	1253 (198-7917)	1408 (560-3539)
2 WPC (visit 6)	0	1.77 (0.16-20)	0	4.4 (1.45-13)	0	18 (3.02-111)	79 (2.56-2416)	23 (4.14-127)	1408 (293-6763)	451 (206-989)	1138 (89-14585)	1288 (360-4611)
4 WPC (visit 8)	0	1.77 (0.27-12)	0	4.4 (1.57-12)	0	24 (3.95-146)	137 (9.7-1940)	59 (16-222)	2079 (486-8898)	468 (226-967)	1018 (79-13052)	2516 (703-9007)
12 WPC (visit 10)	0	12 (0.68-227)	0	4.4 (1.39-14)	0	300 (23-3844)	463 (7.64-28087)	175 (23-1366)	1168 (228-5981)	286 (126-646)	1492 (40-55043)	2458 (405-14931)

*95% CI not available.
Abbreviation: GMC = Geometric Mean Concentration; HP = *Helicobacter pylori*; WPC- = weeks post challenge.
Categorical parameters: GMT (95% Confidence Interval)

Table 11: Number (%) of Subjects with Local and Systemic Adverse Events During the 7 day period after Each Injection

	Number (%) of Subjects With Solicited Reactions					
	First vaccination		Second vaccination		Third vaccination	
	Placebo N=27	HP vaccine N=36	Placebo N=27	HP vaccine N=35	Placebo N=27	HP vaccine N=35
Any	20 (74%)	27 (75%)	16 (59%)	23 (66%)	15 (56%)	24 (69%)
Local	18 (67%)	24 (67%)	14 (52%)	20 (57%)	14 (52%)	21 (60%)
Systemic	13 (48%)	19 (53%)	7 (26%)	16 (46%)	9 (33%)	15 (43%)
Other	3 (11%)	4 (11%)	0	6 (17%)	2 (7%)	2 (6%)

Abbreviation: HP = *Helicobacter pylori*.
Categorical parameters: N (%)

Table 12: Number (%) of Subjects with Local Adverse Events During the 7 day period after Each Injection

		Number (%) of Subjects With Solicited Reactions					
		First vaccination		Second vaccination		Third vaccination	
Injection Site		**Placebo N=27**	**HP vaccine N=36**	**Placebo N=27**	**HP vaccine N=35**	**Placebo N=27**	**HP vaccine N=35**
Erythema (mm)	Any	6 (22%)	3 (8%)	4 (15%)	6 (17%)	5 (19%)	11 (31%)
	> 100 mm	0	0	0	0	0	0
Induration (mm)	Any	2 (7%)	1 (3%)	1 (4%)	4 (11%)	3 (11%)	6 (17%)
	> 100 mm	0	0	0	0	0	0
Swelling (mm)	Any	2 (7%)	1 (3%)	0	1 (3%)	0	4 (11%)
	> 100 mm	0	0	0	0	0	0
Warmth	Any	2 (7%)	1 (3%)	0	3 (9%)	1 (4%)	1 (3%)
	Severe	0	0	0	0	0	0
Tenderness	Any	16 (59%)	19 (53%)	12 (44%)	17 (49%)	9 (33%)	17 (49%)
	Severe	0	0	0	1 (3%)	0	0
Pain	Any	8 (30%)	16 (44%)	8 (30%)	17 (49%)	7 (26%)	14 (40%)
	Severe	0	0	0	0	0	0

Abbreviation: HP = *Helicobacter pylori*.

Table 13: Number (%) of Subjects with Systemic Reactions During the 7 day period after Each Injection

		Number (%) of Subjects With Solicited Reactions					
		First vaccination		Second vaccination		Third vaccination	
Injection Site		**Placebo N=27**	**HP vaccine N=36**	**Placebo N=27**	**HP vaccine N=35**	**Placebo N=27**	**HP vaccine N=35**
Chills	Any	0	1 (3%)	0	2 (6%)	0	1 (3%)
	Severe	0	0	0	0	0	0
Malaise	Any	2 (7%)	2 (6%)	0	2 (6%)	1 (4%)	2 (6%)
	Severe	0	0	0	0	0	0
Myalgia	Any	8 (30%)	10 (2%8)	5 (19%)	9 (26%)	5 (19%)	9 (26%)
	Severe	0	0	0	0	0	0
Arthralgia	Any	1 (4%)	0	0	3 (9%)	0	1 (3%)
	Severe	0	0	0	0	0	0
Headache	Any	6 (22%)	9 (25%)	3 (11%)	7 (20%)	6 (22%)	6 (17%)
	Severe	0	0	0	0	0	0
Fatigue	Any	3 (11%)	10 (28%)	4 (15%)	5 (14%)	2 (7%)	4 (11%)
	Severe	0	0	0	0	0	0

		Number (%) of Subjects With Solicited Reactions					
Rash	Any	0	1 (3%)	0	0	0	1 (3%)
	Urticaria	0	1 (3%)	0	0	0	1 (3%)
Fever (≥ 38 °C)	Yes	0	0	0	0	0	0
Other							
Oral Temp. (°C)	<38 C	27 (100%)	36 (100%)	27 (100%)	35 (100%)	27 (100%)	35 (100%)
	38 - < 39.5 °C	0	0	0	0	0	0
	39.5 - < 40.5°C	0	0	0	0	0	0
	≥ 40.5°C	0	0	0	0	0	0
Stayed Home Due to Reaction	Yes	0	0	0	1 (3%)	0	1 (3%)
Analgesic Antipyretic Medicines Used	Yes	3 (11%)	4 (11%)	0	6 (17%)	2 (7%)	2 (6%)

Abbreviation: HP = *Helicobacter pylori*.

