premier platinum
HpSA® PLUS

Enzyme Immunoassay for the Detection of *Helicobacter pylori* Antigens in Stool Specimens for Diagnosis and Monitoring

REF 601396 IVD Rx Only

INTENDED USE
The Premier Platinum HpSA PLUS enzyme immunoassay (EIA) is an in vitro qualitative procedure for the detection of *Helicobacter pylori* antigens in human stool. Test results are intended to aid in the diagnosis of *H. pylori* infection and to monitor response during and post-therapy in patients. Accepted medical practice recommends that testing by any current method, to confirm eradication, be done at least four weeks following completion of therapy.

SUMMARY AND EXPLANATION OF THE TEST
Since its discovery over 20 years ago by Marshall and Warren,[1] *Helicobacter pylori* is now recognized as one of the most common and medically important pathogens worldwide.[2] *Helicobacter pylori* has been firmly established as an etiologic agent in chronic gastritis and peptic ulcer disease, and has been associated with mucosa-associated lymphoid tissue lymphoma and gastric adenocarcinoma.[1, 3-7]

The ecological niche in humans appears to be restricted to the stomach and the duodenum. Patients who harbor the organism are divided into two basic groups. The first group shows no signs or symptoms of gastrointestinal disease and is considered as "colonized". The second group shows gastrointestinal signs and symptoms and is considered as "infected". The process by which an individual becomes colonized or infected is still under investigation.[3, 4, 8-10] Many possible routes of transmission of *Helicobacter pylori* to humans such as animals, contaminated water and oral reservoirs have been suggested.[11]

Diagnostic tests for *H. pylori* can be categorized as invasive (endoscopy, biopsy) or noninvasive (serology, urea breath test and stool antigen test). In invasive testing, a biopsy is taken from the upper gastrointestinal tract and examined microscopically. The tissue is also cultured for *H. pylori* or evaluated in the rapid urease test. This strategy offers the advantages of detecting an active infection and has high specificity and a high positive predictive value. The disadvantages of invasive testing include risk and discomfort to the patient and colonization in patches that might be missed by biopsy. Culture of biopsy material is time consuming and can yield false-negative results due to inherent technical difficulties.[3, 12-15]

The urea breath test (UBT) is a type of noninvasive test that detects the highly active urease of *H. pylori*. Although UBT is highly sensitive and specific, it has a number of significant drawbacks. UBT is time consuming, requires specialized detection equipment and involves the ingestion of isotopically labeled urea by the patient.[3, 16, 17] Serological tests, also noninvasive, based on the detection of IgG against *H. pylori* are useful for primary screening of patients that present with uncomplicated infections, yet they do not distinguish between past exposure and active infection.[5, 11, 18] The stool antigen test has been evaluated extensively and has been accepted as an accurate non-invasive test both before and after treatment. [19-21] The recent Maastricht V Consensus Report recommends the use of the stool antigen and UBT tests as an aid in the diagnosis of *H. pylori* disease in the primary care setting.[22]

Premier Platinum HpSA PLUS is a microwell-based enzyme immunoassay that detects *H. pylori* antigens present in human stool. No calculations are required and the visual color change makes the interpretation of results objective and simple. In addition, the HpSA test permits assessment of established or novel anti-*H. pylori* treatment during and post-therapy to monitor for treatment effectiveness, relapse or eradication. Premier Platinum HpSA PLUS is a modification of Premier Platinum HpSA that provides increased signal strengths with positive test results and better discrimination between low positive and negative tests.

BIOLOGICAL PRINCIPLES
The Premier Platinum HpSA PLUS test utilizes a plurality of monoclonal anti-*H. pylori* capture antibodies adsorbed to microwells. (Plurality is defined as a mixture of monoclonal antibodies.) Diluted patient samples and a conjugate (peroxidase conjugated to a plurality of monoclonal antibodies) are added to the wells and incubated for one hour at room temperature. A wash is performed to remove unbound material. Substrate is added and incubated for 10 minutes at room temperature. Color develops in the presence of bound enzyme. Stop Solution I is added and the results are interpreted visually or spectrophotometrically.

REAGENTS/MATERIALS PROVIDED
The maximum number of tests obtained from this test kit is listed on the outer box.
1. **Antibody Coated Microwells -** Breakaway plastic wells coated with a plurality of murine monoclonal antibodies specific for *H. pylori*.
2. **Positive Control -** Inactivated *H. pylori* diluted in 10 mM phosphate-buffered solution with 0.02% Thimerosal, pH 7.2.
3. **Sample Diluent/Negative Control -** pH 7.2, 10 mM phosphate-buffered solution with 0.02% Thimerosal.
4. **Premier 20X Wash Buffer I -** pH 6.8, 180 mM phosphate-buffered solution with 0.2% Thimerosal.
5. **Enzyme Conjugate –** A plurality of murine monoclonal antibodies specific for *H. pylori* conjugated to horseradish peroxidase in a pH 7.8, 50 mM Tris-buffered solution containing 0.02% Thimerosal.
6. **Premier Substrate I -** a-buffered solution containing urea peroxide and tetramethylbenzidine. (pH 5.0)
7. **Premier Stop Solution I –** 1 M phosphoric acid. CAUTION: Avoid contact with skin. Flush with water if contact occurs.
8. Transfer pipettes (one for each test sample). Each pipette is marked to indicate 50 µL, 100 µL, 200 µL and 300 µL volumes.
9. Plate sealer.
10. Wooden stick applicators.

MATERIALS NOT PROVIDED
1. Test tubes (12 x 75 mm) for dilution of sample
2. Distilled or deionized water
3. Squirt bottle
4. Graduated cylinder for making 1X Wash Buffer I
5. EIA plate reader capable of reading absorbance at 450 or 450/630 nm*
6. Semiautomated plate washer (e.g., BioTek Elx50) *

* **Note:** It is the operator's responsibility to validate the semiautomated plate washers and readers prior to their use with this product.

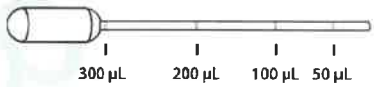
PRECAUTIONS
1. All reagents are for in vitro diagnostic use only.
2. Patient specimens may contain infectious agents and should be handled and disposed of as potential biohazards.
3. All reagents should be mixed gently before use.
4. Do not interchange the Microwells, Enzyme Conjugate, Substrate I Reagent, or Positive Control reagents between lots. (The Sample Diluent, Premier 20X Wash Buffer I and Premier Stop Solution I are interchangeable provided the reagents are within their assigned expiration dates when used.)
5. Allow reagents to warm to 19-27 C before use.
6. Hold reagent vials vertically at suitable distance above the well to insure proper drop size and delivery.
7. Do not use kit components beyond labeled expiration date.
8. Replace colored caps on correct vials.
9. Dispose of used wash buffer and all test materials in an appropriate container. Treat waste as a potential biohazard.
10. The Positive Control reagent contains inactivated *H. pylori*. It should be handled, however, as a potential biohazard.
11. Avoid skin contact with Premier Stop Solution I (1 M phosphoric acid). Flush with water immediately if contact occurs.
12. Do not reuse microwells.
13. Unused microwells must be placed back inside resealable pouch. It is important to protect strips from moisture.
14. The transfer pipettes provided with this kit must be used for specimen preparation and transfer. Use one per specimen.
15. Avoid splashing when dispensing diluted stool into microwells by placing the transfer pipette tip about halfway down the well and dispensing slowly down the side of well.
16. Microwell washing is to be performed precisely as directed in assay procedure. Inadequate washing may be the cause of elevated background in any EIA protocol.
17. All reagents except the Premier 20X Wash Buffer I are provided already diluted to the proper concentration.
18. Any deviation below or above set incubation times may affect sensitivity and specificity and should be avoided.
19. Stool must be mixed thoroughly (regardless of consistency) to insure a representative sample prior to pipetting.
20. Some precipitation may occur in Premier 20X Wash Buffer I when it is stored at 2-8 C. The precipitate will dissolve when a working dilution is made with the Wash Buffer.
21. Do not use vials that lack a label, a lot number, or an expiration date.

HAZARD and PRECAUTIONARY STATEMENTS

 Premier Stop Solution I	**Signal Word** Danger **Hazard Statements** H412 - Harmful to aquatic life with long lasting effects H314 - Causes severe skin burns and eye damage Contains Phosphoric acid **Precautionary Statements - EU (§28, 1272/2008)** P260 - Do not breathe dust/fume/gas/mist/vapors/spray P264 - Wash face, hands and any exposed skin thoroughly after handling P280 - Wear protective gloves/ protective clothing/ eye protection/ face protection P305 + P351 + P338 - IF IN EYES: Rinse cautiously with water for several minutes. Remove contact lenses, if present and easy to do. Continue rinsing P310 - Immediately call a POISON CENTER or doctor/ physician P303 + P361 + P353 - IF ON SKIN (or hair): Remove/ Take off immediately all contaminated clothing. Rinse skin with water/ shower P363 - Wash contaminated clothing before reuse P304 + P340 - IF INHALED: Remove to fresh air and keep at rest in a position comfortable for breathing P310 - Immediately call a POISON CENTER or doctor/ physician P301 + P330 + P331 - IF SWALLOWED: Rinse mouth. Do NOT induce vomiting P405 - Store locked up P501 - Dispose of contents/ container to an approved waste disposal plant.
 Premier 20X Wash Buffer I	**Signal Word** Danger **Hazard Statements** H302 - Harmful if swallowed H311 - Toxic in contact with skin **Precautionary Statements - EU (§28, 1272/2008)** P280 - Wear protective gloves/ protective clothing/ eye protection/ face protection

SHELF LIFE AND STORAGE
The expiration date is indicated on the kit label. Store the kit at 2-8 C and return the kit promptly to the refrigerator after each use.

PROCEDURAL NOTES
The Premier Platinum HpSA PLUS transfer pipette is diagrammed below:



REAGENT PREPARATION
1. Bring the entire kit, including microwell pouch, to 19-27 C before use.
2. Prepare 1X Wash Buffer I as needed. For example: 4.0 mL of Premier 20X Wash Buffer I + 76.0 mL of distilled or deionized water is sufficient to wash one strip. Place in a clean squirt bottle. The 1X Wash Buffer I can be stored at 19-27 C for up to three months.

SPECIMEN COLLECTION AND PREPARATION
The specimen should be received in an airtight transport container and stored at 2-8 C until tested. The specimen should be tested as soon as possible, but may be held up to 72 hours at 2-8 C prior to testing. (See SPECIMEN PREPARATION section for instructions on diluting samples.) If testing cannot be performed within this time frame, specimens should be frozen immediately upon receipt and stored frozen (-20 C to –80 C) until tested. Specimens may be frozen and thawed twice.
NOTE: Stool in transport media, swabs, or preservatives are inappropriate for testing.