Table 14: Number (%) of Subjects Reporting Unsolicited Adverse Events

	Number (%) of Subjects with Adverse Events	
	Placebo N=27	**HP vaccine N=36**
Any AEs	12 (44%)	24 (67%)
At least possibly related AEs	1 (4%)	6 (17%)
Serious AEs	0	1 (3%)
AEs leading to discontinuation	0	1 (3%)
Death	0	0

Abbreviation: AE = Adverse event; HP = *Helicobacter pylori*.

Table 15: Number (Percentages) of Subjects with Serious Adverse Events by Preferred Term sorted by System Organ Class

	Number (%) of Subjects	
MedDRA System Organ Class MedDRA Preferred Term	**Placebo** **N=27**	**HP vaccine** **N=36**
Any Serious Adverse Events	0	1 (3%)
Infection & Infestation	0	1 (3%)
Pilonidal Cyst	0	1 (3%)

Abbreviations: HP = *Helicobacter pylori*; MedDRA = Medical dictionary for regulatory activities.

Number and percent of subjects with one or more events (as reported on Adverse Events form) that map to each MedDRA system organ class or MedDRA preferred term. Hence, MedDRA preferred term counts may not sum to MedDRA system organ class counts, and MedDRA system organ class counts may not sum to overall counts

Table 16: Number (Percentages) of Subjects with Unsolicited Adverse Events Reported by ≥ 5% of Subjects by Preferred Term sorted by System Organ Class

	Number (%) of Subjects	
MedDRA System Organ Class MedDRA Preferred Term	**Placebo N=27**	**HP vaccine N=36**
Any Adverse Events	12 (44%)	24 (67%)
Gen. Disorders &Admin. Site Condition		
Influenza Like Illness	0	8 (22%)
Injection Site Reaction	0	2 (6%)
Pain	0	2 (6%)
Infections & Infestation		
Influenza	3 (11%)	3 (8%)
Nasopharyngitis	2 (7%)	2 (6%)
Nervous System Disorder		
Headache	2 (7%)	7 (19%)
Skin & Subcutaneous Tissue. Disorder		
Erythema	1 (4%)	3 (8%)

Abbreviations: HP = *Helicobacter pylori*; MedDRA = Medical dictionary for regulatory activities.

Number and percent of subjects with one or more events (as reported on Adverse Events form) that map to each MedDRA system organ class or MedDRA preferred term. Hence, MedDRA preferred term counts may not sum to MedDRA system organ class counts, and MedDRA system organ class counts may not sum to overall counts

Table 17: Number (Percentages) of Subjects with Unsolicited Adverse Events Reported by ≥ 5% of Subjects by Preferred Term sorted by System Organ Class with onset after HP challenge

	Number (%) of Subjects	
MedDRA System Organ Class MedDRA Preferred Term	**Placebo** **N=15**	**HP vaccine** **N=19**
Any Adverse Events	15 (100%)	16 (84%)
Cardiac Disorders	1 (7%)	1 (5%)
Cardiovascular Disorder	1 (7%)	1 (5%)
Gastrointestinal Disorder	15 (100%)	16 (84%)
Abdominal Discomfort	1 (7%)	1 (5%)
Abdominal Distention	0	4 (21%)
Abdominal Pain	8 (53%)	9 (47%)
Abdominal Pain Upper	4 (27%)	3 (16%)
Diarrhea	2 (13%)	3 (16%)
Dyspepsia	5 (33%)	4 (21%)
Gastroesophageal Reflux Disease	1 (7%)	1 (5%)
Nausea	8 (53%)	11 (58%)
Vomiting	5 (33%)	3 (16%)
Gen. Disorders & Admin. Site Cond.	1 (7%)	2 (11%)
Influenza like Illness	1 (7%)	2 (11%)
Infections & Infestations	4 (27%)	1 (5%)
Gastroenteritis	1 (7%)	0
Gastroenteritis Viral	1 (7%)	0
Nasopharyngitis	1 (7%)	1 (5%)
Urinary Tract Infection	1 (7%)	0
Injury & Poisoning	1 (7%)	0
Joint injury	1 (7%)	0
Nervous System Disorder	3 (20%)	2 (11%)
Headache	2 (13%)	1 (5%)
Migraine	1 (7%)	0
Skin & Subcutaneous Tis. Disorder	1 (7%)	0
Drug Eruption	1 (7%)	0

Abbreviations: HP = *Helicobacter pylori*; MedDRA = Medical dictionary for regulatory activities.

Number and percent of subjects with one or more events (as reported on Adverse Events form) that map to each MedDRA system organ class or MedDRA preferred term. Hence, MedDRA preferred term counts may not sum to MedDRA system organ class counts, and MedDRA system organ class counts may not sum to overall counts

Conclusion:

The HP vaccine was well tolerated and there were no vaccine-related SAEs reported during the study.
Vaccination induced measurable HP-specific Ab to all three HP antigens (CagA, NAP, and VacA), in contrast to placebo recipients.
Rates of HP infection among the vaccine recipients (36%) and the placebo recipients (46%) were not considered different from one another, suggesting an absence of efficacy. This conclusion is limited however, by lower than expected rates of HP infection in the placebo arm, suggesting failure of the model and futility in continuing with any further challenges.

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