SPECIMEN PREPARATION
1. Using a pipetting device, add 500 µL of Sample Diluent to a clean test tube.
2. Mix stool as thoroughly as possible prior to pipetting.
   a. Liquid or semi-solid stools - Using the supplied transfer pipette, add 100 µL (second mark from the tip of the pipette) of stool into Sample Diluent. Using same pipette, gently withdraw and expel the stool suspension several times, then vortex 15 seconds. Save the transfer pipette in the sample for later use.
   b. Formed/Solid stools - Using a wooden applicator stick, transfer a small portion (5-6 mm diameter) of thoroughly mixed stool into Sample Diluent. Emulsify stool using the wooden applicator stick, then vortex 15 seconds.
3. Stool specimens may be centrifuged after dilution. Centrifuge at approximately 2750 x G for five minutes or until solid matter separates from liquid. Proceed with the assay after recovering supernate.

TEST PROCEDURE
1. After the pouch has reached temperature, break off the required number of microwells (1 well for each specimen, plus 1 positive and 1 negative control well per batch). Place the microwells in the microwell strip holder and record the location of all wells. Unused microwells must be resealed in the pouch immediately.
2. Using the specimen transfer pipette, add 100 µL of diluted stool (second mark from the tip of the pipette) to the appropriate well. (Place the pipette tip halfway into well and let the sample slowly run down side of well.)
3. Add 2 free falling drops of Positive Control and 100 µL of Sample Diluent /Negative Control to the appropriate wells.
4. Add 1 free falling drop (approximately 50 µL) of Enzyme Conjugate to each well. Firmly shake/swirl the plate for 30 seconds.
5. Cut plate sealer to size and press firmly onto top of microwells to seal. Incubate the plate for 1 hour at 19-27 C.
6. Carefully remove the plate sealer and wash wells:
   a. Manual method:
      i Dump plate contents firmly into a biohazard receptacle.
      ii Bang the inverted plate on a clean stack of paper towels.
      iii Fill all wells with 1X Wash Buffer I, directing stream of buffer to the sides of the wells to avoid foaming.
      iv Repeat wash cycle (dump, bang on fresh towels, fill) 4 times for a total of 5 wash cycles. After the last fill, dump and bang plates on fresh towels hard enough to remove as much excess wash buffer as possible, but do not allow wells to completely dry at any time.
   b. Semiautomated method using validated equipment
      i Aspirate the contents of the well.
      ii Fill the wells to the top (approx 300-350 µL/well) with 1X Wash Buffer I then aspirate. The washer manifold should be adjusted to ensure no foaming occurs during the filling of the wells and that the wells are thoroughly aspirated after each wash.
      iii Repeat step ii a minimum of 4 more times. Following the last wash, test wells should be thoroughly aspirated to remove as much moisture as possible.
7. Clean the underside of all wells with a lint-free tissue.
8. Add 2 free falling drops (approx. 100 µL) of Premier Substrate Solution I to each well. Firmly shake/swirl the plate for 30 seconds. Incubate for 10 minutes at 19-27 C.
9. Add 2 free-falling drops (approx. 100 µL) of Premier Stop Solution I to each well. Firmly shake/swirl the plate for 30 seconds.
   Note: Initial color of positive reaction is blue, which changes to yellow upon addition of Premier Stop Solution I.
10. Inspect and record reactions. Test results can be read visually or using a spectrophotometric reader.
    a. Visual Determination - Read within 15 minutes after adding Premier Stop Solution I.
    b. Spectrophotometric Determination - Zero EIA reader on air. Wipe underside of wells with a lint-free tissue. Read absorbance at 450 nm or 450/630 nm within 15 minutes of adding Premier Stop Solution I.

INTERPRETATION OF RESULTS
The following interpretations apply to both initial diagnosis and monitoring of anti-*H. pylori* therapy.
Visual Reading
Negative = colorless to faint yellow
Positive = definite yellow color
To be called positive, a faint yellow color must be confirmed by a spectrophotometric reading. If a spectrophotometer is not available, the cut-off must be determined by an alternative method.

Spectrophotometric Single Wavelength (450 nm)

Negative:	< 0.140
Positive:	≥ 0.140
Negative Control:	< 0.140
Positive Control:	≥ 0.640

Spectrophotometric Dual Wavelength (450/630 nm)

Negative:	< 0.100
Positive:	≥ 0.100
Negative Control:	< 0.100
Positive Control:	≥ 0.600

If a Negative Control is < 0.000, reblank the plate reader to air and reread the plate.

A positive result indicates the presence of *H. pylori* antigens. A negative result indicates the absence of *H. pylori* antigens, or that the level of antigens is below what can be detected by the assay. The magnitude of the OD above the cut-off is not indicative of the severity or extent of *H. pylori* infection, nor can it be correlated to an endpoint titer. Extremely strong positive reactions may yield a purple precipitate within a few minutes of stopping the reaction.

QUALITY CONTROL

This test should be performed per applicable local, state, or federal regulations or accrediting agencies.

1. At the time of each use, kit components should be visually examined for obvious signs of microbial contamination, freezing or leakage. Do not use contaminated or suspect reagents. The Positive and Negative Controls must be used with each test batch. See the INTERPRETATION OF RESULTS section above for a description of the expected results for control reagents. Tests should be considered invalid when either control reagent does not produce the expected results. In such cases, repeat tests and controls. If, on repeat testing, the expected reactions are still not observed and the reagents are still within their expiration date, contact Meridian's Technical Support Services at (800) 343-3858 for assistance (USA) or your local distributor.
2. The controls are used to monitor reagent reactivity. Failure of the controls to produce the expected results can mean that one or more of the reagents are no longer reactive at the time of use, the test was not performed correctly, or that reagents or samples were not added. The Positive Control will not ensure precision at the cut-off.
3. Suspect failure of the washing method or device if the Negative Control and/or Positive Controls consistently produce out of specification results. Increasing the number of washes, washing more vigorously, decanting more thoroughly or recalibrating washing devices should correct the problem. **If the expected control reactions are not observed, repeat the control tests as the first step in determining the root cause of the failure. If control failures are repeated please contact Meridian's Technical Services Department at 1-800-343-3858 (US) or your local distributor.**
4. Specimen matrix interference has not been observed in this assay as samples are significantly diluted before testing in Sample Diluent. For this reason, the positive and negative control reagents supplied as part of this assay are prepared in the matrix of the Sample Diluent. If control materials that are identical in composition to test samples are preferred, the user can prepare these by diluting known positive and negative specimens in Sample Diluent according to the SPECIMEN PREPARATION section of this insert. Add 100 µL of user prepared controls to test wells.

EXPECTED VALUES

Studies on the epidemiology of *H. pylori* have shown that this organism is present worldwide.[16, 23, 24] Gastritis caused by *H. pylori* has been shown to correlate with age, ethnic background, family size and socioeconomic class.[25, 26] The prevalence of *H. pylori* infection in a given population can vary from 20% to 90%. In patients diagnosed with duodenal ulcers, however, it has been shown in every age group to be approximately 80%.[18] Currently recommended eradication treatments have an efficacy rate between 75% and 90%.

The Premier Platinum HpSA PLUS test detects the presence of *H. pylori* antigens in human stool. Expected values for a given population should be determined for each laboratory. The rate of positivity may vary depending on geographic location, method of specimen collection, handling and transportation, test employed and general health environment of patient population under study. As demonstrated by Premier Platinum HpSA in tests conducted in the United States, Canada and Italy, incidence of disease ranged from 34% to 53% to 69% respectively.

LIMITATIONS OF THE PROCEDURE

1. The test is qualitative and no quantitative interpretation should be made with respect to the values.
2. Test results should be used in conjunction with information available from the patient clinical evaluation and other diagnostic procedures.
3. Antimicrobials, proton pump inhibitors and bismuth preparations are known to suppress *H. pylori* and ingestion of these prior to *H. pylori* testing (culture, histology, rapid urease, UBT, antigen) may give a false negative result. If a negative result is obtained for a patient ingesting these compounds within two weeks prior to performing the Premier Platinum HpSA PLUS test, it may be a false-negative result and the test should be repeated on a new specimen obtained two weeks after discontinuing treatment. A positive result for a patient ingesting these compounds, within two weeks prior to performing the Premier Platinum HpSA PLUS test, should be considered accurate. As an example, patients with *H. pylori* were placed on a proton pump inhibitor (Lansoprazole) or bismuth for two weeks, and tested with the Premier Platinum HpSA and a urea breath test. Patients were then taken off treatment for two weeks and retested. At the end of treatment, both assays were negative for some patients, but returned to positive two weeks post-treatment (see table).

		Premier Platinum HpSA		Breath Test	
Treatment	Time Point	Pos/Total	% Positive	Pos/Total	% Positive
PPI	End of Treatment	15/20	75.0%	12/20	60.0%
	2 Weeks Post-Treatment	19/20	95.0%	18/20	90.0%
Bismuth	End of Treatment	15/20	75.0%	11/20	55.0%
	2 Weeks Post-Treatment	19/20	95.0%	18/20	90.0%

4. Performance characteristics have not been established for watery, diarrheal stools.
5. Performance characteristics have not been established in asymptomatic populations.
6. H2 blockers do not interfere with positive results.

SPECIFIC PERFORMANCE CHARACTERISTICS

Clinical evaluations performed with the first generation Premier Platinum HpSA demonstrated that an ELISA -based assay could reliably and predictably detect *H. pylori* antigen in human stool in symptomatic patients. Studies also demonstrated the test can be used to monitor the efficacy of eradication therapy.

The Premier Platinum HpSA was evaluated on 200 symptomatic adults at one Midwestern United States location, one site in Canada, and two sites in Italy. The patients studied had a wide cross-section of gastric pathologies noted, including: antral gastritis (n=81), antral gastropathy (n=25), antral erosions (n=24), esophagitis (n=21), duodenal ulcer (n=15), erosive duodenitis (n=10), GERD (n=10), "normal" (n=10), duodenitis (n=9), gastric ulcer (n=8), total stomach gastritis (n=6), hiatal hernia (n=6), Schatzki's ring (n=4), pyloric ulcer (n=2), and esophageal ulcer (n=1). HpSA test results were compared to diagnosis of *H. pylori* infection as judged by objective reference methods (culture, rapid urease, histology and UBT). Patients were considered positive if culture was positive, or if two or more of the other three tests were positive. Nine patients with negative or no culture results, and only one other test positive, were considered unevaluable. The HpSA test exhibited 96.1% sensitivity and 95.7% specificity when compared to the reference method. Confidence intervals were calculated by the exact binomial method.

Trial Site #1

TEST		DIAGNOSIS		Sensitivity	Specificity	Pos. PV	Neg. PV	Correlation
Method	Result	Infected	Not Infected	± 95% CI	± 95% CI	± 95% CI	± 95% CI	± 95% CI
PPHpSA	Pos	17	3	94.4%	91.4%	85.0%	97.0%	92.5%
EIA	Neg	1	32	72.7-99.9%	76.9-98.2%	62.1-96.8%	84.2-99.9%	81.8-97.9%
	Equ	0	0					

Reference Methods: Histology, Rapid Urease, Breath Test. Readings Single and Dual Wavelength.

Trial Site #2

TEST		DIAGNOSIS		Sensitivity	Specificity	Pos. PV	Neg. PV	Correlation
Method	Result	Infected	Not Infected	± 95% CI	± 95% CI	± 95% CI	± 95% CI	± 95% CI
PPHpSA	Pos	9	0	100.0%	100.0%	100.0%	100.0%	100.0%
EIA	Neg	0	8	66.4-100.0%	63.1-100.0%	66.4-100.0%	63.1-100.0%	80.5-100.0%
	Equ	0	0					

Reference Methods: Histology, Rapid Urease, Culture, Breath Test. Readings Single and Dual Wavelength.

Trial Site #3

TEST		DIAGNOSIS		Sensitivity	Specificity	Pos. PV	Neg. PV	Correlation
Method	Result	Infected	Not Infected	± 95% CI	± 95% CI	± 95% CI	± 95% CI	± 95% CI
PPHpSA	Pos	44	0	97.8%	100.0%	100.0%	96.0%	98.6%
EIA	Neg	1	24	88.2-99.9%	85.8-100.0%	92.0-100.0%	79.6-99.9%	92.2-100.0%
	Equ	1	0					

Reference Methods: Histology, Rapid Urease, Culture, Breath Test. Readings Single Wavelength.

Trial Site #4

TEST		DIAGNOSIS		Sensitivity	Specificity	Pos. PV	Neg. PV	Correlation
Method	Result	Infected	Not Infected	± 95% CI	± 95% CI	± 95% CI	± 95% CI	± 95% CI
PPHpSA	Pos	29	1	93.5%	96.3%	96.7%	92.9%	94.9%
EIA	Neg	2	26	78.6-99.2%	81.0-99.9%	82.8-99.9%	76.5-99.1%	85.6-98.9%
	Equ	2	0					

Reference Methods: Histology, Rapid Urease. Readings Dual Wavelength.

Combined Data From All Sites

TEST		DIAGNOSIS		Sensitivity	Specificity	Pos. PV	Neg. PV	Correlation
Method	Result	Infected	Not Infected	±95% CI	±95% CI	±95% CI	±95% CI	±95% CI
PPHpSA	Pos	99	4	96.1%	95.7%	96.1%	95.7%	95.9%
EIA	Neg	4	90	90.4-98.9%	89.5-98.8%	90.4-98.9%	89.5-98.8%	92.2-98.2%
	Equ	3	0					

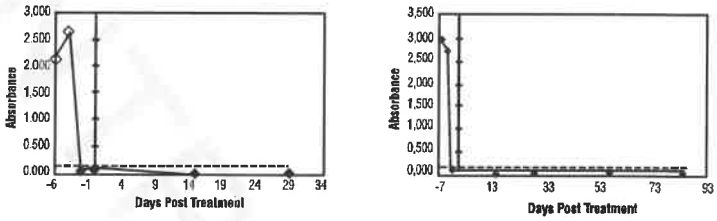
Therapeutic Monitoring:
Four sites examined the utility of the stool antigen test for monitoring anti-*H. pylori* treatment in 97 patients who initially tested positive by endoscopy (culture, histology, and rapid urease). Premier Platinum HpSA testing and endoscopic biopsies were performed four weeks after completion of physician-prescribed, *H. pylori* eradication therapy. The test results are compared in the following table. Culture, histology, and rapid urease were used to determine eradicatio n as defined by FDA guidelines.[22]

Overall: HpSA vs. 4 Week Scope		
HpSA	**4 Weeks Post Treatment**	
Result	**Infected**	**Eradicated**
Positive	18	3
Negative	1	73
Statistic	**Value**	**95% CI**
Sensitivity	94.7%	74.0-99.9%
Specificity	96.1%	88.9-99.2%
Positive PV	85.7%	63.7-97.0%
Negative PV	98.6%	92.7-100%
Correlation	95.8%	89.6-98.8%

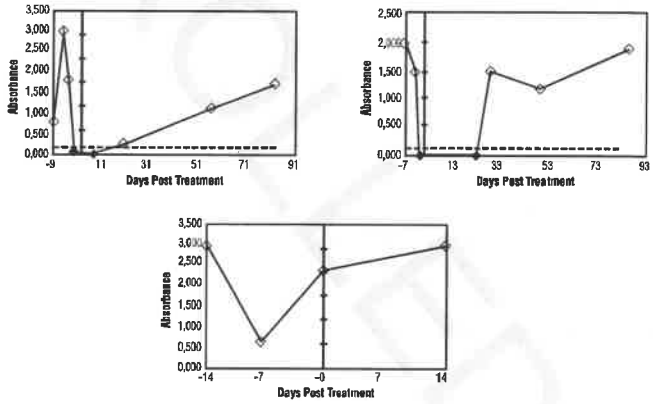
Premier Platinum HpSA correctly identified 18/19 (94.7%) of the infected and 73/76 (96.1%) of the eradicated patients. Two of the 97 stools were e quivocal by HpSA (2%). The false negative stool was from a patient that was positive by culture, histology and rapid urease. Three false positive HpSA results were obtained from patients that were negative by all other methods (culture, histology, and r apid urease).

Response to treatment is generally noted by a negative HpSA test within 5 to 7 days after initiating treatment. Pos itive results at this time, or later, indicate ineffective therapy or recurrence. Recurrence can result from lack of patient compliance with the drug regimen, ineffective drugs, resistant strains of *H. pylori*, improper dosage, etc. Recurrent *H. pylori* infection generally occurs by four weeks after termination of therapy. Occasionally, however, infections will remain cryptic beyond four weeks. This observation supports accepted medical practice that determination of eradication utilizing a ny diagnostic method should be done at least four weeks following completion of therapy. The figures below are typical response profiles for successful and unsuccessful eradication therapies. The vertical bar indicates completion of th erapy (Day 0). Days to the left of Day 0 reflect the period that patients were taking drugs. The positive cut-off is shown as horizontal dashed lines.

Eradicated Patient Profiles



Non-Eradicated (Infected) Patient Profiles



Comparison of Premier Platinum HpSA PLUS to Premier Platinum HpSA:
Tests with 291 samples from symptomatic patients collected either prior to or following treatment were used to demonstrate th at Premier Platinum HpSA PLUS performed similarly to Premier Platinum HpSA. Thirty three of the se samples were originally evaluated in an earlier trial to demonstrate the effectiveness of Premier Platinum HpSA. Test performance in cluding 95% confidence intervals is detailed in the following table.

PP HpSA PLUS	PP HpSA (Predicate)		
	Positive	**Negative**	**Indeterminate**
Positive	94	10	3
Negative	0	183	1
Agreement	**Positive Test**	**Negative Test**	**Overall**
	94/94 = 100%	183/193 = 94.8%	277/287 = 96.5%

Eight of the 10 samples that were positive by Premier Platinum HpSA PLUS, but negative by Premier Platinum HpSA, were positive by CLO, histology or UBT testing. The three samples that were pos itive by Premier Platinum HpSA PLUS but indeterminate by Premier Platinum HpSA were positive by CLO, histology or UBT testing. The one sample, that was negative by Premier Platinum HpSA PLUS but indeterminate by Premier Platinum HpSA, was negative by CLO , histology or UBT testing.

Comparison of Modified Premier Platinum HpSA PLUS to Premier Platinum HpSA PLUS (Predicate):
One hundred and fifty-nine (159) archived, unpreserved stool samples from symptomatic patients were analyzed for *H. pylori* antigen by the modified Premier Platinum HpSA PLUS and Premier Platinum HpSA PLUS (Predicate) to demonstrate that changes to the microwell and conjugate antibodies do not affect assay performance. Test performance including 95% confidence intervals is detailed in the following table.

Modified PP HpSA PLUS	PP HpSA PLUS (Predicate)		
	Positive	**Negative**	**Total**
Positive	57	0	57
Negative	0	102	102
Total	57	102	159
			95% CI
Positive Agreement	57/57	100.0%	93.7-100.0%
Negative Agreement	102/102	100.0%	96.4-100.0%

REPRODUCIBILITY
Assay precision, intra-assay variability and inter-assay variability were assessed with a reference panel prepared from moderately positive samples (n=3), low positive samples (n=3), high negative samples (n=3) and a true negative sample (n=1). In addition, the positive and negative kit controls were run when each panel was tested. Each panel was tested once a day by two technicians, at three different laboratory sites, for 5 consecutive days. Overall, 100% (300/300, 98.7-100%, 95% CI) of results obtained with the Premier Platinum HpSA PLUS were as expected. There were no invalid results generated during the study (0.0%; 0/300; 0.0-1.3%, 95% CI).

CROSSREACTIVITY
The specificity of Premier Platinum HpSA PLUS was tested by utilizing the following bacterial or viral strains. Potentially cross-reactive microorganisms were added at a target concentration of 1.0×10^7 CFU/mL (bacteria or fungi), or a concentration greater than 1×10^5 $TCID_{50}$/mL (viruses), to a natural negative and a contrived positive sample. None of the organisms affected positive or negative test results.

Microorganism or virus
Adenovirus 41, *Aeromonas hydrophila, Bacillus subtilis, Borrelia burgdorferi, Campylobacter coli, Campylobacter fetus, Campylobacter jejuni, Campylobacter lari, Candida albicans, Citrobacter freundii, Clostridium difficile, Clostridium perfringens, Enterobacter cloacae, Enterococcus faecalis, Escherichia coli O157:H7, Escherichia coli, Escherichia coli 8739, Escherichia coli 9637, Escherichia fergusonii, Escherichia hermanii, Escherichia hermanii EMDI-64, Haemophilus influenzae, Klebsiella pneumoniae, Lactococcus lactis, Listeria monocytogenes, Peptostreptococcus anaerobius, Proteus vulgaris, Pseudomonas aeruginosa, Pseudomonas fluorescens,* Rotavirus, *Salmonella dublin, Salmonella hitversum, Salmonella heidelberg* (Group B), *Salmonella minnesota, Salmonella typhimurium, Serratia liquefaciens, Serratia marcescens, Shigella boydii, Shigella dysenteriae, Shigella flexneri, Shigella sonnei, Staphylococcus aureus, Staphylococcus aureus (Cowan Strain I), Staphylococcus epidermidis and Yersinia enterocolitica*

ANALYTICAL SENSITIVITY
The Premier Platinum HpSA PLUS test can detect ≥ 4.66 ng *H. pylori* protein/mL of stool.

TESTS FOR INTERFERING SUBSTANCES
The following substances, that may be present in human stool, do not interfere with positive or negative test results at the stated concentrations per 500 µL human stool: Barium sulfate – 25 mg, Mylanta 11.5 mg, Pepto Bismol – 0.44 mg, Prilosec (omeprazole) – 1 mg, Tagamet (cimetidine) – 1 mg, Tums – 10 mg, Hemoglobin – 62.5 mg, Mucin – 17 mg, NSAID Ibuprofen – 0.25 mg, Stearic acid – 5.3 mg, Palmitic acid – 2.65 mg, White blood cells – 250 µL, Whole blood – 250 µL

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Vergleich des Premier Platinum HpSA Plus Tests mit dem Premier Platinum HpSA Test:
Testresultate mit 291 Proben symptomatischer Patienten, die entweder vor oder nach der Behandlung entnommen wurden, zeigen, dass die Tests Premier Platinum HpSA PLUS und Premier Platinum HpSA ähnliche Leistungen erfüllen. Dreiunddreißig dieser Proben wurden anfangs in einem früheren Versuch evaluiert, um die Wirksamkeit des Premier Platinum HpSA Tests zu demonstrieren. Die Leistungsmerkmale, die 95% Konfidenzintervalle einbeziehen, sind in der folgenden Tabelle detailliert.

PP HpSA PLUS Ergebnis	PP HpSA		
	Positiv	Negativ	Unbestimmbar
Positiv	94	10	3
Negativ	0	183	1
Übereinstimmung	Positiver Test	Negativer Test	Gesamt
	94/94 = 100%	183/193 = 94,8%	277/287 = 96,5%

Acht der 10 Proben, die positiv mit Premier Platinum HpSA Plus waren, aber negativ mit Premier Platinum HpSA, waren positiv mit Urease Schnelltest, Histologie oder Harnstoffatemtest (UBT). Drei Proben, die positiv mit Premier Platinum HpSA Plus waren, aber unbestimmbar mit Premier Platinum HpSA, waren positiv mit Urease Schnelltest, Histologie oder Harnstoffatemtest (UBT). Eine Probe, die negativ mit Premier Platinum HpSA Plus war, aber unbestimmbar mit Premier Platinum HpSA, war negativ mit Urease Schnelltest, Histologie oder Harnstoffatemtest (UBT).

Vergleich des modifizierten Premier Platinum HpSA PLUS Tests mit dem Premier Platinum HpSA PLUS Test (Prädikatstest)
Einhundertneunundfünfzig (159) archivierte, nicht konservierte Stuhlproben von symptomatischen Patienten wurden mit dem modifizierten Premier Platinum HpSA PLUS und dem Premier Platinum HpSA PLUS Test (Prädikatstest) auf H. pylori-Antigen analysiert, um zu zeigen, dass Änderungen an den Antikörpern der Mikrotiterplatte und des Konjugats die Assay-Leistung nicht beeinflussen.

Modifizierter PP HpSA PLUS Test	PP HpSA PLUS (Prädikatstest)		
	Positiv	Negativ	Gesamt
Positiv	57	0	57
Negativ	0	102	102
Gesamt	57	102	159
			95% CI
Positive Übereinstimmung	57/57	100.0%	93.7-100.0%
Negative Übereinstimmung	102/102	100.0%	96.4-100.0%

REPRODUZIERBARKEIT
Die Assay-Präzision, die Intra-Assay-Variabilität und die Inter-Assay-Variabilität wurden mit einem Referenzpanel aus mäßig positiven Proben (n = 3), niedrig positiven Proben (n = 3), hoch negati ven Proben (n = 3) und einer echten negativen Probe (n = 1) bewertet. Zusätzlich wurden die Positiv- und Negativ-Kit-Kontrollen durchgeführt als jedes Panel getestet wurde. Jedes Panel wurde einmal täglich von zwei Anwendern an drei verschiedenen Laborstandorten an fünf aufeinanderfolgenden Tagen getestet. Insgesamt entsprachen 100% (300/300, 98,7-100%, 95% CI) der mit dem Premier Platinum HpSA PLUS Test erzielten Ergebnisse den Erwartungen. Während der Studie wurden keine ungültigen Ergebnisse erzielt (0,0%; 0/300; 0,0-1,3%, 95% CI).

KREUZREAKTIVITÄT
Die Spezifität des Premier Platinum HpSA PLUS Tests wurde unter Verwendung der folgenden Bakterien- oder Virusstämme getestet. Potentiell kreuzreaktive Mikroorganismen wurden in einer Zielkonzentration von $1,0 \times 10^7$ CFU / mL (Bakterien oder Pilze) oder einer Konzentration von mehr als 1×10^6 $TCID_{50}$ / mL (Viren) zu einer natürlichen negativen und einer konstruierten positiven Probe hinzugefügt. Keiner der Organismen beeinflusste die positiven oder negativen Testergebnisse.

Mikroorganismen oder Viren
Adenovirus 41, *Aeromonas hydrophila, Bacillus subtilis, Borrelia burgdorferi, Campylobacter coli, Campylobacter fetus, Campylobacter jejuni, Campylobacter lari, Candida albicans, Citrobacter freundii, Clostridium difficile, Clostridium perfringens, Enterobacter cloacae, Enterococcus faecalis, Escherichia coli O157:H7, Escherichia coli, Escherichia coli 8739, Escherichia coli 9637, Escherichia fergusonii, Escherichia hermanii, Escherichia hermanii EMDI-64, Haemophilus influenzae, Klebsiella pneumoniae, Lactococcus lactis, Listeria monocytogenes, Peptostreptococcus anaerobius, Proteus vulgaris, Pseudomonas aeruginosa, Pseudomonas fluorescens,* Rotavirus, *Salmonella dublin, Salmonella hilversum, Salmonella heidelberg* (Gruppe B), *Salmonella minnesota, Salmonella typhimurium, Serratia liquefaciens, Serratia marcescens, Shigella boydii, Shigella dysenteriae, Shigella flexneri, Shigella sonnei, Staphylococcus aureus, Staphylococcus aureus (Cowan Stamm I), Staphylococcus epidermidis and Yersinia enterocolitica*

TESTEMPFINDLICHKEIT
Der Premier Platinum HpSA PLUS -Test kann ≥ 4,66 ng *H. pylori*-Protein/mL Stuhl nachweisen. (Analytische Sensibilitätsgrenze.)

STÖRSUBSTANZEN -TESTS
Die folgenden Substanzen, die möglicherweise in humanen Stuhlproben vorkommen, beeinflussen nicht die Testergebnisse bei den angegebenen Konzentrationen pro 500 µL humane Stuhlprobe: Bariumsulfat – 25 mg, Mylanta 11,5 mg, Pepto Bismol – 0,44 mg, Prilosec (Omeprazol) – 1 mg, Tagamet (Cimetidin) – 1 mg, Tums – 10 mg, Hämoglobin – 62,5 mg, Mucin – 17 mg, NSAID Ibuprofen – 0,25 mg, Stearinsäure – 5,3 mg, Palmitinsäure – 2,65 mg, Leukozyten – 250 µL, Vollblut – 250 µL.

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LOT	Batch Code / Codice del lotto / Code du lot / Código de lote / chargenbezeichnung	CONTROL −	Negative control / Controllo negativo / Contrôle négatif / Control negativo / Negative Kontrolle
IVD	In vitro diagnostic medical device / Dispositivo medico-diagnostico in vitro / Dispositif médical de diagnostic in vitro / Dispositivo médico para diagnóstico in vitro / In-Vitro-Diagnostikum	EC REP	Authorized representative in the European Community / Rappresentante Autorizzato nella Comunità Europea / Mandataire dans la Communauté européanne / Representante autorizado en la Comunidad Europea / Bevollmächtigter in der Europäischen Gemeinschaft
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REF	Catalogue number / Numero di catalogo / Référence du catalogue / Numero de catálogo / Bestellnummer		Do not freeze / Non congelare / Ne pas congeler / No congelar / Nicht Eingrieren
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	Temperature limitaion / Limiti di temperatura / Limites de température / Límite de temmperatura / Temperaturbegrenzung	CONJ ENZ	Enzyme Conjugate / Coniugato enzimatico / Conjugué enzymatique / Conjugado enzimático / enzymkonjugat
SN	Serial number / Numero di serie / Numéro de série / Número de serie / Seriennummer	CONTROL	Assay Control / Controllo del test / Test de contrôle / Control de Ensayo / Kontrolltest
TEST	Test Device / Dispositivo test / Dispositif de test / Dispositivo de Prueba / testgarät	REAG	Reagent / Reagente / Réactifs / Reactivos / Reagenzien
	Date of manufacture / Data di fabbricazione / Date de fabrication / Fecha de fabricación / Herstellungsdatum	BUF WASH	Wash Buffer / Soluzione di lavaggio / Solution de lavage / Tampón de lavado / Waschpuffer
BUF	Buffer / Soluzione tampone / Solution tamponnée / Tampón / Puffer		Warning / Avvertenze / Mise En Garde / Advertencia / Warnhinweise
CONJ	Conjugate / Coniugato / Conjugué / Conjugado / Konjugat	DIL SPE	Specimen Diluent (or Sample Diluent) / Diluente del Campione / Diluant échantillons / Diluyente de muestra / Probenverdünnungspuffer
SUBS	Substrate / Substrato / Substrat / Substrato / Substrat	BUF WASH 20X	Wash Buffer Concentration 20X / Soluzione di lavaggio 20X / Solution de lavage concentrée 20X / Solución tampón de lavado 20X / 20fach konzentriertes Waschkonzentrat
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Valerie Tyree (VTYREE)	Associate Manager, Lot Release	03 Apr 2020, 08:25:33 AM	Data Approval

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Todd Woodrich (TAW00006)	Sr. Director, Operations	03 Apr 2020, 03:43:51 PM	Data Approval
Chris Larka (CLARKA)	Scientist II Immunoassay	06 Apr 2020, 06:37:02 AM	Data Approval
Carly Magee (CMM00780)	Project Manager	07 Apr 2020, 10:32:49 AM	Data Approval

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